

Section 4

EVALUATION OF THE MAMMALIAN TOXICOLOGY AND METABOLISM/TOXICOKINETICS

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1. INTRODUCTION

1.1 Regulatory History of Health Considerations in Australia

Monocrotophos is an organophosphorothioate insecticide used in agriculture to control a range of pests in a range of horticultural and agricultural crops. Residue levels of monocrotophos were set for apples, pears and cotton seed in 1968, with uses extended into potatoes, tomatoes, sweet corn, bananas, beans and cereals throughout the 1970s and 1980s.

In Australia, public health standards for agricultural and veterinary chemicals, such as the poison schedule, first aid and safety directions and an acceptable daily intake (ADI), are set by the Department of Health and Family Services. Poison schedules are set by the National Drugs and Poisons Schedule Committee (NDPSC) or the Australian Health Ministers' Advisory Council (formerly the Drugs and Poisons Schedule Committee (DPSC) or the National Health and Medical Research Council (NHMRC). In the case of maximum residue limits (MRLs), these were formerly established by the Pesticide and Agricultural Chemicals Committee (PACC) of the NHMRC, however in 1992, the Department of Health became directly responsible for establishing MRLs, a function subsequently transferred to the National Registration Authority (NRA) in June 1994.

Health Standards

NOEL/ADI

The PACC established an acceptable daily intake (ADI) of 0.0003 mg/kg bw/day (December 1990). This ADI was set on a No Observable Effect Level (NOEL) of 0.003 mg/kg bw/day based on plasma ChE inhibition in a human study.

Poisons Schedule

Monocrotophos is in Schedule 7 (S7) of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

MRLs

Monocrotophos has MRLs set for fruits, vegetables, meats, milks and cereal grains. The MRLs for monocrotophos as detailed in the MRL standard (June 30 1994) are outlined in Table 1 below.

Table 1. Australian Maximum Residue Limits for Monocrotophos.

Commodity	MRL (mg/kg)
Apple	0.5
Banana	0.5
Beans, except broad beans and soya bean	0.2
Broad bean (green pods and immature seeds)	0.2
Cereal grains	*0.02
Cotton seed	0.1
Edible offal (mammalian)	*0.02
Eggs	*0.02
Meat (mammalian)	*0.02
Milks	*0.002
Pear	0.5

Potato	0.1
Poultry, edible offal off	*0.02
Poultry meat	*0.02
Sweet corn (corn on the cob)	*0.01
Tomato	0.5
Vegetable oils, edible	*0.05

Existing Chemical Review Program

Monocrotophos is one of some 80 agricultural and veterinary chemicals identified as candidates for priority review under the ECRP. Following data call-in processes, a number of additional studies on the toxicology of monocrotophos have been received from industry. These data, together with all previously submitted data have been evaluated and are detailed in the report below. The data submission details covering toxicological and public health aspects of monocrotophos are summarised in Appendix 1.

1.2 International Toxicology Assessments

Monocrotophos has been evaluated by the Joint FAO/WHO Expert Committee on Pesticide Residues (JMPR) in 1972, 1975, 1991, 1993 and 1995. An ADI of 0.0006 mg/kg bw/day was allocated by JMPR in 1993, and confirmed in 1995.

This ADI was based on the following levels causing no toxicological effects.

Mouse: <1 ppm in the diet, equivalent to <0.15 mg/kg bw/day (2 year study)
Rat: 0.1 ppm in the diet, equivalent to 0.005 mg/kg bw/day (2 year study)
Human: 0.006 mg/kg bw/day (30 day study)

1.3. Chemistry

Chemistry details for monocrotophos are contained in Section 3 of this report

2. METABOLISM AND TOXICOKINETICS

2.1. Rat

Lee PW (1987) Rat Metabolism Study of ¹⁴C-DPX-Y2034 Lab: EI du Pont de Nemours & Co. Inc. Lab Project ID AMR-653-87 RTI-3852 GLP:USEPA

Wistar rats (Crl(W1)BR, Charles River Labs, Kingston NY) (7/sex) were given single gavage doses of ¹⁴C-monocrotophos (radiochemical purity 98.4%, batch E-48043-32, Shell Chemical Co.) at 2 mg/kg bw. Animals were individually housed in metabolism cages and urine, faeces, and CO₂ were collected throughout the study. The study was terminated when either 90% of the radioactive dose had been recovered or at 7 days following dosing. Levels of radioactivity were determined in urine, faeces, expired CO₂ and selected tissues. Urinary metabolites were isolated and identified using TLC, HPLC and MS.

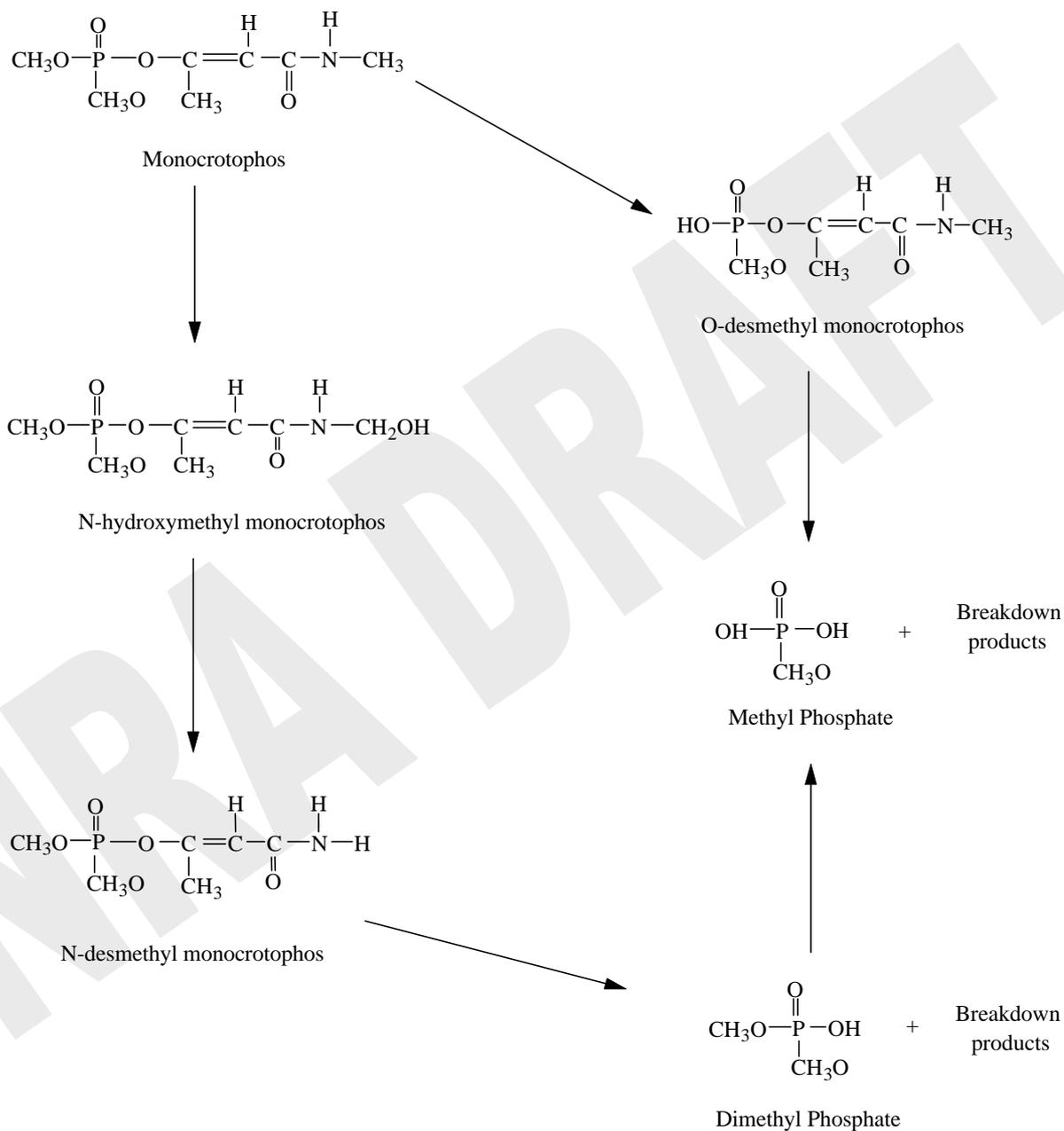
Thirty minutes after dosing, common signs of organophosphate poisoning were evident (trembling, twitching, salivation, chromodachyorrhoea, and piloerection) for up to 3 h.

82% of the administered radioactive dose was detected in the urine after 96 h (76% was detected in the urine after 12 h). After 96 h, excretion of radioactivity in the faeces and expired air accounted for approximately 3% and 6% of the radioactive dose respectively. The rate and route of excretion were independent of sex.

Only low levels of radioactivity were detected in the tissues after 96 h, the highest level being found in adipose tissue (<0.08 ppm). The liver contained <0.05 ppm, while the skin contained approximately 0.04 ppm. Although widely distributed, radioactivity detected in the tissues accounted for less than 1% of the radioactive dose. The distribution of radioactivity was independent of sex.

Unchanged monocrotophos in the urine accounted for 26 to 33% of the radioactive dose. On the basis of TLC and HPLC data, the principal urinary metabolites, N-methyl acetoacetamide (SD9112) and 3-hydroxy-N-methyl butyramide (SD11734), formed following cleavage of the phosphate-vinyl linkage, accounted for approximately 13-17% and 8% of the radioactive dose, respectively. Seventeen to 20% of the radioactive dose remained in the aqueous phase in the urine and could not be extracted using organic solvents. Faecal metabolites were not identified. On the basis of the metabolites identified, it was determined that the metabolism pathway in the rat is basically a detoxification route, involving the ester cleavage of monocrotophos, to first produce N-methyl acetoacetamide, which is then further degraded to produce 3-hydroxy-N-methyl butyramide. Given the excretion seen in expired air (approximately 6% of administered dose), the levels of radioactivity found in tissues were considered to be largely due to incorporation of carbon dioxide into the biological system.

Metabolic Pathway for Monocrotophos



Bull DL & Lindquist DA (1966) Metabolism of 3-hydroxy-N-methyl-cis-crotonamide dimethyl phosphate (AZODRIN) by insects and rats. J Agric Food Chem 14(2):105-109

The metabolism of monocrotophos by insects and rats was investigated by quantifying metabolites present in extracts of animals treated with ^{14}C - and ^{32}P -labelled monocrotophos and by incubating unlabelled monocrotophos with extracts from untreated animals. Metabolites found following this incubation included phosphoric acid, monomethyl phosphate, dimethyl phosphate, O-demethyl monocrotophos, monocrotophos acid and hydroxymethyl monocrotophos, however the relative proportions of metabolites formed were not quantified.

^{32}P -labelled monocrotophos was administered to Wistar rats (source not specified) at 5 mg/kg bw by IP injection. Urine was collected every 2 h for the first 12 h, then at intervals until 48 h after treatment. Faecal samples were also collected over this period. Monocrotophos was excreted rapidly in the urine, with 45% of the administered dose recovered in the first 6 h after treatment. Over the 48-h observation period, 61% of radioactivity was excreted in the urine, with 6% excreted in the faeces. In the first 2 h, the main compound excreted was unchanged monocrotophos (50% of radioactivity excreted), with approximately 30% of the excretion as dimethyl phosphate. At 24 h, dimethyl phosphate made up approximately 50% of the excreted material, while unchanged monocrotophos accounted for approximately 10%. Over 48 h, dimethyl phosphate made up 40% of urinary excreted metabolites, monocrotophos 28%, hydroxymethyl monocrotophos 19%, O-demethyl monocrotophos 10%, and phosphoric acid 3%.

2.2. Rat, goat and mouse.

Menzer RE & Casida JE (1965) Nature of toxic metabolites formed in mammals, insects and plants from 3-(dimethoxyphosphinyloxy)-N, N-dimethyl-cis-crotonamide analog. J Agric Food Chem 13: 102-112.

Monocrotophos technical, and monocrotophos radiolabelled at a number of different sites were used to investigate the metabolism of monocrotophos in the rat and the goat. The radiolabelled compounds were ^{32}P -labelled monocrotophos, N-methyl ^{14}C labelled monocrotophos, and O-methyl ^{14}C labelled monocrotophos. These were administered both separately and in combination to a Saanen goat, and to white rats (supplied by Rolfsmeyer Farms, Wisconsin).

When a Saanen goat was given an unspecified dose of radiolabelled monocrotophos, there were no signs of toxicity. Milk, urine and faeces were collected at 'regular intervals' for 72 h. Radioactivity was determined by a liquid scintillation counter. Radioactivity in milk was 0.05 ppm 1 h after the dose, and decreased progressively from this point. The excreted material was analysed using a chromatograph to determine the metabolites, however the results were not reported.

Rats were treated with 1 mg/kg bw labelled ^{32}P -monocrotophos in aqueous solution by gavage, and faeces and urine were collected. Following the treatment, a number of metabolites were excreted. 13% of the administered dose was excreted as unchanged monocrotophos, while 50% of the administered dose was excreted as hydrolysis products (not further quantified).

N-hydroxymethyl amide and an amide product each were less than 2% of the administered dose. Overall, 63 - 71% of the dose given was excreted in 48 h, with 55% being excreted in the first 6 h.

2.3 Goat

Hall TDJ, Jameson CE & Shaffer SR (1987) Goat Metabolism Study of ^{14}C -DPX-Y2034. Lab: Analytical Bio-Chemistry Laboratories Inc. Sponsor: EI du Pont de Nemours & Company Inc. GLP:USEPA

^{14}C -labelled monocrotophos (radiochemical purity 98.5%, specific activity 21.3 $\mu\text{Ci}/\text{mg}$; Shell Biological Science Research Centre) was administered to goats (Les Finding, Atlanta, Missouri) orally by gelatin capsules at 10 mg/d (approximately 0.2 mg/kg bw/d) for 3 days. Two goats were treated, and one maintained as a control. Goats were housed in individual metabolism cages; urine and faeces were collected daily, milk twice daily. Within 24 h of the final dose, all goats were killed. A gross necropsy examination was done, and samples of blood, omental fat, perirenal fat, muscle, kidneys, liver and GI tract/rumen contents were collected. The total radioactivity in all samples was

quantified. For urine, faeces and milk, the metabolites were identified and quantified, where possible.

Feeding of monocrotophos at this dose did not produce any adverse clinical signs. By the end of the 3 d of collection, 66% of the administered radioactive dose was recovered from the urine, and approximately 13% recovered from the faeces. Overall, 79% of the administered dose was recovered from excreta. The study did not proceed with a sufficient observation period to enable a more complete excretion; additionally, the radioactivity expired as carbon dioxide was not measured. Less than 2% of the administered dose was recovered from the milk. The major metabolites identified were N-methyl acetoacetamide (SD9112) and 3-hydroxy-N-methyl butyramide (SD11734). The presence of 2 minor metabolites was also notified, however it was not possible to identify their structures. Tissue residue examinations were limited to quantifying the 'monocrotophos equivalent' based on radioactivity count. Levels in the kidney were approximately 0.17 ppm monocrotophos equivalents, while in the liver they were approximately 0.13 ppm.

Cattle Feeding Studies with SD-13311. Modesto Technical Report (undated) from Shell Chemical Technical Report Files

SD 13311 (3-dimethyl phosphate of 3-hydroxy-N-(glucosyloxymethyl)-*cis*-crotonamide), a metabolite of monocrotophos found in plants, was fed to two Guernsey cows to determine whether SD 13311 or its hydrolysis products (SD 12657 or SD 11319) would be present in the milk, meat or fat. Cows were milked twice daily. At each milking the cows received an initial 1 kg of grain; when this was consumed an additional 2 kg of grain was supplied. For 9 days, the first kg was treated with a water-alcohol solution to acclimatise the animals to treated grain. Following this, grain treated with water-alcohol solution containing 180 mg of SD 13311 was fed for 10 days. At the end of the 10-day period, the cows were slaughtered and samples of tissue taken for analysis.

Both cows were healthy and free of clinical signs throughout the test. Feeding SD 13311 did not appear to affect milk output. Milk samples were analysed for the presence of SD 12657, SD 11319 and SD 13311, as were tissue samples obtained at the end of the experiment. The results showed that residues were not detectable in this trial.

