Demeton

(CAS No: 8065-48-3)

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 demeton 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 L Portengen, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands)*.

The evaluation of the toxicity of demeton has been based on reviews published by the American Conference of Governmental Hygienists (ACG99) and in the '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: demeton, demeton-O, demeton-S, systox, isosystox, 8065-48-3, 298-03-3, and 126-75-0. The results of unpublished studies were not considered with the exception of studies that were summarised and evaluated by international bodies as the Food and Agricultural Organization/World Health Organization (FAO/WHO: Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticides Residues (JMPR)) (FAO65, WHO87).

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 May 2003 did not result in information changing the committee's conclusions.

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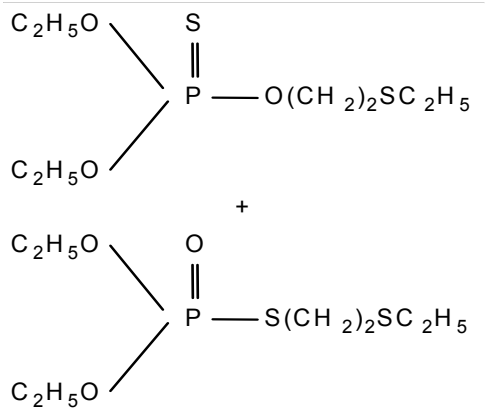
2 Identity

Demeton consists of a mixture of two isomers: demeton-O (thionate isomer) and demeton-S (thiolate isomer), in a ratio of approximately 2:1.

name	:	demeton (mixture of demeton-O and demeton-S)
synonyms	:	phosphorothioic acid, *O*,*O*-diethyl *O*-(ethylthio)ethyl ester (demeton-O); phosphorothioic acid, *O*,*O*-diethyl *S*-(ethylthio)ethyl ester (demeton-S); *O*,*O*-diethyl *O*-(and *S*-)2-(ethylthio)ethyl phosphorothioate; systox; systemox; demox; mercaptofos
molecular formula	:	$C_8H_{19}O_3PS_2$
structural formula	:	
CAS number	:	8065-48-3 (mixture), 298-03-3 (demeton-O), 126-75-0 (demeton-S)

3 Physical and chemical properties

molecular weight	:	258.34
boiling point	:	at 0.2 kPa: 134ºC
melting point	:	> -25ºC
flash point	:	45ºC (closed cup)
vapour pressure	:	at 20ºC : 0.03 Pa
solubility in water	:	at 20ºC: 1.2 mg/100 mL
Log $P_{octanol/water}$	:	4.02
conversion factors	:	not applicable

Data from ACG99, Gal91, NLM02.

The mixture is an oily, colourless to yellow liquid with a characteristic sulphur odour. Contact with strong oxidisers may cause fire and explosions.

4 Uses

Demeton is a systemic insecticide and acaricide effective against sap-feeding insects and mites. It is available as emulsifiable concentrates of varying active ingredient contents (Gal91). According to the database of the Dutch Pesticide Authorisation Board (CTB)*, demeton is at present not registered for its use as an active ingredient in pesticides in the Netherlands. In the USA, demeton as an active ingredient is no longer contained in any registered product, and, thus, the Office of Pesticide Programs of the US Environmental Protection Agency has characterised demeton as 'cancelled' in its Pesticide Registration Status (EPA98) implying that no toxicological review for a reregistration eligibility decision will be prepared.

5 Biotransformation and kinetics

In the mouse, 50-70% of an orally administered dose of demeton was eliminated in the urine within 24 hours. Demeton-S is the same molecule as the oxon metabolite of disulfoton, an analogous insecticide/acaricide (EPA88). Metabolism studies conducted in the 1950's showed that the principal metabolic pathway for both demeton-S and demeton-O is oxidation of the thioether moiety into the corresponding sulphoxides and sulphones. For demeton-O, a secondary pathway involves oxidation of P=S to P=O with subsequent oxidation into its sulphoxide and sulphone. Both isomers and their metabolites are degraded by hydrolysis to form *O,O*-diethylphosphorothiolate (DEPTH) and *O,O*-diethylphosphorothionate (DETP), respectively. By isomerisation, DETP is transformed into DEPTH (Fuk55, Fuk71, Mar55, Men69, WHO87).

