Australian Pesticides &
Veterinary Medicines Authority

The Reconsideration of Registrations of Products containing Carbaryl and their Associated Labels

DRAFT REVIEW REPORT

JUNE 2004

Australian Pesticides &
Veterinary Medicines Authority

Canberra
Australia

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

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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 carbaryl 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 or people using anything containing its residues; and/or
- would not be likely to have an effect that is harmful to human beings.

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 Aging Office of Chemical Safety (OCS), the Department of Environment and Heritage (DEH), the National Occupational Health and Safety Commission (NOHSC), 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

* Prior to March 2003, the APVMA was known as the National Registration Authority for Agricultural and Veterinary Chemicals (NRA). In this report, the name APVMA is generally used even when referring to the organisation prior to March 2003.

these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.

This document is Volume 1 of *'The reconsideration of registrations of products containing carbaryl and their associated labels'* and relates to products containing carbaryl 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 both 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 Carbaryl, Volume 1) and the technical evaluation reports (Volume 2) for registrations and approvals relating to carbaryl 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 draft review report directly to the APVMA. Your comments will assist the APVMA in preparing the final report.

The draft 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 continued registration of carbaryl products. Also included are the full technical assessment reports from the Office of Chemical Safety 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: 27 August 2004

Your comments should be mailed to:

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ACRONYMS AND ABBREVIATIONS

ac	active constituent
ACPH	Advisory Committee on Pesticides and Health
ADI	Acceptable Daily Intake
ai	active ingredient
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
BA	2-bromoacrolein
CRP	Chemistry and Residues Program
ChE	Cholinesterase
CODEX	FAO/WHO Codex Alimentarius Commission
DEH	Department of Environment and Heritage (previously Environment Australia)
EHC	Environmental Health Criteria
F0	parental generation
F1	filial generation, first
F2	filial generation, second
FAISD	Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals
FSANZ	Food Standards Australia and New Zealand
GAP	Good Agricultural Practice
HG	Home Garden
HV	Home Veterinary
ha	hectare
IRED	Interim Re-registration Eligibility Decision
GLP	Good Laboratory Practice
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD_{50}	median lethal dose
LOEL	Lowest Observable Effect Limit
MoS	Margin of Safety
MRL	Maximum Residue Limit
mg/kg bw/d	milligrams/ kilogram of bodyweight/day
NEDI	National Estimated Dietary Intake
NESTI	National Estimated Short-Term Intake
NHMRC	National Health and Medical Research Council
NOEL	No Observed Effect Level
NOAEL	No Observable Adverse Effect Level
NOHSC	National Occupational Health and Safety Commission
NRS	National Residue Survey
OCS	Office of Chemical Safety
OHS	Occupational Health and Safety
PACSC	Pesticide and Agricultural Chemical Standing Committee
PHED	Pesticide Handlers Exposure Database
POEM	Predictive Operator Exposure Model
PHI	Post Harvest Interval
PPE	Personal Protective Equipment
ppm	parts per million
RAC	Raw Agricultural Commodity
RBC	Red Blood Cell
SC	Suspension Concentrate
SUSDP	Standard for Uniform Scheduling of Drugs and Poisons
TMRL	Temporary MRL
WHP	Withholding Period
WP	Wettable Powder

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EXECUTIVE SUMMARY

Introduction

Carbaryl is a carbamate insecticide that is used for the control of insect pests in a broad range of agricultural and domestic situations, including stored grain, ornamentals, lawns, fruit and vegetables and around public buildings. To a lesser extent it is also used in the control of insects on domestic animals. Formulations of carbaryl include emulsifiable concentrates, suspension concentrates, aqueous concentrates, wettable powders, ready-to-use dusts, ready-to-use liquids and solid formulations. There are currently 49 registered products containing the active constituent carbaryl (refer Appendix 1).

Products containing labels and their label approvals were placed under review in 1995 due to potential toxicological and residue human health concerns.

Toxicological Assessment

The toxicological assessment for the review of carbaryl was undertaken by the Office of Chemical Safety (OCS). The OCS assessed all the data and information submitted for the review of carbaryl and provided the APVMA with advice relating to the toxicity of the products. In considering registered carbaryl products, the scope of the toxicological assessment was limited to home garden/domestic and home veterinary products. The APVMA has considered the advice received from the OCS and makes the recommendations relating to the continued use of home garden / domestic and home veterinary products containing carbaryl below.