Potter JC (1965) Residues of AZODRIN insecticide in milk. Modesto, Shell Development Company. Tech Report M-24-65

The excretion pattern of monocrotophos in cattle was investigated by feeding ³²P-labelled monocrotophos twice daily in the feed to 2 lactating cows at doses of approximately 1 mg/kg bw/day (split into 2 doses of 0.5 mg/kg bw). Cattle were fed this dose for 14 days, with collection of milk, urine and faeces. At the end of the feeding period, the cattle were slaughtered and tissue samples collected. Previous investigations had indicated that the main metabolites were likely to be a hydroxy-monocrotophos and N-hydroxymethyl-monocrotophos. Milk was also investigated specifically for the presence of a glucoside of N-hydroxymethyl, which had been previously found in plants.

Over the 14-day feeding period, the residues of monocrotophos in milk were on the order of 0.0061 - 0.022 ppm. The residues of hydroxy-monocrotophos were <0.0005 (LOD) to 0.0037 ppm, and the residues of N-hydroxy monocrotophos were <0.0005 to 0.002 ppm. In urine, the levels of monocrotophos excreted were 0.32 to 1.02 ppm, of hydroxy monocrotophos 0.01 to 0.06 ppm, and of N-hydroxy monocrotophos 0.083 to 0.63 ppm. Therefor there was significantly more excretion of monocrotophos and its metabolites in urine than in milk. Monocrotophos levels in skeletal muscle were 0.023 - 0.041 ppm, while liver levels were 0.11 - 0.13 ppm. Levels of metabolites in these tissues were not quantified.

3. ACUTE TOXICITY

3.1 Technical Grade Active Constituent

3.1.1 Median Lethal Dose Studies

The results obtained from acute toxicity studies conducted with monocrotophos are summarised in the following table.

Median Lethal Dose Studies

Species	Sex	Route	Vehicle	LD50(mg/kg bw) or LC50 (mg/m ³)	Reference
Mouse	M/F	PO	Peanut oil	15	Shellenberger & Newell (1963a)
Mouse	M/F	PO	Peanut oil	10	Shellenberger & Newell (1963b)
Mouse	M/F	PO	Peanut oil	11	Shellenberger & Newell (1963b)
Mouse (Swiss)	M/F	PO	Distilled water	11	Seshaiah (1955a)
Rat (CFE)	M/F	PO	?	8.4 - 8.7	Brown et al (1970)
Rat (Sprague Dawley)	M/F	PO	?	35 (M), 20 (F)	Newell & Dilley (1978)
Rat	M/F	PO	Peanut oil	23	Shellenberger & Newell (1963a)
Rat	M/F	PO	Peanut oil	13	Shellenberger & Newell (1963b)
Rat	M/F	PO	Peanut oil	21	Shellenberger & Newell (1963b)
Rat	M/F	PO	Peanut oil	15	Shellenberger & Newell (1964b)
Rat	M/F	PO	?	15	Shellenberger & Newell (1964d)
Rat	M/F	PO	?	17	Shellenberger & Newell (1964d)
Rat (Tif.RAI)	M/F	PO	Carboxymethyl cellulose	14	Sachsse & Bather (1975)
Rat (Wistar)	M/F	PO	Distilled water	9.6	Seshaiah (1995b)
Rat (Sprague Dawley)	M/F	Dermal	Undiluted	210(M) 206 (F)	Newell & Dilley (1978)
Rat (RAC)	M/F	Dermal	Carboxymethyl cellulose	330	Hurni & Sachsse (1969)
Rat (RifRAI)	M/F	Dermal	Distilled water	>2000 (M), approx 2000 (F)	Hartmann (1992)
Rat (Wistar)	M/F	Dermal	Undiluted	123	Deshmukh et al (1993a)
Rabbit	?	Dermal	Undiluted	354	Shellenberger & Newell (1963a)
Rabbit	?	Dermal	Undiluted	709	Shellenberger & Newell (1963b)
Rabbit	?	Dermal	Undiluted	354	Shellenberger & Newell (1963b)
Rabbit	?	Dermal	Water	420	Shellenberger & Newell (1964a)
Rabbit	?	Dermal	DMSO	223	Shellenberger & Newell (1964a)

Rabbit	?	Dermal	Xylene	149	Shellenberger & Newell (1964a)
Rabbit (NZW)	M/F	Dermal	Undiluted	347	Dushmukh et al (1993b)
Rat (CFE)	F	SC	Saline	7	Reift (1969)
Mice (MF-2)	M/F	IP	Carboxymethyl cellulose	11	Hurni & Sachsse (1970a)
Mice (MF-2)	M/F	IV	Carboxymethyl cellulose	11.5	Hurni & Sachsse (1970b)
Rat (Sprague Dawley)	M/F	IV	?	11.9(M) 9.2 (F)	Newell & Dilley (1978)
Rat	M/F	Inhalation		92 (1h), 80 (4h)	Sachsse et al (1973)
Rat (Tif RAI)	M/F	Inhalation	Distilled water	809 (4h)	Sachsse (1973)

3.1.1.1. Oral

Shellenberger TE & Newell GW (1963a) Report No 97, Ref Project B-1008., Stanford Research Institute, Menlo Park.

Monocrotophos technical (SD 9129, Code 1400, source, purity not specified) in peanut oil was administered orally to mice (10/group: source, strain, sex not specified) at doses of 10, 12.6, 15.9 or 20 mg/kg bw. It was not specified whether animals were fasted or non-fasted, nor was the duration of the observation period stated. Clinical signs included diarrhoea, tremors, salivation and lacrimation, and began within 15 - 30 min of dosing. Survivors appeared normal after 24 h. The acute oral LD50 was determined to be 15 mg/kg bw.

Shellenberger TE & Newell GW (1963b) Report No 105, Ref Project B-1008. Stanford Research Institute, Menlo Park.,

Two compositions of monocrotophos were tested for acute oral toxicity. The first, SD9129 Code 4200 was 95% pure (source not specified) while the second, SD 9129 Code 3500 was approximately 90% pure (source not specified). SD 9129 code 4200 in peanut oil was administered to mice (source, strain, sex not specified) at 7.95, 10, 12.6 or 15.9 mg/kg bw (10/group). The LD50 was 10 mg/kg bw. SD 9129 code 3500 in peanut oil was administered to mice (source, strain sex not specified) at 7.95, 10, 12.6 or 15.9 mg/kg bw (10/group), and the LD50 was 11 mg/kg bw. Clinical signs observed included salivation, diarrhoea, tremors and clonic convulsions, and survivors appeared normal after 24 h.

Seshaiah A (1995a) Acute oral toxicity (LD50) study of monocrotophos technical to mice. Lab: Dept of Toxicology, Jai Research Foundation Sponsor: United Phosphorus Ltd.

Monocrotophos technical (purity 74.4%, batch no 307 supplier United Phosphorus Ltd) in distilled water was administered to Swiss albino mice (Animal House, Jai Research Foundation) in an initial range finding study and in the main study. Mice were housed in groups of 5, with *ad libitum* access to food and water (with the exception of required fasting periods).

In the range-finding study, monocrotophos was administered at 0, 8, 16 and 32 mg/kg bw (2/sex/group). Mice were observed for 5 days after treatment. All mice in the 16 and 32 mg/kg bw groups died. Toxic signs observed were lethargy, tremor, abdominal breathing and piloerection.

In the main study, monocrotophos was administered at 0, 8, 11 and 16 mg/kg bw (5/sex/group). Mice were observed for 5 h after dosing, then checked daily for 14 days. Body weights were recorded prior to administration, then on days 7 and 14. At the end of the study, survivors were euthanised and a gross post mortem examination performed.

Mortalities were observed in all treatment groups at the frequency 0/10, 3/10, 5/10 and 10/10. Clinical signs included gait changes, lacrimation, tremor and abdominal breathing. There were few abnormalities observed on gross post mortem examination, with lung congestion being the most notable. It was determined that the acute oral LD50 to mice was 11 mg/kg bw.

Brown VK, Dean B, Muir CMC, Pickering RG, & Reiff B (1970) Toxicity studies on AZODRIN; the effect of a single oral or subcutaneous dose on rats. Lab., Shell Research Ltd Sittingbourne UK: TLTR.0005.68

The acute oral toxicity of monocrotophos technical (purity not given) and recrystallised monocrotophos (purity 99.8%) was investigated in Carworth Farm E rats (Tunstall Laboratories). The LD50 of technical grade monocrotophos was 8.4 mg/kg bw, that of the recrystallised monocrotophos was 8.7 mg/kg bw.

The effects of a single oral dose of monocrotophos technical on plasma, erythrocyte and brain ChE of female rats was investigated. A dose of 4 mg/kg bw produced significant (>20%) ChE inhibition plasma up to 24 h after dosing. Erythrocyte and brain ChE were inhibited for 15 days after dosing with 4 mg/kg bw.

The effects of concurrent administration of a single oral dose of monocrotophos and atropine sulphate were investigated. A dose of 6 mg/kg bw of either the pure or technical monocrotophos, with or without atropine sulphate, inhibited plasma ChE up to 24 h after dosing. Only pure monocrotophos produced inhibition of plasma ChE for 7 days after dosing. Erythrocyte ChE was inhibited until 10 days after dosing by monocrotophos pure or technical, with or without atropine. Technical monocrotophos, and monocrotophos with atropine produced significant inhibition of erythrocyte ChE at 20 days after dosing. Brain ChE was inhibited until 20 days after dosing by all treatments. Therefore, as expected, atropine sulphate did not appear to change the effect of monocrotophos on ChE inhibition.

Newell CW & Dilley JV (1978) Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Springfield, US Dept of Commerce NTIS-PB-277.077

Monocrotophos technical (purity 61-64%, source: Battelle Memorial Institute Repository, Columbus Lab, Ohio) was administered by gavage to adult Sprague Dawley rats (Simonsen Laboratories, California) at unspecified doses (10/sex/group). Clinical signs included salivation, lacrimation, exophthalmos, defecation, urination and muscle fasciculations. The duration of the signs were dose dependent, with all survivors completely recovered by 10 - 14 days after treatment. The LD50 was determined to be 35 mg/kg bw for males and 20 mg/kg bw for females. Whole blood ChE inhibition was determined 6 h after treatment; in males at 25 mg/kg bw there was 82% inhibition, and in females at 15 mg/kg bw 89% inhibition.

Shellenberger TE & Newell GW (1963a) Report No 97, Ref Project B-1008. Stanford Research Institute Menlo Park.

Monocrotophos technical (SD 9129, code 1400, source, purity not specified) in peanut oil was administered orally by gavage to rats (source, strain, sex not specified) at doses of 16, 20, 25 or 32 mg/kg bw (10/group). It was not specified whether rats were fasted or non-fasted. Clinical signs included diarrhoea, tremors, salivation and lacrimation, and were seen within 15 to 30 min of administration. Survivors appeared normal 24 h after dosing. The LD50 was determined to be 23 mg/kg bw.

Shellenberger TE & Newell GW (1963b) Report No 105, Ref Project B-1008. Stanford Research Institute, Menlo Park.

Two compositions of monocrotophos were tested for acute oral toxicity. The first, SD9129 Code 4200 was 95% pure (source not specified) while the second, SD 9129 Code 3500 was approximately 90% pure (source not specified). SD9129 code 4200 in peanut oil was administered PO by gavage to rats (source, strain, sex not specified) at doses of 10, 12.6, 15.9 or 20 mg/kg bw (10/group). The LD50 was determined to be 13 mg/kg bw. SD9129 code 3500 in peanut oil was administered PO to rats (source, strain, sex not specified) at doses of 15.9, 20, 25.2 or 31.8 mg/kg bw (10/group). The LD50 was determined to be 21 mg/kg bw. Clinical signs included lacrimation, salivation, diarrhoea, tremors and clonic convulsions.

Shellenberger, TE & Newell GW (1964b) Report No 110, Ref Project B-1008. Stanford Research Institute, Menlo Park.

Monocrotophos technical (SD 9129, code 7300, source, purity not specified) in peanut oil was administered in peanut oil to rats (source, strain, sex not specified) at doses of 12.6, 15.9, 20 or 25.2

mg/kg bw. It was not specified whether rats were fasted. Clinical signs were tremors, salivation, lacrimation and diarrhoea. The LD50 was determined to be 15 mg/kg bw.

Shellenberger TE & Newell GW (1964d) Report No 114, Ref Project B-1008. Stanford Research Institute Menlo Park.

Monocrotophos (SD 9129 code 6200, code 9100 and code 9200, source and purity not specified) was administered PO to rats (source, sex, strain not specified) at a range of doses specific for each compound using 10 rats/group. SD 9129 code 6200 was administered at doses of 315, 398, 500 or 630 mg/kg bw; the LD50 was 420 mg/kg bw. SD 9129 code 9100 was administered at doses of 9.9, 12.5, 15.8 or 19.8 mg/kg bw; the LD50 was 15 mg/kg bw. SD 9129 code 9200 was administered at doses of 12.5, 15.8, 19.8 or 25 mg/kg bw; the LD50 was 17 mg/kg bw.

Sachsse K & Bathe R (1975) Acute oral LD50 of technical monocrotophos (C1414) in the Rat. Project No Siss 69 Ciba Geigy Limited, Basle, Switzerland

Technical monocrotophos (Batch OP 50/51, purity not given, source Ciba Geigy Ltd) in carboxymethyl cellulose was administered PO by gavage to fasted Tif.RAI SPF rats (Ciba Geigy Laboratories) at doses of 10, 12, 18 or 30 mg/kg bw (5 rats/sex/group). Rats were maintained in groups of 5 under standard conditions for 7 days. Clinical signs were seen in all treated rats, and included dyspnoea, chromodacryorrhoea, exophthalmus, salivation, hunched position, trismus, tonic-clonic muscle spasms and ruffled fur. Survivors recovered within 3 - 4 days of dosing. All survivors were euthanised after 7 days. Gross autopsy revealed no abnormal findings. The oral LD50 for both males and females was determined to be 14 mg/kg bw.

Seshaiah (1995b) Acute oral toxicity (LD50) study of monocrotophos technical to rat. Lab: Department of Toxicology Jai Research Foundation. Sponsor: United Phosphorus Ltd.

Monocrotophos technical (purity 74.4%, batch no 307, supplier: United Phosphorus Ltd) in distilled water was administered by gavage to Wistar rats (Animal House, Jai Research Foundation) in an initial dose range finding study, and the main trial. Rats were housed in groups of 5, with food and water available *ad libitum*, except during required pre-dosing fasts.

In the dose range-finding study, monocrotophos was administered at 0, 8, 16 or 32 mg/kg bw (2 rats/sex/group). Deaths occurred in the 16 mg/kg bw group. Clinical signs including tremors, abdominal breathing, chromodacryorrhea, exophthalmus and piloerection were observed for up to 5 days after dosing.

The main study used doses of 0, 12, 16, 20 and 25 mg/kg bw (5 rats/sex/group). Animals were observed hourly for 5 h after dosing, then daily for 14 days. Body weights were recorded prior to dosing and on days 7 and 14. A gross pathological examination was performed at the end of the study, and on animals dying during the study. Deaths occurred in all treatment groups (0/10, 8/10, 7/10, 9/10, 10/10). Tremor, lacrimation, exophthalmus and piloerection were seen in all treatment groups. On gross necropsy, there was congestion in the lungs, and patchy white discoloration of the liver. Organs were not preserved for histopathological examination. The acute oral LD50 of monocrotophos was determined to be 9.6 mg/kg bw.

Potrepka, RF (1994) Acute Oral Toxicity study of Monocrotophos Technical in Rats. Ciba Geigy Corporation, Laboratory Study No. F-00189 GLP:USEPA

Monocrotophos technical (C1414, Lot No. FL-940574, Batch No. OP 107001, purity 77.6%, source: Ciba-Geigy Crop Protection Division) was administered to CrI:CD(SD)BR VAF/Plus rats in a number of trials. Animals were housed individually during all trials, with food and water available *ad libitum*, except during pre-dosing fasting periods.

In the first trial, 3 mg/kg bw was administered by oral gavage to 5 rats/sex. Based on these observations, two additional groups were treated at 0.3 and 5 mg/kg bw. General physical examinations were done, and clinical signs recorded at 1, 2, 4 and 6 h after dosing, then daily for 7 days. Body weights were recorded prior to compound administration, and after 7 days. In the 2nd trial, monocrotophos in distilled water was administered by oral gavage at 3 mg/kg bw to 20 female rats, with controls receiving vehicle. The peak inhibition times for plasma, erythrocyte and brain ChE activity was determined by sacrificing 5 animals at 2, 4, 6 and 24 h after treatment. Animals were examined 1, 2, 4, 6 and 24 h after dosing (where applicable) for clinical signs. Body weights were recorded immediately prior to sacrifice. In the 3rd trial monocrotophos in distilled water was

administered by oral gavage at doses of 0, 0.01, 0.03, 0.1, 0.3 or 1 mg/kg bw with 5 rats/sex/group, with doses selected on the basis of results from the first 2 trials. General physical examinations were done prior to dosing, and approximately 1 and 2 h post-dose. ChE activities in plasma, erythrocytes and brain were determined. All animals in all trial were subject to a gross post mortem immediately after sacrifice.

