Monocrotophos

(CAS No: 6923-22-4)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of monocrotophos by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of The Netherlands. The first draft of this document was prepared by JAGM van Raaij, Ph.D. and WK de Raat, Ph.D. (OpdenKamp Registration & Notification, Zeist, the Netherlands) and J Krüse, Ph.D. (Kinetox, Vleuten, the Netherlands).*

The evaluation of the toxicity of monocrotophos has been based on reviews published in the 'Handbook of pesticide toxicology' (Gal91) and by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1999, literature was searched in the on-line databases Toxline, Medline, Chemical Abstracts, covering the period of 1965-1966 until December 1999, and using the following key words: monocrotophos and 6923-22-4. Data from unpublished studies were generally not taken into account. Exceptions were made for studies that were summarised and evaluated by international bodies such as the Food and Agricultural Organization/World Health Organization (FAO/WHO: Joint Meeting of the FAO Panel of Experts on Pesticides Residues on Food and the Environment and the WHO Expert Group on Pesticides Residues - JMPR) (FAO92, FAO94, FAO96). Use was also made of reviews prepared by the Health, Safety and Environment Division, Shell, The Hague, the Netherlands (SIP85) and the Crop Protection Division, Ciba-Geigy Ltd, Basel, Switzerland (Skr94).

In October 2002, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: J Soave (Health and Safety Executive, London, England).

An additional search in Toxline and Medline in April 2003 did not result in information changing the committee's conclusions.

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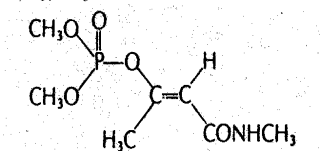
2 Identity

name	:	monocrotophos
synonyms	:	phosphoric acid, dimethyl [1-methyl-3-(methylamino)-3-oxo-1-propenyl] ester; (*E*)-phosphoric acid dimethyl ester, ester with 3-hydroxy-*N*-methylcrotonamide; 3-(dimethoxyphosphinyloxy)-*N*-methyl-*cis*-crotonamide; dimethyl 2-methylcarbamoyl-1-methylvinyl phosphate, Azodrin, Nuvacron
molecular formula	:	$C_7H_{14}NO_5P$
structural formula	:	
CAS number	:	6923-22-4

3 Physical and chemical properties

molecular weight	:	223.2
boiling point	:	At 0.07 Pa:125°C
melting point	:	54-55°C
vapour pressure	:	3×10^{-4} Pa
solubility in water	:	miscible
Log $P_{octanol/water}$	:	-0.22
conversion factors	:	not applicable

Data from ACG99, Gal91, Rob99, Tom97.

The pure compound consists of colourless hygroscopic crystals. The commercial product is a reddish-brown to dark brown clear viscous liquid with a mild ester odour, which eventually forms a semisolid to solid mass through crystallisation (commercial product). The compound is unstable in low molecular weight alcohols and glycols. It is stable in ketones and higher molecular weight alcohols and glycols and when stored in glass and polyethylene containers (Gal91). It is relatively stable at acidic and neutral pH values, but it is hydrolysed in alkaline solutions (Rob99).

4 Uses

Monocrotophos is a systemic insecticide and acaricide belonging to the vinyl phosphate group. It controls pests on a variety of crops, such as cotton, rice, and sugarcane. It is used to control a wide spectrum of chewing and sucking insects and also mites (ACG99, Bur94).

According to the database of the Dutch Pesticide Authorisation Board (CTB)*, monocrotophos is at present not registered for its use as an active ingredient in pesticides in the Netherlands. In the USA, monocrotophos as an active ingredient is no longer contained in any registered product, and, thus, the Office of Pesticide Programs of the US Environmental Protection Agency has characterised monocrotophos as 'cancelled' in its Pesticide Registration Status (EPA98) implying that no toxicological review for a reregistration eligibility decision will be prepared.

5 Biotransformation and kinetics

Human data

In a dermal absorption study, ^{14}C-labelled monocrotophos was applied on the forearms of 6 human volunteers in a quantity of 4 $\mu g/cm^2$. The material remained non-occluded on the skin for 24 hours. After 5 days, 15% of the radioactivity administered was excreted in the urine. The maximum excretion rate was at 24-48 hour after the start of application and amounted on average 0.18% of the applied dermal dose per hour, from which an absorption rate was calculated of 7.3 ng/cm^2/hour. However, skin absorption was reported to be incomplete because much of the applied compound was lost from the skin surface by washing, evaporation, or the gradual exfoliation of outer layers of the stratum corneum (Fel74). It was also shown that 37% of a ^{14}C-labelled intravenous dose of 1 microCurie was excreted in the urine within 24 hours and 68% within 120 hours. The half-life of excretion was 20 h (Fel74).

In 2 field studies, the absorption of monocrotophos into the body during spraying was assessed by measurement of the concentration of the metabolite dimethyl phosphate (DMP) in urine of field workers. Observations during spraying showed the presence of skin exposure, but inhalation of spray mist was negligible. Urinary levels ranging from 0.02 to 1.9 mg monocrotophos

* at: http://www.ctb-wageningen.nl/geel.html.

equivalents/24 hour were reported in one study (Kum86) and from 0.6 to 19 mg over a 3-day exposure period in the second study (Sit90). The levels corresponded to maximal tentative oral doses of 4.2 mg (Kum86) and 42 mg (Sit90), respectively. In the latter study, the average half-life of elimination of DMP from the body was 18 h.

Animal data

In rabbits, dermal absorption was demonstrated by application of unlabelled material to the midshoulder area, using the inhibition of blood cholinesterase as a measure for absorption (Fos71). The metabolic fate of monocrotophos has been investigated in a variety of animal species, such as rats, rabbits, and goats. Rats that received an oral dose of 1.0 mg/kg bw [^{32}P]-monocrotophos excreted 67% and 5% of the radioactivity in urine and faeces, respectively (Men65). Similar percentages were found following oral administration of *N*-[^{14}C-methyl]-monocrotophos (Men65). In a later study, Wistar albino rats, given a single oral dose of 2 mg/kg bw of [3-^{14}C]-monocrotophos, excreted 83%, 3%, and 6% of the administered dose in the urine, in the faeces, and as expired $^{14}CO_2$, respectively, within 96 hours. A very large portion (>90%) of the radiocarbon excreted within 96 hours was produced during the first 24-hour period following administration (Lee87). The main mechanism of biotransformation of monocrotophos was hydrolysis of the P-O vinyl linkage, to give dimethyl phosphate (DMP) and *N*-methylacetoacetamide as major metabolites. The latter was further biotransformed into metabolites 3-hydroxy-*N*-butyramide and $^{14}CO_2$ (Lee87). Another metabolic route is *N*-demethylation giving the *N*-hydroxymethyl derivative and *O*-dealkylation giving des-*O*-methylmonocrotophos (Bul66, Men65, Rob99). *N*-demethylated metabolites are highly active inhibitors of acetylcholinesterase, thus having toxicological significance (Rob99). Following an intraperitoneal dose of 5 mg/kg bw of ^{32}P-monocrotophos, 40% of the dose was excreted in the urine within 24 hours as DMP, 20% as *N*-hydroxymethylmonocrotophos, and 10% as des-*O*-methylmonocrotophos (Bul66).

In summary, the mechanisms involved in the absorption, distribution, metabolism, and elimination of monocrotophos seem to be largely species independent. In the initial biotransformation, 3 different metabolic reactions occur: hydroxylation of the *N*-methyl group, demethylation of the *O*- or *N*-methyl group, and hydrolysis of the phosphate-vinyl linkage. Excretion is predominantly in the urine, typically 70 to 90 % of the dose, and usually less than

10% is voided with the faeces and expired as CO_2. Monocrotophos may therefore contribute to the carbon pool and may thus, via *de novo* synthesis of endogenous compound, lead to non-monocrotophos-related ^{14}C-residues in tissues. The highest concentrations of residues have been found in the liver and the kidneys (Muc94).

6 Effects and mechanism of action

Human data

Cases of poisoning with monocrotophos have occurred following gross spillage of an emulsifiable concentrate formulation, unintended ingestion, or by suicidal intent. A 19-year-old male splashed about 570 mL of an emulsifiable concentrate formulation on his bare chest and arms, washed it off with water, and continued working. Symptoms, becoming manifest 28 hours after exposure, were muscular weakness, blurred vision, chest pain, and blackouts. Clinical recovery, after treatment, occurred within 48 hours. Whole blood cholinesterase (ChE) activity was inhibited by 90% 1.5 days after exposure and returned slowly reaching to normal values 8 weeks after the incident (Sim69). Several cases of poisoning with monocrotophos have been described in Sri Lanka. In one patient, dermal exposure occurred due to spraying while in the second case, poisoning was due to ingestion with a suicidal intent. Patients showed neurological effects manifested as muscle weakness in those innervated by the cranial nerves, paralysis of cranial nerves, and respiratory difficulty. The times to onset and the durations of the effects were 1 to <4 and 16 to 18 days, respectively (Sen87). A third case in Sri Lanka reported respiratory distress and weakness of limbs in a man after accidental dermal exposure to a 60% monocrotophos concentrate. He recovered 16 days after the exposure. However, his plasma ChE levels were still within 37.5-50% of normal on the 20th day (Pei88). The 3 cases did not yield evidence of nerve degeneration. In a review of 20 human cases of poisoning with monocrotophos (including the 3 mentioned above), cases of delayed neuropathy, which may lead to irreversible nerve damage, have not been reported (Sch94).

