REVIEW SCOPE

Australian Pesticides & Veterinary Medicines Authority

The Reconsideration of Registrations of Products Containing Carbendazim or Thiophanate-methyl and Their Associated Approved Labels

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This scope document for the review of CARBENDAZIM and THIOPHANATE-METHYL is published by the Australian Pesticides and Veterinary Medicines Authority. For further information about this review or the Pesticides Review Program, contact:

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Review Scope Document
(CARBENDAZIM & THIOPHANATE-METHYL)

SUMMARY

The APVMA has initiated its reconsideration of the approvals of the active constituents carbendazim and thiophanate-methyl, the registrations of products containing carbendazim or thiophanate-methyl, and the approvals of all associated labels. This document defines the scope of the matters of concern to the APVMA and outlines the kinds of information the APVMA requires to conduct a comprehensive scientific assessment of carbendazim and thiophanate-methyl.

Approvals of the active constituents carbendazim and thiophanate-methyl are being reconsidered because of public health and occupational health and safety concerns. Products containing carbendazim and thiophanate-methyl and all associated labels are being reviewed because of public health, occupational health and safety and residue concerns.

Carbendazim and thiophanate-methyl are evaluated together because thiophanate-methyl rapidly converts mainly to carbendazim in the environment. They share the same residue definition (carbendazim). Benomyl also shares the same residue definition and was placed under review by the APVMA in October 2003.

The APVMA will review the following aspects of active constituent approvals, product registrations and label approvals for carbendazim and thiophanate-methyl.

- Toxicology, including:
  - The potential risks following exposure of humans via the oral, dermal and inhalational routes; and
  - The potential for impairment of reproduction and development.

- Occupational health and safety, including:
  - Risks arising from exposure during handling and applications;
  - Re-entry exposure risks; and
  - Determination of appropriate personal protective clothing requirements.

- Residues, including:
  - Residues in treated produce arising from application of carbendazim in accordance with label instructions; and
  - Determination of dietary exposure resulting from the consumption of produce treated with carbendazim (both chronic and short-term).

The APVMA will also consider whether product labels carry adequate instructions and warning statements. Such instructions include:

- the circumstances in which the product should be used;
- how the product should be used;
- the times when the product should be used;
- the frequency of the use of the product;
- the withholding period after the use of the product;
- the disposal of the product and its container;
- the safe handling of the product.

A decision on the reconsideration (hereafter referred to as the 'review') will be made after the APVMA has reviewed all the data and other information provided to it for this purpose.

1 INTRODUCTION

Section 31 of the Agvet Codes, authorises the APVMA to reconsider:

(a) the approval of an active constituent for a proposed or existing chemical product;
(b) the registration of a chemical product; and
(c) the approval of a label for containers for a chemical product.

The APVMA has decided to reconsider the approvals of the active constituents carbendazim and thiophanate-methyl, the registrations of products containing carbendazim or thiophanate-methyl and the approvals of associated labels, based on toxicological, occupational health and safety and residue concerns.

2 REGULATORY STATUS AND USE OF CARBENDAZIM AND THIOPHANATE-METHYL IN AUSTRALIA

2.1 Active Constituent and Products

At the commencement of the review, there were:

- 9 active constituent approvals for carbendazim;
- 1 active constituent approval for thiophanate-methyl;
- 21 registered products containing the active constituent carbendazim; and
- 3 registered products containing the active constituent thiophanate-methyl.

Details of these active constituents and products can be found in Attachments 1 and 2 respectively.

Of the 21 registered products containing carbendazim, 19 are suspension concentrates (16 containing 500 g/L carbendazim and the other 3 contain between 80-130 g/L carbendazim), 1 is an emulsifiable concentrate (75 g/L) and 1 product is a wettable powder (500 g/kg). Of the 3 registered products containing thiophanate-methyl, 2 are wettable powders (250 g/kg and 156 g/kg thiophanate-methyl) and the third product is a granular formulation (50 g/kg).

These active constituent approvals and product registrations are subject to this review. It should be noted that any active constituent approvals and product registrations that occur after the commencement of the review will be subject to the outcomes of the review.

2.2 Current use patterns

Carbendazim

Carbendazim is a member of the benzimidazole group of fungicides. It is a broad-spectrum systemic fungicide with protective and curative action. It is absorbed through the roots and green tissues, with translocation acropetally and acts by inhibiting development of the fungal germ tubes, the formation of appressoria and the growth of mycelia.

Carbendazim products are used for the control of a wide range of fungal diseases such as mould, spot, mildew, scorch, rot and blight in a variety of crops. The target crops include cereals, fruit (pome, stone, citrus, currants, strawberries, bananas, pineapples, mangoes, avocados, etc.), vines, hops, vegetables, ornamentals, cotton, pasture, turf and mushrooms.

Depending upon the crop, it is applied as either a spray (low and high volume) or a post-harvest dip, with multiple application depending upon the crop and disease. Listed application rates for products are in the range 25-100 ml/100 L (all products registered for use on crops contains 500 g/L or 500 g/kg carbendazim).

Products containing carbendazim are also registered for use as fungicides for the control of sapstain and mould on freshly sawn timber. Application is by spraying or dipping.

There are no home garden uses for registered products containing carbendazim.

The following tables summarise the uses of carbendazim as they appear on product labels.

