10 NEUROTOXICITY

10.1 Mice

Gupta M & Bagchi GK (1982) Behavioural pharmacology of FURADAN and NUVACRON in mice. Ind J Hospital Pharmacy, July/August 136 - 141

Monocrotophos (source, purity unspecified), dissolved in 0.9% sodium chloride was administered IP to male albino mice (UK Horn Huderfield strain: source unspecified) at doses of 0, 2, 3 or 4 mg/kg bw using 15/group. Righting reflex, corneal reflex, pinna reflex and grip strength were measured and a traction test was done. Awareness was evaluated by assessing the movement of the mice when held by the scruff of the neck in a variety of positions, including a normal walking position, vertically or supine. A somersault test, involving tossing the mouse so that it performs 2 or 3 somersaults, and evaluating how the animal lands (on all 4 feet, on one side etc) was performed. Motor activity was assessed using a photo-actometer. The incidences of stereotypy and catalepsy were also evaluated.

Doses of 2 mg/kg bw monocrotophos had a significant effect on awareness in comparison to controls, with the effect being between 'strong effect' and 'very strong effect'. There was no effect on performance in the somersault test. Motor activity was slightly altered by monocrotophos, but not in a dose-related manner. The pinna reflex was absent in all treated groups. There was also a dose related decrease in gripping time, with controls gripping for 35 seconds, and the high dose group gripping for 26 seconds. Mice treated with monocrotophos were inactive for 30 - 60 min after administration, with behaviour gradually returning to normal over 240 min. Therefore there appears to be short term effects on the neurological system in mice; the time frame is consistent with these being related to ChE inhibition.

10.2 Rat

Rose GP & Dewar AJ (1980) Toxicity studies on the RIPCORD/AZODRIN formulation EF 5254: Biochemical and functional studies on the neurotoxicity of the formulation EF 5254 in the rats. Shell Research Ltd, Sittingbourne. TLGR.79.027.

The neurotoxicity potential of a combined formulation of monocrotophos and a pyrethroid was assessed using Wistar rats (Tunstall Breeding Unit). The formulation (EF 5254) contained 50 g/L pyrethroid (unspecified) and 200 g/L monocrotophos in hexylene glycol and Shellsol AB. The LD50 of this formulation had been established at 96 mg/kg bw. Five treatment groups, of 8 rats/sex/group were established. Group 1 received blank formulation at 25 mg/kg bw/day, group 2 received EF 5254, group 3 received EF5254 without monocrotophos and group 4 received EF 5254 without the pyrethroid. Group 5 was a positive control group, receiving a dose of pyrethroid (unspecified) known to be neurotoxic (150 mg/kg bw). Rats were observed for clinical signs, and were also tested for neuromuscular function by being placed on an inclined board; as the angle of the board was increased, the angle at which the rat began to slip was measured.

Three weeks after dosing commenced, rats were euthanised. The right and left sciatic nerves were dissected out to the distal phalangeal branches of the posterior tibial nerves. These nerves were then sectioned into proximal and distal portions. The right and left trigeminal ganglia were dissected free after removal of the brain. The levels of -galactisodase and -glucuronidase in these tissues were analysed.

No mortalities were seen in groups 1 or 3. In the group receiving EF5254, 6/8 females died while all males survived. In group 4, 4/8 females and 2/8 males died, while 1 male in the positive control group died. Males receiving EF 5254 either with or without monocrotophos showed decreased body weights, as did control animals. There were no significant effects on body weights in female animals. Clinical signs observed in animals receiving EF 5254 were ataxia, tiptoe walk, hyperexcitability, convulsions, tremors, unkempt appearance and lethargy. Animals receiving monocrotophos alone showed tiptoe walk, tremors, lethargy and an unkempt appearance. Positive control animals showed ataxia, splayed gait, tiptoe walk, hyperexcitability and lethargy, with one animal showing tremors. There were transient decreases in neuromuscular function in animals receiving EF 5254, monocrotophos and in positive controls. These changes were only significant in female animals.

Analysis of enzyme levels in sciatic nerve revealed a significantly increased ($p<0.01$) level of both -galactisodase and -glucuronidase in the proximal nerve section following EF 5254 administration. Following monocrotophos administration, glucuronidase levels were significantly increased in both the proximal and distal sciatic nerves ($p<0.01$), with a lesser increase ($p<0.05$) in galactosidase levels in both sections. Positive control animals showed increases in both enzymes in both the proximal and distal sections of the nerves. In the trigeminal ganglion, both enzymes were increased following EF 5254 administration, and in the positive control group. Levels of glucuronidase were increased following monocrotophos treatment.

Therefore there is an indication that monocrotophos may cause changes to sciatic nerve enzyme levels similar to those seen following a known neurotoxic pyrethroid. It must be noted however, that the dose of monocrotophos used was relatively high, at around 1/4 of the LD50, and produced deaths and obvious clinical signs. It is of interest that despite the transient changes in neuromuscular function assessed clinically, there was no histopathological examination of the nerves.

Wolthuis GL, Hoodendijk EMG & Vanwersch RAP (1982) Behavioural effects in rats of low doses of insecticides in relation to brain and blood cholinesterase activity. Addendum to the first interim report. Shell Project 7-1-81. Rijswijk Medical Biological Laboratory TNO
Monocrotophos (purity 95%, source: Chrompack BV Middleberg, the Netherlands) was administered to male Wistar rats (MAG/MBL) (source not specified) in a number of experiments. The LD50 of the chemical was determined to be 6.1 mg/kg bw in this strain.

The experiment aimed to determine the peripheral effects of monocrotophos by measuring the respiratory minute volumes and the effects on the neuromuscular junction. This was measured by tetanically stimulating the sciatic nerve, and measuring the contraction of the gastrocnemius soleus muscle. Initially, 12 mg/kg bw was administered. This produced respiratory arrest within 30 min. Neuromuscular transmission was significantly inhibited at this time.
When rats were pretreated with 50 mg/kg bw of atropine sulphate or atropine methylnitrate, the dose of monocrotophos required to induce respiratory failure increased to 15 times the LD50, or approximately 92 mg/kg bw. At this dose, respiratory failure was induced by inhibition of neuromuscular transmission.

A diaphragm strip prepared from a rat which died in one of the above experiments was mounted in a laboratory preparation, and was washed free of monocrotophos. Neuromuscular transmission was restored following washout of the pesticide; a second dose of pesticide resulted in a return of inhibition. These trials indicated that monocrotophos has primarily a peripheral action. This is supported by the significant preventative role of atropine which is unable to cross the blood-brain barrier.

Following the above trials, a number of behavioural trials were performed. A runway performance test using trained rats (9/group) was done. Treated rats were injected SC with approximately 2 mg monocrotophos/kg bw, and control rats injected SC with saline. The reaction time (time from box being opened to rat entering the runway) and the running time were measured using photoelectric beams. Monocrotophos had no effect on the running times in this trial. The reaction time 60 minutes after injection was increased related to monocrotophos dosing; this was related to one rat taking 3 seconds to leave the box.

Open field behavior was measured in rats receiving 0, 0.6, 1.2 or 1.8 mg/kg bw monocrotophos by SC injection, with open field measurements commencing 30 min after injection. Animals were euthanised approximately 2 h later, and the ChE activity in plasma, blood and brain determined. A dose of 0.6 mg/kg bw had no effect on open field behavior, however the higher two doses decreased the distance moved and areas entered in the trial. All doses administered produced significant ChE inhibition in the plasma, blood and brain.

Rats were injected daily with 0.18 mg/kg bw monocrotophos or saline (control). Two rats/group received IP injection, while 3 rats/group received SC injection. Rats were injected 5 days/week for 3 weeks, with body weight and tail length determined at the end of the trial. Open field behavior was measured on days 5 and 12, and was unaffected by this dose of monocrotophos. ChE inhibition was measured 1, 2 and 3 h after injection in rats receiving SC injections. There was significant inhibition of plasma, blood and brain ChE at all three times at this dose.

10.3 Hens

Jenkins LJ (1981a) 14 day neurotoxicity study of AZODRIN in chicken hens. Lab: Food and Drugs Research Laboratories, Report 6535-1 Sponsor: Shell Development Company, Houston WRC RIR-147
Monocrotophos technical (source, purity not specified) was administered by oral gelatin capsules to White Leghorn hens (Babbock Farms, Ithaca NY) at doses of 0, 0.03, 0.1, 0.3 or 1.0 mg/kg bw/d for 14 d using 5 hens/group. There were also 2 positive control groups, receiving 50 or 100 mg/kg bw/d tri-ortho-cresyl-phosphate (TOCP). Negative control animals received a capsule containing ground feed. Capsules were prepared on the day of dosing. Blood was collected from all hens on the d before dosing and on d 1, 7 and 14. Plasma and erythrocyte ChE activity were determined. After 14 d, the hens were euthanised, and the whole brains collected and weighed. The brain ChE activity and neurotoxic target esterase (NTE) levels were determined. Any animals in a moribund condition were sacrificed, and examined as for animals at the end of the study.

