Temephos

(CAS No: 3383-96-8)

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

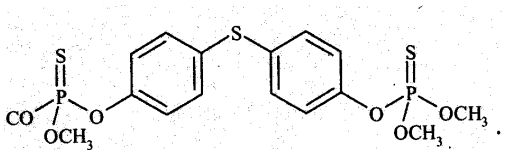
The present document contains the assessment of the health hazard of temephos by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. and MM Verberk, Ph.D. (Coronel Institute of the Academic Medical Centre, Amsterdam, the Netherlands).

The evaluation of the toxicity of temephos was based on reviews published in the 'The handbook of pesticide toxicology' (Gal91) and by the American Conference of Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in July 1998, literature was searched in the databases Medline, Embase, and Chemical Abstracts, starting from 1966, 1988 and 1970, respectively, as well as from the Hazardous Substances Data Bank (HSDB) (NLM02). CD-ROM versions of the databases Poltox (1990-1994) HSELINE, CISDOC, MHIDAS, and NIOSHTIC (from 1998 backwards) were also consulted. In May 2002, a literature search was carried out in Toxline and Medline. The following key words were used: temephos, temefos, abate, and 3383-96-8. Data of unpublished studies were generally not taken into account.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) (FAO75) and the Health Effects Division (HED) of the US Environmental Protection Agency (EPA) as part of their hazard identification assessment review (Lie98, Paq99b).

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.

2 Identity

name	:	temephos
synonyms	:	phosphorothioic acid, *O*,*O*'-(thiodi-1,4-phenylene) *O*,*O*,*O*',*O*'-tetramethyl ester; *O*,*O*,*O*',*O*'-tetramethyl *O*,*O*'-thiodi-*p*-phenylene phosphorothionate; Abate; Abathion; Amercan Cyanamid CL-52160
molecular formula	:	$C_{16}H_{20}O_6P_2S_3$
structural formula	:	
CAS number	:	3383-96-8

3 Physical and chemical properties

molecular weight	:	466.48
boiling point	:	decomposes at 120-125ºC
melting point	:	30.5ºC
vapour pressure	:	at 25ºC: 1 x 10^{-5} Pa
solubility in water	:	insoluble
Log $P_{octanol/water}$	:	4.91
conversion factors	:	not applicable

Data from NLM02, Rob99.

Pure temephos is a white crystalline solid, while the technical grade is a brown viscous liquid. Temephos is hydrolysed by strong acids and alkalis (ACG99).

4 Uses

Temephos is used to control mosquito and black fly larvae in aqueous environments and as a human and veterinary ectoparasiticide. It is also used on crops for the control of cutworms, thrips on citrus, and lygus bugs. Temephos is formulated as emulsifiable concentrates, wettable powders, or granules (Gal91, NLM01). According to the database of the Dutch Pesticide Authorisation Board

(CTB)*, temephos is at present not registered for its use as an active ingredient in pesticides in the Netherlands.

5 Biotransformation and kinetics

Human data

Urine specimens were collected from people residing in an area sprayed by aircraft with naled and temephos. Increased concentrations of the temephos metabolite *O,O*-dimethylphosphorothioate (DMPT) were found in post-treatment samples, indicating absorption of temephos by inhalation of the aerosol or through skin contact (Kut77).

Animal data

In a biokinetic study, Sprague-Dawley rats, New Zealand white rabbits, and beagle dogs were given single intravenous doses of [^{14}C-ring]-labelled Abate (dissolved in methanol) of 0.033 mg each. The amount of radiocarbon recovered in urine and faeces after 7 days was 24.6% of the administered dose for rats, 55% for rabbits, and 35% for dogs. Less than 0.5% of the dose was retained in the tissues. No explanation could be given of these relatively low recoveries. In rats and rabbits, the major portion of the label was excreted in the urine (17.7 and 47% of the dose, respectively), but in dogs most of the radioactivity was excreted in the faeces (23% of the dose). Most of the radiocarbon excreted in the urine over 7 days was produced during the first 24-hour period following administration (69-79%). In dogs, the radioactivity in blood peaked between 5 and 30 minutes after application and then decayed with an initial half-life of about 4 h. The dermal penetration of Abate was studied in the same species. Following topical application of 0.033 mg [^{14}C-ring]-labelled Abate, 6.7% and 24.6% of the applied dose was recovered in the urine and 11% and 9% in the faeces for rats and rabbits, respectively, over 7 days. However, dogs that received a dermal dose of 0.33 mg [^{14}C-ring]-labelled Abate had only 0.5% of the applied dose recovered in the urine and 0.87% in the faeces within 7 days. Most of the radioactivity excreted in the urine over 7 days was produced during the first 2 days following topical application (51-65%). In dogs, nearly all of the unabsorbed compound was recovered from a non-occlusive patch that protected the area and apparently trapped evaporation of the compound. Tissue specimens

