Phorate

(CAS No: 298-02-2)

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

The evaluation of the toxicity of phorate has been based on reviews published by the American Conference of Governmental Industrial Hygienists (ACG99) and in 'Handbook of pesticide toxicology' (Gal91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1999, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts covering the period of 1965/1966 until December 1999, and using the following key words: phorate and 298-02-2. Data of unpublished studies were generally not taken into account.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: Joint Meeting of the FAO Panel of Experts on Pesticides Residues on Food and the Environment and the WHO Expert Group on Pesticides Residues - JMPR) (FAO95, FAO97, WHO88), and the Health Effects Division (HED) of the US Environmental Protection Agency (EPA) (Oli99), as part of its hazard identification assessment review.

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

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

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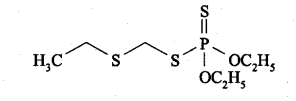
2 Identity

name	:	phorate
synonym	:	phosphorodithioic acid *O*,*O*-diethyl *S*-[(ethylthio)methyl] ester; *O*,*O*-diethyl *S*-(ethylthio)methyl phosphorodithioate; *O*,*O*-diethyl *S*-ethylmercaptomethyl dithiophosphate; Thimet; Timet; Granatox; Rampart
molecular formula	:	$C_7H_{17}O_2PS_3$
structural formula	:	
CAS number	:	298-02-2

3 Physical and chemical properties

molecular weight	:	260.38
boiling point	:	at 0.1 kPa: 118-120°C
melting point	:	-43.7°C
vapour pressure	:	at 25°C: 0.09 Pa
solubility in water	:	slightly soluble (at 25°C: 5 mg/100 mL)
Log $P_{octanol/water}$	:	3.92
conversion factors	:	not applicable

Data from ACG99, Rob99, Tom97.

Phorate is a clear, pale yellow mobile liquid. It is formulated in emulsifiable or granular concentrates (Gal91). Phorate is stable at room temperature and between pH 5 and pH 7 for at least 2 years. However, under very acidic (pH<2) or alkaline (pH>9) conditions, the compound hydrolyses (ACG99).

4 Uses

Phorate is a systemic and contact insecticide and acaricide used to control sucking and chewing pests in a wide range of crops, among others corn, sugar beets, cotton, brassicas, and coffee. It is also used as a nematocide (ACG99, Gal91, Tom97).

According to the database of the Dutch Pesticide Authorisation Board (CTB)*, phorate is at present not registered for its use as an active ingredient in pesticides in the Netherlands.

5 Biotransformation and kinetics

Two studies have been reported on the kinetics of the compound following oral dosing, but the committee did not find information from dermal or inhalation studies.

Male rats were given a single dose of 0.8 mg/kg bw of ^{14}C-labelled phorate (label on methyl group in thioether moiety) in corn oil by gavage. Within the first 24 hours after administration, 77% of the dose was excreted in the urine and 12% in the faeces. Through the 8th day, 83% of the dose was excreted in the urine and 13% in the faeces. Less than 1% of the total radioactivity was found in tissues (highest level in blood) at 24 hours (Hus87).

Similar results were obtained in female rats following a single oral dose of 0.44 mg/kg bw (Mil90).

Phorate is biotransformed by oxidation of the thioether moiety to the corresponding sulphoxide and sulphone and by desulphuration of the P=S moiety to P=O, producing a phosphorothiolate ester. By hydrolysis of these oxidative intermediates, 10 metabolites have been identified in the urine. The 2 major metabolites were the following non-phosphorylated metabolites: sulphoxide(ethylsulphonyl)methyl (43% of urinary metabolites) and methane(ethylsulphonyl)(methylsulphonyl) (24-28% of urinary metabolites). Phosphorylated metabolites accounted for <15% of urinary metabolites in males and no phosphorylated metabolites were identified in the urine of females. The main residues in liver, kidney, and muscle were dephosphorylated metabolites (Hus87, Mil90).

In an older study, male albino rats received a single oral dose of 2 mg/kg bw of ^{32}P-labelled phorate. Only 35% of the administered dose was detected in the urine and 3.5% in the faeces within the first 6 days. Six daily oral doses of 1 mg/kg bw of phorate resulted in an excretion of 12% of the administered dose in the urine and 6% in the faeces within 7 days. The major metabolites identified were *O,O*-diethylphosphorothioate (DEPT; 80% of urinary metabolites) and diethylphosphoric acid (DEP; 17% of urinary metabolites). The brain, liver, and kidney tissues of the repeatedly dosed animals contained unidentified and largely unextractable residues. The authors did not discuss the difference in excretion

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

pattern of single and repeated dosing (Bow58). The aforementioned metabolites were also identified in operator exposure studies (PSD94).