Hens were examined daily for clinical signs, including observations of walking. Delayed neuropathy signs were scored as follows: 0 = no detectable signs, 1 = slight unsteadiness on walking, 2 = marked staggering and occasional falling, 3 = advanced neurotoxic signs, extreme difficulty in walking, falling often, 4 = unable to walk, standing with difficulty, 5 = complete motor paralysis of legs, lying on side.

Hens in the high-dose monocrotophos group were euthanised on day 3. Two of the animals were unable to stand, while the other three were unable to walk or obtain food or water. These effects were considered to be due to acute compound related effects, rather than to any delayed neuropathy. Body weight of hens receiving 0.3 mg/kg bw/d monocrotophos was significantly decreased at the end of the study. No other body weight changes were noted. Egg production was significantly ($p<0.05$) decreased in all treatment groups except the lowest dose. Significant plasma ChE inhibition was seen at 0.1 mg/kg bw/d of monocrotophos, while brain ChE activity was only inhibited by doses of 1.0 mg/kg bw/d. No NTE inhibition was seen at any dose level of monocrotophos, while the positive control produced 90% inhibition. Neurological scoring indicated that, although there was a slight increase in scores at 0.3 mg/kg bw/d (due to a score of 1 in one individual), there was no significant change related to treatment. The animals on 1.0 mg/kg bw/d had high neurological scores prior to their euthanasia, however this was considered to be due to the acute effects of the compound. Therefore there was no evidence in this study of delayed neuropathy related to treatment with monocrotophos.

Owen DE & Butterworth STG (1978) Toxicity of organophosphorus insecticide AZODRIN. Investigation of the neurotoxic potential of AZODRIN-5 to adult domestic hens. Shell Research Ltd, Sittingbourne. TLGR.0066.78
Warren Studdler laying hens (Lervill Farms Ltd, Ken) were premedicated with intramuscular injections of 17.4 mg/kg bw atropine sulphate (British Drug Houses Ltd, Dorset) and 50 mg/kg bw pralidoxime chloride (Ayerst Lab, NY). One h later, one group received 6.7 mg/kg bw of a 60% formulation of monocrotophos in acetone (Azodrin-5, source: Shell Biosciences Laboratory, Sittingbourne) given orally in gelatin capsules. This dose had previously been established as the LD50 for hens; the birds were premedicated to increase survival. A positive control group received 0.5 mL/mg tri-o-tolyl phosphate (TOTP) (source: Kodak Ltd) by gavage and a third control group was not treated. There were initially 6 hens/group, however an addition 8 hens were added to the monocrotophos group after the first treatment. Hens surviving the first injection of monocrotophos were given a second injection 3 weeks later. All animals were euthanised either 3 weeks after their final dose, or when they showed a persistent progressive ataxia.

All animals were observed daily for clinical signs, and tested for the ability to land without staggering after induced flight. On autopsy, the brains, sciatic nerve and spinal cord were removed and preserved in formalin. Sections of the cervical, thoracic and lumbar spinal cords were prepared for histopathological examination, as were section of the sciatic nerve, cerebellum and medulla oblongata.

In the monocrotophos treated group, 3 birds died within 4 days of the first dose, and one after the second dose. Five of the 8 new birds introduced also died. Overall, 5 hens survived 2 doses of monocrotophos. These birds showed no persistent ataxia or histological lesions of the nervous system and were similar to the control group. The positive controls showed ataxia, loss of coordination and loss of balance. There were foci of axonal and myelin degeneration in the spinal cord and sciatic nerves of these animals.

Shellenberger TE (1965c) Letter Report No 7 Ref Project B-4843. Stanford Research Institute, Menlo Park.
Monocrotophos (source, purity not given, code 7-3-0-0) was fed in the diet to White Leghorn hens (source not specified) at doses of 0, 1, 10 or 100 ppm monocrotophos using 10/group. A positive control group received 1000 ppm tri-orthocresyl phosphate (TOCP). After 4-weeks feeding, 5 birds/group were euthanised, and examined for gross pathology. Sections of brain, spinal cord (cervical and lumbar) and sciatic nerve were preserved for histopathological examination. The remaining birds were fed untreated diets for 4 weeks. Body weight, food consumption and egg production were recorded on a weekly basis. Hens were examined daily for any clinical signs.

Body weights were reduced in birds on 10 ppm (by 10 - 12%) and 100 ppm (by 20 - 35%). Egg production was markedly decreased in the 10 and 100 ppm groups, with egg production ceasing totally during the 2nd week of feeding. Egg production was slightly decreased by week 4 in the 1 ppm group. Abnormal clinical signs were observed in the 100 ppm treatment group, with tremors seen after 10 - 12 days of feeding. The birds were able to stand and walk at this stage. Positive control animals showed significant neurotoxic signs after 16 -17 days, including leg weakness and an inability to stand. There were no abnormalities seen on gross pathological examination. On histopathological examination, signs of demyelination were seen at a relatively high frequency in control animals. The frequency was similar in birds treated with monocrotophos. The demyelination was more consistent and severe in the positive control animals.

Jenkins LJ (1981b) Neurotoxicity evaluation of AZODRIN insecticide: Subchronic oral administration in hens. Lab: Food and Drugs Research Laboratories (Report Np 6535-11) Sponsor: Shell Development Company, Houston WRC RIR-148

Monocrotophos (sample no. #14200-5555B, source: Shell Development Company, purity not given) was administered orally in gelatin capsules at doses of 0, 0.03, 0.1, or 0.3 mg/kg bw/d for 78 d to White Leghorn hens (10/group). Additionally, 10 hens received daily oral doses of 7.5 mg/kg bw/d TOCP as a positive control. From days 79 to 96 (the end of the study), the 0.3 mg/kg bw/d group received 0.5 mg/kg bw/d monocrotophos and the dose of TOCP given to the positive control group was increased to 10 mg/kg bw/d, as only one positive control hen had exhibited a positive neurological response at this stage. Hens were housed individually, and food and water were available ad libitum. Hens were observed once daily for clinical signs and mortality, and records of egg production were made throughout the study. All birds were observed walking daily, even where this had to be induced. Clinical signs of neuropathy were rated on a scale from 0 to 5, with 0 being no detectable symptoms, and 5 being complete motor paralysis of legs, lying on side. Blood was collected from all hens on d -1, 1, 30, 58 and just prior to sacrifice. Plasma and erythrocyte ChE activities were determined. At the end of the study, all hens were euthanised, and perfused with saline and a formaldehyde/glutaraldehyde solution for approximately 23 min. The brains, optic and cranial nerves, vertebral columns and the sciatic, tibial and perineal nerves were removed. The vertebral column was decalcified prior to removal of cervical, thoracic and lumbar section of spinal cord and dorsal root ganglion to minimise artifacts produced by tissue stretching. The prepared slides were examined by two histopathologists, and all lesions were graded on numerical scales as to severity.

There were no treatment related effects on body weight seen in this study. Hens in the 0.3 mg/kg bw/d group showed decreased egg production during days 14 - 41, however this then returned to normal levels until the end of the study. There were no clinical signs of neuropathy seen in any animals treated with monocrotophos; a small number of positive control animals showed gait deficits. There was significant inhibition of plasma ChE seen in animals in the mid and high-dose treatment groups from day 30 until the end of the end of the study. Erythrocyte ChE was inhibited only in the high dose group. There were no clinical or histopathological indications of delayed neurotoxicity in hens receiving monocrotophos, whereas those receiving 10 mg/kg TOCP showed neurotoxic signs, particularly swollen axons.

11 HUMAN STUDIES

11.1 Oral or dermal administration

Verberk MM (1977) Incipient cholinesterase inhibition in volunteers ingesting monocrotophos or mevinphos for one month. Toxicol appl Pharmacol 42:345 - 350

Groups of 6 male students, aged 20-30 and weighing 60-90 kg, received daily capsules providing 0, 0.0036 or 0.0057 mg/kg bw monocrotophos (>99% pure, in corn oil, acetone, source not specified) for 28 days. Baseline ChE levels were determined prior to administration. Plasma and erythrocyte ChE activity was determined twice weekly throughout the trial, and for 2 weeks after completion of dosing. ChE inhibition was measured colorimetrically. ALT, AST and AP levels were determined prior to the completion of dosing.