Fruit, vegetables & other crops & situations

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Chickpeas, faba beans, lentils and vetch	Chocolate spot (*Botrytis fabae*), grey mould (*Botrytis cinerea*)	500g/L SC	500mL/ha	4 weeks (H, G)	Apply a maximum of two consecutive applications at 14 day intervals. Apply in a minimum of 100L water per hectare.
Cucurbits	Powdery Mildew (*Sphaerotheca fuliginea*)	500g/L SC 500g/kg WP	50mL/100L or 550mL/ha 50g/100L or 500g/ha	-	Begin application when disease first appears, repeat at 7 to 14 day intervals. Use the higher rate and shorter intervals when disease pressure is high and plants are growing rapidly.
Pasture	Clover scorch (*Kabatiella caulivora*) Cercospora (*Cercospora zebrina*)	500g/L SC	550mL/100L plus 1L/100L summer spray oil	14 days	Apply at 'closing up' of pasture in a minimum spray volume of 150 L/ha. Repeat 30 days later if there is a build up of disease. Use the higher rate if disease is well established at 'closing up', repeat at this rate 30 days later if disease continues to develop.
Red clover, Subterranean clover	Clover scorch (*Kabatiella caulivora*) Cercospora (*Cercospora zebrina*)	500g/L SC 500g/kg WP	550mL/100L plus 1.5L/150L summer spray oil 550g/100L plus 1.5L/100L petroleum oil	14 days	Apply at 'closing up' of pasture in a minimum spray volume of 150 L/ha. Repeat 30 days later if there is a build up of disease. Use the higher rate if disease is well established at "closing up", repeat at this rate 30 days later if disease continues to develop.
Roses	Powdery mildew (*Oidium* or *Sphaerotheca* spp.)	500g/L SC 500g/kg WP	25mL/100L plus 1L summer oil/100L 25g/100L plus 1L summer oil/100L	-	Begin application when disease first appears and repeat at 7 to 14 day intervals throughout the growing season. Shorten intervals during humid weather.
	Black spot (*Diplocarpon rosea*)	500g/L SC 500g/kg	50mL/100L 50g/100L		
Strawberries	Grey mould (*Botrytis cinerea*)	500g/L SC 500g/kg WP	50mL/100L 50g/100L	2 days	Begin application when disease first appears or at flowering and repeat at 7 to 14 day intervals. Use higher rate and shorter intervals when disease pressure is high.

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Turf	Dollar spot (*Sclerotinia homoeocarpa*)	500g/L SC	60mL/100m^2	-	Apply in sufficient water to give good coverage. Commence application at beginning of damp weather and repeat at intervals of 4 weeks.

Tree and vine crops

Crop	Pest	Product description	Maximum rate	WHP (days)	Critical comments
Apples	Powdery Mildew (*Podosphaera leucotricha*) Black spot (Scab) (*Venturia inaequalis*)	500g/L SC 500g/kg WP	50mL/100L 50g/100L	7 days	Apply at 7 to 10 day intervals until petal fall. Use higher rate when disease pressure is high.
Custard apples	*Cylindrocladium* spp., *Pseudocercospora* spp.	500g/L SC	50mL/100L	3 days	DO NOT apply in tank mixes with products containing Copper oxychloride. Apply a maximum of 4 sprays. First spray to be applied at fruit set after flowering. Where disease has occurred previously apply a second spray 2 – 4 weeks later. If high disease pressure should occur, a further two sprays may be applied. All sprays must be applied at a minimum interval of 14 days.
Grapes	Grey mould (Bunch rot) (*Botrytis cinerea*)	500g/L SC 500g/kg WP	100mL/100L or 1.1L/ha 100g/100L or 1.1kg/ha	1 day	Apply at early flowering, 80 to 100% capfall and pre-bunch closure. Further applications may be necessary at veraison and pre-harvest, if wet weather favours infection. Application should be made in sufficient water to obtain thorough coverage of the crop. High volume application should be made in sufficient water to obtain thorough coverage of the crop. For applications close to harvest this would require a minimum of 1100 L/ha. For low volume application, the spray pressure should be high enough to ensure penetration of the leaf canopy and coverage of the bunches.
Macadamia nuts	Macadamia husk spot (*Pseudocercospora* spp.)	500g/L SC	50mL/100L plus wetting agent at 100mL/100L	14 days (H, G) 14 days H 4 weeks G	Apply at 5 and 8 weeks after main flowering – stage 2 anthesis (white flowering stage). Remove any fallen nuts from under trees prior to spraying. DO NOT apply more than 2 applications per season.

Crop	Pest	Product description	Maximum rate	WHP (days)	Critical comments
Pears	Black spot (Scab) (*Venturia pirina*)	500g/L SC 500g/kg WP	50mL/100L 50g/100L	7 days	Apply at 7 to 10 day intervals until petal fall. Use higher rate when disease pressure is high.
Stone fruit	Blossom blight (*Monilinia fructicola*)	500g/L SC 500g/kg WP	50mL/100L 50g/100L	1 day	Apply at pink or white bud stage, 10% blossom and petal fall. Apply the higher rate when disease pressure is high.
	Brown rot (*Monilinia fructicola*)	500g/L SC 500g/kg WP	40mL/100L 40g/100L		Apply 3 and 1 week prior to harvest following earlier application of blossom blight sprays.

Post-harvest

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Apples	Blue mould (*Penicillium expansum*)	500g/L SC 500g/kg WP	50mL/100L 50g/100L	-	Submerge fruit for approximately 30 seconds. Dipping should occur no latter than 24 hours after harvest. Top up dip at the recommended rate of 50mL/100L. **TAS only** : Always apply the treatment whenever the apples are to be dipped in diphenylamine prior to storage.
Bananas	Crown rot (*Colletotrichum musae*)	500g/L SC 500g/kg WP	40mL/100L 40g/100L	-	Submerge fruit for approximately 30 seconds.
Citrus	Blue and green moulds (*Penicillium* spp.)	500g/L SC 500g/kg WP	100mL/100L 100g/100L	-	Submerge fruit for approximately 30 seconds.
Mangoes	Anthracnose (*Colletotrichum* spp.), Stem end rot (*Dothiorella* spp.)	500g/L SC	100mL/100L	-	Submerge for approximately 5 minutes at 52°C.
Pears	Blue mould (*Penicillium expansum*)	500g/L SC 500g/kg WP	50mL/100L 50g/100L	-	Submerge fruit for approximately 30 seconds. Dipping should occur no latter than 24 hours after harvest. Top up dip at the recommended rate of 50mL/100L.

