Methyl-S-demeton

(CAS No: 919-86-8)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of methyl-S-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 JAGM van Raaij, Ph.D. and WK de Raat, Ph.D. (OpdenKamp Registration & Notification, Zeist, the Netherlands) and J Krüse, Ph.D. (Kinetox, Vleuten, the Netherlands).*

The evaluation of the toxicity of methyl-S-demeton has been based on reviews published in the 'Handbook of pesticide toxicology' (Gal91) and by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1999, literature was searched in the on-line databases Toxline, Medline, Chemical Abstracts, covering the period of 1964-1966 until December 1999, and using the following key words: methyl demeton and 919-68-8. Data from unpublished studies were generally not taken into account. Exceptions were made for studies that were summarised and evaluated by international bodies such as the Food and Agricultural Organization/World Health Organization (FAO/WHO: Joint Meeting of the FAO Panel of Experts on Pesticides Residues on Food and the Environment and the WHO Expert Group on Pesticides Residues - JMPR) (FAO90, WHO85) and the International Programme on Chemical Safety/World Health Organization (IPCS/WHO) (WHO97).

The early commercial methyl demeton consisted of methyl-S-demeton and methyl-O-demeton in a ratio of 30:70. From 1957 onwards, this 'methyl demeton' was replaced by a product without methyl-O-demeton. The assessment was, therefore, focussed on methyl-S-demeton; studies with the older 'methyl demeton' were not taken into account; only studies carried out after 1957 were included in the assessment. No assessment is made of oxodemeton-methyl, a metabolite of methyl-S-demeton, which is used as an insecticide in itself.

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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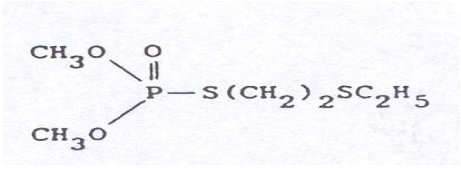
2 Identity

name	:	methyl-S-demeton
synonym	:	phosphorothioic acid *O*,*O*-dimethyl *S*-[2-(ethylthio)ethyl] ester; *S*-(2-ethylthioethyl) *O*,*O*-dimethyl phosphorothioate; *O*,*O*-dimethyl *S*-2-(ethylthio)ethyl phosphorothioate; *O*,*O*-dimethyl-*S*-2-ethylmercaptoethyl phosphorothioate; demeton-S-methyl; metasystox; meta-isosystox; isomethylsystox; methyl-mercaptophos
molecular formula	:	$C_6H_{15}O_3PS_2$
structural formula	:	
CAS number	:	919-86-8

No consistent nomenclature is used in the open literature. Studies on methyl-S-demeton should not be confused with studies on methyl demeton (30:70 mixture of S- and O-isomers) or studies on oxydemeton-methyl (a metabolite of methyl-S-demeton). The CAS registry numbers of methyl demeton, oxydemeton-methyl (metasystox R) or methyl-S-demeton are not always correctly cited in scientific publications.

3 Physical and chemical properties

		methyl-S-demeton	methyl-O-demeton
molecular weight	:	230.29	230.29
boiling point	:	at 0.052 mm Hg: 89°C	at 0.15 mm Hg: 74°C
melting point	:	-	-
flash point	:	-	-
vapour pressure	:	at 20°C: 0.04 Pa	-
solubility in water	:	soluble (at 20°C: 22 9/100 mL	insoluble (33 mg/100 mL)
Log $P_{octanol/water}$	:	at 20°C: 1.32	
Conversion factors	:	not applicable	

Data from ACG99, Gal91, NLM02, Rob99, Tom97.

Technical-grade methyl demeton is a mixture of the O-isomer and the S-isomer in a ratio of approximately 70:30. The purified S-isomer was introduced in 1957 and after some time, it replaced the mixture because it was found to be more toxic to insects than the O-isomer. The S-isomer is a pale yellow oily liquid with an unpleasant odour.

Methyl-S-demeton rapidly hydrolyses after contact with alkaline substances. Under acidic and neutral circumstances methyl-S-demeton is more slowly hydrolysed (Tom97). Methyl-S-demeton is oxidised to the sulphoxide (oxydemeton-methyl) and eventually to the sulphone (demeton-S-methyl sulphone) before it finally decomposes. Furthermore, several sulphonium compounds of variable stability can be found, which are known to be strong inhibitors of ChE activity (ACG99, Hea57). The final toxicity of the methyl demeton formulations may depend on formation of these impurities during storage (Gal91, Mei90).