There were no toxic signs observed, and no changes in ALT, AST or AP activities. Erythrocyte ChE activity was not altered by either dose of monocrotophos. Plasma ChE levels in the 0.0036 mg/kg bw/d group decreased by 15% during the first 18 days and remained at that level. This was not considered to be a significant depression of ChE activity. In the 0.0057 mg/kg bw/day group there was a continuous decrease in plasma ChE throughout the study to a low of 24% inhibition at 28 days. Based on the inhibition of plasma ChE activity seen at 0.0057 mg/kg bw/d, the NOEL may be set at 0.0036 mg/kg bw/d.

Verberk MM (1972) Cholinesterase inhibition in man caused by 30 days administration of monocrotophos (translation). Coronel Laboratories, University of Amsterdam

Monocrotophos (purity 99%) in 90% maize oil and 10% acetone was administered to young male volunteers in two preliminary trials, followed by a longer-term study. In the first trial, 0.015 mg/kg bw/d was administered in gelatin capsules to 8 individuals. Plasma ChE levels had decreased to 65% of pretest levels within 7 days of commencing treatment. In a subsequent trial, 6 individuals were given 0.0036 mg/kg bw/d orally for 21 days. The plasma ChE activity decreased initially, then stabilised with approximately 15% inhibition in comparison to pretest levels. This trial did not maintain a control group, and the results were therefore considered to be of limited use.

In the definitive trial, 3 groups of 6 young male volunteers were administered 0, 0.0036 or 0.0059 mg monocrotophos/kg bw/d by gelatin capsule. The control group received gelatine capsules containing vehicle alone. The ChE activity of each of the volunteers was determined 4 times pretest, during administration, and 4 times up to 12 days after cessation of dosing. A limited blood test (Hb, sedimentation and leucocyte count) and urine test (albumin and sedimentation) were performed pre-test. The AST, ALT and AP levels were determined 10 days pre-test, at the end of administration and 12 days post test.

Plasma and erythrocyte ChE levels were not significantly changed in the low dose group. In the high-dose group, there was significant inhibition of plasma ChE activity from days 18 to 28 of the trial, with levels decreasing to 72% of pretest values. Erythrocyte ChE activity was not affected. Plasma ChE levels had returned to normal by day 9 after cessation of dosing. Based on the effect on plasma ChE seen at 0.0059 mg/kg bw/day, the NOEL can be established at 0.0036 mg/kg bw/d.

Feldman RJ & Maibach HI (1974) Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol 28:126 - 132

^{14}C Labeled monocrotophos (source: either New England Nuclear Corporation, Boston Mass, or Amersham Searle Corporation, Skokie Illinois) was used. An IV dose of 1 Ci/mL was prepared with a propylene glycol solvent, with 1µCi administered to each volunteer (six normal male volunteers; age not specified). Urine was then collected for 5 days. The first 12 h was divided into three 4-h time periods. A 12-h sample was then collected. Samples were then collected every 24 h. The radioactivity present in the urine was determined and was used to quantify the urinary excretion following parenteral administration. The percentage of administered dose excreted following IV administration was used in a trial to determine the degree of absorption following a dermal dose. For dermal application, the dose was dissolved in acetone and applied to either one or both forearms, depending on the skin surface required to reach the dose required. The skin was air dried after application, and subjects were asked not to wash the skin for 24 h after application. Urine collection proceeded following the protocol used for IV administration.

Following IV administration of monocrotophos 68% of the administered dose was excreted in the urine in the 5 d following administration. The half life was determined to be 20 h. Following dermal application of monocrotophos, approximately 15% was excreted in urine in 5 days, indicating incomplete skin absorption of monocrotophos from the forearm skin. This indicated that approximately 22% of the administered dose of monocrotophos was absorbed in this trial.

11.2 Field studies

Guthrie FE, Domanski JJ, Chasson AL, Bradway DE & Monroe RJ (1976) Human subject experiments to estimate reentry periods for monocrotophos-treated tobacco. Arch Environ Contam 4: 217 - 225
Groups of 13-15 volunteers wearing long trousers and short-sleeved shirts worked for 8 h periods in tobacco fields treated 48, 72 or 96 h earlier with 0.5 pounds/acre of monocrotophos. At 48 h, group mean plasma and erythrocyte ChE activities were reduced by 4% and 9% respectively relative to pre-exposure. Rainfall in excess of 25 mm prior to the 72 and 96 h re-entry resulted in plasma and erythrocyte ChE inhibition being little changed from pre-exposure levels. Urine collected from volunteers 3-6 h after each exposure did not identify the presence of any dimethyl phosphate (major metabolite).

Mice (10-15) physically exposed to tobacco leaves taken directly from treated fields (as above) for 10 h/d had almost complete plasma ChE inhibition (99%) immediately after spraying. This inhibition was reduced to 42% (relative to pre-exposure) after 24 h and 40% after 48 h post spraying. This latter result at 48 h contrasts markedly with a second group of mice that had 75% plasma ChE inhibition 48 h after exposure. The reason for this discrepancy in unclear. As expected, the 72 h and 96 h levels of plasma ChE inhibition were both substantially reduced by only 6% (relative to pre-exposure) because the rain had washed the monocrotophos from the leaves.

Van Sittert NJ & Dumas EP (1990) Field study on exposure and health effects of an organophosphate pesticide for maintaining registration in the Phillippines. Med Lav 81.6: 463 - 473
This published report investigated the extent of monocrotophos exposure for 21 spraymen involved in manually spraying rice with pressurised backpack sprayers in the Phillippines. All 28 recruited volunteers (ie. including 7 controls) had no occupational exposure for at least 3 weeks before the study. In the spray operation, groups of 2 spraymen were randomly allocated 11 plots (1 of the 11 plots had only 1 sprayman) that were to be sprayed for 5 h/d over 3 consecutive days. Each group sprayed 1-1.5 ha/d with 120-240 L of 0.09-0.18% (w/v) monocrotophos. During filling and spraying operations, spraymen were clad in normal work clothes, ie. long sleeved shirt and long trousers but without any footwear. The extent of exposure was monitored by two separate methods, namely quantifying the monocrotophos metabolite, dimethylphosphate (DMPO) in pooled urine collected over 24 h the day before, during and the day after spraying, and determining ChE activity in whole blood and erythrocytes (plasma ChE inhibition was calculated by difference). ChE activities were determined 2 h after spraying on days 1, 2 and 3 and 21 h after the third spray, ie. on day 4. DMPO concentration was determined using GC-LC methodology (detection limit 5 µg/mL). ChE activity was measured using a colorimetric assay.

Only one sprayman reported a short episode of blurred vision (duration not reported) following spraying. Excretion of urinary DMPO (expressed as monocrotophos equivalents) increased with successive daily exposure from a median of 0.07 mg/24 h (range, <0.04 to 0.58) on the day before spraying to 0.64 (range, <0.04 to 1.9), 0.74 (range, <0.04 to 5.1) and 1.9 (range, 0.09 to 6.3) mg/24 h respectively on the 3 spraying days. Even on the day following exposure, a median of 0.76 mg/24 h (range 0.07 to 3.5) was observed, indicating a relatively long half life. A mean half life of 18 h was estimated from excreted DMPO levels.

Mean percent inhibition of ChE activity in plasma and erythrocytes relative to activity in the control group are shown below in Table 1. The mean values shown in square brackets are calculated relative to pre-exposure levels in the same individual.

Table 1: Cholinesterase Inhibition - (expressed as % reduction)*

Day	Plasma	Erythrocyte
0	-8	-7
1†	-5 [-5]	-6 [12]
2†	14 [44]	8 [11]
3†	60 [75]	9 [43]
4	54 [71]	8 [36]

* negative values are where test ChE activity exceeds controls; † spraying day.

Although the exact extent of monocrotophos exposure cannot be determined from either urinary excretion of DMPO or ChE inhibition, it is clear that it is substantial. Although there were few overt clinical signs in the

presence of significant ChE inhibition, the possibility of impaired nerve conduction or electromyographic effects were not investigated.

Shell Development Company (1968) Dermal exposure to Azodrin insecticide resulting from aerial application. Modesto, Shell Development Company. M-37-68

An experiment to determine the degree of exposure of workers assisting in the aerial application of monocrotophos was conducted. A 30-acre cotton field was treated with approximately 1.2 L/ha of Azodrin 5 (a 60% formulation) from a plane which made 20 passes at a velocity of 150 km/h at a height generally less than 1 m above the cotton.