Based on the results of the more recent studies (Hus87, Mil90), the committee concludes that phorate and its metabolites are rapidly excreted and that accumulation of a toxic metabolite is not a concern.

6 Effects on mechanism of action

Human data

Several cases of poisoning associated with the use of phorate have been reported. A 16-year-old boy became ill after he had worked for several days with phorate-treated cottonseed. Clinical symptoms of intoxication were lowered blood pressure, pinpoint pupils, convulsions, and unconsciousness. After several treatments with atropine, he recovered. One day after the onset, red blood cell acetylcholinesterase (AChE) and plasma cholinesterase (ChE) activities were 21% and 49% of normal values, respectively, and 15 days later plasma ChE, but not red blood cell AChE, had recovered completely (Gal91, WHO88).

In a pesticide formulation plant, cases of poisoning have been reported for 2 workers who were engaged in Thimet formulation. Symptoms of intoxication were dizziness, nausea, vomiting, constricted pupils, cardiac tachycardia, excessive salivation, respiratory distress, muscle fasciculations, and pinpoint pupils. After treatment with atropine and/or 2-PAM (2-pyridine-aldoxime methiodide), both men recovered. Phorate air concentrations in the plant ranged from 0.07 to 14.6 mg/m^3. No cholinesterase measurements were reported (You79, WHO88). In another incident, a formulator experienced neurological symptoms (not specified) following exposure to phorate while cleaning a mixing tank. Plasma ChE and red blood cell AChE activities were reduced by 50% of base level values and increased concentrations of diethyl phosphate in urine, a metabolite of phorate, were observed (WHO88). Forty male workers who were engaged in formulation of phorate for 2 weeks developed toxic symptoms, including gastro-intestinal effects, bradycardia, and neurological effects (headache, giddiness, fatigue). Skin and eye irritation also occurred. In 60% of the subjects, mean plasma ChE activity was decreased by 55% at the end of the first week and by 71% at the end of the second week compared to pre-exposure activity. Within 10 days after cessation of exposure, ChE activity had recovered to 79% of pre-exposure value (Kas84).

Animal data

Irritation and sensitisation

No data have been reported on irritation and sensitisation in experimental animals, as the high acute toxicity of phorate prohibited administration of appropriate dose levels (Oli99).

Acute toxicity

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

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

exposure route	vehiculum	species (strain)	sex	LC_{50}/LD_{50} (duration)	reference
inhalation[a]		rat (Sprague-Dawley)	male	60 mg/m^3 (1h)	New78
		rat (Sprague-Dawley)	female	11 mg/m^3 (1h)	New78
dermal	xylene	rat (Sherman)	male	6.2 mg/kg bw	Gai69
	xylene	rat (Sherman)	female	2.5 mg/kg bw	Gai69
	propylene glycol	rat (Sprague-Dawley)	male	9.3 mg/kg bw	New78
	propylene glycol	rat (Sprague-Dawley)	female	3.9 mg/kg bw	New78
		rat	male	5.7 mg/kg bw	FAO95
		rabbit	male	5.2 mg/kg bw	FAO95
		rabbit	not specified	99 mg/kg bw	NIO02
oral	peanut oil	rat (Sherman)	male	2.3 mg/kg bw	Gai69
	peanut oil	rat (Sherman)	female	1.1 mg/kg bw	Gai69
		rat	male	2.8 mg/kg bw	FAO95
		rat	female	1.6 mg/kg bw	FAO95
	propylene glycol	rat (Sprague-Dawley)	male	3.7 mg/kg bw	New78
	propylene glycol	rat (Sprague-Dawley)	female	1.4 mg/kg bw	New78
		rat	not specified	1 mg/kg bw	NIO02
		mouse	male	2.25 mg/kg bw	Gal91

intravenous	propylene glycol	rat (Sprague-Dawley)	male	2.2 mg/kg bw	New78
	propylene glycol	rat (Sprague-Dawley)	female	1.2 mg/kg bw	New78

[a] As an aerosol generated from a 1% solution in xylene.

Phorate metabolites, including the sulphoxide and sulphone derivatives of phorate and phorate oxygen analogues, are even more acutely toxic and have greater anticholinesterase activity than phorate (FAO95, Oli99).

