Australian Pesticides & Veterinary Medicines Authority

The Reconsideration of Methiocarb, Registrations of Products containing Methiocarb and their Associated Labels

Volume 1

PRELIMINARY REVIEW FINDINGS

April 2005

Australian Pesticides & Veterinary Medicines Authority

Canberra
Australia

This review report for methiocarb is published by the Australian Pesticides & Veterinary Medicines Authority. For further information about this review or the Pesticides Review Program, contact:

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FOREWORD

The APVMA is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the Agvet Code 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 Code.

The basis for the reconsideration is whether the APVMA is satisfied that continued use of products containing methiocarb in accordance with the instructions for their use:

- would not be an undue hazard to the safety of people exposed to it during its handling; and
- would not be likely to have an effect that is harmful to human beings; and
- would not be likely have an unintended effect that is harmful to animals, plants or things or to the environment; and
- would not unduly prejudice trade or commerce between Australia and places outside Australia.

The requirements for continued approval of a label for containers for a chemical product are that the label contains adequate instructions. Such instructions include:

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

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

The process for reconsideration 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.

In undertaking reviews, the APVMA works in close cooperation with advisory agencies including the Department of Health and Ageing Office of Chemical Safety (OCS), the Department of the Environment and Heritage (DEH), and State Departments of Agriculture as well as other expert advisors, as appropriate.

The APVMA has a policy of encouraging openness and transparency in its activities and community involvement in decision-making. 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. Under this program it is proposed that countries receiving these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.

This report is Volume 1 of '*The Reconsideration of Methiocarb, Registrations of Products containing Methiocarb and their Associated Labels- Preliminary Review Findings'* relates to the active constituent methiocarb, products containing methiocarb and their labels that have been nominated for review by the APVMA. The review's findings and recommendations are based on information collected from a variety of sources. The information and technical data required by the APVMA to review the safety of the active, new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken.

The draft review report containing the APVMA's preliminary assessments (The APVMA Review of Methiocarb, Volume 1) and the technical evaluation reports (Volume 2) for registrations and approvals relating to methiocarb are available from the APVMA website: http://www.apvma.gov.au/chemrev/chemrev.html.

COMMENT FROM THE PUBLIC IS INVITED

The APVMA invites persons and organisations to submit their comments and suggestions on this preliminary review report directly to the APVMA. Your comments will assist the APVMA in preparing the final report.

The preliminary review report outlines the APVMA review process, gives information to the public about how to respond to the review, summarises the technical assessments from the reviewing agencies and outlines the proposed regulatory action to be taken in relation to the registration of methiocarb products. Also included are the full technical assessment reports from the Office of Chemical Safety, Department of the Environment and Heritage, and the Chemistry and Residues Program at the APVMA.

PREPARING YOUR COMMENTS FOR SUBMISSION

You may agree or disagree with or comment on as many elements of the report 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 indicate 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 Review Summary or the technical report. 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.

THE CLOSING DATE FOR SUBMISSIONS IS: 31 JULY 2005

Your comments should be mailed to:

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ACRONYMS AND ABBREVIATIONS

µg	Microgram
ac	Active constituent
ADI	Acceptable Daily Intake
ai	Active ingredient
ALT	Alanine aminotransferase (SGPT)
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
AST	Aspartate aminotransferase (SGOT)
ChE	Cholinesterase
CODEX	FAO/WHO Codex Alimentarius Commission
DEH	Department of Environment and Heritage (previously Environment Australia)
F_0	parental generation
FAISD	Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals
FAO	Food and Agriculture Organisation
FSANZ	Food Standards Australia New Zealand
GAP	Good Agricultural Practice
GI	Gastrointestinal
GLC	Gas Liquid Chromatography
HG	Home Garden
im	Intramuscular
ip	Intraperitoneal
iv	Intravenous
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	Kilogram
LD_{50}	median lethal dose
LH	Luteinising hormone
LOEL	Lowest Observable Effect Limit
mg	Milligram
mg/kg bw/day	mg/kg bodyweight/day
mL	Millilitre
mM	Millimolar
MRL	Maximum Residue Limit
NDPSC	National Drugs and Poisons Scheduling Committee
NEDI	National Estimated Dietary Intake
NESTI	National Estimated Short-Term Intake
ng	Nanogram
Nm	Nanomolar
NOEL	No Observed Effect Level
NOHSC	National Occupational Health and Safety Commission
OCS	Office of Chemical Safety
OHS	Occupational Health and Safety
PHED	Pesticide Handlers Exposure Database
PHI	Post Harvest Interval
po	Oral
POEM	Predictive Operator Exposure Model
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
RBC	Red Blood Cell

sc	Subcutaneous
SUSDP	Standard for Uniform Scheduling of Drugs and Poisons
TLC	Thin layer chromatography
TMRL	Temporary MRL
WHO	World Health Organisation
WHP	Withholding Period
WP	Wettable Powder

EXECUTIVE SUMMARY

Introduction

Methiocarb is a carbamate pesticide that has been registered for use in Australia for over 20 years. Similar to other carbamate pesticides, methiocarb kills insects by interfering with the activity of an enzyme (acetylcholinesterase) in the nervous system.

In Australia, methiocarb is registered for use in the control of snails, slugs, wireworm and birds in a range of agricultural and domestic (in or around the home garden) situations. Major agricultural uses of methiocarb include grapevines, citrus, berries, pastures, cereals, and ornamentals. Methiocarb is available as either bait granules (BA 20g/kg methiocarb) or wettable powder (WP 750g/kg methiocarb) formulations.

The active constituent methiocarb, product registrations containing methiocarb and associated label approvals are under review as part of the APVMA chemical review program. Methiocarb was selected for review from the Priority Candidate Review List (established in 1995 as part of the Existing Chemical Review Program). Concerns were identified for residues in food and trade and worker and environmental exposure. There were also some adverse experience reports relating to domestic animals that were investigated by state departments.

This report summarises the Preliminary Review Findings and includes specific details of the regulatory approach and risk mitigation measures proposed by the APVMA. The list of methiocarb active approvals and registered products is provided in Appendix 1.

Chemistry

The chemistry evaluation found that the active constituent methiocarb meets the required APVMA standard (FAO specification) for that active. The evaluation concluded that the method by which the active is manufactured, batch analysis results and analytical methods were acceptable.

Toxicological Assessment

Methiocarb is highly toxic to humans and animals. Poisoning can occur by oral ingestion or by inhaling the spray or dust, although there is an effective antidote treatment for methiocarb if medical assistance is prompt.

In laboratory studies methiocarb was rapidly absorbed, when swallowed, and did not persist for long periods in the tissues or organs. Absorption of methiocarb through the skin was relatively poor. Long-term exposure to low concentrations of methiocarb in the diet was without serious consequences in animals. Methiocarb does not interact with genetic material, in animals and gave no indication that it would be likely to cause cancer in humans. Similarly, exposure to low doses of methiocarb had no adverse effects on reproduction or on the development of the foetus in experimental animals. Infants and children are not considered to be at an increased risk from methiocarb products, when used according to label instructions.

Home garden uses may give rise to some exposure of the public, but studies indicate that such exposures do not pose a public health risk.

In considering dietary health standards, it has been determined that the current Acceptable Daily Intake (ADI) for methiocarb of 0.002 mg/kg bw/day is acceptable and so amendments to the current ADI are not proposed. Prior to this review no Acute Reference Dose (ARfD) had been established for methiocarb. An ARfD of 0.03 mg/kg bw/day has been determined, based on two developmental toxicity studies in rats and rabbits with a safety factor of 100 being applied to the No Observable Effect Level (NOEL).

The NDPSC consider methiocarb in May 2000 and determined that methiocarb be placed in schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Formulations containing 20% or less of methiocarb were placed in schedule 6, while those products containing 2% or less were to remain in schedule 5 of the SUSDP. Existing products have already had their labels amended to reflect these scheduling changes.

The proposed findings of the toxicology evaluation are that product labels do not contain adequate instructions with regards to the safe handling of the product. It is recommended that the instructions be varied by including further safety directions and warning statements

The toxicology evaluation recommended that, if product labels are varied as proposed, then the APVMA would be able to be satisfied that continued use and other dealings of the active methiocarb and products containing methiocarb would not be likely to have an effect that is harmful to human beings.

Occupational Health and Safety Assessment

No measured worker exposure studies were available for methiocarb. The risk assessment for the WP formulation was based on exposure estimates calculated from the UK Predictive Operator Exposure Model (POEM), Pesticide Handlers Exposure Database (PHED) and sponsor data generated from a German model. For BA formulation, the risk assessment relied on PHED data only.

The risk assessment showed that mixer/loader/applicators applying WP formulation by mechanical means would not be adequately protected when using the product according to current label instructions (including safety directions; dust mask and PVC gloves during spray preparation). However the risk assessment indicated that these workers will be protected if they wear cotton overalls and gloves during both mixing/loading and application and a dust mask during mixing/loading and a face shield during application.

For hand held application of WP formulations, the risk assessment identified concerns for workers. However the use of additional protective clothing will provide adequate worker protection. Respiratory protection is recommended for indoors use as inhalation risk contributed significantly to total exposure.

For BA formulations, the risk during mechanical applications is considered to be low if workers wear coveralls or equivalent clothing. Hand distribution of baits poses an unacceptable risk to workers. Provided that label safety directions are amended to include the use of coveralls and gloves, worker exposure will be reduced to acceptable levels for hand application of baits.

Assessment of re-entry worker exposure indicated a risk for workers handling treated grapevine foliage up to 28 days after treatment. In the absence of crop specific data, this result was used as an approximate guide to estimate dermal exposure to nursery workers

handling treated ornamentals. A re-entry period of 28 days is recommended on the current labels for vineyards, orchards and ornamentals treated by cover spray. The occupational health and safety evaluation proposes that workers be required to wear protective clothing and PVC gloves if prior entry (or rehandling) is required. The assessment also proposes that workers entering greenhouses/glasshouses will require a re-entry period of 28 days to guard against inhalation exposure.

The risk to workers re-handling treated soil, following use of methiocarb as a soil drench on ornamentals, could not be determined due to no available information. Consequently the APVMA would not be able to be satisfied that continued use of methiocarb in ornamentals treated by soil drench is not an undue hazard to the safety of workers exposed to it. It is proposed that labels be varied to delete these uses.

The proposed findings of the occupational health and safety evaluation are that product labels do not contain adequate instructions with regards to the safe handling of the product and re-entry to treated crops for uses other than the soil drench. It is proposed that labels be varied to include further safety directions and a re-entry period after use.

The occupational health and safety evaluation recommended that provided that labels are varied as proposed then the APVMA would be able to be satisfied that continued use and other dealings of the active constituent methiocarb and products containing methiocarb would not be an undue hazard to the safety of people exposed to it during handling.

Residue Assessment

The metabolism of methiocarb in plants and animals occurs by carbamate ester cleavage and oxidation to sulfoxides and sulfones. No change to the current residue definition for methiocarb (the sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb) is necessary. Adequate analytical methods were available to allow determination of methiocarb, its sulfoxide and sulfone, either combined or separately, in a wide variety of plant and animal matrices.

Limited information was available to allow a determination of residues risks in produce treated with methiocarb under Australian use situations. There was insufficient residues data available to accurately calculate the National Estimated Dietary Intake, assess the acute dietary intake, or determine the level of methiocarb residue in animal feed items. Risks to trade and to public health could, therefore, not be assessed. For example:

- There were insufficient data to allow appropriate Maximum Residue Limits (MRLs) to be established in food crops and in animal feed commodities.
- Adequate storage stability studies for crop commodities were not provided.
- Whilst studies were provided in which residue levels were determined for some processed commodities, no data were provided for major processed commodities such as cereal grain fractions, oilseed oils, meals, processed fruit products such as pome and citrus fruit pomace.
- Assessment of the chronic dietary risk to methiocarb was determined using temporary MRLs calculated from residue data assessed during the review. However the NEDI calculation that was determined is not considered to be a true reflection of the actual dietary exposure to methiocarb.
- In the absence of residues data for Australian use patterns, no assessment of the acute dietary risk to methiocarb could be performed.

Consequently the APVMA would not be able to be satisfied that continued use of methiocarb products for food and animal feed uses would not be an undue hazard to the safety of people using anything containing its residues, and would not unduly prejudice trade or commerce between Australia and places outside Australia. It is proposed that the instructions on product labels be varied by deleting all uses on food and animal feed crops.

The residue review recommended that provided product labels are varied as proposed, then the APVMA would be able to be satisfied that continued use and other dealings of methiocarb and products containing methiocarb would not be an undue hazard to the safety of people using anything containing its residues, and would not unduly prejudice trade or commerce between Australia and places outside Australia.

Environmental Assessment

Continued use of methiocarb is not expected to lead to significant environmental contamination or broad scale impacts on populations of non-target organisms. Some invertebrate species, particularly sensitive ground beetles, are likely to be killed where snail baits are applied, but effects will be localised and the ecological function performed by these organisms should not be impaired. Frequent use as occurs in home gardens is likely to be ecologically disruptive, with impacts expected on some beetle species as well as the target snails, slugs, slaters and millipedes. Some earthworms are also likely to be killed, but any impacts are expected to be localised. Small lizards are also likely to be killed if they consume baits.

Similar predictions may be made for agricultural situations. Small birds, mammals and reptiles in cropping areas are likely to be killed if they consume baits, but numbers involved would be expected to remain relatively low and overall populations would not be affected. Impacts on the invertebrate ecology of agricultural fields would be less pronounced than in the home garden because of the lower rates and relative infrequency of use. Short term, localised disruption to aquatic communities may occur in agricultural situations when spray drifts to water, but any such disruption would affect only small areas with no lasting ecological consequences.

The proposed environmental evaluation findings are that the use of methiocarb is not expected to lead to significant environmental contamination or broad scale impacts on populations of non-target organisms. However, it was recommended that product labels were inadequate and proposed that they be varied by amending current protection and cautionary statements to reduce potential environmental exposure.

The environment evaluation recommended that provided the product labels were varied as proposed, then the APVMA would be able to be satisfied that continued use and other dealings of the active constituent methiocarb, products containing methiocarb and associated labels in accordance with the instructions for use would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

Summary of the Preliminary Review Findings

Following consideration of the available data, the following recommendations are made:

1) Affirm active constituent approvals.

The APVMA is satisfied that the requirements for continued approval of the active constituent have been met and proposes that the active constituent approvals of methiocarb listed in Appendix 1, be affirmed.

2) Vary label approvals

The APVMA is not satisfied that the labels of the products listed in Appendix 1, contain adequate instructions pertaining to the circumstances in which the product should be used, how the product should be used, the re-entry period after the use of the product and the safe handling of the product. The APVMA is satisfied that the conditions of label approval for the products (as detailed in Table 24) can be varied in such a way so that they contain adequate instructions in accordance with s 14(3)(g) of the Agvet codes.

Label variations recommended to mitigate identified risks are as follows:

- Instructions for use of methiocarb products on food crops including grapevines, oranges, berry crops, cereals, oilseed crops (including sunflowers), orchards, vegetable crops and pastures are **to be deleted** from labels, as insufficient data was available to accurately calculate the NEDI, assess the acute dietary intake, or determine the level of methiocarb residue in animal feed items.
- Instructions for use of methiocarb on ornamentals for the control of glasshouse sciarids applied as a soil drench is **to be deleted** from labels, as no data was available to accurately asses the risk to workers re-handling treated soil.
- Restraints, protection statements, cautionary statements and safety directions **are to be varied,** in order for the APVMA to be satisfied that labels contain adequate instructions in accordance with s 14(3)(g) of the Agvet codes.
- Re-entry statements **will be added**.

3) Affirm Product Registrations

The APVMA is satisfied that provided product labels (as listed in Table 24) are varied as proposed that the products meet the prescribed requirements for continued registration and therefore affirms product registrations (for use in gardens, ornamentals and hibiscus).

4) **Cancel Product labels**

The APVMA is not satisfied that old approved labels (as listed in Table 25) contain adequate instructions and cancels these approvals.

1. INTRODUCTION

The APVMA has reviewed the active constituent approvals, product registrations and associated label approvals for methiocarb. Methiocarb was selected for review from the Priority Candidate Review List (established in 1995 as part of the Existing Chemical Review Program). The purpose of this report is to provide a summary of the data evaluated and of the regulatory decisions reached.

1.1 Regulatory status of methiocarb in Australia

Methiocarb is a carbamate pesticide of high acute toxicity, marketed in Australia for over 20 years. It was first registered in Australia in the early 1980's. It is a non-systemic pesticide and like other carbamate pesticides methiocarb kills by interfering with enzymes in the nervous system. It is used for snail and slug control in broadacre crops (sunflowers, canola and pastures), berry crops, vegetables, vineyards, greenhouses, citrus and ornamentals (including nurseries and cut flower production). It is also used as a bird and fungus gnat control agent in ornamentals and has been used in the past as a control measure for false wireworm beetle in sunflowers.

Prior to the commencement of the review there were two registered products containing methiocarb and one active constituent approval. A further two products and one active have been registered /approved after the commencement of the review and are subject to review outcomes as conditions of their registration/approval. All registrations and approvals are held by Bayer CropScience Pty Ltd (Table 1).

Table 1: Currently approved actives constituents and registered products

Product/active approval No	Product/active constituent name	Registrant/Approval holder
33274	Mesurol Snail and Slug Bait	Bayer Cropscience Pty Ltd
33276	Mesurol 750 Bird Repellent and Snail and Slug Spray	Bayer Cropscience Pty Ltd
44212	Methiocarb (active constituent)	Bayer Cropscience Pty Ltd
51851*	Baysol Snail and Slug Bait	Bayer Cropscience Pty Ltd
55824#	Methiocarb (active constituent)	Bayer Cropscience Pty Ltd
58652*	Bayer Advanced Garden Baysol Snail and Slug Bait Pellets	Bayer Cropscience Pty Ltd

* Products registered after the commencement of the review that are subject to the outcomes of the review

Approval granted after the commencement of the review, that is subject to the outcomes of the review

1.2 Reasons for Methiocarb Review

Methiocarb was reviewed because of concerns related to public health, occupational health and safety, residues and environment. These include:

- lack of appropriate maximum residue limits (MRLs) for some agricultural uses (including cereal grains and oilseeds;
- residue detections in produce above MRLs (detected through the National Residue Survey);
- MRL inconsistencies with major trading partners (US, Canada, Codex); and

- potential risk from worker exposure.

State department also submitted reports of adverse effects reported for products containing methiocarb in particular in respect of its high toxicity in dogs.

1.3 Regulatory options

There can be three possible outcomes to the reconsideration of the registration and approvals relating to methiocarb. Based on the information reviewed the APVMA may:

- be satisfied that the active and/or products and their labels continue to meet the prescribed requirements for registration and approval and therefore affirm the registrations and/or approvals.
- be 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 and/or approval.
- not be satisfied that the requirements for continued registration and approval continue to be met and suspends or cancels the registration and/or approval.

1.4 Scope of the Review

The scope of the review covered all risk areas associated with registrations and active approvals including:

- Chemistry and manufacture of the active methiocarb;
- Toxicology, including the potential for acute and chronic effects that might pose undue hazards to human health;
- Occupational Health and Safety, including the potential for undue hazards to workers;
- Residues in food, including acute and chronic dietary exposure estimates;
- The potential for undue prejudice to Australian trade; and
- Environment.

The APVMA also considered 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.

1.5 Public submissions

The APVMA has a commitment to transparency in the review process. When the review of methiocarb was announced, the APVMA published notices in the rural and metropolitan press calling for written submissions for the review of the chemical methiocarb. This attracted 2 submissions from industry associations.

Both submissions noted that methiocarb is an important chemical for controlling snails and slugs in crops. It was also emphasised that there is only one alternative bait available for control of snail infestations in cropping systems, being metaldehyde.

A second opportunity for public consultation will occur as a result of this draft review report. Submissions received will be taken into account in the development of this report and recommendations for future use of the chemical.

2 METHIOCARB USE PATTERNS

2.1 Introduction

Methiocarb is supplied as solid bait pellets (BA) (three products) and as a wettable powder (WP) (one product). It may be distributed by hand, hand-propelled fertiliser spreaders, knapsack or garden sprayers or through powered bait spreaders or spraying equipment. Label instructions for bait products indicate that equipment such as fertiliser spinners, combines or sod seeders are satisfactory for spreading the pellets.

2.2 Uses of Methiocarb Products in Australia.

Crop	Pest	Rate	Critical Comments
Methiocarb pellets – 20 mg/kg BA			
Gardens	Snails, slugs, slaters millipedes	100 pellets per square metre (Equivalent to 25 kg/ha)	Sprinkle evenly onto ground. Heaping is unnecessary and wasteful.
Methiocarb pellets – 20 mg/kg BA			
Berry crops, Cereals, Gardens, Nurseries, Oilseed crops, Orchards, Pastures, Vegetables	Common garden snail Slugs White Italian Snail White Snail (Not Qld)	5.5 kg/ha (22 pellets/m^2) or 11 – 22 kg/ha (44 – 88 pellets/m^2)	For most infestations apply low rate. For heavy infestations or where pasture is tall or dense apply higher rate. Scatter bait evenly onto ground where snails or slugs occur. Do not heap pellets. When applying in vegetable crops, ensure pellets do not become lodged in plant foliage. Equipment such as fertilizer spinners, combines or sod seeders are satisfactory for spreading the pellets and can be easily calibrated to apply 5.5 kg/ha. Gloves should be worn when the pellets are spread by hand.
Sunflowers (Qld, SA only)	False wireworm beetle	2.5 kg/ha (10 pellets/m^2)	Apply 1 – 3 days after sowing. Scatter bait evenly onto ground where false wireworm beetles occur.
Methiocarb as a spray – 750 g/kg WP			
Grapevines (WA only)	White Italian snail	100 g/100 L	Apply before flowering as a cover spray when pests become apparent. For greater control spray where they harbour – eg damp, dark areas, dense foliage, compost heaps, fences etc.
	Garden weevil	200 g/100 L	Wet vine thoroughly at or before flowering before foliage is established. Spray in the evening when the weevils are active. Use high volume equipment only. May require a second application 3 weeks after the first spray.
Grapevines (butt treatment only)	White Italian snail (NSW, SA ONLY) Common garden snail *Bradybaena* spp. **Slugs** (QLD, NSW, TAS, SA, WA ONLY)	100 g/100 L	Apply as a cover spray when pests become apparent. For greater control spray where they harbour – eg damp, dark areas, dense foliage, compost heaps, fences etc. Only spray butt of grapevines
Oranges Ornamentals	Common garden snail *Bradybaena* spp. Slugs	100 g/100 L	Apply as a cover spray when pests become apparent. For greater control spray where they harbour – eg damp, dark areas, dense foliage, compost heaps, fences etc.
Hibiscus	Hibiscus Flower Beetle	100 g/100 L	Spray when beetles are first seen, particularly when flowers are present. Repeat spray 3 days later to control beetles in tight buds.
Ornamentals	Glasshouse sciarids (Fungus gnats)	300 g/100 L	Drench soil, potting mix or compost in which infested plants are growing. Apply when larvae are first seen.
Ornamentals	Blackbirds Sparrows Starlings Indian myna	200 g/100 L	Apply as a thorough cover spray when birds begin attacking plants.
Poppies (TAS only)	Slugs	5.5 kg/ha	Apply as a thorough spray to protect seedlings when slugs become apparent.

Table 4: Use patterns of methiocarb

The following withholding periods currently on product labels have been set for methiocarb as a spray:

- Grapes: Do not harvest for 9 weeks after application.
- Citrus fruits: Do not harvest for 6 weeks after application.

An additional warning statement for grapes is also included in label directions:
'Grapevine leaves treated with Mesurol 750 must not be used for human consumption.'

The following withholding periods currently on product labels have been set for methiocarb as bait pellets:

- Edible crops: Do not harvest for 7 days after application (for home garden products – Do not pick edible crops for 7 days after applying)
- Treated Areas: Do not graze or cut for stockfood for 7 days after application

2.2.1 Individual crops and application methods

In general, when used as a bird repellent, methiocarb is applied as a cover spray. When used for control of snails and slugs it can be applied both in pelleted form and by cover spray, with pellets apparently more commonly used. The cover spray is limited to control of snails and slugs in grapevines (WA only - also as a butt treatment in NSW, QLD, SA, TAS, and WA), oranges, ornamentals (including hibiscus) and poppies. It is noted that the pelleted formulation is also widely used in these circumstances. The wettable powder is used to prepare a soil drench (300 g/100 L – 2 L/m^2) for the control of fungal gnats.

Advice from growers indicates that their most favoured method of applying the chemical in small to medium areas is by hand distribution of pellets. Mechanical applicators are normally used in broadacre situations. However, advice was received during the review that in many orchards and vineyards the pellets are distributed by hand. Similarly, areas up to 50 ha of vegetable crops such as cabbages appear to be regularly treated by hand.

2.2.1.1 Orchards (including oranges)

As indicated above, the main formulation used by growers is the pelleted bait formulation. Some orchardists also use equipment such as fertiliser spreaders however growers indicate that most distribution is by hand. The only orchard crop in which respondents indicated methiocarb was applied as a cover spray was for cherries. However, it is noted that the label for the wettable powder includes instructions for application to oranges as a cover spray.

2.2.1.2 Vineyards

Methods of application adopted by growers in this situation are similar to those used in orchards. Both pellets and wettable powder sprays are used in vineyards, with orchard type spraying equipment used for spraying the vines and much of the distribution of the pellets accomplished by hand broadcasting. This distribution tends to be strategic in that the pellets are specifically located around the vine butts or along the rows.

It is noted that the use pattern specified on the label for the wettable powder recommends application in such a way that fruit should not be contacted. Thus, application is recommended as a cover spray at or before flowering (in WA only) or as a spray applied to the butts only of the grapevines (VIC, NSW, QLD, TAS, SA and WA). It is noted that the current labels carry the critical comment to "apply as a cover spray" when the use is intended as a butt treatment only.

2.2.1.3 Ornamentals (including nurseries, quarantined glasshouses, cut flower production, poppies)

Baits are normally used for snail and slug control and cover or spot sprays for control of western flower thrips under permit. Where baits are used in this situation they are most often distributed by hand. Hand wands connected to mobile powered spray equipment are the most usual method used for application as a spray for control of western flower thrips in nurseries and greenhouses.

2.2.1.4 Oilseeds

The pelleted form of methiocarb is most often used for broadacre crops, including sunflowers and canola. When used in this context it is normally applied down crop rows by tractor-operated equipment such as fertiliser spreaders.

3.2.1.5 Berry crops (including strawberries, red and black currents, blueberries

Only limited information on the use of methiocarb on berry crops is available. Information from Queensland agricultural authorities indicates that application of methiocarb to strawberries is normally by hand distribution of pelleted bait. Although there may be problems with birds in crops from time to time, it is not used for bird control in strawberries.

