Australian Government
Australian Pesticides and
Veterinary Medicines Authority

THIOPHANATE-METHYL
PRELIMINARY REVIEW FINDINGS REPORT

The reconsideration of the active constituent thiophanate-methyl, registration of products containing thiophanate-methyl and approvals of their associated labels

AUGUST 2010

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This document is published by the APVMA. In referencing this document the APVMA should be cited as both author and publisher.

ISBN: 978-0-646-54058-0

Website: This publication is available from the APVMA website: http://www.apvma.gov.au

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FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary (Agvet) chemicals in Australia. Its statutory powers are provided in the Agvet Codes scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*.

The APVMA can reconsider the approval of an active constituent, the registration of a chemical product or the approval of a label for a container for a chemical product at any time. This is outlined in Part 2, Division 4 of the Agvet Codes.

A reconsideration may be initiated when new research or evidence has raised concerns about the use or safety of a particular chemical, a product containing that chemical, or the label of a product containing that chemical.

The reconsideration process includes a call for information from a variety of sources, a review of that information, and following public consultation, a decision about the future use of the chemical or product. The information and technical data required by the APVMA to review the safety of both new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken.

In undertaking reconsiderations (hereafter referred to as reviews), the APVMA works in close cooperation with advisory agencies including the Office of Chemical Safety and Environmental Health within the Department of Health and Ageing, the Department of the Environment Heritage and the Arts, and state Departments of Agriculture, and other expert advisers as appropriate.

The APVMA has a policy of encouraging openness and transparency in its activities and community involvement in making decisions. The publication of review reports is a part of that process.

The APVMA also makes these reports available to the regulatory agencies of other countries as part of bilateral agreements. The APVMA recommends that countries receiving these reports should not utilise them unless they are also provided with the raw data from the relevant registrant.

The basis for the current reconsideration is whether the APVMA is satisfied that the active constituent thiophanate-methyl and the use of products containing thiophanate-methyl (when used in accordance with the instructions for their use):

- would not be an undue hazard to the safety of people exposed to them during their handling
- would not be likely to have an effect that is harmful to human beings.

The APVMA also considered whether product labels carry adequate instructions and warning statements.

This document sets out the preliminary review findings relating to the active constituent thiophanate-methyl and the use of products containing thiophanate-methyl when used in accordance with label instructions. The preliminary review findings and proposed recommendations are based on information collected from a variety of sources.

The review summary (Volume 1) and the technical reports (Volume 2) for all registrations and approvals relating to thiophanate-methyl are available from the APVMA website <http://www.apvma.gov.au/>.

SUBMISSIONS FROM THE PUBLIC ARE INVITED

This report of the Preliminary Review Findings:

- outlines the APVMA review process
- advises interested parties on how to respond to the review
- summarises the technical assessments from the reviewing agencies
- outlines the proposed regulatory action to be taken in relation to the continued registration of thiophanate-methyl products.

The APVMA invites persons and organisations to submit their comments and suggestions on this report of the preliminary review findings directly to the APVMA.

This report is the first of two stages in the review process. Comments on this report will be assessed by the APVMA (and partner agencies where required) prior to finalisation of the review and publication of the Final Review Report and Regulatory Decision.

Preparing your comments for submission

You may agree or disagree with or comment on as many elements of the preliminary review findings as you wish. When making your comments:

- clearly identify the issue and clearly state your point of view
- give reasons for your comments, supporting them, if possible, with relevant information and indicating the source of the information you have used
- suggest to the APVMA any alternative solution you may have for the issue.

Please try to structure your comments in point form, referring each point to the relevant section in the preliminary review findings. This will help the APVMA assemble and analyse all of the comments it receives.

Finally, please tell us whether the APVMA can quote your comments in part or in full.

Please note that subject to the *Freedom of Information Act 1982*, the *Privacy Act 1988* and the Agvet Codes, all submissions received may be made publicly available. They may be listed or referred to in any papers or reports prepared on this subject matter.

The APVMA reserves the right to reveal the identity of a respondent unless a request for anonymity accompanies the submission. If no request for anonymity is made, the respondent will be taken to have consented to the disclosure of their identity for the purposes of the Information Privacy Principles of the *Privacy Act 1988*.

The contents of any submission will not be treated as confidential or confidential commercial information unless they are marked as such and the respondent has provided justification such that the material is capable of being classified as confidential or confidential commercial information in accordance with the *Freedom of Information Act 1982* or the Agvet Codes as the case may be.

The closing date for submissions is 31 August 2010.

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EXECUTIVE SUMMARY

Thiophanate-methyl is a member of the benzimidazole group of fungicides. It is used as a broad-spectrum systemic fungicide for agricultural use in Australia. It is absorbed by the roots and leaves of treated plants and has a protective and curative action. Thiophanate-methyl is registered in several other countries (Canada, New Zealand, the USA and the UK) for food and non-food uses. However, in Australia, at the time of this review, thiophanate-methyl was not registered for use on food-producing species; it was only used for the control of soil-borne diseases of ornamental plants. Therefore, there were no dietary residue issues associated with the use of thiophanate-methyl in Australia.

As at July 2010, there was one thiophanate-methyl active constituent approval and three thiophanate-methyl registered products (Appendix A). Thiophanate-methyl is applied either directly to the soil (evenly mixed with the soil), as a post-planting soil drench, or as a foliar spray. The three registered products contain the active constituent at different concentrations, with the application rates adjusted for this.

A review of the active constituents thiophanate-methyl and carbendazim, all products containing thiophanate-methyl and carbendazim, and their associated labels commenced in 2007 because of concerns about potential foetal malformations and also evidence of testicular toxicity in laboratory animals following the use of benomyl, a compound structurally related to thiophanate-methyl and carbendazim. Thiophanate-methyl breaks down rapidly in the environment to form carbendazim and can subsequently lead to residues of carbendazim in treated commodities. However, thiophanate-methyl appears to undergo only very limited metabolic conversion to carbendazim in mammals and did not induce foetal malformations and testicular toxicity in treated animals. Because of the differences between these related benzimidazoles, a separate Preliminary Review Findings (PRF) for thiophanate-methyl has been produced to address specific concerns about the potential risks following exposure to humans, arising from handling and application of thiophanate-methyl. This includes re-handling treated plants and re-entry to treated areas.

A separate PRF will be produced for carbendazim in due course to address the issues applicable to that active constituent.

Preliminary review findings

Toxicological assessment

The toxicological assessment for the review of thiophanate-methyl was undertaken by the Office of Chemical Safety and Environmental Health (OCSEH). The review was initiated because of concerns over the possibility that thiophanate-methyl could cause birth defects or impair male fertility. There were concerns over the risks to workers who could be exposed to products containing thiophanate-methyl during handling, application and re-entry.

The OCSEH considered the toxicological data and information submitted for the review. The APVMA considered the advice received from the OCSEH and has concluded that the use of products containing thiophanate-methyl in accordance with amended label instructions would not be likely to have a harmful

effect on human health. In considering human health issues, no change to the approval status of the active constituent thiophanate-methyl has been proposed. However, the Australian Acceptable Daily Intake (ADI) for thiophanate-methyl has been increased from 0.02 mg/kg bw/d to 0.08 mg/kg bw/d[1]. Furthermore, an Acute Reference Dose (ARfD) of 0.2 mg/kg bw for thiophanate-methyl was established by the OCSEH; prior to this review assessment, no ARfD had been established. A safety factor of 100 was applied to a NOEL of 20 mg/kg bw/d which was derived from a rabbit developmental study that showed increased foetal skeletal variations (supernumerary ribs) following short-term exposure of dams to 40 mg/kg bw/d. The reconsideration of the toxicology database for thiophanate-methyl as part of this review has also enabled the OCSEH to recommend a new health-based guideline value (not previously established) for thiophanate-methyl in Australian drinking water of 0.09 mg/L[2].