The potential of phorate to induce delayed neuropathy was investigated in Leghorn hens (n=50) that were given an oral dose of phorate (purity: 89.5%) of 14.2 mg/kg bw. Before dosing, atropine was administered for protection. At day 21 after dosing, all surviving hens were given a second dose of atropine and 14.2 mg/kg bw phorate. Fifteen hens were used as negative controls and were given atropine but no phorate, and 15 hens, used as positive controls, were given 2 doses of 500 mg/kg bw tri-*ortho*-tolyl phosphate at days 1 and 21. Of the 50 phorate-treated hens, 23 died within 24 hours of the first dose and 13 more within 24 hours of the second dose, 10 hens surviving until the termination of the study at day 42. Vehicle controls and phorate-treated hens had slight generalised limb weakness (lasting for about 2 hours) shortly after each atropine treatment, phorate-treated hens showing slightly more severe reactions as well as slight to moderate ataxia for up to 2 hours after phorate treatment. No clinical signs of delayed neuropathy were observed in any vehicle-control or phorate-treated hens. At necropsy, no effects were seen in any of the 50 phorate-treated animals. Histological examination of the 10 surviving phorate-treated hens revealed minimal to mild focal axonal degeneration of the sciatic nerves, which was not observed in the negative controls. This degeneration was associated with interstitial infiltration of lymphoid cells, which was also seen in other test and vehicle-control hens. This syndrome, which was distinctly different from that observed in the positive-control animals, was ascribed to lesions of a naturally occurring disease, and was considered not to be related to phorate treatment (Fle84).

Recently, an acute neurotoxicity study has been conducted in 7-week-old Sprague-Dawley CD rats. The rats (n=20/sex/group) were given a single oral dose of phorate (purity: 91.8%) by gavage at levels 0, 0.25, 0.50, or 1.0 mg/kg bw. The Functional Observational Battery (FOB) revealed miosis in 2/10 males and 2/10 females of the mid-dose group and in 2/10 males and 5/10 females of the high-dose group, approximately 4-5 hours after dosing. Other effects were tremors, fasciculations, slightly impaired locomotion, and splayed hind limbs in

one high-dose female and moderate tremors in another high-dose female. These symptoms disappeared within the first week and were no longer present during the 8th day of observation. In the male and female rats of the high-dose group, there was significant inhibition of plasma ChE, red blood cell AChE, and brain AChE (not quantified). In the mid-dose group, a small but statistically significant decrease in brain AChE activity (6%) was observed in male rats at 0.5 mg/kg bw. The NOAEL in this acute neurotoxicity rat study was 0.25 mg/kg bw, based on the evidence of miosis and inhibition of brain AChE in males (Oli99).

Short-term toxicity

In a dermal toxicity study, 3 groups of Sprague-Dawley CD rats (n=10/sex/group) received topical applications of granular phorate (20.3%) at 0, 0.41, 0.81, or 3.1 (females) or 4.1 (males) mg active ingredient/kg bw/day, 6 hours/day, 5 days/week, for 4 weeks. High mortality (5 out of 10 animals) was seen in the high-dose female group during the first 3 weeks of the study. In this group, signs of toxicity were lachrymation, lethargy, tremors, and irregular gait. However, male rats were not affected. At the top dose, plasma ChE activity was inhibited up to 61% in males and 91% in females. Inhibition of red blood cell AChE was up to 76% in males and 97% in females, while brain AChE was inhibited by 41% in males and 68% in females. A small but statistically significant decrease in red blood cell AChE and brain AChE was observed in females at 0.81 mg/kg bw/day. The NOAEL in this 4-week dermal rat study was established at 0.41 mg active ingredient/kg bw/day (Oli99).

Rats (n=50/sex/group; strain not specified) were given phorate (purity: 92%) in the diet at levels equivalent to 0, 0.01, 0.03, 0.1, 0.3, 0.6, and 0.9 mg/kg bw/day for 13 weeks. At the 2 highest levels, 25 male and 25 female rats were used. In the 2 highest dose groups, there were severe excitability, intermittent tremors, ataxia, reduced body weight gain and food consumption, and mortality (100% and 50% at 0.9 and 0.6 mg/kg bw/day, respectively). Plasma, red blood cell, and brain cholinesterase activity was significantly depressed (not quantified). At 0.3 mg/kg bw, cholinergic signs of intoxication (excitability, intermittent tremors) were observed occasionally in females only. Plasma ChE, red blood cell AChE, and brain AChE activities were significantly reduced (not quantified). At 0.1 mg/kg bw, red blood cell AChE was reduced (not quantified) in females only. Animals dosed with 0.3 mg/kg bw or less did not show changes in survival, growth, and food intake, or abnormalities at gross necropsy and histological examination (performed on 3/10/sex only). The 13-week oral rat

NOAELs were 0.03 mg/kg bw/day for inhibition of plasma ChE activity and 0.1 mg/kg bw/day for inhibition of red blood cell and brain AChE (Tus56a).