4 Uses

Methyl-S-demeton is applied as insecticide and acaricide for control of aphids, mites, and whiteflies on fruit, vegetables, potatoes, beet and hops (Tom97).

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

5 Biotransformation and kinetics

Methyl-S-demeton absorbs into the human body through the intact skin (Red68), from the gastro-intestinal tract (Sch88), or by inhalation of spray mist (Heg65, Kli58). The committee did not find quantitative data on inhalation or dermal absorption of the compound in humans or experimental species.

The kinetics of methyl-S-demeton were studied by administration of single oral doses of ^{14}C-labelled compound of 0.1, 0.5, 5, or 10 mg/kg bw or single intravenous doses of 0.5 or 1.0 mg/kg bw to male and single oral doses of 0.5 mg/kg bw to female Sprague-Dawley rats (n=5/sex/group). Total recovery of radioactivity was 99-100% in each animal. The authors reported that test results were largely independent of dose level, administration route, and sex of the animals, and presented, therefore, mainly data on male rats receiving a dose of 5 mg/kg. The test material was very rapidly and almost completely absorbed. The blood concentration peaked at about one hour following administration, and

decreased thereafter with half-lives of 2, about 6, and considerably longer than 6 hours during the first 6 hours, the next 48 hours, and thereafter, respectively. Nearly all the radioactivity in blood after 24 hours was accounted for by a high retention in erythrocytes, serum radioactivity levels being low. More than 50% and approximately 90% of the radioactivity administered were eliminated within about 3 and 8 hours following administration, respectively. Forty-eight hours after dosing, radioactivity excreted in urine, faeces, and exhaled air accounted for 98-99, 0.5-2.0, and 0.2% of the amount administered, respectively. The half-life of urinary elimination was 2-3 h during the first 24 hours and 1.5 days thereafter. Except for erythrocytes, radioactivity was distributed rather uniformly in various body tissues and organs and did not concentrate in fat tissue or in the reticuloendothelial system (liver, spleen, bone marrow). The radioactivity remaining in the body was about 60%, 1%, and 0.5% of the administered dose at 2, 24, and 48 hours after dosing, respectively. At 10 days, radioactivity was nearly undetectable in most organs and tissues except in the erythrocytes. In a separate experiment, whole-body autoradiography confirmed these findings regarding distribution of radioactivity but also indicated some localised accumulation in the pineal gland, thyroid, and some genital tract glands (Cowper's gland, seminal vesicle, accessory genital gland). When a dose of 0.5 mg/kg bw was administered into the duodenum of rats with cannulated bile ducts, about 3% of the radioactivity was excreted in the bile within 24 hours (Web78). Analysis of urine sampled from those rats 8 or 24 hours after administration of a single oral dose of 5 or 10 mg/kg bw of ^{14}C-labelled methyl-S-demeton showed almost complete metabolism. The main route was oxidation of the side chain to the corresponding sulphoxide (58%), and further oxidation to the sulphone (6%). Another route involved O-demethylation resulting in the formation of *O*-demethyl-methyl-S-demeton (6%) and the corresponding sulphoxide (6%) and sulphone (4%). Finally, 2 other metabolites, probably the result of cleavage of the *O*-methylphosphoric ester group and subsequent methylation and sulphoxidation, were identified as methyl sulphinyl-2-ethyl sulphinyl ethane (8.4%) and methyl sulphinyl-2-ethyl sulphonyl ethane (10.4%). One other metabolite accounting for less than 1% of the radioactivity administered was not further investigated. There were no indications for the presence of glucuronide or sulphate conjugates (Eck78, Eck83).

Hydrolysis leads to the formation of dimethyl phosphate. The analysis of the metabolite *O,O*-dimethylphosphorothioate (DMPT) has been shown to be a good indicator for the occupational exposure to demeton-S-methyl (Vas87).

