Australian Government

Australian Pesticides and Veterinary Medicines Authority

Reconsideration of Methiocarb: Update to Toxicology Assessment

The reconsideration of the approvals of the active constituent methiocarb, registration of products containing methiocarb and their associated labels

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Comments and enquiries regarding copyright:

Director Public Affairs and Communication
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4988

Email: communications@apvma.gov.au.

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CONTENTS

EXECUTIVE SUMMARY

Methiocarb is a non-systemic, broad-spectrum, residual, contact and stomach acting carbamate pesticide. It kills insects, slugs and snails by interfering with the activity of acetylcholinesterase, an enzyme in the nervous system. Methiocarb has been registered for use in Australia for over 30 years.

In Australia, methiocarb is currently registered for use in the control of snails, slugs, millipedes, slaters and false wireworm beetles in a range of agricultural and home garden situations. At present methiocarb is available only as a bait formulation (BA 20g/kg methiocarb), in two registered products (one for commercial use, one for the home garden).

The reconsideration of the active constituent methiocarb, products containing methiocarb and associated labels includes consideration of public health, occupational health and safety (OHS), residues in food and possible risks to Australian trade and the environment.

After assessing all the available data, the Australian Pesticides and Veterinary Medicines Authority (APVMA) published the toxicology, OHS, environment, and residues and trade assessment reports along with the Preliminary Review Findings (PRF) in 2005. An updated toxicology assessment was published in 2013 and a supplementary OHS assessment in 2017. These assessments recommended continued approval and registration of methiocarb. Revision to safety directions and first aid instructions for all methiocarb products were recommended together with refinements to the re-entry and re-handling periods. All of these reports are available from the methiocarb chemical review webpage (in the Publication Archive).

This document includes an assessment of 24 new toxicological studies on methiocarb, received after the 2013 toxicology update was published.

This assessment recommended the following changes to the toxicology hazard profile of methiocarb, as presented in the 2013 mammalian toxicology assessment of methiocarb:

- The rat oral LD_{50} of methiocarb phenol has been changed from >1000 mg/kg bw to >2000 mg/kg bw;
- A rat oral LD_{50} of > 2000 mg/kg bw has been added for methiocarb sulfoxide phenol (previously not available);
- Metabolites methiocarb phenol, methiocarb sulfoxide phenol and methiocarb sulphone phenol have been added to the genotoxicity section, with a rating of “Not genotoxic” (previously not available);
- A (human) dermal absorption of <1% has been identified for methiocarb (previously not available); and
- The Acute Reference Dose (ARfD) of methiocarb has been amended from 0.03 mg/kg bw to 0.005 mg/kg bw.

The new information from the studies (e.g. dermal absorption), does not require any change to the existing first aid instructions or safety directions of the currently registered methiocarb products.

There are no other changes or updates to the toxicological hazard profile of methiocarb proposed as a result of this current assessment of the new methiocarb toxicological studies.

1 METHIOCARB TOXICOLOGY ASSESSMENT UPDATE

The main update to the methiocarb toxicological profile following assessment of the new studies was the amendment to the ARfD value. This amendment was based on a developmental toxicity study (Young, A.D. (2002)). In this study methiocarb (>99% purity) in 0.5% carboxymethylcellulose/0.4% Tween 80 in water was administered by gavage to groups of 30 pregnant Crl:WI(HAN) rats at 0, 0.5, 1.5, or 5 mg/kg bw per day from gestation days (GD) 6–19 (Young 2002). The study was conducted according to principles of GLP. Dams were observed daily for clinical signs, with body weight and feed consumption recorded regularly throughout the dosing period. On day 20 of gestation, surviving dams were killed and necropsied, and the following parameters recorded: gravid uterine weight, corpora lutea counts, total resorptions, number of implantations, live foetuses, dead foetuses and pup sex ratio. Liver and thyroid weights of dams were recorded. Foetuses were examined for external, visceral and skeletal abnormalities.

