TEMEPHOS

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Explanation

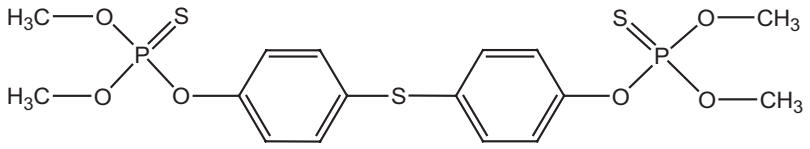
Temephos (*O,O,O'O'*-tetramethyl *O,O'*-thiodi-*p*-phenylene bis(phosphorothioate)) is an organophosphate insecticide. Temephos is one of the compounds recommended by the World Health Organization (WHO) as a mosquito larvicide treatment for potable water. No acceptable daily intake (ADI) had been established previously. For that reason, the WHO Drinking-water Guidelines

programme recommended that temephos be evaluated toxicologically by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Temephos has not been previously evaluated by the Meeting.

For temephos, the specifications were established by the Joint FAO/WHO Meeting on Pesticide Specifications (JMPS) and published as *WHO specifications and evaluations for public health pesticides*: *temephos* (WHO, 1999).[1]

Several studies with temephos, including studies of acute oral toxicity, dermal toxicity inhalation toxicity, irritancy, skin sensitization, genotoxicity and special studies of neurotoxicity in hens, were certified as being compliant with good laboratory practice (GLP). Other available studies were carried out before the Organisation for Economic Co-operation and Development (OECD) guidelines on GLP were promulgated. The Meeting noted that the reports of some of the critical studies were available only as brief published articles that lacked some of the details normally required for completing an adequate risk assessment.

Figure 1. Structural formula of temephos



The specifications for technical temephos (WHO/SIT/19.R4), temephos emulsifiable concentrate (WHO/SIF/31.R4), temephos emulsifiable concentrate for simulium control (WHO/SIF/34.R3) and temephos sand granules (WHO/SIF/40.R1) were last revised on 10 December 1999.

Temephos is a phenyl organothiophosphate insecticide that is mainly used as a larvicide to control mosquitoes, midge, blackfly and other insects. Its toxic action against the target species is by inhibition of cholinesterase in the nervous system. Temephos has been used for the control of mosquito larvae in potable water since the early 1970s (WHO, 1991) and has been recommended for treatment of potable water at a dose not exceeding 1 mg/l (WHO, 1984; Rozendaal, 1997).

Evaluation for acceptable daily intake

1. Biochemical aspects

1.1 Absorption, distribution, excretion and biotransformation

Rats

Groups (number and sex not stated) of Sprague-Dawley rats (body weight, 150–200 g) were given radiolabelled temephos at a dose of 970, 1357, 3164 or 9168 µg (dissolved in acetone and sesame oil) given by oral gavage. The temephos was radiolabelled with tritium at the ortho-position relative to the sulfide linkage on both phenyl rings of the molecule. Samples of urine and faeces were collected for analysis at various times between 7 h and 96 h after dosing. Unspecified numbers of animals from the group at 970 µg were killed at 48 h and rats from the group at 1357 µg were killed at 72 h. Samples of muscle, liver, kidney, stomach, intestines and fat were taken for analysis. The urine for each group at each time was pooled and extracted with chloroform and ethyl ether before analysis

[1] Available from: http://www.who.int/whopes/quality/en/temephos.pdf

by thin-layer chromatography (TLC). Faecal samples were extracted with methanol and analysed by TLC. Residues in fat were extracted with hexane and methanol and analysed by TLC. Identification of metabolites was by chromatographic comparisons with non-radioactive reference compounds. Tissues other than fat contained insufficient residues to permit analysis by TLC. The measurement of amounts of radiolabel in different tissues was by liquid scintillation counting.

More than 95% of the administered radioactivity was recovered in faeces and urine within 98 h, with most being recovered in the first 48 h. The distribution of radiolabel in the various tissues is shown in Table 1, and shows that most of the residues were in the fat.

Table 1. The tissue distribution of radiolabel in rats given tritiated temephos

Tissue	Concentration of radiolabel (µg temephos equivalents per gram tissue)	
	970 µg/rat at 48 h	1357 µg/rat at 72 h
Fat	1.25	1.75
Intestines	NA	0.51
Kidneys	0.07	0.09
Liver	0.17	0.19
Muscle	0.03	0.02
Stomach	0.04	0.24

From Blinn (1966)
NA, no data available.

The metabolites of temephos that were identified were temephos sulfoxide, 4,4'thiodiphenol, 4,4'-sulfinyldiphenol and 4,4'-sulfonyldiphenol. Faeces contained 60% of the total radioactivity recovered, with 30% as temephos, 10% as its sulfoxide, 5% as 4,4'-thiodiphenol, 4% as 4,4'-sulfonyldiphenol and 10.5% as unknowns and unextractables. Urine samples contained 39.5% of the total recovered radiolabel. The amounts of metabolites extractable (as percentages of the total radioactivity recovered from urine, faeces and tissues) from untreated urine were 0.5%, 2%, 1.5% and 2.2% for temephos, 4,4'-thiodiphenol, 4,4'-sulfinyldiphenol and 4,4'-sulfonyldiphenol. These amounts increased to 0.5%, 24%, 2.5% and 4.6%, respectively, when the urine was treated with a mixture of glucuronidases and sulfatases, indicating that some of the urinary metabolites (particularly the 4,4'-thiodiphenol) were present in conjugated form. Only about 0.5% of the total recovered radiolabel was found in samples of fat taken at 48 h and 72 h after dosing. Of this, 0.5% from fat tissue, 0.3% was as temephos and 0.2% as its sulfoxide. It was proposed that the metabolism of temephos can occur by *S*-oxidation to form temephos sulfoxide and by carboxylesterase hydrolysis to form 4,4'-thiodiphenol. Further hydrolysis and *S*-oxidation of these metabolites would result in the formation of 4,4'-sulfinyldiphenol and 4,4'-sulfonyldiphenol. Secondary metabolism by glucuronidation or sulfation of temephos, 4,4'-thiodiphenol, 4,4'-sulfinyldiphenol and 4,4'-sulfonyldiphenol would result in the formation of conjugates (Blinn, 1966).

2. Toxicological studies

2.1 Acute toxicity

(a) Oral toxicity

Mice and rats

Studies of acute oral toxicity were performed with CF-1 mice and CHRCD rats. Certificates of compliance with GLP were not provided with the reports of these studies

In a study in mice, groups of five females were given single doses of temephos at 1250, 2500 or 5000 mg/kg bw in corn oil by oral gavage. The treatment was followed by a 14-day observation period. Body weights were measured at the beginning and end of the study. Necropsies were not performed. All animals at 5000 mg/kg bw died before the end of the observation period. At all doses, ataxia, decreased activity, diarrhoea and prostration were observed. Salivation and diuresis were also observed at 1250 and 2500 mg/kg bw. The oral median lethal dose (LD_{50}) for female mice in this study was estimated to be 2062 mg/kg bw (Fischer, 1986; Nielsson, 1990).

In a study in rats, groups of five males and five females were given single doses of temephos at 2500, 5000 or 10 000 mg/kg bw in corn oil by oral gavage. The treatment was followed by a 14-day observation period, during which body weights were measured weekly. Autopsies were performed on all rats. All of the males at 10 000 mg/kg bw, but none of the females at this dose died during the observation period. Decreased movement was seen in all animals at all doses and diuresis was seen in all rats at 5000 mg/kg bw or more. At autopsy, all of males at the highest dose had discoloured liver and haemorrhagic or dark coloured lungs and three out of five had blood in the lumen of their intestines. No adverse findings were seen in females at the highest dose. The oral LD_{50} was 4204 mg/kg bw in males and > 10 000 mg/kg bw in females (Fischer, 1986; Nielsson, 1990).

In a briefly reported study that did not conform with GLP, groups of 20–58 male and 20–58 female adult Sherman rats were given single doses of three different batches of technical-grade temephos (purity not reported) in undiluted form in various volumes by oral gavage. Similarly, a group of 50 adult female white mice (strain not reported) were treated orally with various volumes of temephos from one of the batches (batch A). In addition, groups of 20 male and 20 female rats received temephos of batch A in various volumes applied to the skin and were restrained to stop them temephos being removed by licking. The animals were observed for 22 days. The lowest oral dose that caused death in rats was 4000 mg/kg bw. The affected animals were reported to show “the classical symptoms of illness and manner of death associated with organic phosphorus poisoning”. The acute oral toxicity of batch A appeared to be lower than that of batches B and C in rats, and was also higher in mice than in rats (Table 2) (Gaines et al., 1967).