Several field studies were carried out to assess the health implications following application of monocrotophos. Monocrotophos (Nuvacron) was applied to cotton by aerial spraying and cholinesterase (ChE) activities were measured in the blood of pilots, engineers, and field workers. Whole blood ChE activities in some cases were inhibited by more than 60%, but no compound-related clinical signs or symptoms were observed (Rao79, Rao80, Ull79). Two

studies have been reported in workers following application of monocrotophos (Azodrin) to cotton and rice, respectively. Application to cotton was carried out by hand-held ULV (ultra low volume application), using a formulation of 20% monocrotophos in a mixture of a glycol and a glycol ether. On average 4 or 10 L per person per day was sprayed on one or 2 consecutive days. Absorption of monocrotophos was confirmed by the presence in the urine of the metabolite DMP. No clinical signs or symptoms of intoxication or significant inhibition of acetylcholinesterase (AChE) activity in red blood cells were observed. However, significant inhibition of plasma ChE up to 59% of pre-exposure value was measured. Below a 24-hour urinary DMP excretion of 650 µg monocrotophos equivalents, no significant whole blood, plasma, or red blood cell ChE inhibition was observed. Furthermore, at 24-hour urinary DMP levels up to 1.9 mg monocrotophos equivalents, corresponding to a tentative oral dose of 4.2 mg monocrotophos (0.06 mg/kg bw), no significant inhibition of red blood cell ChE activity occurred (Kum86).

In another report, 21 applicators had sprayed Azodrin on rice cultures for 3 consecutive days. Average ChE activities at the end of the third day were inhibited by 22% of pre-exposure value in whole blood and by 41% in plasma. However, average red blood cell AChE activity had not been affected. The median total amount of DMP excretion in the urine of the 21 sprayers corresponded to a tentative oral dose of 11 mg monocrotophos, i.e., 3.7 mg (0.05 mg/kg bw/day) (Sit90).

In a study with volunteers, monocrotophos (in capsules) was given daily for 28 days to 3 groups of 6 people. Doses were 0, 3.6, and 5.7 µg/kg bw. No signs of poisoning were recorded, and red blood cell AChE and liver enzyme activities remained unaffected. Plasma ChE activity in the low-dose group decreased slowly during the first 18 days, reaching a mean inhibition of 15%. During the following 10 days of dosing, no further decrease in the activity occurred. In the high-dose group, a mean plasma ChE inhibition of 24% (range 12-29%) was reached after 28 days, and a tendency toward a steady state started to develop. Two weeks after cessation of exposure, plasma ChE activity had not yet returned to baseline levels. In a previous pilot study, a group of 8 subjects received 15 µg/kg bw/day for 8 days and then, after a 3-day pause, for 4 more days. Plasma ChE was inhibited by 51%, but even then, no effect on red blood cell AChE was observed. In the absence of effects on red blood cell AChE, 5.7 µg/kg bw is the NOAEL for humans in this study (Ver77).

Animal data

Irritation and sensitisation

A 4-hour occlusive irritation test in rabbits revealed that monocrotophos was slightly irritating to the skin. In rabbits, monocrotophos was also found to be slightly irritating to the eyes (Skr94). Monocrotophos had no sensitising properties in guinea pigs (Skr94).

Acute toxicity

Results of some acute lethal toxicity tests are summarised in Table 1.

Table 1 Summary of some acute lethal toxicity studies for monocrotophos in mammals.

exposure route (duration)	vehiculum	species (strain)	sex	LC_{50}/LD_{50}	reference
inhalation[a] (4 h)		rat	not given	63 mg/m^3	NIO02
(1 h)[b]		rat	not given	80 mg/m^3	Sac73
(1 h)[b]		rat	not given	94 mg/m^3	Sac73
(1 h)[c]		rat	not given	169 mg/m^3	New78
intratracheal		rat	not given	4.5 mg/kg bw	NIO02
dermal	xylene	rat (Sherman)	male	126 mg/kg bw	Gai69
	xylene	rat (Sherman)	female	112 mg/kg bw	Gai69
	propylene glycol	rat	not given	135 mg/kg bw	New78
	none	rabbit	not given	709 mg/kg bw	She63
	water	rabbit	not given	420 mg/kg bw	She64
	water	rabbit	not given	336 mg/kg bw	Hur69
	DMSO	rabbit	not given	223 mg/kg bw	She64
	xylene	rabbit	not given	149 mg/kg bw	She64
oral	peanut oil	rat (Sherman)	male	18 mg/kg bw	Gai69
	peanut oil	rat (Sherman)	female	20 mg/kg bw	Gai69
	propylene glycol	rat	male	35 mg/kg bw	New78
	propylene glycol	rat	female	20 mg/kg bw	New78
	water	rat	not given	5.7 mg/kg bw	Bro70
	peanut oil	rat	not given	13 mg/kg bw	She63
		rat	not given	8 mg/kg bw	NIO02
	peanut oil	mouse	not given	10 mg/kg bw	She63
		mouse	not given	15 mg/kg bw	NIO02

	aqueous carboxymethylcellulose	rabbit	not given	45 mg/kg bw	Hur70

[a] Aerosols.
[b] Droplet size <7 µm.
[c] Droplet size <3 µm.

When rats (n=10/sex/group) were exposed to air saturated with vapours from technical monocrotophos (purity: not given), for 1 hour, no mortality, clinical signs, body or organ weight changes, or gross or microscopic abnormalities were observed (observation time: 14 days) (New64, She95a).

Occlusive 24-hour dermal exposure of rats during 24 hours, using different vehicles and monocrotophos formulations, resulted in LD_{50}'s between 135 and 1028 mg/kg bw (Skr94). Semi-occlusive exposure of rats yielded an LD_{50} value >2000 mg/kg bw for the active ingredient and a value >500 mg/kg bw for Nuvacron 40 SCW formulation (Skr94).

Several acute oral toxicity studies were specifically focussed on the possible neurotoxic effects.

The effect of monocrotophos on brain AChE, red blood cell AChE, and serum ChE activity was reported in several studies. Inhibition of brain AChE (87%), red blood cell AChE (72%), and serum ChE (80%) activity was observed in female Crl:CD rats, 2 hours after treatment with a single oral dose of 3 mg/kg bw. Recovery of inhibited cholinesterases to approximately 30% inhibition occurred within 24 hours after treatment. In the same study, rats were given single oral doses of 0, 0.01, 0.03, 0.1, 0.3, or 1.0 mg/kg bw by gavage. Brain AChE, red blood cell AChE, and plasma ChE activities were equally sensitive to inhibition by moncrotophos. The NOAEL for this effect was 0.1 mg/kg bw, based on >20% inhibition of brain AChE activity at higher dose levels (Pot94). Male and female Wistar rats, treated with monocrotophos at a dose of 0.96 mg/kg bw by oral intubation, showed decreased red blood cell AChE activity by 12.8 and 16.2% in males and females, respectively. Brain Mg^{2+}-ATP-ase activities were significantly inhibited by 14% in males. Brain Ca^{2+}-ATPases were inhibited about 40% in both males and females (Sid93). The enzyme kinetics of the inhibition of brain AChE activity in rats was studied following a single oral LD_{50} dose of 20 mg/kg bw monocrotophos. Both the degree of AChE inhibition and the enzyme kinetics were determined 1, 3, 5, or 7 days after treatment. AChE activity showed maximum inhibition on day 1, with a significant recovery at day 3. However, the activity was inhibited again at day 5, followed by a recovery at day 7. Enzyme kinetics of the inhibition of brain AChE differed between *in vivo*

and *in vitro* studies, demonstrating that the toxic properties based on *in vitro* studies may not be extrapolated to *in vivo* studies (Rao92).

The acute behavioural toxicity of monocrotophos was assessed in Albino mice and Wistar rats (n=5/group), given doses of 1, 2, and 4 mg/kg bw by intragastric intubation. Observed effects at all dose levels were reduced locomotor activity, hypothermia, and reduced ability of trained mice to ride on a rotating rod (Man95). In an acute neurotoxicity test, 14 adult hens received 2 oral doses of 6.7 mg/kg bw monocrotophos with an interval of 3 weeks. The hens were pre-treated with atropine sulphate and pralidoxime chloride to protect from the acute effects of monocrotophos. Nine hens did not survive the treatment. In the others, no signs of delayed neurotoxicity were detected. Histological examination did not reveal neuropathological changes. All hens treated with a positive control (tri-*o*-tolyl phosphate) developed ataxia and had lesions in the sciatic nerve and spinal cord (Owe78).

Other published acute toxicity studies were focussed on biochemical effects of the compound. Hepatic and extrahepatic glutathione (GSH) depletion and glutathione-S-transferase (GST) inhibition were observed in different tissues of 6 male albino rats, given a single oral dose of 0.96 mg/kg bw monocrotophos (Sid90). Adult male albino rats (n=6/group), given a single oral dose of 2 mg/kg bw monocrotophos, developed hyperglycaemia and showed a decrease of liver glycogen content 12 hours after administration. A reversed effect was found in the next 12 hours: a hypoglycaemia developed accompanied by an increase of glycogen content in the liver. No changes with respect to pre-exposure values were reported for lactic acid, pyruvic acid and protein concentrations in the liver (Sha98). Dose-related decreased cytochrome P450 levels have been observed in the liver, lung, kidney, and brain of rats, treated with single oral doses of monocrotophos (0, 0.96, 1.23, 3 mg/kg bw). Cardiac and splenic cytochrome P450 concentrations were, however, increased. This study suggested organ specificity in modulating the microsomal cytochrome P450 content of hepatic and extrahepatic tissue (Sid92).