There were no treatment-related deaths. Clinical signs were observed at 1.5 and 5 mg/kg bw per day consisting of muscle fasciculations (both doses), coarse tremors and urine staining of fur (5 mg/kg bw per day). Reduced bodyweight gain and feed consumption occurred at the highest dose from GD 6–10 (-12.5 and -11 per cent, respectively). In dams, there were no treatment-related macroscopic findings or effect on organ weights. There were no effects on litter parameters or on the incidence of external, visceral or skeletal abnormalities in foetuses. The NOAEL for maternal toxicity was 0.5 mg/kg bw per day for clinical signs (muscle fasciculations) at 1.5 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 5 mg/kg bw per day, the highest tested dose.

The assessment of the 24 new toxicological studies is summarised in the tables below:

1.1 Acute toxicity

Unless otherwise indicated, all studies reported below were conducted according to principles of GLP and relevant OECD/other-country test guidelines.

Oral

Species	Strain, age weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Rat	Wistar Hannover albino rats *(Rattus norvegicus)* 11–12 wk 189–269 g	F	Oral Gavage	5–50 mg/kg bw Test material purity: 98.2% Observation period: 14 d	Corn oil	**Results:** At 5 mg/kg bw: There were no treatment related deaths, no signs of toxicity in any animal and no abnormalities found during necropsy. At 50 mg/kg bw treatment: There were: ➢ treatment-related deaths, out of 6 animals; ➢ all 6 animals presented 2 or more of systemic signs* of toxicity (at 10 min to 6 h after administration); ➢ the animals found dead had macroscopic changes on the kidneys, liver or digestive tract that characterise possible intoxication signs; and ➢ no abnormalities were noted for the animals that were submitted to euthanasia and necropsy. * ventral position (6/6), muscular tremors (6/6), sialorrhea (3/6), piloerection (1/6), ataxia (3/6) & apathy (3/6). **Conclusion:** The acute oral LD_{50} of methiocarb is 50 mg/kg bw.	Alves, M.C.(2005a) 27-Sept-2005 (Report-No: RF-0030.305.320.05 Document No.: M-261735-01-1)
Rat	Wistar HsdCpb:Wu	F	Oral Gavage	2000 mg/kg bw	PEG 400	**Results:** There were no mortalities or clinical signs observed.	Schuengel, M. 29-Aug-2007

Species	Strain, age weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
	9–13 wk 170–201 g			Test material purity: 99.1% methiocarb-phenol Observation period: minimum 14 d.		**Conclusion:** The acute oral LD_{50} of methiocarb phenol is > 2000 mg/kg bw.	(Study ID: T 5077 957 Report-No: AT04045 Document No.: M-292380-01-1)
Rat	Wistar HsdCpb:Wu 9–13 wk 171–196 g	F	Oral Gavage	2000 mg/kg bw Test material purity: 99.4% methiocarb – sulfone-phenol Observation period: minimum 14 d	PEG 400	**Results:** One mortality only, at 6 h after application. Diverse clinical* signs observed of this animal, as were some organ abnormalities** upon necropsy. For the other 5 animals, the body weight and the body weight gain were not affected by the treatment. Nor did necropsy reveal any treatment-related findings. * decreased motility, poor reflexes, reactivity decreased and lateral position. ** change in contents aqueous and clear in intestine, urinary bladder enlarged, liver spotted brownish-black, lung haemorrhagic, and gas-filled stomach with haemorrhagic change in contents. **Conclusion:** The acute oral LD_{50} of methiocarb-sulfone-phenol is > 2000 mg/kg bw.	Gillisen, U. (2007a) 29-Aug-2007 (Study ID: T 5077 974 Report-No: AT04053 Document No.: M-292392-01-1)

Species	Strain, age weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Rat	Wistar HsdCpb:Wu 9–13 wk 171–189 g	F	Oral Gavage	2000 mg/kg bw Test material purity: 99.3% methiocarb – sulfoxide-phenol Observation period: min 14 d	PEG 400	**Results:** There were no mortalities, clinical signs or gross pathological findings. **Conclusion:** The acute oral LD_{50} of methiocarb-sulfoxide-phenol is > 5000 mg/kg bw	Gillisen, U. (2007b) 29-Aug-2007 Study ID: T 5077 975 Report-No: AT04054 Document No.: M-292384-01-1)