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

collected from each species showed only trace amounts or complete absence of radioactivity 7 days after application. The percentage of dermal absorption was calculated by dividing the percent of the dose excreted in the urine following dermal application by the percent of the dose excreted in the urine following intravenous dosing and then multiplying by 100. The percent dermal absorption was 38% in rats, 52% in rabbits, and approximately 5% in dogs. By comparison of the dermal penetration potential of organophosphorus pesticides between species, the authors concluded that topically applied Abate should not present a dermatotoxic hazard to man following a single application, and that absorption would be expected to be less than 3% of the applied dose (Paq99a, Sno80).

In another paper, it is reported that following administration of either a single oral dose of 300 mg/kg bw of temephos or repeated oral doses of 300 mg/kg bw/day, for 5 days, the elimination of temephos in plasma of Sprague-Dawley rats followed monoexponential kinetics. The half-life of temephos after acute exposure was 7 h and after subchronic exposures 24 h (Fer85).

When Sprague-Dawley rats were given a single oral dose of radiolabelled [^{3}H-phenylene]temephos, 95-98% of the radioactivity was eliminated within 72 hours, the faeces (52-65%) being the principle route of excretion. Parent compound accounted for ca. 60% of the radioactivity in the faeces, while urine contained only trace amounts of unchanged temephos. The concentration of radioactivity in the blood peaked between 5 and 8 hours and then dissipated with a half-life of about 10 h. Appreciable radioactivity was found in the gastrointestinal tract and the fat. The main mechanism of biotransformation of temephos is hydrolysis of the P-O linkages, to give *O,O*-dimethylphosphorothioate (DMPT) and 4,4'-thiodiphenol, which is subsequently biotransformed by oxidation of the thioether moiety into its sulphoxide (4,4'-sulphinyldiphenol) and its disulphoxide (4,4'-sulphonyldiphenol). These metabolites are excreted in the urine as water-soluble sulphate ester conjugates, which together comprised some 80% of total urinary radioactivity (Blin69, Rob99).

6 Effects and mechanism of action

Human data

Two studies were conducted in which human volunteers were given oral doses of technical Abate (purity: not given) to investigate the toxicity of the compound. The aim of first study was to discover the acute dose of Abate necessary to

produce inhibition of red blood cell acetylcholinesterase (AChE) or plasma cholinesterase (ChE) in humans. Two groups of 10 healthy male volunteers were involved, one to receive Abate and one control group. Each subject in the experimental group started with an oral dose of 2 mg Abate and the dose was then doubled every 3 to 4 days to reach a level of 256 mg at day 25. Subjects in the control group were not given Abate. The study was terminated on day 28. Cholinesterase (ChE) activities were examined 3 times a week. Urine samples for the determination of Abate were also collected. The aim of the second study was to determine a NOAEL for inhibition of cholinesterases following repeated oral intake of Abate. One experimental group and one control group of 9 volunteers each were involved. Each subject in the experimental group was given a daily dose of 64 mg Abate, for 4 weeks. Subjects in the control group did not receive Abate. ChE activities were determined twice a week and an additional blood sample was taken 5 days after the last dose. Urine samples for the determination of Abate were collected during dosing of Abate and for 3 weeks following the last dose. At no time in either study, there was a significant difference between the red blood cell AChE or plasma ChE activities of the volunteers receiving Abate and the control groups. No clinical symptoms or other reactions related to Abate were observed. The concentration of Abate in urine was proportional to doses and was still detectable 3 weeks after dosing stopped (Law67). From these studies, the committee concludes that the NOAEL of a 4-week oral study with temephos in man is at least 64 mg/person/day (average of 0.91 mg/kg bw/day).