Based on the data provided, the APVMA is satisfied that the use of registered carbaryl products in pet shampoos, 1% ready to use liquid sprays and home veterinary ear drops would not be likely to be an undue hazard to the safety of people exposed to it during its handling and have an effect that is harmful to human beings. Product labels for these products are considered not to contain the required warning statements and safety directions, therefore labels are to be varied to meet the required standards.

Based on the data provided it was found that user exposure from home veterinary dust preparations for the treatment of companion animals and birds is likely to exceed the Acceptable Daily Intake (ADI) and recommended Acute Reference Dose (ARfD). Revised warning statements and enhanced personal protective equipment are not likely to be effective in protecting users from absorbing systemic doses of carbaryl. Therefore, the APVMA cannot be satisfied that home veterinary dust preparations intended for the treatment of companion animals and birds would not be an undue hazard to the safety of people exposed to it during its handling and would not have an effect that is harmful to human beings. It is recommended that the registrations and label approvals of these products be cancelled.

Insufficient data was received to enable an assessment of householder exposure and assure an adequate margin of safety of carbaryl dusts for treatment of carpets, rugs and animal bedding. Therefore, the APVMA cannot be satisfied that products containing carbaryl for domestic uses would not be an undue hazard to the safety of people exposed to it during its handling and would not have an effect that is harmful to human beings. It is recommended that the registrations and label approvals of these products be cancelled.

The APVMA considers that any product with an acute oral LD_{50} of 1500 mg/kg bw or less is not suitable for domestic/home garden use, because of the toxicological risk. It was found that products containing carbaryl and marketed as 800 g/kg wettable powder and liquids containing 400 and 500 g/L carbaryl are above this safety threshold. Therefore, the APVMA cannot be satisfied that domestic / home garden products with a maximum carbaryl concentration of greater than 160 g/kg (or g/L), 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. Therefore, because of the unacceptable risk the concentration of domestic/home garden products will be restricted to maximum carbaryl concentration 160 g/kg (or g/L). It is recommended that the registrations and label approvals of these products be cancelled.

The toxicological assessment concluded that there was insufficient data to determine user exposure from home garden uses of carbaryl on food producing plants. There was also insufficient data available to ensure dietary intake would not exceed the acute reference dose. Therefore, the APVMA cannot be satisfied that such uses 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. It is recommended that uses of carbaryl on food producing plants in the home garden be deleted and product labels be varied. For other products registered exclusively for these uses it is recommended that registrations be cancelled.

The toxicological assessment identified that one carbaryl product contains a non-active constituent that is potentially carcinogenic and is classifiable as Schedule 7. The registrant has agreed to reformulate the product. It is recommended that after the product is reformulated use can continue after the label is updated to meet required standards.

Safety directions for one home garden product have not been set. Therefore as an out come of the review the registrant will be required to provide information to allow safety directions to be set for this product.

Residue Assessment

The residue assessment for the review of carbaryl was undertaken by the APVMA Chemistry and Residues Program (CRP). The CRP assessed all the data and information submitted for the review of carbaryl. Based on the information provided, the makes the recommendations below.

One carbaryl product is registered for a direct treatment to poultry. Insufficient data was available to assess residues in poultry from direct animal treatment. Therefore, the APVMA cannot be satisfied that the use of the product in accordance with the instructions for its use would not result in residues in poultry commodities exceeding the limits established or that the use of the product would not be an undue hazard to the safely of people using anything containing its residues. Other uses of the product as companion animal dust are also not supported on toxicological grounds. Therefore, it is recommended that this product be cancelled.

Insufficient data were received to enable the assessment of residues in berry fruits (except raspberries and grapes), tropical fruit (both edible and inedible peel varieties), citrus fruits (except oranges), Cape gooseberry, sunflower and linseed, brassica vegetables (except cabbage, broccoli and cauliflower), cucurbit vegetables (except cucumber, cantaloupe, bottle gourd and zucchini), mushrooms, carrots and parsnips, pulses, bulb vegetables and stalk and

stem vegetables (except asparagus). Therefore, the APVMA cannot be satisfied that use of carbaryl products on the above fruit and vegetable crops would not be an undue hazard to the safety of people using anything containing its residues. Instructions for use for the above crops with insufficient data are to be deleted from labels. It is recommended that some product labels be varied. For other products registered exclusively for these uses it is recommended that their registrations be cancelled.