2.2.2 Home garden

The wettable powder formulation is not recommended for home garden use. The pelleted bait formulation recommended for home gardens is the same strength as that recommended for agricultural use and has similar directions for use. The pellets are to be sprinkled evenly onto the ground at the rate of 100 pellets/m^2, which is higher than the rate recommended for agricultural situations (22 – 88 pellets/m^2 depending on ground cover or level of infestation). Although the label does not indicate how the pellets are to be applied, it would appear that there is an underlying assumption that they will be applied by hand.

2.2.3 Usage by Crop or Situation

Information from Bayer CropScience provides a picture of the distribution of methiocarb use between crops. These figures are from **2001/2002** and are on the basis of % sale.

Table 5: Usage by crop/situation

Product	Market	Crop	% split
Mesurol 750WP	Horticulture	Citrus	10
		Ornamentals	50
		Vines	40
Mesurol S/S pellets	Horticulture (42%)	Citrus	2
		Strawberries	6
		Vegetables	8
		Ornamentals	11
		Vines	13
		Other	2
	Broadacre (58%)	Cereals	2
		Oilseeds	43
		Pasture	9
		Pulse crops	4

2.2.4 Alternatives

The major chemical alternative for snail and slug control is metaldehyde. For agricultural use, methidathion and copper as a buffered copper complex are both registered for snail control in some crop/situations. For home garden use, buffered copper complex, copper silicate, ferric EDTA and mustard are registered for snail and slug control.

There are a number of alternatives for the control of false wireworm in sunflower including imidacloprid, chlorpyrifos and fipronil. Methiocarb is now not used often in this situation.

Other strategies for management of snails and slugs involve control of habitat such as damp dark areas, dense foliage, compost heaps etc. As noted above conservation tillage practices encouraged by State agricultural authorities also provide natural harbourages for snails and slugs. One of these authorities indicated that slugs especially, find minimum till methods conducive to build up of populations. Strategic burning, slashing and other habitat destruction techniques are employed in these situations to assist with snail control.

One alternative recommended for some time by NSW Agriculture for control of snails in orchards is ducks. Although this option has been used successfully by at least one citrus orchardist, widespread adoption of this control option has not occurred.

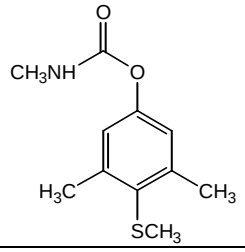
SUMMARY OF DATA ASSESSMENT

3 CHEMISTRY ASSESSMENT

3.1 Chemical Identity

Methiocarb is a non-systemic pesticide belonging to the carbamate chemical family.

Table 2: Chemical Identity

Common name:	Methiocarb
Developmental Codes	Bayer 37344, H321, OMS 93, ENT 25 726
Chemical name:	4-methylthio-3,5-xylylmethylcarbamate (IUPAC) 3,5-dimethyl-4-(methylthio)phenyl methylcarbamate CAS)
CAS Number:	2032-65-7
Molecular formula:	$C_{11}H_{15}NO_2S$
Molecular weight:	225.3 g/mol
Chemical structure:	

3.2 Physical and Chemical Properties of the Active Constituent

Methiocarb is manufactured to a high purity standard (minimum 970 g/kg).

Table 3: Physical and Chemical Properties of the Active Constituent

Physical state:	Crystalline solid
Colour:	Colourless crystals
Odour:	Phenol like
Melting point:	119°C
Density/specific gravity:	1.236 g/cm^3
Solubility in water:	27 mg/L (20°C)
Solubility in other solvents (20°C)	dichloromethane 500 g/L 4.4.7.1.4 Isopropanol80 g/L Toluene 33 g/L
Octanol/water partition coefficient:	LogP = 3.08 (20°C)
Vapour pressure:	0.015 mPa (20°C)
Stability:	Unstable in highly alkaline media. Hydrolysis DT_{50} (22°C) >1y (pH 4), <35 d (pH 7), 6 h (pH 9). Photodegradation contributes to overall elimination of methiocarb from the environment: DT_{50} 6-16 d.
Impurities:	3,5-dimethyl-4-(methylthio)phenol

	4-chloro-3,5-dimethylphenyl methylcarbamate 3,5-dimethyl-2,4-bis(methylthio)phenyl methylcarbamate 3,5-dimethyl-4-(methylthio)phenyl methyl[(methylamino)carbonyl]carbamate 3-methyl-4-(methylthio)phenyl methylcarbamate N,N'-dimethylurea 3,5-dimethylphenyl methylcarbamate 2,4,6-trichloro-3,5-dimethylphenyl-N-methylcarbamate water

3.3 Composition of Methiocarb Active Constituent

Declaration of Composition

Food and Agriculture Organisation Specification

The FAO monograph specification for methiocarb technical

Methiocarb Content	minimum 970 g/kg
Water	maximum 2 g/kg

The APVMA standard for methiocarb is as follows:

Methiocarb Content	minimum 970 g/kg

All APVMA approved sources of methiocarb active constituent comply with the FAO specification.

3.4 Manufacture of Methiocarb Active Constituent

The chemistry aspects (synthetic process, quality control procedures, batch analysis results and analytical methods) of methiocarb were evaluated previously and were found to be acceptable. The levels of methiocarb and its impurities are quantified using reverse phase HPLC with UV detection at 215 nm.

3.5 Conclusions

The chemistry evaluation found that the active methiocarb meets the required APVMA standard (FAO specification) for that active. The evaluation concluded that the method by which the active is manufactured, batch analysis results and analytical methods were acceptable.

4 TOXICOLOGY

4.1 Introduction

Methiocarb has been reviewed by the Joint FAO/WHO Meeting of Pesticide Residues (JMPR) in 1981, 1983, 1984, 1985, 1987 and 1998. In its 1981 evaluation, the JMPR established an ADI of 0.001 mg/kg bw/day for methiocarb on the basis of the NOEL from a 2-year dog study and a safety factor of 100. This ADI remained unchanged up until 1998. In the most recent review in 1998, the JMPR amended the ADI to 0.02 mg/kg bw/day, based on a revised NOEL of 1.5 mg/kg bw/day from the same 2-year dog study and a safety factor of 100. This report presents an evaluation of previously submitted toxicology data together with the data from two new submissions to the APVMA.

4.2 Metabolism and Toxicokinetics

Studies on biotransformation and excretion of methiocarb have been performed using both *in vivo* and *in vitro* systems. *In vivo* studies have used rats, dogs and a dairy cow, the routes of administration being intra-peritoneal in one rat study and oral in the remaining studies. In addition, several *in vitro* studies have been conducted with methiocarb using rat liver microsomal preparations under both activated and non-activated conditions and foetal and maternal rat tissue preparations.

4.2.1 *In vivo* studies

Intra-peritoneal Administration

In a study performed to determine and compare the detoxification and elimination mechanisms and the metabolic fate of the radiocarbon from ten variously labelled methyl and dimethyl insecticides, carbonyl-^{14}C labelled methiocarb in 2-methoxyethanol was administered ip to male SD rats. The rats were sacrificed at 48 h post treatment and the radioactive content of the expired CO_2, urine and faeces and in a range of tissues was determined. Of the radioactivity administered, 66.1% was present in the expired air as $^{14}CO_2$. About 20% and 2.2% of ^{14}C were recovered in 24 h and 24-48 h post treatment urine samples respectively with 2.5% in faeces. A further 8.9% of the administered radioactivity remained within body tissues 48 h post administration with highest residue levels in the spleen, liver, heart and kidney. The study authors hypothesised that the expired radioactivity originated from hydrolysis of the administered compound or its metabolites to yield carbonate, which was subsequently expired as $^{14}CO_2$. The hydrolytic cleavage of the ester group of methiocarb by rat liver microsomes was identified as the probable rate limiting step in the production of $^{14}CO_2$. However, except for $^{14}CO_2$ no other metabolites were characterised in this study and hence only partial interpretation of the nature of the metabolites was possible (Krishna & Casida, 1966).

A metabolism study undertaken by Wheeler and Strother (1974a) examined the quantitative excretion, maternal tissue distribution, placental transfer, and foetal disposition of carbonyl ^{14}C labelled methiocarb following ip administration to 18 or 19 days pregnant SD rats. A range of maternal and foetal tissues including amniotic fluid was studied. Methiocarb and its metabolites in tissues were ether extracted and resolved using TLC and GLC techniques. Rapid placental transfer of radioactivity was observed. A pregnant animal showed a slower

rate of elimination of $^{14}CO_2$ compared to non-pregnant rats. The kinetics of metabolism of methiocarb appeared complex because of a rebound elevation of radioactivity seen in all maternal tissues except RBCs and several foetal tissues at 4 h post treatment. Methiocarb attained higher levels and appeared to remain longer in the foetal tissues compared to the maternal tissues. Foetal kidney retained the highest concentration of radioactivity in the foetal tissues, whereas in dams the highest concentration of radioactivity 8 h post treatment was found in the liver and the lowest in the muscle and bone. A large proportion of metabolic products of methiocarb were not organo-soluble and remained in the aqueous phase suggesting that it was extensively metabolised to form water soluble metabolites. The major ether extractable metabolite identified in this study was methiocarb sulfoxide.

Oral Administration

Van Hoof and Heyndrickx (1975) examined the urinary excretion of 4 insecticidal carbamates including methiocarb, and their phenolic metabolites following oral administration of parent compounds to rats. Up to 2.3% of the administered dose of methiocarb was excreted in urine unchanged within 72 h. The only methiocarb metabolite identified in urine was methiocarb phenol accounting for 2.3% of the administered dose. The marked contrast to the extensive urinary excretion of methiocarb, methiocarb phenol and other metabolites observed in other studies in rats, dogs and cattle possibly arises from the lack of assay for metabolites of methiocarb other than methiocarb phenol.

Metabolism and excretion of metabolites in urine was investigated by Stanley and Johnson, (1976) following a single oral gavage administration of ring-1-^{14}C labelled methiocarb in ethanol to rats at 0.25 or 20 mg/kg bw. Urinary excretion amounted to 95% of administered radioactivity at 20 mg/kg bw and 79/82% in males/females at 0.25 mg/kg bw. The major chloroform extractable metabolites found in urine at 20 mg/kg bw were methiocarb phenol (5%), methiocarb sulfoxide phenol (6%) and an unidentified metabolite (6%) that might correspond to N-hydroxymethyl methiocarb sulfoxide. Methiocarb sulfoxide was detected in trace quantities (about 1%). The major metabolites found in the aqueous fraction were methiocarb sulfoxide phenol (23%), methiocarb phenol (8%) and methiocarb sulfone phenol in trace quantities (about 1%). At 0.25 mg/kg bw, about 15% of the administered radioactivity was recovered in the chloroform extract while 59% remained in the aqueous phase. However, the proportion of organo-soluble and water soluble radioactivity and percentages of major metabolites found in urine were independent of the administered dose. Between 57-72% of the radioactivity present in the aqueous phase was rendered organo-soluble by enzyme incubation. No major difference was seen between sexes.

In a study conducted to evaluate the metabolic fate of methiocarb in dogs, a single oral dose of ring-UL-^{14}C-methiocarb in gelatine capsules was administered to overnight fasted dogs at 2 mg/kg bw. The dogs were sacrificed at 24, 48, 96 and 144 h intervals post treatment and the radioactivity in a range of tissues and blood was determined. Radioactivity in the blood reached its maximum within one hour after administration. Half lives of the total radioactivity in plasma or whole blood were estimated to be about 75-76 h. The total radioactivity recovered in urine ranged from 26-66% of the administered dose; methiocarb phenol sulfone and methiocarb phenol sulfoxide being the two major metabolites found at a ratio of about 3:1. The proportion of unchanged methiocarb excreted in urine was not given. Of the administered dose, between 10-56% was excreted in faecal matter as methiocarb suggesting incomplete gastrointestinal absorption, possible secretion of absorbed but unchanged methiocarb in bile, and lack of degradation by intestinal flora (Bell, 1974). The highest tissue residue level at 144 h post dosing was found in the kidney.

The metabolic fate and urinary excretion of methiocarb in a dairy cow has been studied (Minor & Murphy, 1977) by administering a single dose of ring-1-^{14}C labelled methiocarb at 0.14 mg/kg in a gelatine capsule orally. The general physical condition of the cow and the milk production were unaffected by treatment. The peak blood radioactivity was noted between 2.5-3 h post treatment and of the administered radioactivity, 96% was excreted in urine by 144 h post treatment. Faecal matter and milk samples collected during 144 h contained 1% and <1% of the administered radioactivity respectively. Only about 1% of the metabolites in urine were chloroform extractable. Following enzyme and acid hydrolysis, approximately 78-85% of the urine radioactivity became chloroform extractable suggesting that the primary metabolites of methiocarb were in conjugated form. TLC analysis revealed the presence of three major metabolites: methiocarb phenol (25-29%), methiocarb sulfoxide phenol (22-32%) and methiocarb sulfone phenol (20-23%) with trace quantities of methiocarb sulfoxide, methiocarb sulfone and some unidentified components (<1%). The proportion of parent compound excreted in urine was not given, and about 14-21% of the administered radioactivity in urine remained as aqueous residues.

4.2.2 *In vitro* Studies

In a study conducted to determine the metabolic fate of various methyl and dimethylcarbamate insecticides, carbonyl-^{14}C labelled methiocarb was incubated with rat liver microsome fraction, or microsome plus the soluble fraction for 4 h with NADP, $NADPH_2$, NAD, $NADH_2$ or without any of these chemicals. The extent of metabolism of methiocarb was generally higher in the incubation mixture containing the microsomes plus soluble fraction and NADP. About 8% of methiocarb was metabolised to products, about 43% of which were water soluble. Two hydroxylated metabolites of the s-alkyl group were identified: 4-methylsulfinyl-3,5-xylyl methyl-carbamate (sulfoxide) and 4-methylsulfonyl-3, 5-xylyl methyl carbamate (sulfone). One further metabolite was not identified. It was reasoned that the unidentified metabolite might have formed due to hydroxylation reactions at different sites on the substrate. The sulfoxide metabolite was found to possess plasma ChE inhibitory properties. Neither the metabolites formed by hydrolysis at the carbamic ester site nor those at the origin of the TLC plates were identified (Oonithan & Casida, 1966).

Wheeler and Strother (1971) conducted a comparative study of the metabolism of Zectran (4-dimethylamino-3,5-xylyl methylcarbamate) and Mesurol (methiocarb) to characterise and identify the metabolites, routes of biotransformation and to understand the extent of biodegradability of the parent compounds using 15000 g supernatant fractions of the liver and the kidney homogenates, and blood of dogs and rats. Two major metabolites of methiocarb formed by the dog and rat liver and the dog kidney were identified. They were 4-methylsulfynyl-3,5-xylyl N-methyl carbamate (methiocarb sulfoxide) and 4-methylthio-3,5-xylyl N-hydroxymethylcarbamate (M-NOHME). Methiocarb metabolites following incubation with serum or whole blood were not identified. The greater part of added methiocarb was found to be bound with plasma proteins when added to plasma. However, when the red cells were present, plasma protein binding was diminished by about 2-fold, demonstrating the ability of methiocarb to bind with RBCs. This binding however, appeared rather weak as the majority of the radioactivity was found in the supernatant fractions obtained after trichloroacetic acid (TCA) precipitation and organo-soluble fractions.

A comparative *in vitro* metabolism study of five methylcarbamate insecticides including methiocarb was undertaken by Strother (1972) using human and rat liver fractions. Rat or human liver 15000 g supernatant fractions were incubated with carbonyl ^{14}C-labelled

methiocarb technical for 3 h at 37° C in the presence of NADP. The reaction mixture was then ether extracted and analysed by TLC and GC. With human and rat liver preparations, approximately 45% of the added radioactivity was noted in the aqueous phase suggesting that, *in vitro* metabolism produced more water soluble metabolites than organo-soluble products. Two major metabolites in organo-soluble fractions were identified: 4-methylsulfinyl-3,5-xylyl methylcarbamate (methiocarb sulfoxide, 13% and 16% for human and rat liver respectively), and 4-methylthio-3,5-xylyl N-hydroxymethyl carbamate (8% and 6% for human and rat liver respectively). Both products retained the OC(O)NC group necessary for ChE inhibition. Twelve further metabolites produced by human liver, and 5 formed by rat liver preparations were not identified.

Wheeler and Strother (1974b) investigated the ether extractable metabolites produced from *in vitro* metabolism of three carbamate pesticides including carbonyl ^{14}C-labelled methiocarb following incubation with foetal and maternal tissue preparations. Maternal and foetal brain, liver, and placental tissues were obtained from 18 or 19 days pregnant SD rats. The supernatant fractions fortified with $NADP^+$ were incubated with 0.5 µmol of methiocarb for 2 h. Sulfoxidation was the major pathway of methiocarb metabolism. Foetal and maternal liver converted 23 and 12% respectively of methiocarb to methiocarb sulfoxide. However, other metabolic pathways were also active in the maternal liver. The most prominent of these, accounting for approximately 8% of the added radioactivity was hydroxylation of the N-methyl carbon to form N-OH methiocarb. Rat placenta had some limited ability to sulfoxidate methiocarb, but the foetal and maternal brain had no measurable metabolic activity towards methiocarb.

The role of flavin adenine dinucleotide (FAD)-dependant monooxygenase in the oxidation of 39 thioether containing organophosphate and carbamate pesticides including methiocarb, and the structure-activity relationships of these pesticides were studied by Hajjar and Hodgson, (1982). Methiocarb was incubated in the presence of NADPH and FAD-dependant monooxygenase at 37º C for 30-60 seconds. Methiocarb was oxidised by FAD-dependent monooxygenase, purified from pig liver microsomes. The stoichiometric relationship between NADPH and standard substrates during the course of the oxidation reaction was 1:1. The rate of metabolism of methiocarb was relatively low compared to phosphorodithioates, and was equivalent to about 2.82 ± 0.03 nmoles of NADPH/min/nmole of enzyme. However, the metabolic products of methiocarb metabolism were not identified nor were their optical activity measured.

A study was undertaken to evaluate the enzyme systems involved in microsomal sulfoxidation of methiocarb (MeS), the product enantioselectivity of the reaction and cholinesterase inhibitory properties of the two methiocarb sulfoxide (MeSO) enantiomers by Buronfosse et al, (1995) using microsomes prepared from the livers of either control, 3-methylcholanthrene (3MC), dexamethasone (DEX) or pyrazole (PYR) treated male rats. Microsomal preparations were incubated with MeS at pH 7.4 in the presence of $NADP^+$, glucose-6-phosphate and glucose-6-phophate dehydrogenase. The major metabolite identified was MeSO. Based on the order of elution from the chiral column, two MeSO enantiomers (A and B) were identified and their relative proportions were established. FMO dependant sulfoxidation showed high stereoselectivity with an enantiomeric excess of 88% in favour of A enantiomer. No methiocarb sulfone ($MeSO_2$) in the incubation mixture was detected. Based on the comparative ChE inhibition kinetic data, MeS and its metabolites were arranged according to the order of increasing inhibition: $MeSO_2$, A-MeSO, racemic MeSO, MeS and B-MeSO.

4.2.3 Metabolism and Urinary Excretion of Methiocarb Metabolites

Methiocarb Phenol

The metabolic fate and urinary excretion of orally administered methiocarb phenol in male rats was studied by Stanley and Johnson (1985). Ring-1-^{14}C labelled methiocarb phenol in ethanol/water (1:1) was administered orally to rats. Of the radioactivity administered, 77-81% was excreted in urine within 48 h and of that about 3-4% was organo-soluble while 73-78% remained in the aqueous phase. About 45% of the radioactivity excreted in urine was identified and three compounds were detected: unchanged methiocarb phenol (29-35%), methiocarb sulfoxide phenol (3-5%) and methiocarb sulfoxide (5%). The study authors stated that methiocarb phenol contained about 2% of methiocarb sulfoxide phenol and about 1% of methiocarb phenol can be converted to methiocarb sulfoxide phenol by incubating in pH 5 buffer for about 16 h. The 3-5% methiocarb sulfoxide phenol fraction found in urine therefore could be attributable to impurities in the dosing solution and artefact formation during enzyme hydrolysis. The fraction of methiocarb sulfoxide (5%) identified in urine could be an *in vivo* metabolic product. Apparently, rats did not readily convert methiocarb phenol to methiocarb sulfoxide phenol.

4.3 Acute Toxicity

The acute toxicity of methiocarb technical in mammals is high when administered by the oral route. The oral LD_{50} value in rats ranged from 9.0 to 135 mg/kg bw in a variety of vehicles, and was 52.3 mg/kg bw in mice. The oral LD_{50} in guinea pigs ranged from 12.2 to 100 mg/kg bw, and has been shown to be less than 25 mg/kg bw in the Beagle dog. By the ip route, the LD_{50} values for mice and rats ranged from 5.5 to 6.0 and 25 to 100 mg/kg bw respectively, and in guinea pigs, it was 17 mg/kg bw.

It is moderately toxic in rats by the inhalation route. In a head only 4 h exposure situation, the LC_{50} in rats ranged from 433-1208 mg/m^3.
Generally, the acute dermal toxicity in rats and rabbits was low with LD_{50} values being in excess of 2000 mg/kg bw. However, an early dermal toxicity study conducted in rats using isopropanol as the vehicle, and in which the applied material was not removed after exposure to the chemical for an unspecified duration, reported a dermal LD_{50} of 350-400 mg/kg bw. In contrast, three further dermal studies conducted in rats using polyethylene glycol 400, saline or unspecified type of oil as vehicles reported LD_{50} values in excess of 500 mg/kg bw. Therefore, the worst dermal LD_{50} of 350-400 mg/kg bw therefore, may perhaps be due to the isopropanol vehicle used in that study.

In acute toxicity studies (oral, inhalational and intraperitoneal), cholinergic effects such as diarrhoea, salivation, lacrimation and vomiting (muscarinic effects), muscular tremors and paralysis (nicotinic effects), and restlessness, ataxia and convulsions (CNS effects) have been observed in experimental animals. The signs of acute toxicity appear to be similar to those seen following intoxication with other carbamates.

Methiocarb technical was not an eye or skin irritant in rabbits. Similarly, there was no evidence of skin sensitisation in studies conducted using guinea pigs.

The acute oral toxicity of the formulations varied, with LD_{50} values in rats ranging from 23-140 mg/kg bw for formulations containing 75% methiocarb. The acute oral LD_{50} of products containing 4% methiocarb ranged from 848 to 945 mg/kg bw, and the value for pellets

containing 2% methiocarb was in excess of 2648 mg/kg bw in rats. The formulations were of moderate to low dermal toxicity. Although, technical grade methiocarb was not an eye or skin irritant, or a dermal sensitiser, some products have been found to cause slight to severe ocular irritation in rabbits and one of them was a skin sensitiser. The products that caused severe eye irritation or skin sensitisation are not currently registered in Australia.

4.3.1 Antidote Studies

The effects of pralidoxime (PAM), atropine sulfate or obidoxime chloride (BH6) have been studied in rats when each chemical was administered alone or in combination after administration of a single oral dose of methiocarb. Antidotal chemicals were administered ip before the appearance of cholinergic signs. The LD_{50} value of methiocarb without antidotes was 67 mg/kg bw. Treatment with atropine sulfate alone increased this value by about 7-fold, PAM alone by about 2.8-fold, and BH6 alone by about 3.3-fold. The combined effect of atropine sulfate and PAM or atropine sulfate and BH6 was slightly higher than atropine sulfate alone, the increases being approximately 7.4- and 7.6-fold respectively. Thus, treatment with atropine sulfate alone appears to be more effective as an antidote against methiocarb compared to PAM or BH6 alone. The effect of atropine sulfate was only slightly increased when it combined with PAM or BH6 (Kimmerle, 1966).

Kimmerle (1971) investigated the antidotal effects of tetraethylammonium chloride (TEAC) and atropine sulfate when each was administered alone or in combination after administration of a single oral dose of methiocarb to rats when cholinergic signs of toxicity were evident. The LD_{50} values were: 104.5, 415, 643 and 580 mg/kg bw for the animals receiving no antidote, TEAC, atropine sulfate, and TEAC and atropine sulfate combination respectively. Thus, treatment with atropine sulfate alone produced a 6-fold increase in the LD_{50} value, and appears more effective as an antidote against methiocarb compared to TEAC alone or TEAC and atropine sulfate combination.

4.4 Effects on Acetylcholinesterase Activity

Baron et al (1964) examined the comparative liver and brain esterase inhibiting properties of methiocarb in mice. Female mice were treated ip with 16 mg/kg bw of methiocarb in corn oil. An inhibition of liver esterase activity was seen against acetylcholine and other substrates within 30-60 minutes of administration. The study authors claimed that the enzyme activity was reversed by 24 h post treatment, but no supporting data were provided. No inhibition of brain esterase activity was said to have occurred at or after 1 h post treatment. The absence of some useful supporting data, together with vehicle induced inhibition of liver esterase(s) noted at 24 h post treatment reduced the value of the study findings, and made independent evaluation difficult.

The effects of dermally administered methiocarb and its two plant foliar residue components, methiocarb sulfoxide and methiocarb sulfone, on erythrocyte (RBC) ChE activity in rats were investigated by Knaak et al (1980). Each chemical was applied on the shaven intact skin in 1 mL of acetone. The quantities applied were approximately 22, 44, 87, 174 and 348 µg/kg bw, 17, 35, 70 and 139 µg/kg bw, and 22, 44, 87, 109, 217 and 435 µg/kg bw for methiocarb, methiocarb sulfoxide and methiocarb sulfone respectively. Methiocarb and methiocarb sulfoxide caused biologically significant inhibition in RBC ChE activity (>20%) at 87 and 70 µg/kg bw and above respectively. Methiocarb sulfone did not produce any depression in RBC ChE activity when applied at levels as high as 435 µg/kg bw for a period of 24 h.

4.5 Short-Term Repeat-Dose Studies

Short term repeat dose toxicity studies have been conducted using rats, dogs and rabbits. The routes of administration were oral, intraperitoneal or inhalational in the rat, oral in the dog, and dermal in the rabbit studies. Synopses of these studies are given in the following sections.

In the study of Kimmerle (1960), methiocarb was administered by oral gavage to rats at 3 mg/kg bw/day for three days, and at 4 mg/kg bw/day for the next 24 days. Three animals/group were killed every week and the RBC ChE activity was determined. The RBC ChE activity was depressed to about 80% and 50% of its pre-treatment values after 14 days and at termination respectively. It was stated that the recovery of the enzyme activity was slow during the subsequent observation period and did not return to normal values up until 42 days after the completion of the study. No cholinergic signs were observed and the body weight gain of the animals was normal, but no supporting data for any of these study parameters were provided. No NOEL was established as this was a single dose study.