Dermal

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Rat	Wistar Hannover *(Rattus norvegicus)*, Adult albino 8–14 wk M: 254–278 g F: 221–269 g	M & F	Dermal	2000 mg/kg bw (moistened but undiluted) Test material purity: 98.2% n = 5/sex/treatment Exposure Area: ~10% of the total body surface area Exposure time: 24 h Observation period: 14 d	Distilled water & gauze	**Results:** There were no deaths, behavioural or clinical alterations. No treatment-related macroscopic alterations were observed during the necropsies. **Conclusion:** The dermal LD_{50} for methiocarb is > 2000 mg/kg bw.	Alves, M.C. (2005b) 10-Nov-2005 (Report-No: RF - 0030.310.299.05 Document No.: M-261741-01-1)

Skin irritation

Species	Strain, age weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Rabbit	NZ White Young adult 13–16 wk 2.968–3.417 kg	M & F	Dermal	0.5 g of technical material (moistened but undiluted) Test material: methiocarb purity (98.2%) n = 3 (2M, 1F) Exposure Area: ~6 cm^2 Exposure time: 4 h	Distilled water & gauze patch	**Results:** The test item applied on the skin of the rabbits did not cause any dermal irritation. No treatment-related behavioural or clinical alterations were noted during the observation period.	Collor, L.V.M. (2005a) 23-Sept-2005 (Report-No: RF - 0030.311.318.05 Document No.: M-261812-01-1)

Species	Strain, age weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
				Observation period: 72 h		**Conclusion:** Methiocarb is not a skin irritant.	

Eye irritation

Species	Strain, age weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Rabbit	NZ White Young adult 14–16 wk 3.107–3.398 kg	M & F	Ocular (conjunctival sac of the left eye).	0.1 g dose of test item (undiluted) Test material: methiocarb (purity: 98.2%) n = 3 (2F, 1M) Exposure Time: ~1 h (then eye-rinse) Observation period: 72 h	Nil	**Results:** The test item applied in the eye of the rabbits caused slight changes on the conjunctivae: hyperaemia grade 1, at the 1-h time point in 3/3 test eyes. All irritation signs had returned to normal by the 24-h time point following treatment. Additional ocular effect noted was miosis (contraction of the pupil) at the 1-h time point in 1/3 animals. There were no other behavioural and clinical alterations observed. **Conclusion:** Methiocarb is not an eye irritant.	Collor, L.V.M. (2005b) 27-Sept-2005 (Report-No: RF - 0030.312.405.05 Document No.: M-261818-01-1)

Skin sensitisation

Species	Strain, age weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Guinea Pig (*Cavia porcellus*)	Hartley 9 wk 403-520 g	M	Epidermal	0.5 g dose of test item (undiluted) Test material; methiocarb (purity 98.2%). 7 d gap between inductions (3), & then 14 d to challenge (total: 29 d) n = 10 Exposure Area = 6 cm^2 Exposure Time = 6 h Observation period: 30 d	Buehler's closed patch technique (absorbent cotton lint)	**Results:** No skin reactions were observed. Also no clinical signs nor behavioural alterations were observed. **Conclusion:** Methiocarb is not a skin sensitiser.	Ferreira, T.G. 11-July-2013 (Study/Report-No: RF-0030.318.279.05 Document No.: M-261825-02-1)

1.2 Genotoxicity

Species	Strains	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Salmonellla typhimurium (LT2 mutants)	TA 1535, TA 100, TA 1537, TA98, and TA 102.	Plate incorporation test: 16–5000 µg test material per plate Test material purity: 99.1% methiocarb phenol	Nutrient broth (usually Oxoid No. 2)	**Conclusion:** Methiocarb-phenol was considered to be non-mutagenic without and with S9 mix.	Herbold, B. (2007a) 24-Sept-2007 (Study ID: T 9077 762 Report-No: AT04108 Document No.: M-292915-01-1)