Swiss mice (Crl:CD-1 (ICR) BR; n=20/sex/group) were given phorate (purity: 92.1%) via the diet in concentrations equivalent to 0, 0.18, 0.55, or 1.10 mg/kg bw/day in males, and 0, 0.23, 0.67, or 1.38 mg/kg bw/day in females for 13 weeks. No significant changes in survival rates, food intake, or body weight gain, or remarkable clinical signs were observed in any of the treated groups. Histological examinations were not performed; cholinesterase activities were measured before terminal sacrifice. Plasma ChE activity was reduced by 15% at 0.23 mg/kg bw/day in females and in both sexes at the 2 highest dose levels (not specified). Red blood cell AChE was decreased by 17% at 0.67 mg/kg/day in females and by 50% in males and 61% in females at the top dose. Brain AChE was significantly decreased in both sexes by approximately 10% and 50% at the mid and high dose, respectively. The NOAEL in the 13-week oral mouse study was 0.18 mg/kg bw/day based on inhibition of brain AChE (Tru90).

To study the effect of phorate on AChE and butyrylcholinesterase (ChE) in the olfactory bulb of the mouse brain, adult albino mice (n=10/sex/group; strain not specified) received 1.0 and 1.5 mg phorate/kg bw/day via the diet for 32 weeks. Histoenzymological examination showed that AChE activity in the different layers of the olfactory bulb was reduced only at 1.5 mg/kg bw, whereas reduced ChE activity was found at both dose levels (Van97).

Several short-term studies were carried out with dogs. In a range-finding study, dogs (n=2/sex/group) received oral (capsules) doses of phorate (purity: 92%) of 0.01, 0.05, 0.10, 0.25, or 0.50 mg/kg bw/day for 2 weeks. Controls (n=3/sex) received capsules with corn oil only. At the highest dose, one female dog showed cholinergic effects (excessive salivation and tremors) while decreased body weight gain and decreased total serum protein levels were seen in animals of both sexes. Treatment did not affect survival, food intake, haematological parameters, organ weights, or gross pathology. Histological examinations were not performed. At 0.05 mg/kg bw/day, plasma ChE activity alone was significantly decreased (not specified) in males only. At 0.10 mg/kg bw/day and higher, both plasma ChE and brain AChE activities were significantly reduced in both sexes. Red blood cell AChE activity was significantly reduced at 0.50 mg/kg bw/day only. The 2-week oral dog NOAEL was 0.05 mg/kg bw/day, based on inhibition of brain AChE (Pic87).

In a study conducted in 1961, beagle dogs (n=3/sex/group) that were fed phorate (purity: not given) at dose levels equivalent to 0, 0.012, or 0.025 mg/kg bw/day for 6 weeks, did not show changes in plasma ChE or red blood cell

AChE activity (Kay61). Another study dealt with mongrel dogs (one female and 2 males per group) that received oral (capsules) doses of phorate (purity: 92%) of 0. 0.01, 0.05, 0.25, 1.25, or 2.5 mg/kg bw/day, 6 days/week, for 13-15 weeks. All dogs at the 2 top doses showed typical cholinergic signs and subsequently died. Plasma ChE activity was inhibited at 0.05 mg/kg bw or above and red blood cell AChE at 0.25 mg/kg bw/day or above (not specified). The NOAEL in this 15-week oral dog study was 0.05 mg/kg bw/day, based on inhibition of red blood cell AChE (Tus56b).

A one-year feeding study was carried out in beagle dogs (n=6/sex/group) that were given oral (capsules) doses of phorate (purity: 92%) of 0, 0.005, 0.01, 0.05, or 0.25 mg/kg bw/day. Eight control animals of each sex were used. At the highest dose, clinical signs (tremors) were occasionally observed in both sexes and mean body weights were decreased in males. Treatment did not affect food consumption or haematological parameters for any group. However, serum total protein levels were significantly reduced in males treated at 0.25 mg/kg bw/day. Gross and microscopic examination did not reveal treatment-related abnormalities. With regard to effects on cholinesterase activities, red blood cell AChE (>20%) and brain AChE (43-54%) were significantly reduced at the top dose, but were within normal levels at 0.05 mg/kg bw/day. Plasma ChE activity was decreased at the 2 highest dose levels. The NOAEL in this one-year oral dog study was 0.05 mg/kg bw/day based on decreased body weights, inhibition of red blood cell and brain AChE activities, and clinical signs observed at the next higher dose of 0.25 mg/kg bw (She87).