In a 4-week study, methiocarb in polyethylene glycol 400 was administered by oral gavage to rats at 1, 3 or 10 mg/kg bw/day. Cholinesterase activity in plasma and RBC was determined at 20 minutes post treatment on days 4, 8, 14, 21 and 28, and additionally, 5 h after the last dose. The brain ChE activity was determined 2 h after the final administration. The animals receiving methiocarb at 10 mg/kg bw/day exhibited brief cholinergic signs but details on the type, onset and the duration of such manifestations were not provided. Biologically significant (>20%), consistent plasma and RBC ChE inhibition was seen at 10 mg/kg bw/day in both sexes at the majority of the sampling times. Similarly, the depression in brain ChE activity noted in rats of both sexes at the same dose level was biologically significant and may have been attributable to treatment. The NOEL for plasma, RBC and brain ChE inhibition was set at 3 mg/kg bw/day based on biologically significant inhibition in plasma ChE at 10 mg/kg bw/day (Eben & Kimmerle, 1973).

A study of the effects of methiocarb or methiocarb sulfoxide on cholinesterase activity in rats was undertaken by Hixson (1981). The test chemicals were administered by oral gavage to groups of female rats at 0.5 or 2.0 mg/kg bw/day in Carbowax, 5 days/week for 4 weeks. A concurrent vehicle control group received Carbowax at 0.5 mL/100 g bw. Sporadic tremors were seen in 6/15 rats receiving methiocarb sulfoxide at 2.0 mg/kg during the first five days. In animals at 0.5 mg/kg bw, a biologically significant (≥20%) plasma ChE inhibition was observed at 30 minutes post treatment at week 1 only. A trend towards decreased depression of the plasma ChE activity with time was seen. In rats receiving methiocarb at 2.0 mg/kg bw, plasma and RBC ChE activities were reduced at 30 min post treatment, achieving biological significance during the first 3 weeks and at week 1 respectively. No statistically or biologically significant inhibition of plasma or RBC ChE was seen at 4 h after dosing in rats receiving methiocarb at either dosage. With methiocarb sulfoxide, biologically significant inhibition was observed at 0.5 or 2.0 mg/kg in plasma ChE from weeks 1-4, and RBC ChE during all but second week. RBC ChE was slow to recover, showing biologically significant inhibition at 0.5 and 2.0 mg/kg on 2 of the 4 weeks on study. Both test compounds demonstrated an apparent dose response relationship with respect to ChE inhibition at 30 minutes but not at 4 h post treatment. A NOEL for methiocarb sulfoxide was not observed due to biologically significant inhibition in plasma and RBC ChE activity at 0.5 and 2.0 mg/kg. The NOEL of methiocarb for RBC ChE inhibition was set at 0.5 mg/kg. No NOEL of methiocarb for plasma ChE inhibition was established due to the enzyme inhibition seen at 0.5 mg/kg bw at week one.

A study was undertaken by Dubois and Raymund (1961), in which female SD rats were treated with methiocarb in 20% ethanol and 80% propylene glycol ip at 0, 5, 10 or 15 mg/kg bw/day, daily for 60 days. No mortalities were observed in the control and 5 mg/kg bw/day groups. But the survival rates at 10 and 15 mg/kg bw/day were low, being 40% and 0% respectively. It was claimed that there was no treatment related effect on weight gain of rats at 5 mg/kg bw/day and a "slight gain" in the body weight was seen at 10 mg/kg bw/day. However, no individual data on body weights were provided nor were details of the statistical procedures used supplied to support these claims. The brain, submaxillary gland and serum ChE activity in rats at 5 mg/kg bw/day was unaffected by treatment. The NOEL for this study was established at 5 mg/kg bw/day. However, the validity of the findings is markedly reduced due to methodological deficiencies, lack of absolute data on several useful study parameters and information on clinical observations.

Kimmerle (1960) conducted an inhalation toxicity study, in which 400 mg of methiocarb of unstated purity in ethanol was sprayed using a "Flury type atomiser" into a chamber of 400 litre capacity containing 1 rabbit, 1 guinea pig, 2 rats and 4 mice for 1 h/day, for 5 consecutive days. Two mice died 4 days after the completion of the study. The study author stated that the animals were "observed to suffer from slight irritation of mucous membrane" during the first 4 days. Muscular spasms were observed in the rats and mice on the fifth day. It was stated that the surviving animals recovered soon. No "poisoning symptoms" except for slight mucous membrane irritation were observed when half of the above dose (ie 200 mg/400 litres) was administered to a different group of animals comprising 1 cat, 1 rabbit, 1 guinea pig, 2 rats and 4 mice for 1 h/day, for 5 consecutive days. Because of deficiencies in the study conduct including, lack of a control group, information on experimental animals and clinical observations, this study was of limited regulatory value.

Thyssen and Mohr (1983) exposed rats to aerosols of methiocarb technical at concentrations equivalent to 6, 23 or 96 mg/m^3 daily for 6 h/day for 15 work days within three weeks. Animals in the negative and solvent control groups received air only or 20 mL of the solvent respectively. There were no mortalities. Muscular tremors were observed in animals at 96 mg/m^3 from day 5 persisting until termination of the study. Significant reductions ($p \leq 0.05$) in group mean body weight were noted in males at 96 mg/m^3 after 5 days of exposure compared to the negative controls. Group mean body weight of females in the same dose group was significantly depressed compared to the solvent controls after 15 days. No treatment related changes were seen in haematological parameters. Significant reductions in plasma ChE activities were observed in males at 23 mg/m^3 after the 5 [32% ($p \leq 0.01$)] and 10 [31% ($p \leq 0.05$)] day exposure periods. Percent reductions in plasma ChE activity in rats at 96 mg/m^3 after 5, 10 or 15 days of exposure were 55 ($p \leq 0.01$), 37 ($p \leq 0.05$) and 52 ($p \leq 0.01$) respectively. In females, significant depressions of plasma ChE activity were observed at 96 mg/m^3 after 5, 10 and 15 days of exposure, percent inhibitions being 56%, 60% and 61% ($p \leq 0.01$) respectively. RBC ChE activity in males at 96 mg/m^3 was depressed by about 18% ($p \leq 0.01$) compared to the solvent controls after 5 days of exposure. Brain ChE activity was significantly reduced in male rats exposed to 23 and 96 mg/m^3 after 15 days exposure (35 and 39% respectively, $p \leq 0.01$) compared to the solvent controls. In females, brain ChE inhibition (26%, $p \leq 0.01$) was noted only at 96 mg/m^3, on treatment day 15. No histopathological changes attributable to treatment were seen. Based on statistically and biologically significant inhibition of ChE activity in the plasma and brain at higher exposure levels, the NOEL for male rats was 6 mg/m^3, and the NOEL for females was 23 mg/m^3.

Technical grade methiocarb applied to shaved flanks of adult white rabbits at 500 mg/kg bw/day for 14 consecutive days did not result in any mortalities, behavioural changes or

toxicological symptoms. Weight gain, haematology, and liver and kidney function of treated animals were unaffected by treatment. In addition, urinalysis did not reveal any treatment related variations in the measured parameters. Dermal application of methiocarb at 500 mg/kg bw/day, daily for 14 days appears to have not produced any treatment related effects in rabbits. However, the reliability of the study is reduced due to the absence of any pathological examination (Kimmerle, 1969c).

A 21-day dermal toxicity study of technical grade methiocarb was conducted by Procter (1988). Methiocarb was applied to the shaven intact skin of NZW rabbits at 0, 60, 150 or 375 mg/kg bw, 6 h/day under occluded conditions. Two animals at 60 mg/kg bw/day displayed decreased faecal output, weight loss and decreased motor activity, and died prematurely. Similar symptoms were also observed in three other animals; one each at 60, 150 and 375 mg/kg bw/day. No skin reaction to the test substance was evident. Food consumption in males at 375 mg/kg bw/day was depressed and reached statistical significance ($p \leq 0.05$) on days 9 and 15. The total amount of food consumed by this group during the study was about 13% less than the controls. Likewise, the food consumption in 375 mg/kg bw/day females was reduced, to a biologically significant (≥20%) extent on days 19 and 21. Further reductions in food consumption were noted in females at 150 mg/kg bw/day during the second week. Consequently, biologically significant deficits in weight gain occurred in both sexes at 375 mg/kg bw/day and in 150 mg/kg bw/day females. Group mean plasma ChE activity in males was depressed in a dose related manner at 375 mg/kg bw achieving significance at 6 h post treatment on days 14 ($p \leq 0.05$) and 21 ($p \leq 0.01$). Biologically significant reductions in plasma ChE activity were evident in males on day 7 at 375 mg/kg and on day 14 at 150 mg/kg, 6 h post treatment. No gross or microscopic tissue changes attributable to the treatment were observed. Based on decreased food consumption and weight gain, and plasma ChE inhibition at 150 mg/kg bw/day, the NOEL for this study was 60 mg/kg bw/day.

Procter (1989) conducted another study in which technical grade methiocarb was applied to the shaven intact skin of female NZW rabbits at 0.5 g/kg bw, 6 h/day for 21 days under occluded conditions. No mortalities were observed. Two animals that removed their dressings on treatment day 10 and ingested some test material exhibited clinical signs of cholinergic poisoning, which reversed by the next day. Group mean food consumption was depressed by about 13% in males and 10% in females compared to the controls achieving significance ($p \leq 0.05$) during study days 13-15 in males and 19-21 in female rabbits. The total weight gained by the males during the study was about 63% less compared to the controls. Similarly, treated females were always lighter than the controls and showed statistically significant reductions ($p \leq 0.05$) in group mean body weights and gained about 30% less weight during the study. A statistically significant reduction in plasma ChE activity was noted in treated females on day 14, 6 h post treatment compared to the controls. RBC ChE and brain ChE activities were unaffected by treatment. No inter-group differences in absolute and relative organ weights of the treated animals were seen nor were any gross or microscopic tissue changes attributable to the test chemical observed. The reduced food consumption and body weight gain seen in the treated animals in this study is consistent with the findings of the previous report (Procter, 1988), but ChE inhibition appears to be unexpectedly slight and inconsistent. As this was a single dose study, a NOEL could not be established.

In a 12-week study, technical grade methiocarb was administered to Beagle dogs at 0, 50, 100, or 250 ppm in the diet (equivalent to approximately 0.75, 1.25 or 3.75 mg/kg bw/day). Growth rate of the animals was unaffected by treatment. No inhibition in the weekly serum or erythrocyte ChE activity was noted. Food and water consumption, haematology or clinical chemistry parameters were not examined. Because of the small experimental group size

adopted, and lack of clinical observations and statistical analysis of data, the usefulness of the findings of this study is reduced (Root et al, 1963).

Hayes (1981) investigated the effects of technical grade methiocarb or methiocarb sulfoxide on ChE activity in Beagle dogs. The test chemicals were administered orally at 0, 0.05 or 0.5 mg/kg bw/day in gelatine capsules for 29 days. Occasional slight to heavy salivation, and vomiting were observed in dogs receiving either test compound at 0.5 mg/kg bw/day and in one female receiving methiocarb sulfoxide at 0.05 mg/kg bw/day. Generally, both test compounds throughout the study showed a dose relationship with respect to ChE inhibition. The maximum ChE inhibition usually occurred between 0 and 3 h post dosing at 0.5 mg/kg bw/day with either test compound in both sexes. Plasma ChE inhibition never reached biological significance at the low dose. Twenty percent depression of the RBC ChE activity was noted with methiocarb at 0.05 mg/kg bw/day at week 1 in females and at week 5 in males. Methiocarb sulfoxide was a more potent inhibitor than methiocarb. Greater than 20% inhibition was seen on both plasma and RBC ChE activity with methiocarb sulfoxide at 0.05 mg/kg bw/day in both sexes on several occasions. Plasma ChE depression was slightly more pronounced than RBC ChE depression. Regardless of sex, both plasma and RBC ChE were depressed to biologically significant levels at 0.5 mg/kg bw/day by both test compounds at most of the sampling times. Plasma and RBC ChE activities were generally normal by 6 h post treatment. Although 20% inhibition of RBC ChE activity was seen on 2 isolated occasions with methiocarb at 0.05 mg/kg bw/day, this was not accepted as a true LOEL because the occurrence was sporadic. However, this was not accepted as a NOEL either, because the data are considered unreliable due to the small numbers of dogs/group. Due to treatment related inhibition of either plasma and/or RBC ChE enzyme activity seen in both sexes with methiocarb sulfoxide at both dose levels, no NOEL was established for this compound. This study was not considered adequate for regulatory purposes due to small experimental group size.

4.5.1 Formulations

Flucke and Kimmerle (1977) investigated the toxicity of orally administered Mesurol slug pellets containing 4% methiocarb, with determination of erythrocyte (RBC) ChE activity in rabbits. The test substance was administered orally to a group of 4 adult female Chinchilla rabbits at 100 mg/kg bw, twice a day for 5 consecutive days. No mortalities were reported. Treated animals showed a slight loss of body weight at the end of the treatment period. However, they regained weight by 9 days after cessation of treatment. RBC ChE activity was slightly depressed at 5 h after the first daily dosing compared to the reference value (2-7%). However, the RBC ChE data at 12 h after the second daily dosing were comparable to the reference value and showed the recovery of the enzyme activity within 12 h post treatment. Plasma ChE activity was depressed by about 25-35% at 5 h after the first daily dosing and was biologically significant on all treatment days. Plasma ChE activity at 12 h after second daily dosing also remained depressed (12-17%) throughout the study and appeared slower to recover. The validity of the study findings, however, is reduced due to small experimental group size, lack of controls, clinical observations, and statistical analyses. No NOEL could be established as this was a single dose study.

An inhalation toxicity study was conducted by Groning and Kimmerle (1975) using rats. The animals were exposed to aerosols of methiocarb 50% wettable powder at concentrations of 20.2, 31.5 or 188 mg/m^3, for 4 h/day for 5 days. There was no control group in the study. There were no mortalities, but the authors stated that the general health of the animals at 31.5 and 188 mg/m^3 was affected from the first day of exposure onwards. A depression in the ChE

activity in the animals at 188 mg/m^3 was seen, but no supporting data were provided. The animals at 20.2 mg/m^3 showed unspecified changes in general health on the second and third day on study. Clinical signs in animals persisted for 1 to 3 days after the 5 day exposure period. Lack of a control group and inadequate information on clinical signs, and ChE depression rendered this study inappropriate for regulatory purposes.

In a 3-week dermal study (Dubois et al, 1968) methiocarb 50% wettable powder in water was applied to shaved, abraded skin of rats at 200 mg/kg bw/day, 5 days/week for 3 weeks. There were no mortalities. An inhibition of the growth rate was seen in all animals, which was more pronounced in females. The brain ChE activity was unaffected by treatment, but cholinergic signs were noted after each treatment, particularly at the beginning of the daily treatment period. No gross pathologic changes attributable to treatment were seen. The data showed the potential of the test substance to cause cholinergic effects by repeat administration. However, due to of lack of information on clinical signs, and with no effect seen on brain ChE activity, the ChE inhibitory potential of the formulation at the dose level used cannot be fully explained. The validity of the study findings is reduced due to methodological deficiencies, debatable sensitivity of the ChE assay used, and insufficient use of statistical procedures to analyse the results.

4.6 Subchronic Toxicity

There were only two subchronic toxicity studies in the methiocarb toxicology database. The two studies have been conducted in rats. Both studies, however, were found to be inappropriate for regulatory purposes.

In the dietary study of Doull et al (1962), methiocarb technical was fed to rats at 0, 5, 10 or 50 ppm (equivalent to approximately 0, 0.5, 1.0 or 5.0 mg/kg bw/day) for 16 weeks. No treatment related effect on mortality was evident. Food consumption and the growth rate of the animals were unaffected by treatment. None of the treated rats exhibited any cholinergic or other toxic symptoms. Biologically significant (≥20%) inhibition of the serum ChE activity was seen in both males (21%) and females (28%) at 5 mg/kg bw/day. Submaxillary gland ChE in females was inhibited dose elatedly by 23-33% in all treatment groups compared to the controls. RBC and brain ChE activity were slightly inhibited in 5 mg/kg bw/day males. No data on necropsy, organ weights, histopathology or clinical observations were provided. The validity of the study findings is reduced due to lack of justification for dose selection, statistical analyses, clinical observations, and data limitations. A NOEL could not be established, given the evidence of ChE inhibition in the submaxillary gland at 0.5 mg/kg bw/day.

A 24-week dietary study was carried out by Löser (1969) in which methiocarb technical was fed to rats at 0, 30, 100 or 300 ppm (equivalent to approximately 0, 3, 10 or 30 mg/kg bw/day). The rats were participating in a concurrent single generation study and the studies reported here were performed in animals of F_0 generation at the end of the preliminary treatment period, and after their second litter had been reared. Modest changes in white blood cell counts were seen in both sexes. Perturbations in haematology were noted at 10 weeks at 30 mg/kg bw/day, and not thereafter. The serum AST and ALT levels were higher in animals of both sexes at 30 mg/kg bw/day, 10 weeks after initiation of the study and not thereafter. No clinical observations, data on food and water consumption or body weights of the animals were provided. The modest changes in haematological and clinical chemistry parameters occurred in treated animals appear to be physiological adaptations and were not suggestive of any disease process. However, due to the limitations of the data and lack of statistical

analyses, the reliability of the findings is reduced. The data could be considered as supplementary to other long term toxicity studies.

4.7 Chronic Toxicity

A chronic study was undertaken by Kroetlinger and Janda (1983) in which methiocarb technical was fed to mice in the diet at 0, 67, 200 or 600 ppm (equal to 0, 14.6, 42.8 and 132 mg/kg bw/day for the males and 0, 19.8, 57.0 and 173 mg/kg bw/day for the females) for 2 years. Mortality among the test groups and controls was high. The body weights at 600 ppm were depressed by about 5% during the first year ($p \leq 0.01$ or 0.05). Consistent with biologically significant elevations in leucocyte counts (42% and 67% at 200 and 600 ppm respectively) seen at 12 months, statistically significant increases occurred in females at 24 months ($p \leq 0.01$ or 0.05) and appeared to be treatment related. The ALT activity in both sexes at 200 and 600 ppm was significantly elevated ($p \leq 0.01$ or 0.05) at termination and was also elevated in females at 12 months. Statistically or biologically significant ($p \leq 0.01$ or 0.05) inhibition of plasma ChE was noted at 200 and 600 ppm males and in females at one month but not thereafter. The brain ChE activity was unaffected. Statistically ($p < 0.05$) or biologically significant reductions in absolute (33-42%) and relative (32-44%) spleen weight noted at 200 and 600 ppm at termination may have been attributed to the test compound. The absolute and relative liver weights were elevated at 600 ppm in both sexes at termination. Because of statistically and/or biologically significant perturbations seen in haematological parameters and ALT activity in treated animals at both sampling times, a NOEL for this study was not established.

Methiocarb technical in the diet was fed to rats at 0, 25, 50 or 100 ppm (equivalent to approximately 0, 2, 5 or 10 mg/kg bw/day) for about 80 weeks. Survival was poor, but mortality appeared to be unrelated to treatment, as most of the animals appear to have been distressed during the study due to respiratory tract and renal infections. Food consumption and the growth rate of the animals were unaffected by treatment. No cholinergic or other toxic symptoms were observed. Biologically significant (≥20%) inhibition of the serum (22%) and submaxillary gland (24%) ChE activity was noted in females at 100 ppm. The NOEL for ChE inhibition was 50 ppm. The validity of the study however, is reduced due to lack of justification for dose selection, statistical analyses, clinical observations and data limitations most significantly relating to ChE activity in males. Therefore, the findings of this study were of limited regulatory value (Doull et al, 1967).

Methiocarb technical in the diet was fed to rats at 0, 67, 200 or 600 ppm (equivalent to 0, 3.27, 9.3 and 29 mg/kg bw/day for the males and 0, 4.98, 13.9 and 42 mg/kg bw/day for the females) for 2 years (Kroetlinger et al, 1981, Kroetlinger, 1990). Food consumption in males at 600 ppm was slightly reduced (5%) during the second year. Between weeks 4 and 19 on study, the 200 ppm males showed a statistically significant ($p \leq 0.05$ or 0.01), consistent deficit in body weight (3-8%). At 600 ppm, body weights were significantly depressed ($p \leq 0.05$ or 0.01) in both sexes throughout the study. Statistically significant increase ($p \leq 0.05$ or 0.01) in reticulocyte count and depressed erythrocyte count were seen in females, at months 3 and 6 at 200 and 600 ppm. Significant increases ($p \leq 0.05$) in plasma urea levels were seen in 600 ppm females at 12 months and termination. Plasma ChE activity in both sexes at 600 ppm was inhibited with either statistical ($p \leq 0.05$ or 0.01) or biological significance (>20%). A reduction of plasma ChE activity in 200 ppm males at termination was biologically significant. RBC ChE activity at 600 ppm showed slight depression achieving statistical significance ($p \leq 0.05$ or 0.01). Significant reductions also occurred at 200 ppm ($p \leq 0.05$ or 0.01). No inhibition in the brain ChE activity was seen. Relative and/or absolute spleen

weights in both sexes at 600 ppm were depressed by about 10-18%. In males, relative testes weights were increased by 7% ($p \leq 0.05$) at 600 ppm. Based on transient depression in body weight in 200 ppm males, elevation in reticulocyte counts in 200 ppm females and plasma and RBC ChE inhibition at 200 ppm, the NOEL was established at 67 ppm (3.27 and 4.98 mg/kg bw/day for males and females respectively).

Technical grade methiocarb in the diet was fed to Beagle dogs at 0, 50, 100 or 250 ppm (equivalent to approximately 0, 1.25, 2.5 or 6.25 mg/kg bw/day) for 2 years. No mortalities or clinical signs were reported, though reporting was limited. Food consumption was unaffected by treatment. The average body weight of the animals at 250 ppm was depressed by about 10% from week 32 to 80 and during the same period it was about 10% greater at 100 ppm compared to the controls. The serum ChE activity was inhibited by up to 20% during weeks 15 to 32, in the animals at 100 and 250 ppm. The RBC ChE activity was variable in all dose groups, but rarely inhibited by more than 20%. The brain and liver ChE activities were unaffected by treatment. The absolute and relative liver weights of dogs at 250 ppm were slightly elevated. Due to lack of clinical observations, limitations of the study data and the low number of dogs/group used, this study is not considered appropriate for regulatory purposes (Doull et al., 1968).

A long term toxicity study was conducted in the Beagle dog by Hoffman and Schilde (1980). Technical grade methiocarb in the diet was fed to Beagle dogs at 0, 15 (during the first 15 days), 5 (from week 3 to 104), 60 or 240 ppm (equivalent to approximately 0.6, 0.2, 2.4 and 9.6 mg/kg bw/day respectively) for 104 weeks. Clinical signs such as occasional mild weakness of the hind limbs accompanied by trembling, lameness and infrequent decreased alertness were seen in 5/8 dogs at 240 ppm during the first 14 weeks. Occasional vomiting was seen in all groups, but the incidence was higher at 240 ppm. Food consumption was reduced slightly (5-7%) in 60 ppm females and in both sexes at 240 ppm (12%) during the second year. The body weights, weight gain, and the nutritional state of the animals were unaffected by treatment. Dose related and biologically significant (>20%) depression of the plasma ChE activity was seen at 60 and 240 ppm, 2 h post treatment. The ChE inhibition at 240 ppm pre-treatment was near or above 20% at most of the sampling times, and was more pronounced in the males than in the females suggesting slow recovery of the enzyme. RBC ChE inhibition was variable and inhibition did not reach biological significance at any dose at any of the sampling times. The brain ChE activity was unaffected by treatment. Based on biologically significant plasma ChE inhibition in both sexes and reduced food consumption in females observed at 60 ppm, the NOEL was established at 5 ppm (0.2 mg/kg bw/day).

4.8 Reproductive Toxicity

A reproductive toxicity study was undertaken by Löser and Newman (1970). Technical grade methiocarb was administered to rats at 0, 30, 100, or 300 ppm (equivalent to approximately 0, 3, 10, and 30 mg/kg bw/day) in the diet for three parental generations and their offspring. Each generation was mated twice. The offspring of each of the second matings were used to produce the next generation. Sporadic changes in some reproductive parameters and neonate data were observed in different generations of animals but did not reveal any consistent, statistically or biologically significant treatment related effects in all generations. No gross or histopathological changes attributable to the treatment were noted nor were any treatment related malformations observed in any generation at birth or during lactation. The validity of the findings, however, is reduced due to data limitations.

4.9 Developmental Toxicity

Lorke (1971) undertook a study of teratology and embryotoxicity in rats. Methiocarb was administered once daily by oral gavage to mated female rats at 0, 1, 3 or 10 mg/kg bw/day on days 6-15 post-coitum. No mortalities or premature abortions were recorded during the treatment nor were any clinical signs noted. Food consumption and appearance of the animals were unaffected. The average weight gain during pregnancy was depressed by about 10% at 10 mg/kg bw/day. Maternal reproductive indices were unaffected, and no significant group differences in foetal weights, resorptions, and foetal skeletal development were observed compared to the controls. Further, no treatment related visceral or skeletal malformations were observed (Renhof, 1971). Based on reduced weight gain at the highest dose, the NOEL for maternal toxicity was set at 3 mg/kg bw/day. There were no effects on foetal survival, development or growth at the highest dose of 10 mg/kg bw/day.

In a preliminary dose range finding study (Tesh and Ross, 1981), methiocarb technical was administered by oral gavage to artificially inseminated NZW rabbits at 0, 1, 3 or 10 mg/kg bw/day on days 6 through 18 post insemination. No mortalities were recorded. The animals at 10 mg/kg bw/day showed a marked loss of body weight during the first half of the treatment period compared to the controls. Thereafter the group mean body weight of this group increased and was comparable to that of the controls at termination. Post treatment cholinergic responses such as loss of muscular control, muscular tremors and polypnea of about 3 h duration were noted in all animals at 10 mg/kg bw/day commencing from 15 minutes post dosing. The litter responses were unaffected by treatment. Examination of foetuses at terminal necropsy revealed several anomalies. However, the group incidence of these anomalies did not show any consistent indication of an association with treatment. The study authors concluded that, dose levels of methiocarb up to 10 mg/kg bw/day would be suitable for use in a main teratology study.