Subacute and subchronic toxicity

Monocrotophos (60% w/v formulation) applied to the intact or abraded, occluded skin of rabbits, at doses of 20 and 40 mg/kg bw/day, 6 hours/day, 5 days/week, for 3 weeks, was mildly irritating. No clinical signs of toxicity were recorded. Cholinesterase activities were not determined (Doy65).

In a 4-week dermal study in rats, technical monocrotophos was applied at doses of 0.2, 1, 10, and 100 mg/kg bw/day under semi-occlusive dressing, a NOEL of 1 mg/kg bw was established. This NOEL was based on inhibition of red blood cell and brain AChE and cholinergic signs of toxicity at 10 mg/kg bw and above (no more data presented) (Hag92).

The behavioural tolerance to monocrotophos was studied in male Wistar rats following oral administration of monocrotophos at an initial dose of 9 mg/kg bw, followed by 16 daily doses of 6 mg/kg bw. Observed signs of toxicity were tremors, sweating, salivation, and uncoordinated movements. The animals developed behavioural tolerance, which was evident by the disappearance of signs while dosing continued. Brain AChE and butyryl (plasma) ChE activities were inhibited and brain acetylcholine content elevated up to day 7, followed by recovery towards normal activities. ChE activities correlated well with the appearance and disappearance of the mainly cholinergic signs. The authors concluded that behavioural tolerance to monocrotophos developed despite changes in brain AChE and acetylcholine levels (Swa92).

Wistar rats (n=8/sex/group) were fed technical monocrotophos at doses equivalent to 0, 0.005, 0.025, 0.05, 0.5, or 5 mg/kg bw/day, for 5 weeks. Food and body weight gain were reduced at the 2 highest dose levels and (not specified) clinical signs of intoxication were observed at the top dose. Histological changes in the liver and the kidneys were observed at the highest dose only. Brain and red blood cell AChE, and plasma ChE activity were inhibited by more than 20-30% at dose levels starting at 0.025 mg/kg bw/day and 0.05 mg/kg bw, respectively. The NOAEL in this 5-week oral rat study was 0.005 mg/kg bw (McA79).

In an experiment to study the reversibility of ChE activity, technical monocrotophos (purity: 78.8%) was fed to 5-week-old Wistar rats (n=30/sex/group; controls: n=60/sex) at dose levels equivalent to 0, 0.005, 0.0125, 0.025, 0.1, and 0.4 mg/kg bw/day. The animals in each dose group were divided into 3 subgroups. Rats in subgroup A were treated for 8 weeks, rats in subgroup B for 13 weeks, and rats in subgroup C were treated for 8 weeks, and then given control diets during a 5-week recovery period. A small decrease in body weight gain was observed at 0.4 mg/kg bw/day. A small decrease in brain AChE activity (5% inhibition compared to control level) was already observed at 0.005 mg/kg bw/day. Biologically significant ChE inhibitions (>20%) were measured at 0.025 mg/kg bw/day and above for red blood cell AChE and plasma ChE activity, and at 0.1 and 0.4 mg/kg bw/day for brain AChE activity. In the males and females of

the group receiving 0.4-mg/kg bw/day, brain AChE, red blood cell AChE, and plasma ChE activities were reduced by 72-75%, 84-86%, and 51-79%, respectively. Continuation of treatment in subgroup B beyond 8 weeks did not inhibit ChE activities further. At the end of the recovery period of subgroup C, plasma ChE was comparable to or exceeded control values. The recovery of red blood cell and brain AChE activities was incomplete, still being inhibited by approximately 30% at 0.4 mg/kg bw/day. Other toxicological effects than ChE inhibition were not investigated in this study. In the absence of biologically significant ChE inhibitions, the NOAEL was 0.0125 mg/kg bw/day (Hen81).

Long-Evans rats were given technical monocrotophos (purity: not given) in the diet at dose levels of 0, 0.025, 0.075, 0.75, 2.25, and 6.75 mg/kg bw/day, for 12 weeks. The number of animals of each sex in each dose group was 42, 30, 30, 42, 12, and 12, respectively. At the top dose, all rats exhibited tremors; body weight gain was reduced and liver and kidney weights were increased but no histological effects were observed. Haematology values were unaffected in all dose groups. From 2 weeks onwards, brain AChE activity was significantly inhibited at 0.075 mg/kg bw/day and above, but remained within the normal range at 0.025 mg/kg bw/day. After a 4-week recovery period, AChE activity in the higher dose groups had returned to control levels. The NOAEL in this 12-week oral rat study was 0.025 mg/kg bw/day based on cholinesterase inhibition (no more data presented) (She64).

In a 90-day study, weanling Wistar rats (n=10/sex/group) received daily doses of 0, 0.3, 0.6, and 1.2 mg/kg bw/day of monocrotophos (purity: 70%) by intragastric intubation. Blood samples were collected at 15, 30, 60, and 90 days after the beginning of the study. At the top dose, mortality was reported in both males and females. Growth retardation was observed at all dose levels. Whole blood ChE levels decreased over time at all dose levels in males, but in females, no further inhibition was observed beyond day 15 in the groups fed 0.6 and 1.2 mg/kg bw/day. At termination, no clear dose-effect relationship was seen for inhibition of whole blood ChE and brain AChE activities in males. The average suppression levels of whole blood ChE and brain AChE activities (all dose levels) were 22% and 33% of control levels, respectively. In contrast, female rats showed a dose-related inhibition of whole blood ChE and brain AChE activities. Levels ranged from 73 to 34% and from 72 to 56% of control levels, respectively, at day 90. Dose-related histological effects were reported in liver and kidneys (Jan90). Because of the inconsistencies in the outcome of cholinesterase results, the committee has doubts on the reliability of this study.

Mice (n=8/sex/group) were fed daily dose levels equivalent to 0, 0.005, 0.025, 0.05, 0.5, and 5 mg/kg bw of technical monocrotophos (purity: not given), for 5 weeks. General health and physical appearance of the mice were not affected. Ocular or haematology changes did not occur. Food and body weight gain were reduced at the top dose only. Histological changes of the kidneys and the adrenal glands were also observed at 5 mg/kg bw. Plasma ChE was inhibited in females at 0.05 mg/kg bw/day (by 30%) and above, and in males at 0.5 mg/kg bw (by 80%) and above. Inhibition of red blood cell and brain AChE activities was found at 0.5 (by 60%) and 5 mg/kg bw (by 70-90%). The NOAEL in this 5-week oral mouse study was 0.025 mg/kg bw based on cholinesterase inhibition (Hen79).

Beagle dogs (6-9-month old) were fed diets containing technical monocrotophos (purity: not given) at dose levels equivalent to 0, 0.0125, 0.0375, 0.375, 1.125, and 3.375 mg/kg bw, for 12 weeks. Dose groups up to 0.375 mg/kg bw/day consisted of 4 animals per sex, 2 of which were allowed to recover during a 4-week exposure-free period. The 2 highest dose groups consisted of 2 animals per sex. From week 9 onwards, the concentration in the high-dose group was raised stepwise to 13.5 mg/kg bw/day and to 27 mg/kg bw/day during an extra 13th exposure week, after which these animals were killed. Body weights were reduced only in the highest dose group after the first increase in dosing (to 6.75 mg/kg bw/day). At termination of the study, brain AChE, red blood cell AChE, and plasma ChE activities were inhibited by more than 50% in the animals of the highest dose group. At 0.0375 mg/kg bw, these activities were inhibited by less than 20% while they were comparable to pre-treatment levels at 0.0125 mg/kg bw. In the dogs that were allowed to recover, ChE levels returned to pre-treatment values. Haematology, clinical chemistry and histological examination did not show abnormalities related to treatment with monocrotophos. The NOAEL in this 12-week oral dog study was 0.0125 mg/kg bw based on cholinesterase inhibition (She64, She65b).

In a prolonged feeding study, beagle dogs (n=3/sex/group) received monocrotophos at levels equivalent to 0, 0.004, 0.04, and 0.4 mg/kg bw/day, for 106 weeks. ChE activities were not reduced at and below 0.04 mg/kg bw/day, but significant inhibition occurred at 0.4 mg/kg bw/day (inhibition of plasma ChE and RBC AChE by more than 50%). A satellite dose group (n=2/sex) given 2.5 mg/kg bw/day was started after 52 weeks until the end of the study. During the first weeks of dosing, signs of toxicity (salivation, tremor, diarrhoea, body weight loss) were observed, and plasma ChE and erythrocyte AChE were inhibited by more than 50%. Brain AChE activity was inhibited by 60% in 2 out

of 4 dogs. Mortality rate, clinical signs, body weights, heart rate, blood pressure, haematology, blood chemistry, brain AChE, urinalysis, organ weights, ophthalmoscopy, gross pathology, and histopathology were evaluated but no effects other than those mentioned above were reported. The NOAEL of this study was 0.04 mg/kg bw/day for cholinesterase inhibition and 0.4 mg/kg bw/day for other toxic effects (Jon66, Jon67a). *[The committee notes that actual levels may have been considerably lower since diet analysis at week 15 and 40 showed deviations from above presented nominal values of up to 60% due to compound instability]*.