Species	Strains	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Salmonellla typhimurium (LT2 mutants)	TA 1535, TA 100, TA 1537, TA98, and TA 102.	Plate incorporation test: 16–5000 µg test material per plate Test material purity: 99.3% methiocarb sulfoxide phenol	Nutrient broth (usually Oxoid No. 2)	**Conclusion:** Methiocarb-sulfoxide-phenol is considered to be non-mutagenic without and with S9 mix.	Herbold, B. (2007b) 28-Sept-2007 (Study ID: T 4077 767 Report-No: AT04135 Document No.: M-293116-01-1)
Salmonellla typhimurium (LT2 mutants)	TA 1535, TA 100, TA 1537, TA 98, and TA 102.	Plate incorporation test: 16–5000 µg test material per plate Test material purity: 99.4% methiocarb sulfone phenol	Nutrient broth (Oxoid No. 2)	**Conclusion:** Methiocarb-sulfone-phenol is considered to be non-mutagenic without and with S9 mix.	Herbold, B. (2007c) 22-Nov-2007 (Study ID: T 3077 766 Report-No: ATO 4261 Document No.: M-294754-01-1)
Salmonellla typhimurium (LT2 mutants)	A 1535, TA 100, TA 1537, TA98, and TA 102.	Plate Incorporation test: 0–5000 µg test material per plate Test material purity: 98.2% methiocarb	Nutrient broth	**Conclusion:** Methiocarb technical is considered to be non-mutagenic (as measured in this Salmonella typhimurium reverse mutation assay), at concentrations of ≤ 333 µg.	Henninger, K. 17-June-2015 (Study ID: 1690 601 [Harlan] Document No.: M-524333-01-1)

1.3 Sub-chronic toxicity

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Dog	Beagle Age: Not >6 m Mean bw (g) : M : 9153.5–9437.5 F: 7081.8–8177.0	M & F	Diet	Test material: > 99% purity methiocarb 0, 10, 50 or 250 ppm (equal to 0, 0.3, 1.3 or 5.9 mg/kg bw/d in males and 0, 0.25, 1.3 or 6.5 mg/kg bw/d in females) n = 4/sex/treatment Exposure time: 90 day Observation period: 90 days	-	**Conclusions:** NOAEL for plasma cholinesterase = 10 ppm (0.30 and 0.25 mg/kg bw/d in males and females respectively).	Jones, R.D. & Stuart, B.P. 7-Dec-2000 (Study No.: 99-S76-BG Report-No: 109807 Document No.: BC9387 / MO-00-016374 Record No.: M-064316-01-1)
Rat	SPF-bred Wistar strain Hsd Cpb:WU 5-6 wk Mean initial body weights: M 136–139 g F 132–137 g	M & F	Diet	Test material: 98.9% purity methiocarb 0, 100, 300 or 900 ppm (equal to 0, 7.3, 22.7 or 67.6 mg/kg bw/d in males and 0, 10.0, 30.7 or 90.7 mg/kg bw/d in females respectively) Note: a separate, concurrent recovery-trial used 0 ppm & 900 ppm treatments only. n = 10/sex/group	-	**Conclusions:** Based on reduced relative body weight. NOAEL = 22.7 and 30.7 mg/kg bw/d in males and females respectively.	Kroetlinger, F 11-Dec-2001 (Study No.: T 9069 842 Report-No: PH 31598 Document No.: 31598 / MO-01-021994 Record No.: MO-01-021994 / M-088469-01-1)