When pregnant mice were given a single intraperitoneal injection of 5 mg/kg bw of ^{32}P-labelled demeton at day 14 of gestation, placental tissue, fetal muscle, and osteogenic mesenchyma were highly radioactive within 20 minutes. Fetal tissue showed only a trace of activity after 3 hours, suggesting rapid metabolism and elimination (Bud73a).

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

6 Effects and mechanism of action

Human data

Acute toxicity

A number of cases of serious poisoning and a few deaths caused by intentional or occupational use of demeton have been reported in humans (ACG99, Gal91, WHO87). Death was attributed to demeton in the case of a worker cleaning a plane used in application of the pesticide. Severely depressed plasma ChE and red blood cell AChE activities were measured (Gal91). A case of intoxication has been reported following occupational spraying with demeton by a 16-year-old boy. He suffered general weakness, difficulty in breathing, unconsciousness, and lack of coordination in walking. After 3 months, he still had disturbances of the autonomic nervous system (Gal91).

Short-term toxicity

No clinical symptoms of intoxication were reported in agricultural workers who inhaled demeton at estimated air concentrations between 1 and 6 mg/m^3 during field application of demeton. Most workers had a depressed plasma cholinesterase (ChE) activity (Kag56, Kag58). In a series of controlled human studies over a number of years, test subjects were given daily oral doses of technical grade demeton ('systox') in capsules for 25 days, followed by a recovery period of 32 days. Eighteen different dose levels were given. Beginning at 0.750 mg/person/day, the amount was then increased stepwise with 0.375 mg/person/day until the highest dose of 7.125 mg/person/day was reached. At each dose level, 2 groups were composed: 5 test subjects who were given systox and 2 control subjects who received capsules containing only corn oil. No clinical signs of intoxication were observed at any dose level. At a dose of 4.125 mg/day (0.06 mg/kg bw/day), one out of 5 test subjects showed a marked decrease in plasma ChE and red blood cell AChE activity (59% and 29%, respectively). At dose levels ranging from 4.5 to 6.75 mg/person/day, the average plasma ChE activity was depressed up to 21%, but the average red blood cell AChE activity was not significantly inhibited at any level. However, at the top dose, the average red blood cell AChE activity was inhibited by 16% at the end of administration, while the average plasma ChE activity was decreased by 40%

compared to pre-test levels. Neither inhibition of plasma ChE nor of red blood cell AChE reached a plateau after 25 days of systox administration. Plasma ChE returned to pre-test level within 30 days, but red blood cell AChE was still considerably inhibited. The short-term NOAEL was 3.75 mg/day (i.e., ca. 0.05 mg/kg bw/day), based on inhibition of red blood cell AChE in one out of 5 persons (Rid69).

Animal data

Irritation and sensitisation

The committee did not find data on irritation and sensitisation of demeton using standard methods.

Acute toxicity

Inhalation exposure of 6 Sprague-Dawley rats to commercial systox (60% demeton-O, 40% demeton-S) at an air concentration of 18 mg/m^3 was fatal to all rats within 50-90 minutes after exposure. Following exposure to 3 mg/m^3 for 2 hours, no death or clinical signs of intoxication were reported (Dei55).

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

Table 1 Acute lethal oral and dermal toxicity data for demeton.

exposure route	vehiculum	species (strain)	sex	LD_{50} (mg/kg bw)	reference
dermal	xylene	rat (Sherman)	male	14.0	Gai60
	xylene	rat (Sherman)	female	8.2	Gai60
		rabbit	not specified	24	Tom94
oral	alcoholic solution	rat (‘albino’)	male	10[a]	Bar54
	alcoholic solution	rat (‘albino’)	female	4[a]	Bar54
	corn oil	rat (Sprague-Dawley)	male	5-6	Dei55
	corn oil	rat (Sprague-Dawley)	female	3-5	Dei55
	peanut oil	rat	male	6.2	Gai60
	peanut oil	rat	male	2.5	Gai60
		rat	male	3.8	Bro63

		mouse	not specified	7.85	Tom94
	peanut oil	mouse (Charles River CF-1)	female	14[b]	Bud73b
intravenous		mouse	not specified	1.75	Tom94
		cat	not specified	3.9	Tom94

[a] 'Approximate' LD_{50}.
[b] Observation time: 24 hours.