At the commencement of this review, thiophanate-methyl was not listed in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), because of its low toxicity. The OCSEH determined that thiophanate-methyl should be placed in Schedule 6 for products containing more than 25 per-cent thiophanate-methyl (based on a moderate inhalation toxicity), with a cut-off to Schedule 5 at 25 per-cent or less thiophanate-methyl. All currently registered thiophanate-methyl products contain 25 per-cent or less thiophanate-methyl and contain additional active constituents that are Schedule 5 poisons[3]. Thus, the current signal heading on all thiophanate-methyl product labels are not affected by the changes to scheduling applied by the Department of Health and Ageing.

Occupational health and safety assessment

The occupational health and safety (OHS) assessment for the review of thiophanate-methyl was undertaken by the OCSEH. The OHS assessment was based on previous assessments conducted by OCSEH at the time of registration of the three currently registered thiophanate-methyl products in 2000 and 2001; no additional OHS data were submitted by (or required from) registrants as part of this review. This assessment of the OHS information does not provide any basis to amend the existing thiophanate-methyl active approvals and registrations of existing thiophanate-methyl products.

The APVMA considered the advice provided by the OCSEH and found that the existing safety directions — including the required personal protective equipment (PPE) — for the thiophanate-methyl products remain appropriate, apart from a minor amendment which changes ‘PVC gloves’ to ‘chemical resistant gloves’.

[1] mg/kg bw/d = milligrams of thiophanate-methyl per kilogram of body weight ingested in one day

[2] Measured as total carbendazim levels in drinking water, as thiophanate-methyl rapidly degrades to carbendazim in the environment.

[3] All currently registered thiophanate-methyl products contain either mancozeb or etridiazole, which are Schedule 5 poisons.

In the absence of re-exposure data, the following re-entry statement is proposed on the product label[4]:

> "Do not allow entry into treated areas or rehandle treated plants or soil for 12 hours after treatment unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use."

Public submissions

No public submissions have been received by the APVMA on the thiophanate-methyl review to date.

Proposed review outcomes

The APVMA proposes the following regulatory actions based on consideration of all the data and advice received:

a) Affirm the active constituent approval (Appendix A, Table A1).

b) Vary label approvals (listed in Appendix A, Table A2). To satisfy the requirements for continued registration of products, the APVMA proposes the following label variations:

- amend the existing safety directions of the three registered thiophanate-methyl products to replace 'PVC gloves' with 'chemical resistant gloves'
- amend the following re-entry statement on all product labels to include the appropriate protective equipment for early re-entry:
  "Do not allow entry into treated areas or rehandle treated plants or soil for 12 hours after treatment unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use."
- The current labels for thiophanate-methyl do not specifically exclude use in the home garden, however the use pattern and general information on the product labels suggest that these products are for professional use. Furthermore, thiophanate-methyl products require the use of chemical resistant gloves and goggles under the product label's safety directions. Ag MORAG (the Agricultural Manual of Requirements and Guidelines) states that the use of a home garden product should not require special precautions or equipment, such as PVC gloves or goggles. On this basis, the APVMA requires the restraint "NOT FOR HOME GARDEN USE" to be included on all thiophanate-methyl product labels.

c) Affirm product registrations.

After the proposed label variations are undertaken, then the product registrations and label approvals of three products (Appendix A, Table A2) can be affirmed.

[4] The re-entry statement for thiophanate-methyl products was determined by the OCSEH based on US data and the acute toxicity of the active constituents. The re-entry statement is also consistent with the US thiophanate-methyl product label.

Changes to standards arising from the review

As a result of the evaluation of thiophanate-methyl by the OCSEH, the Department of Health and Ageing has placed all thiophanate-methyl products in Schedule 6 with a cut-off to Schedule 5 for products containing less than 25 per-cent thiophanate-methyl. However, no change to current thiophanate-methyl product labels is required since all currently registered thiophanate-methyl products contain 25 per-cent or less thiophanate-methyl and display a Schedule 5 signal heading on the product label. This signal heading also reflects the additional active constituents contained in thiophanate-methyl products (either mancozeb or etridiazole), which are Schedule 5 poisons. The entry for thiophanate-methyl will be amended in the FAISD handbook[5] to reflect these changes.

In addition, the present review has enabled the OCSEH to increase the Australian Acceptable Daily Intake (ADI) for thiophanate-methyl from 0.02 to 0.08 mg/kg bw/d by applying a safety factor of 100 to the NOEL of 8 mg/kg bw/d derived from a one-year dog study showing reduced thyroxine levels and increased relative thyroid weight following exposure to the next highest dose tested, which was 40 mg/kg bw/d.

A new acute reference dose (ARfD) of 0.2 mg/kg bw for thiophanate-methyl has been established by the OCSEH by applying a safety factor of 100 to the NOEL of 20 mg/kg bw/d from a short-term rabbit developmental study showing increased foetal skeletal variations (supernumerary ribs) following exposure of dams to the next highest dose tested, which was 40 mg/kg bw/d. The developmental effect observed in rabbits was considered by the OCSEH to be possibly elicited by a single exposure and sufficient to establish an ARfD.

[5] *FAISD handbook : handbook of first aid instructions, safety directions and warning statements for agricultural and veterinary chemicals*, Therapeutic Goods Administration, 2009

1 INTRODUCTION

The APVMA has reviewed the approval of the active constituent thiophanate-methyl, registered products containing thiophanate-methyl, and the associated label approvals for products containing thiophanate-methyl. This document summarises the data evaluated and the proposed outcomes of the review.

1.1 Regulatory status of thiophanate-methyl in Australia

Thiophanate-methyl is a member of the benzimidazole group of fungicides. It is used as a broad-spectrum systemic fungicide on soil and plants for both its protective and curative action; it is absorbed by the roots and leaves of treated plants. It is effective against a wide range of fungal diseases in a number of crops. However, in Australia, at the time of this review, thiophanate-methyl was not registered for use on food-producing species; it was only approved for the control of soil-borne diseases of ornamental plants. The current labels for thiophanate-methyl do not specifically exclude these products from home garden use, but suggest they are for professional use.

Thiophanate-methyl is applied either directly to the soil (evenly mixed with the soil), as a post-planting soil drench or as a foliar spray. The three registered products contain the active constituent at different concentrations, with the application rates adjusted for this. If extrapolated to a common concentration of 50 grams of active thiophanate-methyl constituent per kilogram of product, the application rate as a solid mixed with soil is 300 grams of product per cubic metre of soil (equivalent to 15 g thiophanate-methyl active per cubic metre soil). As a foliar fungicide, thiophanate-methyl products are applied at 100–170 g/100 L (15.6–26.5 g thiophanate-methyl active/100 L) to the point of runoff. As a post-planting soil drench, thiophanate-methyl products are applied at 2–4 kg/1000 L (100–200 g thiophanate-methyl active/1000 L) to cover 100 square metres. In contrast, overseas rates of thiophanate-methyl as a post-planting soil drench to ornamentals are significantly higher at 350–595 g active constituent/1000 L (Canada) and 600 g active constituent/1000 L (USA). A review of thiophanate-methyl usage in Canada (in 1997) and the USA (in 2005) considered that there was a risk posed to pesticide workers (particularly mixers, loaders, applicators) and to field workers who come into contact with treated foliage, crops, lawns and turf following application of thiophanate-methyl (refer to Section 3.3 'Overseas regulatory status'). The risks were addressed in the USA by implementation of risk mitigation measures (including reduced turf/home garden application rates, additional safety directions and new re-entry intervals, refer to Section 3.3 'Overseas regulatory status'); the Canadian risk assessment of thiophanate-methyl is yet to be finalised[6]. This in contrast to the assessment by the Office of Chemical Safety and Environmental Health (OCSEH) which found that there is no basis to conclude that persons who followed the label directions when preparing and applying thiophanate-methyl-based products would be likely to be at risk of adverse effects. However, the Australian thiophanate-methyl use pattern is limited to ornamentals only, and at application rates significantly lower than the USA or Canada.