The potential of phorate to induce neuropathy following repeated exposure was investigated in a study in which hens received 5 mg phorate/kg bw/day via the diet for 4 weeks. No treatment-related structural nerve damage, such as myelin loss was found. In contrast, the positive control tri-*ortho*-tolyl phosphate induced myelin loss in each treated hen (Lev65).

The results of these studies are summarised in Table 2. In nearly all studies, inhibition of brain or red blood cell AChE is the critical effect.

Long-term toxicity and carcinogenicity

Five-week-old rats (Crl:COBS CD BR; n=50/sex/group) were fed doses of technical-grade phorate (purity: 84.5%) equivalent to 0, 0.05, 0.16, or 0.32 mg/kg bw/day in males and 0, 0.07, 0.19, or 0.43 mg/kg bw/day in females for 2 years. The mortality rate was increased in females at the highest dose. However, more than 60% of animals in all groups lived more than 90 weeks. Treatment-related effects were growth retardation in females during the first half year and again between weeks 74 and 102, and a decreased red blood cell count, haemoglobin, and haematocrit level in females at month 12. Red blood cell AChE activity was not significantly changed (<20%) at any dose level at any time. After 24 months, plasma ChE was decreased by more than 20% at all dose levels in males and at 0.19 and 0.43 mg/kg bw/day in females. Brain AChE activity was reduced by more than 20% in males at 0.32 mg/kg bw and in females at 0.19 and 0.43 mg/kg bw/day. At sacrifice, females given the highest dose had increased relative adrenal, brain, heart, liver, and spleen weights. Gross and histological examination revealed a significant treatment-related increase of inflammation and hyperplasia of the forestomach in both sexes at the highest dose level. Incidence, type, or time of appearance of tumours were not significantly different between treated and control groups. The 2-year oral rat NOAEL was 0.07 mg/kg bw/day, based on inhibition of brain AChE at 0.19 mg/kg bw/day in female rats (Man81a).

CD-1 outbred Swiss albino mice (n=50/sex/group) were fed technical-grade phorate (purity: 85.5%) at doses equivalent to 0, 0.15, 0.45 or 0.9 mg/kg bw/day for 18 months. Compared with controls, a higher incidence of tremor, hyperactivity, excessive salivation, and growth retardation (in females only) was observed at 0.9 mg/kg bw/day, but survival was not adversely affected. Gross and histological examination did not show alterations related to treatment. There was no significant dose-related increase in the incidence of any particular type of tumour or of animals with malignant or benign tumours. Cholinesterase activities were not measured in this study. The 18-month oral mouse NOAEL was 0.45 mg/kg bw/day, based on growth retardation in female mice at 0.9 mg/kg bw (Man81b).

Mutagenicity and genotoxicity

A battery of assays was performed to test the genotoxicity of phorate. Assays comprised tests for gene mutation, cytogenicity, and other genotoxic effects *in vitro* and *in vivo*.

- *In vitro* tests
  - Gene mutation assays. Phorate was negative in tests for reverse mutation in *S. typhimurium* strains TA100, TA1535, TA 1537, and TA 1538 and in *E. coli* p3478 at doses up to 1000 µg/plate in the presence or absence of an S9 metabolic activation system (Pan86, Sim87, Wat80,). Phorate did not induce gene mutations at the *hprt* locus in cultured Chinese hamster ovary (CHO) cells (Thi85).
  - Cytogenicity assays. No statistically significant changes were found in the frequency of sister chromatid exchanges (SCE) in either cultured human lymphocytes (up to 20 µg phorate/mL), cultured CHO cells (up to 40 µg/mL), or cultured rat tracheal epithelial cells (up to 50 µg/mL), in the presence or absence of S9 (Pan84, Wan87). However, a statistically significant increase in the frequency of SCEs was reported in cultured human lymphoid cells treated with 2 and 20 µg phorate/mL without metabolic activation of S9 (Sob82). The frequency of chromosomal aberrations in cultured CHO cells was increased at 40 µg/mL without S9, but no change occurred in the presence of S9 (Lin87).
  - Other genotoxicity assays. Phorate did not induce mitotic recombination in *S. cerevisae* D3 at a concentration of 5% with and without metabolic activation (Sim77). No unscheduled DNA synthesis (UDS) was seen in cultured human fibroblasts (WI-38 cells) at concentrations up to 1 mM (Sim77).