Guinea-pigs

In another briefly reported experiment that did not conform with GLP, a group of five adult male guinea-pigs was given temephos (purity not stated) as five daily doses at 100 mg/kg bw administered by gavage. The animals showed no clinical signs of toxicity and findings on autopsy were unremarkable. Cholinesterase activities were not measured (Gaines et al., 1967).

Rabbits

In a briefly-reported study that did not comply with GLP, a group of eight rabbits was given temephos at an oral dose at 100 mg/kg bw per day for 5 days, while a control group of six rabbits was not treated. Three treated rabbits died during the dosing period. Autopsies were performed on seven of the treated rabbits and all control animals. No microscopic examination of tissues was conducted. Diffuse necrosis of the liver was reported in two treated rabbits and focal liver necrosis was reported in another two treated rabbits, while no liver necrosis was found in untreated controls (Gaines et al., 1967).

Birds

In a study that complied with GLP, groups of four mature White Leghorn chickens (sex not stated) were given temephos as single oral doses at 215, 464, 681, 1000 or 1470 mg/kg bw by gavage. An acute oral LD_{50} of 500 mg/kg bw was calculated from the mortality results (Fletcher & Leonard, 1986).

In a special study to investigate the potential of temephos to cause neurotoxicity, groups of six adult hens (breed not stated) were given temephos (purity, 99.9%) as single oral doses of 0 (untreated controls), 227, 455, 823, 1137, 1422 or 1705 mg/kg bw by gavage. Mortality in the group at 227 mg/kg bw was no greater than in the untreated control group. The oral LD_{50} calculated from the results for mortality in this study was 579 mg/kg bw (Ross et al., 1976). More details of this study are given in the section "Neurotoxicity studies in hens".

Groups of three adult White Leghorn hens were given various amounts of temephos (purity, 87.1%) as single oral doses. From the mortality results, an oral LD_{50} of 183 mg/kg bw was calculated (McNerney & Levinskas, 1967).

Groups of 2–11 hens were given single oral doses of temephos of three different batches (A, B and C) (purity not stated) at 125, 250, 500 or 1000 mg/kg bw by gavage. All doses caused leg weakness, but the effect was reported as being very mild in the group at 125 mg/kg bw and disappeared within 6 days. The leg weakness lasted longer in the other groups. Half of the animals (5 out of 10) died in the group at 1000 mg/kg bw. No difference in response was detected between groups given the same doses of different batches of temephos (Gaines et al., 1967).

Groups of 5–8 chicks or ducklings were given temephos (purity not stated) as five daily oral doses at 10, 25 or 50 mg/kg bw by gavage. All of the birds at 50 mg/kg bw per day died, as did several of those at 25 mg/kg bw per day (two out of six chicks and five out of eight ducklings). The survivors in the group at 25 mg/kg bw per day were generally weak, but typical leg weakness was not observed. The six chicks at 10 mg/kg bw per day showed no clinical signs at all, but four of the five ducklings at this dose showed mild signs of poisoning over the first 2 days, but had recovered by the end of the dosing period. Autopsy findings were unremarkable (Gaines et al., 1967).

Groups of 10 hens were given temephos (purity not stated) as a single subcutaneous dose at 500 or 1000 mg/kg bw. Five of the hens given 1000 mg/kg bw died and all of the survivors developed leg weakness which persisted for 6 to 38 days (mean, 26 days). All of the hens given 500 mg/kg bw survived, but they all developed leg weakness that persisted for 11 to 31 days (mean, 15 days). The onset of leg weakness was immediate but recovery was gradual (Gaines et al., 1967).

(b) Dermal toxicity

Rabbits

In a briefly-reported study for which a GLP certificate was not supplied, temephos (purity, 94.7%) was applied as single doses at 1000, 2000 or 4000 mg/kg bw to the intact shaved skin of groups of five male and five female New Zealand White rabbits. The application site was covered with occlusive dressing for 24 h, and was then wiped with moistened gauze. The animals were observed for 14 days after treatment and body weights were measured weekly. All animals were killed for autopsy at the end of the observation period. Decreased activity and body-weight loss were reported at all doses and those rabbits at 200 mg/kg bw or more also had diarrhoea, prostration and anorexia. Autopsies showed gross pathology in the animals at the highest dose: blood in the abdominal cavity (7 out of 10 rabbits), haemorrhagic areas in the intestines (8 out of 10), and pale kidneys (7 out of 10). The LD_{50} was estimated to be 2000 mg/kg bw in males and 2378 mg/kg bw in females (combined results for both sexes, 2181 mg/kg bw) (Fischer, 1986).

Table 2. Oral and dermal median lethal doses of temephos

Species	Sex	Route	Batch of temephos	LD_{50} (mg/kg bw)	Reference
Mouse	Male (50/group)	Oral	A	4 700	Gaines et al. (1967)
Mouse	Female (5/group)	Oral	—	2 062	Fischer (1986)
Rat	Male (58/group)	Oral	A	8 600	Gaines et al. (1967)
Rat	Female (50/group)	Oral	A	13 000	Gaines et al. (1967)
Rat	Female (20/group)	Oral	B	4 000	Gaines et al. (1967)
Rat	Female (20/group)	Oral	C	4 000	Gaines et al. (1967)
Rat	Male (5/group)	Oral	—	4 240	Fischer (1986); Nielsson (1990)
Rat	Female (5/group)	Oral	—	> 10 000	Fischer (1986); Nielsson (1990)
Chickens	Not stated (4/group)	Oral	—	500	Fletcher & Leonard (1986)
Chickens	Female (3/group)	Oral	—	183	McNerney & Levinskas (1967)
Rat	Male (20/group)	Dermal	A	> 4 000	Gaines et al. (1967)
Rat	Female (20/group)	Dermal	A	> 4 000	Gaines et al. (1967)
Rabbit	Male (5/group)	Dermal	—	2 000	Fischer (1986)
Rabbit	Female (5/group)	Dermal	—	2 378	Fischer (1986)

LD_{50}, median lethal dose

(c) Inhalation

Rats

The acute toxicity of temephos administered by inhalation was examined in a GLP-compliant study in Sprague-Dawley rats. Groups of 10 male and 10 females were exposed to temephos (purity, 94.7%) at measured concentrations of 3.49, 4.20, 4.37, 4.73 or 4.79 mg/l in an exposure chamber for 4 h. The mass median aerodynamic diameter (MMAD) of the particles to which the groups were exposed ranged from 1.80 to 1.93 μm. The rats were observed for 14 days after exposure. On day 15, all surviving rats were killed for autopsy. There was no significant difference in the findings for the different groups. Body weights increased in all groups over the course of the study. Clinical signs included ruffled fur, hypersensitivity and slight tremors. The clinical signs generally appeared to be more severe in males than in females. Mortality varied between 0% and 30%. In decedent animals, autopsy findings included small spleen and haemorrhages in the thymus, lung and around the kidneys. In animals surviving to the end of the study, the most common finding was congested lungs. It was

concluded that temephos was of low acute inhalation toxicity with a median lethal concentration (LC_{50}) of > 4.79 mg/l (Hershman, 1986).

(d) Dermal irritation

Guinea-pigs

Male Hartley guinea-pigs were given temephos (purity, 94.7%) in a test for dermal irritancy as a screen before a test for dermal sensitization. Groups of one animal received temephos at concentrations of 25, 50, 75 and 100% (w/v) applied to the clipped skin for a contact period of 6 h. When the application sites were examined after 24 h and 48 h, there was no erythema or oedema at any of the application sites. In was concluded that temephos was not irritant to the skin of guinea-pigs (Costello, 1986).

Rabbits

The dermal irritation potential of temephos was investigated in six New Zealand White rabbits. Undiluted temephos (purity, 94.7%) was applied to shaved and to shaved and abraded areas of skin on the flanks of each rabbit. The test material was left for 24 h, after which the application sites were cleaned with moistened gauze. The application sites were examined at the end of the application period and at 72 h after dosing. No signs of irritation were seen at any of the abraded or unabraded sites on any animal at either examination time. It was concluded that temephos was not a skin irritant in this test (Fischer, 1986).