As at July 2010, there was one thiophanate-methyl active constituent approval and three thiophanate-methyl registered products (Appendix A). Of the three registered products containing thiophanate-methyl (refer to

[6] As at the date of the preparation of this manuscript viz. July 2010.

Table 1 below), two are wettable powders (250 g/kg thiophanate-methyl and 156 g/kg thiophanate-methyl) and the third product is a granular formulation (50 g/kg thiophanate-methyl). There are no STOPPED[7] thiophanate-methyl products. Information on the uses of thiophanate-methyl products can be found in Section 2 of this PRF.

Table 1: Formulation types for thiophanate-methyl.

FORMULATION TYPE	LEVEL OF ACTIVE CONSTITUENT	PRODUCT TYPE
Wettable Powder	156 g/kg	Commercial#
	250 g/kg	Commercial#
Granular	50 g/kg	Commercial#

 # The current labels for thiophanate-methyl suggest that these products are not intended for home garden use.

1.2 Reasons for the review of thiophanate-methyl

A review of thiophanate-methyl and carbendazim, all products containing thiophanate-methyl and carbendazim, and their associated labels commenced in 2007 because of concerns about potential foetal malformations and also evidence of testicular toxicity in laboratory animals following the use of benomyl, a compound structurally related to thiophanate-methyl and carbendazim. Initial concerns were raised regarding benomyl in 1993 based on an alleged association between benomyl exposure and the occurrence of eye defects in infants born in Britain. At this time it was considered that residues of benomyl arising in food from pre-harvest application would be unlikely to present a public health hazard. Nonetheless, to prevent possible exposure of pregnant women, benomyl was withdrawn at that time from sale for the home garden market in Australia in 1994. Toxicology assessments were conducted by the Department of Health in 1995 and 1996. Because of concerns about the potential developmental toxicity of benomyl, the APVMA undertook an assessment in 2003 of all data that had become available since 1996. The outcome from this assessment by the OCSEH was that benomyl could cause impairment of reproduction and development in laboratory animals, and that women of childbearing age should avoid contact with benomyl. In addition, the OCSEH recommended that the two chemicals structurally-related to benomyl, carbendazim and thiophanate-methyl, be reviewed.

In contrast to benomyl and carbendazim, thiophanate-methyl did not induce birth defects in laboratory animals even following high oral doses administered by stomach tube. Thiophanate-methyl breaks down in the environment to form carbendazim, however in mammals thiophanate-methyl appears to undergo only very limited metabolic conversion to carbendazim. Because of the difference between these related benzimidazole compounds, a separate PRF for thiophanate-methyl has been produced to address specific concerns about the potential risk to humans following exposure arising from handling and application of thiophanate-methyl. This includes re-handling treated plants and re-entry to treated areas. A separate PRF will be produced for carbendazim to address the issues applicable to that active constituent in due course.

[7] STOPPED products are those products where registration of the product is not renewed. This means that the product may no longer be manufactured, but there is 2-year period during which (a) wholesale and retail stock may be sold and (b) product purchased before and during the 2-year period may be used.

1.3 Scope of the review

When the extent of the review was scoped, the reasons for the nomination of thiophanate-methyl, the information already available on this chemical, and the ways that it is approved for use in Australia were taken into account. In view of the concerns identified and the basis for the concerns, the scope of the review of thiophanate-methyl was confined to assessment of toxicology and occupational health and safety aspects. The OCSEH considered additional submitted toxicology data (that became available after the cessation of the benomyl review) to determine whether products containing thiophanate-methyl could continue to be used without unacceptable risks to human health.

The basis for a reconsideration of the registration and approvals for a chemical is whether the APVMA is satisfied that the requirements prescribed by the Agvet Codes for continued registration and approval are being met. In the case of thiophanate-methyl, these requirements include that the use of the product in accordance with the instructions for its use would not be likely to:

- be an undue hazard to the safety of people exposed to it during its handling; or
- have an effect that is harmful to human beings (e.g. during application, re-handling of treated plants or re-entry to treated areas).

The APVMA reviewed the toxicology and occupational health and safety issues for thiophanate-methyl. There was no environmental assessment for thiophanate-methyl. This was based on advice from the then Department of Environment and Heritage (DEH) in 2006 that there was no basis to consider that thiophanate-methyl could be likely to have a harmful effect on the environment. Similarly, trade and efficacy were not considered in the review of thiophanate-methyl, as these issues were considered during the registration process of thiophanate-methyl products, and there has been no subsequent changes to the use pattern of these products. 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. However, the application of thiophanate-methyl to food crops in Australia may be permitted at a later date if suitable data were submitted to support a registration application.

The APVMA also considered whether product labels carried adequate instructions and warning statements. Such instructions should include (among other things):

- frequency of the use of the product
- safe handling of the product
- re-entry into treated areas.

On the basis of these concerns, it was decided that the active constituent approvals, product registrations and label approvals for thiophanate-methyl should be reviewed under the provisions of Part 2, Division 4 of the Agvet Codes in relation to human health and OHS only.

1.4 Regulatory options

There can be three possible outcomes to the reconsideration of the active constituent thiophanate-methyl, registration of products containing thiophanate-methyl and all associated label approvals. Based on the information reviewed, the APVMA may be:

- satisfied that the products and their labels continue to meet the prescribed requirements for registration and approval and therefore affirms the registrations and approvals
- 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 and approval will be complied with and therefore varies the conditions of registration or approval
- not satisfied that the requirements for continued registration and approval can be met and thus suspends or cancels the registration and/or approval.

2 APPROVED THIOPHANATE-METHYL USE PATTERNS

Thiophanate-methyl is a broad-spectrum systemic fungicide with protective and curative action. It is effective against a wide range of fungal diseases in a number of crops. However in Australia, at the time this review was conducted, it was not registered for use on food-producing species, only for the control of soil-borne diseases of ornamental plants. The current labels for thiophanate-methyl imply that these products are not intended for home garden use.

Thiophanate-methyl is applied either directly to the soil (evenly mixed with the soil), as a post-planting soil drench, or as a foliar spray. The three registered products contain the active constituent at different concentrations, with the application rates adjusted for this.

If extrapolated to a common concentration of 50 grams of active thiophanate-methyl constituent per kilogram of product, the application rate as a solid mixed with soil is approximately 300 g product per cubic metre of soil (equivalent to 15 g thiophanate-methyl active per cubic metre soil). As a foliar fungicide, thiophanate-methyl products are applied at a dilution of 100–170 g/100 L (15.6–26.5 g thiophanate-methyl/100 L) to the point of runoff. As a post-planting soil drench, thiophanate-methyl products are applied at 2–4 kg/1000 L (100–200 g thiophanate-methyl active/1000 L) to cover 100 square metres.