In the first trial, there were no mortalities. There were no treatment related effects on body weight in either sex. Clinical signs of toxicity were seen at 3 and 5 mg/kg bw, and included muscle fasciculations, staining of the eyes, mouth and nose, diarrhoea, miosis, lacrimation and salivation. Signs were first seen at 1 h after dosing, peaked at 2 to 4 h, and were generally absent by 24 h although in some animals miosis persisted for the 7 d examination period. Gross necropsy revealed no treatment related findings. Incidental findings included a malformed/misshapen eye seen at 0.3 mg/kg bw, and a kidney cyst seen at 5 mg/kg bw; no histopathological examination was done.

In the second trial, there were no mortalities. There were decreases in body weight at 2 and 4 h post dosing, however this was not considered of biological significance. Clinical signs including flattened posture, muscle fasciculations, miosis, lacrimation, salivation and staining of the eyes, mouth and nose were seen from 1 to 2 h after dosing, Miosis was the only clinical sign still observed at 24 h after dosing. There were no significant findings on gross postmortem examination; histopathological examination was not done. ChE activities showed significant depression at all time periods examined. Plasma ChE activity was inhibited 80% at 2 h after administration and 32% at 24 h. Erythrocyte ChE was inhibited 72% at 2 h and 32% at 24 h. Brain ChE was inhibited 87% at 2 h and 27% at 24 h.

In the third trial, there were no significant change in bodyweights in the 2 h of observation. Clinical signs in males were muscle fasciculation and salivation at 1 mg/kg bw and miosis (>0.1 mg/kg bw). In females, the only observed abnormal clinical signs were miosis and staining of the nose. These did not show a clear dose relationship. Inhibition of ChE is presented below.

Mean percentage ChE inhibition

Dose (ppm)	Plasma ChE		Erythrocyte ChE		Brain ChE	
	Males	Females	Males	Females	Males	Females
0.01	10	4	0	2	1	3
0.03	21	0	6	7	0	7
0.1	34	0	13	7	17	15
0.3	56	29	44	65	44	26
1	83	57	66	75	72	88

There was significant inhibition of plasma ChE in males at 0.03 mg/kg bw at 2 h after dosing. In females, plasma ChE activity was significantly decreased at 0.3 mg/kg bw. Erythrocyte and brain ChE activity was significantly decreased in both sexes at 0.3 mg/kg bw/day. Based on the inhibition of plasma ChE, the NOEL for the study can be established at 0.01 mg/kg bw.

Hurni PH & Sachsse K (1970) Report on the determination of the acute oral LD50 to the rabbit of C-1414, Technical. Tierfarm AG Biomedical Research

Monocrotophos technical (source, purity, batch no not specified) was administered orally to rabbits (source, strain not specified) at doses of 16.7, 35.9, 46.4, 77.5 or 275 mg/kg bw using an unspecified number of animals/group. Rabbits were maintained for a 14-day observation period following dosing. Clinical signs in the lowest dose group included asynchronism of the extremities, spasm of the limb muscles and diarrhoea. These rabbits had recovered by 24 h after dosing. At the higher doses, signs included tachypnoea, clonic-tonic muscle spasms, hollow flanks, inhalation noises, salivation, lacrimation and diarrhoea. Survivors appeared normal after 48 h. Gross autopsy of animals dying during the study showed atelectases and haemorrhages of the lungs, and congested livers. No gross pathological changes were seen in animals euthanised at the end of the 14-day observation period. The oral LD50 was not determined in this study, and no information was presented on the number of mortalities.

3.1.1.2 Dermal

Newell CW & Dilley JV (1978) Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Springfield, US Dept of Commerce NTIS-PB-277.077

Monocrotophos technical (purity 61-64%, source: Battelle Memorial Institute Repository, Columbus Ohio) was administered to the clipped skin of Sprague Dawley rats (Simonsen Laboratories, California) at unspecified doses, using 10 rats/sex/group. It was not specified how long the compound remained in contact with the skin, or whether the area was covered with an occlusive dressing. The LD50 for this trial were determined to be 210 mg/kg bw for males and 206 mg/kg bw for females.

Hurni H & Sachsse K (1969) Report on the determination of the acute dermal LD50 to the rat of monocrotophos technical. Toxicological Research Centre, Tierfarm Ag, Sisseln Switzerland

Monocrotophos technical (source, purity, batch no not specified) in carboxymethylcellulose was applied to the clipped dorsolumbar skin of RAC rats (Tierfarm AG, Switzerland) at doses of 60, 120, 240, 360, 600 or 1200 mg/kg bw and covered with an occlusive dressing for 24 h. At the end of this time, the dressing was removed, and the skin was washed with warm water. Rats were maintained for a 14-day observation period, with food and water available *ad libitum*. After 24 h, rats showed tachypnoea, clonic-tonic muscle spasms, prostration and lacrimation. The severity of the symptoms increased with increasing doses. The LD50 was determined to be 330 mg/kg bw.

Hartmann HR (1992) C 1414 technical Acute Dermal Toxicity in the Rat. Test No 911264 Ciba Geigy Ltd, Stein Switzerland.GLP - OECD/US EPA

Monocrotophos technical (batch no OP 107001, purity 77.6%, source: Ciba Geigy Ltd) in distilled water was applied to the shorn dorsolumbar skin of Tif RAI f (SPF) rats (source: Ciba Geigy Ltd Animal Production Switzerland) at doses of 100, 500 or 2000 mg/kg bw for males (5/group) and 500, 1000 or 2000 mg/kg bw for females (5/group). The application site was covered with an occlusive dressing for 24 h. All animals were maintained for at least 14 days observation; females receiving 2000 mg/kg bw were monitored for 26 days. All animals were checked at least once daily for mortality and clinical signs. Body weight was determined weekly. A gross autopsy was done as soon as possible after death in the case of animals which died spontaneously. All animals were autopsied after scheduled sacrifice.

Clinical signs included piloerection, abnormal body positions, exophthalmus and dyspnoea. At 500 mg/kg bw and higher doses, tremor and decreased locomotor activity were seen. Ataxia was seen at 500 and 2000 mg/kg bw, while convulsions were seen only at 2000 mg/kg bw. Trismus was seen in males at 2000 mg/kg bw, but was not seen in females. Survivors did not show a decreased body weight at the end of the observation period. In the 1000 mg/kg bw group, 2/5 females died, while 2/5 females at 2000 mg/kg bw also died. There were no abnormalities seen on gross autopsy in any of the animals which died or were sacrificed. The LD50 for male rats was determined to be >2000 mg/kg bw, while the LD50 for females was determined to be approximately 2000 mg/kg bw. Overall, the LD50 for rats was determined to be >2000 mg/kg bw.

Deshmukh PB, Banerize RS & Patel SV (1993a) Acute dermal toxicity studies of monocrotophos technical in rats. Lag: Jai Research Foundation Sponsor: United Phosphorus Ltd.GLP: OECD

Monocrotophos technical (source, batch no, purity not specified) was administered dermally to Wistar:Haffkine strain rats (Jai Research Foundation) in a preliminary trial and main test. In both experiments, the material was applied to the clipped dorsolumbar region, and rats were observed for 15 days after dosing.

In the preliminary experiment, monocrotophos was applied at 100, 200 or 300 mg/kg bw (5/sex/group). It was not stated whether the area was covered with an occlusive dressing. The LD50 was determined to be between 100 and 200 mg/kg bw. For the main experiment, the doses used were 100, 125, 150 or 175 mg/kg bw, and the area was covered with an occlusive dressing for 24 h. It was not stated whether the area was washed following removal of the dressing. Clinical signs seen included lacrimation, salivation, exophthalmus, ataxia, dyspnoea and convulsions. The LD50 was determined to be 123 mg/kg bw.

Shellenberger TE & Newell GW (1963a) Report No 97, Ref Project B-1008. Stanford Research Institute, Menlo Park.

Monocrotophos technical (SD 9129, Code 1400, source, purity not specified) was applied to the skin of rabbits (source, strain not specified) at 125, 250, 500 or 1000 mg/kg bw using 3 rabbits/group. The length of exposure, whether the skin was covered or not, the degree of abrasion and the length of observation following exposure were not specified. Unspecified clinical signs described as 'typical of organophosphate toxicity' were seen within 1 h of application. Survivors were normal after 24 h. Mild erythema at the site of application was noted. The LD50 was determined to be 354 mg/kg bw.

Shellenberger TE & Newell GW (1963b) Report No 105, Ref Project B-1008. Stanford Research Institute, Menlo Park.

Two compositions of monocrotophos were tested for dermal toxicity. The first, SD9129, Code 4200 was 95% pure (source not specified) while the second, SD 9129, Code 3500 was approximately 90% pure (source not specified). The compounds were applied percutaneously to rabbits (source, strain, sex not specified). The application time was not specified, and it was not specified whether the area was covered. The skin was washed after exposure. SD 9129, Code 4200 was applied at doses of 250, 500, 1000 or 2000 mg/kg bw, and the LD50 was 709 mg/kg bw. SD 9129, Code 3500 was applied at doses of 125, 250, 500 or 1000 mg/kg bw, and the LD50 was 354 mg/kg bw. Clinical signs of tremors, diarrhoea, salivation and lacrimation were seen, and mild erythema was observed when the compound was removed.

Shellenberger TE & Newell GW(1964a) Report No 107 Ref Project B-1008. Stanford Research Institute, Menlo Park.

Monocrotophos technical (SD 9129, Code 4200, purity 95%, source not specified) was applied dermally to rabbits (source, strain, sex not specified) in water, DMSO or xylene using 3 rabbits/group. The compound was applied in water at doses of 125, 250, 500 or 1000 mg/kg bw; the LD50 was 420 mg/kg bw. The compound was applied in DMSO at doses of 62.5, 125, 250 or 500 mg/kg bw; the LD50 was 223 mg/kg bw. The compound was applied in xylene at doses of 62.5, 125, 250 or 500 mg/kg bw; the LD50 was 149 mg/kg bw. In all applications, clinical signs included tremors, salivation, diarrhoea and lacrimation; these signs increased in severity with dose, and were also more severe with xylene than with the other solvents.

Shellenberger, TE & Newell GW (1964c) Report No 111, Ref Project B-1008. Stanford Research Institute, Menlo Park.

Monocrotophos (SD 9129, Code 7347, source not specified, 40% in acetone) was applied dermally to rabbits (source, strain, sex not specified). It was not specified whether the hair was shorn, whether the area was occluded, and for how long the compound was applied. The signs observed were miosis, diarrhoea and dyspnoea. The LD50 was determined to be 342 mg/kg bw.

Dushmukh PB, Banerjee RS & Patel SV (1993b). Acute dermal toxicity studies of monocrotophos technical in rabbit. Lab: Jai Research Foundation Sponsor: United Phosphorus Ltd. GLP:OECD
Monocrotophos technical (batch no, source, purity not specified) was applied dermally to the shorn dorso-lumbar region of New Zealand rabbits (source: Jai Research Foundation) in a preliminary and a main trial. Rats were maintained in a specialised rabbit holder for 24 h after application before being returned to individual housing. The application area was not covered with an occlusive dressing.

In the preliminary trial monocrotophos was applied at 250, 500 or 750 mg/kg bw (2/sex/group). The LD50 was determined to lie between 250 and 500 mg/kg bw. In the main trial, monocrotophos was applied at 300, 325, 375 and 400 mg/kg bw (2/sex/group). Clinical signs were seen, including lacrimation, salivation, exophthalmus, ataxia, dyspnea and convulsions. The LD50 was determined to be 347 mg/kg bw.

3.1.1.3 Subcutaneous

Reift B (1969) Pharmacological studies into the toxic actions of cholinesterase inhibitors. Part 9. Shell Research Ltd, Sittingbourne UK TLGR.0008.69

Monocrotophos (analytical grade - 100% pure, source: WARC) in a saline vehicle was injected SC to female Carworth Farm rats (source not specified) at doses of 4.82, 5.79, 6.95, 8.34 or 10.0 mg/kg bw. Deaths were recorded at 24 h intervals over 7 days. The LD50 was determined to be 7 mg/kg bw.

Brown VK, Dean B, Muir CMC, Pickering RG, & Reiff B (1970) Toxicity studies on AZODRIN; the effect of a single oral or subcutaneous dose on rats. Lab: Shell Research Ltd, Sittingbourne UK. TLTR.0005.68

The effect of a single SC dose of 8.4 mg/kg bw monocrotophos on ChE inhibition was investigated in Carworth Farm E rats (Tunstall Laboratories). Plasma ChE was significantly inhibited 24 h after a single SC dose. Erythrocyte and brain ChE were inhibited for 7 days after a single SC dose. The inhibition had resolved by 14 days after dosing.

3.1.1.4 Intraperitoneal

Menzer RE & Casida JE (1965) Nature of toxic metabolites formed in mammals, insects and plants from 3(-dimethoxyphophinyloxy)-N, N-dimethyl-cis-crotonamide analog. J Agric Food Chem 13: 102 - 112

The acute toxicity of monocrotophos and its metabolites was tested by IP administration to mice. The LD50 determined for monocrotophos was 8 mg/kg bw, while the LD50 for the N-hydroxymethyl metabolite was 12 mg/kg bw. The amide metabolite had an LD50 of 3 mg/kg bw, and thus was more toxic than the parent compound.

Hurni H & Sachsse K (1970) Report on the determination of the acute intraperitoneal LD50 to the mouse of C-1414, technical. Biomedical Research, Tierfarm AG, Switzerland

Monocrotophos technical (batch no, purity, source not specified) in carboxymethyl cellulose was administered by IP injection to MF-2 mice (Tierfarm AG, Switzerland) at doses of 4.64, 7.75, 10, 12.9 or 16.7 mg/kg bw using 5 mice/sex/group. Mice were housed in groups of 5 under controlled conditions, with food and water available *ad libitum* for an observation period of 14 days. At approximately 1 h after injection, mice showed slight tonic-clonic muscle spasms and tachypnoea, while mice at the 2 highest doses became recumbent. Gross autopsy of mice dying during the test generally revealed a pale liver, without other visible abnormalities. No abnormalities were found in mice autopsied at the end of the trial. The acute IP LD50 was determined to be 11 mg/kg bw.

3.1.1.5 Intravenous

Hurni H & Sachsse K (1970) Report on the determination of the Acute Intravenous LD50 to the Mouse of C1414 Technical. Tierfarm AG, Sisseln, Switzerland Ciba Geigy Ltd

Monocrotophos technical (source, purity not specified), diluted in sodium carboxymethyl cellulose was administered by IV injections to MF-2 mice (Tierfarm AG, Sisseln, Switzerland) at doses of 6, 10, 12.9 or 16.7 mg/kg bw using 5 mice/sex/group. Mice were housed in groups of 5 under controlled conditions, with food and water available *ad libitum*. Animals were observed for 14 days following treatment. Clinical signs in the animals receiving 6 or 10 mg/kg bw included apathy, tachypnoea and lacrimation. In the animals at the higher doses, dyspnoea, clonic-tonic muscle spasms, and 'anxiety' were observed immediately after administration of the compound. Survivors were normal after 48 h. On gross autopsy, animals dying during the study had slightly congested livers. Animals surviving until the end of the observation period had no abnormal signs. The acute IV LD50 in mice was determined to be 11.5 mg/kg bw for males and females.

Newell CW & Dilley JV (1978) Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Springfield, US Dept of Commerce NTIS-PB-277.077

Monocrotophos technical (source: Battelle Memorial Institute Repository, Columbus Ohio, purity 61 - 64%) was administered by IV injection to adult Sprague Dawley rats (Simonsen Laboratories, California) at unspecified doses using 10 rats/sex/group. Clinical signs included salivation, lacrimation, exophthalmus, defecation, urination and muscle fasciculations. Duration of clinical signs was dose related. The LD50 was determined to be 11.9 mg/kg bw for males and 9.2 mg/kg bw for females. Whole blood ChE inhibition was measured 6 h after treatment. At 12 mg/kg bw in males, inhibition was 92%, while in females at 9 mg/kg bw, inhibition was 79%.

