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

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 Data from unpublished studies were generally not taken into account.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-(dimethoxyphosphinyl)-N-methyl-cis-crotonamide; dimethyl 2-methylcarbarnoyl-1-methylvinyl phosphate, Azodrin, Nuvacron

molecular formula : $C_7H_{14}NO_5P$
structural formula :

\[
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{C} \\
\text{CONHCH}_3
\end{array}
\]

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 : $3 \times 10^{-4}$ 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 Use

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

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 [32P]-monocrotophos excreted 67% and 5% of the radioactivity in urine and faeces, respectively (Men65). Similar percentages were found following oral administration of N-[14C-methyl]-monocrotophos (Men65). In a later study, Wistar albino rats, given a single oral dose of 2 mg/kg bw of [3-14C]-monocrotophos, excreted 83%, 3%, and 6% of the administered dose in the urine, in the faeces, and as expired 14CO2, 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 14CO2 (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 32P-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 CO₂. Monocrotophos may therefore contribute to the carbon pool and may thus, via de novo synthesis of endogenous compound, lead to non-monocrotophos-related 14C-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>
<thead>
<tr>
<th>exposure route (duration) vehiculum</th>
<th>species (strain)</th>
<th>sex</th>
<th>LC₅₀/LD₅₀</th>
<th>reference</th>
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<tbody>
<tr>
<td>inhalation (4 h)</td>
<td>rat</td>
<td>not given</td>
<td>63 mg/m³</td>
<td>NIO02</td>
</tr>
<tr>
<td>(1 h)</td>
<td>rat</td>
<td>not given</td>
<td>80 mg/m³</td>
<td>Sac73</td>
</tr>
<tr>
<td>(1 h)</td>
<td>rat</td>
<td>not given</td>
<td>94 mg/m³</td>
<td>Sac73</td>
</tr>
<tr>
<td>(1 h)</td>
<td>rat</td>
<td>not given</td>
<td>169 mg/m³</td>
<td>New78</td>
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<tr>
<td>intratracheal</td>
<td>xylene</td>
<td>not given</td>
<td>4.5 mg/kg bw</td>
<td>NIO02</td>
</tr>
<tr>
<td>dermal</td>
<td>xylene</td>
<td>rat (Sherman)</td>
<td>male</td>
<td>126 mg/kg bw</td>
</tr>
<tr>
<td></td>
<td>xylene</td>
<td>rat (Sherman)</td>
<td>female</td>
<td>112 mg/kg bw</td>
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<td></td>
<td>none</td>
<td>rabbit</td>
<td>not given</td>
<td>709 mg/kg bw</td>
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<td>water</td>
<td>rabbit</td>
<td>not given</td>
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<td>water</td>
<td>rabbit</td>
<td>not given</td>
<td>336 mg/kg bw</td>
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<td></td>
<td>DMSO</td>
<td>rabbit</td>
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<td>xylene</td>
<td>rabbit</td>
<td>not given</td>
<td>149 mg/kg bw</td>
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<td></td>
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<td>male</td>
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<td></td>
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<td>rat (Sherman)</td>
<td>female</td>
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<tr>
<td></td>
<td>peanut oil</td>
<td>mouse</td>
<td>not given</td>
<td>15 mg/kg bw</td>
</tr>
</tbody>
</table>
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 monocrotophos. The NOAEL for this effect was 0.1 mg/kg bw, based on >20% inhibition of brain AChE activity at higher dose levels (Put94). 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.
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).