Animal data

Irritation and sensitisation

Temephos is slightly irritating to eyes but not irritating to skin of rabbits (EPA99, Lev70). The compound is not a dermal sensitiser (Paq99b). No further details were given.

Acute toxicity

Rats survived an 8-hour inhalation exposure to air almost saturated with temephos (LC_{50}>1300 mg/m^3)(Lev70, Lie98).

Acute inhalation LC_{50} and dermal and oral LD_{50} values in test animals are summarised in Table 1.

Table 1 Summary of acute toxicity studies for temephos in mammals.

exposureoute	vehiculum	species (strain)	sex	LC_{50} or LD_{50}	reference
inhalation		rat	not given	>1300 mg/m^3 (8 h)	Lev70, Lie98
dermal	none	rat (Sherman)	male	>4000 mg/kg bw	Gai67, Gai69
	none	rat (Sherman)	female	>4000 mg/kg bw	Gai67, Gai69
		rat	not given	1200 mg/kg bw	Gon75
		rabbit	male	1850 mg/kg bw	Lie98
		rabbit	female	970 mg/kg bw	Lie98
		rabbit	not given	2000 mg/kg bw	Lev70
oral	none	rat (Sherman)	male	8600 mg/kg bw	Gai67, Gai69
	none	rat (Sherman)	female	13000 mg/kg bw	Gai67, Gai69
		rat	not given	1226 mg/kg bw	Ito72
		rat	not given	2000 mg/kg bw	Lev70
		rat	not given	1650 mg/kg bw	Gon75
		rat	not given	444 mg/kg bw	Lie98
	none	mouse ('white')	male	4700 mg/kg bw	Gai67
		mouse	unknown	460 mg/kg bw	Gon75

In their studies, Gaines et al. found that some manufacturing batches of technical Abate (purity: not given) had an approximately 3-fold lower acute oral LD_{50} in female rats than the value of 13,000 mg/kg bw reported in Table 1 (Gai67, Gai69). The acute dermal or oral LD_{50}s of temephos reported by other authors (Gon75, Ito72, Lev70, Lie98) were appreciably lower than that reported by Gaines et al. It is not known whether this difference in acute toxicity was associated with a difference of Abate manufacture or with some unidentified factor (Gal91).

Sprague-Dawley rats (n=32) given a single oral dose of 300 mg/kg bw of temephos (purity: 93.1%) did not show mortality or clinical signs of intoxication. However, red blood cell AChE activity was depressed by 67% and 47% at 4 and 48 hours after treatment, respectively (Fer85). The same authors studied the influence of temephos on the mixed function oxidase (MFO) system by measuring the hexobarbital sleeping time (HST) 4 hours after oral administration of doses of temephos of 0, 30, and 300 mg/kg bw. Animals in the high-dose group showed a significant increase in duration of HST compared to the control group. The HSTs were significantly correlated with plasma temephos concentrations. This study indicates that at high acute doses, temephos has an

inhibitory effect on the activity of the MFO system (Fer85). In a study to compare the susceptibility to inhibition by temephos of cholinesterase and carboxylesterase enzymes, male Holzman rats (n=3/group) were given single oral (gavage) doses of Abate (purity: 86.2%) of 2.5, 5, 10, 25, 50, 100, or 250 mg/kg bw. Using the 50%-inhibition point, the susceptibility to inhibition by Abate was in the order: liver carboxylesterase > red blood cell AChE > plasma ChE > red blood cell AChE. Carboxylesterase was 3-18 times more sensitive than red blood cell AChE and 8-45 times more sensitive than brain AChE. No signs of intoxication were observed (Mur72). To investigate the effects on behaviour, Sprague-Dawley rats received intraperitoneal injections of Abate (purity: 90%) of 316, 562, or 1000 mg/kg bw and were tested for 16 days. At the top dose, animals showed signs of intoxication and an impaired avoidance performance 6 days after injection, but not 2, 8, 10, or 16 days after treatment. No behavioural changes were observed in the other groups (Kur79).