(e) Ocular irritation

Rabbits

The ocular irritation potential of temephos was investigated in six New Zealand White rabbits. Undiluted temephos (purity, 94.7%) was applied to the conjunctival sac of the right eye of each rabbit. The left eye was left untreated to act as a control. The test material was left for 24 h, after which the eyes were rinsed with tap water and examined for irritation. Further examinations were performed at 1, 24, 48 and 72 h after dosing. No signs of eye irritation were seen in any animal at any examination time. It was concluded that temephos was not an eye irritant in this test (Fischer, 1986).

(f) Dermal sensitization

In a modified Buehler test, guinea-pigs were allocated to a test group, a negative-control group or a positive-control group. Each group consisted of 11 animals. For the test group, 0.42 ml of undiluted temephos (purity, 94.7%) was applied to a gauze patch, which was placed on the clipped skin of each animal. The trunk of the animal was then wrapped in plastic and secured with an elastic bandage. After a contact period of 6 h, the patch was removed. The site of application was examined at 24 h and 48 h. This sequence was repeated three times per week during an induction phase, until nine applications had been made. After a rest period of 2 weeks, a challenge application of temephos was made to the clipped skin and left for 6 h, followed by observations at 24 h and 48 h. In the positive-control group, a suspension of 1-chloro-2,4-dinitrobenzene was used instead of temephos. In the negative-control group, the animals remained untreated during the induction stage and only received the challenge application of temephos. No erythema or oedema was seen in any animal in the test group or the negative-control group during the induction phase or after challenge. Ten out of eleven animals in the positive-control group showed erythema and/or oedema at the challenge application site. It was concluded that temephos showed no skin sensitizing potential in this test (Costello, 1986).

2.2 Short-term studies of toxicity

(a) Oral toxicity

Short-term studies of oral toxicity after repeated doses have been performed in rats and dogs given diets containing temephos. None of the studies were performed to the standards of GLP as they were all conducted before the introduction of GLP standards.

Rats

Groups of 45 male and 45 female Carworth Farms' Nelson strain rats were given diets containing temephos (purity, 96.4%) at a concentration of 2, 6, 18 or 350 ppm for 92 days. These dietary concentrations supplied doses of approximately 0.15, 0.46, 1.41 and 32 mg/kg bw per day, to males and 0.18, 0.54, 1.71 and 35.2 mg/kg bw per day to females. An untreated control group consisted of 65 males and 65 females. A non-standard protocol was used. Food consumption and body weight were measured weekly for 10 males and 10 females in each group. Rats were randomly chosen from the different groups for determination of cholinesterase activity in plasma, erythrocytes and brain. Seven rats of each sex from the control group and four rats of each sex from the groups at 2, 6 and 18 ppm were killed for testing after 1, 3, 5, 9 and 13 weeks, and four rats of each sex at 350 ppm were killed for cholinesterase estimation after 12 weeks. After 13 weeks, 10 rats of each sex selected from the groups at 2, 6 and 18 ppm, and 15 rats of each sex from the control groups were fed control diet for a further 2–4 weeks before testing for cholinesterase activity in plasma, erythrocytes and brain. All animals at 350 ppm were autopsied after 12 weeks of dosing. After 13 weeks, 15 rats of each sex from the remaining groups (including controls) were autopsied. Liver and kidney weights were recorded and a wide selection of tissues was preserved for microscopic examination.

The results showed no effect on feed intake, and body-weight gain was reduced only in females at the highest dose of 350 ppm. There was no treatment-related effect on mortality. At 350 ppm, there was marked inhibition of cholinesterase activity in plasma, erythrocytes and brain in both sexes. At 18 ppm, cholinesterase activity was inhibited in erythrocytes and brain at most time-points throughout the study, with inhibition of erythrocyte cholinesterase activity being greater than 20% after 5 weeks in males and after 3 weeks in females. At 6 ppm, only erythrocyte cholinesterase was inhibited: in males at weeks 9 and 13, and in females at week 13 only. Inhibition in males was less than 20% and was not regarded as toxicologically significant. The 27% inhibition in females at 6 ppm at 12/13 weeks was regarded as an isolated finding and it was considered that there was no consistent adverse effect at this dose. At 2 ppm, there was slight inhibition (9%) of erythrocyte cholinesterase activity only at week 13 in females. After a 4-week recovery period, the cholinesterase activities in the treated groups were no different from those of the controls. The results for effects on erythrocyte cholinesterase activity are summarized in Table 3. Liver weights were statistically significantly lower than control values in males at 2 ppm and 350 ppm and in females at 18 ppm. Kidney weights were unaffected. Microscopic examination of tissues from rats at 350 ppm showed no treatment-related pathology. Tissues from groups given lower doses were not examined microscopically. Less than 20% inhibition of acetylcholinesterase activity was not regarded as being toxicologically significant. The no-observed-adverse-effect level (NOAEL) for the study was 6 ppm (1.41 mg/kg bw per day in males and 1.71 mg/kg bw per day in females) on the basis of consistent inhibition of erythrocyte acetylcholinesterase activity by 20% or more (Levinskas & Shaffer, 1965).

Table 3. Effects on mean erythrocyte cholinesterase activity in rats fed diets containing temephos

Dietary concentration (ppm)	Corrected ΔpH/h per 0.04 ml packed erythrocytes (percentage inhibition compared with value for concurrent control)						
	Treatment period					Recovery period	
	Week 1	Week 3	Week 5	Week 9	Week 12/13	Week +2	Week +4
Males							
0	0.494	0.473	0.446	0.450	0.507	0.579	0.519
2	0.468	0.445	0.458	0.433	0.458	0.565	0.542
6	0.505	0.452	0.442	0.378* (16%)	0.423* (17%)	0.548	0.505
18	0.422* (15%)	0.385* (19%)	0.342* (23%)	0.343* (24%)	0.323* (36%)	0.470* (19%)	0.475
350	—	—	—	—	0.040* (92%)	—	—
Females							
0	0.484	0.501	0.396	0.471	0.666	—	0.569
2	0.473	0.475	0.435	0.438	0.540* (9%)	—	0.562
6	0.468	0.440	0.365	0.433	0.483* (27%)	—	0.542
18	0.430	0.382* (24%)	0.338	0.375* (20%)	0.435* (35%)	—	0.515
350	—	—	—	—	—	—	—

From Levinskas & Shaffer (1965)

* $p < 0.05$ (differs significantly from control values)

In a second feeding study in rats, groups of 20 male and 20 female Carworth Farms' Nelson strain rats were given diets containing temephos (purity, 87.1%) at a concentration of 6, 18 or 54 ppm for up to 90 days (corresponding to doses of approximately 0.26, 0.78 and 2.35 mg/kg bw per day). A control group of 32 male and 32 female rats was given diets without temephos. Limited haematology (erythrocyte volume fraction, haemoglobin, total leukocyte count and differential leukocyte count) was performed on seven males and seven females sexing the control group and five males and five females from each treatment group before the start of treatment and after 11 (males) or 12 weeks (females). Samples were taken from seven males and seven females in the control group and five males and five females from each treatment group after 4, 8 and 13 weeks of treatment and after a recovery period of 2 weeks, for measurement of cholinesterase activity in plasma, erythrocytes and brain. No measurements were made of body weight, feed intake, organ weights, gross or microscopic pathology.

The only effect revealed by haematology was a slight increase in lymphocyte counts in males at 18 ppm, but this was not thought to be caused by the treatment. The results for cholinesterase activities in the erythrocytes and the brain are summarized in Tables 4 and 5. Both sets of results show a dose-related inhibition at dietary concentrations of 18 and 54 ppm at various times, and no statistically significant effect at 6 ppm. The 2-week recovery period was of insufficient duration to allow recovery of cholinesterase activities. For plasma cholinesterase, the dose–response relationship was less clear, with some occasions when cholinesterase was significantly inhibited at 6 ppm, so a

no-observed-effect level (NOEL) for inhibition of plasma cholinesterase activity could not be identified. Statistically significant inhibitions of erythrocyte and brain acetylcholinesterase were seen at 18 ppm, but inhibition was less than 20% (the cut-off for toxicological significance that is used by the Joint Meeting) in all cases but one (males at 4 weeks), which was regarded as an outlier result.

The NOAEL for consistent adverse effects on erythrocyte acetylcholinesterase activity was 18 ppm (0.78 mg/kg bw per day), while for brain acetylcholinesterase activity it was the highest dose tested, 54 ppm (2.35 mg/kg bw per day) (Hutchinson, et al., 1966).