Sufficient data was received to enable the assessment of residues in grapes, oranges, pome fruit (late pre-harvest applications only), stone fruits, cabbage, broccoli and cauliflower, cucumber, cantaloupe, bottle gourd and zucchini, leafy vegetables, fruiting vegetables (except mushrooms and Cape gooseberries), legumes and asparagus. Because of unacceptable residue and acute dietary risk the APVMA cannot be satisfied that use of carbaryl products on the above fruit and vegetable crops would not be an undue hazard to the safety of people using anything containing its residues. It is recommended that product labels be varied, and as all instructions or use for some products are to be deleted, it is recommended that these products be cancelled.

Based on the submitted data the APVMA is satisfied that continued use of registered carbaryl products on raspberries, beetroot, potato, sugarbeet, turnips (Swede), pome fruit (fruit thinning use pattern only), macadamia nuts, pecan nuts, cottonseed, cereal grains, pastures and miscellaneous other forage and fodder crops would not be an undue hazard to the safety of people using anything containing its residues. It is recommended that these use patterns remain and product labels be varied to meet required standards.

One carbaryl product is registered for use as a direct treatment to pigs. Sufficient data was available to assess residues in pigs from direct animal treatment. The APVMA is satisfied that the use of this product in accordance with the instructions for its use would not result in residues in pork commodities exceeding the limits established. Therefore, the APVMA is satisfied that the use of the product would not be an undue hazard to the safety of people using anything containing its residues. It is recommended that this use pattern remain and product labels be varied to meet required standards.

Livestock may be exposed to residues of carbaryl. Sufficient data were available to assess residues in animal commodities resulting from dietary exposure to feeds containing carbaryl residues. The APVMA is satisfied that the use of carbaryl products on potential animal feeds (except cotton) in accordance with the instructions for use would not be an undue hazard to the safely of people using anything containing its residues. It is recommended that these use patterns remain and product labels be varied to meet required standards.

Carbaryl products are also registered for use in various situations considered to be non-food uses (ie. not for human or livestock consumption): as an insecticide in commercial, industrial and domestic areas, tobacco storage sheds and rights of way, in non-crop areas in general, ornamentals, lawns, elm trees (in non-crop areas), kenaf, Duboisia and rosella, and for disinfestation of grain storage buildings. There are no residues issues relating to non-food uses of carbaryl products therefore the APVMA is satisfied that the use of carbaryl products in the above non-crop areas in accordance with the instructions for use would not be an undue hazard to the safely of people using anything containing its residues. It is recommended that these use patterns remain and product labels be varied to meet required standards.

Proposed Final Review Recommendations

Proposed final review recommendations are as follows:

a) Changes to Product Registrations.

- Registrations of carbaryl based home veterinary dusts registered for the treatment of animals and birds are to be **cancelled**, due to unacceptable exposure risk.
- Registration of a carbaryl based treatment for poultry is to be **cancelled**, because of the potential risk of residues in treated animals.
- Registrations of carbaryl dusts for treatment of carpets, rugs and animal bedding are to be **cancelled**, due to unacceptable exposure risk.
- Products for use in domestic/home garden situations are to be restricted to a maximum carbaryl concentration of 160 g/kg or g/L. Products containing 800 g/kg wettable powder and liquids containing 400 and 500 g/L carbaryl for use in domestic/home garden situations are to be **cancelled**, due to an unacceptable exposure risk.
- Use of carbaryl (all forms) is to be **prohibited** for indoor use on domestic premises, due to an unacceptable exposure risk.
- The use of carbaryl products on food producing plants in the home garden is to be **cancelled**, due to an unacceptable exposure risk.

b) Label variations.

Risks identified for some carbaryl uses can be mitigated by label variations as follows:

- Warning Statements and Safety Directions are to be updated.
- Withholding Periods are to be amended
- Deleting those uses where unacceptable risks were identified as in a) above.
- It is also recommended that old approved labels are deemed not to contain adequate instructions and are to be cancelled.
- Label statements to be added to some products as a result of unacceptable risks identified as in a) above.
- A maximum carbaryl concentration of 160 g/kg (or g/L) is recommended for home garden products.
- Instruction for use of carbaryl products on berry fruits (except raspberries), tropical fruit (both edible and inedible peel varieties), citrus fruits, Cape gooseberry, sunflower and linseed, brassica vegetables, cucurbit vegetables, mushrooms, carrots and parsnips, pulses, bulb vegetables and stalk and stem vegetables, grapes, pome fruit (late pre-harvest applications only), stone fruits, cabbage, leafy vegetables, fruiting vegetables, legumes and asparagus are to be deleted from labels, as insufficient data was available to ensure dietary intake would not exceed the acute reference dose.
- The use of carbaryl products as pet shampoos, 1% ready to use liquid sprays and home veterinary ear drops are to remain and product labels are to be varied to meet required standards.
- The use of carbaryl products for raspberries, beetroot, potato, sugarbeet, turnips (Swede), pome fruit (fruit thinning use pattern only), macadamia nuts, pecan nuts, cottonseed commercial, industrial and domestic areas, tobacco storage sheds and

rights of way, in non-crop areas in general, ornamentals, lawns, elm trees (in non-crop areas), kenaf, Duboisia and rosella, cereal crops, pastures and lucerne are to remain and product labels are to be varied to meet required standards.

- The use of carbaryl products for direct treatment to pigs is to remain and product labels are to be varied to meet required standards.
- The use of carbaryl products on potential animal feeds (except cotton) are to remain and product labels are to be varied to meet required standards.

c) Summary of Recommendations.

- The APVMA is satisfied that the conditions to which the registrations of 22 products are currently subject can be varied in such a way that the requirements for continued registration will be complied with and therefore varies registrations and approvals.

- It is then recommended that these variations to label instructions would satisfy the requirements for continued registration of products; and hence 22 product registrations are proposed to be affirmed.

- The APVMA is not satisfied that the requirements for continued registration of 27 products continue to be met and variations can not be made so that the requirements for continued registration will be complied with; and hence it is proposed that these 27 registrations and approvals be cancelled.

1. INTRODUCTION

The APVMA has reviewed the registration of products containing carbaryl and all associated label approvals. The purpose of this document is to provide a summary of the data evaluated and of the regulatory decisions reached, as a result of the review of carbaryl.

1.1 Regulatory status of carbaryl in Australia

Carbaryl has been registered in Australia for over 20 years. There are currently 49 registered products containing the active constituent carbaryl and 21 registrants (Appendix 1). Products formulations contain carbaryl as either the sole active ingredient or in combination with other active constituents. Formulations of carbaryl include emulsifiable concentrates, suspension concentrates, aqueous concentrates, wettable powders, ready-to-use dusts, ready-to-use liquids and solid formulations. The formulation types are set out in Table 1. Information on the uses of carbaryl products can be found in Section 3 of this report.

Table 1: Registered formulations of carbaryl under consideration in review

Formulation type	Level of active constituent	Product type
Emulsifiable concentrates	500 g/L	Agricultural and home garden insecticide concentrate
	100 g/L	Home garden insecticide concentrate
Suspension concentrates	400-500 g/L	Agricultural and home garden insecticide concentrate
	100 g/L	
Wettable powders	800 g/kg	Agricultural and home garden insecticide
	80-120 g/kg	
Ready-to-use dusts	40-50 g/kg	Home garden and commercial bird dusting powder
	50 g/kg	Pet grooming, carpet and pet bedding treatment powder
	18-50 g/kg	Home garden insect bait
	20 g/kg	Agricultural and home garden vegetable dust
	19 g/kg	Home garden flower and vegetable dust
Ready-to-use liquid	0.96 g/L	Home garden insecticide
	2-40 g/L	Pet shampoo
Aqueous concentrate	60 g/L	Domestic lawn insecticide concentrate
	100g/L	Home garden insecticide concentrate
	400g/L	
Solid	37.2g/kg	Pet shampoo tablet
	18 g/kg	Bait pellet
Liquid	10 mg/mL	Ear drop

1.2 Reasons for Carbaryl Review

In 1993 the maximum residue limits (MRLs) for carbaryl use on cereal crops were withdrawn following a residue assessment that showed that the available Australian residue data was inadequate to support the existing MRLs. Temporary MRLs were put in place at that time to allow trials to be carried out.

Insufficient residue data was subsequently provided to support ratification of the temporary MRLs in relation to the use of carbaryl in cereals, either by field application or for stored grain use. A review was initiated in 1995 to reconsider residues in cereals and also to establish MRLs for animals that may be fed on treated cereal products.