White Leghorn chicken hens were tested for leg weakness following a single subcutaneous dose of temephos. All animals were given atropine to protect against the acute toxic effects of the chemical. The lowest dose that caused mortality was 1000 mg/kg bw. Birds that received 125 mg/kg bw showed leg weakness within 24 hours for a period of 6-31 days (Gai69). According to EPA, no evidence of temephos-induced delayed neurotoxicity or neuropathology was observed in 3 acute delayed neurotoxicity studies in hens. However, these studies were judged inadequate for various technical deficiencies, but no details were provided (Paq99b).

Short-term toxicity

Albino rats (n=10/sex/group) received dermal doses of 12 or 60 mg/kg bw of temephos (purity: not given) applied as an aqueous emulsion, 5 days/week, for 3 weeks. No mortality or clinical signs of systemic toxicity were observed, but animals receiving the high dose had lower food intake and lower body weight gain. Gross and microscopic examination revealed increased liver weights in females but no other treatment-related lesions. Cholinesterase activities were not reported (FAO75, Lev70).

Rabbits (strain, sex, and number not given) that received dermal doses of 178 mg/kg bw/day of temephos (purity: not given) for 5 consecutive days showed no mortality, but diarrhoea occurred in 7 treated animals. Cholinesterase activity was reduced, but no further details were given (FAO75).

Sprague-Dawley rats (n=32) receiving temephos at oral (gavage) doses of 300 mg/kg bw/day, for 5 days, did not show mortality. Cholinergic signs such as muscle fasciculations and salivation appeared on day 4 of the treatment. Red blood cell AChE activity was depressed by 100% for all animals at 2 and 48 hours after treatment. Treated animals showed a significant increase in hexobarbital sleeping time compared to the control group (Fer85).

Male rats (Sherman) were given technical-grade Abate (purity not given) by gavage or in the diet. Besides monitoring of symptoms of intoxication and terminal gross and microscopic examinations, only plasma ChE and red blood cell AChE activities were measured. However, since red blood cell AChE activity was always affected more rapidly and to a greater extent than plasma ChE activity, almost only effects on red blood cell AChE activity were presented. Groups of 7 rats received doses of temephos of 0, 1, 10, or 100 mg/kg bw/day by gavage for 44 days (dosing regimen not indicated). After 11 days, administration of the test compound to 'some' of the animals of the high-dose group was stopped. No mortality was reported in any of the groups. Rats given the highest dose developed typical symptoms of organic phosphorus intoxication (not specified) after 3 doses when their red blood cell AChE activity was inhibited by 64%. Gradual recovery from symptoms occurred while dosing progressed, even though the red blood cell AChE activity continued to fall to 87% inhibition after 11 days of dosing. In the animals that were allowed to recover after 11 days, red blood cell AChE activity was inhibited by 27% at the end of the experiment (44 days). The rats receiving 10 mg/kg bw showed no symptoms of intoxication, but red blood cell AChE was inhibited by 31% and 47% after 14 and 44 days, respectively. The NOAEL for inhibition of red blood cell AChE was 1 mg/kg bw/day. Other groups of 11-14 rats received temephos in their diets at levels equivalent to 0, 0.18, 1.8, 18, or 150 mg temephos/kg bw/day, for 99 days (dosing regimen not indicated). In the 150-mg/kg bw group, the red blood cell AChE activity was depressed by 100%, and only 2 animals survived the 99-day treatment period, both showing 100% and 80% inhibition of red blood cell AChE and plasma ChE activity, respectively. Animals in the 18 mg/kg bw group showed no grossly observable signs of toxicity in spite of 71% inhibition of red blood cell AChE at the end of the 99 days. Gross or microscopic examination did not reveal abnormalities in any of the treatment groups. The NOAEL for inhibition of red blood cell AChE was 1.8 mg/kg bw/day (Gai67).