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Rockmelons	Fusarium fruit rot (*Fusarium* spp.), Sour rot (*Geotrichum candidum*), Alternaria fruit rot (*Alternaria* spp.), Rhizopus soft rot (*Rhizopus stolonifer*), Pink mould rot (*Trichothecium roseum*)	500g/L SC	100mL/100L plus 130mL Nufarm Panoctine plus 10mL Chemwet 1000/100L water	-	Dip fruit for 45 seconds within 24 hours of harvest.
Stone fruit	Brown rot (*Monilinia* spp., *Sclerotinia* spp.)	500g/L SC 500g/kg WP	100mL/100L 50g/100L	-	Submerge fruit for approximately 30 seconds. Use higher rate when disease pressure is severe or when longer term storage is required.

Pre-planting

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Ginger seed pieces	Rhizome / seed piece rot (*Fusarium* spp.)	500g/L SC 500g/kg SC	200mL/100L 200g/100L	-	Cut seed pieces to desired length from rhizomes free of rot. Submerge for 5 minutes and allow to dry before planting.
Sugar cane	Pineapple disease (*Ceratocystis paradoxa*)	500g/L SC 500g/kg	65mL/100L 125ml/200L 125g/200L	-	Apply to cut seed pieces as a dip or spray so as to obtain thorough wetting. After dipping allow to drain. When replenishing dip, top up with 65 mL (125mL) in 100L water.

Timber preservative

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Sawn lumber. **Normal conditions. Winter or short stock piling**	Sap stain and mould	75g/L EC	6L/1000L		Freshly sawn lumber should be treated as soon as possible after processing.
Sawn lumber **Severe conditions. Summer or long stock piling**			8L/1000L		Higher rates recommended for mould control.
Round wood / Poles			8L/1000L		Poles should be treated immediately after peeling or shaving.
Boron bath			6L/1000L		Ensure timber is completely wetted by treatment solution.
Sawn lumber. Normal conditions. (temperate conditions and low humidity).		80g/L EC	6L/1000L (dip) or 100L/1000L (spray)		**Dip Applications:** Completely disperse the concentrate in a small amount of water before addition to the final mix solution. **Spray Applications:** Spray application solution strengths are in the range of 60L – 100L per 1,000L. .
Sawn lumber. Severe conditions. (warm to hot temperature and high humidity)			8L/1000L (dip) or 100L/1000L (spray)		
Sawn lumber. export conditions. (hot temperatures in shipping and high humidity)			10L/1000L (dip) or 100L/1000L (spray)		
Poles and rounds			8L/1000L		
Timber – Pine (freshly sawn	Sap stain, mould and decay fungi	100g/L SC	800mL/100L		ANTIBLU CC may be applied by dip or spray treatment. Ensure all surfaces are thoroughly covered with the solution. Use the lower rate for short term storage in cool or dry conditions or where timber is strip stacked. Use the higher rate for longer storage or where conditions are warm and humid and timber is block-stacked.

Thiophanate-methyl

Thiophanate-methyl is a member of the benzimidazole group of fungicides. It is a broad-spectrum systemic fungicide with protective and curative action, and is absorbed by the roots and leaves. It is effective against a wide range of fungal diseases in a number of crops, but in Australia is not registered for use on food-producing species, only for the control of soil-borne diseases of ornamentals plants.

It is applied either directly to the soil (evenly mixed with the soil) or as a spray. The three registered products contain the active constituent at different concentrations, but the application rates are adjusted for this, and if extrapolated to a common concentration of 50 g/kg, the application rate is approximately 300 g/kg (solid mixed with soil) or 2-4 kg /1000 L (to cover 100 m^2) as a spray.

The labels do not indicate that the products are for home garden use.

The following table summarises the uses of thiophanate-methyl as they appear on product labels.

Thiophanate methyl use patterns

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Container grown seedlings, cuttings, transplants – pre-plant soil mix additive	Damping off rot and root and stem diseases caused by – *Pythium, phytophthora and thielaviopsis (chalara)*	50 g/kg (GR) 250g/kg (WP)	50 g/kg 60g/cubic metre	-	Mix evenly into the soil/potting mix before sowing or transplanting. An even mix is essential for effective disease control. Pre-mixing into a small sample of the soil/potting mix before adding may assist even application. One treatment will give control for 4-8 weeks over the establishment or germination period. If longer protection is required then retreat at 4-8 week intervals using the broadcast method.
Container grown seedlings, bedding plants, shrubs and other woody plants, and indoor plants		250g/kg (WP)	2-4kg/100 sq metres (post plant broadcast treatment) 400-800g/100 sq metres in 1000L water (soil drench)		Measure the area covered by the pots/containers to be treated. Weight out the amount of product required to treat that area. Apply evenly over the measured area using a calibrated granule spreader. Irrigate within several days of application to incorporate the granules into the soil. Normal sprinkler irrigation with then continue to move the product into the soil. Re-treat at 4-8 week intervals depending on the disease incidence. Use the lower rate when lower disease pressure is expected and the higher rate for higher disease pressure.
In-ground bedding and other plants – post plant broadcast treatment					Apply as for container grown plants. Harrow, rake or till into the soil to incorporate the granules into the upper 5-15cms of soil. Retreat at 4-8 week intervals. Use the lower rate when lower disease pressure is expected and the higher rate for higher disease pressure
In-ground bedding and other plants – pre plant treatment					Apply as for container grown plants. Rotary hoe, harrow or till into the soil to incorporate the granules into the upper 5-15cms of soil. Retreat at 4-8 week intervals. Use the lower rate when lower disease pressure is expected and the higher rate for higher disease pressure