In 1999, toxicology reviewers also identified the potential for excessive human exposure to carbaryl. This was considered to have serious implications for exposure of consumers through use of carbaryl in the home garden. The scope of the review was therefore extended to reconsider whether the uses of products containing carbaryl for use as home garden or home veterinary applications and associated labels would have an effect that was harmful to human beings.

More recently (June 2003) the APVMA extended the scope of the review a second time when concerns over the implications of acute dietary intake of carbaryl were identified.

1.3 Regulatory options

There can be three possible outcomes to the reconsideration of the registration of products containing carbaryl and their labels. Based on the information reviewed the APVMA may be:

- satisfied that the products and their labels continue to meet the prescribed requirements for registration and approval and therefore affirms the registrations and approvals.
- satisfied that the conditions to which the registration or approval is currently subject can be varied in such a way that the requirements for continued registration and approval will be complied with and therefore varies the conditions of registration or approval.
- not satisfied that the requirements for continued registration and approval continue to be met and suspends or cancels the registration and/or approval.

1.4 Scope of the Review

The scope of the review considered the reasons for the nomination of carbaryl, the information already available on this chemical and the way in which it is approved for use in Australia.

In light of concerns raised by:

- Office of Chemical Safety (OCS) and
- APVMA,

it did not appear that the APVMA could be satisfied that the continued use of or any other dealing with, products containing carbaryl in accordance with the approved instructions for use:

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

The APVMA also considered whether product labels carry adequate instructions and warning statements. The requirements for product labels 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;
- 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.

On the basis of these concerns, it was appropriate that the registrations and label approvals for carbaryl be subject to reconsideration under Part 2, Division 4, of the Agvet Codes.

The APVMA reviewed the following aspects of product registrations and label approvals for carbaryl:

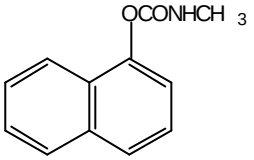
a) Toxicology, including:
   - the potential for home garden/domestic and home veterinary products to cause acute and chronic toxicity, that could be an undue hazard to the safety of people exposed to it during its handling and could have an effect that is harmful to human beings;

b) Residues in food, including:
   - the potential for carbaryl residues, in relation to existing temporary MRLs for cereals treated by field application or storage; and
   - the potential for acute and chronic dietary exposure to carbaryl residues in food commodities; and
   - the potential for consumption of carbaryl residues in food to exceed the ARfD, that may be an undue hazard to the safety of people exposed to its residues in food; and
   - the potential for residues in animals likely to be fed on produce treated with carbaryl.

The APVMA also considered whether product labels carry adequate instructions and warning statements as outline in section 1.4 above.

2. CHEMISTRY ASSESSMENT

2.1 Chemical Identity

Common name:	carbaryl (BSI, E-ISO, ANSI, ESA, BAN, SA)
Synonyms and code number:	Sevin; UC 7744; OMS 629; OMS 29; ENT 23 969
Chemical name:	1-naphthyl methylcarbamate (IUPAC) 1-naphthalenyl methylcarbamate (CAS)
CAS Number:	63-25-2
Molecular formula:	$C_{12}H_{11}NO_2$
Molecular weight:	201.2
Chemical structure:	

2.2 Physical and Chemical Properties of the Active Constituent

Carbaryl is manufactured to a high purity standard (minimum 980 g/kg).

Physical state:	Solid
Colour:	Colourless to light tan crystals
Odour:	Essentially odourless
Melting point:	142°C
Boiling point:	Decomposes
Solubility in water:	120 mg/L (20°C)
Density/specific gravity:	1.232 (20°C)
Solubility in organic solvents:	dimethylformamide and dimethyl sulfoxide 400-450 g/kg; acetone 200-300 g/kg; cyclohexanone 200-250 g/kg; isopropanol and xylene 100 g/kg (all at 25°C)
Octanol/water partition coefficient:	log P = 1.59
Vapour pressure:	4.1×10^{-2} mPa
Flash point:	193°C
Corrosion characteristics:	Not corrosive
Thermal stability:	Stable to heat up to 70°C
Solution stability:	Stable under neutral and weakly acidic conditions. Hydrolysed in alkaline media to 1-naphthol; DT_{50} 12 days (pH 7), 3.2 hours (pH 9).
Storage stability:	Stable for at least 12 months at ambient temperature
Chemical type:	insecticide
Chemical family:	carbamate

2.3 Composition of Carbaryl Active Constituent (AC)

2.3.1 Declaration of Composition

The APVMA has previously evaluated Declarations of Composition (DoC) for all approved sources of carbaryl and found them to be acceptable. In each case the DoC lists the minimum carbaryl content and the maximum content of each relevant impurity present in the active constituent.