Male Holtzman rats were given oral (drinking water) doses of technical-grade Abate (purity: 86.2%) of 0, 0.3, 0.5, 1, 3, or 5 mg/kg bw for 7 days (n=5/group) or of 0, 0.1, 0.3, or 0.5 mg/kg bw/day, 7 days/week, for 8 weeks

(number: not given). At the end of the 7-day study, liver carboxylesterase activity was inhibited by 20% in the lowest dose group, while red blood cell AChE activity was inhibited (20%) at 5 mg/kg bw only. Brain AChE and plasma ChE levels remained unaffected. In the 8-week study, groups of 4-5 rats from each dose group were sacrificed at intervals of 14, 22, 28, and 56 days for cholinesterase and liver carboxylesterase determinations. No inhibition of brain or red blood cell AChE or plasma ChE activity was observed for any dose at any time. However, liver carboxylesterase activity was depressed in a dose-dependent way. The NOAEL for inhibition of cholinesterase activities in the 8-week study was 0.5 mg/kg bw/day, the highest dose tested. No NOAEL could be established for liver carboxylesterase since its activity was depressed at 0.1 mg/kg bw, the lowest level tested (Mur72).

In a 13-week feeding study, groups of rats (strain: not given; n=45/sex/group; controls: n=65/sex) were given temephos (purity: 96.4%) at levels equivalent to 0, 0.1, 0.3, 0.9, or 17.5 mg/kg bw/day. At the top dose, the female body weight gain was significantly depressed. No treatment-related mortality, cholinergic signs of intoxication, ophthalmological abnormalities, changes in food consumption, or changes in clinical chemistry and haematological data were observed. No gross and microscopic treatment-related changes were noted in any of the groups. However, the relative liver weight of males in the highest dose group was significantly decreased. Significantly decreased activities of brain AChE (77%, males and females), red blood cell AChE (89% for males and 91% for females), and plasma ChE (48% for males and 61% for females) were measured in the highest dose group at the end of the 13-week treatment period. At 0.9-mg/kg bw, brain AChE activity was decreased by 17% in males and 14% in females in the first 5 weeks of the study, but these effects disappeared at the end of the 13 weeks with red blood cell AChE activities decreased by 25% for males and 23% for females, but no significant changes found for plasma ChE for either sex. At 0.18 mg/kg bw, the red blood cell AChE activity was inhibited in males only by 16% at week 13 with no changes noted in either brain AChE or plasma ChE. Since inhibition of red blood cell AChE at 0.3 mg/kg bw and brain AChE at 0.9 mg/kg bw were considered equivocal, the study was repeated at dietary levels equivalent to 0, 0.3, 0.9, and 2.7 mg/kg bw/day, for 90 days. Statistically significant decreases were only seen in red blood cell AChE activity in both sexes at 0.9 and 2.7 mg/kg bw. In this 90-day oral rat study, the NOAEL for inhibition of red blood cell AChE activity is, therefore, 0.3 mg/kg bw/day (Lev70, Lie98).

Male rabbits were administered technical-grade Abate (purity: not given) at oral (gavage) doses of 0.1, 1, or 10 mg/kg/day for 35 days (n=4/group) (dosing regimen not indicated) or 100 mg/kg bw/day for 5 days (n=8). Three out of the animals given 100 mg/kg bw died. Out of the 7 animals of this 100-mg/kg bw group autopsied, 4 showed focal or diffuse liver necrosis. Effects on cholinesterase activities were not discussed. None of the animals exposed for 35 days developed any sign of toxicity. At 10 mg/kg bw, red blood cell ACE activity was inhibited by 47% at the end of the 35 days. No significant inhibition of red blood cell AChE activity occurred in the other groups. At autopsy, there were neither liver lesions, such as seen in the 100-mg/kg bw group, nor any other pathological changes in any of the groups treated for 35 days. Brain AChE and plasma ChE activities were not determined in this study (Gai67).

Dogs (n=2/sex/group) were given technical-grade Abate (purity: not given) in drinking water at doses of 0, 0.7, or 3.5 mg/kg bw/day, for 18 weeks (dosing regimen not indicated). No clinical signs of toxicity were observed. At 3.5 mg/kg bw/day, red blood cell AChE was inhibited by 78% in males and 50% in females at the end of the 18 weeks. No effect was found on red blood cell AChE nor on plasma ChE activity of either of the dogs given 0.7 mg/kg bw (Gai67).