The composition of the material and formulation used should be taken into account when evaluating the results of different studies. When orally administered in corn oil, purified demeton-S is appreciably more toxic in rats than purified demeton-O based on LD_{50} values of 1.5 and 117 mg/kg bw, respectively (Dei55). The composition of formulation has great impact on the dermal toxicity of demeton. Addition of extra emulsifier reduced the LD_{50} from <24 mg/kg to approximately 620 mg/kg, whereas dilution to spray-strength greatly enhanced the toxicity (LD_{50}: ca. 5 mg/kg) (Dei52).

Demeton (probably the demeton-S isomer) was found not to be neurotoxic in atropinised Rhode Island Red hens (n=2-10/dose level) observed for 30 days after single subcutaneous doses of 5-80 mg/kg bw. The estimated LD_{50} in this study was 20 mg/kg bw and signs of cholinergic poisoning were already obvious at 10 mg/kg bw (Dur56).

Short-term toxicity

Rats (Sprague-Dawley; n=20; sex not indicated) were exposed by inhalation to 3 mg/m^3 commercial systox, 1 hour/day for up to 12 days. No signs of intoxication were observed following 2 days of exposure. Brain AChE, red blood cell AChE, and plasma ChE activities, measured in 2 rats immediately after the second exposure, were inhibited by about 25%, 30%, and 15%, respectively. Mild tremors were observed after 4 days of exposure, marked tremors and lachrymation after 6 days of exposure. Eight out of 20 rats died during exposure days 6 to 12. Immediately following 6 or 12 days of exposure, cholinesterase activities (measured in 2 rats after each exposure) were reduced to a similar extent; brain AChE activity was inhibited by about 55%, red blood cell AChE by about 52%, and plasma ChE by about 39% (Dei55). Daily 2-hour inhalation of 3 mg/m^3 systox for 2 to 3 days caused tremors and lachrymation; death of 10 out of 17 Sprague-Dawley rats was observed after 4 days of exposure (no more data presented) (Dei55).

Female albino rats (n=12/group) were fed levels equivalent to 0, 0.5, 1.0, and 2.5 mg/kg bw/day of systox (approximately 52% demeton-O and 48% demeton-S) for 16 weeks. Animals at the high dose showed cholinergic signs of toxicity (tremors, salivation, fasciculations, weakness). During the first 4 weeks, food intake and body weight gain were decreased, and after 4 weeks, 3 out of 12 rats were killed because of the severity of their illness. Thereafter, the remaining rats gradually recovered despite continued ingestion of the high-dose diet. However, body weights of the high-dose rats remained below those of control animals throughout the study in spite of a high food intake. Terminal whole blood cholinesterase (combined activity of plasma ChE and red blood cell AChE) and brain AChE activities were inhibited by 92 and 93%, respectively. At 1 and 0.5 mg/kg bw/day, no overt signs of toxicity were observed. However, terminal whole blood cholinesterase activity was inhibited by 85 and 72% and brain AChE by 87 and 73%, respectively (Bar54). In a subsequent experiment by the same authors, female rats (n=18/group) were given systox at dietary levels equivalent to 0, 0.05, 0.15, and 0.5 mg/kg bw/day for 11 weeks. In the mid- and high-dose groups significant decreases in terminal plasma ChE (30 and 72%), red blood cell AChE (20 and 84%) and brain AChE (34 and 80%) activities (measured in 7 or 8 animals) were recorded. At 0.05 mg/kg bw/day, a slight decrease in terminal cholinesterase activities (measured in 7 animals) was still detectable (plasma ChE: 4.5%, red blood cell: AChE 17%, brain: AChE 7%) (Bar54). The committee considers inhibition of red blood cell and brain AChE activity at the lowest dose level tested (0.05 mg/kg/day) not biologically significant, and, therefore, the NOAEL for red blood cell and brain AChE inhibition in this study was 0.05 mg/kg/day.

In a 90-day oral study, Sprague-Dawley rats (n=5/group; sex not indicated) were given systox (approximately 60% demeton-O and 40% demeton-S) in corn oil at levels equivalent to 0, 0.4, 0.66, 0.9, or 1.89 mg/kg bw (0, 4, 7, 10, and 20% of previously determined oral LD_{50}) by stomach tube, for 5 days/week. No signs of intoxication were observed at the 2 lower doses, but at 0.9 mg/kg bw, animals displayed hyperexcitability and tremors, and at 1.89 mg/kg bw, 1 out of 5 animals died after 17 days. Gross and microscopic examination of the major organs of the treated animals revealed no significant differences when compared to controls. Cholinesterase activities were not reported. The NOAEL for signs and symptoms was 0.66 mg/kg/day (Dei55).