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

<table>
<thead>
<tr>
<th>exposure route</th>
<th>species (strain; number; sex)</th>
<th>dose levels (mg/kg bw/d)</th>
<th>exposure duration</th>
<th>critical effect¹</th>
<th>NOAEL (mg/kg bw/d)</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>dermal</td>
<td>rabbit (‘albino’; n=10/sex/group)</td>
<td>20, 40</td>
<td>3 w</td>
<td>clinical signs</td>
<td>20</td>
<td>Doy65</td>
</tr>
<tr>
<td></td>
<td>rat (not given)</td>
<td>0.2, 1, 10, 100</td>
<td>4 w</td>
<td>BAChe, RAChe</td>
<td>1</td>
<td>Hag89</td>
</tr>
<tr>
<td>oral</td>
<td>rat (Wistar; male)</td>
<td>6 (1st d: 9)</td>
<td>17 d</td>
<td>behaviour</td>
<td>6</td>
<td>Swa92</td>
</tr>
<tr>
<td></td>
<td>rat (Wistar; 8/sex/group)</td>
<td>0, 0.005, 0.025, 0.05, 0.5, 5</td>
<td>5 w</td>
<td>BAChe, RAChe</td>
<td>0.005</td>
<td>McA79</td>
</tr>
<tr>
<td></td>
<td>rat (Wistar; n=30/sex/group; controls: n=60/sex)</td>
<td>0, 0.005, 0.0125, 0.025, 8-13 w 0.1, 0.4</td>
<td>12 w</td>
<td>BAChe, RAChe</td>
<td>0.0125</td>
<td>Hen81</td>
</tr>
<tr>
<td></td>
<td>rat (Long-Evans; n=12-42/sex/group)</td>
<td>0, 0.025, 0.075, 0.75, 2.25, 6.75</td>
<td>12 w</td>
<td>BAChe</td>
<td>0.025</td>
<td>She64</td>
</tr>
<tr>
<td></td>
<td>rat (Wistar; n=10/sex/group)</td>
<td>0, 0.3, 0.6, 1.2</td>
<td>90 d</td>
<td>BAChe, liver effects, kidney effects</td>
<td>LOAEL: 0.3</td>
<td>Jan90</td>
</tr>
<tr>
<td></td>
<td>mouse (CD; n=8/sex/group)</td>
<td>0, 0.005, 0.025, 0.05, 0.5, 5</td>
<td>5 w</td>
<td>BAChe, RAChe</td>
<td>0.025</td>
<td>Hen79</td>
</tr>
<tr>
<td></td>
<td>dog (beagle; 2-4/sex/group)</td>
<td>0, 0.125, 0.375, 1.125, 13 w 3.375</td>
<td>12 w</td>
<td>BAChe, RAChe</td>
<td>0.125</td>
<td>She64; She65</td>
</tr>
<tr>
<td></td>
<td>dog (beagle; n=3/sex/group)</td>
<td>0, 0.004, 0.04, 0.4b</td>
<td>106 w</td>
<td>BAChe, RAChe</td>
<td>0.04b</td>
<td>Jon66; Jon67a</td>
</tr>
<tr>
<td></td>
<td>hen (Cofal/Marek; n=10/group)</td>
<td>0, 0.03, 0.1, 0.3</td>
<td>96 d</td>
<td>neurotoxicity, RAChe 0.3</td>
<td></td>
<td>Bec81</td>
</tr>
</tbody>
</table>

¹ BAChe= brain AChE; RAChe= red blood cell AChE.
² 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).

073-16 Health-based Reassessment of Administrative Occupational Exposure Limits
**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. cerevisiae 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).
  • 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 mg/kg 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/kg bw/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 1 and 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/m³, 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 organophosphorus pesticide as brain AChE, is used as a surrogate for brain AChE.

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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 m³ 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/m³ is recommended for monocrotophos.

The committee recommends a health-based occupational exposure limit for monocrotophos of 0.02 mg/m³, 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.

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073-29 Monocrotophos


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### Annex

Occupational exposure limits for monocrotophos in various countries.

<table>
<thead>
<tr>
<th>country</th>
<th>organisation</th>
<th>occupational exposure limit</th>
<th>time-weighted average</th>
<th>type of exposure limit</th>
<th>note&lt;sup&gt;a&lt;/sup&gt;</th>
<th>reference&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>the Netherlands</td>
<td>Ministry of Social Affairs and Employment</td>
<td>-</td>
<td>0.25</td>
<td>8 h</td>
<td>administrative</td>
<td>S</td>
</tr>
<tr>
<td>Germany</td>
<td>AGS</td>
<td>-</td>
<td>0.25&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 h</td>
<td>S</td>
<td>TRG00</td>
</tr>
<tr>
<td>Great Britain</td>
<td>HSE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>HSE02</td>
</tr>
<tr>
<td>Sweden</td>
<td>-</td>
<td>-</td>
<td>0.25</td>
<td>8 h</td>
<td></td>
<td>Swe00</td>
</tr>
<tr>
<td>Denmark</td>
<td>-</td>
<td>-</td>
<td>0.25</td>
<td>8 h</td>
<td></td>
<td>Arb02</td>
</tr>
<tr>
<td>USA</td>
<td>ACGIH</td>
<td>-</td>
<td>0.25&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 h</td>
<td>TLV</td>
<td>S, A4&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OSHA</td>
<td>-</td>
<td>0.25</td>
<td>10 h</td>
<td>REL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIOSH</td>
<td>-</td>
<td>0.25</td>
<td>8 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Union</td>
<td>SCOEL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>EC03</td>
</tr>
</tbody>
</table>

<sup>a</sup> S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

<sup>b</sup> Reference to the most recent official publication of occupational exposure limits.

<sup>c</sup> Measured as inhalable fraction.

<sup>d</sup> 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.
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