Crop	Pest	Product description	Maximum rate	WHP	Critical comments
Ornamental plants – shrubs, bedding plants, indoor plants including African violet, azalea, begonia, carnation, chrysanthemum, dahlia, ferns, geranium, gladioli, hollyhock, poppy, roses, snapdragon, zinnia	Includes control of: Grey mould (*Botrytis cinerea*), petal blight (*Ovulinia azaleae),* powdery mildew (*erysipe cichoraceanum*), rust (*uromyces spp.),* fungal leaf spots and blights (*mycosphaerella and septoria spp.)* rust (*puccinia spp*.), mildew, black spot	156 g/kg (WP)	170g/100L water	-	Apply as a high volume spray to the point of run-off covering all foliage, stems and flowers. Commence spraying on the first appearance of disease or when conditions are suitable for disease infection. Apply at intervals of 7-14 days. Use shorter interval under severe disease pressure or when heavy rain has occurred since the last spray and the longer interval under lighter disease pressure.

3 REASONS FOR REVIEW

In October 2003 the APVMA initiated a review of the active constituent benomyl, registrations of products containing benomyl and associated label approvals. The APVMA had received advice from the Office of Chemical Safety (OCS) that benomyl may cause impairment of reproduction and development in laboratory animals, and that women of childbearing age should avoid contact with benomyl.

The scope of the benomyl reconsiderations was limited to:

- Toxicology including:
  - the potential for impairment of human reproduction and development;
  - the toxicological exposure to humans via the oral, dermal and inhalation routes.
- Occupational health and safety, including:
  - short and intermediate occupational exposure to hazards to human safety (health); and
  - the potential for risks arising from exposure including re-entry of treated areas and handling of treated produce.
- The adequacy of instructions and warnings on product labels.

At the commencement of the benomyl review the APVMA suspended all registrations and approvals pending the outcome of the review and issued new instructions for use. These instructions included provision of the MSDS with the product and addition of the following warning statement: **"Contains benomyl which cause birth defects in laboratory animals. Women of child bearing age should avoid contact with benomyl".**

In December 2004, at the request of the registrant and prior to the completion of the review, the APVMA cancelled the approvals for benomyl and the registration of the only benomyl product **Farmoz Marvel Fungicide (54552)**. The supply and use of this product was to cease 6 December 2006.

New information available since the cessation of the benomyl review, not previously evaluated by OCS, identifies the possibility that exposure to carbendazim and thiophanate-methyl could also cause developmental abnormalities in experimental animals, as identified for benomyl. There is also data available to suggest the potential for worker exposure during application and post application to exceed established health standards.

On this basis it was recommended by OCS that both carbendazim and thiophanate-methyl be reviewed and that any review should encompass both public health and occupational health and safety.

The details of the concerns that have been raised forming the basis for this review can be found in Sections 5 to 7 of this scope document.

4 SCOPE OF THE REVIEW

The scope of the review has been defined taking into consideration the reasons for the nomination of carbendazim and thiophanate-methyl, the information already available on this chemical, and the way in which it is approved for use in Australia.

In light of concerns raised by the Office of Chemical Safety (OCS) as detailed in Section 5 and 6 and the APVMA Chemistry and Residues Program (CRP) as detailed in Section 7, the APVMA needs to determine whether it can be satisfied that continued use of or any other dealing with, the active constituent carbendazim and thiophanate-methyl or products containing carbendazim or thiophanate-methyl in accordance with the approved instructions for use:

- would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues; and/or
- would not be likely to have an effect that is harmful to human beings.

It also appears that the labels for products containing carbendazim and thiophanate-methyl may not contain adequate instructions and warning statements.

On the basis of these concerns, it is appropriate that the registrations and approvals of carbendazim and thiophanate-methyl be subject to reconsideration under Part 2, Division 4, of the Agvet Codes.

Therefore the APVMA will review the following aspects of active constituent approvals, product registrations and label approvals for carbendazim and thiophanate-methyl:

- Toxicology, including:
  - The potential risks following exposure of humans via the oral, dermal and inhalational routes; and
  - The potential for impairment of reproduction and development;

- Occupational health and safety, including:
  - Risks arising from exposure during handling and applications;
  - Re-entry exposure risks; and
  - Determination of appropriate personal protective clothing requirements.

- Residues, including:
  - Residues in treated produce arising from application of carbendazim in accordance with label instructions; and
  - Determination of dietary exposure resulting from the consumption of produce treated with carbendazim (both chronic and short-term).

- The adequacy of instructions and warnings on product labels.

Registrants and approval holders will be required to undertake certain actions aimed at securing relevant data that might address these matters. However, the public is invited to make submissions to the APVMA about any of the matters raised in the scope document (see Section 9).

5 TOXICOLOGICAL ISSUES

Both carbendazim and thiophanate-methyl are classified as benzimidazole fungicides. Carbendazim is a major metabolite of benomyl with closely similar structural and toxicological characteristics. Thiophanate-methyl is also structurally related to both carbendazim and benomyl.

Previous considerations

In 1992 the Pesticide and Agricultural Chemicals Committee (PACC) considered the toxicology and Maximum Residue Limits (MRLs) of benomyl, carbendazim and thiophanate-methyl. The Committee considered the need to rationalise existing MRLs for the three compounds, combining them into a single list under carbendazim. The method of analysis for benomyl, thiophanate-methyl and carbendazim does not differ and measures the total residues as carbendazim plus 2-aminobenzimidazole.

Hazards associated with exposure

Previous consideration of carbendazim found that it has low acute oral, dermal and inhalational toxicity in animals. It is not an eye irritant in rabbits or a skin sensitiser in guinea pigs. There was no information available on the skin irritation testing on animals.