In a teratology study methiocarb technical was administered by oral gavage to artificially inseminated NZW rabbits at 0, 1, 3 or 10 mg/kg bw/day on days 6 through 18 post insemination (Tesh et al, 1981). There was no treatment related maternal mortality. The animals at 10 mg/kg bw/day showed a marked loss of body weight during the first two days of treatment. Consequently, their overall body weight gain was decreased during the remaining test period achieving statistical significance ($p \leq 0.01$) on day 18 of gestation compared to the controls. Post-treatment cholinergic signs were noted at 10 mg/kg bw/day. Post mortem examinations of animals either found dead or sacrificed during the experiment revealed evidence of respiratory tract infection and/or gastro-intestinal tract disorder or accidental tracheal intubation. The incidence of pale areas on the foetal liver was increased at 10 mg/kg/day by about 3.5-fold and 17-fold compared to mean concurrent and background control data respectively. Reproductive indices were comparable among groups. No evidence of teratogenicity of methiocarb was reported. However, maternotoxicity characterised by cholinergic signs and weight loss was evident at 10 mg/kg bw/day. Therefore, a maternotoxicity NOEL was established at 3 mg/kg bw/day. Based on the effects seen in the foetal liver, the embryo/foetotoxicity NOEL was also set at 3 mg/kg bw/day.

In the dose range finding embryotoxicity and teratogenicity study of Dotti and Biedermann (1993), methiocarb technical was applied dermally to shaved, occluded skin of the backs of rabbits at 0, 250, 500 or 750 mg/kg bw, 6 h/day from days 6 through 18 post coitum. No mortalities, clinical signs or skin reactions related to treatment were noted. The mean food consumption was markedly depressed in all groups during treatment compared to the controls, achieving statistical significance at 250 and 750 mg/kg bw/day. Overall, the does at 750

mg/kg bw/day consumed about 27% less food compared to the controls. Statistically insignificant moderate loss in body weight was noticed in all groups from days 6 through 12 post coitum. The trend was similar to that observed for food consumption, being most marked at 250 and 750 mg/kg bw/day. Group mean foetal body weights were depressed by about 20% at 750 mg/kg bw/day and by 12% at 500 mg/kg bw/day. One foetus at 500 mg/kg bw/day and all foetuses of one doe at 750 mg/kg bw/day were of less than 19 g body weight. No information on skeletal abnormalities was provided. Because of effects seen in maternal food consumption and body weight gain, and foetal findings at 500 and 750 mg/kg bw/day, dose levels of 10, 50, and 250 mg/kg bw/day were selected for the main embryotoxicity study.

A study of the teratogenic and embryotoxic potential of methiocarb was undertaken by Dotti and Beidermann (1992). Methiocarb technical was applied dermally to the shaved, occluded skin of the backs of rabbits at 0, 10, 50 or 250 mg/kg bw, 6 h/day from days 6 through 18 post coitum. The mean food consumption was depressed at 250 mg/kg bw/day during days 6-11, 11-15 and 15-19 by about 6%, 19.5% and 7.3% respectively. Overall, the does at 250 mg/kg bw/day consumed about 4.5% less food compared to the controls. Weight loss at 250 mg/kg bw/day was distinct during days 6 through 22, being significant on days 13 and 16 ($p \leq 0.01$). The mean foetal body weights were depressed by about 4% at 250 mg/kg bw/day. The foetal incidence of incompletely ossified or non-ossified forelimb phalanges was significantly increased ($p \leq 0.05$ or 0.01) at all three doses but lay within the historical control range. Hind limb phalangeal ossification appeared to be retarded at 50 and 250 mg/kg bw/day only ($p \leq 0.05$ or 0.01), and the dose response relationship evident is suggestive of a treatment related effect. The litter incidences of retarded hind limb ossification were significant ($p \leq 0.05$) at 250 mg/kg bw/day. Because of reduced food consumption in does at 250 mg/kg bw/day, and the weight loss during days 6 through 22 post coitum the maternotoxicity NOEL was established at 50 mg/kg bw/day. Owing to reduced mean foetal body weight at 250 mg/kg bw/day, and retarded ossification of hind limb phalanges seen at 50 and 250 mg/kg bw/day, the foetotoxicity NOEL was established conservatively at 10 mg/kg bw/day.

4.10 Genotoxicity

Genotoxicity of methiocarb has been examined using a battery of *in vitro* and *in vivo* tests. The studies include *in vitro* gene mutation, DNA damage and repair, unscheduled DNA synthesis, chromosomal aberration, micronucleus formation and *in vivo* dominant lethal mutation assays. Eight out of 9 genotoxicity studies reviewed, produced negative results indicating by weight of evidence that methiocarb is not genotoxic. The *in vitro* study of Murli (1990) performed using Chinese hamster ovary (CHO) cells was the only study showing positive results for inducing chromosomal aberrations at the dose levels tested under both activated and non-activated assay conditions.

4.11 Neurotoxicity

The neurotoxicity of methiocarb has not been studied extensively. The results of two studies conducted on hens are summarised in the following sections.

The neurotoxicity of methiocarb in relation to its demyelinating potential was studied in hens by Ives (1965). In this study, hens were fed with diets containing either 0, 200, 400 or 800 ppm (equivalent to approximately 25, 50 and 100 mg/kg bw/day respectively) of methiocarb *ad libitum* daily, for 30 days. All birds survived the experimental period. No treatment related effects on body weight were noted and nor were any histopathological evidence of myelin degeneration or clinical signs of cholinesterase inhibition noticed in any of the treated birds.

No other clinical observations or methodological information were provided. However, when age and source of the study, lack of detailed methodology, and the data limitations are considered, the findings of this study are of limited regulatory value.

Thyssen and Schilde (1978) conducted a neurotoxicity study in hens. Methiocarb was administered twice at 380 mg/kg bw (equivalent to LD_{50}) to hens orally at an interval of 3 weeks. The birds were treated with 50 mg/kg bw of atropine sulphate im prior to each treatment. Following the first treatment with methiocarb, the birds manifested unspecified light behavioural changes of brief duration and lethargy on the first day. Two methiocarb treated hens died after an unspecified period. Similar "symptoms" were noted after the second treatment, following which 2 further mortalities occurred after an unspecified period. No delayed neurotoxic effects of methiocarb in the central or peripheral nervous system were observed. The positive control, tri-ortho-cresyl-phosphate produced the classical signs and of delayed polyneuropathy. In histopathology, 9/10 methiocarb treated hens showed occasional very minimum to minimum peri-vascular round cell infiltration in one or several of the nerve tissues examined. Four out of 5 positive controls showed "minimal" degeneration of individual fibres in the sciatic nerve, vacuolar distension of myelin sheaths, Schawnn cell proliferation, presence of eosinophilic particles and occasional peri-vascular round cell infiltration. The validity of the findings of the study however, was reduced due to lack of negative control data.

4.12 Immunotoxicity

Casale et al (1993) performed an *in vitro* study using mouse CTTL2 cells. Plates containing CTLL2 cells in a growth medium supplemented with human recombinant IL2 were incubated in the presence of 100 µL of either 0, 0.5, 5.0 or 50 µM methiocarb in 0.2 M acetone for 16 h. IL2 dependent cell proliferation was evaluated by measuring the ^{3}H-thymidine uptake. Under the study conditions, *in vitro* T cell proliferation was inhibited by methiocarb at 50 µM by about 80% compared to the untreated cells, in the absence of metabolic activation. No inhibition was noticed at other concentration levels. However, no reference to the cytotoxicity of methiocarb was made. It was stated that the potency to produce acute cholinergic toxicity by the tested chemicals did not predict the potency to inhibit T cell proliferation.

4.13 Human Studies

4.13.1 Dermal Irritation

In the study of Dubois and Raymund (1961), cotton wool compresses containing an unidentified quantity of methiocarb of unstated purity in dry form, moistened with either an unidentified type of oil or with water were applied to the forearm of 8 persons for 8 and 24 h respectively. In some cases symptoms of irritation were noticeable at the site of application after 8 h. Inflammation and swelling were observed at application sites of all test persons after 24 h. Based on the information provided, methiocarb was an irritant to the human skin. However, it is not possible to comment on the severity of irritation or influence of the vehicle ("oil") on the skin reaction observed, with the limited information provided.

4.13.2 Occupational Exposure

A dermatological effect ascribed to methiocarb was reported by Willems et al (1997) in a published case study. A 35 year old carnation grower developed acute severe hand eczema, who continued his work in spite of this dermatological condition. Though several topical

corticosteroids were used, they did not bring about any therapeutic benefit. A patch test conducted with a methiocarb based product yielded a positive result. However, it is unclear whether the allergic reaction occurred in response to methiocarb or non-active constituents in the formulation.

About 250 employees in two methiocarb manufacturing plants were subjected to yearly medical examinations including assay of whole blood ChE activity for more than 20 years. The medical tests also included, examination of the work and health history, measurement of the height and weight, a detailed clinical examination and laboratory tests to determine blood sedimentation rate (BSR), blood count, urinalysis, AST and ALT levels. An X-ray examination of the thoracic organs was conducted at 2-3 year intervals. The study authors stated that, under the conditions prevailed in the plants, no adverse health effects related to methiocarb were noted in any of the employees nor were changes in any of the laboratory parameters observed (Faul, 1993).

4.14 Discussion

4.14.1 Metabolism and Toxicokinetics

According to absorption, metabolism and excretion studies in rats, dogs and cattle, methiocarb is reasonably well absorbed when administered orally. It has been demonstrated that more than 75% of the administered dose was excreted in urine by rats within 48 h, mostly as phenolic derivatives. The findings of the *in vivo* studies suggest that methiocarb is extensively metabolised to form a range of metabolic products such as methiocarb phenol, methiocarb sulfoxide phenol, and methiocarb sulfone phenol. In some studies, the formation of N-hydroxymethyl methiocarb sulfoxide, and trace quantities of methiocarb sulfoxide have also been reported. Both of these products retained the OC(O)NC functional group that is necessary for cholinesterase inhibition. Initial hydroxylation of the ester bond followed by sulfoxidation appeared to be the primary steps involved in the formation of methiocarb sulfoxide phenol. However, in the formation of methiocarb sulfoxide, the metabolite which possessed significant anticholinesterase activity, sulfoxidation reaction preceded the hydrolysis of the ester bond.

One of the major *in vivo* metabolic pathways for many carbamates is hydrolysis of the ester bond and release of the resultant carbonate in exhaled air as CO_2. *In vivo* studies with carbonyl-^{14}C labelled methiocarb have shown elimination of about 66% of the administered dose in the expired air as CO_2 following metabolism of methiocarb or its metabolites by microsomal enzymes. However, under *in vitro* conditions with hepatocytes, the formation of CO_2 during metabolism is low, generally accounting for about 2% of the administered radioactivity. It is likely that under *in vivo* conditions physiological and biochemical processes other than the hepatic microsomal enzymes are involved in methiocarb metabolism and elimination.

A large proportion of methiocarb metabolites formed under *in vivo* conditions and excreted in urine appeared to be water soluble metabolites while the faeces contained largely unchanged methiocarb. The major metabolites excreted in urine by rats and cattle following oral administration are methiocarb phenol, methiocarb sulfoxide phenol and methiocarb phenol sulfone, whereas in dogs, the primary urinary metabolites are methiocarb sulfoxide phenol and methiocarb phenol sulfone.

The major metabolic products formed under *in vitro* conditions were methiocarb sulfoxide, methiocarb sulfone and N-hydroxymethyl methiocarb sulfoxide. A recent study conducted using rat liver microsomes, however, revealed only the presence of methiocarb sulfoxide in the incubation mixture with no methiocarb sulfone being detected. In general, sulfoxidation or N-methyl oxidation appeared to be the main routes of methiocarb metabolism under *in vitro* conditions. Methiocarb was oxidised relatively slowly by the dog liver or kidney supernatant fractions compared to the rat liver supernatant.

Studies conducted in pregnant animals show rapid metabolism, placental transfer and excretion of the compound following ip administration, without producing any gross teratogenic effects in the foetus. As revealed in elimination and tissue distribution studies, foetal tissues appear to retain elevated levels of methiocarb for longer compared to maternal tissues. Although these levels did not cause maternotoxicity or teratogenic lesions in the foetus, there may be potential for alterations in such enzyme systems as ChE. Additionally, foetal uptake and retention may perhaps slow the rate at which the chemical could be metabolised by the maternal tissues.

4.14.2 Acute Toxicity

The acute toxicological profile of methiocarb appears to be similar to those of other insecticide carbamates, and most organophosphorous ChE inhibiting pesticides. The clinical signs commonly observed in experimental animals following acute exposure were salivation, lacrimation, vomiting, diarrhoea, muscular tremors, restlessness, convulsions, and paralysis in some animals. It was noted that more than 60% of the acute oral toxicity studies reported LD_{50} values ranging from 9.0 to 50 mg/kg bw, while the remainder presented values in excess of 50 mg/kg bw for rats (range 9-135 mg/kg bw). A credible explanation for the wide variability of the acute oral LD_{50} value in rats could not be found from the data provided for individual studies. The lowest acute inhalation LC_{50} of methiocarb in rats was 433 mg/m^3. Methiocarb acute toxicity was not substantially increased by ip administration, for which the rat LD_{50} ranged from 25 to 100 mg/kg bw. The acute dermal toxicity in rats and rabbits is generally low, with LD_{50} values being in excess of 2000 mg/kg bw.

Amongst methiocarb metabolites, methiocarb sulfoxide appears to be toxicologically significant with oral LD_{50} in rats ranging from 6.0 to 9.0 mg/kg bw. Clinical signs observed in rats and dogs treated with methiocarb sulfoxide by oral gavage (2.0 and 0.5 mg/kg bw respectively) were similar to those observed in methiocarb acute toxicity studies. The rat oral LD_{50} values of N-hydroxymethyl derivatives of methiocarb, methiocarb sulfone and methiocarb sulfoxide were greater than 112 mg/kg bw whilst those of methiocarb phenol, methiocarb sulfone, methiocarb phenol sulfoxide and methiocarb phenol sulfone were in excess of 1000 mg/kg bw.

The LD_{50} values that have been reported for end-use products containing methiocarb are generally representative of the percentage of active ingredient present in the formulation.

4.14.3 Acetylcholinesterase Inhibition

A summary of NOEL findings for plasma, RBC and the brain ChE in different species of experimental animals in a range of repeat dose studies is presented in Table 6.

Table 6 : Summary of doses (mg/kg bw/day or mg/m^3) at which no inhibition of ChE activity following methiocarb administration was seen

Species	Duration	Route	Plasma	Erythrocyte	Brain	E:P ratio
Mice	2 years	Oral	14.6	ND	132/173 (M/F)	-
Rat	4 weeks	Oral	3.0	3.0	3.0	1.0
	4 weeks	Oral	<0.5	0.5	ND	-
	24 days	Oral	ND	<3.0	ND	-
	2 months	IP	5.0	ND	5	-
	3 weeks	Inhalation	6.0	>23.0	6.0	3.8
Rat	16 weeks	Oral	1.0	ND	ND	-
	80 weeks	Oral	5.0	>10	>10	>2.0
	2 years	Oral	3.27	3.27	>29/42 (M/F)	1.0
Rabbit	3 weeks	Dermal	60.0	>375.0	>375.0	>6.25
Dog	29 days	Oral	<0.05	<0.05	ND	-
	2 years	Oral	1.25	>6.25	>6.25	>5.0
	2 years	Oral	0.2	>9.6	>9.6	>48

ND = not determined.

The data presented in the Table above indicates that the inhibition of ChE in plasma occurs at relatively low dose levels. Due to wide intra- and inter- species variability observed, and the data limitations, no appropriate short-term repeat dose study could be selected for establishment of an acute reference dose (ARfD). The 2-year toxicity study in dogs conducted by Hoffman and Schilde (1980), which yielded the lowest NOEL of 0.2 mg/kg bw/day based on plasma ChE inhibition, and related acute clinical signs, has therefore been chosen to establish the ADI recommended in this review.

4.14.4 Neurotoxicity Studies

The neurotoxic potential of methiocarb has not been studied extensively. Nevertheless, in two early studies conducted in hens, methiocarb has not been shown to produce delayed polyneuropathy of the organophosphorus type. However, both these studies provided limited methodological information and/or data for independent evaluation, and hence were found to be of limited regulatory value.

The antidotal studies conducted in rats using chemicals such as atropine sulfate, pralidoxime (PAM), obidoxime chloride (BH6) and tetraethylammonium chloride (TEAC) indicate that atropine sulfate alone is more effective as an antidote against methiocarb acute toxicity compared to treatment with PAM, BH6 or TEAC alone. The effect of atropine sulfate was only slightly increased when it was combined with any of these chemicals. Further, the effectiveness of the procedures that have been adopted by veterinarians to treat accidentally poisoned animals are consistent with this finding.

4.14.5 Genotoxicity and Carcinogenicity

Methiocarb has been evaluated for genotoxicity using a battery of tests under both *in vivo* and *in vitro* conditions using various end points such as gene mutation, sister chromatid exchange, unscheduled DNA synthesis, micronucleus formation and dominant lethal assay. The weight of evidence indicates that methiocarb is not mutagenic. In an *in vitro* chromosomal effect assay, methiocarb has been found to cause chromosomal aberrations under both activated and non-activated conditions in the absence of cytotoxicity. However, this study used a higher dose range compared to the doses used in an *in vitro* sister chromatid exchange assay which yielded negative results, and an *in vivo* mouse micronucleus assay was negative. Moreover, there was no evidence of carcinogenicity from long term studies in rats and mice.

4.14.6 Reproduction and Development

An old reproduction study conducted using three parental generations of rats did not reveal any consistent statistically or biologically significant treatment related effects of methiocarb on fertility, litter size, pup birth weight and survival, or lactation in any generation. Histopathological examination of the pups did not reveal any treatment related abnormalities. This study, however, failed to provide absolute data on several useful study parameters such as maternal body weights, post cull survival, pup sex ratio and ChE activity, and therefore falls short of the standard that would be expected in a modern reproduction study.

The teratogenicity of methiocarb has been investigated in one rat study, and two rabbit studies following administration of the chemical to the pregnant animal during the period of organogenesis. In the rat study, based on reduced weight gain of the dams at the highest dose, the NOEL for maternotoxicity was established at 3 mg/kg bw/day, and because there were no effects on foetal survival, development or growth at the highest dose tested, the NOEL for foetotoxicity was 10 mg/kg bw/day.

When methiocarb was administered to pregnant rabbits at doses up to 10 mg/kg bw/day by oral gavage, maternotoxicity characterised by cholinergic signs and weight loss, and embryo/foetotoxicity as manifested by the occurrence of pale areas in the liver were evident at the highest dose. The NOEL for maternotoxicity and embryo/foetotoxicity was set at 3 mg/kg bw/day. In the remaining rabbit study, methiocarb was administered at 0, 10, 50 or 250 mg/kg bw/day dermally. Because of reduced food consumption and weight loss seen in does at the highest dose tested in this study, the maternotoxicity NOEL was 50 mg/kg bw/day. In addition, a depression in mean foetal body weights was noted at the highest dose tested, together with retarded ossification of hind limb phalanges at 50 and 250 mg/kg bw/day, the findings which led to the establishment of a conservative foetotoxicity NOEL at 10 mg/kg bw/day. In contrast to the previous oral gavage study, foetotoxic events in the subsequent dermal study occurred only at maternotoxic dose levels. However, no teratogenic effect of methiocarb was observed in any of these studies.

4.14.7 Human Studies

Only one human study was found in the methiocarb toxicology database. This study investigated the effects of technical grade methiocarb following application of an unidentified quantity of the chemical to the forearm. Based on the information provided, methiocarb was classified as an irritant to the human skin, but it is not possible to grade the skin irritation, and quantify the irritant potential of the chemical due to lack of experimental details. A single

report exists of sensitisation to a methiocarb based product, but it is unclear whether the allergy was caused by the active constituent or an excipient.

4.14.8 Accidental Poisoning in Animals

Although there were no reports on human poisoning incidents involving methiocarb in the toxicology database provided, poisoning of domestic cats and dogs following ingestion of snail and slug baits containing 2% methiocarb has been reported in Australia and several other countries. A survey conducted in Australia found that snail and slug bait to be the most common cause of poisoning in dogs and cats, accounting for about 43% of accidental poisoning (Studdert, 1985). The incidence of poisoning and fatality rates were independent of body size of the animals. Similar incidents involving poultry, sheep, cattle and horses have also been reported. However, the snail and slug bait products registered in Australia at present contain a non-active ingredient denatonium benzoate (Bitrex) which is a pet deterrent. Published case reports of methiocarb poisoning in dogs and sheep indicated rapid appearance of typical cholinergic signs and successful treatment with atropine sulfate in cases accurately diagnosed in time.

4.15 NOEL Considerations

In order to establish the lowest NOEL for methiocarb, a summary of the NOELs determined in those studies deemed appropriate for regulatory purposes are presented in Table 7.

Table 7: Summary of NOELs from various studies

Study Type	NOEL (mg/kg bw/day)	LOEL and Toxic Effects
Mice 2-year dietary	Not established (<14.6 for males and <19.8 for females)	Dose related increase in MCHC values in males, elevation of leucocyte counts in females (at 14.6 mg/kg bw/day in males and 19.8 mg/kg bw/day in females)
Rats 2-year dietary	3.27 for males and 4.98 for females	Transient depression in body weight in males, elevation of reticulocyte counts in females, plasma ChE inhibition in males and RBC ChE inhibition in females (at 9.3 mg/kg bw/day in males and 13.9 mg/kg bw/day in females).
Beagle dog 2-year dietary	0.2	Plasma ChE inhibition in both sexes and reduced food consumption in females at 1.5 mg/kg bw/day.
FB strain rats Oral gavage, teratology	3.0	Reduced maternal weight gain at 10 mg/kg bw/day. No foetotoxicity was observed at the highest dose tested.
NZW rabbit Oral gavage, teratology	3.0	Maternal cholinergic signs and weight loss, and pale areas in the foetal liver at 10 mg/kg bw/day.
Chinchilla rabbit Dermal occluded, teratology	50.0 (maternotoxicity) 10.0 (foetotoxicity)	Reduced maternal food consumption and weight loss at 250 mg/kg bw/day. Retarded ossification of foetal hind limb phalanges at 50 mg/kg bw/day.

4.16 Determination of Public Health Standards

4.16.1 Acceptable Daily Intake

The current acceptable daily intake (ADI) is 0.002 mg/kg bw/day which was derived by applying a 100-fold safety factor to a NOEL of 0.2 mg/kg bw/day, based on plasma ChE depression and reduced food consumption observed in a 2-year dog study.

No change to the current ADI is proposed, as this review has not identified any other study that is more suitable for setting the pivotal NOEL, and both the current and previous evaluators have reached the same conclusion as to the value of the NOEL. Nor is there any need to revise the safety factor of 100.

In the 1998 review by JMPR, this same 2-year dog toxicity study was used to set an ADI of 0.02 mg/kg bw/day. The JMPR ADI is 10-fold higher than the Australian value because the JMPR reviewer established a NOEL at the mid-dose of 1.5 mg/kg bw/day. Plasma ChE inhibition and reduced food intake at this dose were not taken into account, and the NOEL was based on clinical signs at the highest dose. Again, a safety factor of 100 was used.

4.16.2 Acute Reference Dose (ARfD)

The acute reference dose (ARfD) is an estimate of the amount of a chemical in food or water, expressed on a body weight basis, that can be ingested over a short period of time, usually during a meal or in one day, without any appreciable health risk to the consumer on the basis of all the known facts at the time of evaluation. The studies usually considered appropriate to estimate this value are short-term dietary repeat dose studies as acute studies only report a very limited number of end-points. Prior to this review no Acute Reference Dose (ARfD) had been established for methiocarb. An ARfD of 0.03 mg/kg bw/day has been determined from the review 2 developmental toxicity studies in rats and rabbits with a safety factor of 100 being applied to the No Observable Effect Level (NOEL).

4.16.3 Poisons Scheduling

Prior to this review, methiocarb was placed in Schedule 6 of the SUSDP and in Schedule 5 for pelleted preparations containing 2% or less of the active ingredient. The 75% wettable powder formulations were covered by the S6 classification.

The previous classification for methiocarb was established prior to the submission of numerous acute oral toxicity studies in rats, over a half of them demonstrating LD_{50} values of 50 mg/kg bw or less, ranging down to 9 mg/kg bw. Examination of the data has not revealed any aspect of the experimental methods which would account for the wide range (9-135 mg/kg bw) of oral LD_{50} values in rats. Consequently, there is no basis upon which to discount any of these studies from being used for regulatory purposes. Estimates of acute oral LD_{50}s in guinea pigs lie between 12 and 100 mg/kg bw, while the corresponding value in dogs is approximately 25 mg/kg bw. Given that the acute oral toxicity of methiocarb appears to have been hitherto underestimated, it was recommended that its Poisons Schedule classification be amended from S6 to S7. The fact that the worst inhalation LC_{50} for methiocarb [433 mg/m^3 (4 h) in female rats] also lies within the criterion for S7, further justifies the proposed revision.

No toxicology studies have been performed with the Australian registered 750 g/kg WP formulations, but the worst rat oral and inhalation LD and LC_{50} values for 75% test

formulations were 23 mg/kg bw and 403 mg/m^3, respectively. A cut-off to S6 for the 750 mg/kg WP formulations would therefore appear to be unwarranted.

Again, the only experimental acute toxicity data available for 20 g/kg pellets is derived from a test formulation that differs from Australian registered products. However, its toxicology characteristics are consistent with the existing S5 status.

The NDPSC consider methiocarb at its May, 2000 meeting and determined that Technical grade methiocarb is in schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Formulations containing methiocarb 20% or less have been placed in schedule 6, while those products containing 2% or less methiocarb will remain in schedule 5 of the SUSDP. Existing products have already had their labels amended to reflect these scheduling changes.

4.16.4 Proposed Safety Directions

750 g/kg wettable powder (WP) formulations

750 g/kg wettable powder formulation sold in commercial packs, used for the control of snails, slugs, hibiscus flower beetle, garden weevil and glasshouse sciarids (fungus gnats) and for repelling birds on ornamental plants. These products are applied by spray to grapevines, oranges, ornamentals and hibiscus at a dilution from 100 to 200 g/100 L, or to poppies at 5.5 kg/ha, and to ornamentals as a soil drench at 300 g/100 L. The spraymix is prepared by mixing the product with water in a bucket before addition to the partly filled spray tank under agitation. Label directions recommend use of boom spray or air mist equipment for application. The most probable route of exposure to mixer/loaders would be dermal contact with the powder or concentrated premix, whereas spray operators would be exposed to the dilute spray mix by inhalation and dermal contact.