In a subchronic neurotoxicity study in hens (Cofal/Marek; n=10/group), animals were dosed daily with 0, 0.03, 0.1, and 0.3 mg/kg bw/day, for 96 days. The high dose was raised to 0.5 mg/kg bw/day on day 79. Tri-*o*-cresyl phosphate (7.5 mg/kg bw/day, raised to 10 mg/kg bw/day on day 79) was used as a positive control. Body weights were slightly decreased in the high-dose and in the positive control group. Brain weight was increased in the high-dose group only. Plasma ChE was inhibited dose dependently in all groups receiving monocrotophos by 15 and 47% in the low- and high-dose group, respectively. However, neither changes in red blood cell AChE, nor clinical signs of delayed neurotoxicity, nor neuropathological changes were observed in any of the groups receiving monocrotophos. The positive control showed typical signs of neurotoxicity (not specified) (Bec81).

Haematological effects in mice were studied following weekly intraperitoneal doses of Nuvacron (0.8 mg/kg bw), for 6 weeks. Significant decreases in haemoglobin concentration, red blood cell count, platelet count, haematocrit, and erythrocyte sedimentation rate were found, while clotting time was prolonged and white blood cell count was increased. Neutrophil and basophil counts were increased and lymphocyte count decreased. In addition, bone marrow depression and splenic hyperplasia were observed (Gup82). The author also reported increased concentrations of brain neurotransmitters (e.g., acetylcholine, epinephrine, dopamine) and a decrease in AChE activity of the brain (Gup84).

The results of various subacute and subchronic toxicity studies in experimental animals are summarised in Table 2. In nearly all studies, inhibition of brain or red blood cell AChE is the critical effect.

Table 2 Summary of subacute and subchronic dermal and oral toxicity studies for monocrotophos.

exposure route	species (strain; number; sex)	dose levels (mg/kg bw/d)	exposure duration	critical effect[a]	NOAEL (mg/kg bw/d)	reference
dermal	rabbit ('albino'; n=10/sex/group)	20, 40	3 w	clinical signs	20	Doy65
	rat (not given)	0.2, 1, 10, 100	4 w	BAChE, RAChE	1	Hag89
oral	rat (Wistar; male)	6 (1st d: 9)	17 d	behaviour	6	Swa92
	rat (Wistar; 8/sex/group)	0, 0.005, 0.025, 0.05, 0.5, 5	5 w	BAChE, RAChE	0.005	McA79
	rat (Wistar; n=30/sex/group; controls: n=60/sex)	0, 0.005, 0.0125, 0.025, 0.1, 0.4	8-13 w	BAChE, RAChE	0.0125	Hen81
	rat (Long-Evans; n=12-42/sex/group)	0, 0.025, 0.075, 0.75, 2.25, 6.75	12 w	BAChE	0.025	She64
	rat (Wistar; n=10/sex/group)	0, 0.3, 0.6, 1.2	90 d	BAChE, liver effects, kidney effects	LOAEL: 0.3	Jan90
	mouse (CD; n=8/sex/group)	0, 0.005, 0.025, 0.05, 0.5, 5	5 w	BAChE, RAChE	0.025	Hen79
	dog (beagle; 2-4/sex/group)	0, 0.125, 0.375, 1.125, 3.375	13 w	BAChE, RAChE	0.125	She64; She65
	dog (beagle; n=3/sex/group)	0, 0.004, 0.04, 0.4[b]	106 w	BAChE, RAChE	0.04[b]	Jon66; Jon67a
	hen (Cofal/Marek; n=10/group)	0, 0.03, 0.1, 0.3	96 d	neurotoxicity, RAChE	0.3	Bec81

[a] BAChE= brain AChE; RAChE= red blood cell AchE.
[b] Actual levels might have been considerably lower since diet analysis at week 15 and 40 showed deviations from nominal values of up to 60% due to compound instability.

In summary, subacute or subchronic exposure of rats, mice, dogs, and rabbits to monocrotophos caused inhibition of brain, red blood cell, and/or plasma ChE activities and cholinergic symptoms. The committee considers a NOAEL of 0.0125 mg/kg bw/day, based on biologically significant inhibition of brain and red blood cell AChE in rats. Subchronic oral exposure of rats to monocrotophos may also cause dose-dependent liver and kidney damage (LOEL: 0.3 mg/kg bw).

Chronic toxicity and carcinogenicity

In a 2-year study, rats (Charles River; n=25/sex/group) were given technical monocrotophos (purity: not given) in dietary levels equivalent to 0, 0.05, 0.5, and 5 mg/kg bw/day. However, actual levels may have been considerably lower since diet analysis at week 15 and 40 showed deviations from above presented nominal values of up to 60% due to compound instability. In the high-dose group, signs of toxicity, reduced body weight gain accompanied by reduced food intake in males only, and, in females only, decreased absolute liver, gonads, thyroid, and pituitary gland weights were observed. No other changes were seen at post-mortem gross and microscopic examination. Plasma ChE and red blood Cell AChE activities were inhibited in the mid-dose group by more than 50% from week 6 onwards but were not affected on the low-dose group (no data given for the high dose group). Brain AChE activities measured at the end of the study did no show significant changes in the low-dose group (no data given for the 2 higher dose groups) (Jon66, Jon67b).

In a 2-year study with Wistar rats (n=85/sex/group), the animals received technical monocrotophos (purity: 78.7%) in dietary concentrations equivalent to 0.0005, 0.0015, 0.005, 0.05, and 0.5 mg/kg bw/day. The control group comprised 170 rats of each sex. At 0.5 mg/kg bw, survival, body weight gain, and feed consumption were reduced. No changes were found in haematology and in clinical chemistry test results. There was no evidence of carcinogenic effects, and no gross and microscopic lesions attributable to treatment were found. Brain AChE, red blood cell AchE, and plasma ChE activities were reduced throughout the study by up to 75, 85, and 80%, respectively, at 0.5 mg/kg bw, and by up to 30, 50, and 30, respectively, at 0.05 mg/kg bw. At and below 0.005 mg/kg bw, ChE activities remained within the normal range. The NOAEL for inhibition of brain and red blood cell AChE and plasma ChE activities was therefore 0.005 mg/kg bw/day; the NOAEL for reduced body weight gain and feed consumption was 0.05 mg/kg bw/day (Bro83).

In a 2-year study, CD mice (n=77/sex/group) were fed technical monocrotophos (purity: 78.7%) at doses equivalent to 0.15, 0.30, 0.75, or 1.5 mg/kg bw/day. The control group comprised 154 animals of each sex. A dose-related increase in the number of mice showing convulsions was seen. Survival, body weight gain, haematological parameters, and organ weights were not adversely affected. No gross or microscopic lesions, and no evidence of a carcinogenic effect were seen. Dose-related inhibition of brain AChE, red blood cell AChE, and plasma ChE was observed at all levels. A NOAEL could not be

established since at the lowest dose ChE activities were still inhibited by 30-35% (Bro82).

In summary, long-term studies in mice and rats did not show evidence for a carcinogenic potential of monocrotophos. Brain AChE, red blood cell AChE, and plasma ChE were inhibited by monocrotophos in a dose-dependent manner. The overall 2-year rat oral NOAEL was 0.005 mg/kg bw based on inhibition of brain AChE and red blood cell AChE activities.

Mutagenicity and genotoxicity

Mutagenicity and genotoxicity assays comprised tests for the detection of gene mutations in bacteria, yeast, and mammalian cells (*in vitro*) and *in vitro* and *in vivo* cytogenicity and other genotoxicity assays.

- *In vitro* tests
  - Gene mutation assays. Tests for reverse mutations in *S. typhimurium* strains TA100, 1535, 1537, and 1538 were negative at concentrations up to 1 mg/plate (Sim77) and positive at concentrations up to 20 mg/plate (Hoo86, Mor83, San85, Wat82) in the presence and absence of metabolic activation. Positive results were also found in *S. cerevisae* D7 in concentrations up to 30 mg/mL (San85, Wat82). In *E.coli* WP2, gene mutation tests were negative at doses up to 10 mg/plate in the presence and absence of metabolic activation (San85, Sim77, Wat82). Monocrotophos induced gene mutations in cultured mouse lymphoma L5178Y cells at levels up to 1200 µg/mL in the presence or absence of metabolic activation (Jot80, San85, Wat82). The genotoxicity of a 'farm-grade' formulation of monocrotophos was studied in *D. melanogaster* using the wing mosaic test and the sex-linked recessive lethal test. At concentrations between 0.5-10 x 10^{-5}%, the compound was genotoxic in both somatic and germ cells of *Drosophila* (Tri92), confirming findings in previous studies (San85, Wat82).
  - Cytogenicity assays. In cultured Chinese hamster ovary (CHO) cells, monocrotophos induced sister chromatid exchanges (SCE) at levels ranging from 25 up to 2000 µg/mL and chromosome aberrations at levels >200 µg/mL with and without metabolic activation (Lin87, San85, Wan87, Wat82). No chromosome aberrations were observed at doses between 9.8-78.1 µg/mL monocrotophos (Her92a). At concentrations between 1 and 10 µg/mL, Nuvacron induced a significant increase in the

frequencies of micronuclei in CHO cells (Pei96). In human lymphocyte cultures, increased frequencies of chromosome aberrations and SCEs were seen at monocrotophos concentrations of 0.05 and 0.1 μg/mL (in DMSO) and at >0.0125 μg/mL, respectively (Rup88). Chromosome aberrations were also observed in another study at monocrotophos concentrations between 0.001 and 10 μM (Vai82). A SCE test in cultured human lymphoid cells was positive at monocrotophos levels up to 2 μg/ml (Sob82).