3.1.1.6 Inhalation

Newell GW & Shellenberger TE (1964) Letter Report No 2, Project B-4843. Stanford Research Institute, Menlo Park and

Shellenberger TE (1965a) Letter Report No 5 Ref Project B-4843. Menlo Park, Stanford Research Institute

Monocrotophos technical (batch 4-5-0-0) was administered to 10 rats/sex (strain, source not given) in a vapor chamber for 1 h, with whole body exposure. The air flow was 3L/min saturated with the test solution. Rats were weighed before and after exposure, then weekly during the 14-d monitoring period. At the end of this time, rats were killed and examined grossly. The liver, kidney, spleen and heart of each animal was weighed, and these organs plus the lung, bronchial tube, testes/ovaries, prostate/uterus, lymph nodes, bone marrow, skeletal muscle, adrenals, thyroid and parathyroid were preserved for histopathology. There were no changes in body weight or organ weight relating to treatment. On gross necropsy, one treated male had a lung abscess, and one treated male had thyroid glands which were greatly increased in size. On histopathological examination, there was evidence of peribronchial infiltrate with lymphocytes associated occasionally with mild interstitial fibrosis or mild chronic bronchopneumonia. There were also signs of fibrosis in the thyroids. All effects were seen in both treated and control animals, and are not considered to be related to treatment.

Newell CW & Dilley JV (1978) Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Springfield, US Dept of Commerce NTIS-PB-277.077

Monocrotophos technical (purity 61-64%, source: Battelle Memorial Institute Repository, Columbus Ohio) was administered by inhalation to adult Sprague Dawley rats (Simonsen Laboratories, California) at doses of 90, 97, 151, 162, 210, 308, 321 or 740 mg/m³ with a particle size of 0.3 - 3 µm for an unspecified durations, using whole body exposure. Clinical signs included salivation, lacrimation, exophthalmus, defecation, urination and muscle fasciculations, and their duration was dose related. All survivors had were normal by 10 to 14 d after treatment. The LD50 was determined to be 162 mg/kg bw for males and 176 mg/kg bw for females. Whole blood ChE inhibition was measured 6 h after treatment. For males at 156 mg/kg bw, there was 74% inhibition, and for females at 192 mg/kg bw there was 69% inhibition of ChE.

Sachsse K, Ullmann L, Voss G & Hess R (1973) Measurement of inhalation toxicity of aerosols in small laboratory animals. in: Experimental model systems in toxicology and their significance to man. Proc. Eur. Soc. Study of Drug Toxicity Vol XV. Excerpta Medica Intern. Congress Series No 311, Zurich

Rats (strain not specified) were exposed to monocrotophos technical (source not specified) for either 1 or 4 h by nose-only inhalation. The doses used were not specified, and there was no description of clinical signs, or detailed presentation of mortality. The LD50 for a 1 h exposure was determined to be 94 mg/m³, and for a 4 h exposure, 80 mg/m³.

Sachsse K (1973) Acute inhalational toxicity of technical C-1414 (monocrotophos) in the rat. Project No Siss 2780, Ciba Geigy Ltd

Monocrotophos technical (source, batch no. and purity not specified) was administered as an aqueous dilution to Tif.RAI SPF rats (Ciba Geigy Laboratories) by inhalation, with nose-only exposure, for 4 h at doses of 38, 100 or 208 mg/m³ with 9 rats/sex/group. Two control groups were maintained: one was exposed in to distilled water, the other control group was not exposed. Within 1 h of exposure commencing, rats showed dyspnoea, exophthalmus, trismus and tonic-clonic muscle spasms. Later rats also showed salivation. Rats were maintained under observation for 7 days. Survivors were normal by 48 h after exposure. At the end of the observation period, all rats were euthanised and a gross autopsy performed. Animals dying during the study showed lung and intestinal haemorrhages, and congested organs. There were no abnormal findings in animals surviving until the end of the study. The LC50 was determined to be 809 mg/m³.

Deshmukh PB, Banerjee RS & Patel SV (1993c) Acute inhalation toxicity studies of monocrotophos technical in rat. Study no. NCTCF/R/006/91/01300. Report No.

366/JAIREF/TOXT/93 Lab: Jai Research Foundation. Sponsor United Phosphorus. GLP:OECD
Rats (source, strain unspecified) were exposed to monocrotophos technical (source, batch no, purity unspecified) for 4 h at 11 mg/L, with an air flow of 1.5 L/min. It was not specified whether the exposure was whole body or nose only. The concentration of monocrotophos maintained in the

exposure chamber was not reported. Rats were observed every 15 min for 1 h, then hourly for 3 h. After exposure, rats were observed daily for 14 days. No mortality, abnormal clinical signs or weight loss were seen. Gross post mortem examination revealed no abnormalities.

3.1.2 Skin Irritation and Sensitisation Studies

Scibor G (1977a) Primary skin irritation test with AZODRIN insecticide, Code 288-55, 99.5% in albino rabbits. Industrial Biotest Laboratories Inc, Northbrook. Report No. 8530-10808 and

Sawin VL & Sommer KR (1981) Audit of Industrial Bio-Test Laboratories Study No. 8530-10808, "Eye irritation test and primary skin irritation with AZODRIN insecticide in albino rabbits". Shell Development Company, Houston. WRC RIR-92

Skin irritation tests were carried out with 6 New Zealand White rabbits (Pel Freeze Inc, 3/sex) using 99.5% pure monocrotophos (source:Shell Chemical Co, Code 288-55). The dorso-lumbar region was clipped, and one intact and one abraded area of skin was treated with monocrotophos (250 mg/site) and occluded for 24 h. The skin was washed with water, and the sites were examined and scored for irritation 1 h after removal of the dressing. The sites were assessed again 72 h after treatment. Monocrotophos produced a mild erythema and was classified as slightly irritant to rabbit skin.

Hagemann (1992a) Acute Dermal Irritation/Corrosion Study in the Rabbit. Test No 911265 C 1414 tech. Ciba Geigy Ltd Plant Protection. GLP: OECD/USEPA

Monocrotophos technical (Batch no. OP 107001, purity 77.6%, source not specified) was applied to the shaved right flank of 3 female NZW rabbits (Chemisch-Pharmazeutische Fabrik). The monocrotophos (0.5 g) was applied to a gauze patch previously moistened with 0.5% carboxymethylcellulose and aqueous polysorbate 80. The left flank was used as a control, and had a gauze patch moistened with solvents applied. The patches were covered with an occlusive bandage for 4 h. Skin reactions were assessed 1, 24, 48 and 72 h after removing skin patches. Body weight was assessed pretest and on days 3 and 7. Animals were housed individually with food and water available *ad libitum*.

The mean skin reaction scores for erythema using the Draize scoring system for each rabbit over the 24-72 h period were 0.67, 0.67 and 1.67. No erythema was evident after 7 days. The mean skin reaction scores for oedema for each rabbit over the same period were 0, 0, and 1. No oedema was evident after 7 days. There was a slight weight loss in 2 rabbits after 3 days, however this had recovered by 7 days. Monocrotophos was classed as a mild skin irritant.

Seshaiah S (1995c) Acute dermal irritation study of monocrotophos technical to rabbit. Lab: Jai Research Foundation. Sponsor United Phosphorus GLP: OECD

Monocrotophos technical (purity 74.4%, batch no 307, source: United Phosphorus Ltd) was tested for skin irritation in New Zealand White rabbits (source: Jai Research Foundation). The dorso-lumbar region of each of 3 rabbits (sex not specified) was clipped at 2 sites, one treated with monocrotophos, and the other acting as control. Monocrotophos (100 mg) was applied to the treated site and covered with a gauze swab for 4 h. The area was then wiped with moist cotton prior to assessment of skin reaction. The skin reaction was assessed 1, 24, 48 and 72 h after the end of treatment. The Draize score for erythema and oedema was 1 in each rabbit at the end of 1 h. The scores were 0 for the rest of the test. Therefore monocrotophos technical was classes as a mild irritant to rabbit skin.

Deshmukh PB, Banerjee RS & Patel SV (1993c) Mucous membrane irritation studies of monocrotophos technical in rabbit. Lab: Jai Research Foundation. Sponsor United Phosphorus Ltd GLP:OECD

Monocrotophos technical (source, batch no, purity not specified) was applied to the vaginal mucous membranes of 6 female New Zealand White rabbits (Jai Research Foundation). The volume of monocrotophos applied was unspecified. Irritation was scored at 24 and 72 h. Very slight erythema was seen in the mucous membranes of 4/6 rabbits at 24 h; no oedema was seen. The mucous membranes were fully recovered at 72 h. Therefore monocrotophos was determined to cause very slight irritation to mucous membrane of rabbits.

Hurni H & Sachsse K (1970) Sensitizing effects on guinea pigs of C-1414, technical. Toxicological Research Centre, Tierfarm Switzerland

Monocrotophos technical (source, batch no, purity not specified) in carboxymethylcellulose was administered by intracutaneous injection to Pirbright White guinea pigs. The back and upper flanks of the guinea pigs were shorn, and a 1% solution administered, with the first injection being 0.05 mL, and the next 9 injections being 0.1 mL administered every 2nd day. Two weeks after the final injection, a challenge injection of 0.05 mL was administered.

Animals were examined 24 h after each injection to determine the reaction. Each of the intracutaneous injections produced a slight necrosis, of about 1 mm diameter surrounded by slight erythema. The reaction following the challenge injection was not more intense than that following each of the sensitising injections. Therefore, no sensitisation reactions were observed at the challenge sites. No raw data on individual animals was presented.

3.1.3 Eye Irritation Studies

Scibor G (1977b) Eye irritation test with AZODRIN insecticide in albino rabbits. Industrial Biotech Laboratories Inc, Northbrook. Report No. 8530-10808 and

Sawin VL & Sommer KR (1981) Audit of Industrial Bio-Test Laboratories Study No. 8530-10808, "Eye irritation test and primary skin irritation with AZODRIN insecticide in albino rabbits". Shell Development Company, Houston. WRC RIR-92

Monocrotophos (source: Shell Chemical Co, purity 99.5%, Code:288-55) was applied to the right conjunctival sac of 6 New Zealand White rabbits (Pel-Freez Inc, Arkansas), with the left eye serving as control. Seventy mg of the material was applied; the eyes were not washed. Within 30 min of application, the rabbits showed hyperpnea, hyperexcitability and miosis, with one rabbit showing salivation. All animals had recovered within 22 h of ocular exposure. Eye irritation was scored at 1, 24, 48, 72 and 96 h and 7 days after treatment, using the Draize scoring system. Irritation was present at 1 and 24 h, however no irritation was observed from 48 h. Monocrotophos was classed as mildly irritating to the rabbit eye.

Hagemann (1992) Acute Eye Irritation/Corrosion Study in the Rabbit. Text No 911266. C1414 tech. Ciba Geigy Ltd, Switzerland.

Monocrotophos technical (batch no. OP 107001, purity 77.6%, source not specified) was applied to the left conjunctival sac of 3 female New Zealand White rabbits (source: Chemisch Pharmazeutische Fabrik), with 100 mg applied. The right eye was used as an untreated control. The ocular reactions were assessed 1, 24, 48 and 72 h after treatment. Miosis was seen from 10 min until 3 h after treatment in all treated eyes. Clinical signs included tremors, trismus, dyspnea, ataxia and diarrhoea, with some incidences of muscle twitching. Two animals showed weight loss on day 3. Mean scores for irritation using the Draize scoring system for each animal over the 24-72 h period were 0.33, 0 and 0 for the iris, for redness of the conjunctiva 1.67, 1.67 and 1.67 and for chemosis 0.33, 0.33 and 1 respectively. No effects to the cornea were reported and after 14 days no abnormal signs were detected. Monocrotophos was classed as a minimal irritant to the eye.

Seshaiah S (1995d) Acute eye irritation study of monocrotophos technical to rabbit. Lab: Jai Research Foundation. Sponsor United Phosphorus. GLP:OECD

Monocrotophos technical (purity 74.4%, batch no 307, source: United Phosphorus Ltd) in distilled water was applied in a volume of 0.1 mL (containing 10 mg) to one eye of each of 3 New Zealand White rabbits (source: Jai Research Foundation). Observations were made for reactions at 1, 24, 48 and 72 h after treatment. All rabbits showed conjunctival reactions at 1 h. No iris or cornea signs were seen at any stage, and the redness and discharge from the conjunctiva had resolved by 24 h. Based on this, monocrotophos was determined to be a minimal irritant to the rabbit eye.

3.1.4 Potentiation/Interaction studies

Shellenberger TE (1965e) Letter Report No 9, Ref Project No B-4843. Stanford Research Institute, Menlo Park.

Oral LD50 values in male Long Evans rats for monocrotophos (technical grade, 7-3-0-0) and 24 other cholinesterase-inhibiting pesticides were determined. The oral LD50 of monocrotophos was determined to be 10 mg/kg bw. Potentiation was determined by giving monocrotophos in combination with each of the pesticides. Initially, the LD10 of both pesticides was administered simultaneously. If mortality was less than 50%, the effect were considered to be merely additive,

with no potentiation, and no further investigation was done. If mortality was greater than 50%, both chemicals were administered at 1/2 the LD50. If mortality was greater than 50%, it was assumed that potentiation was occurring, and the LD50 of an equitoxic mixture of the chemical was determined.

Chemicals showing additive effects included dimethoate, malathion, parathion, azinphos and carbaryl. Potential potentiation was identified in chemicals including dicrotophos, crotoxyphos, diazinon, guthion, parathion-methyl, phosphamidon and fenclorphos. Potentiation of lethality occurred only in the case of monocrotophos given with fenclorphos.

3.2 Isomers, Metabolites and Impurities

3.2.1 Median Lethal Dose Studies

A summary of the median LD50s following administration of the *trans*-isomer of monocrotophos is presented in the table below.

Species	Sex	Route	Vehicle	LD50 (mg/kg bw) or LC50 (mg/m ³)	Reference
Mouse Tif:MAG	M/F	PO		118	Sachsse & Bathe (1976a)
Rat Tif:RAIf	M/F	PO	carboxymethyl cellulose	207	Sachsse & Bathe (1976b)
Rabbit Himalayan	M/F	PO		485	Sachsse & Ullman (1976a)
Rat Tif:RAIf	M/F	Dermal		>3170	Sachsse & Bathe (1976c)
Rat Tif:RAIf	M/F	Inhalation		805	Sachsse & Ullman (1976b)
Rat Tif:RAIf	M/F	IP		202	Sachsse & Bathe (1976d)

3.2.1.1 Oral

Sachsse K & Bathe R (1976a) Acute oral LD50 in the mouse of monocrotophos, trans isomeres. Project No: Siss 5559 Ciba Geigy Ltd

Monocrotophos (trans isomer - source, batch no, purity not specified) was administered PO by gavage to fasted Tif MAG(SPF) mice (source: Ciba Geigy Ltd) at doses of 46.4, 77.5, 100, 129, 147 or 167 mg/kg bw using 5 mice/sex/group. Mice were housed in groups of 5 under controlled conditions with food and water available *ad libitum*. Signs included sedation, dyspnoea, chromodacryorrhea, exophthalmus, trismus, clonic-tonic muscle spasms and ruffled fur. Survivors had returned to normal within 9 days. There were no abnormalities found on gross post-mortem examination, either of animals dying during the study or animals examined at terminal sacrifice. The LD50 was determined to be 118 mg/kg bw.

Shellenberger TE (1966) Subacute toxicity and cholinesterase study of Shell Compound SD 13311 - Rat. SRI Project SS05908. Stanford Research Institute, Menlo Park

The oral LD50 of the beta-D-glycosyl conjugate of hydroxymethyl monocrotophos, a monocrotophos metabolite produced in mammals, was determined in non-fasted Long-Evans rats (source not specified). The compound was administered at doses of 126, 159, 200 or 252 mg/kg bw PO by gavage. Clinical signs included tremors, salivation, diarrhoea and tonic and clonic convulsions. The LD50 was determined to be 168 mg/kg bw.

Sachsse K & Bathe R (1976b) Acute oral LD50 in the rat of monocrotophos, trans isomeres. Project No: Siss 5559. Ciba Geigy Ltd

Monocrotophos, trans-isomer (purity, batch no, source not specified) diluted in carboxymethyl cellulose was administered PO by gavage to fasted Tif:RAIf rats (source: Ciba Geigy Ltd) at doses of 167, 180, 200, 205, 215 or 230 mg/kg bw (5/sex/group). Rats were housed in groups of 5 under controlled conditions, with food and water supplied *ad libitum*. Within 2 h of treatment, clinical signs included sedation, dyspnoea, chromodacryorrhoea, exophthalmus, curved or ventral body

positions, tonic-clonic muscle spasms, trismus and ruffled fur. Survivors had recovered within 9 - 12 days. On post mortem examination, no gross abnormalities could be seen either in animals dying during the study, or those killed at the termination of the study. The LD50 was determined to be 207 mg/kg bw.