No toxicology studies have been performed with the Australian registered products of 750 g/kg WP formulation. By extrapolation from the individual acute toxicity profiles of methiocarb and the non-active constituents present in the product, it is anticipated that this product would have high to moderate acute oral toxicity (based on a 75% methiocarb content and taking into account the full range of its rat LD_{50} values), low acute dermal toxicity, and moderate acute inhalation toxicity. These products would also be expected to cause slight eye and skin irritation and there is no evidence that it would cause dermal sensitisation, although relevant data on the non-active constituents are lacking.

Two 750 g/kg methiocarb powder formulations have been subjected to acute toxicity studies. Both of these formulations contain non-active constituents that differ from those present in Australian formulations. Methiocarb 75% Concentrate yielded an oral LD_{50} of 82 mg/kg bw in male rats and 23 mg/kg in females, while Methiocarb 75% WP/Seed Treatment demonstrated values of 100-130 and 60-140 mg/kg bw in male and female rats, respectively. Both formulations caused slight eye irritation in rabbits. Methiocarb 75% concentrate was not a skin sensitiser in guinea pigs. In these respects, the toxicological characteristics of the two test formulations are consistent with those extrapolated for Australian 750 WP formulations. Both test formulations were non-irritant to the rabbit skin.

Although Methiocarb 75% Concentrate had a worst acute dermal LD_{50} of 704 mg/kg bw in female rabbits and an inhalation LC_{50} of 403 mg/m^3 (4 h) in female rats, markedly lower

dermal and inhalation toxicity was observed with Methiocarb 75% WP/Seed Treatment. These were, respectively, >5000 mg/kg bw in rabbits and >20000 mg/m^3 (1 h) in rats. Differences between the non-active constituents do not explain these discrepancies between the two test formulations. Droplet/particle sizes were not measured in the inhalation toxicity study with Methiocarb 75% WP/Seed Treatment, and so methodological deficiencies may account for the apparently high LC_{50} value obtained. By contrast, droplet sizes were measured in the corresponding study with Methiocarb 75% Concentrate, and so its results are considered as being more reliable. There is no explanation as to why Methiocarb 75% Concentrate had markedly greater dermal toxicity than Methiocarb 75% WP/Seed Treatment. Given that the dermal toxicity study on Methiocarb 75% Concentrate was GLP-compliant and much more recent than those performed with Methiocarb 75% WP/Seed Treatment (1988 vs. 1972-79), its results are preferred.

Therefore, safety directions have been set assuming that Australian 750 WP formulations have moderate to high oral toxicity, moderate dermal and inhalation toxicity, and is a slight skin and eye irritant, but not a dermal sensitiser.

The principal hazards of 750 g/kg WP formulations to the operator are expected to be dermal and inhalation toxicity when opening the container and preparing the spraymix. Given that dilution rates of 333-fold or greater are used, the toxicological hazard posed by the spray mixture will be low.

The current safety directions for 750 g/kg WP formulations are shown in Table 8.

Table 8: Current safety directions

WP 750 g/kg or less	
Product is poisonous if absorbed by skin contact or swallowed	120 130 131 133
Avoid contact with eyes and skin	210 211
Do not inhale dust or spray mist	220 221 223
When preparing wear elbow-length PVC gloves face shield	279 281 290 294 296
If product on skin, immediately wash area with soap and water	340 342
After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water	350
After each day's use, wash gloves and face shield	360 361 362

Given that the 750 g/kg WP products is expected to be of high to moderate acute oral toxicity, addition of the 100 ("Very dangerous") statement is warranted, together with the warning statement 132 ("inhaled"). A 160 162 164 statement ("May irritate the eyes and skin") should be added in view of the anticipated slight dermal and ocular irritancy of the product. It is noted there is currently no precaution statement 373 ("Obtain an emergency supply of atropine sulfate 0.6 mg"). The 373 statement should be added because of the potent anticholinesterase effects of methiocarb and the high level at which it is present in the product.

The revised warning statements* for 750 g/kg WP formulations, based on toxicological hazard alone, are presented in Table 9.

Table 9: Proposed Safety Directions

WP 750 g/kg or less	
Very dangerous	**100**
Product is poisonous if absorbed by skin contact, **inhaled** or swallowed	120 130 131 **132** 133
May irritate the eyes and skin	**160 162 164**
Avoid contact with eyes and skin	210 211
Do not inhale dust or spray mist	220 221 223
When preparing wear elbow-length PVC gloves face shield	279 281 290 294 296
If product on skin, immediately wash area with soap and water	340 342
After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water	350
After each day's use, wash gloves and face shield	360 361 362
Obtain an emergency supply of atropine tablets 0.6 mg	**373**

*The statements shown in bold text are those recommended in the present review.

20g/kg bait formulations (commercial packs)

No toxicology studies have been performed with 20g/kg bait formulations. By extrapolation from the toxicity of methiocarb and the non-active constituents present in the product, it is expected to be of moderate to very low acute oral toxicity (taking into account the full range of LD_{50} values for methiocarb), low acute dermal and very low inhalation toxicity, and slight eye irritancy, and not to cause irritation to the skin. Dermal sensitisation data are lacking on most of the non-active constituents, except for Bitrex (denatonium benzoate), which is a sensitiser at 10% w/v in guinea pigs. However this agent is present in the product at a very low concentration, and is therefore unlikely to pose a significant sensitisation hazard.

A 2% methiocarb slug and snail pellet test formulation was of very low oral toxicity in rats, low dermal toxicity in rabbits, did not cause any deaths in rats when inhaled at 835 mg/m^3, was a slight eye irritant in rabbits but did not irritate the rabbit skin. A dermal sensitisation study was not performed. These results are consistent with the anticipated toxicological characteristics of 20 g/kg bait formulations.

The principal hazards to the user from the product would therefore be expected to arise from skin or eye contact with any dusts that may be generated during loading and application. Eye irritation is considered to be the most probable hazard. The current safety directions for 20g/kg bait formulations (in commercial packs) are presented in the Table 10.

Table 10: Current Safety Directions

BA 20 g/kg or less	
Poisonous if swallowed	130 133
Avoid contact with eyes and skin	210 211
If product on skin, immediately wash area with soap and water	340 342
After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water	350
Obtain an emergency supply of atropine tablets 0.6 mg	373

Given that these bait formulations are expected to be a slight eye irritant, a 160 162 ("May irritate the eyes") statement should be added. Otherwise, the existing warning statements for the product are considered appropriate, from a toxicological viewpoint.

The revised warning statements* for 20g/kg bait formulations (in commercial packs), based on toxicological hazards alone, are provided in Table 11.

Table 11: Proposed Safety Directions

BA 20 g/kg or less	
Product is poisonous if swallowed	**120** 130 133
May irritate the eyes	**160 162**
Avoid contact with eyes and skin	210 211
If product on skin, immediately wash area with soap and water	340 342
After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water	350
Obtain an emergency supply of atropine tablets 0.6 mg	373

*The statement recommended in the present review is shown in bold text.

20g/kg bait formulations (home garden packs less than 1 kg)

Although these home garden products are the same as the commercial bait formulations, no safety directions are currently specified**,** consistent with small size (≤1 kg) pack size and the fact that domestic users will be treating smaller areas for shorter durations than agricultural users, the potential for exposure will be low. However, as the toxicological profile of these products are similar to that of commercial products, and there is some potential for dermal contact with the pellets when opening and closing the container or scattering its contents, it is appropriate to include a 351 ("Wash hands after use") statement on the respective product labels.

The warning statements recommended for 20g/kg bait formulations (home garden packs less than 1 kg), based on toxicological hazards alone, are provided in Table 12.

Table 12: Proposed Warning statements

BA 20 g/kg or less (1 kg pack or less)	
Wash hands after use	351

4.16.5 First Aid Instructions

At present, the standard statements 'a' and 'h' are specified in the First Aid Instructions and Safety Directions Handbook for Agricultural and Veterinary Chemicals (TGA, 1999). No changes to the current first aid instructions are proposed.

4.16.6 Conclusion

The toxicological evaluation found that product labels do not contain adequate instructions with regards to the safe handling of the product and proposes that the instructions are varied by including further safety directions and warning statements.

The toxicological evaluation concluded that provided product labels are varied as proposed, then the APVMA could be satisfied that continued use and other dealings of the active methiocarb, and products containing methiocarb would not be likely to have an effect that is harmful to human beings.

5 OCCUPATIONAL HEALTH AND SAFETY

5.1 Introduction

The Occupational Health and Safety (OHS) review of methiocarb is based on the hazard assessment, information obtained from: Industry submissions, responses to an APVMA user questionnaire, state agriculture departments, published literature and overseas reviews.

5.2 Use Patterns

Commercial use patterns of methiocarb products are summarised in Table 13.

Table 13: Use Pattern of Registered Methiocarb Products

Crop/ Situation	Product: application rate/dilution	Alternative chemicals/ strategies used*	Comments/ label instructions	Application methods
Grapevines	**750 WP**: 100 g/100 L or 200 g/100 L	N/A	Applied at or before flowering	Boom or air mist Orchard type spraying equipment**
Oranges	**750 WP**: 100 g/100 L	metaldehyde (citrus)	Apply as a cover spray when pests become apparent	Although this is a label use, most applications to orchards (including oranges) are expected to be by hand distribution of pellets (**20 BA**)**
Hibiscus	**750 WP**: 100 g/100 L	N/A	Spray when beetles are first seen and 3 days later to control beetles in tight buds	Cover spray**
Ornamentals	**750 WP**: 300 g/100 L or 200 g/100 L	N/A	Higher rate applied as a soil drench (Ag report specifies an application volume of 2 L/m^2), lower rate applied as a cover spray	Cover or spot spray** Hand wand connected to mobile powered spray equipment **
Poppies	**750 WP**: 5.5 kg/ha	N/A	Applied at seedling stage as a "thorough spray"	Cover spray**
Gardens	**20 BA**: 100 pellets per m^2	N/A	Sprinkle evenly onto ground. Heaping is unnecessary and wasteful	Assumed to be applied by hand**
Berry crops, cereals, gardens, nurseries, oilseed crops, orchards, pastures, vegetable crops	**20 BA**: 5.5 kg/ha or 11-22 kg/ha	metaldehyde (avocado, pulses, cereals, pasture)	Lower rate used for most infestations, higher rate for heavy infestations or tall/dense pasture Gloves should be worn when pellets are spread by hand	Applied by hand, fertiliser spinners, combines or sod seeders Hand distribution around vine butts or along the rows**
Sunflowers	**20 BA**: 2.5 kg/ha (10 pellets/m^2)	N/A	Scatter evenly on ground 1-3 days after sowing	Method not specified, assumed to be as above

Information derived from labels unless otherwise indicated
* Information provided by survey respondents
** Information provided by APVMA (Agricultural assessment)
N/A – not available
750 WP: wettable powder containing 750 g/kg methiocarb
20 BA: bait containing 20 g/kg methiocarb

The frequency of application is not specified on product labels. Information from survey respondents suggests a range of application frequencies from less than once per year to 2 applications per year for all label situations. Although application frequencies are low, work is generally conducted on consecutive days to cover large treatment areas.

5.3 Occupational Exposure and Risk Assessment

The occupational risk assessment takes into consideration the hazard of the chemical as determined by toxicology testing, its use pattern in Australia and worker exposure for each exposure situation.

In order to adequately determine the risk associated with the end use or post-application exposure to methiocarb, Margins of Exposure (MOE) were calculated by comparing the most appropriate NOELs with exposure data obtained from end use exposure data (surrogate exposure studies, predictive modelling or exposure database estimates) or post-application exposure data (measured exposure studies or dislodgeable foliar residue data).

The main acute health effect of methiocarb exposure is ChE inhibition with clinical effects characteristic of other carbamates. To estimate methiocarb risk, a rabbit dermal No Observable Effect Level (NOEL) (60 mg/kg bw/day) was available to assess risk from dermal exposure, while a rat inhalational study was considered suitable to estimate risk from inhalation exposure (NOEC 6 mg/m^3). The NOEC (6 mg/m^3) was converted to a daily systemic dose by assuming that the respiratory volume/h and bodyweight of the rats was 0.01 m^3 and 0.23 kg respectively (ie. 6 mg/m^3 x 0.01 m^3/h x 6 h/day (exposure duration)/0.23 kg = 1.6 mg/kg bw/day).

Where a human NOEL is used to estimate risk, MOE of approximately 10 or more are considered to be acceptable, to account for intra-species (10x) variability. For animal NOEL, MOE of approximately 100 or more are considered to be acceptable, to account for intra-species (10x) and inter-species (10x) variability. The methiocarb risk assessment relies on animal data only, therefore MOE of 100 or more are considered to represent acceptable risk.

5.3.1 End Use Exposure

Methiocarb products are used in a number of crop and garden situations. To facilitate the exposure assessment and risk assessment, rather than consider each individual use situation separately, exposure scenarios were developed, coded and grouped where possible according to application method. This allows maximisation of available data and simplifies the assessment.

Methiocarb is available in two different formulation types to be used outdoors as a foliar spray, a soil drench or bait. The extent of exposure is dependent on the formulation type and method of application. On the whole, exposure is expected to be limited to inhalation and dermal exposure during mixing/loading (if applicable) and application.

The agricultural exposure scenarios identified for use of methiocarb are summarised in Table 14.

Table 14: Agricultural Exposure Scenarios

Scenario (1) Mixing/loading and application of WP by mechanical application
Scenario (2) Mixing/loading and application of WP by hand held application - soil drench
Scenario (3) Mixing/loading and application of WP by hand held application - cover spray
Scenario (4) Application of BA by mechanical applicator - orchard applications
Scenario (5) Application of BA by mechanical applicator - broadacre applications
Scenario (6) Application of BA by hand distribution - all situations

The following table details the use pattern parameters identified for use in the occupational exposure assessment.

Table 15: Use Pattern Parameters used in Exposure Assessment

Situation	Scenario number and description	Product application rate, spray volume and concentration of ai in spray	Work rate	Total ai handled per day
ornamentals (nurseries, cut flowers, greenhouses, poppies, hibiscus) vineyards orchards (including oranges)	**Scenario (1)*** Mixing/loading and application of **WP** by mechanical application	150 g/100 L 2000 L/ha (2.25 kg ai/ha) 0.11%[1]	12 ha/6 hr/day [2]	27 kg
	Scenario (2)* Mixing/loading and application of **WP** by hand held application - soil drench	300 g/100 L 2 L/m^2 (45 kg ai/ha) 0.23%[3]	0.1 ha/6 hr/day (vehicle mounted spray tank) [4]	4.5 kg
			0.02 ha/6 hr/day (knapsack tank)**	0.9 kg
	Scenario (3)* Mixing/loading and application of **WP** by hand held application - cover spray	200 g/100 L 2000 L/ha (3 kg ai/ha) 0.15%[5]	0.5 ha/3 hr/day (vehicle mounted spray tank)[6]	1.5 kg
			0.2 ha/6 hr/day (knapsack tank)**	0.6 kg
gardens broadacre crops (cereals, sunflower, oilseeds, pasture) ornamentals (nurseries, cut flowers, greenhouses) orchards (including oranges) vegetable crops berry crops	**Scenario (4)** Application of **BA** by mechanical applicator - orchard applications	5.5 kg/ha[7]	5 ha/2 hr/day[8]	0.55 kg
	Scenario (5) Application of **BA** by mechanical applicator - broadacre applications	17 kg/ha[9]	5 ha/2 hr/day[10]	1.7 kg
	Scenario (6) Application of **BA** by hand distribution - all situations	5.5 kg/ha[11]	2 ha/2 hr/day[12]	0.22 kg

* open mixing and loading using non-water soluble 400 g packs

** area to be treated is limited by total spray volume achievable using knapsack per day: 400 L (default maximum used in UK Predictive Operator Exposure Model)

[1] mean label rate; spray volume based on APVMA advice (airblast application in cherries); equivalent to 3 kg product/ha

[2] based on survey information; crop areas ranged from 1-50 ha for orchards

[3] label rate for soil drench; spray volume based on APVMA advice for application by soil drench

[4] based on survey information for nurseries and greenhouses; average crop area 1 ha; soil area to be treated expected to be a fraction of total crop area, assumed 10%

[5] label rate for cover spray; spray volume based on volume for mechanical applications

[6] based on survey information for flowers (cut flowers, gerberas, roses); most ornamentals grown in small areas (~1 ha), poppies grown in larger areas (over 50 ha)

[7] label rates for most orchard infestations

[8] based on survey information for orchards; crop areas ranged from 1-50 ha for orchards

[9] mean label rate for tall/dense pasture (11-22 kg/ha)

[10] based on survey information for applications by fertilizer spreaders; broadacre crop area ~200 ha

[11] application rate for the majority of label situations

[12] based on survey information for hand applications; APVMA advice suggests up to 50 ha of vegetable crops are treated by hand, mean vegetable farm size reported in survey ~30 ha

End Use Risk Assessment – Wettable Powder Formulation

Scenario (1) Mixing/loading and application of WP by mechanical application

Mechanical application of WP methiocarb as a cover spray is expected to be limited. The label suggests grapevines and oranges may be treated this way. Mechanical application of

WP involves workers mixing the product with water and applying the final spray mixture by orchard sprayer.

Exposure estimates for this scenario are based on applications by orchard sprayer. Applications by boom spray or mister are indicated on the label but are uncommon and unlikely to result in any additional exposure.

The exposure assessment for this scenario relied on PHED data. The risk assessment results showed similar MOE for mixer/loader or applicators based on PHED with a value of 154 and 189 respectively. The majority of exposure occurred during application, with dermal exposure contributing the most to risk. Exposure during mixing/loading was also significant, with the majority of the risk associated with inhalation exposure. The use of a face shield is recommended on the current safety directions. However a dust mask will offer better protection during mixing/loading as the product is in powder form.

The overall conclusion is that mixer/loader/applicators applying WP formulation by mechanical application will not be adequately protected when using the product according to current label instructions (including safety directions: face shield and PVC gloves during spray preparation).

The risk assessment indicated that these workers would be protected if they wear cotton overalls and gloves during both mixing/loading and application and a dust mask/face shield during mixing/loading and application respectively.

Scenario (2) Mixing/loading and application of WP by hand held application - soil drench

Methiocarb WP formulation will be applied as a soil drench to ornamentals including nurseries, cut flowers, greenhouses, poppies and hibiscus. Applications are expected to be made either with a vehicle-mounted spray gun or for smaller areas by knapsack sprayer.

The exposure assessment for this scenario relied on POEM and PHED data. The POEM data represent outdoor applications while the PHED data represent indoor applications.

Outdoor knapsack and vehicle-mounted applications

POEM showed unacceptable risk for workers using methiocarb as a soil drench by either knapsack or vehicle-mounted spray gun.

The overall conclusion is that mixer/loader/applicators applying WP formulation outdoors by soil drench will not be adequately protected when using the product according to current label instructions (including safety directions: face shield and PVC gloves during spray preparation).

In order to reduce risk to an acceptable level workers should wear cotton coveralls, a dust mask and gloves during mixing/loading and chemical resistant overalls, face shield and gloves during application.

Indoor knapsack applications

PHED data showed unacceptable risk for workers using methiocarb as a soil drench by knapsack. There was however a large discrepancy between data generated from individual

mixer/loader and applicator data sets compared to data generated from the combined mixer/loader/applicator data set. Given the uncertainty of the PHED data the more conservative estimates will be used. These estimates indicate the need to reduce inhalation exposure in order to reach an overall acceptable risk level.

The use of a face shield is recommended on the current safety directions for mixer/loaders only. As the relative contributions of inhalation exposure during mixing/loading or application cannot be determined, applicator inhalation exposure should also be minimised as much as possible.

The overall conclusion is that mixer/loader/applicators applying WP formulation indoors by soil drench will not be adequately protected when using the product according to current label instructions (including safety directions: face shield and PVC gloves during spray preparation).

In order to reduce risk to an acceptable level, workers should wear cotton coveralls, gloves and respiratory protection during mixing/loading and application.

Scenario (3) Mixing/loading and application of WP by hand held application - cover spray

Methiocarb WP formulation will also be applied to ornamentals as a cover spray. As with soil drench applications, either vehicle-mounted spray guns or knapsack sprayers will be used. The product is applied at a much lower application rate and lower final spray concentration than in scenario (2) and this is reflected in the lower estimated risks.

The exposure assessment for this scenario relied on sponsor supplied surrogate data as well as OCS generated model (POEM) and database (PHED) data. Outdoor applications are represented by the POEM data. Indoor applications are represented by surrogate and PHED data.

Outdoor applications using vehicle-mounted spray guns and knapsack

POEM data were the only source available for this situation. Vehicle mounted spray tank with H-nozzle was considered relevant for this exposure estimation (as this is a worst case scenario, this can be used for outdoor knapsack application also). It showed acceptable risk for workers wearing their own clothing and gloves during mixing/loading and application.

The overall conclusion is that mixer/loader/applicators applying WP formulation as a cover spray using vehicle-mounted spray guns will not be adequately protected when using the product according to current label instructions (including safety directions: face shield and PVC gloves during spray preparation).

In order to reduce risk to an acceptable level workers should wear cotton overalls and gloves during mixing/loading (and a dust mask) and application (and a face shield).

Indoor knapsack applications

The sponsor provided surrogate data showed acceptable risk for workers applying WP formulation to high or low crops in greenhouses by knapsack, while wearing protective clothing and gloves.

Given the uncertainties associated with the sponsor provided data, the overall risk assessment relies more on PHED data.

The overall conclusion is that mixer/loader/applicators applying WP formulation as a cover spray by knapsack will not be adequately protected when using the product according to current label instructions (including safety directions: face shield and PVC gloves during spray preparation).

Given that PHED data indicate significant inhalation exposure relative to total exposure, inhalation exposure during both mixing/loading and application should be minimised as much as possible.

In order to reduce risk to an acceptable level workers should wear cotton overalls, respiratory protection and gloves during mixing/loading and application.

End use risk assessment – bait formulations

The exposure assessment of BA formulations relied on PHED data only. No other data were available in the literature or provided by the sponsor. Additionally, POEM was not suitable for this product or application type.

The safety directions for BA products do not recommend gloves or any other PPE. PHED data generated for workers using mechanical application equipment was estimated for workers wearing normal work clothing and no gloves. PHED data for workers applying bait by hand were estimated for workers wearing normal clothing and gloves. This was done because there were no data available for workers without gloves. The data are considered relevant because gloves are currently recommended on the product labels for hand application, although the recommendation is not located in the safety directions. Given that the risk assessment relied only on one data source, exposure for workers wearing protective clothing and gloves was also estimated and served as a comparison.

Baits containing methiocarb will be applied to gardens, broadacre crops (cereals, sunflower, oilseeds and pasture) ornamentals (nurseries, cut flowers and greenhouses) orchards (including oranges) vegetable crops and berry crops. All of these crops may be treated by either mechanical applicator (sod seeder, combine, fertiliser spreader) or by hand distribution. The mechanical applications are separated into two scenarios based on different application rates for different crops (scenario (4) and (5)). These two scenarios cover exactly the same application methods and therefore rely on the same PHED data for their exposure estimates. The third scenario (scenario (6)) covers the application of bait by hand application to any of the label crops.

Scenario (4) Application of BA by mechanical applicator - orchard applications, and **Scenario (5)** Application of BA by mechanical applicator - broadacre applications

PHED estimates for workers applying methiocarb baits by tractor mounted equipment or hand held/pulled equipment showed acceptable risk to workers wearing long pants, long sleeved shirt and no gloves. Australian workers are expected to wear similar clothing during the working day, although there may be exceptions. Tractors with open cabs showed greater risk to applicators than tractors with closed cabs, but in both cases risk was very low.

The lowest MOE was 150, obtained for operators using hand operated equipment and applying product at the higher application rate. This level of risk suggests that workers wearing less clothing than that specified above could be exposed to unsafe levels of product.

The overall conclusion is that the risk during mechanical applications of bait is acceptable provided workers' clothing is appropriate. Label safety directions should be amended to recommend the use of cotton overall (ie one layer of protection).

Scenario (6) Application of BA by hand distribution - all situations

PHED estimates for workers applying methiocarb baits by hand distribution showed unacceptable risk to workers wearing long pants, long sleeved shirt and gloves. An estimate based on workers wearing cotton overalls and gloves showed acceptable risk.

5.4 Post-application Exposure

The potential for exposure will exist during worker re-occupation of treated crops. The level of exposure will be dependent on a number of factors, including the amount of active applied, the timing of the post-application activity, the nature and duration of the work done, as well as ambient (atmospheric) conditions.

Limited information was available to estimate re-entry worker exposure following methiocarb use. Measured re-entry exposure, dislodgeable residue and dissipation data which are relevant for the assessment of re-entry exposure are described below.

5.4.1 Post-application Risk Assessment – Wettable Powder Formulation

There are no re-entry periods on the current label for WP formulation. The available studies indicate an unacceptable risk for workers handling treated blueberry or grapevine foliage until 6 or 28 days after treatment, respectively.

Vineyards and orchards

Methiocarb is used in vineyards and orchard as a cover spray or tree butt treatment.

Based on label withholding periods, vineyards will not be harvested for 6 weeks after application, while citrus orchards will not be harvested for 9 weeks after application. Additionally, the label states that grapevine leaves are not permitted to be used for human consumption.

Under normal use situations significant foliar contact is not expected until harvest time. However to prevent any dermal contact during other activities (such as pruning or crop checking), a re-entry period of 28-days should be included on the label. Workers will be required to wear protective clothing and chemical resistant gloves if prior entry is required.

Inhalation exposure is not a significant concern for re-entry workers given that the chemical has low volatility and outdoor locations should have adequate natural ventilation.

Ornamentals – cover spray

There is no withholding period for ornamentals. The labels advise that methiocarb may be used as a cover spray in nurseries and does not exclude use in greenhouses for the control of a variety of pests. Methiocarb has also been used under permit for control of Western flower thrips used as a cover spray. Crop handling may be required soon after spraying and may be intensive, particularly in the cut flower industry.

The available information indicates an unacceptable risk for workers handling treated blueberry or grapevine foliage until 6 or 28 days after treatment, respectively. In the absence of crop specific data, these results will be used as a rough estimate of dermal exposure to nursery workers handling treated ornamentals. Based on this information, a re-entry period of 28-days should be included on the label. Workers will be required to wear protective clothing and chemical resistant gloves if prior entry (or rehandling) is required.

Dermal exposure to soil could be significant during some nursery activities, such as plant re-potting. No information is available to assess the risk to workers handling treated soil. Given that most of the spray will be deposited on the foliage, the PPE requirements recommended above may be adequate to protect workers from dermal exposure to soil residues.

Workers entering treated greenhouses/glasshouses soon after application may be exposed to significant amounts of methiocarb in the air. However, given the chemical's low volatility air concentrations should not be significant after the enclosures have been ventilated.