6 Effects and mechanism of action

Human data

Ingestion of 50 to 500 mg methyl-S-demeton/kg bw resulted in acute cardiovascular collapse and death 83 hours after exposure (Gos84). Another case involved a 65-year-old man who died following ingestion of approximately 15 mL of a mixture of methyl-S-demeton (25% w/w) and benzene methylchloride. The subject developed severe signs of poisoning such as perspiration, pulmonary discharge, and other characteristic symptoms of organophosphorus intoxication 32 hours after exposure. Acute pulmonary embolism was responsible for his death. It is unclear from this study to which extent benzene methylchloride contributed to the toxic effects (Bar64). A farmer who drunk about 90 mL of an old type formulation in which 70% of the active ingredient was present as methyl-O-demeton, developed nervous excitation, salivation, coughing of mucus, and muscle fasciculations. Gastric lavage in hospital improved his condition (UKM69). Headaches, nausea, and dizziness were observed in a farmer 2 weeks after he started handling/spraying methyl-S-demeton ('metasystox new formula'). He was exposed to the chemical on at least 23 occasions for periods varying from 20 minutes to 6¾ hours, and was mostly engaged with flagging during aerial spraying but also in the preparation of the formulation. Clinical signs and symptoms of intoxication gradually increased, and he collapsed while using another organophosphorus pesticide. Serum ChE activity was depressed by 90%. Following treatment with atropine, he fully recovered. The author suggested that absorption through the skin contributed to the toxic effects of methyl-S-demeton and that the acute exacerbation of the symptoms were possibly the result of inhalation of the chemical (Red68). A 2-year-old boy who ingested 10 mL methyl-S-demeton was admitted to the hospital and treated with atropine and obidoxime for 5 days. Clinical signs and symptoms were excessive salivation, vomiting, bronchial hypersecretion, muscarinic effects on pulse rate and pupil size, and slight bradycardia. Initial values of plasma-ChE concentrations were depressed by 90%, but returned to baseline levels 8 days after admission to the hospital (Rol98).

Lethal suicidal intoxication with methyl-S-demeton has been reported for a man who deliberately ingested an estimated amount of 5 g of the chemical. Chromatographic analysis of various body tissues revealed that the concentrations of methyl-S-demeton varied from 7 mg/kg in the liver to 165.3

mg/kg in the upper intestinal tract. A remarkably high concentration of methyl-S-demeton was observed in the liquor (83.8 mg/L) when compared with heart blood (16.1 mg/L) (Sch88).

One field study has been reported in which the health implications following application of methyl-S-demeton were assessed. The study dealt with a number of sprayers and bystanders who had been exposed occupationally or accidentally to the chemical during cotton spraying. Serum ChE activity was measured following the onset of toxic signs and symptoms. At day one after the signs of intoxication, serum ChE activity was inhibited in 25 sprayers by 64% when compared to the average activity in 53 control persons. Recovery to normal values occurred 21 days after the intoxication. ChE activity in bystanders was not changed. The main signs of toxicity in the accidentally exposed bystanders included drowsiness, vomiting, and abdominal pain. These symptoms were also observed in the occupationally exposed sprayers, who further showed diarrhoea, nausea, fatigue, headache, respiratory problems, salivation, and lachrymation. A correlation between serum ChE levels and symptomatology was found for sprayers but not for bystanders (Heg65). Two groups of 2 human volunteers applied metasystox (a 30:70 mixture of the S- and O-isomers) in greenhouses for 5 consecutive days, 5 hours/day. No significant changes were found in serum ChE or red blood cell AChE activities. Two different types of spray equipment were used. The average airborne concentrations were 1.9 mg/m^3 and 0.28 mg/m^3. Haemoglobin, erythrocyte count, and lymphocyte count were not altered. However, a marked increase (400%) in mean reticulocyte count was observed (Kli58).

Animal data

Irritation and sensitisation

Following instillation of 0.1 mL of a 0.5% aqueous solution of a commercial formulation of methyl-S-demeton (50% active ingredient) into the eyes of New Zealand white rabbits (n=3) for 24 hours, no signs of irritation were observed. Instillation of undiluted test substance caused severe lachrymation and miosis on application. Mild corneal opacity and discrete redness and oedema of conjunctivae were observed and recovered in about 7 days (Flu83). Testing a ca. 50% solution in xylene showed slight eye irritation in rabbits but this was attributed to xylene (Thy81).

Occluded application of 0.5 mL of a similar formulation to the shaved skin of New Zealand white rabbits (n=3) for 4 hours caused mild erythema and oedema, which generally disappeared within 3 days (Flu83). Testing a ca. 50% solution in xylene showed slight skin irritation in rabbits but this was attributed to xylene (Thy81).

In a Magnusson-Kligman maximisation test, 20/20 guinea pigs reacted positively to a the first challenge with a 10% solution of methyl-S-demeton (purity: 96.3%), after a intradermal induction with a 0.1% solution, and 16/20 to a second challenge with a 1% solution *vs.* 4/10 and 3/10 positive reactions in controls, respectively (Hei87a). When testing methyl-S-demeton (purity: 95.6%) in the Buehler epidermal patch test on 12 guinea pigs (topical induction with a 10% solution, once a week, for 3 weeks; 1st challenge: 10% solution; 2nd challenge: 20% solution), there were no indications for a skin-sensitising potential of methyl-S-demeton (Hei87b).