- *In vivo* tests

There was no increase in the incidence of chromosomal aberrations in bone marrow cells of male and female Sprague-Dawley rats (number not specified) receiving phorate capsules at doses varying from 0 to 2.5 mg/kg/day (duration of study not specified) (Ive86). No increased incidence of micronucleated bone marrow cells of Swiss albino mice (3/sex/group) was reported following 2 intraperitoneal doses of 1.5 mg/kg bw of phorate at 24-hour intervals (Pan86). In contrast, a statistically significant increase was found in the frequency of micronuclei in bone marrow cells of male Wistar rats (n=5/group) after a single

intraperitoneal dose of 0.75 mg/kg bw. No changes were observed at 0.25 and 0.50 mg/kg bw. The frequency of chromosomal aberrations in bone marrow cells of Wistar rats (n=5/group) was increased following daily intraperitoneal injections of 0.15 and 0.30 mg phorate/kg bw/day for 5 days (Gro85, Mah87). These effects were confirmed in another study with Wistar rats following administration of 2 intraperitoneal doses of phorate at 24-hour intervals. Increased chromosome aberrations and micronuclei were observed in bone marrow cells of rats that received of 0.09-0.37 and 7.5-15 mg/kg bw, respectively (Dhi90). Dominant lethal mutations were not found in male mice given dietary phorate levels varying from 0 to 20 mg/kg bw for 7 weeks (Sim77).

Based on these results, the committee concludes that phorate does not induce gene mutations *in vitro,* but conflicting results have been reported for cytogenicity effects, both *in vitro* and *in vivo*.

Reproduction toxicity

A 2-generation study was conducted in groups of Sprague-Dawley rats (COBS CD (SD); n=25/sex/group) that were fed phorate (purity: 92%) at dose levels equivalent to 0, 0.09, 0.17, 0.35, or 0.52 mg/kg bw/day for males and 0, 0.10, 0.20, 0.40, or 0.62 mg/kg bw/day for females for a minimum of 60 days before mating. The second-generation parental animals (n=25-30/sex/group) were treated for a minimum of 100 days before mating. Animals were exposed continuously to phorate before mating and throughout weaning of the offspring in both generations. Treatment-related effects in parental animals were tremors and decrease in body weight at 0.35 and 0.40 mg/kg bw/day in males and females, respectively. At the top dose, clinical signs, mortality, and ocular effects were observed. In F1 males, plasma ChE, red blood cell AchE, and brain AChE activities were inhibited at 0.52 mg/kg bw/day by >30, 11, and 40%, respectively. In F1 females, brain AChE was reduced by 59 and 83% and plasma ChE by more than 30% at 0.40 and 0.62 mg/kg bw/day, respectively. Red blood cell AChE was reduced at the top dose only. Mating or fertility indices, pregnancy rate, length of gestation, gestation index, sex distribution ratios, and reproductive organ morphology did not show treatment-related changes. Pup survival during the lactation period and mean pup weights were reduced at the 2 highest doses and litter size at the highest dose. The NOAEL in this 2-generation oral rat study was 0.17 mg/kg bw/day for both parental and offspring toxicity (Sch91).

In an older reproduction study in mice (8 males and 16 females/group), carried out in 1965, phorate (purity: unknown) was given at dietary levels equivalent to 0, 0.09, 0.23, or 0.45 mg/kg bw/day. Compound administration was initiated 7 weeks before the first mating. The study involved 3 generations with 2 litters per generation. No effects on fertility, gestation length, or on gross and microscopic alterations of tissues were observed. The lactation and viability indices were only slightly decreased at the highest dose. The NOAEL in this 3-generation mouse study for parental and reproduction toxicity was 0.23 mg/kg bw/day (FAO95, Oli99).

Several developmental toxicity studies have been reported for phorate. Groups of pregnant Sprague-Dawley rats (n=10/group) were exposed to aerosols of phorate (purity: 78-90%), generated from a 1% solution in xylene, 1 hour/day, on days 7-14 of gestation, at concentrations 0.15, 0.4, or, 1.94 mg/m^3. Controls received xylene or air only. Signs of toxicity in the dams that received the highest dose were death (5/10), tremors, lachrymation, and exophthalmus. No treatment-related effects on body weight, food consumption, or pregnancy rate were observed. However, the average percentage of fetal mortality was significantly increased at the top dose. Average number of implants, average fetal weight, average number of ossification centres, or the incidence of supernumerary ribs were not affected by phorate. The NOAEL for maternal and offspring toxicity was 0.4 mg/m^3 (New78). The committee considers this study to have a limited value due to the possible role of xylene as a solvent on these results.