Sachsse K & Ullman L (1976a) Acute oral LD50 in the rabbit of monocrotophos, trans-isomeres. Project No Siss 5559. Ciba Geigy Ltd

Monocrotophos (trans isomer - source, batch no, purity not specified) in carboxy-methylcellulose was administered PO by gavage to fasted Himalayan rabbits (source Ciba Geigy Ltd) at doses of 100, 215, 359, 464 or 600 mg/kg bw using 2 rabbits/sex/group. Rabbits were maintained under controlled conditions, and food and water were available *ad libitum*. Clinical signs were seen within 1 h of treatment at doses of 215 mg/kg bw and greater, and included tonic-clonic muscle spasms, ataxy, tremor, lateral or ventral position and sedation. Survivors had recovered within 2 or 3 days. No gross post mortem signs were seen in any animals, either those dying during the study, or those euthanised at the end of the study. The LD50 was determined to be 485 mg/kg bw.

3.2.1.2 Dermal

Sachsse K & Bathe R (1976c) Acute dermal LD50 in the rat of monocrotophos, trans-isomeres. Project No Siss 5559. Ciba Geigy Limited.

Monocrotophos (trans-isomer - source, batch no, purity not specified) was applied to the shorn dorso-lumbar skin of Tif: RAIf (SPF) rats (3/sex/group) at doses of 1000, 2150, 2780 or 3170 mg/kg bw and covered with an occlusive dressing for 24 h. After 24 h, the dressing was removed and the skin cleaned with lukewarm water. Rats were maintained under controlled conditions with food and water available *ad libitum*.

Within 24 h, rats in all dosage groups showed sedation, dyspnoea, chromodacryorrhoea, exophthalmus, curved position, trismus, tonic-clonic muscle spasms and ruffled fur. One female each at 2150 and 2780 mg/kg bw died within 48 h; all other rats survived. No local skin irritations were observed. Survivors had recovered from all clinical signs within 10 to 13 days. Gross autopsies revealed no abnormalities in any animals. The LD50 was determined to be in excess of 3170 mg/kg bw.

3.2.1.3 Inhalation

Sachsse K & Ullman L (1976b) Acute Inhalation Toxicity in the rat of monocrotophos, trans-isomeres. Project No Siss 5559. Ciba Geigy Ltd.

Monocrotophos (trans isomer - batch no, source, purity not given) was administered by nose-only inhalation exposure to Tif RAIf (SPF) rats (source: Ciba Geigy Ltd) at 360, 530 or 710 mg/m³ for 4 h using 9 rats/sex/group. The concentration and particle size of the administered material was monitored at 1 h intervals throughout the exposure. Following the 4 h exposure, rats were returned to their cages and monitored for 14 d. Rats were housed in groups of 9, and food and water were available *ad libitum*.

Within 2 h of the start of the exposure, rats in all concentrations showed dyspnoea, exophthalmus, tremor, tonic-clonic muscle spasms, curved positions and ruffled fur. The symptoms increased in severity with dose. Surviving animals recovered were normal within 3 to 6 days. Gross autopsies on animals dying during the study showed haemorrhages in the lungs and intestines, while there were no abnormalities seen in the animals surviving until the end of the study. The LD50 was determined to be 805 mg/m³.

3.2.1.4 Intraperitoneal

Sachsse K & Bathe R (1976d) Acute Intraperitoneal LD50 in the rat of monocrotophos, trans-isomer. Project No Siss 5559. Ciba Geigy Ltd, Switzerland

Monocrotophos (trans isomer - batch no, source, purity not specified) in carboxy-methylcellulose was administered by IP injection to Tif RAI f (SPF) rats (source - Ciba Geigy Ltd) at doses of 77.5, 147, 167, 215, 278, 359 or 600 mg/kg bw using 5 rats/sex/group. Rats were housed in groups of 5 under controlled conditions, with *ad libitum* access to food and water and were maintained for a 14-d observation period after injection.

Signs of toxicity were seen within 2 h after treatment, and were dyspnoea, trismus, chromodacryorrhea, exophthalmus, tonic-clonic muscle spasms and ruffled fur. Survivors were normal in 8 - 12 days. On gross examination of animals dying during the study and those sacrificed at the end of the study, no abnormalities were found. The LD50 was determined to be 202 mg/kg bw.

3.2.2 Skin irritation

Sachsse K & Ullman L (1976c) Skin irritation in the rabbit after single application of monocrotophos, trans isomeres. Project No Siss 5559. Ciba-Geigy Ltd.

Monocrotophos (trans isomer - batch no., source, purity not given) was applied to the skin of Himalayan rabbits (source not specified). Rabbits were housed individually under controlled conditions. The back and flank of the rabbits was clipped 2 days prior to the test. Immediately before application, the left side of each rabbit (3/sex) was scarified. Gauze patches with 0.5 mL of test material was applied and covered with an occlusive dressing for 24 h. Skin irritation was scored immediately following removal of the gauze patch, and 48 h later (ie. 24 and 72 h after treatment).

On the intact skin after 24 h, one rabbit had well defined erythema. No other signs of irritation were seen at any time on intact skin.

On the scarified skin at 24 h, all rabbits showed either slight (5/6) or well defined (1/6) erythema. Rabbits also showed very slight (2/6), slight (2/6) or moderate (2/6) oedema. At 72 h, 4/6 showed very slight erythema, with no other signs seen. Therefore the test material caused a mild skin irritation to rabbits.

Sachsse K & Ullman L (1976a) Repetitive skin irritation test in rabbits of monocrotophos, trans isomeres. Project No. Siss 5559 Ciba Geigy Ltd

Monocrotophos (trans isomer - batch no, purity, source not specified) was applied to the shorn dorsolumbar skin of Himalayan rabbits (source not specified) once daily for 5 d (3/sex). Five mL of the material was applied to a gauze patch, placed on the shorn skin area and covered with an occlusive bandage for 24 h. At the end of the 24-h period, the dressing was removed, and the skin reaction evaluated using the Draize index before another gauze patch and occlusive dressing was applied. Rabbits were maintained for observation following the 5-d treatment period in individual housing under controlled conditions, with free access to food and water.

Within 48 h of commencing treatment, rabbits showed salivation, trismus, convulsions, ataxia, diarrhoea and sedation. Signs became more severe over time, and all animals died between days 5 and 7. The body weight of all animals decreased over the test period. The skin reaction after the first 24 h was scored at 0.83. The mean reaction score for days 1 to 5 was 1.9, and the final reaction score for day 5 was 2.5. Based on these scores, monocrotophos trans-isomer was determined to be a mild irritant to rabbit skin following repeated exposure.

3.2.3 Eye irritation

Sachsse K & Ullman L (1976d) Eye irritation in the rabbit of monocrotophos, trans-isomeres. Project No. Siss 5559. Ciba Geigy Ltd.

Monocrotophos (trans isomer - source, batch no, purity not specified) was applied (0.1 mL) to the left conjunctival sac of 3 male and 3 female Himalayan rabbits (source not specified), with the right eye an untreated control. In 3 rabbits, the test solution was rinsed out after 30 seconds. Rabbits were housed individually under controlled conditions, with *ad libitum* food and water. Eye irritation was assessed on days 1, 2, 3, 4 and 7. There was no evidence of any irritation to the cornea, conjunctiva

or iris at any assessment time, in either the rinsed or unrinsed eyes. Therefore the trans isomer of monocrotophos was non-irritating to the eye.

Sachsse K & Ullman L (1976b) Repetitive eye irritation test in rabbits of monocrotophos, trans isomeres. Project No. Siss 5559 Ciba Geigy Ltd

Monocrotophos (trans isomer - source, batch no, purity not specified) was tested for repetitive irritation in Himalayan rabbits. 0.1 mL of monocrotophos trans isomer was placed in the left eye of 6 rabbits (3/sex). The right was maintained as an untreated control. In 3 animals, the treated eye was rinsed 30 seconds after application. The treatments were repeated once daily for 5 days. The reaction was assessed 24 h after each application and scored using the Draize system, and also assessed 8, 9 and 10 days after commencement of treatment. Animals were housed individually under controlled conditions with free access to food and water.

No adverse clinical signs were reported during the trial, and there was no loss in body weight in any of the treated animals. The primary reaction score after 24 h was 1, the mean reaction score over days 1 to 5 was 0.4, and the score on day 5 was 0. Monocrotophos, trans isomer, was therefore considered to be a minimal irritant to the rabbit eye.

3.2.4 Skin sensitisation

Sachsse K & Ullman L (1976e) Skin sensitizing (Contact allergenic) effect in guinea pigs of monocrotophos, trans isomeres. Project No. Siss 5559. Ciba Geigy Ltd

Monocrotophos (trans isomer - source, purity, batch no not specified) was administered by intracutaneous injection to Pirbright white guinea pigs (source: Ciba Geigy Ltd) using 10 animals/sex/group. A 0.1% dilution in saline was administered in 0.1 mL injections, with saline used as negative control and dinitrochlorobenzene (DNCB) used as positive control. On the first d, animals received an injection in the right flank and in the back; every second d they received an injection in the back, for a total of 10 injections. Fourteen d after the final induction injection, animals received a challenge injections of 0.1 mL of the test solution in the left flank. Animals were housed individually under controlled conditions with *ad libitum* food and water.

Reactions were scored based on the diameter and skin thickness of the reaction seen. Each injection was scored 24 h after administration. The injections administered during the first week of induction were used to establish a standard of reactivity for each animal. Any reaction greater than one standard deviation above this reaction in this animal was considered to be positive, and to be an allergic reaction. No allergic reactions were seen in the negative control, while all animals administered DNCB showed positive reactions. In the monocrotophos (trans isomer) test animals, 9/20 showed positive reactions. Many of these animals showed no skin reaction at all during induction, and the magnitude of the reaction was considerably less than that seen with the positive control. Therefore monocrotophos, trans isomer, was determined to induce allergic responses.

3.3 Monocrotophos formulations

3.3.1 Median Lethal Dose Studies

A summary of the median lethal dose studies with different monocrotophos formulations are presented in the table below.

Formulation	Species	Sex	Route	LD50 (mg active/kg bw) or LC50 (mg/m ³)	Reference
60%:acetone	Rat	M/F	PO	5.8	Brown et al (1968)
60%; acetone	Rat	M/F	PO	10	Muir (1970a)
24%; acetone and isopropyl alcohol	Rat	M/F	PO	11.9	Brown et al (1968)
24%; isopropyl alcohol	Rat	M/F	PO	7.7	Brown et al (1968)

24%; acetone	Rat	M/F	PO	7.7	Brown et al (1968)
10%; hexylene glycol	Rat	M/F	PO	4.5	Brown et al (1970)
24%; isopropanol and acetone	Rat	M/F	PO	12	Brown et al (1970)
24%; hexylene glycol	Rat	M/F	PO	3.6	Carter (1976)
15%; acetone	Rat	M/F	PO	7.8	Cassidy (1978)
40%; hexylene glycol	Rat	M/F	PO	7.1	Muir (1970a)
60%; acetone	Rat	M/F	PO	6.1	Muir (1970a)
10%; hexylene glycol	Rat	M/F	PO	4.1	Muir & Brown (1968)
15%; hexylene glycol	Rat	M/F	PO	4.5	Muir & Brown (1968)
10%; acetone	Rat	M/F	PO	7.2	Muir & Brown (1968)
15%; acetone	Rat	M/F	PO	7.7	Muir & Brown (1968)
40%; acetone	Rat	M	PO	8.4	Newell (1965)
20%; oxitol acetate	Rat	M/F	PO	m: 10.4, f: 1.08	Price (1982b)
20%; hexylene glycol	Rat	M/F	PO	m: 9.8, f: 8	Price (1982b)
5%; oil	Rat	M/F	PO	5.5	Simpson & Carter (1975)
60%; acetone	Rat	M/F	Dermal	80-100	Brown et al (1968)
24%; acetone, isopropyl alcohol	Rat	M/F	Dermal	<80	Brown et al (1968)
24%; isopropyl alcohol	Rat	M/F	Dermal	>125	Brown et al (1968)
24%; acetone	Rat	M/F	Dermal	<80	Brown et al (1968)
24%; hexylene glycol	Rat	M/F	Dermal	m: 114, f: 143	Carter (1976)
15%; acetone	Rat	M/F	Dermal	75 - 78	Cassidy (1978)
57%; hexylene glycol	Rat	M/F	Dermal	m: 86-114, f: 57-86	Muir (1968)
40%; hexylene glycol	Rat	M/F	Dermal	114	Muir (1970a)
60%; acetone	Rat	M/F	Dermal	78.6	Muir (1970a)
5%, granules	Rat	M/F	Dermal	>500	Muir (1970b)
25%; dioxitol	Rat	M/F	Dermal	m: 197, f: 227	Price (1982b)
15%; hexylene glycol and Shellsol AB	Rat	M/F	Dermal	11-17	Price (1982b)
20%; oxitol acetate	Rat	M/F	Dermal	m: 135, f: 132	Price (1982b)
20%; hexylene glycol	Rat	M/F	Dermal	m: 189, f: 145	Price (1982b)
40%; excipient not specified	Rat	M/F	Dermal	155	Hurni & Sachsse (1969)

60%; acetone	Rabbit	M/F	Dermal	>120	Lazzara & Paa (1975) Sawin (1980)
40%; hexylene glycol	Rabbit	M/F	Dermal	210	Coombs (1975)
40%; acetone	Rabbit	M/F	Dermal	137	Newell & Shellenberger (1964)
40%; acetone	Rabbit	M/F	Dermal	338	Shellenberger (1965a)

3.3.1.1 Oral

Brown VK, Muir CMC & Barrett J (1968) The acute oral and percutaneous toxicities of four AZODRIN formulations. Lab: Shell Research Ltd, Sittingbourne UK. TLTR.0005.68.

Monocrotophos in one of 4 formulations was administered to fasted Carworth Farm E rats (Tunstall Laboratories) in a single gavage dose using 4 rats/sex/group. The formulations were Azodrin 5 (60% monocrotophos in acetone), EF 2629 (24% monocrotophos; Azodrin 5 in isopropyl alcohol), EF 2448 (24% monocrotophos in isopropyl alcohol) and EF 2672 (24% monocrotophos in acetone) and were administered at 5, 10 or 20 mg monocrotophos/kg bw. Water was available *ad libitum*, and food was available after dosing. No detail of the clinical signs observed were given. The LD50s, based on active ingredient, were 5.8, 11.9, 7.7 and 7.7 mg/kg bw respectively. The LD50s based on administration of formulation were 10.2, 42.3, 26.6 and 28.6 mg/kg bw.

Brown VK, Dean B, Muir CMC, Pickering RG, & Reiff B (1970) Toxicity studies on AZODRIN; the effect of a single oral or subcutaneous dose on rats. Lab: Shell Research Ltd Sittingbourne UK. TLTR.0005.68

Monocrotophos formulations were administered to fasted Carworth Farm E rats (Tunstall Laboratory) by gavage. Rats were observed for at least 10 days after dosing; observation time was continued where rats showed any sign of poisoning at the end of 10 days. No details on the clinical signs observed were presented. The LD50s ranged from 4.5 mg active/kg bw for a 10% solution of monocrotophos in hexylene glycol, to 12 mg active/kg bw for a 24% solution of monocrotophos in isopropanol and acetone.

Carter BI (1976) The acute toxicity of AZODRIN 24% in hexylene glycol (FX 1363). Lab: Shell Research Ltd, Sittingbourne UK. TLTR.0015.76

Monocrotophos (24% in hexylene glycol) was administered as a single oral dose to fasted Wistar or CFE rats (Shell Toxicology Laboratory, Tunstall) at doses of 10, 20, 30, 40 or 50 mg formulation/kg bw using 5 rats/sex/group. All doses resulted in clinical signs including piloerection, fibrillation, fasciculations, salivation and chromolacrimation. The acute oral LD50 was 15 mg formulation/kg bw, equivalent to 3.6 mg active/kg bw.

Cassidy SL (1978) Toxicology of insecticides: Acute toxicity of a 15% AZODRIN in acetone formulation to rats. Lab: Shell Research Ltd, Sittingbourne UK. TLTR.003.78

Monocrotophos technical (78.1% purity, source: Shell Toxicology Laboratory) was mixed with acetone to give a 15% w/v formulation, which was administered to fasted SPF Wistar rats (Tunstall Breeding Unit) at doses of 40, 50, 63, 80 or 100 mg formulation/kg bw using 6 rats/sex/group. Rats were maintained for 14 days with free access to food and water. A gross post mortem examination was done, however the results were not reported. Rats were described as showing signs typical of cholinesterase inhibition for the first day after dosing, however the signs were not specified. The LD50 was determined as either 52 or 53 mg formulation/kg bw, depending on the method of determination, equivalent to 7.8 mg active/kg bw.