2.1 Specific use patterns

At July 2010, thiophanate-methyl was registered for the following crops, fungal diseases and use patterns:

1. As a pre-plant soil mix additive or post planting soil drench (in combination with etridiazole) for control of damping off and root and stem diseases caused by *Phythium, Phytophthora, Rhizoctonia* and *Thielaviopsis (Chalara).* Refer to Table 2 for crop uses covered on the product label.
2. As a post-plant foliar fungicide (in combination with mancozeb) for control of leaf and flower diseases including leaf spots, blights, powdery mildew, downy mildew, petal blight, grey mould and rusts in a range of ornamentals (as listed in Table 2).

Table 2: Approved uses of thiophanate-methyl as a pre-plant soil mix additive or post planting soil drench to control fungal diseases.

BEDDING PLANTS	WOODY PLANTS	HERBACEOUS PERENNIALS	UNROOTED CUTTINGS	INDOOR PLANTS
Ageratum, Alyssum, Aster, Balsam, Begonia, Calendula, Carnation, Coleus, Celosia, Cosmos, Cornflower, Dahlia, Gynura, Impatiens, Larkspur, Marigold, Nasturtium, Pansy, Petunia, Phlox, Salvia, Snapdragon, Sweet Pea, Verbena, Zinnia	Azalea, Camelia, Gardenia, Roses, Hydrangea, Acacia, Melaleuca, Callistemon, Banksia, Grevillea, Leptospermum, Tibouchina, Viburnum, Pittosporum, Poinsettia	Chrysanthemum, Delphinium, Geranium, Gerbera, Pelargonium, Fuchsia	Impatiens, Geranium	African violet, Aluminium plant, Boston fern, Dieffenbachia, Dracaena, Maidenhair fern, Maranta, Syngonium, Philodendron, Schefflera, Compact Boston fern

3 SUMMARY OF DATA ASSESSMENTS

3.1 Toxicology

The toxicological assessment for the review of thiophanate-methyl was undertaken by the OCSEH (refer to Volume 2 for full report). The OCSEH considered the extensive toxicological data for thiophanate-methyl in the form of unpublished data generated by industry, in addition to a number of published studies. The toxicological findings are summarised below.

Approval status

No change was recommended to the approval status of the active for thiophanate-methyl on the basis of toxicology data. Continued approval of the active thiophanate-methyl was supported.

Product registration

As a result of the evaluation of thiophanate-methyl by OCSEH, The Department of Health and Ageing determined that thiophanate-methyl should be placed in Schedule 6 with a cut-off to Schedule 5 at 25 per-cent thiophanate-methyl; previously it was not scheduled. However, no change to current thiophanate-methyl product labels was required since all currently registered thiophanate-methyl products contain 25 per-cent or less thiophanate-methyl and display a Schedule 5 signal heading on the product label. This signal heading is based on the additional active constituents contained in the thiophanate-methyl product's formulation (either mancozeb or etridiazole), which are Schedule 5 poisons. The entry for thiophanate-methyl will be added to the SUSDP handbook to reflect these changes.

Continued registration of existing thiophanate-methyl products is supported, providing that product labels are amended to reflect the findings of the review, specifically:

- amend the existing safety directions of the three registered thiophanate-methyl products to replace 'PVC gloves' with 'chemical resistant gloves'
- amend the following re-entry statement on the product label to include appropriate PPE:
  "Do not allow entry into treated areas or rehandle treated plants or soil for 12 hours after treatment unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use."

Acceptable daily intake (ADI)

At the commencement of the review, the Australian acceptable daily intake (ADI) for thiophanate-methyl was 0.02 mg/kg bw/d based on a no observable effect level (NOEL) of 2 mg/kg bw/d in a 2-year rat study (established in 1991). The present review enabled the OCSEH to determine that it is appropriate to increase the ADI for thiophanate-methyl to 0.08 mg/kg bw/d, by applying a safety factor of 100 to the NOEL of 8 mg/kg bw/d derived from a one-year dog study. This study reported the most sensitive toxicological effects to be a significant decrease in the levels of thyroxine and an increase in relative thyroid weight at the next highest dose tested, which was 40 mg/kg bw/d.

Acute reference dose (ARfD)

A new acute reference dose (ARfD) of 0.2 mg/kg bw for thiophanate-methyl was established by the OCSEH; prior to this review assessment, no ARfD had been established. A safety factor of 100 was applied to the NOEL of 20 mg/kg bw/d which was derived from a short-term rabbit developmental study showing increased foetal skeletal variations (supernumerary ribs) following exposure of dams to the next highest oral dose tested, which was 40 mg/kg bw/d. The developmental effect observed in rabbits was considered by the OCSEH to be possibly elicited by a single exposure and therefore was an appropriate endpoint to establish an ARfD.

Water quality guidelines

A new National Health and Medical Research Council (NHMRC) health-based guideline value (not previously established) for thiophanate-methyl in drinking water of 0.09 mg/L was proposed by the OCSEH, based on a NOEL of 2.5 mg/kg bw/d from a 2-year dog study with carbendazim.

Poisons schedule

At the time of this review, thiophanate-methyl was not listed in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). However, as a result of this review, the OCSEH recommended that thiophanate-methyl be placed in Schedule 6 of the SUSDP, with a cut-off to S5 for preparations containing 25 per-cent or less of thiophanate-methyl. The National Drugs & Poisons Schedule Committee (NDPSC) adopted this recommendation at its 57th meeting on 20–21 October 2009.

First aid instructions and warning statements

There were no first aid instructions for thiophanate-methyl in the FAISD Handbook prior to the commencement of this review. However the first aid instruction ‘a’ appeared on the labels of all registered thiophanate-methyl product labels (due to the presence of either etridiazole or mancozeb in the product formulation).

CODE	FIRST AID INSTRUCTION
a.	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126

Based on the acute hazard of thiophanate-methyl, the existing first aid instruction ‘a’ was considered to be appropriate by OCSEH. As a result, a new row entry for thiophanate-methyl was recommended for the FAISD handbook. No warning statements are required for thiophanate-methyl products.

3.2 Occupational health and safety (OHS)

The OHS assessment for the review of thiophanate-methyl was undertaken by the OCSEH, which considered previous OHS and toxicology assessments of thiophanate-methyl (for product registration in 2000, 2001, 2002), as well as all the OHS data and information submitted for the review (refer to Volume 2 for full report). The OHS findings are summarised as follows.

1. The OCSEH reported that there was no basis to conclude that thiophanate-methyl-based products will have an adverse effect on persons involved in preparing and applying thiophanate-methyl-based products, when used according to the directions on the product label.
2. The current registered uses of thiophanate-methyl are supported without change to the current conditions of application. These include:
   - application to ornamental plants by mechanical tractor and hand-held equipment
   - application to soil by hand or hand held equipment.
3. Re-entry statement: Workers entering treated areas can be exposed to product residues and degradation products during plant scouting as well as re-handling activities such as thinning, weeding, flower cutting and re-potting. In 2000 and 2001, in the absence of re-exposure data, the National Occupational Health and Safety Commission (NOHSC) determined the re-entry exposure by the product toxicity profile as well as the US EPA regulations, which are based on the acute toxicity of the active constituent. Therefore, the following re-entry statement is recommended by the OCSEH on the product label:

   > "Do not allow entry into treated areas or rehandle treated plants or soil for 12 hours after treatment unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use."

   This statement is consistent with the USA thiophanate-methyl product label.
4. Safety directions[8]: the existing safety directions of the three registered thiophanate-methyl products remain appropriate, except that 'PVC gloves' are to be replaced by 'chemical resistant gloves' (refer Table 4). In addition, the two entries for thiophanate-methyl alone (HG[9] LD[10] 1.5 g/L or less and WP[11] 700 g/kg or less, refer Table 3) were recommended for deletion as there are no registered products.