- Other genotoxicity assays. Positive results were seen in a mitotic-recombination assay in *S. cerevisiae* D3 and D7 at concentrations 10-50 mg/mL in the presence or absence of metabolic activation (Mor80, San85, Sim77, Wat82). Monocrotophos induced DNA repair or unscheduled DNA synthesis (UDS) in cultured human fibroblasts at levels in the range of 10^{-4}-10 mM, with and without metabolic activation (Sim77). Positive UDS results were also obtained in later studies (San85, Wat82). In a study on the alkylating properties of organophosphorus compounds, it was demonstrated that monocrotophos is a weak alkylating agent, e.g., 30 times less potent than the standard alkylating agent methyl methanesulfonate. Monocrotophos might, therefore, form adducts with DNA *in vitro* (Bed72).

- *In vivo* tests

Male and female Swiss mice treated with single intraperitoneal doses of 1.25, 2.5, and 5.0 mg/kg bw monocrotophos (Nuvacron-400) showed a significantly increased incidence of micronuclei in polychromatic bone marrow erythrocytes at the 2 highest dose levels (Pei96). Increased frequencies of micronuclei and chromosome aberrations were also observed in bone marrow cells of Swiss mice after 2 intraperitoneal doses of 1.5 and 2 mg/kg bw monocrotophos on 2 consecutive days (Vai82). However, monocrotophos did not induce micronuclei in bone marrow cells of mice following 2 intraperitoneal doses in the range of 2-8 mg/kg bw (Kir80) or following 5 intraperitoneal doses in the range of 1.25-5 mg/kg bw. In the latter study, chromosome aberrations were induced by intraperitoneal administration, but no significant effects were detected when monocrotophos was given orally at doses of 5 mg/kg bw (Bhu88). No increased frequency of micronuclei was observed in bone marrow cells of mice treated with a single oral dose of 9 mg/kg bw (Her92b). In Wistar rats, monocrotophos induced chromosome aberrations in bone marrow cells following 2 intraperitoneal doses of 2 mg monocrotophos/kg bw (interval 24 hours). At

lower doses, no aberrations were induced (Adh88). No increased frequency of chromosome aberrations was observed in bone marrow cells of Chinese hamsters after 2 oral doses up to 5.6 mg/kg bw, 24 hours apart (Str86). Dominant lethal effects were not observed in mice fed monocrotophos at levels equivalent to 0.75, 1.5, and 3.0 mg/kg bw, for 7 days or 7 weeks (Wat82, Sim77). Hens given either intraperitoneal doses of 1.25, 2.5, and 5 mg/kg bw or an oral dose of 5 mg/kg bw showed a significant increased frequency of chromosome aberrations and micronuclei in bone marrow cells and peripheral red blood cells (Bhu93). A significant increase in frequency of micronuclei was also observed in bone marrow cells and peripheral red blood cells of 1-week-old chicks, fed 5 mg monocrotophos/kg for 30 days (Jen92). A statistically significant, dose-related increase in mean comet tail length indicating DNA damage was seen in peripheral blood leukocytes 24 hours after treating male Swiss mice (n=6/group) with single (gavage) oral doses of 0, 0.046, 0.093, 0.186, 0. 373, and 0.746 mg/kg bw. At 48 hours post-treatment, mean tail lengths were gradually decreased in all dose groups, but still statistically significantly increased while they returned to control levels at 72 hours post-administration indicating repair of damaged DNA (Mah02).

The committee concludes that monocrotophos is mutagenic both in *in vitro* and *in vivo* assays. However, apart from a positive result in a test indicative of DNA damage in mouse, oral genotoxicity studies in either mice or rats were negative.

Reproduction toxicity

Male Swiss Albino mice (n=9-10/group) were given monocrotophos (0, 0.9, 1.8, 3.6 mg/kg) by intragastric intubation, for 5 days. The percentage of abnormal sperms increased with the dose from 2.1% in the control and low-dose groups to 3.6 and 5.4% in the 2 higher dose groups (Kum88). When female virgin Swiss albino mice (n=10/group) were given oral doses of technical grade monocrotophos (purity: 75%) of 0, 1.6, 3.3, 6.6, 10, and 13 mg/kg bw/day, for 30 days, dose-dependent decreases in the number of oestrus cycles and in the duration of pro-oestrus, oestrus, and metoestrus with concomitant increases in di-oestrus duration were found reaching statistically significance at doses of 3.3 mgkg bw and above. Morphometric follicular analysis in 4 animals per group, showed dose-dependent decreases in the sizes and number of healthy follicles and increases in the sizes and number of atretic follicles, reaching statistically significance at doses of 6.6 mg/kg bw and higher. Statistically significant

decreased ovary and uterus weights were seen at 3.3 mg/kg bw and above and 10 mg/kg bw and above, respectively. At the 2 higher dose levels, body weights were significantly decreased, while treatment did not cause changes in relative weights of liver, kidneys, adrenals, thymus, thyroid, spleen, and pituitary gland (Rao02).

A 2-generation reproduction study was carried out in rats (13 male and 26 female rats per dose group) that were given doses equivalent to 0, 0.005, 0.05, 0.15, and 0.5 mg/kg bw via the diet. Parental effects noted before mating were lower body weights in the male rats of the F0 and F1 generation at 0.5 mg/kg bw, and small dark faecal pellets at 0.5 and 0.15 mg/kg bw. At 0.5 mg/kg bw/day, the mating, fertility, and gestation indices were not different among F0 groups, but the mating index of F1 males was lower compared to the control group. Gestation length was increased, but mean litter size, mean pup weight, and viability and lactation indices were significantly reduced. Three total litter losses were observed in both F1 and F2 generations. At 0.15 mg/kg bw, one total litter loss was observed in the F2 generation. In addition, mean pup weight and viability index were significantly reduced. F2 female weanlings showed higher kidney and liver weights at 0.15 and 0.5 mg/kg bw compared to the controls. A NOAEL of 0.05 mg/kg bw/day was established for parental and reproduction toxicity (Dix81).

In another study, doses of 0, 0.3, 0.6, and 1.2 mg/kg bw/day were administered by gavage to female rats (n=10/group), for 2 weeks prior to mating with non-treated males. The female rats had dose-dependent lower body weights, lower resorptions, enlarged ovaries, and reduced fertility and parturition indices. These changes already started at 0.3 mg/kg bw. The gestation index was not affected. Pups showed also a dose-dependent reduction of average birth weight, average crown-rump length, and of viability and lactation indices at 0.3 mg/kg and higher. However, the average litter size was not affected in any of the groups (Adi94).

In a developmental study, monocrotophos was given to pregnant Sprague-Dawley rats (number not specified) by gavage at doses of 0, 0.3, 1, and 2 mg/kgbw/day, during days 6 to 15 of pregnancy. Dams were killed on gestation day 20. Maternal toxicity was evident by muscle tremors and twitching, listlessness, salivation, perianal urine-soaked fur, and crusty eyes at 2 mg/kg bw/day, and maternal body weight was reduced at 1 and 2 mg/kg bw/day. No compound-related effects on maternal reproduction parameters, i.e., number of corpora lutea, of implantations, of resorptions, and number of dead and viable fetuses, were found. At 2 mg/kg bw/day, fetuses had a decreased body weight, a

decreased crown-rump length, and delayed ossification of sternebrae, and at 1and 2 mg/kg bw, the number of runt fetuses was increased. Fetal visceral examination did not reveal abnormalities. The findings in fetuses were considered to be secondary to maternal toxicity. Brain defects were observed in all groups but were considered unspecific and unrelated to the test compound. The NOAEL for maternal and developmental toxicity was 0.3 mg/kg bw (Bor83). In order to evaluate the relevance of the brain defects observed in the above study, a new study was performed in female rats that were given doses of 0, 0.1, 0.3, 1, and 2 mg/kg bw during days 6 through 15 of gestation. The animals were killed on pregnancy day 20. Clinical signs of intoxication were seen in most animals at 2 mg/kg bw and tremors in one female at 1 mg/kg bw. Body weight gain was reduced at 2 mg/kg bw. There were no treatment-related necropsy findings. Pre- and post-implantation losses, mean litter size, mean fetal weight, and sex ratio were unaffected. No treatment-related external, visceral, and skeletal changes were found in fetuses. This study confirmed the conclusion that the brain defects observed in the preceding study were not related to treatment. This study confirmed the maternal NOAEL value of 0.3 mg/kg bw, and further, a NOAEL for developmental toxicity of at least 2 mg/kg bw was established (Fuc92).

In a developmental toxicity in rabbits, the animals received oral doses of 0, 0.1, 1, 3, or 6 mg/kg bw monocrotophos during days 6 through 18 of gestation. The animals were sacrificed at day 29 of gestation. Maternal effects observed at the top dose were mortality of 13 animals, weight loss, signs of cholinergic toxicity (such as hyperpnoea, tremor, ataxia, salivation, excitation, faecal changes, and constricted pupils). Necropsy revealed gastrointestinal ulceration and pulmonary oedema. At 3 mg/kg bw, diarrhoea and related faecal changes and transiently reduced body weights were seen. Average numbers of late resorptions were slightly increased, and mean live fetal weights and maternal uterine weights marginally reduced at 6 mg/kg bw. Average numbers of corpora lutea, implantations, early resorptions, litter size, dead fetuses, and fetal sex ratio were comparable among all groups. Fetuses did not show treatment-related malformations externally, in soft tissues, or in skeletal structures at any dose level. The maternal NOAEL was 1 mg/kg bw and the NOAEL for developmental toxicity 3 mg/kg bw (Dea87).