The exposure of a swamper and 2 flagmen was assessed. A pre-exposure blood sample was taken, and blood was taken 4 h after exposure. Blood samples were also taken 3 and 7 days after exposure. All samples were analysed for plasma and erythrocyte ChE. Gauze patches were attached to each man on the right and left shoulders, legs, thighs and wrists, and in the middle of the chest and back. No protective clothing was worn by any of the subjects. Exposed patches were analysed for monocrotophos residues.

Three days after spraying, 2 field checkers checked the cotton field for a 1-h period. These workers had had ChE levels determined on the day of spraying. They wore no protective clothing, and had similar gauze patches attached as did the swamper and flagmen. Blood samples were taken 3 h after the end of the exposure, and also on the 3rd and 7th days after exposure.

Of the workers, the swamper, one of the flagmen and one of the field checkers reported that they worked with organophosphorous and carbamate insecticides on a daily basis.

The gauze samples analysed showed a range of residues. The swamper samples showed a very high level (1.8 mg) on the left wrist. All other samples from this worker had residues of 6 µg or less. One of the flagmen had residues around 20 µg on the shoulders; in the other flagmen, there was no such increase. The field checkers had more consistently raised residue levels, with between 10 and 40 µg on the wrist, thigh and legs, with <10 µg on the shoulders, chest and back. These residues reflect the activities the workers were involved in; the high levels on the swampers left wrist may be the result of wiping his face.

There was no clear pattern of ChE inhibition resulting from the exposure. Two worker (one flagman and one field checker) showed either plasma or erythrocyte ChE inhibition on day 3 after exposure, but the inhibition was marginal and had resolved by day 7 after exposure. Thus it appear that in this trial, despite the lack of protective clothing, the ChE inhibition resulting from exposure to monocrotophos was minimal.

Blok AC & Mann AH (1977) Organophosphorus insecticide exposure of spraying under field conditions on rice in India. II Azodrin (Monocrotophos) The Hague, Shell International Research Maatschappi, BV Report Series Tox 77-006

The effects of monocrotophos on workers involved in its application to rice fields in India was assessed in field conditions. Five workers were involved in the application of the pesticide on 6 consecutive days, working 7 h/day. A 40% water soluble solution of monocrotophos was diluted to 0.06% and applied from a knapsack sprayer containing 10 L of formulation. On the first day of spraying, the formulation was accidentally made up at 0.12%; all other days used the correct dilution. Workers applied an average of 66 g monocrotophos/day. Workers did not use protective clothing; their normal clothing exposed the arms, legs and feet. Clean clothes were worn for each day's work, and the workers washed their hands before meals. Workers were trained in common sense ways of avoiding contamination, such as avoiding direct contact with formulation and spray mix, giving attention to the containers to ensure they were not leaking, and avoiding spraying against the wind or upwind of other workers. All workers were normal farmhands, aged between 17 and 40 years, and described as healthy and fit, with normal nutritional status. They had not had contact with pesticides for 2 weeks prior to the trial.

Five pre-test blood samples were taken from the workers applying monocrotophos, and also from 5 workers not involved in pesticide applications to act as controls, to determine plasma and erythrocyte ChE levels. Samples were taken regularly throughout the trial, and for two days at the end of the trial. It was recognised that there were practical difficulties with the sampling and testing methods, due to the uncontrolled field conditions.

No clinical signs of exposure were seen during the trial. Plasma ChE appeared to be inhibited on the evening of the first day, and morning of the second day. Control workers also had some depression of ChE, so there may have been a problem with the testing method at these times. No inhibition of plasma or erythrocyte ChE was seen for the rest of the trial. Therefore it appears that there is little effect from applying monocrotophos from a knapsack spray without protective clothing, however the quality of the assay method may obscure any real effects.

Rao RR, Marathe MR & Gangoli SD (1979) Effect of exposure of human volunteers to the aerial spray of monocrotophos. Ecotoxicol environ Safety 3: 326 - 334
Volunteers were exposed to an aerial spray of monocrotophos (40% formulation in water). In the first trial, 12 male and 5 females volunteers (aged 13 - 57) were exposed to a single aerial spray. Volunteers were examined for clinical signs, erythrocyte and leucocyte counts, Hct and ChE activity pre-test, and at 2, 24, 48 and 72 h after exposure. In the second trial, 12 male volunteers were exposed to either 1, 2 or 3 sprays (4 men/group). Hct and ChE activity were determined 2 h after exposure, then once daily for seven days, then 3 times in the next week. In both trials, men removed their shirts and women wore light clothing. They remained in the cotton field during aerial spraying and for 1 h after spraying. The only protective equipment worn was rubber finger gloves on the fingers used to take blood samples. In both trials, no abnormal clinical signs were observed. There were no significant variations in ChE activity or haematological findings, although there was a non-significant decrease in ChE activity in a number of individuals 2 h after exposure, which had completely resolved by 24 h.

Rao RR, Quadros Fmazmudar RM, Marathe MR & Gangoli SD (1980) Toxicological effects of aerial applications of monocrotophos. Arch environ Contam Toxicol 9:473-481
Twelve volunteers were exposed to monocrotophos during aerial spraying of a cotton field and adjoining grazing area with a 40% solution of monocrotophos, further diluted using 400 mL in 9L of water. The dose delivered to the area was not specified. Additionally, 2 cows, 2 bulls, 3 buffaloes and 6 chickens were exposed. Blood samples were taken 2 h and 1, 2, 3, 7 and 15 days after exposure. No abnormal clinical signs were observed. Hct, erythrocyte and leucocyte counts and ChE activity were normal in all exposed humans and animals.

Nayak NJ, Shingatgeri MK, Rao RR, Marathe MR & Gangoli SD (1975) Toxicological, residual and biological evaluation of NUVACRON 40 (monocrotophos) by aerial application under Indian field conditions. Ciba-Geigy of India Ltd. Bombay
Monocrotophos (Nuvacron 40, 40% w/v) was diluted in water (400 mL/8.5L) and applied aerially at 8.5L/acre to a 10-acre plot using a helicopter flying at 2 to 3 metres, and spraying approximately a 40 m swath. There was approximately 2 kg of monocrotophos applied overall. Workers, cattle and fowls were exposed, with the domestic animals being tethered along footpaths at the edges of the sprayed plot, while workers continued to work in the plot during spraying. Only light clothing was worn, and men remover their shirts. The only protective clothing used was a rubber finger glove to protect the blood sampling site.

Blood was taken from each volunteer 1 to 2 days before spraying, and then between 1 and 3 h after spraying. Samples were also taken 24, 48 and 72 h after the application of the monocrotophos. No abnormal clinical signs were noted in the volunteers. There were no changes in ChE activity, erythrocyte or leucocyte counts or Hct values, either before or after spraying.

Ullmann L, Phillips J & Sachase K (1979) Cholinesterase surveillance of aerial applicators and allied workers in the Democratic Republic of the Sudan. Arch environ Contam Toxicol 8:703 - 712.
Whole blood cholinesterase activity of all personnel engaged in seasonal aerial spraying with Nuvacron 40 SCW (40% formulation of monocrotophos in water) and Nuvacron Ulvair Combi C500 (monocrotophos and DDT) in the Sudan was monitored. No baseline figures could be obtained for the groups, as they had been working with pesticides previously. Control values from similar populations were used. The Hct of these workers was also determined to rule out anaemias which may have altered the results. In all cases, blood was taken from washed fingertips of the left hand. Four groups were investigated: pilots, aircraft engineers, aircraft, landing strip and ground personnel and entomologists. All checks were done between 8 am and 10 am, with some regions being checked 3 times over the 4 week spraying period, and others being checked twice. In total, 70 600 ha were sprayed, with a total of 148 445 L of 40% monocrotophos in water, and 4795 L of the monocrotophos/DDT mixture.

Protective clothing was supplied, and workers were encouraged to wear it, however it was unpopular as the conditions were very hot. Overalls were supplied to landing strip and ground personnel, and were laundered 2 to 3 times per week, depending on use. Goggles and gas masks were used when handling pesticides, and gloves were used when handling any chemicals or chemical equipment.