The main hazards associated with repeated exposure to carbendazim are systemic effects on liver and thymus and effects on reproduction. Carbendazim has also been shown to produce numerical aberrations (aneuploidy) in mammalian cells exposed *in vitro* and *in vivo.* The European Union (EU) has classified carbendazim as a potential genotoxic chemical.

Relatively recent information that has not been assessed by the OCS, has highlighted health concerns associated with exposure to carbendazim.

- Following an investigation to the effects of carbendazim on various cell types in the testis, Kadalmani *et al*[1]. (2002) observed that spermatocytes are a target for carbendazim.
- Lu *et al*[2]. (2004) concluded that carbendazim causes losses of spermatozoa, decrease in testis weight and decrease in sperm concentration in rats.
- The US EPA has classified both carbendazim and thiophanate-methyl as probable human carcinogens. Aggregate cancer risk estimates for both carbendazim and thiophanate-methyl from all uses including residential (lawn treatment and post-application exposure) and dietary exposure exceeded EPA's level of concern (US EPA 2001).

Established health standards

Acceptable daily intakes (ADIs) have been established for both carbendazim and thiophanate methyl. The ADI for carbendazim is 0.03 mg/kg/day established in 1979, and the ADI for thiophanate methyl is 0.02 mg/kg/day, set in 1991.

[1] Kadalmani B, Girija R, Faridha A and Akbarsha MA (2002). Male reproductive effects of carbendazim: Hitherto unreported targets in testis. Indian Journal of Experimental Biology 40, 40-44 (2002).
[2] Lu Shui-Yuan *et al* (2004). Endocrine disrupting activity in carbendazim-induced reproductive and developmental toxicity in rats. Journal of Toxicology and Environmental Health Part A, 67 (19), October 2004.

No acute reference dose (ARfD) has been established for either carbendazim or thiophanate-methyl.

Conclusion

New information regarding a range of toxicological endpoints are available which have either not previously been investigated or have now been studied more extensively. These include binding studies on target cells (testis and embryonic tissue) and other studies as noted from the US EPA reports and newly submitted genotoxicity and reproductive toxicity data considered by JMPR. A review of these studies and all other new data is considered important to determine whether products containing carbendazim or thiophanate-methyl can continue to be used without unacceptable risks to human health (public health and occupational health and safety). The appropriateness of current health standards, established some time ago, will be considered as part of this review to ensure the continued protection of the general public and workers handling such products.

6 OCCUPATIONAL HEALTH AND SAFETY ISSUES

In its benomyl assessment the OCS concluded (based on a study in strawberries) that exposure to benomyl during strawberry harvesting may exceed the ARfD for women harvesters. The OCS considers that a review of this study from the OHS perspective would be helpful in estimating worker exposure to carbendazim during various post application activities.

The OCS used a 10% default absorption factor for worker exposure estimates in the assessment of benomyl. Advice from the OCS has noted that there is a possibility that dermal absorption for carbendazim may be significantly more than for benomyl.

In 1995 the registrant of benomyl provided the OCS with a set of studies (conducted in 1978/79) investigating the potential for worker exposure during mixing/loading, ground application and during hand-harvesting of strawberries treated with Benlate (one of the registered benomyl products). The OCS has also received a copy of the report of a study conducted by the National Institute of Occupational Safety and Health (1994) investigating the potential for worker exposure to Benlate among nursery workers in Florida. The OCS has not assessed these studies. Review of these studies would be expected to provide additional information on worker exposure to carbendazim.

It is also to be noted that the EU has recently classified carbendazim as a potential genotoxic chemical, with the following risk phrase:

R68/22 Harmful. Possible risk of irreversible effects if swallowed.

Conclusion

Assessment of new toxicology data is likely to identify new toxicological findings of relevance to occupational health and safety. On this basis, an OHS risk assessment would appear to be essential.

The OHS risk assessment would require information on:

- Physico-chemical properties of all products containing thiophanate-methyl and carbendazim;
- Details of use patterns and method of application;

- Number of applications;
- Worker exposure studies; and
- Re-entry information (including dislodgeable foliar data where applicable)

7 RESIDUE ISSUES

Registered uses of carbendazim are similar to previously registered uses for benomyl, including post-harvest dips and foliar sprays. Current Maximum Residue Limits (MRLs) exist for many commodities, although a number of these have a 'temporary' status. A table of current MRLs as published in the MRL Standard can be found at Attachment 3.

As thiophanate-methyl is not registered for use in food-producing situations (use in ornamentals only) there are no residue concerns associated with products containing thiophanate methyl.

The residue definition for benomyl and thiophanate-methyl is included under carbendazim, as benomyl and thiophanate-methyl to carbendazim.

The Australian National Estimated Dietary Intake (NEDI) is almost 80% of the current carbendazim ADI of 0.03 mg/kg bw/day. However this NEDI includes MRLs established on the basis of benomyl uses that no longer exist. An Acute Reference Dose (ARfD) has not been established in Australia.

If current dietary exposure calculations are not reflective of current uses of carbendazim, as may be the case based on examination of current MRLs alone, the levels of carbendazim in food may exceed standards designed to protect human health.

It is anticipated that exceedence of the ARfD established by JMPR is likely to occur in relation to those use patterns examined by JMPR, although these determinations have yet to be made. The establishment of an ARfD for carbendazim in Australia would require a more detailed assessment of the toxicology and likely dietary exposure associated with the use patterns. Exceedence of the ARfD could occur even in the absence of MRL violations.

In the last three National Residue Survey 'Report on Results' (2003 to 2006) no MRL violations attributed to carbendazim have been reported.

Conclusion

On the basis of the above concerns, and in the absence of a contemporary toxicological review of carbendazim and thiophanate-methyl, the APVMA cannot be satisfied that products containing carbendazim would not be an undue hazard to the safety of people using anything containing its residues. The Residues assessment of carbendazim would focus primarily on short-term and chronic dietary estimates. These estimates will have regard to the ADI and ARfD established by the OCS.