In summary, these studies indicate that the overall NOAEL for reproduction toxicity in rats or rabbits is 0.05 mg/kg bw monocrotophos/day.

7 Existing exposure limits

The current administrative exposure occupational limit (MAC) for monocrotophos in the Netherlands is 0.25 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for monocrotophos in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The health hazard assessment of monocrotophos is based mainly on toxicology reviews issued by the FAO/WHO (Joint Meeting of the FAO Panel of Experts on Pesticides Residues on Food and the Environment and the WHO Expert Group on Pesticides Residues - JMPR) (FAO92, FAO94, FAO96), the Health, Safety, and Environment Division, Shell, The Hague, The Netherlands (SIP85), and the Crop Protection Division, Ciba-Geigy Ltd, Basel, Switzerland (Skr94). The toxicity profile in these reviews is obtained mainly from unpublished reports of toxicology studies conducted for registration purposes by the chemical companies manufacturing or marketing the compound.

Workers can be exposed to monocrotophos through inhalation of aerosols or by direct skin contact with a formulation of the compound. Skin absorption has been demonstrated by detection of large amounts of the metabolite dimethyl phosphate (DMP), excreted in the urine of sprayers following 3-day monocrotophos application. The maximum dermal absorption is estimated to be 0.18% of the dose per hour, 24-48 hours after application. The extent of absorption following oral intake is 90-100% in the rat. Following absorption, the compound is rapidly metabolised into breakdown products (e.g., DMP), which are mainly excreted in the urine. There is no evidence of accumulation of the compound in any of the tissues.

Human case studies show a high acute toxicity of monocrotophos following accidental exposures. Effects observed in these studies were typical cholinergic symptoms such as reversible nerve weakness, paralysis, and respiratory difficulty. Two field studies on occupational exposure during application of monocrotophos on crops showed no compound-related clinical signs of intoxication or inhibition of red blood cell AChE activity. However, serum ChE was inhibited up to 59% of pre-exposure levels. Estimated dose levels were on average equivalent to an oral intake of 0.05 mg/kg bw/day. In a human volunteer study, oral intake of 0.0057 mg/kg bw/day for 28 days produced inhibition of

serum ChE (24%), but AChE activity in red blood cells remained unaffected and no cholinergic symptoms were observed. The NOAEL for inhibition of red blood cell AChE is >0.006 mg/kg bw/day. The committee concludes that in humans, red blood cell AChE is much less sensitive to inhibition by monocrotophos than plasma ChE. In addition, the rate of recovery of inhibited serum ChE in humans in slow in comparison to test animals.

Based on results of acute lethal toxicity studies in test animals and case reports in humans, the committee considers the compound as very toxic after oral and respiratory exposure, and as toxic after dermal exposure. Monocrotophos did not cause neurological changes indicative of acute delayed neurotoxicity. No significant systemic effects have been reported in short- or long-term toxicity studies in test animals, except liver and kidney injury in one short-term study in which rats were given high oral doses of monocrotophos. However, these studies showed inhibition of plasma ChE and of red blood cell and brain AChE in dogs, rats, and mice. These cholinesterases have approximately the same sensitivity for inhibition by monocrotophos in these species. NOAELs for brain and red blood cell AChE inhibition were 0.04 mg/kg bw for dogs (2-year oral study), 0.005 mg/kg bw for rats (2-year feeding study), and <0.15 mg/kg bw for mice (2-year feeding study). Monocrotophos caused gene mutations *in vitro* and cytogenetic effects both *in vitro* and *in vivo*. The induction of mutations is in accordance with its weak DNA alkylating potency. In mammals, cytogenicity effects were found if monocrotophos was given by intraperitoneal injections; apart from a positive result in a Comet assay suggesting - repairable - DNA damage in mouse leukocytes, studies following oral administration were negative. Carcinogenicity studies in rats and mice did not show a treatment-related increase in tumour incidence. The committee concludes that the positive genotoxic effects of monocrotophos were thus not reflected in carcinogenicity. Monocrotophos was not embryotoxic or teratogenic. At doses below those causing parental toxicity, reproduction performance was not affected. The overall NOAEL associated with reproduction toxicity was 0.05 mg/kg bw/day.

Based on the above data, the committee concludes that the mechanism of toxicity of monocrotophos in mammals is through inhibition of AChE activity in nerve tissue. The committee identifies inhibition of AChE in brain tissue as the most sensitive adverse toxic effect of monocrotophos in animal studies, occurring at dose levels that are lower than those causing other toxic effects. In human beings, for obvious reasons, brain AChE cannot be measured. Instead, red blood cell AChE, being the same molecular target for inhibition by organophosporus pesticide as brain AChE, is used as a surrogate for brain AChE

in assessing the human health risk of exposure to monocrotophos (Jey94). Studies in experimental animals showed that red blood cell AChE and brain AChE are equally sensitive for inhibition by monocrotophos, and it may be assumed that this is also the case in humans.

The committee takes the NOAEL of 0.006 mg/kg bw/day, derived from the 28-day human volunteer study, as a starting point in establishing a health-based recommended occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week, this NOAEL from a continuous study (i.e., 7 days a week) is adjusted by multiplying with a factor of 7/5 resulting in a no-adverse-effect level (NAEL) of 0.008 mg/kg bw. For extrapolation to a HBROEL, an overall assessment factor of 3, covering intraindividual variation, is used. This results in a NAEL for humans of 0.003 mg/kg bw/day. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day, and a retention of 100%, and applying the preferred value approach, a health-based occupational exposure limit of 0.02 mg/m^3 is recommended for monocrotophos.

The committee recommends a health-based occupational exposure limit for monocrotophos of 0.02 mg/m^3, as an 8-hour time-weighted average (TWA). Because monocrotophos can be absorbed through the skin in significant amounts, the committee recommends a skin notation.

References

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Monocrotophos. In: TLVs® and other occupational exposure values - 1999. [CD-ROM]. Cincinnati OH, USA: ACGIH®, Inc, 1999.

ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 91.

ACG03b American Conference of Governmental Industrial Hygienists (ACGIH). 2003 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2003: 42.

Adi94 Adilaxmamma K, Janardhan A, Reddy KS. Monocrotophos: reproductive toxicity in rats. Indian J Pharmacol 1994; 26: 126-9.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002; At-vejledning C.0.1.

Adh88 Adhikari N, Grover IS. Genotoxic effects of some systemic pesticides: In vivo chromosomal aberrations in bone marrow cells in rats. Environ Mol Mutagen 1988; 12: 235-42.

Bec81 Becci PJ, Parent RA. Neurotoxicity evaluation of Azodrin insecticide: subchronic oral administration in hens. Waverly NY, USA: Food and Drug Research Laboratories, 1981; unpublished report, cited in FAO92, SIP85, and Skr94.

Bed72 Bedford CT, Robinson J. The alkylating properties of organophosphates. Xenobiotica 1972; 2: 307-37.

Bhu88 Bhunya SP, Behera BC. Mutagenicity assay of an organophosphate pesticide, monocrotophos in mammalian in vivo test system. Cytologia 1988; 53: 801-7.

Bhu93 Bhunya SP, Jena GB. Studies on the genotoxicity of monocrotophos, an organophosphate insecticide, in the chick in vivo system. Mutat Res1993; 292: 231-9.

Bor83 Borders CK, Salamon CM, Mayhew DA. Technical Azodrin (SD9129) teratology study in SD CD rats. USA: Toxi-Genics, Inc, 1983; unpublished report, cited in FAO92 and Skr 94.

Bro70 Brown VK, Dean B, Muir CMC, et al. Toxicity studies on Azodrin; the effect of a single oral or subcutaneous dose on rats. Sittingbourne, UK: Shell Research Ltd, 1970; rep no TLGR.0002.70; unpublished report, cited in SIP85.

Bro82 Brown VK. A two-year oncogenicity study in mice fed Azodrin. Sittingbourne, UK: Shell Research Ltd, 1982; rep no SBGR.81.218; unpublished report, cited in SIP85 and Skr94.

Bro83 Brown VK, Gellatly JBM. A long-term feeding study with Azodrin in rats to investigate chronic toxicity and oncogenicity (6, 12, 18 and 24 month necropsies). Sittingbourne, UK: Shell Research Ltd, 1983; rep no SBGR.82.062; unpublished report, cited in SIP85 and Skr94.

Bul66 Bull DL, Lindquist DA. Metabolism of 3-hydroxy-N-methyl-cis-crotonamide dimethyl phosphate (Azodrin) by insects and rats. J Agric Food Chem 1966; 14: 105-9.

Bur94 Burkhard N, Drabek J. Monocrotophos - Chemical and physical properties. Rev Environ Contam Toxicol 1994; 139: 1-12.

Dea87 Dearlove GE. Development toxicity study of Azodrin insecticide (technical) in New Zealand white (NZW) rabbits. Horsham PA, USA: Argus Research Laboratories, 1987; proj no 619-005; unpublished report, cited in FAO94 and Skr94.