Table 4. Effects on mean erythrocyte cholinesterase activity in rats fed diets containing temephos

Dietary concentration (ppm)	Corrected ΔpH/h per 0.04 ml packed erythrocytes (percentage inhibition compared with value for concurrent control)			
	Treatment period			Recovery period
	Week 4	Week 8	Week 13	Week +2
Males				
0	0.471	0.411	0.486	0.389
6	0.465	0.360	0.482	0.370
18	0.358* (24%)	0.340* (17%)	0.400* (18%)	0.405
54	0.248* (44%)	0.220* (46%)	0.220* (55%)	0.260* (33%)
Females				
0	0.404	0.476	0.511	0.493
6	0.418	0.420	0.510	0.478
18	0.350* (13%)	0.402* (16%)	0.458	0.480
54	0.290* (28%)	0.315* (34%)	0.395* (23%)	0.438

From Hutchinson et al. (1966)
* $p < 0.05$ (differs significantly from control values)

Table 5. Effects on mean brain cholinesterase activity in rats fed diets containing temephos

Dietary concentration (ppm)	Corrected ΔpH/h per 2.0 ml homogenate (percentage inhibition compared with value for concurrent control)			
	Treatment period			Recovery period
	Week 4	Week 8	Week 13	Week +2
Males				
0	1.239	1.336	1.229	1.191
6	1.222	1.290	1.205	1.150
18	1.092	1.190	1.078* (12%)	1.048* (12%)
54	1.242	1.105* (17%)	1.023* (18%)	1.015* (12%)

Females				
0	1.091	1.224	1.324	1.394
6	1.070	1.200	1.320	1.358
18	1.020	1.140	1.250	1.255* (10%)
54	1.015	1.048*	1.265 (10%)	1.242* (11%)

From Hutchinson et al. (1966)
* $p < 0.05$ (differs significantly from control values)

A series of experiments that did not comply with GLP, in which male Sherman-strain rats were given temephos of unstated purity in the diet or by oral gavage in peanut oil, were briefly reported.

In the experiment in which temephos was administered by oral gavage, groups of eight rats were given temephos at a dose of 0, 1, 10 or 100 mg/kg bw per day for up to 28 days, and groups of seven rats were given temephos at a daily oral dose of 0, 1, 10 or 100 mg/kg bw for up to 44 days. No adverse effects were reported for the group at 1 mg/kg bw per day. Rats receiving temephos at 10 mg/kg bw per day showed a 31% inhibition in erythrocyte cholinesterase activity after 14 days and a 47% inhibition after 44 days. None of these animals displayed signs of organophosphate poisoning. At 100 mg/kg bw per day, the rats showed signs that were reported to be "typical of organic phosphate poisoning" after three daily doses, at which time their erythrocyte cholinesterase activity was inhibited by 64%. As dosing progressed, the group at 100 mg/kg bw per day showed some recovery in the severity of their signs of toxicity, although inhibition of erythrocyte cholinesterase activity rose to 87% after 11 days of dosing. At this point in the experiment, dosing was stopped for an unspecified number of animals from this group and they were allowed a recovery period of 32 days. At the end of the recovery period, erythrocyte cholinesterase activity was inhibited by 27%, compared with controls. Findings from gross pathology and histopathology on rats from all groups showed no treatment-related effects. The NOAEL for this experiment was 1 mg/kg bw per day, with toxicologically significant inhibition (i.e. > 20%) of erythrocyte cholinesterase activity at 10 mg/kg bw per day or more.

In the dietary dosing experiment, groups of 10–14 rats were given diets containing temephos at a concentration of 0, 2, 20, 200 or 2000 ppm for 99 days. The doses received by the groups of rats over the course of the experiment were calculated to be approximately 0 mg/kg bw per day (untreated controls), 0.12 to 0.24 mg/kg bw per day (2 ppm), 1.2–2.4 mg/kg bw per day (20 ppm), 11–24 mg/kg bw per day (200 ppm) and 150 mg/kg bw per day (2000 ppm). All the rats in the group at 2000 ppm showed signs of organophosphate poisoning and 8 out of the 10 rats in the group died between days 5 and 10, having 100% inhibition of erythrocyte cholinesterase activity. The two remaining rats in this group survived until the end of the 99-day study, despite having a reported 100% and 80% inhibition of erythrocyte and plasma cholinesterase activities, respectively. Rats at 200 ppm or less did not show signs of cholinesterase poisoning. At 200 ppm, the rats showed a progressive inhibition of erythrocyte cholinesterase activity that was almost complete by day 14, but gradually reduced to 71% by day 99. No significant inhibition of cholinesterase activity (not stated whether this refers to erythrocyte or plasma activity or both) occurred at 2 or 20 ppm (equal to mean doses of 0.18 and 1.8 mg/kg bw per day respectively). Findings from gross pathology and histopathology on rats from all groups showed no treatment-related effects. The NOAEL was 20 ppm (equivalent to an average dose of 1.8 mg/kg bw per day or a range of doses of 1.2 to 2.4 mg/kg bw per day), with inhibition of erythrocyte cholinesterase activity at 200 ppm (equal to 11–24 mg/kg bw per day) or more.

The authors reported that temephos was slightly less toxic when given in the diet than when given by gavage. However, there was a greater degree of inhibition of erythrocyte cholinesterase activity (> 71%) seen at 200 ppm (11–24 mg/kg bw per day) in the dietary study than in the gavage

study (31–47%) at 10 mg/kg bw per day. The small differences in the NOAELs for the different ways of administering temephos orally can be explained by dose spacing and do not necessarily reflect a difference in toxicity (Gaines et al., 1967).

Rabbits

In one of a series of briefly reported experiments that did not comply with GLP, groups of four weanling male white rabbits (strain not stated) were given temephos (batch A; purity not stated) at a daily oral gavage doses of 0.1, 1.0 or 10 mg/kg bw for up to 35 days. It was not clear whether a control group had been used. None of the animals developed clinical signs of poisoning. After 7 days of treatment, the rabbits at 10 mg/kg bw per day showed a 26% inhibition of erythrocyte cholinesterase activity when compared with values for concurrent controls. At the end of 35 days, the degree of inhibition had risen to 47%. No treatment-related pathology was seen at autopsy. The NOAEL was 1.0 mg/kg bw per day on the basis of inhibition of erythrocyte cholinesterase activity at 10 mg/kg bw per day (Gaines et al., 1967).

In further experiments, groups of three to four rabbits were given temephos from one of three different batches (batches A, B and C, as fed to rats in a separate experiment described previously) at a daily oral dose of 10 mg/kg bw for 30 days by gavage, while groups of 4–12 rabbits were given a daily oral dose of 100 mg/kg bw per day by gavage for 5 days. The results for the different batches of temephos were similar. A dose of 10 mg/kg bw per day for 30 days caused "mild changes in liver pathology" in one out of three rabbits given temephos of batch A, one out of four given batch B and two out of three given batch C. While a dose of 100 mg/kg bw per day caused death in about one third of the animals (batch A, 4 out of 12; batch B, 1 out of 4; batch C, 1 out of 4) and in several animals caused focal necrosis (batch A, 6 out of 12; batch B, 1 out of 4; and batch C, 0 out of 4) or diffuse necrosis (batch A, 2 out of 12; batch B, 1 out of 4; and Batch C, 1 out of 4) of the liver. It was not clear whether the descriptions of liver changes were based on histopathological examination or solely on observations at autopsy. The lowest-observed-adverse-effect level (LOAEL) for this experiment was 10 mg/kg bw per day, with mild hepatotoxicity seen in some animals at this dose (Gaines et al., 1967).

Dogs

In a 90-day study, groups of beagle dogs were given diets containing temephos (purity, 96.4%) at a concentration of 0, 2, 6, 18 or 700/500 ppm (equivalent to approximately 0, 0.1, 0.3, 0.9 and 35/25 mg/kg bw per day). Each group consisted of two male and two female dogs, except for the group at 18 ppm which consisted of one male and three females. The highest dose was 700 ppm (17.5 mg/kg bw per day), which was given for the first 15 days, after which the dose was reduced to 500 ppm (12.5 mg/kg bw per day), until the end of week 12, when dogs receiving the highest dose were killed for necropsy. After 13 weeks of treatment with temephos at 0, 2, 6 or 18 ppm, the dogs were fed untreated diet for a 2-week recovery period. Dogs were weighed at approximately weekly intervals and physical examinations were carried out at 1–2 month intervals. Cholinesterase activity was measured in plasma and erythrocytes taken before treatment and after 1, 3, 5, 9 and 12/13 weeks of treatment (12 weeks for the group at the highest dose; 13 weeks for other groups) and at the end of the 2-week recovery period. Weights of liver, heart, kidneys and testes were measured in dogs in the group receiving the highest dose that underwent necropsy, brain cholinesterase activity was measured and a wide range of organs were examined microscopically.