Tests on ground personnel revealed significant ChE inhibition. On the first check in the Medani region, 82% of ground personnel had inhibition of >20%, while 41% had >60% inhibition. At the second check, 90% had >20% inhibition, however 25% had >60% inhibition. On the 3rd check, 86% had >20% inhibition, while 11% had >60% inhibition. The techniques to reduce exposure appeared to be effective in decreasing the more significant exposures, but were not effective on lower level exposure. On the first check in the Suki region all workers showed inhibition of >20%, with 67% showing inhibition of >60%. On the second check, 80% of workers had inhibition of >20% while 30% had inhibition of >60%. In the Managil region, no workers had inhibitions of >60%, while approximately 50% had inhibitions greater than 20% in both tests. The ChE inhibition seen in other

workers (pilots, entomologists and aircraft engineers) was significantly less, with very few workers showing inhibition of >60%. Among the engineering staff, many had inhibitions of >20% on the first 2 tests.

Therefore, there was significant exposure of many staff involved in aerial spraying in the Sudan. Exposure was reduced, but not eliminated by attempts to limit exposure. Ground personnel were the most exposed group, with pilots, entomologists and engineers showing lower levels of inhibition.

Gaeta R, Puga FR & Mello D. de (1975) Determination of cholinesterase activity in workers exposed to the action of monocrotophos, an organic phosphorus insecticide. O Biologico 41: 73 (translated from Portuguese)
Monocrotophos (60% EC, diluted at application to 0.25% aqueous solution) was applied by 2 groups of workers, 46 working on immature plants, and 26 working on mature plants. All workers were male, aged between 15 and 54 years. No protective clothing was worn, and clothes were not washed after each day's work. Blood samples were taken one day before and one day after each application cycle. ChE activity in whole blood was determined on site; additional samples were collected and the plasma ChE activity determined in a laboratory.

During the study, one individual showed clinical symptoms of intoxication, and a number of workers on the property who were not involved in the study required hospitalisation. There was no difference in the pattern of ChE activity in the workers applying chemicals to mature or immature plants. There were significant decreases in plasma ChE (to approximately 10% of pre-exposure values) and whole blood (to approximately 65% of pre-exposure values) on the first day after spraying. These had not returned to normal after 31 days.

Sittert NJ van & Tordoir WF (1981) Exposure and biomedical monitoring study of AZODRIN/DDT hand-held ULV application on cotton in South Africa. The Hague, Shell International research Maatschappij BV Report Series TOX 81-002
and
Sittert NJ van, Tordoir WF & Kummer R (1985) Exposure and biomedical monitoring study of AZODRIN/DDT hand-held ULV application on cotton in South Africa. A re-evaluation after reconsideration of cholinesterase results. The Hague, Shell International research Maatschappij BV Report Series TOX 85-005
Two monocrotophos formulations were tested under field conditions in cotton for their potential to inhibit ChE activity. The first formulation contained 250 g/L monocrotophos and 300 g/L DDT in Emulsogen, cylcohexanone and Shellsol AB. The second formulation contained 250 g/L monocrotophos and 300 g/L DDT in cyclohexanone and ethyl dioxitol, while the third formulation contained only the hexylene glycol, cyclohexanone and Shellsol AB solvents. The formulations were applied by hand-held ULV applicators, with the flow rate set at 1 mL/sec. Sprayers were not involved in mixing, loading or filling activities; therefore their total exposure can be assumed to be related to spraying activities. Most workers wore long-sleeved overalls and boots, while some wore long trousers and long sleeved shirts. Most wore a hat. Face masks, face shields, respirators, goggles or gloves were not worn.

In the initial protocol, spraying was to occur on 5 consecutive days. Spraying with pesticides actually occurred on 2 days, with a 2-day break between spraying days. While spraying, workers wore alfoil strips attached to the chest, back and both forearms. There were removed immediately after spraying and analysed for DDT deposition. The DDT levels in the blood were also measured. The level of dimethyl phosphate in a 24-h urine sample following spraying was analysed to determine exposure to monocrotophos. Medical examinations were done both before and after spraying, including an examination of neurological functions and blood tests including glucose, urea, total bilirubin, total protein, calcium, inorganic phosphorus, uric acid, AP, AST, ALT, LDH, creatinine and cholesterol. Blood for ChE activity determination was taken in capillary tubes from finger-tip punctures. Fingers were well washed prior to sampling, however this method was later called into question.

During the study, no toxic signs were observed. The urinary excretion of dimethyl phosphate was much higher in workers spraying the formulation containing Shellsol AB than workers using the formulation containing ethyl dioxitol. This indicates a greater absorption of monocrotophos in workers using Shellsol AB, probably indicating a greater dermal penetrance. Whole blood and plasma ChE activities were significantly inhibited in both spraying groups, with levels in some cases showing 80% inhibition. This resulted in the second day's spraying being canceled due to concern for workers health. The study recommended that due to the significant inhibition of plasma ChE, the ULV formulations should not be used for hand-held application. Later re-evaluation of the study suggested that skin contamination may have partly contributed to the depressed ChE levels. It also suggested that plasma ChE may not be a suitable indicator, and that erythrocyte ChE inhibition should be used as a preferred measure of anticholinesterase activity. The re-evaluation did not amend the initial recommendations. The study authors felt that, as there was not data available on the effects of five days consecutive spraying, it was inappropriate to amend these recommendations.

Kummer R & van Sittert NJ (1985) Field study on health effects from the application of a 20% AZODRIN formulation by hand-held ULV to cotton in South-East Celebes. Report no HSE 85.001. Shell Internationale Petroleum Maatschappij.
Monocrotophos (20% ULV formulation in hexylene glycol and ethyloxitol acetate) was handsprayed to cotton, and the exposure and effects assessed. There were five groups of workers with a variety of exposures. Group 1 was a control group of 7 workers. Group 2 consisted of 1 filler and 4 spraymen who sprayed 10 L/person in one day. Group 3 consisted of 1 filler and 4 spraymen who sprayed 10 L/person/day on 2 consecutive days. On their second day of spraying, the filler worked as a sprayman, and all workers filled their own spraytanks. Group 4 had 3 spraymen, spraying 10 L/person, with each person doing their own filling and cleaning. Group 5 had 4 spraymen applying 4 L/person in one day. The recommended protective equipment for workers was long pants and a long sleeved shirts. Workers specifically involved in filling wore overalls, mask, rubbers boots and gloves; this equipment was not worn when sprayers filled their own drums. Not all workers wore the recommended clothing, with some choosing to wear shorts and short sleeved shirts.

The study involved observing spraying, to determine possible times and degrees of exposure, checking workers for signs of intoxication either during or after spraying, determining the ChE activity in whole blood, erythrocytes and plasma, using blood collected either from a finger prick or from the earlobe, and collecting a 24-h urine sample to determine the excretion of dimethyl phosphate, a monocrotophos metabolite.

Exposures were noted in the fillers when they touched contaminated equipment with ungloved hands, and also an occasion where a filler adjusted his mask with contaminated gloved hands. Sprayers were occasionally contaminated following changes in wind velocity or direction. Where they were filling their own containers, there was significant exposure both at filling and cleaning of the containers. All workers washed their hands after filling; this was likely to significantly reduce the absorption of monocrotophos.

No adverse clinical signs were noted during the trial. Urinary dimethyl phosphate concentrations were higher when sprayers also acted as fillers and equipment cleaners. Whole blood ChE activity was inhibited up to 19 and 36% after the first and second applications, respectively. This probably reflected plasma ChE activity, which was inhibited up to 50 and 74% after the first and second applications, respectively. Erythrocyte ChE activity was not altered.

Ware GW, Morgan DP, Estesen BJ & Cahill WP (1974) Establishment of reentry intervals for organophosphate-treated cotton fields based on human data: II AZODRIN, ethyl- and methyl parathion. Arch environ Contam Toxicol 2(2):117 - 129
In a re-entry exposure study, 4 men worked in a cotton field in Arizona for a 5-h period 24 h after the field was sprayed with 1.3 kg monocrotophos/hectare (formulation not stated). A number of measurements of contamination were done. These included foliar residue levels of applied pesticide, pesticide contamination of the hands and lower arms of workers (measured by collection of wash samples after exposure), adsorption onto clothing, concentration of pesticide in air samples (collected by 2 workers), and the effect on plasma and erythrocyte ChE levels. The foliar residues were approximately 4.7 mg/m². No clinical signs of intoxication were observed. Residues extracted from hands and clothing were: hands 3 mg; shirts 16 mg; trousers 71 mg. A respiratory dose of 27 µg/5 h was estimated. Therefore, the main exposure was dermal. Plasma ChE activity was not altered, whilst erythrocyte ChE activities were decreased, showing between 15 and 30% inhibition. In 2 subjects, erythrocyte ChE activity was beginning to rise by 24 h after exposure.