1.4 Reproductive toxicity

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Rat	Wistar Hsd Cpb: WU F0 animals: 10–11 wk F0 animals: M:296–325 g F:180–211g	M & F	Diet (ad libitum) for F0 animals (parents) only Via dam milk for F1-pups	<u>Pilot 1-gen study</u> Test material: >99% purity methiocarb Mean daily active-intake/animal of F0 (mg/kg bw/d), per treatment: 0 ppm/animal M & F: 0 100 ppm/animal M = 6.1 ; F = 8.1 300 ppm/animal M = 18.5 ; F = 22.4 900 ppm/animal M = 52.4 ; F = 76.5 n = 10/sex/dose	Feed: Altromin® 1321 meal + 1% peanut oil (DAB 10)	**<u>Conclusions:</u>** NOAEL reproductive toxicity = 900 ppm : M = 52.4 & F = 76.5 (highest tested dose) NOAEL parental toxicity = 300 ppm: M = 18.5 & F = 22.4 [LOAEL = 900 ppm: decreased body weight & erythrocyte AChE] NOAEL offspring toxicity = 100 ppm: M = 6.1 & F = 8.1 [LOAEL = 300 ppm: decreased pup weight during lactation]	Eiben, R. (2002a) 8-February-2002 (Study No.: T 1068 700 Report-No: PH 31755 Document No.: 31755 / MO-02-002325 Record No.: M-035507-01-1)
Rat	Wistar Hsd Cpb:WU F0 animals: 5–6 wk F0 animals:	M & F	Diet (ad libitum) and in dam milk during non-weaned period for pups 2-generation study: F0, F1	Test material: ≥99% purity methiocarb Mean daily active-intake/animal of F0 & F1 (mg/kg bw/d), per treatment: <u>F0</u> <u>F1</u> <u>0 ppm:</u> M & F 0 0	Feed: Altromin® 1321 meal + 1% peanut oil (DAB 10)	**<u>Conclusions:</u>** NOAEL reproductive toxicity = 500 ppm: M = 41.0 & F = 52.1 [highest tested dose] NOAEL parental toxicity = 50 ppm: M = 4.3 & F = 5.5	Eiben, R., Bach, U. & Popp, A. (2002b) 11-February-2002 (Study No.: T 4096 306 Report-No: PH 31760 Document No.: 31760 / MO-02-002596

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
	M: 115 g F: 101 g		& F2 generations	<u>50 ppm:</u> M 4.3 4.2 F 5.5 6.0 <u>150 ppm:</u> M 12.5 13.5 F 15.4 18.6 <u>500 ppm:</u> M 41.0 43.5 F 52.1 61.3 n = 25 animals/sex/dose/generation		[LOAEL = 150 ppm: decreased body weight] NOAEL offspring toxicity = 50 ppm: M = 4.3 & F = 5.5 [LOAEL = 150 ppm: decreased lactation index]	Record No.: MO-02-002596 / M-036790-01-1)
Rat	Wistar CrlGlxBrlHan: WI F0 animals: 5–6 wk F0 animals: M: 126 g F: 109 g	M & F	Diet (ad libitum) and in milk during non-weaned period for pups 2-generation study: F0, F1 & F2 generations	Test material: ≥ 99% purity methiocarb Mean daily active-intake/animal of F0 & F1 (mg/kg bw/d), per treatment: <u>F0</u> <u>F1</u> <u>0 ppm:</u> M & F 0 0 <u>50 ppm:</u> M 4.6 5.6 F 6.9 7.6 <u>150 ppm:</u> M 14.8 16.3 F 21.3 22.3	Feed Altromin® 1321 meal + 1% peanut oil (DAB 10)	**<u>Conclusions:</u>** NOAEL reproductive toxicity = 500 ppm: M = 55.1 & F = 83.9 [highest test dose] NOAEL parental toxicity: could not be set: At all doses for parental males, decreased erythrocyte AChE NOAEL offspring toxicity = 150 ppm: M = 14.8 & F = 21.3 [LOAEL = 500 ppm: decreased pup weight, lactation index & litter size]	Eiben, R. & Bach, U. (2002c) 23-October-2002 (Study No.: T 6070 298 Report-No: AT00047 Document No.: AT00046 / MO-02-0015935 Record No.: MO-02-0015935 / M-064945-01-1)

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
				500 ppm: M 55.1 69.0 F 83.9 89.0 n = 25/sex/dose/generation			
Rat	Wistar CrlGlxBrlHan: WI F0 animals: 13–15 wk F0 animals: Weight not recorded	M & F	Diet (ad libitum) and in milk during non-weaned period for pups	Test material: ≥ 99% purity methiocarb Estimated mean daily active-intake/ animal of F0 & F1(mg/kg bw/d), per treatment: F0 F1 0 ppm: M & F 0 0 50 ppm: M 4.6 U* F 6.9 U 150 ppm: M 14.8 U F 21.3 U 500 ppm: M 55.1 U F 83.9 U	Feed Altromin® 1321 meal + 1% peanut oil (DAB 10)	**Conclusions:** NOAEL parental toxicity = 50 ppm: M = 4.6 & F= 6.9 [LOAEL = 150 ppm: based on AChE activity]	Eiben, R. (2003d) 31-March-2003 (Study No.: T 7071 667 Report-No: AT0341 Document No.: AT00341 / MO-03-004371 Record No.: M-088195-01-1 / MO-03-004371)