New Zealand rabbits (n=6/group; sex not indicated) were fed systox-contaminated greens at levels equivalent to 0.07, 0.15, 0.5, 1.5, and 2.3 mg/kg bw/day for 94, 98, 100, 30, and 40 days respectively. At 2.3 mg/kg bw/day, 3 out

of 6 animals died during treatment days 14-30. Plasma ChE activity was reduced immediately after dosing levelling off after 15 days of treatment at 70% of normal. Treatment was discontinued after 40 days. Ingestion of 1.5 mg/kg/day caused mortality in 4 out of 6 animals during days 15-30, after which treatment was discontinued. Plasma ChE activity was promptly reduced levelling off after about 12 days at about 45%. Determination of plasma ChE activity in the 2 surviving animals 3 weeks after ending treatment showed values within the normal range. Feeding 0.5 mg/kg bw for 100 days caused mortality in one out of 6 animals (at day 64). Treatment gradually decreased plasma ChE activity, which levelled off after 30 days at 85% of normal. At 0.15 and 0.07 mg/kg bw/day, fed for 98 and 94 days, respectively, neither fatalities nor reduced plasma ChE levels occurred. Generally, no animal showed any obvious signs of toxicity at a time when marked reductions in plasma ChE activities were observed. In animals that died, symptoms observed 3 to 5 days preceding death included respiratory distress, frothing at nose and mouth, marked diarrhoea, muscular paralysis, coma, and mild asphyxial convulsions. The NOAEL for plasma ChE inhibition was 0.15 mg/kg/day (Dei55).

Groups of young adult dogs (mixed breed; n=1/sex/group) were given dietary levels of systox equivalent to 0, 0.025, 0.047, and 0.149 mg/kg bw/day for 24 weeks. Only effects on plasma and red blood cell cholinesterase activity were studied. Blood samples were regularly drawn during a 3-week pre-treatment period (5 times), during treatment (at weekly intervals for the first month, at biweekly intervals for the next 5 months), and during the exposure-free recovery period (weekly for the first month, 2- or 3-weekly thereafter) until normal activity was restored. Dogs receiving 0.149 mg/kg bw/day showed decreases in plasma ChE and red blood cell AChE activities reaching maximum inhibition by approximately 70% and 30%, when compared to pre-treatment levels, after about 12 weeks of feeding. Recovery of plasma activity to ‘ normal’ levels was complete within 4 weeks after ending treatment. Recovery of red blood cell activity was much slower. Although levels were comparable to those of control animals after an 11-week exposure-free period, they were still only about 80-85% of the pre-treatment activities. At 0.047 mg/kg bw/day, significant plasma ChE inhibition (ca. 25%) was found only after 16 weeks of feeding, returning to ‘normal’ levels within 2-4 weeks post-exposure. Red blood cell AChE activity was not affected. At 0.025 mg/kg bw/day, no significant inhibition of plasma ChE or red blood cell AChE was found. The NOAEL for ChE inhibition in this study was 0.025 mg/kg/day, based on inhibition of plasma ChE and 0.047 mg/kg bw for inhibition of red blood cell AChE (Fra57).

The above studies are summarised in Table 2.

Table 2 Summary of short-term toxicity studies for demeton.

exposure route	species (strain; number; sex)	dose levels	exposure duration	critical effect[a]	NOAEL	reference
inhalation	rat (Sprague-Dawley; n=20; ?)	0, 3 mg/m^3	1 h/d, up to 12 d	BAChE	<3 mg/m^3	Dei55
	rat (Sprague-Dawley; n=17; ?)	0, 3 mg/m^3	2 h/d, up to 4 d	cholinergic symptoms	<3 mg/m^3	Dei55
oral	rat ('albino'; n=12/group; female)	0, 0.5, 1.0, 2.0 mg/kg bw/d	16 w	BAChE	<0.5 mg/kg bw/d	Bar54
	rat ('albino'; n=18/group; female)	0, 0.05, 0.15, 0.5 mg/kg bw/d	11 w	BAChE and RAChE	0.05 mg/kg bw/d	Bar54
	rat (Sprague-Dawley; n=5/group; ?)	0, 0.04, 0.66, 0.9, 1.89 mg/kg bw/d	90 d	cholinergic symptoms	0.66 mg/kg bw/d	Dei55
	rabbit (New Zealand; n=6/group; ?)	0, 0.07, 0.15, 0.5, 1.5, 2.3 mg/kg bw/d	94-30 d	cholinergic symptoms or plasma ChE	0.15 mg/kg bw/d	Dei55
	dog (mixed breed; n=1/sex/group)	0, 0.025, 0.047, 0.149 mg/kg bw/d	24 w	RAChE	0.047 mg/kg bw/d	Fra57

[c] BAChE= brain AChE; RAChE= red blood cell AchE

Long-term toxicity and carcinogenicity

The committee did not find data from long-term or carcinogenicity studies.