Table 3: Deleted safety direction entries for thiophanate-methyl.

CODES	SAFETY DIRECTIONS
THIOPHANATE METHYL HG LD 1.5 G/L OR LESS	
210 211	Avoid contact with eyes and skin
219 223	Avoid inhaling spray mist
351	Wash hands after use
THIOPHANATE METHYL WP 700 G/KG OR LESS	
210 211	Avoid contact with eyes and skin
220 221 223	Do not inhale dust or spray mist
351	Wash hands after use.

[8] Safety Directions which relate to safety in handling, use and storage of a product can be obtained from *Handbook of First Aid Instructions and Safety Directions for Agricultural and Veterinary Chemicals (PDF)* (including Pesticides), published by the Commonwealth Department of Health and Aged Care and NOHSC.

[9] HG: Home Garden

[10] LD: Liquid

[11] WP: Wettable Powder

Table 4: Amended safety direction entries for thiophanate-methyl.

CODES	SAFETY DIRECTIONS
ETRIDIAZOLE WP 161 G/KG OR LESS WITH THIOPHANATE-METHYL 270 G/KG OR LESS	
161 162 164	Will irritate eyes and skin
210 211	Avoid contact with eyes and skin
340 342	If product on skin, immediately wash area with soap and water
340 343	If product in eyes, wash it out immediately with water
279 280 281 282 290 292 294c 297	When opening the container and preparing mix/drench and using the prepared mix/drench, wear cotton overalls buttoned to the neck and wrist and a washable hat and chemical resistant gloves and goggles
351	Wash hands after use
360 361 363 366	After each day's use, wash goggles, gloves and contaminated clothing
ETRIDIAZOLE GR[12] 34 G/KG OR LESS WITH THIOPHANATE-METHYL 57 G/KG OR LESS	
161 162 164	Will irritate eyes and skin
210 211	Avoid contact with eyes and skin
279 280 283 290 292b 294c 306	When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist, and chemical resistant gloves and a disposable dust mask
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing
MANCOZEB WP 700 G/KG OR LESS WITH THIOPHANATE-METHYL 200 G/KG OR LESS WHEN PACKED IN SEALED WATER SOLUBLE SACHETS (APPLICATION BY HAND SPRAYING)	
161 162	Will irritate eyes
210 162	Avoid contact with eyes
279 282 290 292b 294c 298	When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat and elbow length chemical resistant gloves and impervious footwear
340 343	If product in eyes, wash it out immediately with water
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing
MANCOZEB WP 700 G/KG OR LESS WITH THIOPHANATE-METHYL 200 G/KG OR LESS WHEN PACKED IN SEALED WATER SOLUBLE SACHETS (APPLICATION BY MECHANICAL SPRAYING)	
161 162	Will irritate eyes
210 162	Avoid contact with eyes
279 282 290 292b 295	When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow length chemical resistant gloves
340 343	If product in eyes, wash it out immediately with water
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing

[12] GR: Granular

Worker exposure during mixing, loading and application

On the basis of available information, there was no basis to alter the existing finding that thiophanate-methyl-based products will not have an effect that is harmful to workers, when used according to the directions on the product label.

3.3 Overseas regulatory status

According to the Pesticide Action Network (PAN) North America Pesticides Database, thiophanate-methyl is registered for use in the following countries:

South Africa, Tanzania, India, New Zealand, Philippines, Germany, Hungary, Netherlands, Finland, Portugal, United Kingdom, Canada and the United States. Additional information in relation to some of these uses is given below.

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 and 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 or feed uses include ornamentals (greenhouses, interior-scapes, landscaping) and nursery (including forest nurseries) and turf (sod farms, residential and recreational lawns).

Thiophanate-methyl formulations include dusts, granules, wettable powders, water-dispersible granules and flowable concentrates ranging from 1.5 per-cent to 90 per-cent active ingredient. Application methods for thiophanate-methyl include aerial, chemigation (chemical injection into irrigation water) 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 post emergent broadcast applications.

US EPA Re-registration Eligibility Decision (RED) document (October 2005)

In October 2005 the US EPA published a Re-registration Eligibility Decision (RED) for thiophanate-methyl and the primary metabolite carbendazim. The review was ongoing at the time of this review as the outcomes are yet to be implemented. The review found that thiophanate-methyl can induce developmental toxicity in laboratory animals. Foetal effects in rabbits from thiophanate-methyl exposure include an increase in supernumerary ribs and reduced foetal weight. Thiophanate-methyl has also been associated with an increased incidence of liver tumours in mice.

Thiophanate-methyl was found to exhibit low acute oral, dermal and inhalational toxicity. Long-term dietary studies show the liver and thyroid are the primary target organs of thiophanate-methyl toxicity in several species following sub-chronic and chronic dietary exposure. Thiophanate-methyl is not a skin irritant, but it is a slight eye irritant and a skin sensitiser. An acute RfD (Reference Dose) for the general population of 0.4

mg/kg bw/d was set, based on a No Observable Adverse Effect Level (NOAEL[13]) of 40 mg/kg/d from a one-year dog study where there were tremors two to four hours post-dosing in seven out of eight dogs at 200 mg/kg bw/d. The US EPA added a 'Food Quality Protection Act' (FQPA)[14] Safety Factor of 3, taking the value to 0.13 mg/kg bw/d. For females (13–50 years), the USEPA set an acute RfD of 0.2 mg/kg bw/d, based on a NOAEL of 20 mg/kg bw/d for supernumerary ribs in foetuses and decreased foetal weight of exposed dams in a rabbit developmental toxicity study and using a 100-fold uncertainty factor (analogous to a safety factor). The US EPA added a FQPA Safety Factor of 3, taking the value to 0.067 mg/kg bw/d. A chronic RfD (analogous to an ADI) was set at 0.08 mg/kg bw/d, based on a NOAEL of 8 mg/kg bw/d for liver and thyroid toxicity in a one-year dog study and using a 100-fold uncertainty factor. The FQPA Safety Factor was also 3, taking the chronic RfD value to 0.027 mg/kg bw/d.

Thiophanate-methyl was classified by the US EPA as likely to be carcinogenic to humans based on dose-dependent increases in liver tumours in male and female mice. Aggregate cancer risk estimates for thiophanate-methyl from all uses, including residential (lawn treatment and post-application exposure) and dietary exposure in the USA, exceeded the US EPA's level of concern.

Of greater concern to the US EPA was the risk posed to pesticide workers (particularly mixers, loaders and applicators) and field workers who come into contact with treated foliage, crops, lawns and turf following pesticide application. This is in contrast to the findings by the OCSEH under Section 3.2 of this PRF, 'Worker exposure during mixing, loading and application'. The OCSEH reported persons involved in preparing and applying thiophanate-methyl-based products, according to label directions, would be unlikely to suffer an adverse effect. However, higher rates of thiophanate-methyl used in the US as a foliar fungicide (60 g thiophanate-methyl/100 L) compared to the more limited Australian registered use patterns (26.52 g thiophanate-methyl/100 L) may form the basis of these contrasting findings.

To mitigate human health risks of concern posed by thiophanate-methyl, the US EPA introduced significant risk mitigation measures. These included:

- reduced application rates for cut flowers (560 g thiophanate-methyl/ha, as a foliar application) and turf application (3.07–9.15 kg thiophanate-methyl/ha as a soil drench) in residential and public areas (such as parks, athletic fields, lawns) and golf courses. Maximum application rates of 24.4 kg thiophanate-methyl/ha/year (golf) and 12.19 kg thiophanate-methyl/ha/year (turf) are also required. The application rate for potted plants remains at 3.36 kg thiophanate-methyl/ha (as a foliar application). By comparison, the application rate in Australia for container grown plants is 10–20 kg thiophanate-methyl/ha.
- a 14-day re-treatment interval for most turf applications.
- water soluble packaging for wettable powder formulations for aerial and chemigation applications.