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
				** : U = Unknown* n = 10/sex/dose/generation			
Developmental Toxicity							
Rat	Wistar (Hannover) Crl:WI[Glx/BRL/ Han]IGS BR Age: F: 15 w 2 d Mean body weight females: 211.6–214.0 g	F only	Oral gavage	Test material: ≥ 99% purity methiocarb <u>Doses:</u> 0, 0.5, 1.5 or 5 5 mg/kg bw/d n = 30	0.5% Carboxy- Methyl- cellulose and 0.4% Tween 80 in deionized water	**<u>Conclusions:</u>** Maternal NOAEL: 0.49 mg/kg bw/d LOAEL = 1.49 based on muscle fasciculations Developmental NOAEL: >5 mg/kg bw/d [LOAEL: >5]	Young, A.D. 18-Jan-2002 (Study No.: 01-T12-DV Report-No: 10923 Document No.: 01-T12-DV / M-038693-01-1)

1.5 Dermal absorption

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
Rat & human	Sprague Dawley 25 d	M & F	Dermal absorption (*in vitro*)	Methiocarb µg/cm^2 4738.4 2283.4 (repeat) 5.51	FS*(High dose) FS (mid dose) FS (low dose)	**<u>Results:</u>** <u>Relative 24 h skin absorption (%) via epidermis:</u>	Maas, W.J.M. 9-Nov-2001 (TNO Report No.: V 3859

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
	Human 33 & 34 yr		[Epidermal membranes]	16.36 (average) n= 3–4 (rats) n= 3–4 (humans) Exposure area = 0.64 cm^2 Exposure time = 24 h (continuous)	Contaminated corn dust** *: [phenyl-I-^{14}C] Methiocarb 500 FS (44.7–46.3% methiocarb) ** : 0.0056 mg/mg-dust Radio-labelled active used: > 99% radio-purity	Dose - µg/cm^2 (FS-low) (Corn-Dust) (FS-mid) (FS-high) 5.5 16.36 2283.4 4738.4 Human [H]: 71.6% 25.67% 0.80% 0.22% Rat [R]: 89.62% 22.5% 0.99% 0.44% **Conclusions:** Relative 24 h (continuous exposure) *in vitro* absorption of Methiocarb in 500 FS through human epidermal membranes, was < 1 % for the high & mid dose groups and 71 % for the low dose group. When applied as compound-contaminated corn dust, the relative absorption through human skin was 26%. **Comments:** Lag time 0.3–0.9 h [H] & 0–1.4 h [R]. Rat epidermis 1 .3 - 4.2 times more permeable to Methiocarb, than human epidermis. Mean recovery active: 74–95% [H] & 66–95% [R].	Document No.: V 3859/ MO-02-002326)
Rat & human	Wistar Rj WI (IOPS HAN) young adult 230–356 g Human 56–64 yr	M & F	Dermal absorption (*in vitro*) [Flow through diffusion cells using	Methiocarb: Single dose to exposure area: 5 mg/dust = 0.42 mg Dose: 420 µg per cm^2	Corn dust contaminated with [^{14}C]-methiocarb (0.084 mg/mg- dust [nominal])	**Results/Conclusions:** Skin absorption % at 24 h after application of 420 µg/cm^2: Human Rat % directly absorbed dose: 0.141% 0.323% % potentially absorbed dose: 0.162% 0.775% **Comments:**	Rascle, J.B. 1-March-2005 (Study ID: SA 04232 / Document ID: SA 04232 /