Ornamentals – soil drench

Ornamentals are the main crops to be treated by soil drench. The application rate is much higher for this method compared to cover spray (15-20 times), contact with plant foliage is unlikely.

Given that:

(i) there is potential for exposure to soil by nursery workers (eg during re-potting activities),

(ii) the application rate is high, and

(iii) no information is available to assess the risk to workers from treated soil,

Continued use of methiocarb by soil drench cannot be supported.

5.4.2 Post-application Risk Assessment – Bait Formulations

Crops treated with BA formulations include berry crops, cereals, gardens, nurseries, oil seed crops, orchards, pastures, vegetable crops and sunflowers. The current BA labels advise that edible crops should not be harvested for 7 days after application and treated areas should not be grazed or cut for stock food for 7 days after application.

There are no data available to assess the post-application risk to workers following bait application to these crops. The application rate for BA formulations is similar to WP formulation (2.25-45 kg ai/ha and 5.5-17 kg ai/ha, respectively). However, as the product is not expected to come in contact with crop foliage, data from the sponsor studies cannot be extrapolated to this situation.

Given the method of application (bait distribution), most of the applied product will be present on or in the soil surrounding the plants. Shoes or boots worn by re-entry workers are expected to provide adequate protection in most situations. Exposure may however be significant during activities that involve direct contact with the soil, such as during manual harvest of vegetable crops (eg carrots) or during some nursery activities (re-potting of plants).

Most vegetables are harvested mechanically, however manual harvesting is also conducted when checking for optimal harvest times. In these situations relatively small sample sizes are involved. The withholding period for edible crops (7 days) is expected to provide adequate protection for workers involved in manual harvest.

There is no information available to quantify the risk to nursery workers during re-potting activities.

However, as indicated above workers will be required to wear protective clothing and chemical resistant gloves if prior entry (or rehandling) is required.

A re-entry statement is recommended for BA products in pack sizes greater than 1 kg on the basis that these packs would be used commercially. Methiocarb (BA) products in pack sizes under 1 kg currently do not require any safety directions.

5.5 Conclusion

The end use risk assessment indicated that use of methiocarb products according to current label directions will result in unacceptable risk to workers in the following situations:

- All uses of methiocarb wettable powder
- Hand distribution of methiocarb baits
- Post application activities associated with ornamental soil drench

However, all registered end uses (except soil drench) are considered to provide acceptable margins of exposure provided that:

- exposure mitigation methods specified earlier are instituted where applicable
- the products are used in accordance with label instructions recommended above
- safe work practices are followed

The OH&S evaluation found that there are unacceptable risks for worker exposure. However, it was concluded that for all uses, except ornamentals as a soil drench, the risks can be mitigated if labels are varied to include new safety directions, re-entry statements and to require specified PPE

The risk to workers re-handling treated soil following use on ornamentals as a soil drench was unable to be determined due to no available information. Consequently the APVMA cannot be satisfied that continued use of methiocarb in ornamentals treated by soil drench in not an undue hazard to the safety of workers exposed to it. It is proposed that this use be deleted from labels.

The occupational health and safety evaluation found that the APVMA could not be satisfied that the continued use of products containing methiocarb in all situations as currently permitted would not be an undue hazard to the safety of workers exposed to it during its

handling. The evaluation proposes that instructions on product labels be varied by deleting the use on ornamentals as a soil drench. The occupational health and safety evaluation also found that product labels did not contain adequate instructions with regards to the safe handling of the product and re-entry to treated crops and proposes that labels be varied to include further safety directions and re-entry period after the use of the product.

The occupational health and safety evaluation concluded that provided that labels are varied as proposed then the APVMA could be satisfied that continued use and other dealings of the active methiocarb and products containing methiocarb would not be an undue hazard to the safety of people exposed to it during handling.

The following table summarises all end use situations and the required regulatory action.

Table 16: Proposed Regulatory Action – End Use

End use	**Relevant mitigation method/label requirement**
Mechanical application of **WP**	Cotton overalls, dust mask/face shield and gloves
Hand spraying of **WP** as cover spray	Cotton overalls and dust mask during mixing/loading and chemical resistant overalls, gloves and face shield during application
Hand spraying of **WP** as a soil drench or	Not supported
Mechanical application of **BA**	Cotton overalls
Hand distribution of **BA**	Cotton overalls and gloves

The post-application risk assessment indicated that the risk to most (except for soil drench use) re-entry workers will be acceptable, provided the following re-entry statements are included on all methiocarb WP products and BA products over 1 kg:

RE-ENTRY TO TREATED AREA: DO NOT PERMIT re-entry until 28 days after application. If prior entry (or rehandling) is required, wear cotton overalls buttoned to the neck and wrists and elbow length PVC gloves. Clothing must be laundered after each day's use.

6 RESIDUES

6.1 Introduction

This report considers residues aspects of methiocarb in human food and animal feed crops from commercial uses only, however use in the home garden situation may be effected as a result of the findings for the commercial uses.

The Pesticides and Agricultural Chemicals Committee (PACC) first considered methiocarb in 1971 for home garden uses. MRLs were recommended for grapes, wine, cherries, oranges, berry fruit, stone fruit and vegetables between 1979 and 1988. A summary of the PACC proceedings is presented in Volume 2 of this report..

6.1.1 Current MRLs

Australian MRLs[1] for methiocarb are listed below.

Table 1 of the MRL standard

Commodity	MRL (mg/kg)
Citrus fruits	0.1
Fruits (except citrus fruits; grapes)	T0.1 (T-temporary)
Grapes	0.5
Vegetables	0.1
Wine	0.1

Table 5 of the MRL standard

-In baits for the control of garden pests

T -In baits for the control of garden pests on herbs, lemon balm, lemon grass, kaffir lime leaves, lemon verbena and tumeric

The Australian residue definition is:

Methiocarb Sum of methiocarb, its sulfoxide and sulfone, expressed as methiocarb.

6.1.2 Maximum Treatment Regime

The maximum treatment regime for methiocarb on food and animal feed crops, as shown on labels of currently registered products, are summarised below. Most respondents to the Agricultural Assessment questionnaire indicated that treatment is required once or twice per season/year.

[1] MRL Standard, as at June 2004.

Table 17: Maximum Treatment Regime

Formulation type	Crops	Maximum application rate
20 g/kg bait	Berry crops (incl grapevines) Cereals Oilseeds Orchards Pastures Vegetables [1]	22 kg product/ha (440 g ai/ha)
	Gardens	100 pellets/m^2 (500 g ai/ha)
750 g/kg WP	Grapevines (foliar spray)[2]	200 g product/100 L (150 g ai/100 L)
	Grapevines (butt treatment)[3] Oranges	100 g product/100 L (75 g ai/100 L)

[1] When applying in vegetable crops ensure pellets do not become lodged in foliage.
[2] Apply as a cover spray at or before flowering using boom spray or mist equipment. A second spray 3 weeks later may be required.
[3] Apply as a cover spray when pests become apparent. Only spray the butt of grapevine.

Withholding periods and restraints

20 g/kg baits
Edible crops:
DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION
Treated areas:
DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 7 DAYS AFTER APPLICATION

750 g/kg WP (spray)
Citrus fruits:
DO NOT HARVEST FOR 6 WEEKS AFTER APPLICATION
Grapes:
DO NOT HARVEST FOR 9 WEEKS AFTER APPLICATION

The following statement also appears on the label of the 750 g/kg WP product: "Grapevine leaves treated with Mesurol 750 must not be used for human consumption"

Home garden products:
DO NOT PICK EDIBLE PLANTS FOR 7 DAYS AFTER APPLYING

The following restraint appears on the label of all products:

DO NOT TREAT AREAS ON WHICH POULTRY GRAZE

6.1.3 Residue Monitoring Data

Results of residue testing carried out by the Victorian Department of Natural Resources and the Environment were reported in the Agricultural Assessment for methiocarb. Between 1987 and 1996, 1 of 44 grape, 3 of 31 cherry, 1 of 6 broccoli, and 1 of 3 cauliflower samples tested contained detectable methiocarb residues. Only the single broccoli sample contained methiocarb residues above the MRL. In addition, 23 of 23 grape samples tested in 2001-2001 contained residues below the limit of detection.

No methiocarb residues were detected in strawberries (23 samples tested), blackberry (1), lemon (7), orange (3), avocado (4), kiwifruit (5), apple (6), nashi fruit (1), pear (6), apricot (4), nectarine (7), peach (4), plum (5), leek (2), onion (1), Brussels sprout (2), cabbage (2), honeydew melon (3), jam melon (1), melon (1), pumpkin (1), rockmelon (3), watermelon (2), zucchini (3), Chinese cabbage (1), lettuce (14), silverbeet (1), capsicum (3), sweetcorn (2), tomato (10), carrot (9), parsnip (1), potato (7), celery (3) and rhubarb (1).

Results of analysis of fruit and vegetable samples purchased weekly from the Sydney wholesale markets from 1989 to 1995 were reported by the JMPR in 1999; the results are reproduced in Table 18.

Table 18: Residue Analysis of Fruit and vegetable Samples – Sydney 1989-1995

Commodity	No. of samples	No. with residues >0.01 mg/kg
Grapes	94	5 (< MRL of 0.1 mg/kg)
Strawberries	113	1 (< MRL of 0.1 mg/kg)
Citrus	1	0
Apples	1	0
Pears	2	0
Cherries	48	0
Nectarines	28	0
Peaches	139	0
Onion	1	0
Broccoli	2	0
Zucchini	1	0
Lettuce	1	0
Capsicum (pepper)	1	0
Mushroom	1	0
Tomato	1	0
Beans	2	0
Carrot	1	0
Potato	1	0
Celery	102	0

Residues of methiocarb were below the limit of reporting (<0.5 mg/kg) in 113 vegetable and 65 fruit samples tested from the Pooraka Food Markets between April 1999 and March 2000 (SA, Heanes, 2001).

Methiocarb was not included as an analyte in the 1992 or 1996 Australian Market Basket Survey (now referred to as Australian Total Diet Surveys). No additional residue monitoring information was available.

6.2 Discussion

Data were provided by Bayer CropScience Pty Limited to support the review of methiocarb. Metabolism studies were provided for apples, beans, lettuce, tomatoes, rice and rotational crops (wheat, red beets, sugarbeets, kale and spinach), rats, lactating cows and poultry. Details of metabolism studies are given in Volume 2 of this report. Residue trials were provided for various crops, however the majority of the trials were only brief summaries of the studies without detailed field and analytical reports. The trials were not comparable to Australian GAP.

Methiocarb was reviewed by the JMPR several times between 1981 and 1988 and again in 1999 as part of the Periodic Review program. Some of the data reviewed by the JMPR were

made available to APVMA evaluators, however many of the studies were not submitted to the APVMA. Data reviewed by the JMPR are included where relevant.

6.2.1 Grapes

Methiocarb is approved for use on grapevines at 0.44 kg ai/ha, PHI 7 days (20 g/kg bait formulation). The 750 g/kg WP formulation is approved for use on grapevines as a directed butt spray at 75 g ai/100 L and as a cover spray applied at or before flowering (WA only) at 150 g ai/100 L (PHI 9 weeks).

The use of methiocarb on grapevines is covered by the MRLs for grapes (0.5 mg/kg) and wine (0.1 mg/kg). Residue data for grapes are presented in Volume 2 of this report.

Of the trials provided for the WP formulation none addressed Australian GAP for either the directed butt treatment or the pre-flowering cover spray treatment. All of the available residue trials involved foliar spray application of methiocarb to grapevines when fruit were present. In the trials where the application rates were similar to the maximum label rate residues ranged from 0.05 mg/kg to 4.5 mg/kg following applications using 0.1-0.24% solutions (100-240 g ai/100 L) of methiocarb (PHI 36-42 days).

No residues trials were provided which addressed Australian GAP for the 20 g/kg bait formulation.

There are insufficient data available to determine whether the current grape MRL of 0.5 mg/kg is adequate to cover residues occurring in treated produce. The available residue trial data therefore do not support the continued use of either the methiocarb 20 g/kg bait or the 750 g/kg WP formulations on grapevines.

It is recommended that the MRLs for grapes (0.5 mg/kg) and wine (0.1 mg/kg) will be made temporary. Registrants would need to provide data from residue trials carried out according to Australian GAP for the bait and/or WP formulations to support future registration of uses on grapevines.

6.2.2 Fruits (except grapes)

Methiocarb is approved for use on berry crops and orchard crops (citrus fruits, pome fruits, stone fruits) at a maximum application rate of 0.44 kg ai/ha using the 20 g/kg bait formulation (PHI 7 days). The 750 g/kg WP formulation is approved for use on oranges at a maximum label rate of 75 g ai/100 L (PHI 6 weeks) for control of snails and slugs. Label directions on the WP product indicate the spray should be applied as a “cover spray where the pests harbour, such as in damp dark areas, dense foliage, compost heaps and fences etc”, which suggests that direct application to fruit could occur. There are no approved uses of the WP formulation on fruit crops other than grapevines and citrus.

The use of methiocarb on orchard crops and berry fruits is covered by the MRLs for citrus fruits (0.1 mg/kg) and Fruits (except citrus fruits and grapes) (T0.1 mg/kg).

Respondents to the user questionnaire indicated that methiocarb may be used off-label as a foliar spray on berry crops in some States, however full details of the actual use pattern were not available.

Berry Fruits

Residue trials on berry fruits are presented in Volume 2 of this report. None of the residue trials provided addressed the Australian use pattern.

Orchard Crops

Residue trials on citrus fruits, stone fruits and pome fruits are presented in Volume 2 of this report. The residue trials provided for citrus fruits or pome fruits did not address the Australian use pattern. No residue data on stone fruit using the bait formulation were available, however several trials involving spray application of methiocarb to cherries, peaches and apricots were available. None of the trials address the Australian use pattern.

The available residue data are not sufficient to support the continued use of methiocarb 20 g/kg pellets on berry crops or orchard crops or the 750 g/kg WP formulation on oranges. Insufficient data are available to set appropriate MRLs for the purpose of monitoring GAP in Australia on these crops. It is recommended that the Fruits (except citrus fruits and grapes) MRL of T0.1 mg/kg be deleted and a new entry for Fruits (except grapes) of T0.1 mg/kg be added to the *MRL Standard*. This new MRL will cover the uses on all fruits including citrus fruits, except grapes.

Registrants would need to provide residue data on all fruit crops for which future registration is sought, using both the bait and WP formulations. Residue trials carried out on representative crops may be sufficient to support the use of the bait formulation on some crop groups.

6.2.3 Vegetables

Methiocarb is approved for use on "vegetable crops" at a maximum application rate of 0.44 kg ai/ha using the 20 g/kg bait formulation (PHI 7 days). Methiocarb formulated as the 750 g/kg WP is not approved for use on any vegetable crops. The use of methiocarb baits on vegetables is covered by the Vegetable MRL of 0.1 mg/kg.

Leafy Vegetables

Residue trials on leafy vegetables are presented in Volume 2 of this report. Only two residue trials were provided in which leafy vegetables were treated with Mesurol 20 g/kg pellets, and of these only one addressed the Australian use pattern. In this trial, lettuce seedlings treated four times (14 day intervals, first application at 7 cm plant height) at 40 mg ai/m^2 (400 g ai/ha) gave methiocarb residues of <0.1 mg/kg 7 days after the last application.

Several other trials were available in which methiocarb was applied either as 40 g/kg pellets or as a foliar spray, however in each case the use patterns did not correspond to GAP in Australia. Residue trials carried out in the USA were evaluated by the JMPR in 1981 and these involved application of methiocarb 40 g/kg pellets at a rate of 1.1 kg ai/ha, 2.5× higher than the Australian rate. Results from the trials were highly variable, with residues ranging from <0.01 mg/kg to 11 mg/kg at 7 days after the last application at 1.1 kg ai/ha.

Overall there were insufficient residues data available to allow a suitable MRL to be established for leafy vegetables, however the data from the USA trials suggests that residues should not exceed approximately 5 mg/kg at the Australian application rate.

Brassica vegetables

Residue trials on brassica vegetables are presented in Volume 2 of this report. The residue data were not comparable to GAP in Australia.

Residue trials on brassica vegetables (broccoli, Brussel sprouts, cabbage, cauliflower) using a 20 g/kg bait formulation were reviewed by the JMPR in 1981. Most trials involved 5-6 applications of Mesurol 20 g/kg baits at 1.1 kg ai/ha, 2.5 times higher than the approved maximum Australian rate of 0.44 kg ai/ha. At 7-8 days after the last application at 1.1 kg ai/ha, methiocarb residues were reported In Table 19.

Table 19: Residues of methiocarb in brassica vegetables (5-6x1.1 kg ai/ha, PHI 7-8 days)

Crop	Methiocarb residues	Mean residues
Broccoli (head)	0.03, 0.04 and 0.2 mg/kg	0.09 mg/kg (n=3)
Cauliflower (head)	<0.01-1.1 mg/kg	0.29 mg/kg (n=6)
Brussels sprouts (whole)	<0.01, 0.06, 0.18 and 0.3 mg/kg	0.14 mg/kg (n=4)
Cabbage (whole)	0.3-4.5 mg/kg	2.0 mg/kg (n=7)

Additional trials on Brussels sprouts and cabbages were also provided. In the trials on Brussels sprouts the application rate of 0.2 kg ai/ha was approximately half the maximum approved Australian rate and samples were not collected at the Australian 7 day WHP. In the cabbage trials the residues of (total) methiocarb were <0.03 (3 trials) and 0.08 mg/kg (1 trial) following application at 0.2 kg ai/ha (PHI 7 days).

The levels of methiocarb residues were highly variable, and in general the highest residues were detected in outer wrapper leaves. Given the non-systemic nature of methiocarb,[2] it is likely that the high variability in residues in brassica and leafy vegetables is due to pellets becoming lodged within plant foliage during application.

The trials described above indicate that the current vegetable MRL of 0.1 mg/kg may not be adequate to cover residues found in brassica or leafy vegetables. It is recommended that temporary MRLs of T5 mg/kg be established for both VB 0040 Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead cabbages, and VL 0053 Leafy vegetables, based on the trials reported by the JMPR.

Pulse and legume vegetables

Residue trials on legume vegetables using the 20 g/kg bait formulation were reviewed by the JMPR in 1981 and are presented in Volume 2 of this report. Three residue trials on legumes using the WP formulation are also presented. The trials did not address Australian GAP.

Trials involving 4-6 applications of methiocarb 20 g/kg baits at 1.1 kg ai/ha, 2.5 times the approved maximum application rate in Australia, are considered here. At 7 days after the last application, methiocarb residues in beans (snap and lima beans) were, in rank order, <0.01 (4), <u>0.01</u>, 0.02 (2) and 0.04 mg/kg (median underlined). Residues in pods (lima beans only) at 7 DALA were <0.01, <u>0.02</u> (2) and 0.03 mg/kg. Residues in bean vines were <0.01, 0.04, <u>0.06</u>, 0.1 and 0.3 mg/kg.

[2] Pesticide Manual, 12th Edition. CDS Tomlin, British Crop Protection Council.

Based on the above trials, the current vegetable MRL of 0.1 mg/kg appears to be adequate, as an interim measure, to cover residues in pulses and legumes from registered uses of methiocarb. No new MRLs are recommended for pulse and legume vegetables at this time. There were insufficient data available to recommend an MRL for legume animal feeds.

Root and Tuber Vegetables

Residue trials on root and tuber vegetables are presented in Volume 2 of this report. Four trials were presented where potato crops were treated twice with methiocarb 20 g/kg pellets at a rate of 0.15 kg ai/ha, approximately one third of the maximum Australian rate. Residues of methiocarb (total) in potatoes were <0.03 mg/kg in all four trials (PHI 7 days). The trials involving application of the WP formulations are not relevant to the Australian use patterns.

Fruiting Vegetables

Residue trials on fruiting vegetables using both methiocarb formulated as baits or as a wettable powder are presented in Volume 2 of this report. The residue trials did not address Australian GAP. Methiocarb residues in sweetcorn on the cob and green forage were <0.01-0.04 mg/kg and 0.07-3.4 mg/kg, respectively, after the last of 4 bait applications at 1.1 kg ai/ha (PHI 7 days). Residues in tomatoes after 5-6 bait applications at the same rate were <0.01-0.3 mg/kg (PHI 7 days). The application rates used in these trials were 2.5 times the maximum registered rate in Australia. In other sweetcorn trials crops were treated with 4% baits at 0.12 kg ai/ha, approximately 0.3× the maximum Australian rate. Samples harvested 4-5 months after the last application were <0.03 mg/kg in samples of plants without roots, cobs without husks and kernels.

Additional trials on tomato, peppers and melons were also provided. Tomato crops treated twice with 4% baits at a rate of 0.12 kg ai/ha resulted in residues below 0.03 mg/kg in fruit 71-81 days after the last application. The trial did not address the Australian rate or WHP. The other trials on peppers, melons and tomatoes involved application of methiocarb 50% WP formulation and therefore did not address Australian GAP.

Stalk and Stem Vegetables

Two residue trials on stalk and stem vegetables involving application of a WP formulation and two trials for 20 g/kg baits were available for review and are presented in Volume 2 of this report. None of the available trials addressed the Australian use pattern.

Following 5 applications of methiocarb 20 g/kg baits to artichokes at 1.1 kg ai/ha methiocarb residues were detected at 0.05 mg/kg (PHI 7 days) in 1 trial and <0.01 mg/kg (PHI 1 day) in a second trial. Treatment of artichokes with methiocarb 75% WP gave much higher residues. Residues at day 0 after treatment were 8.9 mg/kg, declining to 0.9 mg/kg after 13-14 days.

Overall the residue data available for vegetable crops were limited and did not address the Australian use pattern. The data are insufficient for the purposes of establishing appropriate MRLs for monitoring compliance with GAP in Australia.

Registrants will need to provide suitable residue data to support each of the vegetable uses for which future registration is sought. Residue trials carried out according to Australian GAP on representative crops from each group may be sufficient to support the use on all vegetables.

Residue data on animal feed commodities would also be required for crops such as pulses and legumes.

It is recommended that the Vegetable MRL of 0.1 mg/kg will be deleted and replaced with a temporary MRL for Vegetables [except Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead cabbages; Leafy vegetables] at T0.1 mg/kg and MRLs of T5 mg/kg for Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead cabbages and VL 0053 Leafy vegetables.

6.2.4 Broad acre crops

Methiocarb is approved for use on broadacre crops (cereals, oilseeds, pastures) at a maximum application rate of 0.44 kg ai/ha using the 20 g/kg bait formulation (PHI 7 days). There are no approved uses of the 750 g/kg WP formulation on broadacre crops, however the use of methiocarb spray on some broadacre crops was identified in the Agricultural Assessment questionnaire as an important use in some states in the control of snail and slug pests. Details of the actual use pattern in these situations were not available. There are currently no specific MRLs that cover the use of methiocarb on broadacre crops.

Residues trial data were provided for barley, wheat, sunflower and rape seed crops, where crops were treated with 4% methiocarb baits at application rates of 0.12 kg ai/ha. In the eight trials on wheat and barley residues were <0.03 mg/kg in all forage (PHI 14-71 days) and all straw and grain samples (PHI 91-120 days). In trials on sunflower crops residues in seed were <0.03 mg/kg following application at 0.12 kg ai/ha (PHI 84 days). In the four trials on winter rape residues of methiocarb were <0.03 mg/kg in all seed samples (PHI 266-284 days). Residues in green plant collected 0-4 days after application were as high as 0.07 mg/kg (assumed fresh weight) but <0.03 mg/kg in all other plant samples collected from 7-154 days after application.

In trials reviewed by the JMPR (see Volume 2 of this report. and the JMPR 1999 review[3]), quantifiable methiocarb residues (either total methiocarb residues or individual metabolites) were not detected in grain of cereals and oilseed crops following application at rates up to approximately 0.2 kg ai/ha. Residues were below quantifiable levels in all forage and straw samples with the exception of three rape forage samples taken on the day of application with a bait formulation at 0.12 kg ai/ha, where residues of up to 0.07 mg/kg were detected.

Although none of the trials available for cereals and oilseeds addressed the Australian use pattern, significant residues of methiocarb are not expected to occur in cereal grains or oilseeds at the registered Australian application rate and withholding period. It is recommended that MRLs be established for cereal grains and oilseeds at T0.1 mg/kg. Residues above this level should not occur in cereal and oilseed grains treated with methiocarb baits.

In the absence of suitable residue data for animal feeds appropriate MRLs cannot be recommended for feed items derived from cereals, oilseed and pasture crops. Residue data are required for the use of methiocarb in all broadacre crops so that appropriate MRLs for cereal grains and oilseeds and associated animal feed commodities may be set. Data on representative crops may be sufficient for the purposes of establishing group MRLs.

[3] JMPR (1999) FAO Plant Production and Protection Paper, 157. Evaluations. Part 1-Residues. Volume 1. 20-29 September 1999, Rome, 2000.

6.2.5 Other Uses

Home garden uses

Methiocarb is approved for use in home gardens. The APVMA's Ag Requirements Series Report states that "In the case of products intended for application in the home garden to food crops, and where no MRL and withholding period has been established for the same use-pattern in broad-scale agriculture, the applicant is expected to produce residue data from home garden applications and/or argument to justify the safety of the proposed use."

In the event that broad scale agricultural uses of methiocarb baits on fruits and vegetables are not supported in this review, the use of methiocarb in home garden situations should not continue.

6.2.6 Fate of Residues during Processing

The effect of the vinification process on methiocarb, methiocarb sulfoxide and sulfone residues in Pinot Noir and white Riesling grapes was investigated by Miller et al. (1985). This study is presented in Volume 2 of this report. Similar results were obtained from the two grape varieties and for both methiocarb and methiocarb sulfone. Residues concentrated in pomace (1.05 – 1.47×) but were reduced in juice (0.30 – 0.47×), must (0.31 – 0.43×) and wine (0.13 – 0.38×) during vinification.

Residues in processed grape fractions and wine (total methiocarb) were also reported in the 1981 JMPR review. Processing factors for wine and grape juice ranged from 0.42 – 0.76× (average 0.54×) and 0.65 – 0.90× (average 0.81×), respectively. From the available data, concentration factors for wine and grape pomace are estimated at 0.4× and 1.3×, respectively.

A processing study on strawberries was provided in which fruit was washed, and processed into jam and preserve. Residues of methiocarb and methiocarb sulfoxide in fruit were reduced by washing and during the processing of fruit to jam and preserve.

Processing studies, in which the effect on methiocarb residues from washing, peeling and cooking of potatoes were also reviewed by the JMPR in 1999 however these studies were not made available to the APVMA.

Processing studies for cereal grains, oilseeds or fruits (eg pome fruit pomace) were not provided. Registration would need to provide appropriate data for crops for which future registration is sought.