8 INTERNATIONAL REGULATORY STATUS OF CARBENDAZIM AND THIOPHANATE-METHYL

Registration status

According to the PAN* database, carbendazim and thiophanate-methyl are registered for use in the following countries:

- South Africa, Tanzania, India, New Zealand, Philippines, Germany, Hungary, Netherlands, Portugal, Sweden (restricted) United Kingdom, Canada, United States.

Thiophanate-methyl is also listed as being registered in Finland, with carbendazim listed as holding registration in Denmark.

The PAN Pesticides database lists carbendazim as a suspected endocrine disruptor, but, due to lack of specific information, does not categorise its reproductive or developmental toxicity effects. Thiophanate-methyl is noted as exhibiting reproductive or developmental toxicity effects, but, due to lack of specific information, does not categorise it as an endocrine disruptor.

United States (USA)

Use patterns

Thiophanate-methyl is used in agricultural food and feed crops, residential settings and non-food situations such as golf courses, turf production and nurseries.

It is registered for use on the following food/feed crops: almonds, apples, apricots, canola, dry beans, grapes, green beans, cantaloupes, cherries, cucumber, garlic, melons, nectarines, onions, peaches, peanuts, pears, pecans, pistachios, plums, potatoes, pumpkins, soybeans, squash, strawberries, sugar beets, watermelons and wheat. Non-food/feed uses include ornamentals (greenhouses, interiorscapes, landscaping) and nursery (including forest nurseries) and turf (sod farms, residential and recreational lawns).

Thiophanate-methyl formulations include dusts, granules, wettable powders, water-dipersible granules and flowable concentrates ranging from 1.5% to 90% active ingredient. Application methods for thiophanate-methyl include aerial, chemigation or ground equipment (airblast, broadcast, band or soil drench). It can also be applied as a dip or seed treatment under certain situations. The majority of crops are treated with postemergent broadcast applications.

Carbendazim is registered as a systemic fungicide in paints in residential settings, but has no registered food uses in the USA, nor import tolerances.

USEPA Re-registration Eligibility Decision (RED) document (October 2005)

In October 2005 the USEPA published a RED for thiophanate-methyl and the primary metabolite carbendazim. The review found that both thiophanate-methyl and carbendazim can induce developmental toxicity. Foetal effects from thiophanate-methyl exposure include an increase in supernumerary ribs and reduced foetal weight. Foetal effects attributed to carbendazim exposure

* Pesticide Action Network (PAN) North America Pesticides Database. http://www.pesticideinfo.org

include increases in skeletal variations and malformations, and ocular and brain malformations. Carbendazim is also associated with adverse reproductive effects. Both thiophanate-methyl and carbendazim have also been associated with an increased incidence of liver tumours and can cause aneuploidy (abnormal number of chromosomes).

Thiophanate-methyl and carbendazim were found to exhibit low acute oral/dermal/inhalational toxicity. Thiophanate-methyl is not a skin irritant but is a slight eye irritant and a skin sensitizer. Carbendazim is a slight skin irritant but not a skin sensitizer.

The liver and thyroid are the primary target organs of thiophanate-methyl and carbendazim in several species following sub-chronic and chronic dietary exposure. The testes are also a known target organ of carbendazim.

Thiophanate-methyl is classified as likely to be carcinogenic to humans based on dose-dependent increases in liver tumors in make and female mice. Carbendazim is classified as a possible human carcinogen based on hepatocellular tumors in female mice. Developmental toxicity based on decreased foetal body weight and increases in skeletal variations was observed in the foetuses of rabbits exposed to thiophanate-methyl. Carbendazim was also associated with adverse reproductive effects in rats.

Of greater concern is the risk posed to pesticide workers, particularly mixers/loaders/applicators, and field workers who come into contact with treated foliage/crops/lawns/turf/etc. following pesticide application.

Aggregate cancer risk estimates for both thiophanate-methyl and carbendazim from all uses including residential (lawn treatment and post-application exposure) and dietary exposure, exceeded EPA's level of concern.

To mitigate human health risks of concern posed by carbendazim and thiophanate-methyl, the EPA introduced significant risk mitigation measures to allow the ongoing use of thiophanate-methyl. These included:

- Reduced application rates for cut flowers and turf application in residential/public areas (e.g. parks, athletic fields, lawns) and golf courses;
- A 14-day re-treatment interval for most turf applications;
- Water soluble packaging for wettable powder formulations for aerial/chemigation application;
- Enclosed cabs for planters/operators while planting treated potato seed;
- Double-layer PPE, chemical-resistant gloves, and a chemical-resistant apron to be worn when mixing/loading/applying dip treatment;
- Single-layer PPE (baseline) and chemical-resistant gloves for other tasks;
- New re-entry intervals:
  - almonds and peanuts: 3 days
  - apples, cherries, peaches, nectarines, apricots, and plums/prunes: 2 days
  - strawberries, blueberries, wheat, celery, cucurbits, soybeans, and green beans: 24 hours
  - woody ornamentals: 12 hours.
- A maximum single application rate for product applied by homeowners to ornamentals;
- Liquid formulations for broadcast turf/lawn use restricted to commercial pest control operators (PCOs); and
- Reduction in the concentration of carbendazim in paint from 0.5% to 0.35%.

The continued registration of thiophanate methyl products is not only subject to adherence to the mitigation measures outlined above, but to the provision of additional data including:

- toxicology (neurotoxicity, inhalational and dermal toxicity (MBC only));
- chemistry and residue data; and
- occupational exposure and post application exposure.

United Kingdom (UK)

In the UK carbendazim is contained in 47 registered products. These are either formulated with carbendazim as the sole active ingredient or with other compounds such as chlorothalonil, iprodione, epoxiconazole, flusilazole, vinclozalin, prochloraz, tebuconazole or maneb.