No mortality occurred at any dose. The group at the highest dose showed cholinergic signs during the initial 2 weeks during which they were given temephos at 700 ppm, and showed lesser cholinergic signs during the rest of the study when they received temephos at the lower dietary concentration of 500 ppm. There was no treatment-related effect on body-weight gain. There was no significant inhibition of plasma or erythrocyte cholinesterase activities at dietary concentrations

of up to 18 ppm. In the group at the highest dose, there were inhibitions of plasma and erythrocyte cholinesterase (> 95%) at week 1 when they were fed temephos at 700 ppm and at subsequent weeks when they received temephos at 500 ppm. Marked inhibition of brain cholinesterase activity was also reported as occurring in the group at the highest dose, but control values were not given. Necropsies and microscopic examinations of the animals receiving the highest dose showed no treatment-related pathology. The NOAEL was 18 ppm, equivalent to 0.9 mg/kg bw per day, on the basis of inhibition of brain and erythrocyte activity at the highest dose, 700/500 ppm (35/25 mg/kg bw per day) (Hutchinson & Levinska, 1965).

In a briefly-reported study that did not comply with GLP, groups of one male and one female adult dogs (breed not stated) were given temephos (purity not stated) at a concentration of 10 or 50 ppm (equivalent to 0.6–0.8 or 3–4 mg/kg bw per day) for 129 days. None of the dogs showed clinical signs of toxicity. In the male given temephos at 50 ppm, erythrocyte cholinesterase activity fell to 67% of normal values (33% inhibition) in the first week and 22% of normal values (78% inhibition) by the end of the experiment. In the female given temephos at 50 ppm, erythrocyte cholinesterase activity remained normal until day 60, but fell to 50% of normal values (50% inhibition) on day 90 and remained similarly low until the end of the experiment. In the dogs at 10 ppm, erythrocyte cholinesterase activity was normal throughout the study. Plasma cholinesterase activity remained normal throughout the study in both groups. The NOAEL was 10 ppm, equal to 0.6–0.8 mg/kg bw per day, on the basis of inhibition of erythrocyte cholinesterase activity at 50 ppm, equal to 3–4 mg/kg bw per day (Gaines et al., 1967).

(b) Dermal toxicity

Rabbits

In a 21-day study that complied with GLP, undiluted temephos (purity, 93.1%) was administered to the clipped skin of groups of 12 male and 12 female New Zealand White rabbits (half of which had abraded skin) for 6 h/day (with site of exposure wrapped), 5 days/week for 3 weeks at volumes to achieve doses of 9, 25, 50 and 100/75 mg/kg bw. The group at the highest dose received 100 mg/kg bw for the first 2 weeks and 75 mg/kg bw for the last week. After the treatment period, all of the animals at the highest dose and six animals (three with abraded skin and three with non-abraded) of each sex from each of the other groups were kept for a 14-day observation period before being killed. The other animals were killed at the end of the treatment period. Dermal reactions and clinical condition were recorded daily. Body weights and feed consumption were recorded weekly. Blood samples for haematology and clinical chemistry (including plasma cholinesterase activity) were taken before treatment, on day 21 and at termination. Necropsies were performed on all animals. Selected organs were weighed, brain cholinesterase activity was measured and a wide range of tissues was taken for microscopic examination.

There was a high rate of treatment-related clinical signs and mortality at doses of 50 mg/kg bw or greater. Body-weight gains were also reduced at these doses. There were signs of dermal irritation in all treated groups, with a dose-related severity. Erythrocyte count, haematocrit (erythrocyte volume fraction) and haemoglobin were decreased at 50 mg/kg bw or greater. Albumin and total protein were decreased at the top dose only. Plasma cholinesterase was inhibited at all doses. Brain cholinesterase was inhibited at doses of 50 mg/kg bw or greater. Plasma and brain cholinesterase activities had returned to normal after, respectively, 10 days and 14 days recovery. There were no treatment-related effects on organ weights, gross pathology or histopathology. As plasma cholinesterase activity was inhibited at all doses, no NOEL was identified in this study. However, the NOAEL was 25 mg/kg bw on the basis of effects on haematology and brain cholinesterase activity that were seen at 50 mg/kg bw or greater (Thompson & Rao, 1981).

2.3 Long-term studies of toxicity and carcinogenicity

Rats

A non-GLP combined study of the long-term oral toxicity and carcinogenicity of temephos (purity, 93.5%) was performed with Sprague-Dawley rats. The study incorporated an in-utero phase of exposure. Dosing with diets containing temephos at 100 ppm began on day 12 of pregnancy. At weaning, the offspring were randomly divided into three groups of 60 males and 60 females that were given diets containing temephos at 10, 100 or 300 ppm for 24 months. These dietary concentrations were equivalent to doses of approximately 0.5, 5 and 15 mg/kg bw per day. An additional group of 60 male and 60 female rats from the same supplier received no temephos in utero or in life and were used as controls. Feed intake and body weights were measured weekly during the first 3 months, and during weeks 25, 53, 79, and 104. Urine analysis and haematology were conducted on five males and five females from each treatment group at 6 weeks, 3 months, 6 months and at the conclusion of the study. Blood clinical chemistry was performed on five rats of each sex from each group at the end of the study only. All rats were autopsied, selected organs were weighed and a wide range of organs were examined microscopically. There were no treatment-related effects on survival, body-weight gain, haematology, urine analysis, clinical chemistry, gross pathology, organ weights or histopathology. The treatment did not cause an increase in the incidence of any tumour type. The NOAEL was 300 ppm, equivalent to 15 mg/kg bw per day, the highest dose used (Tegeris, 1977; Shaffer, 1978).

2.4 Genotoxicity

Temephos has been tested for genotoxicity in vitro in several assays, which are summarized in Table 6. Certificates of compliance with GLP were supplied with most of the reports (Allen, 1986, Traul, 1988, Thilagar, 1986 and Barfknecht, 1986), but Brusick (1976) was performed before the requirement to comply with GLP. All except one of the tests was performed using the same batch of temephos (lot No. AC 5105-43; purity, 94.7%). All the assays (apart from the study using a primary culture of hepatocytes, which did not require an external metabolizing system) were performed in the presence and absence of metabolic activation from S9 mix from the livers of rats that had been treated with Araclor 1254. All of the tests gave negative results for genotoxicity in vitro. No studies of genotoxicity in vivo were available.

Table 6. Results of studies of genotoxicity with temephos in vitro

End-point	Test object	Concentration	Purity (%)	Result	Reference
Reverse mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 and *Escherichia coli* WP2 *uvrA*-	Up to 5000 µg/plate	94.5	Negative[a]	Allen (1986)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100 and *Saccharomyces cerevisiae* D4	Up to 100 µg/plate	90	Negative[a]	Brusick (1976)
HGPRT gene mutation	CHO K[1] BH[4] cells	Up to 5000 µg/ml	94.5	Negative[a]	Traul (1988)

Chromosomal aberration	CHO K-I cells (ATCC No CCL 61) with harvest times at 10 h and 20 h	Up to 7.5 µg/ml	94.5	Negative[a]	Thilagar (1986)
DNA repair (unscheduled DNA synthesis)	Rat primary hepatocytes	Up to 5000 µg/ml	94.5	Negative	Barfknecht (1986)

[a] In the presence and absence of S9 mix (9000 × *g* supernatant fraction from liver of rats treated with Araclor 1254).

2.5 Reproductive toxicity

(a) Multigeneration studies

Rats

A non-standard non-GLP one-generation study of the effects of temephos on reproduction was performed in Sherman-strain rats. A brief report of the study stated that groups of rats were given diets containing temephos (purity, 90%) at a concentration of 0 or 500 ppm, equivalent to pure temephos at a dose of 22.5 mg/kg bw per day. Fifteen litters were produced from 15 matings of the group given temephos. There were no treatment-related effects on litter size, viability of young or incidence of congenital defects. After 48 days of dosing with temephos, the mothers' mean erythrocyte cholinesterase activity was inhibited by 90% when compared with that of the untreated controls. Erythrocyte cholinesterase was inhibited by 30% in the pup aged 21 days in the treated group (Gaines et al., 1967).