Acute toxicity

Four-hour LC_{50} values for methyl-S-demeton in rats were 500 (sex not specified), 310 (male Wistar), and 210 mg/m^3 (female Wistar) (Flu83, NIO02). The dermal LD_{50} value for undiluted methyl-S-demeton in male rats was 250 mg/kg bw (Dub62) while values ranging from about 10 (25% formulation) to 100-200 ('technical') mg/kg bw were listed as well for rats (WHO97). Oral LD_{50} values in rats were between 33 and 129 mg/kg bw (WHO97).

Hens, given 2 oral doses of 100 mg/kg bw methyl-S-demeton (about the LD_{50} value) with a 21-day interval, and atropinised to survive, did not show nerve injury. No organophosphate-induced delayed polyneuropathy (OPIDN) was observed in the animals (Flu88a). In another study, neuropathy target esterase (NTE), an enzyme which may be predictive for delayed polyneuropathy, was not inhibited in hen brain and spinal cord 1, 2, and 7 days after treatment with an oral dose of 80 mg/kg bw (Flu88b).

Subchronic toxicity

In a one-year study, dogs (n=6/sex/group) were fed diets containing 52.2% methyl-S-demeton in xylene at dose levels equivalent to 0, 0.036, 0.36, or 3.6 mg/kg bw/day. From week 37 onwards, the concentration in the high-dose group was reduced to 1.8 mg/kg bw/day. No mortality was reported. Clinical signs (vomiting, diarrhoea) were most frequently seen in the high-dose group.

Reduced food intake occurred in the high-dose group before dosage reduction. Body weights were not affected in any of the groups. Abnormalities were neither detected in haematological and clinical chemical parameters, nor in organ weights and gross examination at termination. Hepatic cytochrome P450 and *N*-demethylase activity were not altered by the treatment. However, hypertrophy of the proximal tubules was observed in 3 males and 3 females of the high-dose group. Brain AChE activity was suppressed by 64% in the males and by 15% in the females of the high-dose group when compared to their control counterparts; red blood cell AChE by 80-90% and 55-65% in males and females, respectively, and plasma ChE by 45-65% (males) and 50-70% (females). In the mid-dose group, brain AChE activity was suppressed when compared to controls by 25% in males. Red blood cell AChE activity was also reduced by 25-35% in males and by 30-45% in females, and plasma ChE by 20-30% in males and by 5-20% in females. The one-year dog NOAEL for brain and red blood cell AChE inhibition was 0.036 mg/kg bw (Bat83).

Chronic toxicity and carcinogenicity

In a 2-year study with Wistar rats (n=60/sex/group), the animals were given methyl-S-demeton (50% in xylene) in dietary concentrations equivalent to 0, 0.05, 0.35, or 2.5 mg/kg bw/day. Rats in the control group were given xylene at a concentration of 2.5 mg/kg bw. Clinical signs (hair loss, diarrhoea) were observed in the high-dose group. Clinical chemical and haematological parameters were not affected by the treatment. Histological examination did not reveal an increased incidence of neoplastic lesions in treated groups. Retinal atrophy and keratitis were observed in animals of both sexes given 2.5 mg/kg bw. Red blood cell AChE activity was reduced at 0.35 mg/kg bw (by 12-31%) and 2.5 mg/kg bw (by 20-44%) from the third month onwards. AChE activity in the brain was reduced by 67-75% in the high-dose group and by 15-47% in the mid-dose group. The 2-year rat NOAEL for inhibition of brain and red blood cell AChE activity was 0.05 mg/kg bw/day (Sch88b).

In a 21-month study, groups of NMRI mice (n=70/sex/group) were fed methyl-S-demeton (50% in xylene) at levels equivalent to 0, 0.25, 3.75, or 18.75 mg/kg bw/day. The control group was fed xylene at a dose of 18.75 mg/kg bw in the diet. No clinical signs of cholinesterase inhibition were observed. Food intake and body weight were reduced in the high-dose group. Clinical chemical and haematological parameters were not affected by the treatment, except plasma urea that was lower in the high-dose males. Histopathology did not reveal an

increased incidence of tumours and of non-neoplastic lesions. At the 2 highest dose levels, red blood cell AChE activity was reduced up to 70% in males and 38% in females. The 21-month mouse NOAEL for inhibition of brain and red blood cell AChE activity was 0.25 mg/kg bw/day (Sch88a).