Muir CMC (1970a) The acute oral and percutaneous toxicities to rats of an AZODRIN 40% WSC (EF 2820) in comparison with AZODRIN 5. Shell Research Ltd, Sittingbourne UK. TLGR.0066.70

Monocrotophos, either as a 40% solution in hexylene glycol, or a 60% solution in acetone was administered by gavage to fasted Carworth Farm E rats (Tunstall Breeding Unit). The doses used were not specified; 5 rats/sex/dose were used. Rats were then observed for 10 days following treatment. The oral LD50 for the 40% formulation was 17.7 mg formulation/kg bw (equivalent to 7.1 mg active/kg bw), and the oral LD50 for the 60% formulation was 10.2 mg formulation/kg bw (equivalent to 6.1 mg active/kg bw).

Muir CMC & Brown VKH (1968) The acute oral toxicity of some AZODRIN formulations. Shell Research Ltd, Sittingbourne UK. TLTR.0012.68

Four formulations of monocrotophos, all supplied by the Physical Chemistry Division of Woodstock Agricultural Research Centre (location not specified) were used. The formulations were a 10% and 15% solution in hexylene glycol, and a 10% and 15% solution in acetone. The formulations were administered to fasted Carworth Farm E rats (Tunstall Breeding Unit) at doses not specified, using 4 rats/sex/group. Rats were initially maintained for 10 d; at the end of this period some rats showing weight loss were maintained for a continued period (unspecified). Clinical signs observed included trembling, salivation and chromodacryorrhoea, however the doses at which these signs were seen was not specified. The LD50 determined in this trial were: 15% monocrotophos in hexylene glycol - 30 mg formulation/kg bw (4.5 mg active/kg bw); 10% monocrotophos in hexylene glycol - 41 mg formulation/kg bw (4.1 mg active/kg bw); 15% monocrotophos in acetone - 51 mg formulation/kg bw (7.65 mg active/kg bw) and 10% monocrotophos in acetone - 72 mg formulation/kg bw (7.2 mg active/kg bw).

Newell GW (1965) Letter Report No 3 Project B-4843. Stanford Research Institute, Menlo Park

Monocrotophos (40% in acetone, source not specified) further diluted in peanut oil was administered by gavage to young male non-fasted Long Evans rats (source not specified) at doses of 15.2, 20, 25.5 or 31.8 mg formulation/kg bw. At the higher doses, signs of toxicity, including lacrimation, salivation, diarrhoea, tremors and clonic convulsions were observed. Deaths occurred between 25 min and 20 h after dosing, with the survivors appearing normal after 24 h. The LD50 was determined to be 21 mg formulation/kg bw (8.4 mg active/kg bw).

Price JB (1982b) Toxicology of AZODRIN formulations; The acute percutaneous toxicity of EF 5801 and EF 5803 and the acute oral and percutaneous toxicity of EF 5811 and EF 5843. Shell Research Ltd, Sittingbourne SBGR.81.112

In two studies, monocrotophos formulations, 200 g/L in oxitol acetate (EF 5811), and 200 g/L in hexylene glycol (EF 5843), were administered to fasted Wistar rats (Tunstall Breeding Unit) by gavage. The first trial was a dose-ranging study, and the rats received doses between 2.5 and 80 mg formulation/kg bw. The second study was a definitive study to determine the LD50. EF 5811 was administered at doses between 30 and 95 mg formulation/kg bw, and EF 5843 was administered at doses between 25 and 80 mg formulation/kg bw. Rats were observed for 14 d after dosing. Clinical signs included salivation, lacrimation and muscle fasciculations. The LD50 for EF 5811 was 52 mg formulation/kg bw (10.4 mg active/kg bw) for males and 54 mg formulation/kg bw (10.8 mg active/kg bw) for females. The LD50 for EF 5843 was 48 mg formulation/kg bw (9.8 mg active/kg bw) for males and 40 mg formulation/kg bw (8 mg active/kg bw) for females.

Shellenberger TE (1965a) Letter Report No 5 Ref Project B-4843. , Stanford Research Institute, Menlo Park.

Monocrotophos (40% in acetone, source: Shell Chemical Co, Code 8-10-4-13) was diluted in water and administered by gavage to fasted rats (source, strain not specified). The doses for males were 15.8, 19.9, 25 or 31.5 mg formulation/kg bw, and the doses for females were 12.5, 15.8, 19.9 or 25 mg formulation/kg bw, using 10 rats/sex/group. Signs of salivation, lacrimation and tremors were observed. Survivors were normal 24 h after treatment. The acute oral LD50 for males was 23 mg formulation/kg bw (9.2 mg active/kg bw), and the acute oral LD50 for females was 18 mg formulation/kg bw (7.6 mg active/kg bw).

Simpson BJ & Carter BI (1975) Acute oral toxicity of AZODRIN, Formulation EF 3668 to rats. Shell Research Ltd, Sittingbourne UK. TLTR.0023.75

Monocrotophos (50 g/L in an unspecified oil) was administered orally by gavage to fasted rats (strain not specified, source: Tunstall Laboratories) at doses of 20, 40, 80, 121, 141 or 161 mg formulation/kg bw. Rats were observed for 9 d, during which period food and water were available *ad libitum*. Signs of toxicity associated with organophosphorous poisoning (not specified) were seen at doses of 40 mg formulation/kg bw and above. The LD50 was determined to be 111 mg formulation/kg bw (equivalent to 5.5 mg active/kg bw).

3.3.1.2 Dermal

Brown VK, Muir CMC & Barrett J (1968) The acute oral and percutaneous toxicities of four AZODRIN formulations. Lab: Shell Research Ltd, Sittingbourne UK. TLTR.0005.68.

Monocrotophos in one of 4 formulations was administered to Carworth Farm E rats (Tunstall Laboratories) by percutaneous application (4/sex/group). The formulations were Azodrin 5 (60% monocrotophos in acetone), EF 2629 (24% monocrotophos: as Azodrin 5 in isopropyl alcohol), EF 2448 (24% monocrotophos in isopropyl alcohol) and EG 2672 (24% monocrotophos in acetone). Undiluted formulation was applied to the shaved dorso-lumbar area at doses of 60, 80, 100, 125 or 150 mg monocrotophos/kg bw, and a waterproof occlusive dressing applied for 24 h. After 24 h, the dressing was removed and the skin washed with a dilute detergent solution. Water was available *ad libitum*, however food was removed during the exposure period. The LD50s were: Azodrin 5 - 140 - 170 mg formulation/kg bw (80 - 100 mg active/kg bw), EF 2629 - <257 mg formulation/kg bw (<80 mg active/kg bw), EF 2448 - >415 mg formulation/kg bw (>125 mg active/kg bw) and EF 2672 - <268 mg formulation/kg bw (<80 mg active/kg bw).

Carter BI (1976) The acute toxicity of AZODRIN 24% in hexylene glycol (FX 1363). Lab: Shell Research Ltd, Sittingbourne UK. TLTR.0015.76

Monocrotophos (24% in hexylene glycol) was applied to the shorn dorso-lumbar area of Wistar or Carworth Farm E rats at doses of 208, 313, 417, 625, 834, 1042 or 1251 mg formulation/kg bw (4 /sex/group). The area was covered with an occlusive dressing for 24 h, after which the dressing was removed and the skin was washed. Rats were observed for 12 d after exposure. All animals had slightly splayed back legs on the day of dosing. Animals dosed at 417 mg formulation/kg bw and higher showed signs typical of organophosphorus poisoning. An unspecified number of animals lost weight in the days after exposure. The LD50 was 475 mg formulation/kg bw for males and 596 mg formulation/kg bw for females (equivalent to 114 mg active/kg bw and 143 mg active/kg bw respectively).

Cassidy SL (1978) Toxicology of insecticides: Acute toxicity of a 15% AZODRIN in acetone formulation to rats. Lab: Shell Research Ltd, Sittingbourne.. TLTR.003.78

Monocrotophos (78.1% purity, source: Shell Toxicological Laboratory) was formulated as a 15% solution in acetone, and applied to the shorn dorso-lumbar skin of SPF Wistar rats (Tunstall Breeding Unit) under an occlusive dressing for 24 h at doses of 320, 400, 500, 630, 790 or 1000 mg formulation/kg bw (4/sex/group). At 24 h the dressing was removed and the skin washed. Rats were observed for 14 days following treatment, and it was noted that they showed signs of cholinesterase inhibition for 24 h after dosing, and lost weight from then until the end of the trial. The LD50 was determined to be 498, 521 or 523 mg formulation/kg bw (equivalent to 75 or 78 mg active/kg bw)

Muir CMC (1968) Azodrin FX 1364 WMC. Shell Research Ltd, Sittingbourne: Bioassay Card dated 5/12/68.

Monocrotophos (57% in hexylene glycol) was applied to the skin of CFE rats (source not specified) for an unstated time. It was not indicated whether this was an occluded or a non occluded test. Clinical signs included convulsions and considerable weight loss (not quantified). The LD50 was determined to be 150 - 200 mg formulation/kg bw in males and 100 - 150 mg formulation/kg bw in females (equivalent to 86 - 114 mg active/kg bw in males and 57 to 86 mg active/kg bw in females).

Muir CMC (1970a) The acute oral and percutaneous toxicities to rats of an AZODRIN 40% WSC (EF 2820) in comparison with AZODRIN 5. Shell Research Ltd, Sittingbourne. TLGR.0066.70

Monocrotophos, as either a 40% solution in hexylene glycol, or a 60% solution in acetone was applied to the shorn dorso-lumbar skin of Carworth Farm E rats (Tunstall Breeding Unit) and covered with an occlusive dressing for 24 h. The dressing was then removed and the skin washed. The doses applied were not stated, however 4 rats/sex/group were used. The animals were observed for 10 days, and the LD50 of the 40% solution was determined to be 285 mg formulation/kg bw (equivalent

to 114 mg active/kg bw), and the 60% solution to be 132 mg formulation/kg bw (equivalent to 78.6 mg active/kg bw).

Muir CMC (1970b) The acute percutaneous toxicity of AZODRIN 5% Granules (FX 1551) to rats. Shell Research Ltd, Sittingbourne. TLGR.0010.70

Monocrotophos (FX1551, 5% granules) was applied to the shorn dorso-lumbar skin of Carworth Farm E rats (source not specified) at doses of 2500, 5000, 7500 or 10 000 mg formulation/kg bw (8/sex/group), and covered with an occlusive dressing for 24 h. The skin was then washed, and animals were observed for 24 h. The LD50 was determined to be greater than 10 000 mg formulation/kg bw (>500 mg active/kg bw).

Muir CMC (1971) Toxicity studies on Azodrin. The effect of time of exposure on the acute percutaneous toxicity to rats of a 40% w/v WSC (EF 2820) and dilutions of this concentrate in Shellsol A and water. Shell Research Ltd, Sittingbourne TLGR.0020.71

Three formulations of monocrotophos were used to determine the effect of dermal exposure time on toxicity. The formulations were a 40% solution in hexylene glycol, a 40% solution in hexylene glycol diluted to 20% in Shellsol A, and a 40% solution in hexylene glycol diluted to 20% in water. The 24-h occluded LD50 was determined by applying the formulation to the shaved dorso-lumbar skin of Carworth Farm E rats (Tunstall Breeding Unit), and covering the area with an occlusive dressing for 24 h; the skin was then washed. Animals were observed for 10 days. The doses used were not specified. There were 4 rats/sex/group. The LD50 determined were 107 mg active/kg bw for the 40% in hexylene glycol (268 mg formulation/kg bw), 17 mg active/kg bw (85 mg formulation/kg bw) for the Shellsol A dilution, and 113 mg active/kg bw (565 mg formulation/kg bw) for the water dilution. The effect of time of exposure on toxicity was investigated by applying the formulation to shorn skin for periods of time ranging between 1 min and 4 h, then washing the skin and observing the animals for 10 d. The results are set out in the table below.

Effect of time of exposure on toxicity

Exposure time	Percutaneous LD50 value (mg active/kg bw)		
	40% in hexylene glycol	Shellsol A dilution	Aqueous dilution
1 min	>1000	821	>500
10 min	796	130	>500
30 min	846	-	-
1 h	868	-	-
4 h	467	-	-

It can be seen that the toxicity of the compounds increases significantly with the length of time in contact with the skin, and rapid washing is important in order to reduce toxicity. The LD50 determined for each of the formulations indicated that the formulation with Shellsol A had the highest toxicity, while the aqueous formulation had the lowest toxicity.

Price JB (1982b) Toxicology of AZODRIN formulations; The acute percutaneous toxicity of EF 5801 and EF 5803 and the acute oral and percutaneous toxicity of EF 5811 and EF 5843. Shell Research Ltd, Sittingbourne. SBGR.81.112

Monocrotophos formulations were assessed for percutaneous toxicity. The formulations used were 250 g/L in dioxitol (EF 5801), 150 g/L in hexylene glycol and Shellsol AB (EF 5803), 200 g/L in oxitol acetate (EF 5811) and 200 g/L in hexylene glycol (EF 5843). The formulations were applied to the shorn dorso-lumbar skin of Wistar rats (Tunstall Breeding Unit) over a range of doses and covered with an occlusive dressing for 24 h. The skin was then washed with a detergent solution, and the animals were observed for 14 d. The doses used are set out in the following table:

Doses, expressed as active, applied to shorn dorso-lumbar skin

Formulation	Range finding study - 1 rat/sex/group	Definitive study 6 rats/sex/group
EF 5801	32.5 - 527 mg/kg bw	39.5 - 395 mg/kg bw
EF 5803	3.75 - 30 mg/kg bw	2.85 - 28.5 mg/kg bw
EF 5811	25.8 - 412 mg/kg bw	76.2 - 247 mg/kg bw
EF 5843	25 - 401 mg/kg bw	74.2 - 240 mg/kg bw

The clinical signs observed during the trial included fasciculations, tremors, increased lacrimation and salivation, chromodacryorrhea and signs of ocular damage. Signs with EF 5803 were of shorter duration than those observed with other compounds. The LD50s determined are set out below.

Dermal LD50 for formulations, expressed as active.

Formulation	Males	Females
EF 5801	196.5 mg/kg bw	227 mg/kg bw
EF 5803	11 - 18 mg/kg bw	11 - 18 mg/kg bw
EF 5811	136 mg/kg bw	152 mg/kg bw
EF 5843	189 mg/kg bw	195 mg/kg bw

Hurni H & Sachsse K (1969) Report on the determination of the Acute Dermal LD50 to the rat of NUVACRON 40. Tierfarm AG, Sisseln, Switzerland.

Monocrotophos (as Nuvacron 40; no other formulation details, source or batch no. specified) was applied to the shorn dorso-lumbar skin of RAC rats (source: Tierfarm AG, Switzerland) at doses of 100, 200, 300, 500 or 800 mg formulation/kg bw (3/sex/group). The lowest dose was diluted in sodium carboxymethylcellulose; the other doses were applied undiluted. The test area was shorn 6 h prior to application. After application, the area was covered with an occlusive bandage for 24 h. The bandage was then removed and the skin washed with warm water. Animals were housed individually for the 14-d observation period, with free access to food and water.

Clinical signs were seen during and after the application period, and included dyspnoea, exophthalmus, lacrimation and prostration. At 800 mg/kg bw muscle spasms, erection of the tail, and salivation were also seen. Gross pathological examination of animals dying during the study revealed bloating in the gastrointestinal tract and 'stained' livers. In animals euthanised at the end of the study, gross pathological findings included stained livers, inflamed intestines with haemorrhagic contents, and pale kidneys. The LD50 was determined to be 388 mg formulation/kg bw (approximately 155 mg active/kg bw).

Hurni H & Sachsse K (1969) Report on the determination of the Acute Dermal LD50 to the rat of NUVACRON EC 40. Tierfarm AG, Sisseln, Switzerland.

Monocrotophos (as Nuvacron 40EC; formulation details, batch no, and source not specified) was applied to the shorn dorso-lumbar skin of RAC rats (source: Tierfarm AG, Switzerland) at doses of 100, 200, 400, 500 or 1000 mL formulation/kg bw (3/sex/group). As the specific gravity of the formulation was not supplied, a dose in mg/kg bw could not be calculated. The application area was covered with an occlusive dressing for 24 h, after which the dressing was removed and the skin washed with warm water. Rats were housed individually with *ad libitum* food and water for the 14-d observation period.