A three-generation study of reproductive toxicity with temephos was performed in CFE Albino rats. The protocol did not comply with GLP, nor did it conform to modern standards. For the F_0 generation, groups of 24 females and 12 males were fed diets containing temephos (purity 87.1%) at a concentration of 0, 25 or 125 ppm for 8 weeks before mating and during 10 days of mating. The doses were equivalent to 0, 1.1 and 5.4 mg/kg bw per day of pure temephos. The pups of each subsequent generation were weaned directly onto the same diets as their parents. For the F_1 and F_2 generations, 16 pairs (one male and one female) were chosen for each dose and mated when aged 14–17 weeks (F_1 generation), 16–20 weeks (first mating of F_2 generation) or 31–36 weeks (second mating of F_2 generation). Body weights were measured only until the first mating of each generation and food consumption was measured only for parents in the F_0 and F_1 generations and these data were not examined statistically. Any effects on the mating and/or reproductive performance of the parent animals were reported. Pups were sexed and evaluated for health and viability. Gross pathological examinations were performed on all parents and offspring. More detailed examination was performed only on the first litter of offspring of the F_2 parents (i.e. pups of the F_{3i} generation), with the two weakest pups from each litter being set aside at age 21 days, one being examined microscopically for visceral defects and histopathology and the other being examined for skeletal defects.

Treatment with temephos had no adverse effect on reproduction or lactation in any of the generations studied. Litter size, fertility index, gestation index, lactation index and the gross appearance of the pups were not affected by treatment. Mean pup weights were generally higher than values for concurrent controls for the group at 25 ppm and lower than controls for the group at 125 ppm, but the effects were slight and were not considered to be treatment-related. No treatment-related effects on visceral or skeletal abnormalities were observed. Microscopic examination of pups of the F_{3i} generation showed a high incidence of pups having a large amount of splenic extramedullary haemopoiesis in the control group and in the group at 125 ppm, but this was not regarded as a

treatment-related effect. The NOAEL for reproductive effects was the highest dose used, 125 ppm, equivalent to 5.4 mg/kg bw per day (McNerney et al., 1968).

(b) Developmental toxicity

Rabbits

In a study of developmental toxicity, which did not comply with GLP, groups of 15–16 pregnant New Zealand White rabbits were given technical-grade temephos (purity, 90.4%) at a dose of 3, 10, or 30 mg/kg bw per day by oral gavage during days 6–18 of gestation. A control group of 21 pregnant rabbits was not given temephos. On day 29 of gestation, the pregnant rabbits were killed and autopsied. Brain, liver and kidneys were weighed and preserved for possible future examination. The uterine contents were examined for implantation sites, live and dead fetuses and resorption sites. The uterus and ovaries were preserved for possible future examination. The fetuses were examined for external abnormalities, weighed and measured (crown to rump length). Autopsies were performed to examine the thoracic and abdominal viscera of the fetuses. The fetuses were then skinned and prepared for skeletal examination.

During the course of the study, five adults in the control group and one in the group at 3 mg/kg bw per day died of causes unrelated to the oral toxicity of temephos (mostly intubation accidents). There were no treatment-related effects on the body-weight gain or absolute organ weights of the adults, but kidney weight relative to body weight in the group at 30 mg/kg bw per day was significantly lower than the control value. The tissues were not examined microscopically, so it was not possible to tell if the effect on relative kidney weight was associated with any histopathology. Examination of the uterine contents revealed no treatment-related adverse effects. The treatment had no effect on the type or number of abnormalities of the soft tissues or skeleton. It was concluded that doses of up to 30 mg/kg bw per day did not produce embryotoxicity, fetotoxicity or teratogenicity in rabbits. The NOAEL was 10 mg/kg bw per day on the basis of reduced relative kidney weight seen in pregnant adults at 30 mg/kg bw per day. The NOEL for developmental toxicity was the highest dose administered, 30 mg/kg bw per day (Beliles & Makris, 1978).

2.6 Special studies: neurotoxicity in hens

The potential of temephos to cause delayed neurotoxicity in mature White Leghorn chickens was investigated in a study that complied with GLP. Ninety chickens (sex not stated) were given intramuscular injections of atropine sulfate at a dose of 10 mg/kg bw. The birds were then divided into three groups: test group, 60 birds; treated control group, 15 birds; and positive control group, 15 birds. One hour after the initial injection of atropine and again 21 days later, the test birds were each given temephos (purity not reported) at an oral dose of 550 mg/kg bw and the birds in the positive-control group were given tri-ortho-tolyl phosphate (TOTP) at an oral dose of 500 mg/kg bw. Further antidote doses of atropine at 30 mg/kg bw were given 1.5, 2.5, 4, 5 and 6.5 h after the first dose and a similar dosing regime of atropine was given before and after the second dose. The birds were observed daily for mortality and neurotoxicological signs for 21 days after each dose. All birds that died during the study were necropsied and at the end of the study the survivors were killed for necropsy, with particular attention being paid to examination of the nervous system. Numerous sections of the brain, the spinal cord and the sciatic nerves were examined microscopically, using standard haematoxylin-eosin staining and Luxol Fast Blue staining for myelin.

Twenty-one of the 60 birds in the test group died during the first 21 days of the study. After the second dose of temephos, 5 out of 32 birds died. Signs of toxicity included severe lethargy, hypersalivation, ataxia and anorexia. Most of the survivors recovered by day 8 after dosing and all appeared well by 21 days after each dose. There were no clinical signs of delayed neurotoxicity in any

of the birds treated with temephos. Microscopic examination of central and peripheral nerve tissues revealed no treatment-related lesions. It was concluded that temephos at a oral doses of 550 mg/kg bw caused no neurotoxicity or delayed toxicity (Fletcher & Leonard, 1986).

In a study to investigate the potential of temephos to cause neurotoxicity, which did not comply with GLP, groups of six adult hens (breed not stated) were given temephos (purity, 99.9%) as a single oral doses at 0 (untreated controls), 227, 455, 823, 1137, 1422 or 1705 mg/kg bw by gavage. A positive-control group was given TOCP at a dose of 450 mg/kg bw. The animals were observed over 21 days. On day 21, the surviving birds in the groups at 227 and 455 mg/kg bw were given a second dose of temephos at 227 or 455 mg/kg bw, after being protected with pyridine-2-aldoxime methane sulfonate (PAM) at a dose of 43 mg/kg bw and atropine at 6.5 mg/kg bw. An additional group, also pre-treated with PAM and atropine, were given a single dose of temephos at 433 mg/kg bw. This group and the groups receiving a second dose were observed for a further 21 days. The hens were observed for signs of neurotoxicity six times per day and for other clinical signs on a daily basis. All birds were killed at the end of the observation periods, but histopathological examinations were performed on only three hens from the positive-control group and three hens from the group given two doses of temephos at 455 mg/kg bw.

Mortality in the group at 227 mg/kg bw was no greater than in the untreated control group. The single-dose oral LD_{50} calculated from the results for mortality in this study was 579 mg/kg bw. There was no treatment-related effect on body-weight gain. Most (five out of six) of the birds in the positive-control group became ataxic, but none of those given temephos became ataxic. While birds given temephos became lethargic and some exhibited tremors, surviving birds recovered within 72 h of dosing and no further signs of toxicity were seen. The microscopic examination of tissues from the birds given temephos at 455 mg/kg bw showed no abnormalities, but birds in the positive-controls group had histopathological lesions in the mid-brain, spinal cord, peripheral nerve, lungs and skeletal muscle.

The Meeting concluded that single oral doses of temephos at up to 1705 mg/kg bw or two oral doses at up to 455 mg/kg bw did not produce neuropathy in hens (Ross et al., 1976).

In a study of the potential of temephos to cause demyelination, which did not comply with GLP, groups of eight adult White Leghorn hens were given diets containing temephos (purity, 87.1%) at a concentration of 230, 460 or 920 ppm (approximately equivalent to 11, 23 and 46 mg/kg bw per day). A negative-control group of six hens received diet containing no temephos and a positive-control group of six hens received TOCP at 4000 ppm. After 30 days, four hens from the group at 920 ppm and two from each control group were killed for autopsy, with samples of brain, thoracic spinal cord and sciatic nerve being taken for microscopic examination (stained with osmic acid to highlight myelin). The remaining birds were then given basal diet for recovery periods of 1 week (groups at 230 and 460 ppm) or 4 weeks (group at 920 ppm), but were not autopsied.