During the gestational period (days 6-15), 25 Sprague-Dawley rats (Crl:COBS CD (SD) BR) received phorate (purity: 92%) at doses of 0, 0.125, 0.25, or 0.5 mg/kg bw/day by gavage. Maternal toxicity resulting in death occurred in 7/23 of the high-dose dams. No effects on food intake, body weight, or general health condition were observed in the surviving dams. The incidence of cardiac hypertrophy was increased among the fetuses at the highest dose. The number of implantation sites, resorptions and dead fetuses, the mean live litter size, average fetal weight, and sex ratio were not significantly affected compared with controls. The NOAEL was 0.25 mg/kg bw/day for maternal and fetal toxicity (Bel79). In another study, Sprague-Dawley rats (CrL:CDBRVAF/Plus SD, n=24-25/group) received phorate (purity: 92%) at doses of 0, 0.1, 0.2, 0.3, or 0.4 mg/kg bw/day by gavage on pregnancy days 6-15. Maternal toxicity at the highest dose was evident from death (6/25 animals), clinical signs (tremors, excessive salivation, stained fur, laboured breath, decreased motor activity, impaired righting reflex), and significantly decreased body weights, body weight gain, and food intake. Fetotoxicity at the highest dose was demonstrated by

decreased fetal body weight and delayed ossification of the sternum and pelvis when compared with controls. The NOAEL for fetal and maternal toxicity was 0.3 mg/kg bw/day (Loc90). In a range-finding study, pregnant New Zealand white (NZW) rabbits (n=5/group) were given phorate (purity: 92%) in corn oil by gavage at dose levels 0, 0.3, 0.6, 0.9, 1.2, or 1.5 mg/kg bw/day on days 6-18 of gestation. Death occurred in all exposed groups in a dose-dependent way. Mean body weight loss was seen at 1.2 mg/kg bw/day. Increased numbers of resorptions and post-implantation losses were reported at 0.6 mg/kg bw and higher. Decreased mean fetal body weights and shorter crown-rump lengths were found at 1.2 mg/kg bw/day. Gross examination of the fetuses did not show treatment-related malformations. The LOAEL for maternal toxicity and NOAEL for developmental toxicity were 0.3 mg/kg bw/day (Sch86). The same authors carried out a more extensive study in NZW rabbits (n=20/group) that were treated by gavage with phorate (purity: 92%) dissolved in corn oil, during days 6-18 of gestation at doses of 0, 0.15, 0.5, 0.9, or 1.2 mg/kg bw/day. Maternal death occurred at the highest dose (8/20), 0.9 mg/kg bw/day (2/20), and at 0.5 mg/kg bw/day (1/20). Reduced body weight gain, and decreased food consumption were observed at 0.5 mg/kg bw/day and above. Treatment had no effect on pre-implantation loss, number of resorptions, number of live fetuses, fetal body weight, or sex ratio. At the top dose, 3 remaining fetuses in a single litter (5/8 implantation sites showed early resorptions) showed open eyelids, curved scapulae, an absent supraorbital process, an irregular margin of the frontals, and a displaced anterior fontanel. Ocular and scapular defects were not seen in other fetuses from dams treated at this dose and the incidence of open eyes was within that of historical controls. The authors, therefore, considered this findings spurious and not phorate-treatment related. The maternal NOAEL, based on mortality and body weight loss was 0.15 mg/kg, and the developmental NOAEL 1.2 mg/kg/day (Sch87).

The committee concludes that phorate showed effects on reproduction only at dose levels, which produce parental/maternal toxicity.

7 Existing exposure limits

The current administrative occupational exposure limit (MAC) for phorate in the Netherlands is 0.05 mg/m^3, 8-hour TWA, with a skin notation.

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

8 Assessment of health hazard

The health hazard assessment of phorate is based mainly on toxicology reviews issued by the Health Effect Division of the United States EPA for reregistration eligibility (Oli99) and by the FAO/WHO Joint Meeting on Pesticide Residues for recommendation of an acceptable daily intake (FAO95, FAO97). The toxicity profile in these reviews is obtained mainly from unpublished reports of toxicology studies conducted for registration purposes by the chemical companies manufacturing or marketing the compound. It should be realised that some of these studies were conducted in the 1960s and 1970s and do not meet current requirements.

Workers can be exposed to phorate through inhalation of aerosols or by direct skin contact with a formulation of the compound, but the committee did not find quantitative data on dermal or inhalation absorption. In view of the high acute dermal toxicity in rats (LD_{50}: 2.5-9.3 mg/kg bw), it is expected that a substantial percentage of a dermal dose will be absorbed through the skin. The extent of absorption following oral intake is essentially 100% in the rat. Following absorption, the compound is rapidly metabolised into breakdown products (e.g., DEPT, DEP), which are mainly excreted in the urine. There is no evidence of accumulation of the compound in any of the tissues.