Clinical signs were seen after 24 h, and included clonic-tonic muscle spasms, prostration, exophthalmus, lacrimation, dyspnoea and salivation. The severity of the symptoms increased with increasing dosage. Survivors were normal within 7 to 10 days. Gross pathological examination of animals dying during the study revealed haemorrhages in the small intestine and colon, atelectases in lungs, fatty degeneration in the liver and congested organs. No abnormalities were seen in the

animals euthanised at the end of the trial. The LD50 was determined to be 350 mL formulation/kg bw.

Lazzara K & Paa H (1975) Acute dermal toxicity study with AZODRIN 5 water miscible insecticide in male albino rabbits. Lab: Industrial Bio-Test, Report No 601-07485 and

Sawin VL (1980) Audit of Industrial Bio-Test Laboratories Study No 601-07485, "Acute dermal toxicity study in rabbits" Shell Development Company, Houston WRC RIR-13

Monocrotophos (60% in acetone, Code AC 14150, batch 2-TCL-23) was applied to the shaved dorso-lumbar skin of 6 male albino rabbits (source, strain not specified) at a dose of 200 mg/kg bw. The application site was covered with impervious plastic sheeting for 24 h, after which the skin was washed. Test sites were examined for local skin reactions, and the animals were observed for 14 d for mortality, local skin reactions, and behavioural abnormalities. Initial, 7- and 14-d body weights were recorded, and necropsies were done on all animals at the end of the observation period.

No animals died during the study, and there was no significant weight loss during the 14-d observation period. The material was slightly irritating to unabrased skin, producing pale red erythema at 24 h. No skin reactions were seen at 7 or 14 d. No gross pathologic abnormalities were found. The LD50 was determined to be >200 mg/kg bw. This IBT study was independently validated.

Coombs AD (1975) Acute percutaneous toxicity of AZODRIN formulation EF 2820 in the rabbit (non occluded). Shell Research Ltd, Sittingbourne. TLTR.0025.75

Monocrotophos (400 g/L in hexylene glycol) was applied to the shorn dorso-lumbar area of New Zealand White rabbits (Ranch Rabbits, Crawley, Sussex) at doses of 0.322, 0.386, 0.463, 0.556 or 0.667 mL/kg bw using 2 rabbits/sex/group. The skin was left non-occluded during the experiment. Food and water were available *ad libitum* after dosing; the rabbits were observed over a 9-d period. At the end of 9 d, rabbits that had lost weight were kept until their weight had returned to normal. Typical signs of poisoning were seen at doses of 0.556 mL/kg bw and above. Diarrhoea and weight loss were also observed, with the majority of affected animals not regaining normal weight for 2 -4 weeks after dosing. The LD50 was calculated at 0.49 mL/kg bw, equivalent to 527 mg formulation/kg (210 mg active/kg bw).

Newell GW & Shellenberger (1964) Letter Report No 2, Project B-4843. Stanford Research Institute, Menlo Park.

Monocrotophos (40% in acetone, batch no 7-3-4-7) was applied to the closely clipped dorso lumbar skin of New Zealand White rabbits (source not specified) at 96, 192, 384, and 784 mg/kg bw (3/group). The application was not occluded, and skin was washed with water after 6-h exposure. Symptoms included diarrhoea, miosis and dyspnoea, with the severity related to dose. The dermal LD50 for this 6 h nonoccluded trial was 342 mg formulation/kg bw (137 mg active/kg bw).

Shellenberger TE (1965a) Letter Report No 5 Ref Project B-4843. Stanford Research Institute, Menlo Park

Monocrotophos (40% in acetone, source: Shell Chemical Co, Code 7-3-4-7) was applied to the closely clipped skin of New Zealand White rabbits at doses of 237, 474, 948 or 1895 mg formulation/kg bw (3/group). The application area was not covered, and the material was removed by washing after 6-h exposure. Diarrhoea, miosis and dyspnoea were observed. The LD50 was determined to be 845 mg formulation/kg bw (338 mg active/kg bw).

3.3.1.3 Inhalation

Blair D & Wilson AB (1972) Toxicity studies on insecticide AZODRIN (SD 9129): Acute inhalation exposure of rats to aqueous mist (median droplet size less than 10 µm) Lab: Shell Research Ltd, Sittingbourne. TLTR.0002.72.

Azodrin soluble concentrate (40% monocrotophos in hexylene glycol) (source: Woodstock Agricultural Research Centre, Sittingbourne) was administered as an aerosol to Carworth Farm E strain rats (Tunstall Laboratories). Rats (2/sex/group) were restrained with their heads in an exposure chamber and exposed for 4 h. The estimated concentrations of monocrotophos in the atmosphere were 2, 4, 7, 10, 17, 18 or 36 µg/L.

All exposed animals exhibited tremors, excess salivation and dyspnoea. At 4 µg/L, the animals were exposed for 90 min before tremor was observed. At concentrations of 17 µg/L and above, all rats died, while all rats exposed to 7 µg/L or less survived. One female exposed at 10 µg/L died. No NOEL could be established for this study, as signs were seen at the lowest dose tested. There was no calculation of the LD50.

Wilson AB (1970) Toxicity studies on the insecticide AZODRIN (SD 9129): Acute inhalational exposure of rats to a 40% w/v soluble concentrate in an aqueous spray. Shell Research Ltd, Sittingbourne. TLGR.0078.70

Monocrotophos (40% solution in hexylene glycol) was administered by inhalation as an aqueous spray to Carworth Farm E rats (Tunstall Laboratories) at concentrations of 0.4% and 0.75% for 4 h, using 4 rats/sex/group. One group of rats at each dose were not protected from spray deposition on their body; an additional group at 0.4% received exposure only to their heads, with the rest of the body protected. Rats were fitted with collars to prevent grooming during exposure. Immediately following exposure, rats were washed, dried and returned to the cage for 10 d observation.

During exposure, treated rats showed tremors, dyspnoea and lethargy, and several died. The mortality in the unshielded group at 0.4% was 1/3 males and 1/3 females. One rat escaped, and another removed its collar and commenced washing. These animals were not included in the final result. In the 0.4% head only exposure group, 1/4 males died during the experiment. In the 0.75% group, 1/4 males and 4/4 females died. Therefore there appeared to be lower mortality when head-only exposure was used. No LC50 was determined.

3.3.2 Skin irritation Studies

Cagen SZ (1981a) Primary skin irritation of AZODRIN-5. Shell Development Company, Houston. WRC RIR-171

Azodrin 5 (60% monocrotophos in acetone; source: Shell Biological Sciences Research Centre) was applied at 0.25 mL/rabbit to shaved abraded and non abraded skin of New Zealand White rabbits (Ray Nicholls Rabbitry, Lumberton, Texas) under an occlusive dressing for 24 h (6/sex/group). Sites were assessed shortly after removal of dressing and at 72 h after application. The formulation was determined to be slightly irritating, with erythema and oedema the only signs. No clinical signs were reported for this investigation.

Shellenberger TE (1965a) Letter Report No 5 Ref Project B-4843. Stanford Research Institute, Menlo Park

Monocrotophos (40% solution in acetone, Shell Chemical Co, Code 8-10-4-13) was applied to the closely clipped skin of 6 rabbits (source, strain not specified). The material was applied to two spots, each area receiving 0.5 mL. Following application, the area was covered (type of covering not specified) for 24 h. The area was then washed with warm tap water, and sites graded for erythema and edema development. The average erythema at 24 h was 0.8, and at 72 h was 1.0. The average edema score was 0 at 24 h, and mild edema was seen at 2 sites at 72 h. Thus, the compound was deemed to be mildly irritating.

3.3.3 Eye irritation

Cagen SZ (1981b) Eye irritation of AZODRIN-5. Shell Development Company, Houston. WRC RIR-173

A 60% formulation of monocrotophos in acetone (Azodrin 5; undiluted, source, batch no not specified) was applied in a volume of 0.1 mL to the right eyes of 5 New Zealand White Rabbits (Roy Nicholls Rabbitry, Lumberton, Texas). Three males also had 0.1 mL applied, with the eye washed with tap water 30 seconds after application. Based on assessment of irritation at 1, 24, 48 and 72 h and 7 and 14 d after application, Azodrin 5 was found to be severely irritating to rabbit eyes. Washing the eye 30 seconds after application did not diminish the effect. The irritation was considered to be due to the acetone solvent.

Newell GW & Shellenberger TE (1964) Letter Report No 2, Project B-4843. Stanford Research Institute, Menlo Park.

Monocrotophos (40% in acetone, batch 8-10-21-1, source not specified) was instilled into the left eye of 9 rabbits at a dose of 0.1 mL/eye. The solution was washed out of the eyes after 30 sec, after 5

min or was not washed out (3/group). Control animals had the left eye treated with acetone. Eyes were graded for ocular lesions over the next 24 h, and on 3 occasions during the 14-d observation period. Monocrotophos induced transitory ocular effects, with corneal opacity, miosis and chemosis resolving within 24 h. Monocrotophos was classed as mildly irritating, given the transitory nature of the signs.

3.4 Monocrotophos mixtures with other pesticides

Cassidy SL (1979) Toxicology of insecticides: Acute toxicity of AZODRIN/DDT ULV formulation EF 5485 to rats. Shell Research Ltd, Sittingbourne. TLTR.79.010

A ULV formulation of monocrotophos (in cyclohexanone and ethyl dioxitol, percentage of monocrotophos not stated) (EF 5485) was administered to fasted SPF Wistar rats (Tunstall Breeding Unit) by gavage at doses of 44, 55, 69, 77, 110, 137, 158 or 217 mg formulation/kg bw using 6 rats/sex/group. Additionally, the formulation was applied to the shorn dorso-lumbar areas of similar rats with an occlusive dressing for 24 h at doses of 200, 250, 320, 400, 500, 630 or 790 mg formulation/kg bw using 6 rats/sex/group.

In the oral gavage study, all rats showed tremors and lacrimation within 5 h of dosing, with survivors recovering on day 2. In the dermal study, these signs were seen at doses of 320 mg formulation/kg bw and above, and resolved on day 3. At day 7, a dose related bodyweight loss (amount of loss not specified) was observed; this was resolving by day 14. The oral LD50 was calculated to be 123 mg formulation/kg bw, and the dermal LD50 was calculated to be 358 mg formulation/kg bw. It was not possible to determine the LD50 based on quantity of active.

Cassidy SL (1980a) Toxicology of insecticides; Acute oral and percutaneous toxicity of a RIPCORDER/AZODRIN ULV formulation, EF5254, to rats. Shell Research Ltd, Sittingbourne. TLGR.79.182

Monocrotophos (100 g/L in hexylene glycol and Shellsol AB, with RIPCORDER 25 g/L (not otherwise identified)) was administered by gavage to fasted SPF Wistar rats (Tunstall Breeding Units) at 48, 60, 77, 96, 120, 151, or 189 mg formulation/kg bw. Additionally, the formulation was applied to the shaved dorso-lumbar region of rats (6/sex/group) at doses of 125, 160, 200 or 250 mg formulation/kg bw and covered with an occlusive dressing for 24 h.

At oral dose levels of 60 mg formulation/kg bw and above, salivation, tremors and lacrimation were observed within 3 h of dosing. Survivors showed a decreased body weight over the first 7 d, followed by recovery by day 14. In the dermal study, salivation, tremors and lacrimation were observed within 90 min of dosing in all rats. Survivors showed a decreased body weight over the first 7 d, with the majority recovering by day 14. The oral LD50 was calculated to be 89 mg formulation/kg bw (8.9 mg active/kg bw), while the dermal LD50 was calculated to be 186 mg formulation/kg bw (18.6 mg active/kg bw).

Cassidy SL (1980b) Toxicology of insecticides: Acute oral and percutaneous toxicity of a RIPCORDER/AZODRIN ULV formulation, EF 4830, to rats. Shell Research Ltd, Sittingbourne. TLGR.80.007.

Monocrotophos (20% formulation in Shellsol AB) was administered to fasted SPF Wistar rats (Tunstall Breeding Unit) by gavage at doses of 20, 40 or 80 mg formulation/kg, using 2 rats/sex/group. Additionally, the formulation was applied to the shaved dorso-lumbar skin of similar rats under an occlusive dressing for 24 h at 125, 250, 500 or 1000 mg formulation/kg bw, using 2 rats/sex/group. The acute oral LD50 was estimated to be between 20 and 40 mg formulation/kg bw (between 4 and 8 mg monocrotophos/kg bw), while the acute dermal LD50 was estimated to be between 125- 250 mg formulation/kg bw (between 25 and 50 mg monocrotophos/kg bw).

Cassidy SL (1980c) Toxicology of insecticides: Acute oral and percutaneous toxicity of a RIPCORDER/AZODRIN ULV formulation, EF 4831, to rats. Shell Research Ltd. Sittingbourne. TLGR.80.009

Monocrotophos (20% formulation in isopropyl alcohol, diluted in hexylene glycol) was administered to fasted SPF Wistar rats (Tunstall Breeding Unit) by gavage at doses of 20, 40 or 80 mg formulation/kg bw, using 2 rats/sex/group. Additionally the formulation was applied to the shaved dorso-lumbar skin of similar rats at doses of 125, 250, 500, 1000 or 2000 mg formulation/kg bw

under an occlusive dressing for 24 h, using 2 rats/sex/group. The estimated acute oral LD50 was between 20 and 40 mg total formulation/kg bw (between 4 and 8 mg monocrotophos/kg bw), while the acute percutaneous LD50 was estimated to be 500 mg formulation/kg bw (100 mg monocrotophos/kg bw).

Cassidy SL (1980d) Toxicology of insecticides: Acute oral and percutaneous toxicity of a RIPCORD/AZODRIN EC formulation, EF 5312, to rats. Shell Research Ltd, Sittingbourne TLGR.80.006

Monocrotophos (25% in mixed petroleum/xylene: diluted to 2.5% in water) was administered to fasted SPF Wistar rats (Tunstall Breeding Unit) by gavage at doses of 6.25, 12.5, 25 or 50 mg total formulation/kg bw, using 2 rats/sex/group. Additionally, the formulation was applied to the shaved dorso-lumbar skin of similar rats at doses of 30, 60, 130, 250 or 500 mg formulation/kg bw, using 2 rats/sex/group.

Rats in the oral study showed lethargy, piloerection and chromodacryorrhoea at all dose levels. Deaths occurred approximately 5 h after dosing. Rats in the dermal study showed tremors, lachrymation and lethargy, with death occurring approximately 1 h after dosing. The acute oral LD50 was estimated to be approximately 25 mg total formulation/kg bw (6 mg monocrotophos/kg bw), while the acute percutaneous LD50 was estimated to be between 60 and 130 mg formulation/kg (between 15 and 33 mg monocrotophos/kg bw).

Cassidy SL (1980e) Toxicology of insecticides: Acute oral toxicity of a RIPCORD/AZODRIN EC formulation, EF 4832, to rats. Shell Research Ltd, Sittingbourne. TLGR.80.008

Monocrotophos (24% in mixed petroleum/xylene diluted in water) was administered to fasted SPF Wistar rats (Tunstall Breeding Unit) at doses of 20, 40 or 80 mg formulation/kg bw, using 2 rats/sex/group. The estimated acute oral LD50 was estimated to be between 20 and 40 mg formulation/kg bw (between 5 and 10 mg monocrotophos/kg bw).

Dewar AJ (1981a) Toxicology of RIPCORD/AZODRIN formulations: The acute percutaneous toxicity of the ULV formulations EF 5832 and EF 5833. Shell Research Ltd, Sittingbourne. SBGR.81.032

Monocrotophos (150 g/L ULV formulation with (EF 5832) or without (EF 5833) hexylene glycol, source: Physical Chemistry Division, Sittingbourne Research Centre) was applied to the shaved dorso-lumbar area of Wistar rats (Tunstall Breeding Unit).

In an initial dose ranging study, EF 5832 was applied at doses of 100, 200, 300, 500, 750 or 1000 mg total formulation/kg bw and covered with an occlusive dressing for 24 h. Based on the results of this study, the doses for a definitive LD50 determination were 314, 396, 500, 630, 793 and 1000 mg total formulation/kg bw. Clinical signs in the dose-ranging study included salivation, lacrimation, fasciculation, tremor, lethargy and in some cases ataxia. A marked loss in body weight was also seen. In a number of animals, the eyes became swollen, discoloured, bloody and opaque towards the end of the first week of dosing. Clinical signs persisted in survivors into the second week of testing. The LD50 for EF 5832 was determined to be 811 mg formulation/kg bw (122 mg active/kg bw) in males and 619 mg formulation/kg bw (93 mg active/kg bw) in females.