Treatment with temephos caused no deaths, but four of the birds in the positive-control group died. During the treatment period, there was significant body-weight loss in birds fed temephos and in the positive-control group, and there was some recovery of body weight when treatment was ceased for 1–4 weeks. Feed intake was not measured, but it was noted that birds treated with temephos and birds in the positive-control group generally ate less diet during the treatment period than did birds in the negative-control group. The hens given temephos at 920 ppm had diarrhoea for the first 2 weeks of the study, but the temephos-treated birds otherwise appeared in good health throughout the study. In contrast, birds in the positive-control group suffered muscle weakness and/or paralysis from 2 weeks until termination. Microscopic examination of the sampled nervous tissues did not find any myelin loss in birds in the negative-control group or in those given temephos at 920 ppm for 30 days. Microscopic findings were not presented for the birds given temephos at 230 or 460 ppm. The two birds in the positive-control group that were examined showed myelin loss and/or myelin damage in the brain, thoracic spinal cord and sciatic nerve.

The Meeting concluded temephos at dietary concentrations of up to 920 ppm (46 mg/kg bw per day) for 30 days did not cause demyelination of nerves of hens (McNerney & Levinskas, 1967).

3. Observations in humans

3.1 Studies in volunteers

Temephos was given orally to human volunteers in two experiments designed to determine the dosage needed to produce depression of cholinesterase activity in plasma and in erythrocytes. Twenty-eight healthy male volunteers (aged between 22 and 44 years) were selected from a Puerto Rican prison. For the first week of the study, all the men were given daily doses of milk containing no added temephos; during this week, three blood samples were taken for measurement of baseline activities of cholinesterase in plasma and in erythrocytes. At the end of the first week, 20 of the men were randomly assigned to two groups of 10 men for the first experiment. One group received daily glasses of milk containing technical-grade temephos of unreported purity and the other group received milk containing no temephos and served as a control group. The dosage of temephos was initially 2 mg/person per day and was doubled every 3–4 days for 4 weeks, when the dose reached 256 mg/person per day (given for 5 days). Dosing with temephos ceased after 4 weeks and the men were observed for a further 3 weeks, during which they received no temephos. Blood samples were taken three times per week for measurement of plasma and erythrocyte cholinesterase activity. Urine was collected while the men received the highest dosage and during the 3 weeks after the treatment period; measurements of ether-extractable organic phosphorus were made from the urine. The high concentrations of temephos in the milk given to the experimental group in the final week of the treatment period were sufficiently high to flavour the milk, so that the volunteers became aware of whether they were in the control or test group. One man felt nauseous, but apart from this there were no treatment-related adverse reactions. Activities of cholinesterase in the plasma and erythrocytes of the treated group were no different from the values for the control group. The mean concentration of ether-extractable organic phosphorus was 1.15 ppm of temephos equivalents at the end of the treatment period.

In the second experiment of the study, a control group of nine men and an experimental group of nine men were chosen. None of the men in the experimental group had previously received temephos. The control group was given milk containing no temephos and the experimental group was given milk containing temephos at a dose of 64 mg/person per day for 4 weeks. During the treatment period, blood samples were taken twice per week and an additional sample was taken 5 days after the last dose. Urine samples were collected during weeks 1, 3 and 4 of dosing and for 3 weeks after the last dose. Cholinesterase activity was measured in plasma and erythrocytes and ether-extractable organic phosphorus was measured in the urine samples. One man developed a transitory fever, with coryza and myalgia, which disappeared after 3 days, and 4 other men briefly suffered headache and coryza. The affected men came from the control group as well as the treated group, with no clear effect of treatment being evident. At no time during the experiment were there any significant effects on cholinesterase activities in plasma and erythrocytes. Mean urinary ether-extractable organic phosphorus rose to 1.8 ppm of temephos equivalents in the treated group at 21 days and then went down to 1.25 ppm at 28 days.

The Meeting concluded that the volunteers tolerated of temephos at a dose of 256 mg/person per day (4.27 mg/kg bw per day for a 60-kg person) for 3–4 days (preceded by progressively escalating doses before this) or a dose of 64 mg/person per day (1.1 mg/kg bw per day) for 4 weeks (Laws et al., 1967).

3.2 Field studies

A 19-month study of a village community of approximately 2000 people was conducted. Temephos was added to all cisterns and other potable water available to the community. The treatment occurred once per month and consisted of 1% temephos adsorbed to sand in sufficient quantity to achieve a calculated

concentration of 1 ppm. Only one sample ever contained temephos at a concentration of greater than 0.5 ppm. This was attributed to the combined effects of adsorption, solubility and dilution over time. No significant change was measured in either plasma or erythrocyte cholinesterase activities of the villagers at any time during the study. Urinary excretion of temephos reached a steady state after 4 months. No illness attributable to the insecticide occurred and all eight babies born were normal (Laws et al., 1968).

A 2% formulation of temephos in pyrax powder was applied to participants and their bedding from a shaker (57 g, equivalent to 1.1 g of temephos) or to clothed subjects from a powder duster (31 g, equivalent to 0.62 g of temephos). The treatment was reported to be safe and effective (Steinberg et al., 1972).

3.3 Health monitoring of workers

No data were available.

Comments

Biochemical aspects

When given to rats as an oral dose, temephos was rapidly absorbed. At least 40% of the administered dose was absorbed into the blood plasma. Clearance was rapid (mostly within 48 h), with about 40% of an orally administered dose being excreted in the urine and about 60% recovered in the faeces. Very little of the orally administered dose remained in tissues, but most (about 3% of the administered material) was in adipose tissue.

Metabolism in rats is by *S*-oxidation to form the primary toxicant, temephos sulfoxide, and by carboxylesterase-mediated hydrolysis to form 4,4'-thiodiphenol. Temephos and these primary metabolites can undergo secondary metabolism by glucuronidation or sulfation to form conjugates.

Toxicological data

Temephos was of low acute oral toxicity in rats (LD_{50}, 4000–13000 mg/kg bw) and the mouse (LD_{50}, 2062 mg/kg bw).

Temephos did not cause irritancy to rabbits' eyes or to the skin of rabbits or guinea-pigs. It was not a skin sensitizer when tested on guinea-pigs in the Buehler test.

In short-term studies with temephos administered in the diet or by gavage in rats (28–92 days), rabbits (30–35 days) and dogs (90–129 days), acetylcholinesterase activity in erythrocytes and, in some instances, in the brain was measured and animals were observed for clinical signs. The overall NOAEL for clinical signs was 10 mg/kg bw per day as derived from a study in rats treated by gavage for 28- and 44-days and from a study in rabbits treated by gavage for 35 days. This NOAEL is supported by the absence of clinical signs at 5.4 and 30 mg/kg bw per day, the highest doses tested, in the multigeneration study in rats and in a study of developmental toxicity in rabbits treated by gavage, respectively. Additional support is provided by the presence of mild signs in dogs given diets containing temephos at a concentration of 500 ppm for about 11 weeks, approximately equivalent to 25 mg/kg bw per day. The NOAEL for biologically significant (i.e. 20% greater than control values) inhibition of brain acetylcholinesterase activity was 54 ppm (2.3 mg/kg bw per day) in a 90-day dietary study in rats. In a 90-day dietary study in dogs, "marked" inhibition (no control values provided) in brain and > 95% inhibition of erythrocyte acetylcholinesterase activity were reported after treatment at 500 ppm (25 mg/kg bw per day), and there was no inhibition of erythrocyte acetylcholinesterase activity at 18 ppm (about 1 mg/kg bw per day). The overall NOAEL for biologically significant (i.e. 20% greater than control values) inhibition of erythrocyte acetylcholinesterase activity was 1.8 mg/kg

bw per day in a 99-day dietary study in rats. Occasional and inconsistent reductions of erythrocyte acetylcholinesterase activity observed at lower doses in some studies in rats were not considered to be significant. The Meeting noted that between 80% and more than 90% inhibition of erythrocyte acetylcholinesterase activity was not associated with clinical signs of cholinergic toxicity in a 99-day dietary study in rats or in a limited 129-day dietary study in dogs, and this suggested that inhibition of erythrocyte acetylcholinesterase activity was not an appropriate indicator of inhibition of the activity of acetylcholinesterase in the peripheral nervous system. Consequently, the Meeting considered that the critical end-point for human risk assessment was inhibition of brain acetylcholinesterase activity and the NOAEL was 2.3 mg/kg bw per day.