DFG02 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2002. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH, 2002; rep no 38.

Dix81 Dix KM, Thorpe E. A reproduction study in rats fed Azodrin. Sittingbourne, UK: Sittingbourne Research Centre, 1981; unpublished report, cited in SIP85 and Skr94.

Doy65 Doyle RL, Elsea JR. Repeated application of technical Bidrin insecticide and Azodrin (C 1414) to skin of rabbits. Miamiville OH, USA: Hill Top Research, Inc, 1965; unpublished report, cited in SIP85 and Skr94.

EPA98 US Environmental Protection Agency (EPA). Status of pesticides in registration, reregistration, and special review (rainbow report). Washington DC, USA: US EPA, Office of Pesticide Programs, Special Review and Reregistration Division, 1998: 134.

EC03 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs). http://europe.eu.int/comm/employment_social/h&s/areas/oels_en.htm.

FAO92 Food and Agricultural Organization/World Health Organization (FAO/WHO): Joint Meeting of the FAO Panel on Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (JMPR). Monocrotophos. In: Pesticides residues in food – 1991 evaluations. Part II- Toxicology. Geneva, Switzerland: WHO, 1992; rep no WHO/PCS/92.52; http://www.inchem.org/documents/jmpr/jmpmono/v91pr16.htm.

FAO94 Food and Agricultural Organization/World Health Organization (FAO/WHO): Joint Meeting of the FAO Panel on Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (JMPR). Monocrotophos. In: Pesticides residues in food – 1993 evaluations. Part II- Toxicology. Geneva, Switzerland: WHO, 1994; rep no WHO/PCS/94.4; http://www.inchem.org/documents/jmpr/jmpmono/v93pr14.htm.

FAO96 Food and Agricultural Organization/World Health Organization (FAO/WHO): Joint Meeting of the FAO Panel on Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (JMPR). Monocrotophos (addendum). In: Pesticides residues in food – 1995 evaluations. Part II. Toxicological and environmental. Geneva, Switzerland: WHO, 1996; rep no WHO/PCS/96.48; http://www.inchem.org/documents/jmpr/jmpmono/v95pr12.htm.

Fel74 Feldmann RJ, Maibach HI. Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol 1974; 28: 126-32.

Fos71 Foster DF, Shellenberger TE, Gough BJ. Effect of solvents on percutaneous absorption of organophosphate pesticides in rabbits. Toxicol Appl Pharmacol 1971; 19: 398.

Fuc92 Fuchs A. C1414 tech., Oral (gavage) teratogenicity study in the rat. Münster, Germany: Hazleton Deutschland GmbH, 1992; unpublished report, cited in Skr94.

Gai69 Gaines TB. Acute toxicity of pesticides. Toxicol Appl Pharmacol 1969; 14: 515-34.

Gal91 Gallo MA, Lawryk NJ. Monocrotophos. In: Hayes WJ Jr, Laws ER Jr, eds. Classes of Pesticides. San Diego CA, USA: Academic Press, Inc, 1991: 1012-4 (Handbook of pesticide toxicology; Vol 2, Sect 16.6.11).

Gup82 Gupta M, Bagchi G, Bandyopadhyay S, et al. Hematological changes produced in mice by nuvacron or furadan. Toxicology 1982; 25: 255-60.

Gup84 Gupta M, Bagchi G, Gupta SD, et al. Changes of acetylcholine, catecholamines and amin acid in mice brain following treatment with nuvacron or furadan. Toxicology 1984; 30: 171-5.

Hag92 Hagemann C, Waller A, Heider K, et al. 28-day repeated dose dermal toxicity study in the rat. Stein, Switzerland: Ciba-Geigy Ltd, 1992; unpublished report, cited in Skr94.

Har92 Hartmann HR. C 1414 tech.: Acute dermal toxicity in the rat. Stein, Switzerland: Ciba-Geigy Ltd, 1992; unpublished report, cited in Skr94.

Hen79 Hend RW, Gellatly JBM. Toxicity studies on the insecticide Azodrin: a five week feeding study in mice. Sittingbourne, UK: Shell Research Ltd, 1979; unpublished report, cited in SIP85.

Hen81 Hend RW, Brown V. A reversibility study of cholinesterase activity in rats fed Azodrin for 8 weeks. Sittingbourne, UK: Shell Research Ltd, 1981; unpublished report, cited in FAO92, SIP85, and Skr94.

Her92a Hertner T. Cytogenetic test on Chinese hamster cells in vitro. Basle, Switzerland: Ciba-Geigy Ltd, 1992; unpublished report, cited in FAO94 and Skr94.

Her92b Hertner T. Micronucleus test, mouse-in vivo study. Basle, Switzerland: Ciba-Geigy Ltd, 1992; unpublished report, cited in FAO94 and Skr94.

Hoo86 Hool G, Arni P. Salmonella/mammalian-microsome mutagenicity test. C1414 techn. Basle, Switzerland: Ciba-Geigy Ltd, 1986; unpublished report, cited in FAO92 and Skr94.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), UK: HSE Books, 2002.

Hur69 Hurni H, Sacchse K. Report on the determination of the acute dermal LD_{50} to the rat of monocrotophos technical (C1414). Sisseln, Switzerland: Tierfarm AG (now: Ciba-Geigy Ltd), 1969; unpublished report, cited in Skr94.

Hur70 Hurni H, Sacchse K. Report on the determination of the acute oral LD_{50} to the rabbit of monocrotophos technical (C1414).). Sisseln, Switzerland: Tierfarm AG (now: Ciba-Geigy Ltd), 1969; unpublished report, cited in Skr94.

Jan86 Janardhan A, Rao AB, Sisodia P. Species variation in acute toxicity of monocrotophos and methyl benzimidazole carbamate. Indian J Pharmacol 1986; 18: 102-3.

Jan90 Janardhan A, Sisodia P. Monocrotophos: Short-term toxicity in rats. Bull Environ Contam Toxicol 1990; 44: 230-9.

Jen92 Jena GB, Bhunya SP. Thirty day genotoxicity of an organophosphate insecticide, monocrotophos, in the chick in vivo system. In Vivo 1992; 6: 527-30.

Jey94 Jeyaratnam J, Maroni M. Health surveillance of pesticide workers. A manual for occupational health professionals. Organophophorous compounds. Toxicology 1994; 91: 15-27.

Jon66 Johnston CD. Azodrin (C1414) safety evaluation by chronic feeding studies in the rat and the dog for two years, interim report: 52 weeks. New Haven CT, USA: Woodard Research Corporation, 1966; unpublished report, cited in SIP85 and Skr94.

Jon67a Johnston CD, Thompson WM, Donoso J. Azodrin (C1414) safety evaluation by chronic feeding study in the dog for 2 years, final report. New Haven CT, USA: Woodard Research Corporation, 1967; unpublished report, cited in SIP85 and Skr94.

Jon67b Johnston CD, Thompson WM, Donoso J. Azodrin (C1414) safety evaluation by chronic feeding study in the rat for 2 years, final report. New Haven CT, USA: Woodard Research Corporation, 1967; unpublished report, cited in SIP85.

Jot80 Jotz MM, Mitchell AD, Jones DCL, et al. An evaluation of mutagenic potential of monocrotophos employing the L5178Y $TK^{+/-}$ mouse lymphoma assay. Menlo Park CA, USA: SRI International, 1980; unpublished report, cited in FAO92 and Skr94.

Kir80 Kirkhart B, Jones DCL, Skinner WA. Micronucleus test onmonocrotophos. Menlo Park CA, USA: SRI International, 1980; unpublished report, cited in FAO92 and Skr94.

Kum86 Kummer R, Van Sittert NJ. Field studies on health effects from the application of two organophosphorus insecticide formulations by hand-held ULV to cotton. Toxicol Lett 1986; 33: 7-24.

Kum88 Kumar DV, Janardhan A. Mutagenicity of monocrotophos in mice. Bull Environ Contam Toxicol 1988; 41: 189-94.

Lee87 Lee PW. Rat metabolism study of ^{14}C-DPX-Y2034. Wilmington DE, USA: EI du Pont de Nemours & Co, Inc, 1987; report no AMR-653-87; unpublished report, cited in Muc94.

Lin87 Lin MF, Wu CL, Wang TC. Pesticide clastogenicity in Chinese hamster ovary cells. Mutat Res 1987; 188: 241-50.

Mah02 Mahboob M, Rahman MF, Danadevi K, et al. Detection of DNA damage in mouse peripheral blood leucokytes by the comet assay after oral administration of monocrotophos. Drug Chem Toxicol 2002; 25: 65-74.

Man95 Mandhane SN, Chopde CT. Neurobehavioural effects of acute monocrotophos administration in rats and mice. Indian J Pharmacol 1995; 27: 245-9.

McA79 McAusland HE, Gellatly JBM. A five week feeding study of Azodrin in rats. Sittingbourne, UK: Shell Research Ltd, 1979; unpublished report, cited in SIP85.

Men65 Menzer RE, Casida JE. Nature of toxic metabolites formed in mammals, insects, and plants from 3-(dimethoxyphosphinyloxy)-N,N-dimethyl-cis-crotonamide and its N-methyl analog. J Agric Food Chem 1965; 13: 102-12.