2.3.2 Food and Agriculture Organisation Specification

The FAO specification for technical grade carbaryl [FAO Specification 26/TC/S (1989)] is as follows:

Carbaryl	Not less than 980 g/kg
2-Naphthol	Maximum 0.5 g/kg
2-Naphthyl methylcarbamate	Maximum 0.5 g/kg
Loss of vacuum drying	Maximum 10 g/kg

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

2.3.3 APVMA Minimum Compositional Standard

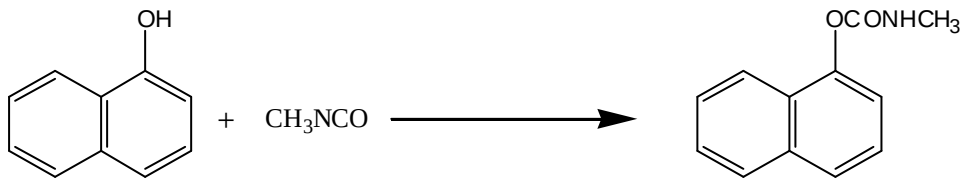
The APVMA minimum compositional standard for carbaryl is as follows:

Carbaryl	980 g/kg minimum

All currently approved sources comply with the APVMA Minimum Compositional Standard.

2.4 Manufacture of Carbaryl Active Constituent

All approved sources of carbaryl are manufactured by the same basic process. 1-Naphthol is reacted with methyl isocyanate in the presence of a catalyst. Carbaryl is crystallised from the reaction mixture at a purity of >980 g/kg.



3. CARBARYL USE PATTERNS

3.1 Introduction

Carbaryl is a broad spectrum, general purpose carbamate insecticide effective against a range of insects, mites, lice, millipedes and other pests. It is used in a diverse range of situations encompassing agricultural crops, veterinary treatments and use in the home garden and has a very short persistence.

3.2 Uses of Carbaryl Products in Australia

3.2.1 Cereal use

Carbaryl is registered for use on cereal crops and is applied during the growing stages for control of certain insect pests (Table 2). It is also registered for use as a grain protectant chemical used during grain storage and for treatment of structures where grain is stored.

Table 2: Uses of carbaryl in cereal crops and in stored grain.

Crop/ Situation	Pests	Product description	Application instructions	Comments
Cereals (general)	Rutherglen Bug, Heliothis spp. Armyworm, Cutworm, Australian plague locust, wingless grasshopper, yellow-winged locust, migratory locust	500 g/L EC or 800 g/kg wettable powder	80-100 g ai/100L or 900-1100 g ai/ha 160-200mL/100L water	Apply at first sign of pest activity and repeat as necessary. For aerial application – apply in not less than 15-20L water (Do not apply by air in NSW)
Sorghum	Sorghum midge (plus pests noted above)	500 g/L	2-2.5 L/ha	First application when 1-2 midges per head present and when 90% heads emerged. Further application at 4 day intervals may be required depending on crop potential.
Rice	Brown planthopper	500 g/L	2.2 L/ha	Apply as pest populations indicate. Under heavy pressure, re-treatment after 14 days may be necessary
Cereal grain storage up to 3 months (except malting barley)	Lesser Grain Borer	500 g/L	10 per L water per tonne of grain (0.8% ai)	Applied through conventional grain spraying equipment
Cereal, grain storage from 3 months up to 9 months			16 mL/L per tonne grain	Applied through conventional grain spraying equipment
Grain stores (surface spraying)			10 mL/L water per 10 square meters	Applied to surfaces of storage areas – spray to runoff

3.2.2 Fruit and vegetable crops.

Carbaryl products are used for the control of a large number of insect pests in a wide variety of fruit and vegetable crops (Table 3). Application of carbaryl on crops is dependant on a number of variables, including crop type and pest pressure. Types of application can be either dilute high volume spraying or concentrate low volume spraying.

Table 3: Uses of carbaryl in fruit and vegetable crops.