Mutagenicity and genotoxicity

In vitro, methyl-S-demeton (purity: not known) induced reverse gene mutations in *S. typhimurium* strains TA1530 and TA1535, but not in several other strains, such as TA1531, TA1532, TA1534, *hisC117*, and *hisG46* (tests without metabolic activation only) (Han75). Tested both with and without metabolic activation, methyl-S-demeton (purity: >98%) was positive in *S. typhimurium* strains TA100 and TA1535 and negative in strains TA98 and TA100 (Her80a) while an overall positive result was reported for a 50.2% formulation using the same 4 strains (Her79). Testing in several *E.coli* strains without metabolic activation resulted in positive results in strain WP2 *uvrA* only (not tested with metabolic activation) (Han75). Methyl-S-demeton as a 53% formulation in xylene did not induce mutations in *S. cerevisiae* strains S138 and S211a when tested in the presence or absence of an S9 mix (Hoo83). The chemical induced recessive-lethal mutations in *D. melanogaster* (Han75). A test for forward gene mutations in cultured mouse lymphoma L5178Y cells was positive at doses of 50-500 µg/mL in the presence and absence of metabolic activation (Cif84).

Methyl-S-demeton (purity: 93%) was negative when tested with and without metabolic activation the *E. coli* polA (W3110/p3478) assay, a test indicative for DNA damage (Her83a).

In vivo, in NMRI mice, methyl-S-demeton (purity: >98%) was negative in a dominant lethal assay (route: oral; highest dose tested: 5 mg/kg bw; no more data available) (Her80b) as well as in a bone marrow micronucleus test (route: oral; highest dose tested: 2 x 5 mg/kg bw; no more data available) (Her80c). Methyl-S-demeton (purity: 94%) did not cause a significant increase in the frequency of sister chromatid exchanges in bone marrow cells of Chinese hamsters at oral doses of 5-20 mg/kg bw (Her83).

Reproduction toxicity

In a 2-generation study, SPF rats (10 males and 20 females) were given 0, 0.07, 0.35, or 1.75 mg/kg bw of methyl-S-demeton in the diet. Controls received 1.25

mg/kg bw of xylene. The chemicals were administered to 42-49-day-old F0 generation rats and continued uninterrupted throughout the successive generations. No mortality occurred in the F0 generation groups, but in the F1 generation, one animal died at 0.35 mg/kg bw and one at 1.75 mg/kg bw. Reduced body weight gain and food intake were observed at the highest dose in both F0 and F1 generations compared to the xylene-treated animals. Animals in the control group also showed a reduced body weight. Fertility index was not affected by the treatment. The number of pups at birth was reduced in the high-dose group and pup viability was decreased at 0.35 and 1.75 mg/kg bw in a dose-related manner. Body weight at birth was comparable among groups while body weight gain was reduced by 8-10% in pups in the high-dose group. Lactation index was also reduced in the high-dose group. No compound-related malformations were found in any of the treatment groups. The NOAEL for maternal and reproduction toxicity was 0.07 mg/kg bw/day (Eib84).

Oral treatment of fertilised female rats (BAY:FB 30; n=25/group) with 0, 0.3, 1, or 3 mg methyl-S-demeton/kg bw/day (52.6% in xylene), during days 6-15 of pregnancy did not result in clinical signs of intoxication. Body weight gain was reduced in the high-dose group. Pups were delivered at day 20. The number of resorptions, implants and live fetuses, fetal body weight, and fetuses with malformations were comparable among groups. No treatment-related external, visceral, or skeletal abnormalities in fetuses were observed. There was no evidence of embryotoxicity or teratogenicity at any of the doses tested. The NOAEL for maternal toxicity was 1 mg/kg bw/day and for developmental toxicity 3 mg/kg bw/day, the highest dose tested (Ren85).

Methyl-S-demeton (52.2% in xylene) was orally (gavage) given to mated female rabbits (Chinchilla Hybrid; n=16/group) at doses of 0, 3, 6, and 12 mg/kg bw/day during gestation days 6 to 18. Caesarean sections were performed on gestation day 28. There was no mortality. Maternal toxicity was limited to the high-dose group and included diarrhoea - after 4 to 10 days of treatment; beginning 1-2 hours after dosing and persisting for 6-24 hours – and decreased food consumption and body weight gain. Apart from a decrease in mean fetal body weight of 6.6% in the high-dose group when compared to mean control weight, no treatment-related effects were seen on reproductive parameters or on incidences of external, visceral, or skeletal malformations in fetuses in any of the treated groups. In this oral developmental toxicity in rabbits, the NOAEL for both maternal and developmental toxicity was 6 mg/kg bw (Bec83).