Ware GW, Morgan DP, Estesen BJ & Cahill WP (1975) Establishment of reentry intervals for organophosphate-treated cotton fields based on human data: III 12 to 72 hours post-treatment exposure to monocrotophos. Arch environ Contam Toxicol 3:9113 - 9130
Monocrotophos was applied to cotton at approximately 1 kg active/ha. Five volunteers entered the cotton fields 48 or 72 h after application. The air concentration of the pesticide was analysed via collection devices carried by 2 volunteers. Foliar residues were determined immediately after application, and after 24, 48 and 72 h. Clothes and hand rinse samples of the volunteers were analysed for residues, and the plasma and erythrocyte ChE activities of volunteers were determined.

Foliar residues of monocrotophos decreased over the sampling time from 12.8 mg/m^2 immediately after exposure to 4.3 mg/m^2 after 72 h. The air samples did not reveal detectable monocrotophos levels. The monocrotophos residues after 48 h were 2 mg from hand rinses, 13.5 mg on the shirt and 20 mg on trousers. After 72 h, residues were very similar, with 2 mg on hands, 13.4 mg on the shirt and 29 mg on the trousers. No toxic signs were observed in any of the workers. Plasma ChE levels were slightly depressed following exposure at 48 and 72 h, while erythrocyte ChE activity was slightly depressed at 48 h. All decreases in ChE activity were less than 20% in comparison to pre-exposure levels, and were not considered to be of biological significance.

Guthrie M, Domanski JJ, Chasson AL, Bradway DE & Monroe RJ (1976) Human subject experiments to estimate reentry periods for monocrotophos treated tobacco. Arch Environ Contam Toxicol 4:217 - 225.
Monocrotophos was applied at 450 g/ha, using a 300 g/L water miscible formulation. Volunteer workers, wearing long pants and short sleeved shirts entered the are 48, 72 or 96 h after spraying. The volunteers were required to remove the blossom, sucker or top-most leaf of the plant. Pre-exposure blood samples were obtained on the evening before exposure. Post-exposure samples were obtained in the evening of the day of exposure. Pre- and post-exposure urine samples were obtained. Leaves were collected at random from the upper portion of the plant for residue analysis. Mice were also exposed to treated leaves, and the ChE activities determined. The mean ChE inhibition following exposure of workers was 9% for both plasma and erythrocyte activity at 48 h after treatment; inhibition at 72 and 96 h was less than this. Therefore no significant ChE inhibition was seen. Information on the exposure of mice to treated leaves was not supplied.

11.3 Poisoning studies

Simson RE, Simpson GR & Penney DJ (1969) Poisoning with monocrotophos, an organophosphorus pesticide. Med J Aust pp 1013 - 1016, November 15 1969
A 19-year old male splashed approximately 600 mL of an emulsifiable concentrate formulation of monocrotophos onto his bare arms and chest and washed it off with water. Clinical signs including muscle weakness, blurred vision, chest pain and blackouts occurred 28 h after exposure. Signs on admission to hospital included lethargy, dry retching, inability to stand, constricted pupils and increased salivation. After repeated doses of atropine and 2-PAM, recovery from the acute signs occurred after 3 days of treatment. When examined 11 days after exposure, the patient reported slight numbness in the arms and hands. Whole blood ChE activity decreased to 10% of normal reference values at 1.5 days after exposure and returned to normal after 8 weeks.

Przezdziak, J & Wisniewsa W (1975) (A case of acute organophosphorus poisoning) Wiad Lek 28(12) 1093 - 1095 (In Polish - abstract translated)
A 54-year old man was severely intoxicated after accidentally swallowing 1/2 teaspoon of monocrotophos (Nuvacron). He was administered to hospital with general symptoms of organophosphorus poisoning. Consciousness returned on the fourth day. Recovery was complicated by bilateral bronchopneumonia and extensive thrombophlebitis, but was complete after 33 days.

Gelbke LC & Schlicht HJ (1978) Fatal poisoning with a plant protective containing monocrotophos, dodine and dinocap. Toxicol Eur Res 1(3): 181 - 184
A 22-year old woman, weight 52 kg, was found dead, with 6 empty vials which had each previously containing 0.2 g monocrotophos, 0.06 g dodine and 0.12 g dinocap, beside her. Her blood alcohol level was 0.12%. There were no abnormal macroscopic or microscopic observations at autopsy apart from vascular congestion in the abdominal organs. Monocrotophos was detected in stomach (350 ppm - 52 mg total), liver (1.8 ppm) and other tissues, including blood (11 - 13 ppm). Dodine and dinocap were not detected. Death was thought to be due to monocrotophos poisoning since the ingested dose of 23 mg/kg was similar to the oral LD50 for rats, whereas dodine and dinocap have low acute oral toxicity.

Senanayake N & Karalliedde L (1987) Neurotoxic effects of organophosphorus insecticides. N Engl J Med 316: 761 - 763
"Intermediate Syndrome" experienced after OP poisoning can be distinguished from the characteristic muscarinic, nicotinic and CNS effects observed soon after exposure and from the delayed neurotoxicity effects seen 2-3 weeks later. Intermediate syndrome occurs 24-96 h after exposure and is characterised by muscular weakness affecting neck, proximal limb and respiratory muscles. Since only some OPs are capable of inducing this phenomenon, this study retrospectively (last 3 years) reviewed 10 OP oral poisoning cases (9M & 1F; 9 attempting suicide and 1 after spraying) that exhibited this condition. Although the ingested volumes were unknown, 4 had consumed fenthion, 2 had dimethoate, 2 had monocrotophos, 1 had methamidophos and an unknown OP for the remaining one. The age of most patients ranged between 22-27 with two being substantially older; 55 and 60 respectively. Treatment with pralidoxime (1g, bid) and atropine (40 mg) was initiated immediately upon admission and continued for up to 48 h. ChE activity was not measured, however, nerve conduction velocity measurements (median nerve, motor and sensory; and peroneal nerve, motor) and electromyography (distal and proximal limb muscles) were performed.

Three patients (2 with fenthion and one with dimethoate) died within 3-15 days after exposure despite atropine and oxime therapy. After the classical clinical signs of OP poisoning, namely miosis, salivation, sweating, and fasciculations lasting 24-96 h, the first sign to indicate onset of Intermediate Syndrome was respiratory insufficiency in the absence of any classical signs of OP poisoning. Three of the 7 survivors required assisted ventilation (1 monocrotophos, 1 dimethoate and 1 unknown OP) for up to 18 days. Delayed polyneuropathy, characterised by paralysis of distal muscles of limbs 2-3 weeks after poisoning, was observed in the one patient on

methamidophos. Nerve conduction and routine electromyography appeared normal in all cases, however, the tetanic stimulation of the abductor pollicis brevis (thumb or first digit muscle) *via* surface electrodes on the median nerve at the wrist during active Intermediate Syndrome symptoms revealed marked fade at 20 (20-80%) and 50 Hz (30-70%). There was no post-tetanic facilitation.

Therefore, in one case involving monocrotophos a patient required assisted ventilation for a period beyond that of severe acute signs. It is difficult to determine whether this was a sign of Intermediate Syndrome, as there was no measurement of ChE activity at the time.

Mani A, Thomas MS & Abraham AP (1992) Type II paralysis or intermediate syndrome following organophosphate poisoning. JAPI 40: 542 - 544

This report describes the case histories of 3 patients who ingested Ops. One of the 3 had taken monocrotophos whereas the others took parathion and an unidentified OP (only details referring to monocrotophos will be detailed in this summary). A 19-year old male was admitted to hospital 14 h after ingesting an unknown volume of monocrotophos. Despite gastric lavage and 2-PAM/atropine therapy for 48 h, he had difficulty breathing, thereby necessitating ventilator support. Neurological examination revealed bilateral facial paresis together with neck and proximal leg muscle weakness. Ventilator support was removed on day 9 and after further improvement, he was discharged on day 16 with slight proximal limb muscle weakness. An outpatient visit two weeks later did not reveal any neurological sequelae.

Peiris JB, Fernando R & De Abrew K (1988) Respiratory failure from severe organophosphate toxicity due to absorption through the skin. Forensic Sci Internat 36: 251 - 253

A 32-old man was admitted to hospital with a 50 mm gash above left eyebrow. The injury sustained 3-4 h earlier was the result of a glass bottle, containing 100 mL of 60% monocrotophos, being thrown and breaking on impact. The excess liquid was wiped off but the skin was not washed. After admission, nausea, vomiting, muscle fasciculations, pinpoint pupils, excessive sweating and abdominal pain developed, prompting atropine and pralidoxime therapy 22 h after the initial exposure. Little change occurred until day 4 when respiration became difficult, necessitating assisted ventilation. By day 6, sweating and vomiting had subsided but generalised muscle weakness and respiratory difficulties persisted up until day 15. On day 16, the patient was ambulatory with apparently normal muscle strength, but his blood ChE activity was still between 37.5% and 50% of normal on day 21. Given the low ChE activity at this stage, it is difficult to determine that this was a case of Intermediate Syndrome, but may be more directly related to inhibition of ChE activity.