6.2.7 Animal Feed Commodities

Methiocarb is approved for use on several crops from which animal feed items are derived. These include pastures, cereal grains, forage and straw of pulses, legumes, cereal and oilseed crops, pomace from pome fruit and grapes, and waste material from various vegetable crops.

There are currently no Table 4 (animal feed commodity) MRLs for methiocarb.

Limited residue data for animal feed commodities were available to the APVMA for this review (see Volume 2 of this report.). Of the data that was available, most did not address GAP in Australia. In the absence of suitable residue data no animal feed commodity MRLs can be recommended at this time. Registrants would need to provide residue data for animal fed commodities derived from crops for which future registration is sought.

6.2.8 Animal Commodity MRLs

Results from a poultry feeding study and two cattle feeding studies are presented in Volume 2 of this report.. The complete poultry transfer study was provided however only summary reports were available for the cow transfer studies. The same studies were reviewed by the JMPR in 1999.

In the poultry feeding study, groups of laying hens were fed a feed pre-mixture containing a 9:1 mixture of methiocarb and methiocarb sulfoxide at 0, 20, 60, 120 or 360 ppm for 28 consecutive days. Combined residues of methiocarb and methiocarb sulfoxide were determined in tissues and eggs at the end of the dosing period.

Table 20: Methiocarb residues in tissues and eggs of poultry

Sample	Methiocarb + methiocarb sulfoxide residues (mg/kg)[a]				
	0 ppm	20 ppm	60 ppm	120 ppm	360 ppm
Giblets[b]	<0.02	<0.02	0.07	0.28	0.13
Fat	<0.02	NA	NA	<0.02	<0.02
Muscle	<0.02	NA	NA	<0.02	<0.02
Skin	<0.02	NA	<0.02	<0.02	0.06
Egg	<0.02	<0.02	<0.02	<0.02	0.06

[a] Highest residues in each group shown. [b] Includes heart, gizzard, liver

Lactating dairy cows were fed a feed pre-mixture containing methiocarb at 10, 30 or 100 ppm for 28-29 consecutive days. Total methiocarb residues in milk were determined on days 28 and 29 of the dosing period. In a separate study, cattle were fed a feed pre-mixture containing methiocarb at 10, 30 or 100 ppm for 28 consecutive days. Residues were determined in various tissues and organs and fat. Results from the two studies are summarised in Table 21.

Table 21: Total methiocarb residues in tissues and milk

Tissue	Total methiocarb residues (mg/kg)			
	Control	10 ppm	30 ppm	100 ppm
Liver	<0.05	<0.05	0.08	0.10
Kidney	<0.05	<0.05	<0.05	0.08
Muscle [a]	<0.05	<0.05	<0.05	<0.05
Fat [b]	<0.05	<0.05	<0.05	<0.05
Milk (28 day)	-	0.006	0.016	0.030
Milk (29 day)	-	0.007	0.020	0.033

[a] Includes loin steak, round steak and flank steak. [b] Includes omental fat, renal fat and back fat.

In the absence of suitable information regarding residue levels in animal feed commodities, it is considered appropriate to recommend animal commodity MRLs based on a conservative estimate of the animal exposure to residues. It is proposed that animal commodity MRLs be established based on the 120 ppm results in the poultry feeding study and the 100 ppm results in the cow feeding study.

On this basis, the following MRLs are recommended:

ML 0105	Edible offal (mammalian)	T0.2
PE 0112	Eggs	T*0.02
MM 0095	Meat (mammalian)	T*0.05
ML 0106	Milks	T0.1
PM 0110	Poultry meat	T*0.02
PO 0111	Poultry, edible offal of	T0.5

The animal commodity MRLs will be reassessed if residues data for feed items are provided and a more realistic estimate of livestock exposure to methiocarb residues can be determined. The complete cow transfer studies are required.

6.2.9 Residue Storage stability

Two storage stability studies were available to APVMA reviewers. In the first study, beef liver was fortified at 200 µg/kg with methiocarb and its sulfoxide then stored for 6 months at -4°C. Residues of both methiocarb and the sulfoxide were highly variable over the storage period.

In a second study the storage stability of methiocarb, methiocarb sulfoxide and methiocarb sulfone were investigated for periods up to 24 months in matrices of potato, field pea seed, canola seed and grapes. Recovery of total methiocarb residues was acceptable for storage periods up to 24 months, ranging from 73-98% in all matrices except a single canola seed sample.

A number of residue storage stability studies were also reviewed by the JMPR in 1999, however these studies were not made available to the APVMA. From the data provided, the JMPR concluded that the information on storage stability was inadequate (except for berries),

and that the residues reported from field trials might be understated if methiocarb and its sulfone and sulfoxide metabolites are unstable under the storage conditions used for the samples. Since the validity of the trials (except on berries) could not be determined the JMPR (1999) recommended the withdrawal of all existing Codex MRLs.

In animal feeding studies provided, poultry commodities and milk were stored frozen for less than 1 month prior to analysis, and tissues from the cattle feeding study were stored for less than 3 months prior to analysis. Given the short storage period prior to residue analysis it is concluded that the results reported in the animal transfer studies are a true reflection of actual residues present at the time of sampling. Further storage stability data for animal commodities are not required.

6.2.10 Dietary Exposure to Methiocarb Residues

The National Estimate of Dietary Intake (NEDI) for methiocarb based on the temporary MRLs proposed in this review is calculated at 121% of the ADI of methiocarb (see Volume 2 of this report.). Although this calculation exceeds the acceptable daily intake of 0.002 mg/kg, it is noted that the dietary exposure to methiocarb residues is unchanged from the present situation.

No realistic assessment of the dietary exposure to methiocarb residues can be undertaken until such time as residue studies are provided and appropriate MRLs are established for animal commodities and crops for which registration is sought. Once suitable residue data are provided in support of uses for which registration is sought, an assessment of both the chronic and acute exposure to methiocarb residues in Australia could be undertaken.

6.3 Overview

The metabolism of methiocarb in plants occurs by carbamate ester cleavage and oxidation to sulfoxides and sulfones. The predominant residue components in plants treated with methiocarb were methiocarb and methiocarb sulfoxide, with lesser amounts of methiocarb sulfone and methiocarb sulfoxide phenol. In animals, methiocarb is metabolised extensively by carbamate ester cleavage followed by oxidation of the resulting phenol to the sulfoxide and sulfone. Predominant residues in animal tissues and excreta were methiocarb phenol, methiocarb sulfoxide phenol and methiocarb sulfone phenol. No change to the current residue definition for methiocarb of sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb, is necessary.

Adequate analytical methods were available which allow determination of methiocarb, its sulfoxide and sulfone, either combined or separately, in a wide variety of plant and animal matrices.

The residue trial data provided did not address the Australian use patterns for either the 20 g/kg bait formulation or the 750 g/kg wettable powder formulation. There were insufficient data to allow appropriate MRLs to be established in food crops and in animal feed commodities. Registrants will be required to provide residue trial data for all crops for which future registration is sought.

Adequate storage stability studies for crop commodities were not provided. Storage stability data are required for representative crops or alternatively for each individual crop proposed for which future registration is sought.

Insufficient residue data were available to determine the level of methiocarb residues in animal feed items. MRLs for animal commodities were recommended on the basis of conservative estimates of residues in animal feeds. Animal MRLs will be reassessed once a more realistic estimate of livestock exposure to methiocarb residues can be determined from residue data for crops for which future registration is sought.

Studies were provided in which residue levels were determined in processed commodities during vinification. No data were provided for major processed commodities such as cereal grain fractions, oilseed oils, meals, processed fruit products such as pome and citrus fruit pomace. Processing data (or argument) will be required for major processed commodities for which future registration is sought (other than wine).

Assessment of the chronic dietary risk to methiocarb has been carried out using the temporary MRLs recommended in this report. The NEDI is calculated at 121% of the ADI, and is based on MRLs for uses in which no residues data for Australian GAP were available. The NEDI calculation is therefore not considered to be a true reflection of the actual dietary exposure to methiocarb. In the absence of residues data for Australian use patterns, no assessment of the acute dietary risk to methiocarb has been performed.

6.4 Conclusions

The residues evaluation found that the APVMA could not be satisfied that use of products containing methiocarb would not be an undue hazard to the safety of people using anything containing its residues, and would not unduly prejudice trade or commerce between Australia and places outside Australia. The evaluation proposes that instructions on product labels be varied by deleting all food and feed uses.

The residue review concluded that provided product labels are varied as proposed, then the APVMA could be satisfied that continued use and other dealings of the active methiocarb, and products containing methiocarb would not be an undue hazard to the safety of people using anything containing its residues, and would not unduly prejudice trade or commerce between Australia and places outside Australia.

1. Based on the residues evaluation it is proposed that the following changes be made to the *MRL Standard* if uses in food producing crops are retained.

Compound		Food	MRL (mg/kg)
Methiocarb			
DELETE	FC 0001	Citrus fruits	0.1
		Fruits (except citrus fruits; grapes)	T0.1
	FB 0269	Grapes	0.5
		Vegetables	0.1
		Wine	0.1
ADD	VB 0040	Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead cabbages	T5
	GC 0080	Cereal grains	T0.1
	MO 0105	Edible offal (mammalian)	T0.2
	PE 0112	Eggs	T*0.02
		Fruits (except grapes)	T0.1
	FB 0269	Grapes	T0.5
	VL 0053	Leafy vegetables	T5
	ML 0106	Milks	T0.1
	MM 0095	Meat (mammalian)	T*0.05
	SO 0088	Oilseed	T0.1
	PM 0110	Poultry meat	T*0.02
	PO 0111	Poultry, Edible offal of	T0.5
		Vegetables [except Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead cabbages, and Leafy vegetables]	T0.1
		Wine	T0.1

2. Crop residue data would be required for all crops for which future registration is sought, for both the bait and wettable powder formulations. Residue data are also required for commodities that may constitute significant animal feeds, such as pulse and legume vegetables, oilseeds, cereals, pastures and some fruit by-products (eg pome fruit pomace). Data on representative crops may be sufficient to set group MRLs.

3. The temporary MRLs recommended above will be deleted from the *MRL Standard* after finalisation of this review. The adequacy of the above temporary MRLs will be assessed if residues data are submitted for crops and animal feed commodities.

4. Complete cow transfer studies were not provided for review. To allow permanent mammalian animal commodity MRLs to be recommended complete cow transfer studies would be required.

5. Processing data are required for major processed commodities of crops proposed for continued registration. Processed commodities requiring data include fruit pomace, oilseed oils and meals, and cereal milled fractions. Suitable argument may be accepted in the absence of processing studies.

6. The critical comments statement on the 750 g/kg wettable powder formulation for the use on grapevines (butt treatment) is inconsistent and contradictory to the intended use pattern.

Since the use pattern is intended to be for butt treatment only, should use on grapevines be retained, it is recommended that the statement:

"*Apply as a cover spray when pests become apparent. Spray where they harbour – eg damp, dark areas, dense foliage, compost heaps, fences etc. Only spray butt of grapevines*"

be amended to read

"*Only spray butt of grapevines. Apply when pests become apparent*".

7. The continued use of methiocarb baits in home garden situations is subject to the outcomes of the review for the commercial uses of methiocarb. The APVMA's Ag Requirements Series Document states that "*In the case of products intended for application in the home garden to food crops, and where no MRL and withholding period has been established for the same use-pattern in broad-scale agriculture, the applicant is expected to produce residue data from home garden applications and/or argument to justify the safety of the proposed use*."

In the event that broad scale agricultural uses of methiocarb baits on fruits and vegetables are not supported in this review, the use of methiocarb in home garden situations should not continue.

8. The chronic and acute dietary exposure will need to be assessed once residues data are reviewed for crops for which future registration is sought.

9. The potential prejudice to Australian trade from the use of methiocarb will be assessed once residues data are reviewed for crops for which future registration is sought.

7 ENVIRONMENT

7.1 Introduction

Methiocarb is mainly used in pelletised forms for control of slugs and snails in home garden and cropping situations. Registrations exist in broadacre crops (including sunflowers and canola), berry crops, vegetables, vineyards, greenhouses, citrus and ornamentals (including nurseries and cut flower production). Methiocarb is also formulated as a cover spray for insect and bird control, and is an important bird, fungus gnat and western flower thrip control agent in ornamentals. Ground application methods only are used.

Methiocarb does not appear to have been subjected to regulatory action in overseas jurisdictions. However, all food uses were voluntarily withdrawn in the USA between 1989 and 1992 after the registrant made a commercial decision not to generate the data necessary to support them. A reregistration eligibility decision report has been prepared, and the associated fact sheet (dated February 1994) can be downloaded from the US EPA's website. Methiocarb has not been specifically reviewed by international organisations.

7.2 Environmental exposure

Several hundred tonnes are used in Australia each year, the vast bulk as baits in the home garden and cropping situations where their scattering on the ground leaves them vulnerable to consumption by a wide variety of non-target organisms as well as slugs and snails. Spray drift and run-off into surface waters is also possible though few contamination incidents are recorded. For example, the extensive US Geological Survey has detected methiocarb residues only one study unit, with a 1% rate of detection at concentrations in the order of 0.1 μg/L in surface waters.

7.3 Summary of environmental fate

Information has been presented in the following areas to determine the environmental fate of methiocarb.

7.3.6 Hydrolysis

Two studies were submitted. Results indicate that methiocarb is susceptible to hydrolysis about the carbamate linkage, which detoxifies the molecule. The half-life is about a month at neutral pH, extending to around a year under acidic conditions (pH 4-5) but decreasing to a few hours in alkaline solution (pH 9). Hydrolysis is likely to be a significant pathway for degradation of methiocarb under neutral to alkaline conditions.

7.3.7 Photolysis

Two unpublished studies on the photodegradation of methiocarb were presented, one in aqueous solution and one on the soil surface. A published paper confirming the results on soil surfaces was also submitted. Methiocarb undergoes relatively slow photo oxidation to its sulfoxide, probably through reaction with singlet oxygen. Note that this reaction leaves the carbamate linkage intact, so that the degradation product is likely to retain the toxic properties of the parent. Half-lives for photodegradation in aqueous solution and on the soil surface are likely to be in the order of 1-2 months.

7.3.8 Metabolism

Four test reports were submitted, describing the aerobic and anaerobic degradation of methiocarb in soils and water. Methiocarb can be persistent in acidic soils, but degrades with initial half-lives of a few days or weeks in neutral to alkaline soils. In each case, detoxification follows a hydrolytic pathway, but proceeded by a slower oxidation to methiocarb sulfoxide in acidic soils. Chemical catalysis or microbial metabolism may intervene. Sulfoxide metabolites revert to sulfides under anaerobic conditions. Methiocarb degrades completely in a matter of days in alkaline waters but is likely to be more persistent in acidic media, although this has not been tested.

7.3.9 Mobility

Two conventional batch adsorption studies with methiocarb were submitted, together with additional studies on the sulfoxide metabolite and the phenol derived from its hydrolysis. Two column leaching studies, one following prior incubation, confirmed the batch adsorption results.

Methiocarb sorbs strongly to soils and has low mobility. However, the main metabolites (methiocarb sulfoxide and the corresponding phenol) are highly mobile in soils, although methiocarb sulfoxide is unstable with respect to hydrolysis. Sulfone metabolites are likely to share these properties, but this has not been specifically tested.

7.3.10 Field dissipation

Only very limited and rather old information was presented on the dissipation of methiocarb under field conditions. Bayer Germany has advised that a field dissipation study is not required in the EU as the DT_{50} in the laboratory is less than 60 days. A recent paper calculates the DT_{50} to be between 1.0 and 1.6 days based on data from unsubmitted laboratory aerobic degradation studies. Residue analysis in a range of soils found half-lives ranging from a week to 2 months, in the same order as those obtained from laboratory investigations and with no obvious distinction between spray and bait formulations. Small plot studies with spray formulations indicated that runoff losses should remain below 10% of applied methiocarb, although large storms soon after treatment may cause greater losses (26% of applied). When applied as the pelletised formulation, methiocarb would be expected to be less mobile, but this has not been investigated. Leaching potential appears low based on the limited information presented, but monitoring studies in Spain indicate that residues of methiocarb and metabolites can leach through no-till soils to contaminate groundwater.

7.3.11 Bioaccumulation

A single test was submitted, confirming that methiocarb is a typical carbamate insecticide in having limited bioaccumulation potential.

7.4 Summary of Environmental Toxicity

Toxicity tests with methiocarb have been conducted in the following organisms.

7.4.6 Birds

Acute oral toxicity data are available for a wide range of birds. Most of the data are old and poorly described, but results are consistent with those from more recent, well reported studies. Methiocarb is highly to very highly toxic to birds by the acute oral route of exposure, with most LD50s in the 5-15 mg/kg range. Intoxication is characterised by a rapid onset of paralysis, progressing to mortality within a few hours. Remission is fairly rapid in sublethally dosed birds. Methiocarb sulfoxide appears to be even more toxic than methiocarb. Methiocarb sulfone appears less toxic and has an immobilising effect on birds at doses an order of magnitude below those that cause death.

From more limited data, dietary toxicity is variable, ranging from slightly to highly toxic. Testing is compromised in most species by strong repellent effects. Mortality tends to be delayed for some days as birds starve to death.

Reproductive testing with quail and ducks found that these species can tolerate dietary concentrations of 50-100 ppm without adverse effects on health or food consumption. Higher doses in Japanese quail led to anorexia and impaired reproductive capacity.

Palatability tests were also conducted in order to further investigate the anorexic effects apparent in dietary studies. Most of the tests are rather old, but both old and newer studies provide consistent evidence for a strong repellent effect of methiocarb to birds, whether mixed with normal feed or scattered as baits at typical rates of use. Quail were able to discriminate between clean and contaminated food, under both laboratory and simulated field conditions, with feed offered in separate hoppers or mixed together. Mild symptoms such as weight loss and apathy were seen in some quail when only limited amounts of clean food were offered. Similar discrimination was displayed by blackbirds and starlings offered contaminated earthworms or cutworms. Some consumption occurred when clean food was in short supply, but without causing any obvious harm. Methiocarb has been registered by the US EPA for aversive conditioning of corvids predating on eggs. This apparent safety does not extend to small and sensitive species. Captive canaries suffered heavy mortality on exposure to treated oat seeds, each of which may have contained a lethal dose.

Field studies also returned favourable results, with most reporting neither mortality nor aberrant behaviour. One detailed study in English cherry orchards sprayed for bird control found a limited number of non-target casualties but could not detect any impacts on overall numbers or breeding success.

7.4.7 Aquatic organisms

Static testing with three species of fish found methiocarb to be moderately to highly toxic (96 hour LC50s typically in the order of 1-5 mg/L based on nominal concentrations). Life cycle studies found significant toxic effects at 0.1 mg/L. Tadpoles appear to share similar acute sensitivity. Available data indicate that methiocarb is very highly acutely toxic to aquatic invertebrates. The 48-hour LC50 to *Daphnia magna* was 19 µg/L. Reproductive impairment in this species occurred at concentrations below 1 µg/L. Limited data indicate that methiocarb is moderately to highly toxic to molluscs and moderately toxic to algae.

7.4.8 Non-target terrestrial invertebrates

Methiocarb is acutely toxic to bees by contact and oral exposure routes. However, exposure of bees will be low when the snail bait formulation is used.

The acute and reproductive effects of methiocarb on earthworms were studied in three artificial soil tests and in four field studies. Methiocarb is slightly to moderately toxic to earthworms when distributed through the soil, with LC50s in the order of 100 mg/kg. Toxicity is moderated when the snail bait formulation is used, except for surface feeding species. Effects on cocoon production are evident at concentrations an order of magnitude lower than those that cause mortality. Reproductive success is impaired when earthworms are tested in boxes at typical application rates, but major population effects do not appear to occur in the field, notwithstanding the deaths of litter feeding species.

A range of laboratory and field tests were conducted with carabid and rove beetles, and effects on numerous other arthropod fauna were studied in the field. These tests generally did not follow established protocols. Predatory insects as represented by carabid beetles feed on pellets and suffer heavy mortality when snail baits are applied under laboratory conditions. Population reductions occur under field conditions. In contrast, rove beetles do not feed on pellets, but suffer heavy mortality through contact under highly exposed laboratory conditions when no refuge is available. Predatory fauna are not expected to be adversely affected in the field by single applications of methiocarb for snail and slug control. Any effects on the function of the decomposer community are expected to be small.

Methiocarb does not appear to impair soil microbial functions.

7.4.9 Mammals

Available data indicate that methiocarb is highly toxic to mammals by the acute oral route, but that aversive effects moderate the dietary hazard as occurs for birds. Methiocarb sulfoxide is more toxic than methiocarb, and methiocarb sulfone much less toxic. Kills of rodents have been reported from the field, including one Australian trial investigating the potential of methiocarb pellets for controlling plague mice, but no significant population impacts have been recorded.

7.5 Prediction of Environmental Hazard

The vast bulk of methiocarb is used as baits in the home garden and cropping situations where their scattering on the ground leaves them vulnerable to consumption by a wide variety of non-target organisms. Spray drift and run-off (of pellets or in dissolved form) into surface waters is also possible though few contamination incidents are recorded.

7.5.6 Birds

Birds will mainly be exposed through the ingestion of granular pesticide when foraging for food or grit.

The US EPA has adopted a level of concern (roughly equivalent to 10 LD50s/m^2) as a screening tool to identify low risk granular pesticides for which no further work is needed. Potential exposure based on an avian LD50 of 1 mg/kg for a small bird weighing 20 g equates to 2500 LD50s/m^2 for the home garden rate of 25 kg/ha product (50 mg/m^2 methiocarb).

Furthermore, the average pellet contains 500 μg methiocarb, or 25 LD50s for a sensitive small bird. Methiocarb pellets are clearly hazardous to sensitive small birds, as they are readily available at the soil surface and each contains multiple lethal doses. Heavy mortality of canaries offered treated oat seeds in the laboratory supports this analysis, but field evidence to confirm it is very limited.

Hazard to larger and less sensitive birds is less clear cut. The LD50 for a 200 g bird with a sensitivity of 5 mg/kg is 1 mg, or two average pellets. The US EPA's screening tool still identifies a potential hazard to birds, as the home garden rate of 25 kg/ha equates to 50 LD50s/m^2. However, the hazard is moderated by aversive effects. This larger bird would probably survive consumption of a single pellet, provided that the subsequent aversion is strong enough to deter further consumption. Available data indicate that birds are likely to be temporarily immobilised by sub-lethal doses of methiocarb. The general agricultural rate of 5.5 kg/ha pellets only marginally exceeds the US EPA threshold of 10 LD50s/m^2, indicating that field use is unlikely to be hazardous to larger birds.

For spray applications, maximum residues on food items may be estimated. The approach is conservative as it assumes that birds obtain all their dietary requirements from food that has just been contaminated and contains the highest possible residue. It is estimated use at 4.1 kg/ha to protect poppy seedlings would leave maximum residues in the order of 500-900 ppm on foliage, and around 50 ppm on insects. Similarly, use at 1.5 kg/ha on ornamentals would leave maximum residues of around 200 ppm on the crop and 20 ppm on insects. Maximum residues measured on cherries are 26 ppm following spray application at 4.3 kg/ha methiocarb. These residues are much lower than those in pellets, suggesting a greater margin of safety. Predicted and measured residues are generally well below all recorded LC50s, most of which exceed 1000 ppm.

The hazard analysis suggests that most birds should survive exposure to methiocarb snail bait formulations, even if there is some initial attraction. Mortality may occur in small, sensitive species if they are attracted to the baits. Experience with the use of snail baits suggests that this would be an unlikely occurrence. No avian incidents have been linked to methiocarb pellets in Australia, notwithstanding their widespread use in home gardens and in agriculture. Methiocarb was not involved in any of the avian incidents described in the most recent incident report from the UK. Even when the field use of methiocarb for bird control (a high rate use) is intensively monitored, only a few small birds are discovered dead as a result, and impacts on populations or breeding success remain undetectable.

7.5.7 Mammals

Mammals appear to respond similarly to methiocarb exposure as do birds, with toxicity moderated by aversive effects. Field studies indicate that some rodents consume methiocarb snail baits with fatal consequences, but have been unable to demonstrate a significant effect on populations.

7.5.8 Invertebrates

Laboratory studies can be used to assess hazard to earthworms. The highest rate of bait application for methiocarb (500 g/ha) would leave residues of 8.3 mg/kg if evenly distributed through 5 cm soil (density 1.2). This prediction is well below 100 mg/kg, a concentration that caused no earthworm mortality in laboratory exposures, but approaches the concentration of 10 mg/kg at which weight reduction and effects on cocoon production were evident. Spray

application at the high rate of 4 kg/ha would leave initial soil residues of about 65 mg/kg in the surface 5 cm. These simple calculations indicate that methiocarb residues dispersed through the soil should not exert lethal influences on earthworms, but may give rise to sub-lethal effects. Some mortalities may occur among surface or litter feeding species where baits are laid.

Field observations confirm the above analysis. In general, earthworms appear unaffected by methiocarb treatments. Some individuals of some species are killed, apparently by feeding on baits rather than contact with contaminated soil, but numbers involved appear too low to affect populations. Short-term population declines are apparent in some species, but populations then recover.

Laboratory studies with carabid and rove beetles indicate that these organisms also can be lethally affected by methiocarb treatment. Carabids die after eating methiocarb baits, but rove beetles appear unaffected by this exposure route. Their survival and reproduction can, however, be affected by residues dispersed in the soil at exaggerated rates.

Field evaluations of the effects on invertebrate communities at application rates typical of Australian agricultural uses have shown that methiocarb causes short term disruption, particularly to beetles, but that most species recover by the following season. Surface feeding predators such as carabids have been shown to be particularly sensitive, with sensitive species eliminated in overseas field trials. However, the ecological function of these predatory organisms should not be significantly impaired as only a small minority of species is affected in this way.

7.5.9 Reptiles

No information was submitted, but a toxic hazard to reptiles must be assumed to exist. Toxicity data for methiocarb to reptiles are not available from Bayer Germany. A literature search on various data bases did not produce any information.
Bayer Australia has stated that no reports of reptile deaths or toxic effects from the use of pelleted methiocarb have been received during the 30 years of use in Australia.

7.6 Aquatic hazard

Aquatic exposure to methiocarb and its toxic metabolites may arise via spray drift or when drainage water enters natural bodies of water.

For drift, screening level risk assessments assume transfer of 10% of the application rate to 15 cm water. Resultant concentrations would be 1 mg/L for spray application at 1.5 kg/ha to ornamentals, and 2.8 ppm for application at 4.1 kg/ha to poppy seedlings.