[13] The No Observable Adverse Effect Level (NOAEL) is the highest dose of a substance at which no toxic (i.e. adverse) effects are observed in the test animal. The No Observable Effect Level (NOEL) is the highest dose of a substance which causes no changes (adverse or not) distinguishable from those observed in the normal (control) animals. Australian ADI and ARfD levels are based on the NOEL, which is commonly less than the NOAEL.

[14] The FQPA safety factor is not used in Australia for the determination of the ADI or ARfD. This additional safety factor, used by the USA, is intended to provide extra protection where it is assessed that infants and children may be more sensitive than adults, or to compensate for an incomplete database relating to this part of the population.

- enclosed cabs for planters and operators while planting treated potato seed.
- double-layer PPE, chemical-resistant gloves, and a chemical-resistant apron to be worn when mixing, loading or applying dip treatment.
- single-layer PPE (baseline) and chemical-resistant gloves for other tasks.
- new re-entry intervals
  - almonds and peanuts: three days;
  - apples, cherries, peaches, nectarines, apricots, and plums/prunes: two days;
  - strawberries, blueberries, wheat, celery, cucurbits, soybeans, and green beans: 24 hours;
  - woody ornamentals: 12 hours.
- a maximum single application rate of 2.02 kg thiophanate-methyl/ha applied by homeowners to ornamentals using spraying products.
- liquid formulations for broadcast turf and lawn use restricted to commercial Pest Control Operators (PCOs).

The continued registration of thiophanate-methyl products in the USA is not only subject to adherence to the mitigation measures outlined above, but to the provision of additional data[15] including:

- toxicology (neurotoxicity, inhalation and dermal toxicity (MBC only, or Methyl 2-benzimidazolycarbamate, the major degradate of thiophanate-methyl));
- chemistry and residue data;
- occupational exposure and post application exposure data.

European Commission

In February 2005, the European Commission conducted a review of the toxicology of thiophanate-methyl. An acute RfD of 0.2 mg/kg bw was set, based on a NOAEL of 20 mg/kg bw/d for supernumerary ribs in foetuses of exposed dams in a rabbit developmental toxicity study and using a 100-fold uncertainty factor (analogous to a safety factor). A chronic RfD (analogous to an ADI) was set at 0.08 mg/kg bw/d, based on a NOAEL of 8 mg/kg bw/d for liver and thyroid toxicity in a one-year dog study and using a 100-fold uncertainty factor.

United Kingdom (UK)

At the time of this review, there were seven products registered in the UK containing thiophanate-methyl formulated alone or with iprodione. Approved uses included application to oilseed rape, field beans, broccoli, Brussels sprouts, cabbage, cauliflower, swede, turnip, apple, pear and amenity turf.

[15] As at the date of preparation of this manuscript, there has been no assessment of thiophanate-methyl data submitted to the US EPA since the Re-registration Eligibility Decision (RED).

New Zealand (NZ)

At the time of this review, thiophanate-methyl was contained in six products in NZ, most of which are also formulated with chlorothalanil. These products can be applied to ornamentals, roses, tomatoes, potatoes, beans, brassicas, grapes and stonefruit.

The NZ Food Safety Authority had previously adopted the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) 1998 ADI determination of 0.08 mg/kg bw/d for thiophanate-methyl. It was also determined that an ARfD wasn't necessary. However since 2004 all health standard settings have been undertaken by the Environmental Risk Management Authority in NZ. The authority has not set an ADI or an ARfD for thiophanate-methyl.

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

Canada

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. Maximum residue limits 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.

In September 2007, the Canadian Pest Management Regulatory Agency (PMRA) conducted a preliminary risk assessment of thiophanate-methyl. An acute RfD for the general population was set at 0.13 mg/kg bw. This was based on a NOAEL of 40 mg/kg bw/d for tremors that occurred within two to four hours of dosing at 200 mg/kg/d in a one-year study in dogs. A safety factor of 300 was applied, the additional three-fold being for the lack of an acute neurotoxicity study in rodents. For females 13–50 years of age, an acute RfD of 0.067 mg/kg bw/d was set, based on a NOAEL of 20 mg/kg bw/d for supernumerary ribs in foetuses of exposed dams in a rabbit developmental toxicity study at 40 mg/kg/d. This effect was considered relevant to a single-dose exposure. The acute RfD incorporates a 300-fold uncertainty factor (the additional threefold for the lack of neurotoxicity and developmental neurotoxicity studies). A chronic RfD (analogous to an ADI) was set at 0.008 mg/kg bw/d, based on a NOAEL of 8 mg/kg bw/d for liver and thyroid toxicity in a one-year dog study and using a 1000-fold uncertainty factor (increased 10-fold for lack of developmental neurotoxicity and endocrine disrupting compound studies).

In addition, the Canadian review raised concerns of long-term worker exposure to thiophanate-methyl during application to ornamentals under low-pressure and high-pressure handwand situations. This is in contrast to the findings by the OCSEH under Section 3.2 of the PRF, ‘Worker exposure during mixing/loading and application’. The OCSEH reported persons involved in preparing and applying thiophanate-methyl-based products, according to label directions, are unlikely to suffer adverse effects. However, higher rates of thiophanate-methyl used in Canada as a foliar fungicide (45.5–59.5 g thiophanate-methyl/100 L) compared to the Australian registered use patterns (26.52 g thiophanate-methyl/100 L) may form the basis of these contrasting findings.

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) considered thiophanate-methyl in 1973, 1975, 1977, 1995, 1998 and 2006.

An ADI of 0–0.08 mg/kg bw/d was established in 1973 by the JMPR on the basis of the NOAEL of 8 mg/kg bw/d in a three-generation study of reproductive toxicity in rats and in a one-year study in dogs, both of which were evaluated at earlier meetings, and a safety factor of 100.

An ARfD was not required because thiophanate-methyl is of low acute toxicity when administered orally or dermally and is only slightly toxic when administered by inhalation. In 2006, the JMPR conducted an evaluation for an ARfD for thiophanate-methyl. Acute effects seen in the one-year dog study at 200 mg/kg bw/d, used by other international agencies to establish an ARfD for the general population, were discounted by JMPR as not relevant to human health as they were not seen in a three-month dog study at 800 mg/kg bw/d. Further, the developmental effects observed in rabbits at 40 mg/kg bw/d were not considered to be elicited by a single exposure. It was concluded that an ARfD was not necessary for thiophanate-methyl in view of its low acute toxicity, the absence of relevant developmental toxicity that could be a consequence of acute exposure, the absence of relevant findings in a study of acute neurotoxicity, and the absence of any other toxicological effect that would be likely to be elicited by a single dose.

3.4 Summary of public submissions

No public submissions have been received by the APVMA on the thiophanate-methyl review to date.

4 PROPOSED REVIEW FINDINGS

On the basis of the evaluation of the submitted data and information, the APVMA proposes to find as follows with regard to the continued approval of the active constituent thiophanate-methyl, registration of thiophanate-methyl products and label approvals in Australia.

4.1 Affirm approvals of the active constituent

The APVMA is proposing to be satisfied that, provided the conditions to which the approval is currently subject are complied with, the continued use if, or any other dealings with, the active constituent thiophanate-methyl would not be likely to have an effect that is harmful to human beings. The APVMA proposes to affirm the active constituent approval listed in Table 5.