No carcinogenicity was observed for disulfoton, of which demeton-S is a metabolite (HCN03).

Mutagenicity and genotoxicity

Mutagenicity and genotoxicity assays comprised *in vitro* tests for the detection of gene mutations in bacteria and *in* vitro cytogenicity and other genotoxicity assays.

- Gene mutation assays. *In vitro* tests for reverse mutations in several strains of *S. typhimurium* (TA98, TA100, TA 1535, TA 1537, TA 1538) and in *E. coli* WP2 were positive both with and without metabolic activation (Bru80, Kie86, Sim79, Wat80). Demeton was negative in a sex-linked recessive lethal test with *D. melanogaster* (Lee83).

- Cytogenicity assays. In cultured Chinese hamster V79 cells, the chemical induced sister-chromatid exchanges (SCE) in the presence of a metabolic activation system (Che82). An increase in the frequency of SCE was also observed in cultured lymphocytes (source not specified) (Dzw89).
- Other genotoxicity assays. Demeton induced mitotic recombination in *S. cerevisiae* D3 both with and without metabolic activation (Zim84). The chemical was positive in DNA-repair-deficient *B. subtilus* but negative in DNA-repair-deficient *E. coli* polA (Lei81).

In summary, demeton is an *in vitro* mutagen, but the committee did not find data from genotoxicity studies in test animals.

Reproduction toxicity

The teratogenic and embryotoxic potential of demeton was studied in Charles River CF-1 mice that were given demeton as single or as 3 consecutive intraperitoneal doses on specific days of gestation. Single doses of 7 or 10 mg/kg bw were administered to groups of mice (number not specified) on either day 7, 8, 9, or 10 of gestation, single doses of 7, 10, or 14 mg/kg bw on day 11 of gestation, and a single dose of 10 mg/kg bw on day 12 of gestation. Consecutive doses of 10 mg/kg bw/day were administered on days 7-9, 8-10, or 9-11 of gestation. In some groups of pregnant mice, fetuses were removed by caesarean section on days 16 and 18 of gestation; other groups were allowed to deliver pups. A dose-related decrease in 16-day fetal weights was observed if demeton was given as single doses on or after day 9 of gestation. These effects were not seen in 18-day fetuses. The percentage of resorptions was not affected by demeton treatment; however, the percentage of dead fetuses was increased, the increase being statistically significant with treatment on day 12. A dose-related increase was found in the number of anomalies of the digestive and skeletal systems in 16-day fetuses compared to control animals. However, no such effects were observed in 18-day fetuses, indicating that the majority of the abnormalities in 16-day fetuses may have been due to growth retardation. Single treatment of 10 mg/kg bw on days 8, 9, or 10 of gestation had no effect on litter size and stillbirths at delivery or on 28-day pup survival. However, at birth, pup weights were lower than that of the controls. Growth rate of pups was comparable to controls, but was lower if treatment was given on day 10 of gestation. Administration of 3 consecutive doses of 5 mg/kg bw each did cause some minor skeleton abnormalities. The frequency of dead fetuses was not increased, but 16-

day fetal weight was significantly lower than that of the controls. The author's conclusion was that embryotoxic and teratogenic effects, observed at high doses (10 mg/kg bw) of demeton, were probably the result of maternal toxicity (Bud73b, WHO87).

Ducklings hatched from eggs inoculated with 10 or 100 µg demeton on day 13 via the yolk were hyperexcitable and in some cases had leg paralysis and body tremors with intermittent convulsions. Average body weight and growth rate during the 2-week observation period were lower than in controls (Khe65).