The standard runoff scenario entails a treated area of 10 acres draining into a 1 acre pond with a depth of 6 feet. A generalised maximum runoff figure of 1.5% is used. Predicted concentrations of methiocarb in a 2 m pond, based on this model, would be 3.75 µg/L following bait application at 25 kg/ha (500 g/ha methiocarb), or 28 µg/L following spray application at 4.1 kg/ha to poppy seedlings. Predicted environmental concentrations in a shallow (20 cm) wetland contaminated in this way would be 37.5 and 280 µg/L, respectively.

7.6.6 Vertebrates (fish and tadpoles)

The most sensitive acute LC50 for fish is 440 µg/L in rainbow trout. Predicted concentrations in deeper or shallow water from runoff (see above) remain below 44 µg/L (10% of the LC50 for rainbow trout). This screening level assessment is considered robust enough to exclude hazard to fish from methiocarb-contaminated runoff.

Concentrations from spray drift exceed those calculated for runoff. Predicted concentrations arising from 10% drift to shallow (15 cm) water extend into the low ppm range for higher rate spray treatments, which would be lethal to more sensitive fish based on laboratory results for rainbow trout and bluegill sunfish. This screening level assessment highlights the importance of avoiding insecticide drift to waterways. However, drift of 10% to water is an unlikely occurrence that would reflect poor agricultural practice, given that methiocarb is only applied using ground based equipment.

A 1% level of drift from boomspray application at the high rate of 4.1 kg/ha as used in poppy seedlings would leave an estimated 0.28 mg/L in 15 cm water, for a hazard quotient of 0.6 based on the LC50 of 0.44 mg/L for rainbow trout. Water depth would have to increase to nearly a metre in order to reduce the hazard quotient below 0.1 and allow confidence that acute risk to fish is low.

Spray application is not commonly used for methiocarb, with most product used having a very low drift potential because it is pelletised for snail control. Use of more sophisticated computer modelling techniques provides less conservative exposure predictions that essentially eliminate concerns for fish, as outlined below.

7.6.7 Invertebrates

For invertebrates, the usual indicator organism is *Daphnia magna*. Some other invertebrates (mayfly nymphs and caddisfly larvae) appear to share the high sensitivity of daphnids to methiocarb.

Predicted concentrations from runoff to deeper water only marginally exceed the acute LC50 of 19 µg/L for *Daphnia magna*, even at the high rate of 4.1 kg/ha for poppy seedlings, and significant ecological impacts from runoff contamination are not expected. Runoff to shallow wetlands may be expected to exert more significant ecological effects, particularly following high rate treatments. However, this risk will decline with time since application as methiocarb residues become less prone to transport in runoff.

Predicted concentrations from drift to shallow water extend into the low ppm range, considerably above the above LC50 for *Daphnia magna*. Based on these simple worst case calculations, drift contamination would be expected to have a short term impact on invertebrate populations where drift enters the water body and every effort should be made to avoid localised disruptions likely to result from drift contamination.

7.6.8 Computer modelling

Predictions of aquatic exposure can be obtained from the AgDRIFT™. AgDRIFT is a computer code that models the aerial application of pesticides, with a validated solution technique against a series of studies conducted by the Spray Drift Task Force (SDTF).

The model predicts that initial concentrations in wetland and pond environments following application of methiocarb at 4.1 kg/ha (the highest rate use for slug and snail control in poppy

seedlings) by low boomspray would be 29.3 and 2.2 µg/L, respectively. Application to ornamentals by orchard air blast at the high rate of 2 kg/ha would give rise to initial predictions of 2.6 and 0.2 µg/L. These predictions indicate that aquatic invertebrates inhabiting shallow wetlands may be adversely affected by spray drift from high rate application as occurs for poppy seedlings. However, the hazard appears relatively low, and longer-term effects on these organisms would not be expected given their high capacity for recovery. These predictions indicate that fish are very unlikely to be affected, as noted above.

In Germany and some other EU member States, basic drift values obtained from the Ganzelmeier tables are used for predicting aquatic exposure. Outdoor drift trials with conventional equipment have been used to complete basic drift values for field crops, grapes, orchards and hops. Estimates for drift are given as the 95th percentile of mean values, quoted as percentage of the application rate.

In Australia, spray formulations of methiocarb are applied to field crops (canola and poppies, up to 4.1 kg/ha), orchards (oranges are listed on the label, but the only reported use is for bird control in cherries at 1.5 kg/ha), grapevines (early season use, not expected to exceed 750 g/ha) and ornamentals (typically 1.5 kg/ha). The basic drift values can be used to determine buffer zone distances for protection of fish and invertebrates. The following hazard quotients are obtained for shallow water, based on toxicity results of 0.44 mg/L for fish and 19 µg/L for invertebrates.

Table 22: Hazard quotients

Crop	Application rate	Buffer	Concentration in 15 cm water	Hazard quotient	
				Fish	Invertebrates
Field	4100 g/ha	3 m	0.32 mg/L	0.73	16.8
		5 m	0.19 mg/L	0.43	10
		10 m	0.10 mg/L	0.23	5.3
		30 m	0.034 mg/L	0.08	1.8
Orchard (late season treatment)	1500 g/ha	3 m	0.14 mg/L	0.31	7.4
		5 m	0.09 mg/L	0.20	4.7
		10 m	0.05 mg/L	0.11	2.6
		30 m	0.0097 mg/L	0.022	0.5
Grapevines (early season treatment)	750 g/ha	3 m	0.018 mg/L	0.041	0.95
		5 m	0.008 mg/L	0.018	0.42
		10 m	0.0015 mg/L	0.0034	0.079

The Ganzelmeier prediction of 0.034 mg/L at 30 m for field crops sprayed at 4.1 kg/ha aligns well with the AgDRIFT prediction of 0.029 mg/L. The Ganzelmeier predictions remain conservative in making no allowance for dissipation processes. They indicate that fish inhabiting shallow water should not be adversely affected by spray application of methiocarb, with hazard quotient values only exceeding 0.5 for application within 3 m of the water's edge. Invertebrates are at higher risk because of their greater sensitivity, but populations of these organisms tend to be more resilient because of their rapid regeneration times. Based on the limited use of methiocarb as a spray, mitigation of these hazards is not required.

The toxicity to aquatic invertebrates is much higher than to fish and the inclusion of aquatic invertebrates on the warning statement on the label would relay to the user that it might affect the aquatic environment more than just to fish.

7.7 Conclusions

Methiocarb is mainly used in pelletised form for control of slugs and snails in agricultural and home garden situations. Application occurs when pests become active, for example when rain occurs or when newly sown seedlings are watered in. The pellets begin to disintegrate through weathering within a week but are likely to remain visible for up to a month unless consumed. Smaller amounts are formulated for spray application to control slugs, snails, hibiscus flower beetles, garden weevils, western flower thrips and glasshouse sciarids in various crops (grapevines, hibiscus, ornamentals and poppies) and to repel birds attacking ornamentals and canola seedlings.

Sufficient information has been presented to allow assessment of the likely environmental impact associated with the use of methiocarb, with the exception of modern field dissipation data, and no information on toxicity to reptiles (a deficiency not specific to methiocarb but common to all agricultural chemicals). Assessment indicates that methiocarb should not persist in the environment but that it has a very broad spectrum of biological activity consistent with its ability to inhibit acetylcholinesterase. Non-target organisms such as birds, mammals, reptiles, earthworms and beetles are likely to be killed by use of methiocarb, particularly the snail bait formulations. Populations of these organisms are not expected to be affected by such impacts, but some sensitive beetle species may be eliminated from treated areas by frequently repeated applications.

7.7.6 Adequacy of labels

750 g/kg wettable Powder (WP) formulations
The label for Mesurol 750 contains the following warnings of toxicity to bees and fish:

- "Dangerous to bees. Do not spray any plants in flower while bees are foraging."
- "Dangerous to fish. Do not contaminate dams, rivers, ponds, waterways or drains with the chemical or used containers."

The hazard assessment has confirmed the toxicity of methiocarb to bees. The warning and accompanying instruction not to spray when bees are actively foraging are adequate.

The hazard assessment has concluded that the toxicity of methiocarb to aquatic invertebrates is much higher than to fish. It is considered that the current label's warning in respect of hazard is inadequate and should be varied to read:

- "Dangerous to fish and aquatic invertebrates. Do not contaminate dams, rivers, ponds, waterways or drains with the chemical or used containers".

20 g/kg Bait formulations

The label for Mesurol Snail and Slug Bait contains the following instruction aimed at minimising harmful effects to aquatic organisms: "Do not contaminate dams, rivers, ponds, waterways or drains with the chemical or used containers". Instructions to "clean up spilled pellets so that they are not eaten by animals and birds" are also included, as are instructions to scatter bait pellets evenly and not to heap pellets. It is considered that these instructions, together with the other instructions and warnings on the label, are adequate.

20 g/kg Home garden bait formulations

In essence, the same instructions together with an illustration appear on labels for the home garden product Baysol. The cautionary statement "DO NOT allow chemical containers or product to get into drains, sewers, streams or ponds" is also featured. A side panel warns that: "Pets may find the bait attractive. If eaten, they will be poisoned which could lead to death". There is no reference to the toxicity of methiocarb to other organisms.

Based on the hazard assessment, which found toxicological hazards to birds and mammals that consume baits, it is considered that the label should be varied so that it includes the following instructions within the label's CAUTION section:

Clean up spilled pellets so that they are not eaten by animals and birds.

Varying the labels, as proposed, would ensure that use of products containing methiocarb would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

On the basis of these findings, the environment evaluation concluded that the APVMA could be satisfied that continued use and other dealings of the active methiocarb, and products containing methiocarb would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment, and affirm the active approval and product registrations from an environmental perspective.

8 OVERSEAS REGULATORY STATUS

- United Kingdom – The UK Reviewed methiocarb in 1997. Data on worker exposure and dermal absorption were not submitted. Data requirements were set to allow further assessment of operator exposure. Limited residue data were presented. Data requirements were set for a full residues package to enable reliable estimates of consumer exposure to be made. According to the OECD database a second review of methiocarb is underway and was in preparation in 1999, as part of the anticholinesterase review. No further information is available at this time.

- United States of America – methiocarb was first registered in the US in 1972. EPA issued a Registration Standard for methiocarb in March 1987, requiring additional product chemistry, residue chemistry, ecological effects, environmental fate, toxicology and occupational and residential exposure data. The methiocarb producers deleted all food uses from their product labels between 1989-92.

- JMPR - Methiocarb has been reviewed by the Joint FAO/WHO Meeting of Pesticide Residues (JMPR) in 1981, 1983, 1984, 1985, 1987 and 1998. In the most recent review in 1998, the JMPR amended the ADI to 0.02 mg/kg bw/day, based on a revised NOEL of 1.5 mg/kg bw/day from the same 2-year dog study and a safety factor of 100.

- Canada – In 2003 the PMRA re-evaluation program 1 announced that "since the initiation of the re-evaluation program, the registrations of methiocarb and there associated end-use products have been discontinued by registrants. The use of methiocarb in food producing plants was already discontinued at this time.

- EU – Methiocarb is currently under review in the EU. The rapporteur country is the United Kingdom and is currently in preparation (1993)

9 PROPOSED REVIEW FINDINGS

9.1 Chemistry

The chemistry evaluation found that the active constituent methiocarb meets the required APVMA standard (FAO specification) for that active. The evaluation concluded that the method by which the active is manufactured, batch analysis results and analytical methods were acceptable.

9.2 Toxicology

The proposed findings of the toxicology evaluation are that product labels do not contain adequate instructions with regards to the safe handling of the product. It is recommended that the instructions be varied by including further safety directions and warning statements.

The toxicology evaluation recommended that, if product labels are varied as proposed, then the APVMA would be able to be satisfied that continued use and other dealings of the active methiocarb and products containing methiocarb would not be likely to have an effect that is harmful to human beings.

9.3 Occupational Health and Safety

The proposed findings of the OH&S evaluation are that there are unacceptable risks for worker exposure. However, it was recommended that for all uses, except ornamentals as a soil drench, the risks can be mitigated if labels are varied to include new safety directions, re-entry statements and to require specified PPE

The risk to workers re-handling treated soil, following use of methiocarb as a soil drench on ornamentals, could not be determined due to no available information. Consequently the APVMA would not be able to be satisfied that continued use of methiocarb in ornamentals treated by soil drench is not an undue hazard to the safety of workers exposed to it. It is proposed that labels be varied to delete these uses.

The proposed findings of the occupational health and safety evaluation are that product labels do not contain adequate instructions with regards to the safe handling of the product and re-entry to treated crops for uses other than the soil drench. It is proposed that labels be varied to include further safety directions and a re-entry period after use.

The occupational health and safety evaluation recommended that provided that labels are varied as proposed then the APVMA would be able to be satisfied that continued use and other dealings of the active constituent methiocarb and products containing methiocarb would not be an undue hazard to the safety of people exposed to it during handling.

9.4 Residues

Limited information was available to allow a determination of residues risks in produce treated with methiocarb under Australian use situations. The proposed findings of the

residues evaluation are that there was insufficient data to accurately calculate the National Estimated Dietary Intake (NEDI), assess the acute dietary intake, or determine the level of methiocarb residue in animal feed items. Risks to trade and to public health could, therefore, not be assessed.

Consequently the APVMA would not be able to be satisfied that continued use of methiocarb products for food and animal feed uses would not be an undue hazard to the safety of people using anything containing its residues, and would not unduly prejudice trade or commerce between Australia and places outside Australia. It is proposed that the instructions on product labels be varied by deleting all uses on food and animal feed crops.

The residue review recommended that provided product labels are varied as proposed, then the APVMA would be able to be satisfied that continued use and other dealings of methiocarb and products containing methiocarb would not be an undue hazard to the safety of people using anything containing its residues, and would not unduly prejudice trade or commerce between Australia and places outside Australia.

9.4.1 Advice to Future Registrants: Data Requirements

- Crop residue data would be required for all crops for which registration is sought, for both the bait and wettable powder formulations. Residue data are also required for commodities that may constitute significant animal feeds, such as pulse and legume vegetables, oilseeds, cereals, pastures and some fruit by-products (eg pome fruit pomace). Data on representative crops may be sufficient to set group MRLs.

- Complete cow transfer studies would be required to allow permanent mammalian animal commodity MRLs to be recommended.

- Processing data would be required for major processed commodities of crops proposed for registration. Processed commodities requiring data would include fruit pomace, oilseed oils and meals, and cereal milled fractions.

- The critical comments statement on the label for 750 g/kg wettable powder formulation for the use on grapevines (butt treatment) is inconsistent and contradictory to the intended use pattern. Since the use pattern is intended to be for butt treatment only, it is recommended that any future label statement should be:

"*Apply as a cover spray when pests become apparent. Spray where they harbour – eg damp, dark areas, dense foliage, compost heaps, fences etc. Only spray butt of grapevines*"

be varied to read

"*Only spray butt of grapevines. Apply when pests become apparent*".

The chronic and acute dietary exposure of methiocarb will need to be assessed before registration is granted.

The potential prejudice to Australian trade from the use of methiocarb will also need to be assessed during any new data assessment for methiocarb product registrations.

9.5 Environment

The environmental evaluation reported that the use of methiocarb is not expected to lead to significant environmental contamination or broad scale impacts on populations of non-target organisms. However, the proposed findings are that product labels were inadequate and should be varied by amending current protection and cautionary statements to reduce potential environmental exposure. Varying the labels, as proposed, would ensure that use of products containing methiocarb would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

The environment evaluation recommended that provided the product labels were varied as proposed, then the APVMA would be able to be satisfied that continued use and other dealings of the active constituent methiocarb, products containing methiocarb and associated labels in accordance with the instructions for use would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

10 PROPOSED REVIEW RECOMMENDATIONS

Following consideration of the available data, the following recommendations are made:

1) Affirm active constituent approvals.

2) Vary conditions of label approval.

3) Provided product labels are varied affirm product registrations.

4) Cancel old product labels.

10.1 Affirm approval of active constituent

The APVMA is satisfied that the requirements for continued approval of the active constituent have been met and proposes that the active constituent approvals of methiocarb, as listed in Appendix 1 be affirmed.

10.2 Vary conditions of label approval

The APVMA is satisfied that the conditions to which the label approval is currently subject can be varied in such a way that the requirements for continued label approval will be complied with and therefore varies the conditions of label approval for labels listed in Table 24.

Proposed label variations

750g/kg wettable powder (WP) formulations

a) Delete all uses on food crops including grapevines, oranges, berry crops, cereals, oilseed crops (including sunflowers), orchards, and vegetable crops;
b) Delete use on pastures and animal feed crops;
c) Delete use on ornamentals as a soil drench; and
d) Changes to label instructions.

Add the following restraint statements:

- **DO NOT apply to food producing crops**
- **DO NOT use on animal feed producing crops**

Replace the existing protection statement (warning of toxicity to fish):

- "Dangerous to fish. Do not contaminate dams, rivers, ponds, waterways or drains with the chemical or used containers"

with:

- "Dangerous to fish and aquatic invertebrates. Do not contaminate dams, rivers, ponds, waterways or drains with the chemical or use containers"

Replace the existing safety directions with:

Safety Directions (changes underlined)

Very dangerous. Product is poisonous if absorbed by skin contact, inhaled or swallowed. May irritate the eyes and skin. Avoid contact with eyes and skin. DO NOT inhale dust or spray mist.
Mixer/loader: When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist, a washable hat, dust mask and elbow length PVC gloves.

Applicator: When using the prepared spray wear cotton overalls buttoned to the neck and wrist, a washable hat, face shield and elbow length PVC gloves, and if applying by hand wear chemical resistant clothing, a washable hat, face shield and elbow-length PVC gloves and if applying in enclosed areas wear cotton overalls buttoned to the neck and wrist, a washable hat, elbow length PVC gloves and a face shield.

If product on skin, immediately wash area with soap and water After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves, contaminated clothing and face shield.
Obtain an emergency supply of atropine tablets 0.6 mg.

Add the following Re-entry statement:

RE-ENTRY TO TREATED AREA: DO NOT PERMIT re-entry until 28 days after application. If prior entry (or rehandling) is required, wear cotton overalls buttoned to the neck and wrists and elbow length PVC gloves. Clothing must be laundered after each day's use.
Well ventilate greenhouses/glasshouses before re-entry.

20g/kg bait formulations (commercial packs over 1kg)

a) Delete all uses on food crops including grapevines, oranges, berry crops, cereals, oilseed crops (including sunflowers), orchards, and vegetable crops;
b) Delete use on pastures and animal feed crops; and
c) Changes to label instructions.

Add the following restraint statements:

- DO NOT apply to food producing crops
- DO NOT use on animal feed producing crops

Replace the existing safety directions with:

Safety Directions (changes underlined)

Product is poisonous if swallowed. May irritate the eyes. Avoid contact with eyes and skin.
Applicator: When using the product, wear cotton overalls buttoned to the neck and wrist, a washable hat and if dispensing by hand also wear elbow-length PVC gloves.
After each day's use, wash gloves, and contaminated clothing.

If product on skin, immediately wash area with soap and water.

After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water.
Obtain an emergency supply of atropine tablets 0.6 mg.

Add the following Re-entry statement:

RE-ENTRY TO TREATED AREA: DO NOT PERMIT re-entry until 28 days after application. If prior entry (or rehandling) is required, wear cotton overalls buttoned to the neck and wrists and elbow length PVC gloves. Clothing must be laundered after each day's use.

20g/kg bait formulations (home garden packs less than 1kg)

a) Delete the statement "DO NOT PICK EDIBLE CROPS FOR 7 DAYS AFTER APPLYING"; and
b) Changes to label instructions as follows:

Include the following restraint statements:

- DO NOT apply to food producing crops

Replace the existing CAUTION statement:

- "Avoid application of pellets to foliage of edible crops. DO NOT allow chemical containers or product to get into drains, sewers, streams or ponds."

with:

- "DO NOT apply to edible crops. Clean up spilled pellets, so that they are not eaten by animals and birds. DO NOT allow chemical containers or product to get into drains, sewers, streams or ponds"

Add new safety directions:

Safety Directions

Wash hands after use.

Summary of proposed label changes

Table 23: Summary of label changes by situation and pest

Situation	Pest	Recommendations
750g/kg WP		
Grapevines	White Italian snail, Garden weevil, common garden snail *Bradybaena spp*., slugs	Insufficient data to establish MRL **Delete from labels**
Oranges	Common garden snail *Bradybaena spp*., slugs	Insufficient data to establish MRL **Delete from labels**
Hibiscus	Hibiscus flower beetle	**Retain use with label variations**
Ornamentals	Common garden snail *Bradybaena spp*., slugs, Glasshouse sclarids, blackbirds, sparrows, starlings, Indian myna	**Delete the use on Glasshouse sclarids using soil drench** **Retain other uses with label variations**
Poppies	Slugs	**Retain use with label variations**
20g/kg Bait (Pack size >1kg)		
Berry crops	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	Insufficient data to establish MRL **Delete from labels**
Cereals	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	Insufficient data to establish MRL **Delete from labels**
Gardens (ornamentals, flowers)	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	**Retain use with label variations**
Nurseries (ornamentals, flowers)	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	**Retain use with label variations**
Oilseed crops	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	Insufficient data to establish MRL **Delete from labels**
Orchards	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	Insufficient data to establish MRL **Delete from labels**
Pastures	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	Insufficient data to establish MRL **Delete from labels**
Vegetable crops	Common garden snail *Bradybaena spp*., slugs, white Italian snail, White snail	Insufficient data to establish MRL **Delete from labels**
Sunflowers	False wireworm beetle	Insufficient data to establish MRL **Delete from labels**
20g/kg Home Garden Bait (Pack size < 1kg)		
Gardens (ornamentals, flowers)	Snails, slugs, slaters, Millipedes	**Retain use with label variations**

9.3 Affirm registrations

The APVMA is satisfied that provided product labels are varied as proposed that the products meet the prescribed requirements for continued registration and therefore affirms product registrations as listed in Table 24.

Table 24: Product registrations to be affirmed with label variations.

Product Number	Product Name	Registrant	Label approval numbers
33274	Mesurol Snail and Slug Bait	Bayer Cropscience Pty Ltd	33274/0304^
33276	Mesurol 750 Bird Repellent and Snail and Slug Spray	Bayer Cropscience Pty Ltd	33276/0304^

^ Labels approved after the commencement of the review, that are subject to the outcomes of the review.

9.4 Cancellation of label approvals

The APVMA is not satisfied that old approved labels (Table 25) contain adequate instructions and cancels these approvals.

Table 25: The following label approvals are deemed not to contain adequate instructions and are proposed to be cancelled.

Product Number	Label approval numbers
33274	Ψ 33274/1097 33274/0100^
33276	Ψ 33276/02 33276/0300^ 33276/0803^

Ψ Labels transitioned from the states and not having an approval number.

^ Labels approved after the commencement of the review, that are subject to the outcomes of the review.

11 AMENDMENTS TO STANDARDS

As a result of the methiocarb review, the Office of Chemical Safety recommends the following amendments to public health standards:

11.1 Acceptable Daily Intake

This review does not recommend any amendments to the current ADI.

11.2 Acute Reference Dose

An ARfD of 0.03 mg/kg bw/day has been determined from the review 2 developmental toxicity studies in rats and rabbits with a safety factor of 100 being applied to the No Observable Effect Level (NOEL).

11.3 Poisons Scheduling

The NDPSC consider methiocarb at its May, 2000 meeting and determined that Technical grade methiocarb is in schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Formulations containing methiocarb 20% or less have been placed in schedule 6, while those products containing 2% or less methiocarb will remain in schedule 5 of the SUSDP. Existing products have already had their labels amended to reflect these scheduling changes.

11.4 Safety Directions

Table 27: Safety Directions

BA 750 g/kg or less	
Very dangerous	100
Product is poisonous if absorbed by skin contact, inhaled or swallowed	120 130 131 132 133
May irritate the eyes and skin	160 162 164
Avoid contact with eyes and skin	210 211
Do not inhale dust or spray mist	220 221 223
When opening the container and preparing spray wear elbow-length PVC gloves and disposable dust mask	279 280 281 290 294 296
When using the prepared spray wear cotton overalls buttoned to the neck and wrist and a washable hat, elbow-length PVC gloves and a face shield	306 279 282 290 292 294 296
If applying by hand wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow length PVC gloves and a face shield	289 290 291b 294 296
If product on skin, immediately wash area with soap and water	340 342
After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water	350
After each day's use, wash gloves and face shield and contaminated clothing	360 361 362 366
Obtain an emergency supply of atropine tablets 0.6 mg	373
BA 20 g/kg or less	
Product is poisonous if swallowed	120 130 133
May irritate the eyes	160 162
Avoid contact with eyes and skin	210 211
When using the product wear cotton overalls buttoned to the neck and wrist and a washable hat and if applying by hand elbow-length PVC gloves	279 283 290 292 289 294
If product on skin, immediately wash area with soap and water	340 342
After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water	350
After each day's use, wash gloves and contaminated clothing	360 361 366
Obtain an emergency supply of atropine tablets 0.6 mg	373

BA 20 g/kg or less (1 kg pack or less)	
Wash hands after use	351

11.5 First Aid Instructions

No changes to the current first aid directions (methiocarb; a, h) are recommended.

Appendix 1:

Active Constituent Approvals

Approval Number	Active Name	Approval holder
44212	Methiocarb	Bayer Cropscience Pty Ltd
55824#	Methiocarb	Bayer Cropscience Pty Ltd

Approval granted after the commencement of the review, that is subject to the outcomes of the review

Product registrations and associated label approvals

Product Number	Product Name	Registrant	Label approval Numbers
33274	Mesurol snail and Slug bait	Bayer Cropscience Pty Ltd	Ψ 33274/1097 33274/0100^ 33274/0304^
33276	Mesurol 750 Bird Repellent and Snail and Slug Bait	Bayer Cropscience Pty Ltd	Ψ 33276/02 33276/0300^ 33276/0803^ 33276/0304^
51851*	Baysol Snail and Slug Bait	Bayer Cropscience Pty Ltd	51851/0599^
58652*	Bayer Advanced Garden Baysol Snail and Slug bait Pellets	Bayer Cropscience Pty Ltd	58652/0504^

Ψ Labels transitioned from the states and not having an approval number.
* Products registered after the commencement of the review that are subject to the outcomes of the review
^ Labels approved after the commencement of the review, that are subject to the outcomes of the review.

Methiocarb Products included in the review that have had their registrations lapse prior to the completion of the review.

Product Number	Product Name	Registrant	Label Approval Number/s
45935	Baysol Snail and Slug Bait	Bayer Cropscience	45935/02
49404	Baysol Snail and Slug bait contains Bitrex Pet Taste deterrent	Bayer Cropscience	49404/01