Approved uses include application to turf, french beans, mushrooms, ornamentals, berry crops, tomato, barley, wheat, oilseed rape, ornamentals and sugar beet.

There are 7 products registered in the UK containing thiophanate-methyl formulated alone or with iprodione. Approved uses include application to oilseed rape, field beans, broccoli, Brussels sprouts, cabbage, cauliflower, swede, turnip, apple, pear and amenity turf.

New Zealand (NZ)

Carbendazim is registered for use in NZ in 19 products, two of which are formulated with triadimenol and one with chlorpyrifos and mancozeb. Uses include application to apples, beans, barley, wheat, citrus, cucurbits, grapes, kiwifruit, kumara, lettuce, maize, onions, raspberries, strawberries, ryegrass, stonefruit and tomatoes.

Thiophanate-methyl is contained in 6 products, most of which are also formulated with chlorothalanil. These products can be applied to ornamentals, roses, tomatoes, potatoes, beans, brassicas, grapes and stonefruit.

The residue definition is the sum of benomyl, carbendazim and thiophanate methyl.

PMRA Canada

In 2006 a review examining the use of carbendazim as a fungicide for the control of Dutch elm disease in elm species (*Ophiostoma and Ophiostoma novo-ulmi*) was completed. There is only one end-use product containing carbendazim registered for use in Canada. Application is by root flare injection (essentially a closed application system), used only by trained aborists and others trained in the identification of Dutch elm disease and injection techniques. The review found that continued use presents minimal risks to workers and the environment, with only minor revisions to personal protective equipment requirements for application made.

Thiophanate-methyl is contained in 13 registered products in Canada. These are intended for use as insecticides and fungicides on food crops as well as potato seed treatments, turf applications and flower dusts. MRLs are established in citrus fruits, peaches, nectarines, berry crops, apples, apricots, carrots, cherries, grapes, mushroom, pears, plums, tomatoes, beans, pineapples, cucumbers, melons, pumpkin and squash.

The Joint Meeting on Pesticide Residues (JMPR)

JMPR has considered carbendazim, thiophanate methyl and benomyl on a number of occasions.

- Carbendazim – 1973, 1976, 1977, 1978, 1983, 1985, 1995.
- Thiophanate-methyl – 1973, 1975, 1977, 1995, 1998.
- Benomyl – 1973, 1975, 1983, 1995.

The most recent consideration was of thiophanate-methyl in October 2006 where they reconsidered the need to established an ARfD (deemed not necessary at an earlier meeting). Thiophanate-methyl was not selectively toxic to embryo or foetal development not teratogenic in laboratory animals. Again it was determined that no ARfD was necessary because thiophanate-methyl was of low acute toxicity and the intake of residues was unlikely to present a risk to consumers.

In their 2005 consideration of carbendazim, the JMPR evaluated developmental toxicity studies that clearly demonstrated that carbendazim is a developmental toxicant and teratogen. An ARfD of 0.1 mg/kg bw for women of childbearing age (based on developmental toxicity) and an ARfD of 0.5 mg/kg bw for the general population, including children, were established.

International Program on Chemical Safety (IPCS)

Carbendazim was reviewed by the IPCS in 1993. The conclusions drawn were that toxicity data were limited and that further elucidation of the mechanism of toxicity of carbendazim in mammals may enable a better definition of a NOEL where binding studies on target cells (testis and embryonic tissues) may facilitate inter-species comparisons.

9 SUBMISSIONS FROM THE PUBLIC INVITED

The formal review will now commence and will deal with the aspects outlined in this scope document.

Interested parties are invited to provide information or data relevant to the issues raised in this scope document. These must reach the APVMA by no later than **30 June 2007**. Submissions can be sent either by email to chemrev@apvma.gov.au or by mail to:

Manager Pesticides Review
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
KINGSTON ACT 2604
Telephone: (02) 6210 4749
Facsimile: (02) 6210 4776

10 DATA ASSESSMENT AND POSSIBLE OUTCOMES

The Office of Chemical Safety and the APVMA Chemistry and Residues Program (CRP) will conduct the technical assessment of data submitted for the review of carbendazim and thiophanate-methyl and advise the APVMA regarding the concerns raised in Sections 5, 6, and 7.

Depending on the findings of the technical assessment, a review can result in one of three broad outcomes:

- The APVMA is satisfied that active constituents and products containing carbendazim or thiophanate-methyl continue to meet the conditions to which registration or approval are currently subject and affirms the registration and approvals; or
- The APVMA is satisfied that the conditions to which the registration or approval is currently subject can be varied in such a way that the requirements for continued registration or approval will be complied with, and varies the conditions of approval or registration; or
- The APVMA is not satisfied that the conditions continue to be met and suspends or cancels the registration or approvals.

The data might lead agencies that provide expert advice to the APVMA to consider setting appropriate public health standards, which in this case might involve:

- the OCS revising the Acceptable Daily Intakes (ADIs);
- the OCS establishing acute reference doses (ARfDs);
- the NDPSC[3] revising the existing poisons schedules;
- the APVMA revising or establishing Maximum Residue Limits (MRLs); or
- the NHMRC[4] revising the drinking water standards.

The APVMA will have regard to the appropriate public health standards in its reconsideration of approvals and registrations.

11 CONSULTATION THROUGHOUT THE REVIEW PROCESS

From initiation of the review through to the implementation of the review outcomes, the APVMA will consult with relevant stakeholders and interested parties. Prior to finalisation of any report, comments from key stakeholders and the public will be sought.

The draft of the review summary along with proposed recommendations will be made available to the stakeholders and public through the APVMA website or direct communication. A period will be allowed for the stakeholders and the public to comment on the draft.