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
	[Abdomen]		epidermal membranes (dermatomed skin)]	n = 5 (rat) n = 5 (human) [3 donors] Exposure time: 8 h [Swab-washes of skin at 8 h & 24 h] Exposure area = 1 cm^2 Measure of methiocarb: - in skin, at 24 h; - on skin, at 8 & 24 h	Radio-Labelled active used: ≥ 99% radio-purity	Approximately 92% of dose was not absorbed, for both rat and human. Percent recovery* was ~92% for human and ~93% for rat. * recovery = surface + skin + receptor compartments	MO-05-008896 Record No.: M-251996-01-1)
Rat	Wistar HsD Cpb:WU (Albino) 9–10 wk (young adult)	M	Dermal absorption (*in vivo*)	Methiocarb Single dose to exposure areas: 2 x 30 mg/dust = 5.04 mg Dose; 420 µg per cm^2: n = 4 Exposure area = ~ 2 x 6 cm^2 Exposure time: 8 h	Corn dust contaminated with [^{14}C]-methiocarb (0.084 mg/mg- dust [nominal]) Radio-labelled active used: > 99% radio-purity	**Results**: Skin absorption % at 8–168 h after application of 420 µg/cm^2: 8 h / 24 h / 72 h / 168 h Direct* 0.631% 2.577% 5.268% 7.819% Total Potential** 6.711% 5.130% 8.016% 9.150% * = systemic compartment (e.g. excreta, blood)	Muriel Odin Feurtet 11-March-2005 (Study ID: SA 04293 Document No.: SA 04293/ MO-05-005737)

Species	Strain, age, weight	Sex	Route	Test parameters (e.g. dose)	Vehicle	Toxicology conclusion/s	Reference information
				Measure of methiocarb, both in and on skin at: 8, 24, 72, 168 h; [Swab-washes of skin at 8, 24, 72 & 168 h, before animal sacrifice]		** = % direct dermal absorption, plus total % in skin compartment (at dose-site plus not-at dose- site) **<u>Conclusion</u>:** The total amount of [^{14}C]-methiocarb absorbed systemically in an 8 h working day for humans was <1% of the dose applied.	
Rat & human	See relevant studies above	See relevant studies above	Dermal absorption (evaluation of the 4 studies above) [Weber 2001, Maas 2001, Odon-Fuertet 2005, Rascle 2005)	2001: Dose 5–5000 µg per cm^2. [~0.0056 mg/mg-dust] 2005: Dose: 420 µg per cm^2. [0.084 mg/mg-dust]	Corn dust contaminated with [^{14}C]-methiocarb See relevant purity information above.	**<u>Conclusions:</u>** - *in vivo* potential absorption, rat skin: <1% - potential *in vitro* absorption: rat skin: 0.8% & human skin: 0.2% - potential *in vivo* human absorption rate, (using above results) is <1%, from methiocarb contaminated corn dust. The following equation was used to calculate the potential *in vivo* human absorption rate: *in vivo* rat x [(*in vitro* human) ÷ (*in vitro* rat)]	Fisher, P. 14-March-2006 (Document ID: M-267700-01-1)

2 CONCLUSIONS

The results obtained from the assessment of the new studies necessitate the following amendments to the Toxicological Hazard Profile of methiocarb described in the 2013 toxicology report:

Acute toxicity of metabolites – rat oral LD_{50} (mg/kg bw)		
Methiocarb phenol	> 2000	(previously > 1000)
Methiocarb sulfoxide-phenol	> 2000	(previously not available)
Genotoxicity		
Methiocarb phenol	Not genotoxic	(previously undetermined)
Methiocarb sulfoxide phenol	Not genotoxic	(previously undetermined)
Methiocarb sulfone phenol	Not genotoxic	(previously undetermined)
Dermal Absorption	<1%	(no previous value)

A new developmental study assessed as part of this update revealed a NOAEL that is relevant for the establishment of an ARfD. The NOAEL for clinical signs (muscle fasciculations) in dams was 0.5 mg/kg bw/d. This clinical sign, which is likely to arise following a single exposure, was considered suitable to establish an amended ARfD for methiocarb. Furthermore, the NOAEL is lower than previously observed in other rat and rabbit developmental studies. There were no studies identified that would necessitate an amendment of the ADI. As a result of this change in the numerical value of the ARfD, the acute dietary risk posed by methiocarb residues has been recalculated and found to be acceptable.