A dose-ranging study for EF 5833 was carried out at the same doses as for EF 5832. A definitive study was carried out at doses of 314, 396, 500, 630, 793 or 1000 mg formulation/kg bw, in a similar manner to the above study. Clinical signs were similar to those seen for EF 5832, including ocular effects. The LD50 for EF 5833 was determined to be 682 mg formulation/kg bw (102 mg active/kg bw) in males and 690 mg formulation/kg bw (104 mg active/kg bw) in females.

Dewar AJ (1981b) Toxicology of AZODRIN/DDT formulations: The acute percutaneous toxicities of the ULV formulations SEF 0001/81 and SEF 0002/81. Shell Research Ltd, Sittingbourne. SBGR.81.143

The formulations SEF 0001/81 and 0001/82 both contain 125 g/L monocrotophos and 300 g/L DDT. SEF 0001/81 is based on Shellsol AB solvent, while SEF 0002/81 is based on Dioxitol solvent. The acute percutaneous toxicities of both of these mixtures was investigated in Wistar rats (Tunstall Breeding Unit), housed under controlled conditions. The pesticides were applied to intact shaved dorsal skin. The area of application was covered by an occlusive dressing for 24 h after application.

At this time, the dressing was removed and the area washed. Animals were observed for 14 days for signs of toxicity.

SEF 0001/81 was applied at doses of 9, 15, 23, 30, 38 or 60 mg formulation/kg bw, using 6 rats/sex/group. Clinical signs observed included lethargy, bleeding from the nose, and chromodacryorrhoea, however the occurrence of these were sporadic, and all animals had recovered by day 3. Following this, SEF 0001/81 was applied at doses of 30, 48, 76, 121, 192 or 305 mg formulation/kg bw. At doses of 76 mg/kg bw and above, clinical signs including muscle fasciculations, salivation and lacrimation were seen. Survivors had generally recovered by day 3, however in one individual tremor persisted until day 7. The LD50 was determined to be 159 mg formulation/kg bw.

SEF 0002/81 was applied at doses of 94, 150, 238, 300, 378, or 600 mg formulation/kg bw. Some animals in the top two dose groups showed signs of intoxication, including salivation, fasciculation and ataxia. Signs appeared either on or after day 2, and recovery had occurred by day 8. The LD50 was determined to be 539 mg formulation/kg bw.

Price JB (1982a). Toxicology of AZODRIN mixtures: The acute percutaneous toxicities of AZODRIN/DDT (EF 5837), AZODRIN/BELMARK (EF 5741) and AZODRIN/RIPCORDER (EF 5798). Shell Research Ltd, Sittingbourne. SBGR.81.111.

The acute percutaneous toxicity of Azodrin/DDT (90/200 g/L), Azodrin/Belmark (100/25 g/L) and Azodrin/Ripcord (100/50 g/L) was investigated using Wistar rats (Tunstall Breeding Unit). A dose-ranging study for each formulation was carried out, using one rat/sex/group, prior to a determination of the LD50 using 6 rats/sex/group. For each trial, the dose was applied to the shaved dorso-lumbar skin and covered with an occlusive dressing for 24 h. At the end of this time, the dressing was removed and the skin washed with detergent solution. The animals were observed for 14 days after dosing. Where rats had a lower body weight at 14 days than at the start of the trial, they were maintained until they had returned to at least 95% of initial weight. Clinical signs seen in all three trials included tremors, increased salivation and lacrimation, muscle fasciculation and chromodacryorrhoea. Additionally, a number of animals in each study showed corneal opacity suggestive of ocular damage. In one animal this resolved within 7 days; the remainder of the animals showing this sign were euthanised on humane grounds due to significant weight loss.

In the Azodrin/DDT trial, the doses for the dose ranging trial were 602, 1183, 1828, 2365, 3010 or 3548 mg/kg bw. In the definitive trial the doses used were 1183, 1505, 1935, 2365, 3010 or 3768 mg/kg bw, and the LD50 for males was 1729 mg/kg bw and for females was 1398 mg/kg bw.

In the Azodrin/Belmark trial, the doses for the dose-ranging trial were 511, 1022, 1544, 2044, 2555 or 3066 mg/kg bw/day, and for the definitive trial were 1022, 1329, 1635, 2044, 2555 or 3270 mg/kg bw. The LD50 for males was 1533 mg/kg bw and for females was 1329 mg/kg bw.

In the Azodrin/Ripcord trial, the doses for the dose-ranging trial were 257, 515, 772, 1029, 1286 or 1544 mg/kg bw, and for the definitive trial were 123, 206, 319, 515, 823 or 1338 mg/kg bw. The LD50 for males was 823 mg/kg bw. The LD50 for females could not be calculated, however was between 319 and 515 mg/kg bw.

Rose GP (1980) Toxicology of RIPCORDER/AZODRIN formulations: The acute oral and percutaneous toxicity of EF 5632 and EF 5644. Shell Research Ltd, Sittingbourne. TLTR.80.003

The acute oral and percutaneous toxicity of two formulations of monocrotophos were tested using Wistar rats (Shell Toxicology Lab Breeding Unit). EF 5632, containing monocrotophos at 125 g/L and Ripcord at 30 g/L in dioxitol, and EF 5644, containing monocrotophos at 125 g/L and Ripcord at 30 g/L in hexylene glycol and Shellsol A were used. The formulations were administered orally, initially at 2% in corn oil, and then in 4% in corn oil, by gavage, to fasted rats using 6 rats/sex/group. The formulations were also applied to the shorn dorso-lumbar skin of rats (6/sex/group), and covered with an occlusive dressing for 24 h. All rats were observed for 14 d following treatment.

EF5632 was initially administered orally at doses between 10 and 160 mg formulation/kg bw. The oral LD50 was estimated to be approximately 160 mg formulation/kg bw. Clinical signs of lacrimation, salivation and muscle fasciculations were seen at doses above 64 mg/kg bw. A second study was done, using doses ranging from 80 to 252 mg formulation/kg bw, and the LD50 was determined to be 168 mg/kg bw in males and 140 mg/kg bw in females.

EF 5644 was initially administered orally at doses between 9 and 149 mg formulation/kg bw. The oral LD50 was estimated to be approximately 149 mg/kg bw. A second study using doses ranging between 93 and 372 mg/kg bw was done, and the oral LD50 for males was determined to be 171 mg/kg bw, and for females 145 mg/kg bw.

EF 5643 was applied dermally at doses from 50 to 500 mg formulation/kg bw. The LD50 was estimated to be >500 mg/kg bw. A second trial was done, using doses from 500 to 2000 mg/kg bw. The LD50 was estimated to be >2000 mg formulation/kg bw. There were no clinical signs seen in rats at any dose.

EF 5644 was administered at doses between 47 and 239 mg formulation/kg bw, and the LD50 was determined to be >239 mg/kg bw. Typical clinical signs were seen at all doses. A second trial using doses between 149 and 735 mg formulation/kg bw was performed. Tremors and ataxia were seen at doses of 288 mg/kg bw and greater. The LD50 was determined to be 288 mg formulation/kg bw.

Rost GP (1984) Toxicity of pyrethroids plus AZODRIN: The acute oral and percutaneous toxicity of AZODRIN ULV. Shell Research Ltd, Sittingbourne SBGR.83.368

A ULV formulation containing 100 g/L monocrotophos and 16 g/L Ripcord in trioxitol G was evaluated for acute oral and percutaneous toxicity using STCF Wistar rats (Tunstall Breeding Unit). In the oral trial, the formulation was administered by gavage to fasted rats (6/sex/group) at doses of 82, 104, 125, 166, 208 or 160 mg/kg bw. Animals were observed for 14 d after dosing. Deaths occurred in the first 24 h after dosing. Clinical signs included muscle fasciculations, ataxia, tremor, splayed hind-leg gait, salivation, lacrimation, lethargy, piloerection and chromodacryorrhea. The acute oral LD50 was determined to be 198 mg/kg bw for males and 125 mg/kg bw for females.

In the percutaneous trial, the formulation was applied to the shaved dorso-lumbar skin of the rats at doses of 655, 822, 1040, 1310, 1664 or 2080 mg/kg bw, and covered with an occlusive dressing for 24 h. At the end of this time, the skin was washed with a detergent solution, and the animals were observed for 14 d. Clinical signs were similar to those seen in the oral study. The LD50 was determined to be >2080 mg/kg bw for males, and 1706 mg/kg bw for females. Deaths occurred mainly in the first 3 d after dosing, however delayed deaths occurred until 14 d after dosing.

3.5 Antidote Studies

Reift B (1969) Pharmacological studies into the toxic actions of cholinesterase inhibitors. Part 9. Shell Research Ltd, Sittingbourne. TLGR.0008.69

Monocrotophos (analytical grade, purity 100%, source WARC) was administered in a saline vehicle by SC injection to female CF rats. This was followed by injections of atropine methonitrate (18.02 mg/kg bw), atropine sulphate (17.4 mg/kg bw), P-2-S (50 mg/kg bw), Toxogonin (dichloride bis[4-hydroxyiminomethyl pyridinium-(1)-methyl]) (90 mg/kg bw), atropine sulphate and P-2-S (dose as previously) or atropine sulphate and Toxogonin (dose as previously) administered when signs of toxicity were observed. Deaths were recorded at 24 h intervals for 7 days. Additionally, monocrotophos was administered SC at doses of 10 mg/kg bw either with or without antidotal treatment. Immediately after death, or after 2 h, the brains were perfused, removed and the ChE activity determined.

The LD50 of monocrotophos in this strain of rats had previously been determined at 7 mg/kg bw. All antidotes were effective in lowering the toxicity; results are presented below.

SC LD50 of monocrotophos following antidote administration

Chemical	LD50 (mg/kg bw)
Monocrotophos	7
Monocrotophos + atropine methonitrate	21.1
Monocrotophos + atropine sulphate	81.5

Monocrotophos + P-2-S	18.3
Monocrotophos + atropine sulphate + P-2-S	198.7
Monocrotophos + Toxogonin	32.6
Monocrotophos + atropine sulphate + Toxogonin	163

In rats given 10 mg/kg bw monocrotophos SC, signs were seen after 9 min, with death following at approximately 23 min after dosing. The brain ChE activity was 63% inhibited in comparison to controls. When antidotes were administered, rats survived to the 2 h scheduled sacrifice. The brain ChE activity following atropine sulphate treatment was 58% inhibited, following atropine sulphate and P-2-S was 60% inhibited, and following atropine sulphate and Toxogonin administration was 61% inhibited. It appears that the brain ChE inhibition it not altered significantly following antidote administration, although the LD50 is substantially changed.

Mehani, S, El-Habashi A & Soliman S (1978) Evaluation of certain oximes and atropine in the treatment of rats intoxicated with organophosphorus insecticides. Ain Shams Med J 29(5/6): 383-389

Monocrotophos (as Azodrin and Nuvacron, source, purity not specified) was administered orally to Wistar rats (source not specified) by gavage at doses of 10 mg/kg bw for Azodrin, or 20 mg/kg bw for Nuvacron using 5 rats/sex/group. This was immediately followed by an IP injection of an antidote, or combination of antidotes. The antidote was repeated by SC injection after 4 h. The antidotes used were 2-PAM, dichloride bis[4-hydroxyiminomethyl pyridinium-(1)-methyl](Toxogonin), parliodixime hydroxyiminomethyl-2 methyl-1 pyridinium (Contrathion) and atropine sulphate. 2-PAM was administered at 100 mg/kg bw, Toxogonin at 5 mg/kg bw, Contrathion at 4 mg/kg bw and atropine sulphate at 20 mg/kg bw. Additionally, atropine was administered in combination with 2-PAM, with Toxogonin and with Contrathion.

Azodrin administered with no antidote resulted in 5/10 rats dying within 24 h. Following atropine, PAM, atropine and PAM, or atropine and Contrathion in combination, all rats survived this dose of Azodrin. Atropine and Toxogonin in combination resulted in 1/10 rats dying, with both Toxogonin or Contrathion alone, 2/10 rats died. Following Nuvacron administration with no antidote 9/10 rats died within 2 days. The only fully effective antidotes was atropine in combination with either Toxogonin or Contrathion. Atropine, 2-PAM or Toxogonin alone resulted in 2/10 rats dying, while a combination of atropine and PAM resulted in mortality in 3/10 rats. Contrathion alone resulted in 5/10 rats dying.

Therefore atropine and 2-PAM either alone or in combination effectively reduce the mortality following an administered dose of monocrotophos.

Gough BJ & Shellenberger TE (1977-78) In vivo inhibition of rabbit whole blood cholinesterase with organophosphate inhibitors and reactivation with oximes. Drug Chem Toxicol 1(1): 25-43

Monocrotophos technical (source: Shell Development, purity not given) in saline solution was administered by IV infusion to adult male New Zealand White rabbits (3/group) at 0.106 mg/min for 60 minutes, followed by treatment with one of five oxime reactivators, 2-PAM, P-2-S, 1,1'-trimethylene-bis-[4-(hydroxyiminomethyl)-pyridinium bromide] (TMB4), isonitrosoacetone (MINA) and diacetyl monoxime (DAM). Whole blood ChE activity was measured prior to, during and after the chemical infusion.

Monocrotophos produced significant inhibition of ChE activity by 20 minutes after the commencement of infusion. Levels decreased to approximately 40% of preadministration levels (estimated from graph) by the end of the infusion, and recovered gradually from this point. The administration of 50 mg/kg bw 2-PAM did not change the ChE activity from that which would be expected with spontaneous recovery. In a second test comparing the 5 oxime reactivators, MINA and DAM at high doses did not affect ChE activity recovery. 2-PAM and TMB-4 administration at 50 mg/kg bw resulted in a return to normal values at 60 minutes after the administration of the reactivator. P-2-S administration at 50 mg/kg bw also produced an increase in ChE activity over 60 minutes, however the levels had not returned to normal. When the rabbits were not dosed with the oxime reactivator, ChE activity did not return to normal over the period of examination.

Brown AK (1964) *The efficacy of atropine and oxime therapy as an antidote to poisoning by SD9129 in guinea-pigs. Shell Research Ltd, Sittingbourne. Tech Memo Tox 20/64*

A series of 2 experiments was conducted using monocrotophos (batch no FC 1342, source not given). The first involved establishing the LD50 by the SC route in guinea-pigs of the 'P' strain (source not given), and the second was to determine the effectiveness of atropine alone or in combination with P-2-S.

In the first test, a 2% aqueous solution of monocrotophos was injected SC into the flank of guineapigs (1/sex/group) at doses of 37.5, 40, 45 or 60 mg/kg bw. The LD50 was determined to be 45 mg/kg bw. For the antidote test either 5 times the LD50 was administered to controls, and either 5 or 10 times the LD50 was administered to animals treated with atropine alone (17.4 mg/kg bw SC) or atropine and P-2-S (17.4 mg/kg bw and 50 mg/kg bw respectively). At 5 times the LD50, all control animals died, while no deaths were seen in either of the antidote groups. Ten times the LD50 was not administered to controls, as complete mortality was assumed. With atropine treatment, mortality following this dose was 3/5 males and 5/5 females. With atropine and P-2-S, mortalities were 1/5 males and 2/4 females. The mortalities seen in these groups were delayed by several hours in comparison to deaths seen in control animals. Therefore, it appears that atropine plus P-2S is an effective antidote, and has a greater affect than atropine alone at high doses.

Shellenberger (1980) *Organophosphate pesticide inhibition of cholinesterase in laboratory animals and man and effects of oxime reactivators. J environ Sci health B 15(6): 795-822*

Monocrotophos (source, purity not given) was administered to New Zealand White rabbits by IV infusion via the lateral ear vein at the rate of 0.106 mg/min. The oxime reactivators 2-PAM, P-2-S and TMP4 were administered at 25 or 50 mg/kg bw, and the level of cholinesterase inhibition determined. 2-PAM at 50 mg/kg bw resulted in minimal ChE inhibition 1 h after commencement of treatment, as did 50 mg/kg bw of TMP4. P-2-S was not as effective at decreasing inhibition. At the lower dose of 25 mg/kg bw, none of the antidotes were effective at preventing ChE inhibition.

An absorption study was also done. Monocrotophos technical, and combined with water, acetone, DMSO or xylene was administered percutaneously to the clipped skin of New Zealand White rabbits, and exposed for a period of time. The dose applied and the period of exposure were not specified. The absorption was estimated using ChE inhibition. Water did not increase the penetrance of monocrotophos. Including acetone or DMSO increased absorption to approximately twice that seen with monocrotophos alone. The use of xylene as a solvent dramatically increased the absorption of monocrotophos, estimated to increase it by approximately 40 times.