Crop	Pest	Product Description	Maximum Rate	Comments
Avocados	Redshouldered leaf beetle	500 g/L	200 mL/100 L	Apply when infestation is first observed and repeat as swarms re-infest
	Monolepta beetle (NSW + QLD)	800 g/kg	130 g/100L	
Beans, cucurbits	Heliothis (budworms), pumpkin beetle, 28-spotted ladybird	500 g/L 800 g/kg	200 mL/100 L 130 g/100L	Apply at first sign of pest activity and repeat at as necessary
Blueberries	Grasshoppers	500 g/L	200 mL/100L	Apply at first sign of pest activity and repeat at 2 week intervals or as necessary
Cape gooseberry	Threelined potato beetle	500 g/L	200 mL/100L	Apply at first sign of pest activity and repeat at 2 week intervals or as necessary
Capsicum	Beetles, weevils	500 g/L	200 mL/100L	Apply at first sign of pest activity and repeat at as necessary
Carrots	Vegetable weevil	500 g/L 800 g/kg	200 mL/100L 130 g/100L	Apply at first sign of pest activity and repeat at as necessary
Citrus	Lightbrown apple moth, yellow peach moth, fruitpiercing moth, citrus leaf-eating caterpillar, Fuller's rose weevil	500 g/L 800 g/kg	160-200 mL/100 L 100-130 g/100L	Apply at first sign of pest activity and repeat at intervals of 2 weeks or as necessary. Use higher rate when higher insect pressure occurs
Cotton	Rough bollworm	500 g/L	200 mL/100 L or 2.2 L/ha	Apply when pest appears and repeat at 7-14 day intervals as necessary. DO NOT use on cotton after 25% of bolls have opened
Cucurbits	Cucurbit stemborer	500 g/L	200 mL/100 L	Apply at first sign of pest activity and repeat at as necessary
Dubosia	Australian plague locust, cluster caterpillar, grasshoppers, leaf eating ladybirds, sandal-box hawk moth	500 g/L 800 g/kg	200 mL/100 L or 2.2 L/ha 130 g/100L	Apply when pest appears and repeat as necessary
Feijoa, guavas	Orange fruit borer	500 g/L	200 mL/100L	Spray trees thoroughly to dripping point in late November to early December followed by a second application in late January to early February. Add summer oil
Fruit – general	Wingless grasshopper	500 g/L	175 mL/100 L	Spray infested area thoroughly as required

Grapes	Grapeleaf blister mite, grapevine hawk moth, grapevine moth, lightbrown apple moth, cutworms, mealybugs, scale	500 g/L 800 g/kg	160-200 mL/100L 100-130 g/100L	Apply at first sign of pest activity and repeat at intervals of 2 weeks or as necessary. Use higher rate when higher insect pressure occurs
Jaboticaba, Jackfruit	Swarming leaf beetle	500 g/L	200 mL/100 L	Several applications may be needed. Do no apply during flowering
Kenaf	Redshouldered leaf beetle		2.2 L/ha	Apply as pest pressure indicates
Kiwi fruit	Lightbrown apple moth	500 g/L	160-200 mL/100 L	Apply when pests appear and repeat as necessary. Apply as high volume spray at 7-10 day intervals when pests present. Use higher rate where high insect pressure occurs
Leafy & root vegetables	Vegetable weevil	500 g/L	300 mL/100 L	Apply at first sign of pest activity and repeat at as necessary
Linseed	Heliothis (budworm)	500 g/L	200 mL/100 L or 2.2 L/ha	Apply when pest appears and repeat as necessary
Loquats	Light brown apple moth	500 g/L	200 mL/100 L	Apply at first sign of pests and repeat as necessary
Lucerne	Heliothis (budworms), leafhoppers (Jassids) Leaf roller, lucerne flea	500 g/L 800 g/kg	2.2 L/ha 1-104 kg/ha	Apply at 1st sign of pest activity and repeat as necessary. Use sufficient water for adequate coverage
Lychees	Caster oil looper, leaf eating looper, macadamia nutborer, redshouldered leaf beetle, swarming leaf beetle	500 g/L	200 mL/100 L	Apply at first sign of pests and repeat as necessary
Macadamias	Macadamia nutborer, macadamia twig-girdler, reshouldered leaf beetle, cornelian (butterfly), macadamia cup moth, macadamia nut moth, yellow peach moth	500 g/L 800 g/kg	200 mL/100 L or 2.2 L/ha 130 g/100L	Apply a preventative spray after moths have been flighting Four sprays at 2-3 week intervals during late Nov. to Feb.
Mangoes	Fig leafhoppers Pink wax scale, flattids	500 g/L 800 g/kg	200 mL/100 L 90 g/100L	Apply when populations appear on leaf stalks (Oct-Nov)
Pastures, pasture seed crops	Lucerne leafroller	500 g/L	1.8-2.2 L/ha	
Pears	Pear and cherry slug	500 g/L	200 mL/100L	Apply as pest populations indicate
Pecans	Orange fruitborer, yellow peach moth	500 g/L	200 mL/100 L	Apply to mature trees carrying nuts. Direct spray to clusters of nuts where pests build up
Pome fruit Apples, pears	Early fruit caterpillars, codling moth, lightbrown apple moth, pearleaf blister mite, fruit thinning Pear and cherry slug	500 g/L 800 g/kg	160-200 mL/100 L 100 – 130 g/100L	Apply at 1st sign of pest activity. Repeat spray at 21 day intervals during the season. Use higher rate where high insect pressure occurs
Potatoes	Potato moth	500 g/L 800 g/kg	200 mL/100 L or 2.2 L/ha 1.4 kg/ha	Apply at 1st sign of moth activity. Use sufficient water for goo coverage. One or two sprays at 3-4 weeks intervals could be required
Rambutans	Caster oil looper, Redshouldered leaf beetle, swarming leaf beetle	500 g/L	200 mL/100 L	Apply at 1st sign of pests and repeat as required