3 UPDATED TOXICOLOGICAL HAZARD PROFILE OF METHIOCARB

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of absorption	Oral: rapid and extensive in rats and cattle, moderate to variable in dogs
Distribution	Highest tissue concentrations were found in the kidney and the spleen
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid and excreted extensively in urine
Metabolism	Well metabolised forming at least 3 major metabolites in urine
Toxicologically significant metabolites	Methiocarb sulfoxide

Acute toxicity

Rat oral LD_{50} (mg/kg bw)	9–135
Worst oral LD_{50} in other species	12.2 in guinea pigs
Rat dermal LD_{50} (mg/kg bw)	>2000
Worst dermal LD_{50} in other species	>2000 in rabbits
Rat inhalation LC_{50} (mg/m^3)	433
Worst inhalation LC_{50} in other species	>39 in mice
Eye irritation	non-irritant
Skin irritation	non-irritant
Skin sensitisation	non-sensitiser

Metabolites of methiocarb - Rat oral LD50 (mg/kg bw)

Methiocarb sulfoxide	6–9
Methiocarb phenol	>2000
N-hydroxymethyl methiocarb	>112
N-hydroxymethyl methiocarb sulfone	>112
N-hydroxymethyl methiocarb sulfoxide	>160
Methiocarb sulfone	>1000
Methiocarb phenol sulfoxide	>1000
Methiocarb phenol sulfone	>1000
Methiocarb sulfoxide-phenol	>2000

Short-term toxicity

Target/critical effect	Plasma ChE inhibition
Lowest relevant oral NOAEL (mg/kg bw/d)	Not established
Lowest relevant dermal NOAEL (mg/kg bw/d)	Not established
Lowest relevant inhalation NOAEL (mg/m^3)	6 (nose-only exposure daily for 6 h/day for 15 work days within 3 weeks)

Genotoxicity	Non-genotoxic

Long-term toxicity and carcinogenicity

Target/critical effect	Plasma ChE inhibition
Lowest relevant NOAEL (mg/kg bw/d)	0.2 (2-year study in dogs)
Carcinogenicity	No evidence of oncogenic potential

Reproductive toxicity

Reproduction target/critical effect	No effects in rats
Developmental target/critical effect	Pale areas on the foetal liver at maternotoxic doses (in rabbits)
Lowest relevant developmental NOAEL (mg/kg bw/d)	0.5 (rats)

Delayed neurotoxicity	No effects
Immunotoxicity	No effects
Dermal absorption	<1%

Summary	**NOAEL** (mg/kg bw/d)	**Study**	**Uncertainty Factor**
ADI [0.002 mg/kg bw/d] (plasma ChE inhibition)	0.2	2-year study in dogs	100
ARfD [0.005 mg/kg bw] (clinical signs - muscle faciculations)	0.5	developmental toxicity in rats	100

A more detailed discussion of these endpoints is available in the 2013 mammalian toxicology assessment of methiocarb.

ABBREVIATIONS

AChE	Acetyl cholinesterase—an enzyme essential for the regulation of nerve tissue function
ADI	Acceptable Daily Intake : for humans, it is considered to be a level of intake of a chemical that can be ingested daily over an entire lifetime, without any appreciable risk to health
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute reference dose: the estimated amount of a substance in food or drinking-water, (expressed on a body weight basis), that can be ingested or absorbed over 24 hours or less, without an appreciable health risk. The ARfD is expressed as milligrams per kilogram of body weight (mg/kg bw).
BA	Bait – a formulation type
bw	Body weight
ChE	Cholinesterase
cm^2	Square Centimetre
d	Day
g	Gram
GLP	Good laboratory practice
h	Hour
kg	Kilogram
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
LOAEL	Lowest Observed Adverse Effect Level
m^2	Square metre
m^3	Cubic metre
mg	Milligram
min	Minute
ml	Millilitre
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development

OHS	Occupational health and safety
PEG	Polyethylene glycol
PRF	Preliminary Review Findings, an interim report published during a reconsideration
μg	Microgram
wk	Week
yr	Year

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