Table 5: Active constituent approval to be affirmed.

APPROVAL NUMBER	APPROVAL HOLDER
44214	Mitsui and Co (Australia) Ltd

4.2 Vary conditions of label approval

The APVMA is currently not satisfied that the current approved labels of the products in Table 6 contain adequate instructions in relation to the criteria set out in 14(3)(g) of the Agvet Codes as well as those referred to in Regulations 11 and 12 of the Agvet Code Regulations. However, the APVMA is proposing to be satisfied that the conditions of label approval for the products in Table 6 can be varied in such a way that they do contain adequate instructions in accordance with section 14(3)(g) of the Agvet Codes.

The following variations to the product label apply:

1. The following re-entry statement to be amended on the product label:

   Re-entry statement:

   > "Do not allow entry into treated areas or rehandle treated plants or soil for 12 hours after treatment unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use."

2. Safety directions, first aid instructions and warning statements: the existing FAISD Handbook safety directions for the three registered thiophanate-methyl products remain appropriate, except that 'PVC gloves' are to be replaced by 'chemical resistant gloves'. The existing first aid instructions for thiophanate-methyl formulations remain appropriate. No warning statements are required for thiophanate-methyl products.
3. No first aid instructions for thiophanate-methyl currently exist in the FAISD Handbook. However the first aid instruction 'a' appears on the labels of all currently registered thiophanate-methyl product labels (due to the presence of either etridiazole or mancozeb in the product formulation).

CODE	FIRST AID INSTRUCTION
a.	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126

Based on the acute hazard of thiophanate-methyl, the existing first aid instruction 'a' is considered to be appropriate by OCSEH. As a result, a new row entry for thiophanate-methyl is recommended for the FAISD handbook. No warning statements are required for thiophanate-methyl products.

4. The current labels for thiophanate-methyl indicate that these products are not for home garden use. Furthermore, thiophanate-methyl products require the use of chemical resistant gloves and goggles under the product label's safety directions. Ag MORAG (Agricultural Manual of Requirements and Guidelines) states that the use of a home garden product should not require special precautions or equipment, such as PVC gloves or goggles. On this basis, the APVMA requires the restraint "NOT FOR HOME GARDEN USE" to be included on all thiophanate-methyl product labels.

The APVMA also proposes to cancel obsolete labels that do not contain adequate instructions.

As a result of the evaluation of thiophanate-methyl by OCSEH, the Department of Health and Ageing has recommended to the NDPSC that thiophanate-methyl be placed in Schedule 6 with a cut-off to Schedule 5 at 25 per-cent thiophanate-methyl. However, no change to current thiophanate-methyl product labels is required since all currently registered thiophanate-methyl products contain 25 per-cent or less thiophanate-methyl and display a Schedule 5 signal heading on the product label. This signal heading is based on the additional active constituents contained in the thiophanate-methyl product's formulation (either mancozeb or etridiazole), which are Schedule 5 poisons. The entry for thiophanate-methyl will be amended in the SUSDP to reflect these changes.

4.3 Affirm product registrations and label approval

Section 4.2 above identifies various changes to labels as an outcome of the thiophanate-methyl review. These variations to label instructions would satisfy the requirements for continued registration of the products listed in Table 6 and the APVMA proposes to affirm these product registrations.

Table 6: Products affected by proposed review findings*.

PRODUCT NUMBER	PRODUCT NAME	REGISTRANT	LABEL APPROVAL NUMBERS TO BE CANCELLED	NEW LABEL APPROVAL NUMBERS
52741	Banrot 400WP Broad Spectrum Fungicide for Ornamentals	Scotts Australia Pty Ltd	52741/907/0706 52741/0601	
53163	Banrot 80G Broad Spectrum Fungicide for Ornamentals	Scotts Australia Pty Ltd	53163/5kg/1007 53163/12kg/1007 53163/18.14kg/1007 53163/5kg/0601 53163/12kg/0601 53163/18.14kg/0601	
53760	Zyban WP Broad Spectrum Fungicide for Ornamental Plants	Scotts Australia Pty Ltd	53760/080353760/0602	

** No products have been withdrawn or voluntarily cancelled since the commencement of the review of thiophanate-methyl.*

4.4 Public health standards

Approval status

The ongoing approval of the current thiophanate-methyl active constituent is supported by the OCSEH.

Impurity limits

No change.

Acceptable daily intake (ADI)

The Australian ADI for thiophanate-methyl in place at the commencement of this review was 0.02 mg/kg bw/d established in 1991. The current review of thiophanate-methyl enabled the OCSEH to determine that the most sensitive toxicological end points in mice, rats and dogs were liver, thyroid and testes toxicity and the NOEL for these effects should be the basis for the establishment of the ADI. The lowest NOEL was 8 mg/kg bw/d in a one-year study in dogs based on thyroid toxicity and a 100-fold safety factor. Consequently, a revised ADI of 0.08 mg/kg bw/d for thiophanate-methyl has been established by the OCSEH.

Acute reference dose (ARfD)

An Australian ARfD has not been previously established for thiophanate-methyl. However, following a review of submitted and archived data by the OCSEH, an ARfD of 0.2 mg/kg bw for thiophanate-methyl has been established, based on a rabbit development study where an increase in foetal skeletal variations (supernumerary ribs) was observed at 40 mg/kg bw/d. Although these variations occurred only in conjunction with maternotoxicity, it is possible that they were related to a single exposure. Therefore, to be protective of developmental effects which can occur following exposure *in utero*, a NOEL of 20 mg/kg bw/d from this rabbit developmental study was used to establish the ARfD. A 100-fold safety factor is used, incorporating 10-fold each for intra and interspecies variation. On this basis, an ARfD of 0.2 mg/kg bw was established by the OCSEH for thiophanate-methyl. This ARfD was also supported by observations from a one-year dog study, in which tremors occurred at doses of 200 mg/kg bw/d. As the tremors occurred shortly after dosing, they are considered to be an acute effect and support the establishment of an ARfD for thiophanate-methyl. No acute effects were noted at the next lowest dose of 40 mg/kg bw/d.

The establishment of an Australian ARfD for thiophanate-methyl is the same as that set by the European Commission (0.2 mg/kg bw), below the USA value (0.4 mg/kg bw), and slightly above the Canadian value (0.13 mg/kg bw). There has been no ARfD set by NZ or the JMPR. In 2006 the JMPR conducted an evaluation for an ARfD for thiophanate-methyl. Acute effects seen in the one-year dog study at 200 mg/kg bw/d, used by other international agencies to establish an ARfD for the general population, were discounted as not relevant as they were not seen in a three-month dog study at 800 mg/kg bw/d. The developmental effects observed in rabbits at 40 mg/kg bw/d were not considered to be elicited by a single exposure. It was concluded by the JMPR that an ARfD was not necessary for thiophanate-methyl, in view of its low acute toxicity, the absence of relevant developmental toxicity that could be a consequence of acute exposure, the absence of relevant findings in a study of acute neurotoxicity, and the absence of any other toxicological effect that would be likely to be elicited by a single dose.

Water quality guidelines

A NHMRC health-based guideline value for thiophanate-methyl in drinking water had not been previously established.

The OCSEH recommended a health-based guideline value of 0.09 mg/L for thiophanate-methyl (measured as total carbendazim levels) to the National Health and Medical Research Council (NHMRC).

Poisons schedule

The OCSEH recommended that products containing more than 25 per-cent thiophanate-methyl be placed in Schedule 6, based on a moderate inhalation toxicity, and Schedule 5 for products containing 25 per-cent or less thiophanate-methyl.