In a study in human male volunteers who were prisoners, 10 men were given temephos at a dose of 1.1 mg/kg bw per day for 4 weeks and 9 men took temephos at a dose of 4.27 mg/kg bw per day for 5 days. There was no inhibition of cholinesterase activity in the plasma or in erythrocytes. This study in human volunteers who were prisoners was considered to be ethically acceptable according to the standards of the time it was performed (1967), although it would not be acceptable by current standards applied to new studies. The Meeting considered that the doses and the outcomes in this study in humans were not sufficiently well described for the results of this study to be used in isolation to set an ADI or an acute reference dose (ARfD).

Hepatotoxicity was inconsistently seen in a series of briefly reported experiments in rabbits. However, there was no evidence of any hepatotoxicity at doses of up to 30 mg/kg bw per day in a well-conducted and well-reported study of developmental toxicity in rabbits.

In a long-term combined study of toxicity and oncogenicity in rats, no adverse effects on neoplastic or non-neoplastic pathology were found at any dietary dose tested, up to the highest dose of 15 mg/kg bw per day. Cholinesterase activities were not measured in this study.

Temephos gave uniformly negative results in an adequate range of tests for genotoxicity in vitro and in vivo. The Meeting concluded that temephos is unlikely to be genotoxic.

Studies of reproductive toxicity in rats showed that temephos did not adversely affect reproduction when given as oral doses of up to 125 ppm (5.4 mg/kg bw per day) for up to three generations. In a one-generation study, temephos at a dose of 500 ppm (22.5 mg/kg bw per day) inhibited erythrocyte cholinesterase in mothers (90%) and in 21-day-old pups (30%), but other doses were not tested. There was no developmental toxicity or hepatotoxicity in rabbits given temephos at oral doses of up to 30 mg/kg bw per day.

Studies in hens showed that temephos did not have the potential to cause organophosphate-induced delayed neuropathy and did not cause demyelination of nerves.

Although, for the purposes of vector control, temephos is used at a concentration of up to 1 mg/l in drinking-water, only one report of an investigation of possible effects in exposed people was available. Approximately 2000 people were exposed to drinking-water containing temephos for 19 months without any adverse effects on plasma or erythrocyte cholinesterase activity. No illness attributable to the treatment was seen and all eight babies born during the study period were normal. The drinking-water was treated monthly with temephos. The intended concentration of 1 ppm was not achieved and only one sample contained temephos at a concentration of more than 0.5 ppm.

Toxicological evaluation

Temephos is recommended by WHO for addition to potable water as larvicide treatment at an application rate not exceeding 1 mg/l. Assuming that an adult weighing 60 kg would consume 2 l per day of drinking-water containing temephos at 1 mg/l, this would be equal to an oral exposure of 0.033 mg/kg bw. However, given the limited solubility of temephos in water, incomplete dissolution in drinking-water would be expected and this could result in actual exposures

being appreciably less than this estimate. Consequently, 0.033 mg/kg bw per day was regarded as a worst-case upper limit of exposure.

Some of the studies that were critical to the assessment were of poor quality. The Meeting considered that the database was insufficiently robust to serve as the basis for establishing an ADI or an ARfD for temephos.

The Meeting concluded that the relevant NOAEL for human risk assessment is 2.3 mg/kg bw per day on the basis of inhibition of brain acetylcholinesterase activity in rats. This NOAEL provides a margin of exposure (MoE) from the estimated oral exposure derived from drinking-water treated with temephos of about 70. The MoE for clinical signs and the, possibly secondary, effects on development and reproduction are in the range of > 160 (highest dose tested in rat multigeneration study) to 900 (study of developmental toxicity in rabbits). In addition, reassurance is provided by the MoEs of 130 and 33 provided by the absence of clinical signs and erythrocyte cholinesterase inhibition in the poorly described study in volunteers treated for 5 or 14 days, respectively.

In addition to this safety assessment, the concerned WHO programmes will consider efficacy of the treatment and additional relevant exposure scenarios before further recommending such a treatment and deriving water-guideline values.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	28-day and 44-day study of toxicity[b]	Clinical signs	10 mg/kg bw per day	100 mg/kg bw per day
	90-day study in rats[a]	Inhibition of acetylcholinesterase in brain	2.3 mg/kg bw per day[d]	—
	2-year study of toxicity and carcinogenicity[a]	Carcinogenicity (cholinesterase activity not measured)	300 ppm (15 mg/kg bw per day)[d]	—
	Three-generation study of reproduction[a]	Maternal	125 ppm (5.4 mg/kg bw per day)[d]	—
		Offspring	125 ppm (5.4 mg/kg bw per day)[d]	
Rabbit	35-day study of toxicity[b]	Clinical signs	10 mg/kg bw per day[d]	—
	Study of developmental toxicity[b]	Maternal	30 mg/kg bw per day[d]	—
		Developmental	30 mg/kg bw per day[d]	—
Dog	90-day study of toxicity[a]	Inhibition of acetylcholinesterase in erythrocytes	18 ppm (0.9 mg/kg bw per day)	700/500 ppm (35/25 mg/kg bw per day)
		Inhibition of acetylcholinesterase in brain	—	700/500 ppm (35/25 mg/kg bw per day)[e]
	129-day study of toxicity[a]	Inhibition of acetylcholinesterase in erythrocytes	10 ppm (0.6–0.8 mg/kg bw per day)	50 ppm (3–4 mg/kg bw per day)
Chickens	Neurotoxicity[b]	No organophosphate-induced delayed neurotoxicity observed	1705 mg/kg bw[e]	—

Humans	Investigation of clinical signs and effects on cholinesterase activities in erthrocytes and plasma[c]	No adverse effects reported	1.1 mg/kg bw per day for 4 weeks or 4.27 mg/kg bw per day for 5 days[e]	—

[a] Dietary administration
[b] Oral gavage
[c] Administration in a drink
[d] Highest dose tested
[e] Only dose at which measurements of the critical end-point were made.

Critical end-points for setting guidance values for exposure to temephos

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	At least 40% of administered dose absorbed.
Distribution	Most of the retained residues were in the fat (about 0.5% of administered dose)
Potential for accumulation	Low
Rate and extent of excretion	Most of the administered oral dose recovered in the urine and faeces within 48 h. About 40% in urine.
Metabolism in mammals	By hydrolysis and *S*-oxidation plus conjugation.
Toxicologically significant compounds	Temephos and temephos sulfoxide
Acute toxicity	
Rat, LD_{50}, oral	4000 to 13 000 mg/kg bw
Rat, LD_{50}, dermal	2000 to > 4000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.79 mg/l
Rabbit, skin irritancy	Non-irritant
Rabbit, eye irritation	Non-irritant
Guinea-pig, skin sensitization (test method)	No skin sensitizing potential (modified Buehler test)
Short-term studies of toxicity	
Critical effects	Inhibition of brain acetylcholinesterase activity
Lowest relevant oral NOAEL	2.3 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	25 mg/kg bw per day (rabbit)
Genotoxicity	
	Not genotoxic (on the basis of tests in vitro)
Long-term studies of toxicity and carcinogenicity	
Critical effects	No adverse effects detected at any dose tested (cholinesterase activities not measured)
Lowest relevant oral NOAEL	15 mg/kg bw per day (rats, highest dose tested)
Carcinogenicity	Not carcinogenic in rats
Reproductive toxicity	
Reproductive target/critical effects	None
Lowest relevant reproductive NOAEL	5.4 mg/kg bw per day (rats, highest dose tested)
Developmental critical effect	None

Lowest relevant developmental NOAEL	10 mg/kg bw per day for maternal toxicity 30 mg/kg bw per day (highest dose tested) for developmental effects
Neurotoxicity studies in hens	
Lowest relevant neurotoxicity NOAELs	1705 mg/kg bw (highest dose tested caused no neuropathy)
Observations in humans	
Volunteer studies	No effects on plasma or erythrocyte cholinesterase activity at 1.1 mg/kg bw per day for 4 weeks, or at 4.27 mg/kg bw per day for 5 days

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