Mor80 Mortelmans KE, Shepherd GF, Jones DCL, et al. In vitro detection of mitotic crossing-over, mitotic gene conversion and reverse mutation with Saccharomyces cerevisae D7 for seven pesticides. Menlo Park CA, USA: SRI International, 1980; unpublished report, cited in FAO92 , SIP85, and Skr94.

Mor83 Moriya M, Ohta T, Watanabe K, et al. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 1983; 116: 185-216.

Muc94 Mucke W. Metabolism of monocrotophos in animals. Rev Environ Contam Toxicol 1994; 139: 59-65.

New64 Newell GW, Shellenberger TE. Letter Report No 2. Ref. Project B-4843. Menlo Park CA, USA: SRI International, 1964; unpublished report, cited in SIP85

New78 Newell GW, Dilley JV. Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Research Triangle Park , USA: U.S. Environmental Protection Agency, 1978; EPA rep no 600/1-78-003; cited in Skr94.

NIO02 National Institute for Occupational Safety and Health (NIOSH), ed. Phosphoric acid, dimethyl ester, ester with (E)-3-hydroxy-N-methylcrotonamide. In: Registry of Toxic Effects of Chemical Substances (RTECS). (last update: July 2000); http://www.cdc.gov/niosh/rtecs/tc42c1d8.html.

Owe78 Owen DE, Butterworth STG, Brown VKH, et al. Toxicity of organophosporus insecticide Azodrin: Investigation of the neurotoxic potential of Azodrin-5 to adult domestic hens. Sittingbourne, UK: Shell Research Ltd, 1978; unpublished report, cited in SIP85 and Skr94.

Pei88 Peiris JB, Fernando R, De Abrew K. Respiratory failure from severe organophosphate toxicity due to absorption through the skin. Forensic Sci Int 1988; 36: 251-3.

Pei96 Peitl PJ, Sakamoto-Hojo ET, De Syllos Colus IM. Genotoxic activity of the insecticide Nuvacron (Monocrotophos) detected by the micronucleus test in bone marrow erythrocytes of mice and in CHO cells. Braz J Genet 1996; 19: 571-6.

Pot94 Potrepka RF. Acute oral toxicity study of monocrotophos technical in rats. Farmington CT, USA: Ciba-Geigy Corp; unpublished report, cited in FAO96.

Rao79 Rao RR, Marathe MR , Gangoli SD. Effect of exposure of human volunteers to aerial spray of monocrotophos. Ecotoxicol Environ Safety 1979; 3: 325-34.

Rao80 Rao RR, Quadros F, Mazmudar RM, et al. Toxicological effects of aerial application of monocrotophos. Arch Environ Contam Toxicol 1980; 9: 473-81.

Rao92 Rao JV, Swamy AN, Yamin S. Rat brain acetylcholinesterase response to monocrotophos and abate. Bull Environ Contam Toxicol 1992; 48: 850-6.

Rao02 Rao RP, Kaliwal BB. Monocrotophos induced dysfunction on estrus cycle and follicular development in mice. Ind Health 2002; 40: 237-44.

Rob99 Roberts TR, Hutson DH, eds. In: Insecticides and Fungicides. Cambridge, UK: Royal Society of Chemistry, 1999: 388-93 (Metabolic pathways of agrochemicals, Pt 2).

Rup88 Rupa DS, Laksman Rao PV, et al. In vitro effect of monocrotophos on human lymphocytes. Bull Environ Contam Toxicol 1988; 41:737-41.

Sac73 Sacchse K. Acute inhalation toxicity of technical C 1414 (monocrotophos) in the rat. Sisseln, Switzerland: Ciba-Geigy Ltd, 1973; unpublished report, cited in SIP85 and Skr94.

San85 Sandhu SS, Waters MD, Simmon VF, et al. Evaluation of the genotoxic potential of certain pesticides used in Pakistan. Basic Life Sci 1985; 34: 185-219.

Sch94 Schulze-Rosario C, Loosli R. Monocrotophos - Worker Safety. Rev Environ Contam Toxicol 1994; 139: 47- 57.

Sen87 Senanayake N, Karalliede L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. N Engl J Med 1987; 316: 761-3.

Sch86 Schoch M. C 1414 SCW 40 (A-3805 A) acute dermal toxicity in the rat. Basle, Switzerland: Ciba-Geigy Ltd, 1986; unpublished report, cited in Skr94.

Sha98 Sharma NJ, Kushwah A, Kushwah HS. Protective action of dietary protein against monocrotophos toxicity on some biochemical constituents in rats. Indian J Animal Sci 1998; 68: 1078-81.

She63 Shellenberger TE, Newell GW. Report No105, Ref. Project B-1008. Menlo Park CA, USA: SRI International, 1963; unpublished report, cited in SIP85 and Skr94.

She64a Shellenberger TE, Newall GW. Report No 107, Ref. Project B-1008. Menlo Park CA, USA: SRI International, 1964; unpublished report, cited in SIP85 and Skr94.

She64b Shellenberger TE, Newal GW. Subacute toxicity and cholinesterase study of Shell compound SD 9129 (C1414)-rat and dog. Menlo Park CA, USA: SRI International, 1964; unpublished report, SIP85 and Skr94.

She65a Shellenberger TE. Letter Report No 5. Ref. Project B-4843. Menlo Park CA, USA: SRI International, 1965; unpublished report, cited in SIP85.

She65b Schellenberger TE. Subacute toxicity study of Shell compound SD 9129 (C1414) - dog. Addendum to tech.report/part 1. Menlo Park CA, USA: SRI International, 1965; unpublished report, cited in SIP85 and Skr94.

Sid90 Siddiqui MKJ, Mahboob M, Mustafa M. Hepatic and extra hepatic glutathione depletion and glutathione-S-transferase inhibition by monocrotophos and its two thiol analogues. Toxicology 1990; 64: 271-9.

Sid92 Siddiqui MKJ, Mahboob M, Mustafa M. Interaction of monocrotophos and its novel thion analogues with microsomal cytochrome P-450: in vivo and in vitro studies in rat. Toxicology 1992; 76: 133-9.

Sid93 Siddiqui MKJ, Rahman MF, Mustafa M. Target enzyme inhibition by novel thion analogues of monocrotophos: An acute in vivo study in the rat. Bull Environ Contam Toxicol 1993; 51: 409-15.

Sim69 Simpson RE, Simpson GR, Penney DJ. Poisoning with monocrotophos, an organophosporus pesticide. Med J Aust 1969; 2: 1013-16.

Sim77 Simmon VF, Mitchell AD, Jorgenson T. Evaluation of selected pesticides as chemical mutagens "in vitro" and "in vivo" studies. Menlo Park CA, USA: SRI International, 197; unpublished report cited in FAO94 and Skr94.

SIP85 Shell International Petroleum Maatschappij (SIPM). Review of mammalian and human toxicology Azodrin. Proprietary information for use by regulatory authorities. The Hague, the Netherlands: Shell Internationale Petroleum Maatschappij, 1985; Review series HSE 85.001.

Sit90 van Sittert NJ, Dumas EP. Field study on exposure and health effects of an organophosphate pesticide for maintaining registration in the Philippines. Med Lav 1990; 81: 463-73.

Skr94 Skripsky T, Loosli R. Toxicology of monocrotophos. Rev Environ Contam Toxicol 1994; 139: 13-39.

Sob82 Sobti RC, Krishan A, Pfaffenberger CD. Cytokinetic and cytogenetic effects of some agricultural chemicals on human lymphoid cells in vitro: organophosphates. Mutat Res 1982; 102: 89-102.

Str86 Strasser F, Arni P. Chromosome studies on somatic cells of Chinese hamster. Basle, Switzerland: Ciba-Geigy Ltd, 1986; unpublished report, cited in FAO92 and Skr94.

Swa92 Swamy KV, Ravikumar R, Murali Mohan P. Effect of chronic sublethal daily dosing of monocrotophos on some aspects of protein metabolism in rat brain. Bull Environ Contam Toxicol 1992; 49: 723-9.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW03 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2003. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2003: 35.

Tom97 Tomlin CDS, ed. In: The Pesticide Manual. A world compendium. 11th ed. Farnham (Surrey), UK: British Crop Protection Council, 1997: 849-51.

TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Tri92 Tripathy NK, Patnaik KK. Studies on the genotoxicity of monocrotophos in somatic and germ-line cells of Drosophila. Mutat Res 1992; 278: 23-9.

Ull79 Ullmann L, Phillips J, Sachsse K. Cholinesterase surveiilance of aerial applicators and allied workers in the democratic Republic of the Sudan. Arch Environ Contam Toxicol 1979; 8: 703-12.

Vai82 Vaidya VG, Patanakar N. Mutagenic effect of monocrotophos- An insecticide in mammalian test systems. Indian J Med Res 1982; 76: 912-7.

Ver77 Verberk MM. Incipient cholinesterase inhibition in volunteers ingesting monocrotophos or mevinphos for one month. Toxicol Appl Pharmacol 1977; 42: 345-50.

Annex

Occupational exposure limits for monocrotophos in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	0.25	8 h	administrative	S	SZW03
Germany						
- AGS	-	0.25[c]	8 h		S	TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	-	0.25	8 h			Arb02
USA						
- ACGIH	-	0.25[c]	8 h	TLV	S, A4[d]	ACG03b
- OSHA	-	-				ACG03a
- NIOSH	-	0.25	10 h	REL		ACG03a
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Measured as inhalable fraction.

[d] Classified in carcinogen category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.