First-aid instructions

No first aid instructions for thiophanate-methyl exist in the FAISD Handbook. However, the first aid instruction 'a' appears on the labels of all currently registered thiophanate-methyl product labels (due to the addition of either etridiazole or mancozeb in the product formulation).

CODE	FIRST AID INSTRUCTION
a.	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126

Based on the acute hazard of thiophanate-methyl, the existing first aid instruction 'a' remains appropriate. No warning statements are required for thiophanate-methyl products.

Safety directions and personal protective equipment (PPE)

The existing safety directions for Australian products containing thiophanate-methyl, as recommended in the FAISD Handbook, are shown in Table 7.

Amendments to existing safety directions and PPE

Based on a consideration of the toxicity of each constituent in registered thiophanate-methyl products, the following amended hazard-based safety directions and PPE (refer Table 8) are considered to be appropriate by the OCSEH.

Deleted safety directions and PPE

The following entries for thiophanate-methyl (refer Table 9) will be deleted from the FAISD by the OCSEH, as there are no registered products containing thiophanate-methyl alone.

Table 7: Existing safety directions and PPE for thiophanate-methyl.

CODE	SAFETY DIRECTIONS
THIOPHANATE-METHYL HG LD 1.5 G/L OR LESS	
210 211	Avoid contact with eyes and skin
219 223	Avoid inhaling spray mist
351	Wash hands after use
THIOPHANATE-METHYL WP 700 G/L OR LESS	
210 211	Avoid contact with eyes and skin
220 221 223	Do not inhale dust or spray mist
351	Wash hands after use
ETRIDIAZOLE WP 161 G/KG OR LESS WITH THIOPHANATE-METHYL 270 G/KG OR LESS	
161 162 164	Will irritate eyes and skin
210 211	Avoid contact with eyes and skin
340 342	If product on skin, immediately wash area with soap and water
340 343	If product in eyes, wash it out immediately with water
279 280 281 282 290 292 294 297	When opening the container and preparing mix/drench and using the prepared mix/drench, wear cotton overalls buttoned to the neck and wrist and a washable hat and elbow-length PVC gloves and goggles
351	Wash hands after use
360 361 363 366	After each day's use, wash goggles, gloves and contaminated clothing
ETRIDIAZOLE GR 34 G/KG OR LESS WITH THIOPHANATE-METHYL 57 G/KG OR LESS	
161 162 164	Will irritate eyes and skin
210 211	Avoid contact with eyes and skin
279 280 283 290 292b 294 306	When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist, and elbow-length PVC gloves and a disposable dust mask
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing
MANCOZEB WP 700 G/KG OR LESS WITH THIOPHANATE-METHYL 200 G/KG OR LESS WHEN PACKED IN SEALED WATER SOLUBLE SACHETS	
161 162	Will irritate eyes
210	Avoid contact with eyes
340 343	If product in eyes, wash it out immediately with water
279 282 290 292 292b 295 298	When using the prepared spray, wear cotton overalls buttoned to the neck and wrist and a washable hat (application by hand spray) and elbow-length nitrile or PVC gloves and impervious footwear (application by hand spray)
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing

Table 8: Amendments to existing safety directions and PPE for thiophanate-methyl.

CODE	SAFETY DIRECTIONS
ETRIDIAZOLE WP 161 G/KG OR LESS WITH THIOPHANATE-METHYL 270 G/KG OR LESS	
161 162 164	Will irritate eyes and skin
210 211	Avoid contact with eyes and skin
340 342	If product on skin, immediately wash area with soap and water
340 343	If product in eyes, wash it out immediately with water
279 280 281 282 290 292 294c 297	When opening the container and preparing mix/drench and using the prepared mix/drench, wear cotton overalls buttoned to the neck and wrist and a washable hat and chemical resistant gloves and goggles
351	Wash hands after use
360 361 363 366	After each day's use, wash goggles, gloves and contaminated clothing
ETRIDIAZOLE GR 34 G/KG OR LESS WITH THIOPHANATE-METHYL 54 G/KG OR LESS	
161 162 164	Will irritate eyes and skin
210 211	Avoid contact with eyes and skin
279 280 283 290 292b 294c 306	When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist, and chemical resistant gloves and a disposable dust mask
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing
MANCOZEB WP 700 G/KG OR LESS WITH THIOPHANATE-METHYL 200 G/KG OR LESS WHEN PACKED IN SEALED WATER SOLUBLE SACHETS (APPLICATION BY HAND HELD SPRAYING)	
161 162	Will irritate eyes
210 162	Avoid contact with eyes
279 282 290 292b 294c 298	When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat and elbow length chemical resistant gloves and impervious footwear
340 343	If product in eyes, wash it out immediately with water
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing
MANCOZEB WP 700 G/KG OR LESS WITH THIOPHANATE-METHYL 200 G/KG OR LESS WHEN PACKED IN SEALED WATER SOLUBLE SACHETS (APPLICATION BY MECHANICAL SPRAYING)	
161 162	Will irritate eyes
210 162	Avoid contact with eyes
279 282 290 292b 295	When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow length chemical resistant gloves
340 343	If product in eyes, wash it out immediately with water
351	Wash hands after use
360 361 366	After each day's use, wash gloves and contaminated clothing

Table 9: Deleted safety directions and PPE for thiophanate-methyl.

CODE	SAFETY DIRECTIONS
THIOPHANATE-METHYL	HG LD 1.5 G/L OR LESS
210 211	Avoid contact with eyes and skin
219 223	Avoid inhaling spray mist
351	Wash hands after use
THIOPHANATE-METHYL	WP 700 G/L OR LESS
210 211	Avoid contact with eyes and skin
220 221 223	Do not inhale dust or spray mist
351	Wash hands after use

APPENDIXES

APPENDIX A—Active constituents and registered products included in the review

Table A1: Active constituent approval included in the review.

APPROVAL NUMBER	PRODUCT NAME	REGISTRANT
44214	Thiophanate-methyl	Mitsui and Co (Australia) Ltd

Table A2: Commercial products included in the review.

PRODUCT NUMBER	PRODUCT NAME	REGISTRANT	LABEL APPROVAL NUMBER
52741	Banrot 400WP Broad Spectrum Fungicide for Ornamentals	Scotts Australia Pty Ltd	52741/907/0706 52741/0601
53163	Banrot 80G Broad Spectrum Fungicide for Ornamentals	Scotts Australia Pty Ltd	53163/5kg/1007 53163/12kg/1007 53163/18.14kg/1007 53163/0601
53760	Zyban WP Broad Spectrum Fungicide for Ornamental Plants	Scotts Australia Pty Ltd	53760/0803 53760/0602

ABBREVIATIONS AND ACRONYMS

AERP	Adverse Experience Reporting Program
ADI	Acceptable Daily Intake (for humans)
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
Ag MORAG	Agricultural Manual of Requirements and Guidelines
Codex	FAO/WHO Codex Alimentarius Commission
FQPA	Food Quality Protection Act
g	gram
GAP	Good Agricultural Practice
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	kilogram
L	Litre
mg	Milligram
mL	Millilitre
MRL	Maximum Residue Limit
NHMRC	National Health and Medical Research Council
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
NOHSC	National Occupational Health and Safety Commission
NDPSC	National Drugs & Poisons Schedule Committee
OCSEH	Office of Chemical Safety and Environmental Health (previously OCS)
OHS	Occupational Health and Safety
PAN	Pesticide Action Network
PCO	Pest Control Operator
PPE	Personal Protective Equipment
PRF	Preliminary Review Findings
RED	Re-registration Eligibility Decision
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
US EPA	United States Environmental Protection Agency