DISCUSSION

Acute Toxicity

The acute toxicological profile of monocrotophos is typical of organophosphorus anti-ChE pesticides, with clinical symptoms being similar in experimental animals and humans.

Monocrotophos is extremely toxic by the oral route, with a median LD50 in rats of 8.4 mg/kg bw. Dermal toxicity of this compound is related to the solvent used, with significant variability observed. In rats, the dermal toxicity ranges from high to low (LD50 199 - >2000 mg/kg bw), while in rabbits monocrotophos is of moderate to high toxicity (LD50 130 - 709 mg/kg bw). It also has a high inhalation toxicity. The metabolites of monocrotophos are less toxic than the parent compound, although still extremely toxic. The trans-isomer of monocrotophos is significantly less toxic, with an oral LD50 of 207 mg/kg bw in rats.

Cholinesterase Inhibition

As ChE inhibition is a primary target for monocrotophos toxicity, a summary of the NOEL findings for ChE inhibition in a range of repeat-dose studies is shown in the Table below. NOELs are presented for plasma, erythrocyte and brain ChE activity.

Summary of NOELs (mg/kg bw/d) for Cholinesterase Activity Inhibition Following Monocrotophos Administration

Species	Duration	Plasma ChE	Erythrocyte ChE	Brain ChE
Mice	5 week	<0.015	<0.015	1.5
Mice	2 year	<0.15	<0.15	<0.15
Rat	5 week	0.005	0.005	0.005
Rat	13 week	<0.005	0.0125	0.025
Rat (dermal)	28 day	1	1	1
Rat	12 week	0.03	0.03	0.03
Rat	2 year	<0.05	0.05	<0.05
Rat	2 year	0.005	0.005	0.005
Dog	13 week	0.038	0.038	0.038
Dog	2 year	0.04	0.04	0.004
Human	28 day	0.0036	0.0059	Not tested

There appears to be no clear difference in binding affinity with plasma (a pseudo- or butyryl-ChE), erythrocyte or brain ChE (acetyl- or true ChE). There is considerable variation between studies, with brain ChE on occasions shown as either the most sensitive (particularly in the 2-year dog study, or the least sensitive (in short term mice and rat studies). Other studies show no difference in sensitivity between the different ChE activities.

Neurotoxicity

The anticipated clinical signs associated with OPs and attributable to an excessive interaction of ACh with the muscarinic and nicotinic cholinergic receptors were common to all animal studies using monocrotophos. Measurements of plasma, erythrocyte and brain ChE activity in a variety of studies did not reveal a clear hierarchy of inhibition.

There was no evidence for delayed neurotoxicity effects in a range of studies using hens, varying from single oral administration to a 78-day study. A 2-year rat study investigated histopathological changes in peripheral and central nerves, and found no evidence for a dose-related increase in abnormalities. Progressive examinations through the 2-year period did not provide evidence for any acceleration of normal age-related changes.

In reports of human poisonings, there were a number of cases of 'intermediate syndrome', involving muscular weakness and paralysis. In many of these reports, ChE activity had not been measured. Overall, the weight of evidence would suggest that monocrotophos does not produce chronic neuropathological changes.

Genotoxicity

Monocrotophos was positive for gene mutation in a number of the *in vitro* assays, including tests in bacteria, fungi and cultured mammalian cells. There was also evidence of chromosomal damage both *in vitro* and *in vivo*, as well as other nuclear damage. Metabolic activation was not required for the genotoxic effects to become apparent. In many of these studies, the dose of monocrotophos required to produce effects was quite high, and cell survival in some trials was low. In *in vivo* trials, monocrotophos was a weak mutagen at relatively high doses. Monocrotophos would appear to be a weak mutagen, however mutagenic effects *in vivo* are only observed at doses significantly greater than those producing ChE inhibition in mammals.

Reproduction and Development

A development study using Sprague Dawley rats showed a dose-related decrease in the percentage of male foetuses. However, this effect was not seen in a developmental study using Charles River rats, or in a number of multi-generation reproduction studies in Wistar or Long-Evans rats.

In New Zealand rabbits, there was an increase in the incidence of premature deliveries seen at 3 mg/kg bw/d. It was not possible to assess whether this was dose related, as the survival rate at the highest dose level (6 mg/kg bw/d)was very low. The effect was not seen in a second study using another strain of rabbits.

Overall, development signs were seen only at doses at or near maternotoxic doses, and there were no significant teratogenic findings.

Carcinogenicity

There were no carcinogenic effects seen over 2 years with monocrotophos at the highest dose tested in CD mice (approximately 1.5 mg/kg bw/d)), in Charles River rats (approximately 5 mg/kg bw/d), in Wistar rats (approximately 0.5 mg/kg bw/d) or Beagle dogs (approximately 0.4 mg/kg bw/day).

Human Studies

Monocrotophos mainly produced classical signs of OP toxicity, however there were a few reports of intermediate syndrome. An absorption study indicated that 22% of monocrotophos applied to forearm skin was absorbed. A field trial involving the use of hand-held ULV spray devices resulted in significant ChE inhibition in applicators. Ground crew involving in loading and cleaning aircraft involved in aerial spraying had significant plasma ChE inhibition. Repeated testing, combined with increased use of protective clothing, decreased the severity of the inhibition, but did not eliminate it during a trial period.

NOEL considerations

A summary of the NOELs determined for monocrotophos are shown in the Table below.

Study Type	NOEL (mg/kg bw/day)	LOEL and Toxic Effect
CD mouse: 5 week dietary	<0.015	Plasma and erythrocyte ChE inhibition in males at 0.015 mg/kg bw/day
CFE rats: 5 day dietary	< 1.68	Slight cholinergic signs seen at 1.68 mg/kg bw/day
Wistar rat: 13 week dietary	< 0.005	Plasma ChE inhibition in females at 0.005 mg/kg bw/day
Wistar rat: 5 week dietary	0.005	Plasma and erythrocyte ChE inhibition at 0.025 mg/kg bw/day
TifRAIf rat: 28 day dermal	1	Plasma, erythrocyte and brain ChE inhibition at 10 mg/kg bw/day
NZW rabbit: 3 week dermal	< 42	Clinical signs at 42 mg/kg bw/day
Albino rabbit: 3 week dermal	22	Skin irritation and kidney and splenic enlargement at 44 mg/kg bw/day

Long Evans rats: 12 week dietary	0.03	Blood and brain ChE inhibition at 0.15 mg/kg bw/day
Beagle dogs: 13 week dietary	0.038	Plasma, erythrocyte and brain ChE inhibition at 0.38 mg/kg bw/day
Beagle dogs: 12 week dietary	1.2	Tremors at 3.6 mg/kg bw/day
CD mice: 2 year dietary	< 0.15	Plasma, erythrocyte and brain ChE inhibition at 0.15 mg/kg bw/day
Charles River rats: 2 year dietary	<0.05	Plasma and brain ChE inhibition at 0.05 mg/kg bw/day
Wistar rats: 2 year dietary	0.005	Plasma, erythrocyte and brain ChE inhibition at 0.05 mg/kg bw/day
Beagle dogs: 2 year dietary	0.004	Brain ChE inhibition in females only at 0.04 mg/kg bw/day
Wistar rats: 2 generation	0.05	Impaired teat development, decreased pup survival at 0.15 mg/kg bw/day
Long-Evans rats; 3 generation	maternal effects: 0.25 reproductive effects: 0.1	Body weight decreases in adults at 0.6 mg/kg bw/day; decreased pup survival at 0.25 mg/kg bw/day
Long Evans rats: 3 generation	Maternal effects: 0.25 reproductive effects: 0.1	Body weight decreases in adults at 0.6 mg/kg bw/day; decreased litter size at 0.25 mg/kg bw/day
Sprague Dawley rats: gavage teratology	maternotoxicity: 0.3 foetotoxicity: 0.1	Clinical signs in dams at 1 mg/kg bw/day; delayed ossification at 2 mg/kg bw/day
Charles River rats; Gavage teratology	1	Clinical signs in dams at 2 mg/kg bw/day; decreased mean foetal bodyweight and crown-rump length at 2 mg/kg bw/day
New Zealand White rabbits: gavage teratology	1	Maternal deaths and clinical signs at 3 mg/kg bw/day; agenesis of lung lobe at 3 mg/kg bw/day
Dutch banded rabbits: Gavage teratology	0.8	No abnormalities observed at 0.8 mg/kg bw/day (highest dose tested)
Male humans:28 day oral gelatin capsule	0.0036	Plasma ChE inhibition at 0.0057 mg/kg bw/day
Male humans:28 day oral gelatin capsule	0.0036	Plasma ChE inhibition at 0.0059 mg/kg bw/day

A NOEL of 0.0036 mg/kg bw/day was observed in 2 studies using human volunteers in 28-day oral dosing trials. This is comparable to the lowest NOEL found in long term animal studies, with a NOEL of 0.004 mg/kg bw/day in a 2-year dog study, and 0.005 mg/kg bw/day in a 2-year rat study. The similarity in NOELs indicates that there may be limited interspecies variation in the potency of monocrotophos inhibition of cholinesterases.