In a 13-week dog study, Abate caused severe cholinergic signs of intoxication at a dietary level equivalent to about 17.5 mg/kg bow/day. Reduction of the dose level of Abate to about 12.5 mg/kg bw/day during the rest of the study markedly decreased cholinergic signs. However, brain and red blood cell AChE and plasma ChE activities were severely inhibited. No gross or microscopic treatment-related lesions were noted. No effects on cholinesterase activities were found at about 0.45 mg/kg bw/day. No further details were provided (Lev70, Lie98, Paq99b).

Male guinea pigs (n=5) given a daily dose of 100 mg/kg bw/day by stomach tube for 5 days showed no signs of intoxication. No pathological changes were observed. Cholinesterase activities were not investigated (Gai67).

Hens (n=2/group) were given dietary levels of technical-grade Abate (purity: not given) of 0, 7.4, or 15.3 mg/kg bw, for 108 days. Hens in the high-dose group developed leg weakness after 30 days of treatment. The hens given 7.4 mg/kg bw/day did not show symptoms of leg weakness during the 108 days of treatment (Gai67).

To investigate the effects of repeated administration of technical-grade Abate (purity: 90%) on behaviour, Sprague-Dawley rats (n=10/group) received daily intraperitoneal injections of 167 mg/kg bw/day, for 6 days. Groups were tested one day and 6 days after treatment. At either day, no changes in avoidance

performance were noted. However, motor activity was depressed by 56% and 78%, red blood cell AChE by 100%, brain AChE by 85% and 78%, and plasma ChE by 39% and 8% at post-treatment day 1 and day 6, respectively (Kur79).

CFHB-remote Wistar rats were given Abate (purity: not given) daily by intraperitoneal injection at doses between 10 and 300 mg/kg bw (not further specified) for 4, 7, or 10 days. A dose-related decrease in whole blood cholinesterase and brain AChE was noted. No effects were observed on liver enzymes alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) or on acid phoshatase. However, significant reductions were found of glutamate dehydrogenase (GLDH) and aminopyrine demethylase levels after all dose periods (doses not specified). Cytochrome P450 activity was reduced after 7 and 10 days treatment, but the activity was increased at the higher doses (doses not specified) after 4 days of treatment (Enn79).

Short-term toxicity studies are summarised in Table 2 (see page 14).

Long-term toxicity and carcinogenicity

In a 2-year study, rats (n=60/sex/group) were fed levels of temephos (purity: 95.5%) equivalent to 0, 0.5, 5.0, or 15 mg/kg bw/day. Rats used for the treated groups were derived from the offspring of 140 pregnant Sprague-Dawley CD rats that were given temephos via the diet at a level of 5 mg/kg bw (length of treatment not given). The controls were derived from offspring of untreated female rats. Neither signs of toxicity nor treatment-related effects on survival, body weight gain, food consumptions, or haematology and clinical chemistry data were observed in any of the treatment groups. Gross post-mortem examination revealed an increase in both absolute and relative liver weight in the high-dose group. According to EPA, these increases were not related to treatment. Histological examination showed tumour incidences evenly distributed among the treated groups and the control group, and no statistically significant differences among groups were found. According to EPA, the NOAEL for long-term toxicity in this study was 15 mg/kg bw/day (Lie98).

Mutagenicity and genotoxicity

The committee did not find any data on the mutagenic and genotoxic potential of temephos.

Table 2 Summary of short-term toxicity studies for temephos in experimental animals.

exposure route	species (strain; number, sex))	dose level (in mg/kg bw/d)	exposure duration	critical effect[a]	NOAEL (mg/kg bw)	reference
dermal	rat ('albino'; n=10/sex/group)	12 or 60	21 days	systemic toxicity	12	Lev70, Lie98
dermal	rabbit	178	5 days	systemic toxicity	LOAEL: 178	FAO75
oral (gavage)	rat (Sherman; n=10 males/group)	0, 1, 10, 100	44 days	RAChE	1	Gai67
oral (diet)	rat (Sherman; n=11-14 males/group)	0, 0.18, 1.8, 18, 150	99 days	RAChE	1.8	Gai67
oral (diet)	rat (n=45/sex/group)	0, 0.1, 0.3, 0.9, 17.5	92 days	RAChE BAChE	0.3	Lev70, Lie98
oral (gavage)	rat (Spague-Dawley; n=32 females)	300	5 days	RAChE	LOAEL: 300	Fer85
oral (drinking water)	rat (Holtzman; n=5 males/group)	0, 0.3, 0.5, 1, 3, 5	7 days	RAChE liver carboxyl esterase	3 LOEL:0.3	Mur72
oral (drinking water)	rat (Holtzman; n=16-20 males/group)	0, 0.1, 0.3, 0.5	8 weeks	RAChE liver carboxyl esterase	0.5 LOEL:0.1	Mur72
oral (gavage)	rabbit (n=4 males/group)	0.1, 1, 10	35 days	RAChE	1	Gai67
oral (drinking water)	dog (n=2/sex/group)	0, 0.7, 3.4	129 days	RAChE	0.7	Gai67
oral (diet)	dog	0, 0.45, 12.5/17.5	13 weeks	RAChE	0.45	Lev70, Lie98, Paq99b
oral (gavage)	guinea pig (n=5 males)	100	5 days	systemic toxicity	100	Gai67