[3] National Drugs and Poisons Scheduling Committee (NDPSC)
[4] National Health and Medical Research Committee (NHMRC)

ATTACHMENT 1: Active constituent approvals

Carbendazim (10)

Approval Number	Approval Holder
44099	Du Pont (Australia) Ltd
44446	4Farmers Pty Ltd
44469	BASF Australia Ltd
52717	Colin Campbell (Chemicals) Pty Ltd
52720	Farmoz Pty Limited
53485	BASF Australia Ltd
53851	Bayer Cropscience Pty Ltd
55520	Imtrade Australia Pty Ltd
58049	Redox Pty Ltd
58228	Sinon Australia Pty Limited

Thiophanate-methyl (1)

Approval Number	Approval Holder
44214	Mitsui & Co (Australia) Ltd

ATTACHMENT 2: Product registrations

Carbendazim (21)

Product Number	Product Name	Registrant	Label Approval Number/s
30399	BASF Bavistin FL Systemic Fungicide	BASF Australia Ltd	30399/02 30399/1100
30740	Hylite Timber Preservative	Osmose Australia Pty Ltd	30740/0799 30740/0500 30740/1100
47708	Hylite 80 Anti-Sapstain	Osmose Australia Pty Ltd	47708/0799
50528	4Farmers Carbendazim 500 Fungicide WP	4Farmers Pty Ltd	50528/0599
51514	Antiblu CC Concentrate Timber Fungicide	Koppers Arch Wood Protection (Aust) Pty Limited	51514/0299
52878	Farmoz Howzat SC Systemic Fungicide	Farmoz Pty Limited	52878/0600 52878/0202 52878/0906 52878/1005 52878/1204
53061	Boomer Systemic Fungicide	Sipcam Pacific Australia Pty Ltd	53061/0600 53061/0505
53390	Chemag Carbendazim 500 SC Fungicide	Imtrade Australia Pty Ltd	53390/0101 53390/0203
53587	Campbell Goldazim 500 SC Systemic Fungicide	Colin Campbell (Chemicals) Pty Ltd	53587/1200 53587/0805 53587/1004
54167	Kendon Carbendazim SC Systemic Fungicide	Kendon Plant Care Pty Ltd	54167/1201
54269	Nufarm Carbend Fungicide	Nufarm Australia Limited	54269/0701 54269/0402 54269/0502
55949	Rotate SC Systemic Fungicide	Kendon Chemicals & MNFG Co Pty Ltd	55949/0602
56497	Sava 500 Fungicide	Allfire Enterprises Pty Ltd	56497/1102
56692	Superway Carbendazim 500 Systemic Fungicide	Superway Garden Ag & Pest Products Pty Ltd	56692/0703
56783	Halley Carbendazim 500 Systemic Fungicide	Halley International Enterprise (Australia) Pty Ltd	56783/0103
58452	Kenso Agcare Carbendazim 500 SC Systemic Fungicide	Kenso Corporation (M) SDN BHD	58452/0105
58832	Conquest Commodore 500 Fungicide	Conquest Agrochemicals Pty Ltd	58832/0604
58886	Crop Care Bavistin FL Systemic Fungicide	Crop Care Australasia Pty Ltd	58886/1105 58886/0705 58886/0804
59434	Shincar 500 SC Fungicide	Sinon Australia Pty Limited	59434/0905
59815	Nufarm Spin flo Systemic Fungicide	Nufarm Australia Limited	59815/0705 59815/1105
60942	Ospray Carbendazim 500 Fungicide	Ospray Pty Ltd	60942/0906

Thiophanate-methyl (3)

Product Number	Product Name	Registrant	Label Approval Number/s
52741	Banrot 400WP Broad Spectrum Fungicide for Ornamentals	Scotts Australia Pty Ltd	52741/0601
53163	Banrot 80G Broad Spectrum Fungicide for Ornamentals	Scotts Australia Pty Ltd	53163/0601
53760	Zyban WP Broad Spectrum Fungicide for Ornamental Plants	Scotts Australia Pty Ltd	53760/0602 53760/0803

ATTACHMENT 3: MRL Standard entries for carbendazim

Compound	Food	MRL mg/kg
FI 0326	Avacado	3
FI 0327	Banana	1
FB 0018	Berries and other small fruits [except grapes]	5
GC 0080	Cereal grains	*0.05
FC0001	Citrus fruits	10
FI 0332	Custard apple	1
MO 0105	Edible offal [mammalian]	0.2
PE 0112	Eggs	*0.1
VC 0045	Fruiting vegetables, cucurbits [except melons, except watermelons]	2
VO 0050	Fruiting vegetables other than cucurbits [except mushrooms]	2
HS 0784	Ginger, root	10
FB 0269	Grapes	3
HH 0092	Herbs [kaffir lime leaves, lemon balm, lemon grass]	T3
DT 1111	Lemon verbena	T3
FI 0343	Litchi	10
FI 0345	Mango	5
MM 0095	Meat [mammalian]	0.2
VC 0046	Melons, except watermelons	4
ML 0106	Milks	*0.1
TN 0669	Macadamia nuts	0.1
VO 0450	Mushrooms	10
FI 0350	Papaya	T20
SO 0697	Peanut	0.2
TN 0675	Pistachio nut	T0.1
FP 0009	Pome fruits	5
PO 0111	Poultry, edible offal of	*0.1
PM 0110	Poultry meat	*0.1
VD 0070	Pulses	0.5
FS 0012	Stone fruits	10
GS 0659	Sugar cane	0.1
HS 0794	Tumeric root vegetables [except fruiting vegetables, cucurbits, fruiting vegetables, other than cucurbits, mushrooms, pulses]	T3

***** - MRL has been set 'at or about' the limit of analytical detection.

T – denotes that the MRL, residue definition of use is temporary to enable further experimental work to be carried out in Australia or overseas, and will be reconsidered at some future date. This symbol is also used in cases where an MRL is being phased out.