7 Existing exposure limits

The current administrative exposure occupational limit (MAC) for methyl-S-demeton in the Netherlands is 0.5 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for methyl-S-demeton in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The health hazard assessment of methyl-S-demeton is based mainly on a toxicology review issued by the FAO/WHO Joint Meeting on Pesticide Residues for recommendation of an acceptable daily intake (FAO90). The toxicity profile in this review is obtained mainly from unpublished reports of toxicology studies conducted for registration purposes by the chemical companies manufacturing or marketing the compound.

Methyl-S-demeton is absorbed into the body through the intact skin, by inhalation of the spray mist, and from the gastro-intestinal tract. The committee did not find quantitative data on kinetics and metabolism. Case studies in humans show a high acute toxicity of methyl-S-demeton following accidental and occupational exposures. Effects observed in these studies were typical clinical symptoms of cholinergic toxicity, such as drowsiness, vomiting, salivation, nervous excitation. Inhibition of serum ChE activity has been observed during occupational exposure. In a human volunteer study, exposure to a 30:70 mixture of *S*- and *O*-isomers, 5 hours/day, for 5 days, did not produce effects on red blood cell AChE and plasma ChE at 5-hour TWA airborne levels up to 1.9 mg/m^3.

Skin sensitisation tests in test animals, using the ‘guinea-pig maximisation test’ and the ‘occluded-patch test’ produced conflicting results. Based on results of acute lethal toxicity studies, the committee considers the compound as toxic after respiratory, dermal, and oral exposure. No significant systemic effects have been reported in short-term and long-term toxicity studies in test animals. Inhibition of serum ChE and of red blood cell and brain AChE was found in dogs, rats, and mice following short-term and long-term exposure. NOAELs for brain and red blood cell AChE inhibition were 0.036 mg/kg bw for dogs (one-year study), 0.05 mg/kg bw for rats (2-year study), and 0.25 mg/kg bw for mice (21-month study). Methyl-S-demeton produced gene mutations in *in vitro* tests in bacteria and mouse lymphoma cells. However, the only test performed in

mammals (Chinese hamster) did not show an increased frequency of sister chromatid exchanges. Carcinogenic effects were not observed following long-term oral exposure of rats and mice to methyl-S-demeton. The committee concludes that the positive genotoxic effects of methyl-S-demeton were thus not reflected in carcinogenicity. Methyl-S-demeton was not embryotoxic or teratogenic. However, the compound showed a dose-dependent reduction in number of live pups and pup viability in a 2-generation study in rats, probably due to maternal toxicity. The overall NOAEL associated with reproduction toxicity was 0.07 mg/kg bw/day.

Based on the above data, the committee concludes that the mechanism of toxicity of methyl-S-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 methyl-S-demeton 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 in assessing the human health risk of exposure to methyl-S-demeton (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 decided to select the 2-year feeding study in rats as a starting point. In this study, the NOAEL was 0.05 mg/kg bw/day, based on inhibition of brain and red blood cell AChE activity. 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 0.07 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, covering inter- and intraspecies variation, are applied, resulting in a NAEL for humans of 0.002 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 0.01 mg/m^3 is recommended for methyl-S-demeton.

The committee recommends a health-based occupational exposure limit for methyl-S-demeton of 0.01 mg/m^3, as an 8-hour time-weighted average (TWA).

Methyl-S-demeton 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 methyl-S-demeton, the committee recommends a skin notation.

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Annex

Occupational exposure limits for methyl demeton (CAS number: 8022-00-2) 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	-	0.5	8 h	administrative	S	SZW03
Germany						
- AGS	0.5	5	8 h		S	TRG00
	2	20	15 min			
- DFG MAK-Kommission	0.5	4.8	8 h		S	DFG02
	1.0	9.6	15 min[c]			
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	0.05[d]	0.5	8 h		S	Arb02
USA						
- ACGIH	-	0.5	8 h	TLV	S	ACG03b
- OSHA	-	-	-			ACG03a
- NIOSH	-	0.5	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 sensitilisation.
[b] Reference to the most recent official publication of occupational exposure limits.
[c] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.
[d] Holds also for individual isomers (CAS numbers: 867-27-6, 919-86-8).