The committee considers these studies not adequate for the assessment of reproduction toxicity.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for demeton in the Netherlands is 0.1 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

Workers can be exposed to demeton through inhalation or by direct skin contact with a formulation of the compound. However, the committee did not find quantitative data on absorption of demeton through the lungs or the skin. The extent of absorption following oral intake is at least 50-70% in mice, but the committee did not find data for other species. Demeton-S is a metabolite of disulfoton. Based on the rapid excretion of repeated oral doses of disulfoton (approximately 90% of the doses are excreted in the urine within 24 hours), the committee expects that, following absorption, demeton is rapidly metabolised and excreted and does not accumulate in tissues.

Case studies in humans show a high acute toxicity of demeton following accidental exposures. Demeton-S was considerably more toxic than the O-isomer. Effects observed in these studies were typical cholinergic symptoms such as weakness, respiratory difficulty, and lack of coordination in walking. In a human volunteer study, oral intake of approximately 0.10 mg/kg bw/day for 25 days produced inhibition of average red blood cell AChE (16%) and plasma ChE (40%) without cholinergic symptoms. The NOAEL for red blood cell AChE or plasma ChE inhibition in humans was 0.05 mg/kg bw/day.

The committee did not find data from studies on eye or skin irritation or on skin sensitisation of the compound. Based on results of acute lethal toxicity studies in test animals, the committee considers the compound as very toxic after respiratory, dermal, and oral exposure. In a limited acute neurotoxicity study in hens, the compound did not cause acute delayed neurotoxicity. No significant systemic effects have been reported in short-term studies in test animals. However, these studies showed inhibition of red blood cell and brain AChE in rats and of red blood cell AChE in dogs (brain AChE not measured). For the rat, the NOAEL for inhibition of brain and red blood cell AChE was 0.05 mg/kg bw/day (11-week oral study). For the dog, the NOAEL for inhibition of red blood cell AChE was 0.047 mg/kg bw/day (24-week oral study).

Results of *in vitro* mutagenicity tests indicate that demeton has significant genotoxic potential. However, no data are available on the genotoxicity in test animals. No data on long-term or carcinogenicity studies are available for demeton. Since disulfoton, of which demeton-S is a metabolite, was not carcinogenic in experimental animal studies (see HCN03), the committee expects that demeton is not carcinogenic. The committee considered a developmental toxicity study of demeton in mice not to be adequate for the assessment of reproduction toxicity.

Based on the above data, the committee concludes that the mechanism of toxicity of demeton in mammals is through inhibition of AChE activity in nerve tissue. The committee identifies inhibition of AChE in brain tissue as the most sensitive adverse toxic effect of demeton in animal studies, occurring at dose levels, which are lower than those causing other toxic effects. In human beings, for obvious reasons, brain AChE cannot be measured. Instead, red blood cell AChE, being the same molecular target for inhibition by organophosporus pesticide as brain AChE, is used as a surrogate for brain AChE in assessing the human health risk of exposure to demeton (Jey94).

The committee takes the NOAEL of 0.05 mg/kg bw/day derived from the 25-day human volunteer study as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week, this NOAEL from a continuous study (i.e., 7 days a week) is adjusted by multiplying with a factor of 7/5 resulting in a no-adverse-effect level (NAEL) of 0.07 mg/kg bw. For extrapolation to a HBROEL, an overall assessment factor of 6 is used, covering the following aspects: intraindividual variation and confidence in the database. This results in a NAEL for humans of 0.01 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 0.1 mg/m^3 is recommended for demeton.

The committee recommends a health-based occupational exposure limit for demeton of 0.1 mg/m^3, as an 8-hour time-weighted average (TWA).

In view of the high acute lethal dermal toxicity in rats, the committee recommends a skin notation.

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Annex

Occupational exposure limits for demeton 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	0.01	0.1	8 h	administrative	S	SZW03
Germany						
- AGS	0.01	0.1	8 h		S	TRG00
	0.04	0.4	15 min			
- DFG MAK-Kommission	-[c]	-			[d]	DFG02
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Arb02
Denmark	0.01	0.1	8 h		S	Swe00
USA						
- ACGIH	-	0.05[e]	8 h	TLV	S	ACG03b
- OSHA	-	0.1	8 h	PEL	S	ACG03a
- NIOSH	-	0.1	10 h	REL	S	ACG03a
European Union						
- SCOEL	-	-				EC03

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

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

[c] Listed among substances for which studies of the effects in man or in experimental animals have yielded insufficient information for the establishment of MAC values.

[d] Compound is not registered as a pesticide.

[e] Measured as inhalable fraction of vapour and aerosol.