Case studies in humans showed a high acute toxicity of phorate following accidental exposure. Effects observed in these studies were typical clinical symptoms of cholinergic toxicity such as salivation, constricted pupils, and muscle fasciculations.

Based on results of acute lethal toxicity studies in test animals, the committee considers the compound as very toxic after dermal, inhalation, and oral exposure. Phorate did not cause neurological changes indicative of delayed neurotoxicity.

Inhibition of serum ChE and of red blood cell and brain AChE were the main effects found in dogs, rats, and mice following short-term and chronic exposure, and, generally, no other systemic effects have been reported. The oral NOAELs for brain and red blood cell AChE inhibition were 0.05 mg/kg bw for dogs (one-year study), 0.07 mg/kg bw (brain AChE only) for rats (2-year study), and 0.18 mg/kg bw for mice (13-week study).

Phorate did not induce gene mutations in *in vitro* tests, but conflicting results were reported for cytogenicity effects, both *in vitro* and *in vivo*. In the latter, abnormalities were found if phorate was given by intraperitoneal injections, but not following oral administration. Carcinogenicity studies in rats and mice did

not show a treatment-related increase in tumour incidence. The committee concludes that the positive genotoxic effects of phorate were thus not reflected in carcinogenicity. The committee did not consider phorate as a reproduction toxicant, as effects occurred at doses above those causing parental or maternal toxicity. The NOAEL for reproduction toxicity in the rat was 0.17 mg/kg bw/day. The NOAELs for developmental toxicity were 0.25 and 1.2 mg/kg bw/day in rats and rabbits, respectively.

Based on the above data, the committee concludes that the mechanism of toxicity of phorate in mammals is through inhibition of AChE activity in nerve tissue. The committee identifies inhibition of AChE activity in brain tissue as the most sensitive adverse toxic effect of phorate in animal studies, occurring at dose levels that are lower than those that cause other toxic effects. In human beings, for obvious reasons, brain AChE cannot be measured. Instead, red blood cell AChE, being the same molecular target for inhibition by organophosporus pesticide as brain AChE, is used as a surrogate for brain AChE in assessing the human health risk of exposure to phorate (Jey94). However, no data is available in the literature of effects of the compound on red blood cell AChE in human beings and, therefore, studies in test animals have to be used for the assessment of a health-based recommended occupational exposure limit (HBROEL).

Because no short- or long-term inhalation toxicity studies are available, the committee takes the 2-year oral toxicity study in rats as a starting point in deriving a HBROEL. In this study, the NOAEL was 0.07 mg/kg bw/day. Since workers are exposed for 5 days a week, this NOAEL from a continuous feeding study (i.e., 7 days a week) is adjusted by multiplying with a factor of 7/5 resulting in a no-adverse-effect level (NAEL) of 0.098 mg/kg bw/day. For the extrapolation to a HBROEL, a factor of 4 for allometric scaling from rats to humans, based on caloric demand, and an overall factor of 9 for inter- and intraspecies variation are applied, resulting in a NAEL for humans of 0.003 mg/kg bw/day. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day, and a retention of 100%, and applying the preferred value approach, a health-based occupational exposure limit of 0.02 mg/m^3 is recommended for phorate.

The committee recommends a health-based occupational exposure limit for phorate of 0.02 mg/m^3, as an 8-hour time-weighted average (TWA).

Phorate showed a high acute lethal dermal toxicity in rats. A ratio of the dermal LD_{50} and the calculated inhalation LD_{50} of less than 10 is proposed as one

of the criteria for assigning a skin notation (ECE98). Since this criterion is met for phorate*, the committee recommends a skin notation.

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* The dermal LD_{50} in male rats is 5.7-9.3 mg/kg bw; the inhalation LD_{50} calculated from the 1-hour LC_{50} of 60 mg/m^3 in male rats (assuming a retention of 1.0 and a minute volume of 125 mL/min for a 200-g weighing rat) is ca. 2.3 mg/kg bw.

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Annex

Occupational exposure limits for phorate in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	0.05	8 h	administrative	S	SZW03
Germany						
- AGS	-	0.05			S	TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	-	0.05	8 h	OES	S	HSE02
	-	0.2	15 min			
Sweden	-	-				Swe00
Denmark	-	0.05	8 h		S	Arb02
USA						
- ACGIH	-	0.05	8 h	TLV	S	ACG03b
	-	0.2	15 min	STEL		
- OSHA	-	-				ACG03a
- NIOSH	-	0.05	10 h	REL	S	ACG03a
	-	0.2	15 min	STEL		
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.