[a] RAChE=red blood cell AChE; BAChE= brain ACHE.

Reproduction toxicity

In a one-generation reproduction study, groups of male and female Sherman rats (numbers not given) were fed dietary levels of technical-grade Abate (purity: not

given), equivalent to 0 or 25 mg/kg bw/day at the time they were placed together for breeding. This dose was sufficiently high to cause (not specified) symptoms of toxicity in some animals and was maintained during mating, gestation, parturition, and lactation. After 48 days of treatment, red blood cell AChE activity of females was inhibited by 90% while that of their 21-day-old young was inhibited by 30%. No significant differences in the fertility or gestation indices, number of litters produced, litter size, viability or lactation indices, or incidence of teratological defects were observed between the treated and the control group (Gai67).

In a 3-generation study, albino rats were fed levels of temephos (purity: 87%), equivalent to 0, 1.25, or 6.25 mg/kg bw/day, from weaning through reproductive age. The number of rats that were mated was 24/dose for the P generation and 16/dose for either the F1 or F2 generations. No treatment-related parental toxicity was observed at any dose level in any of the generations. Cholinesterase levels were not measured. The fertility, gestation, viability, and lactation indices for the temephos-fed animals were comparable to those of the controls. The combined (of all matings) mean pup weight at weaning was slightly higher in the low-dose groups and slightly lower in the high-dose groups when compared to the controls. The P generation fed 1.25 and 6.25 mg/kg bw and the F1 generation fed 6.25 mg/kg bw produced pups with a slight reduction in mean body weights at weaning for both males and females. No gross abnormalities were observed for all P and F1 pups and no gross and microscopic abnormalities for F2 pups of the control and high-dose groups. The NOAEL in this study for both the parental and reproduction toxicity was 6.25 mg/kg bw, the highest level tested (Lev70, Lie98).

Pregnant New Zealand rabbits (no numbers given) were given oral doses of temephos (purity: 90.4%) at levels 0, 3, 10, or 30 mg/kg bw/day, during days 6 through 18 of gestation. No maternal or reproduction toxicity was observed (Lie98).

In a prenatal dermal developmental toxicity study, pregnant New Zealand rabbits (no numbers given) received repeated dermal applications of Abate formulations (purity/composition: not given) at 0, 12.5, 25, or 50 mg/kg bw/day, during days 6 through 18 of gestation. Decreased maternal body weights were observed in the high-dose group. Maternal plasma ChE activity was inhibited at all dose levels (brain or red blood cell AChE not evaluated). No reproductive abnormalities were noted. Further details were not provided. In this study, the maternal NOAEL could not be determined (LOAEL for inhibition of plasma

ChE activity: 12.5 mg/kg bw/day), the NOAEL for reproduction toxicity was 50 mg/kg bw/day, the highest level tested (Lie98).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for temephos in the Netherlands is 10 mg/m^3, 8-hour TWA.

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

8 Assessment of health hazard

The health hazard assessment of temephos is based to a great extent on a toxicology review issued by the EPA for the reregistration eligibility decision (Lie98, Paq99b). The toxicity profile in this review is obtained mainly from unpublished reports of toxicology studies conducted for registration purposes by chemical companies manufacturing or marketing the compound.