Determination of Public Health Standards

Acceptable Daily Intake

The current acceptable daily intake (ADI) is 0.0003 mg/kg bw/d. This ADI was derived from a NOEL of 0.0036 mg/kg bw/day, based on plasma ChE inhibition in human oral dosing experiments.

No change is recommended to the current ADI. The NOELs found in a short-term human study are similar to those found in long term animal studies.

Public exposure

In Australia, monocrotophos does not have any registered domestic uses, and the greatest potential for public exposure is via ingestion of monocrotophos residues in food. Monocrotophos has MRLs established in a wide range of foods, including fruits and vegetables and cereal grains; the current Australian MRL list is outlined below.

Australian Maximum Residue Limits for Monocrotophos

Commodity	MRL (mg/kg)

Apple	0.5
Banana	0.5
Beans, except broad beans and soya been	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

* denotes the MRL has been set at or about the limit of analytical determination.

Dietary Exposure Considerations

In estimating dietary exposures, the "Guidelines for Predicting Dietary Intake of Pesticide Residues (Revised)" circulated by the Codex Alimentarius Commission in November 1996 recommends the use of National Theoretical Maximum Daily Intakes (NTMDI) as an initial estimate, while admitting that these can produce a gross overestimation of the exposure for a number of reasons. The calculation involves the use of the MRL as an estimate of the amount of pesticide in the food, and national estimates of consumption for the quantity of food consumed.

When this procedure is followed for monocrotophos, using the 1983 survey of average food consumption in Australia, it was calculated that a 75 kg adult male (weight as used by the Australian Market Basket Survey) could possibly consume 0.0012 mg/kg bw/day, as would a 60 kg adult female. This is approximately four times the current ADI (0.0003 mg/kg bw/d).

A more reliable estimate of monocrotophos intake may be derived from the Australian Market Basket Survey, a procedure which uses the measure of monocrotophos residues found in that year, rather than assuming that the pesticide is present at the MRL. The estimated intake in the group with the highest consumption of monocrotophos residues (toddlers aged two), based on the average energy intake in 1994, was 0.0000072 mg/kg bw/day. This makes up less than 3% of the ADI. Estimated intake of all groups in 1992 was approximately 10 times lower than the intake in 1994.

Market Basket Survey

The 1994 Market Basket Survey found detectable levels of monocrotophos in a small range of products. Residues were found at a maximum level of 0.01 mg/kg in white bread, 0.02 mg/kg in wholemeal bread and 0.12 mg/kg in capsicum. The residue in capsicum is a violation, as there is no registered use on this vegetable. The residues in bread are lower than the MRL for cereal grains.

Acute Reference Dose

To reflect safe/acceptable exposure from a single or short exposure to monocrotophos, an acute reference dose (acute RfD) may be derived using appropriate data. No human studies using a single oral dose are available for monocrotophos; the only human trials were the 28-day oral dosing trials used to set the ADI, with a NOEL of 0.0036 mg/kg bw/d. The only short term animal studies have NOEL which would result in an acute RfD lower than the ADI. An acute RfD for monocrotophos may be set at 0.0003 mg/kg bw, based on a 28-day human oral gelatin capsule study, ie. the same as the ADI.

Safety Directions

The current safety directions are as follows:

Monocrotophos

AC 400 g/L or less	
Very dangerous, particularly the concentrate	100, 101
Product and spray are poisonous if absorbed by skin contact, inhaled or swallowed	120, 121, 130, 131, 132, 133
Repeated minor exposure may have a cumulative poisoning effect.	190
Avoid contact with eyes and skin	210,211
Do not inhale spray mist	220, 223
Obtain an emergency supply of atropine tablets 0.6 mg	373
When preparing spray and using the prepared spray,	279, 281, 282
wear protective waterproof clothing, cotton overalls buttoned to the neck and wrist and a washable hat,.	291, 292
elbow-length PVC gloves, goggles and half facepiece respirator with combined dust and gas cartridge	294, 297, 300, 303
If product or spray on skin, immediately wash area with soap and water.	340, 341, 342
After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.	350
After each day's use, wash gloves, goggles, respirator and if rubber wash with detergent and warm water and contaminated clothing.	360, 361, 363, 364, 366

EC 400 g/L or less in ethylene glycol, monomethyl ether	
Very dangerous, particularly the concentrate	100, 101
Product and spray are poisonous if absorbed by skin contact, inhaled or swallowed	120, 121, 130, 131, 132, 133
May irritate the eyes and skin.	160, 162, 164
Repeated minor exposure may have a cumulative poisoning effect.	190
Avoid contact with eyes and skin	210,211
Do not inhale spray mist	220, 223
Obtain an emergency supply of atropine tablets 0.6 mg	373
When opening the container, preparing spray and using the prepared spray or product	279, 281, 282, 283
Wear cotton overalls buttoned to the neck and wrist and a washable hat,	290, 292
elbow-length PVC gloves, goggles and half facepiece respirator with combined dust and gas cartridge	294, 297, 300, 303

If clothing becomes contaminated with product or wet with spray, remove clothing immediately	330, 331, 332
If product or spray on skin, immediately wash area with soap and water.	340, 341, 342
After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.	350
After each day's use, wash gloves, goggles, respirator and if rubber wash with detergent and warm water and contaminated clothing.	360, 361, 363, 364, 366

These Safety Directions are considered to be acceptable for public health considerations.

First Aid Instructions

Currently a, h. No changes to the first aid directions are recommended.

The T-value is currently 0.8. No change is recommended.

DRAFT RECOMMENDATIONS FOR PUBLIC HEALTH STANDARDS

1. Acceptable Daily Intake

The current acceptable daily intake (ADI) for monocrotophos is 0.0003 mg/kg bw/day. This ADI was derived from a NOEL of 0.0036 mg/kg bw/day, based on plasma ChE inhibition seen in a 28-day human oral dosing study.

No change to the current ADI of 0.0003 mg/kg bw/day is recommended.

2. Acute Reference Dose

An acute RfD for monocrotophos may be set as 0.0003 mg/kg bw, based on plasma ChE inhibition seen in a 28-day human oral dosing study.

3. Poisons Scheduling

No change to the current Schedule 7 of the SUSDP is proposed for monocrotophos.

4. First Aid and Safety Directions

No changes to the current safety directions are recommended.

Note: Safety Directions recommendations relating to the use of personal protective equipment are to be provided by National Occupation Health and Safety Commission.

No changes to the current first aid directions (monocrotophos: a, h) and T-value (currently 0.8) are recommended.

5. Clearance Status

No change is recommended to the clearance status of monocrotophos.

SUMMARY OF ACUTE TOXICOLOGY HAZARD

Date of Preparation:	November, 1997
Chemical name:	Monocrotophos
Worst oral LD50 in rats:	8.4 mg/kg bw
Worst oral LD 50 in other species:	10 mg/kg bw, in mice
Worst dermal LD50, rat:	123 mg/kg bw
Worst inhalation LC50, rat:	80 mg/m^3
Skin irritation:	Slight
Eye irritation:	Slight
Skin sensitisation:	Negative
T-value:	0.8
NOEL:	0.0036 mg/kg bw/day (28-day human)

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APPENDIX I

MONOCROTOPHOS TOXICOLOGY DATA SUBMISSION DETAILS

Sponsor/Provider	Submission Number	Data Details
Shell Chemical Co.	3308	22 volumes (153 studies)
Ciba-Geigy Ltd	00035	3 volumes (24 studies)
Ciba-Geigy Ltd	10662	6 volumes (46 studies)
United Phosphorus Ltd	11544	1 volume (10 studies)
Novartis Crop Protection Australasia Ltd	11523	1 volume (4 studies)