Workers can be exposed to temephos through inhalation of the dust or by direct skin contact with a formulation of the compound. No data is available of the percentage uptake of the compound through the lungs. The dermal absorption of temephos is of little significance and expected to be less than 3% of the applied dose in humans. Following oral administration to rats, the compound is metabolised into several breakdown products. Elimination half-lives from the blood ranged from ca. 10 to 24 hours following single and repeated exposure, respectively. After a single oral dose, the faeces were the major route of excretion accounting for 52-65% of the dose, 60% of which was parent compound; excretion was complete within 72 hours.

In a human volunteer study, an oral dose of temephos of 0.9 mg/kg bw/day for 4 weeks did not inhibit the cholinesterase activities in red blood cells and in plasma. There were no clinical symptoms or other adverse effects found in the volunteers.

In experimental animals, the compound is slightly irritating to the eyes, but is not irritating to skin or a skin sensitiser. Based on the results of acute lethal toxicity studies in test animals, the committee considers the compound of low toxicity by inhalation and of moderate toxicity by the dermal and oral route. Temephos did not cause neurological changes indicative of acute delayed neurotoxicity. With the exception of mild pathological changes in the liver in a short-term study with rabbits, no significant systemic effects have been reported

in test animals. However, acute and short-term oral studies showed inhibition of red blood cell AChE, brain AChE, and plasma ChE in rats, rabbits, and dogs. Red blood cell AChE was more sensitive for inhibition by temephos than brain AChE or plasma ChE in these species. In one study, it was demonstrated that liver carboxylestererase is even more sensitive for inhibition by temephos than red blood cell AChE. The 13-week oral NOAELs for red blood cell AChE inhibition were 0.3 and 0.45 mg/kg bw/day for rats and dogs, respectively. The LOEL for carboxylesterase was 0.1 mg/kg bw/day for the rat (8-week study). However, carboxylesterase does not appear to be critical for normal physiological function and inhibition of its activity is not considered as an adverse effect (WHO90). Therefore, the committee will not consider the data on carboxylesterase inhibition in the risk assessment. A carcinogenicity study in rats did not show a treatment-related increase in tumour incidence. There were no data available of the mutagenic and genotoxic potential of the compound. At doses below those causing parental toxicity, reproductive performance is not affected. The overall NOAEL associated with reproduction toxicity in rats was ≥6.25 mg/kg bw/day.

Based on the above data, the committee concludes that the mechanism of toxicity of temephos in mammals is through inhibition of AChE activity in nerve tissue, occurring at dose levels that are lower than those that cause other toxic effects. Therefore, the committee identifies inhibition of brain AChE as the critical effect. 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 pesticides as brain AChE, is used as a surrogate for brain AChE in assessing the human health risk of exposure to temephos (Jey94). Studies in rats, rabbits, and dogs showed that red blood cell AChE is more sensitive for inhibition by temephos than brain AChE, and it may be assumed that this also is the case in humans.

The committee prefers to use the human data as a basis in deriving a health-based recommended occupational exposure limit (HBROEL). The NOAEL of 0.91 mg/kg bw/day, derived from the 4-week human volunteer study, is taken as a starting point. For extrapolation to a HBROEL, an overall assessment factor of 3, covering for intraindividual variation, is used. This results in a NAEL for humans of 0.30 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 2 mg/m^3 is recommended for temephos.

The committee recommends a health-based occupational exposure limit for temephos of 2 mg/m^3, as an 8-hour time-weighted average (TWA).

In view of the relatively low (estimated) skin absorption in humans and the relatively low acute lethal toxicity in experimental animals, the committee does not recommend a skin notation*.

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* See ECE98 for criteria to assess the need to assign a skin notation.

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

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Annex

Occupational exposure limits for temephos 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	-	10	8 h	administrative		SZW03
Germany						
-AGS	-	-				TRG00
-DFG MAK-Kommission	-	-				DFG02
Great-Britain						
-HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	-	-				Arb02
USA						
-ACGIH	-	10	8 h	TLV		ACG03b
-OSHA	-	15[c]	8 h	PEL		ACG03a
	-	5[d]	8 h			
-NIOSH	-	10[c]	10 h	REL		ACG03a
	-	5[c]	10 h			
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] Total dust.
[d] Respirabe fraction.