Raspberries	Grasshoppers, lightbrown apple moth, raspberry fruit caterpillar	500 g/L	200 mL/100 L	Apply at 1st sign of pests and repeat as required
Rosella	Leaf-eating beetles	500 g/L	200 mL/100L	Apply at first sign of pest activity and repeat at as necessary
Stone fruit Apricots, nectarines, peaches, plums, prunes	Green treehopper, lightbrown apple moth, oriental fruit moth, pear and cherry slug, redshouldered leaf beetle, orange fruit borer, heliothis (budworms), European earwig	500 g/L 800 g/kg	160-200 mL/100 L 100-180 g/100L	Apply at first sign of pest activity and repeat at intervals of 2 weeks or as necessary. Use higher rate when higher insect pressure occurs
Strawberry	Grasshoppers	500 g/L	200 mL/100 L	Apply at 1st sign of pests and repeat as required
Sunflower	Black sunflower scarab	500 g/L	1 L/ha	Apply to newly emerged plants when pest pressure and repeat as necessary
Sweet corn	Red-shouldered leaf beetle	500 g/L	1.6-2.0 L/ha	Apply at first sign of pest activity and repeat at as necessary
Tomatoes	Leafminer caterpillars Tomato leaf borer False wireworm	500 g/L 800 g/kg	200 mL/100 L or 2.2 L/ha 130 g/100L	Spray plants thoroughly to the point of wetness at the first sign of attack
Vegetables – general	Vegetable weevil	500 g/L 800 g/kg	320 mL/100 L 100-190g/100L	Apply when pest appears and repeat as necessary

3.2.3 General purpose non-crop uses.

Products containing carbaryl are used in a number of non-crop situations (Table 4). These uses include controlling insect pests around outbuildings or sheds and in right of way areas. Application in theses areas is dependant on the pest and is mostly applied as a spray from an agricultural spray unit or handheld spray pack and by direct application of liquid from a squirt bottle.

Table 4: General purpose non crop uses of carbaryl.

Situation	Pest	Product Description	Maximum Rate	Comments
Non-crop, commercial and industrial areas, Right-of-way	European earwig	500 g/L	55ml/10L	Spray on exterior walls of houses and outbuildings, boundary fences and breeding places such as wood piles and reserves
	Plague grasshopper, plague locust, wingless grasshopper	500 g/L	160mL/100 L	For treatment of swarms by high volume ground equipment. Use sufficient volume of water to get a good coverage, usually between 220 and 1100 L / ha.
Domestic pests	Ants, fleas, moths, weevils, European earwig	500 g/L	2.2L/100L	Spray thoroughly all surfaces to be treated. DO NOT uses as a space spray.
Concealed or underground nests in and around home garden, shed	Vespulid wasp (English/European Wasps)	500 g/L	320ml/L	Pour or squirt down the entrance to under ground nests or spray semi-concealed nests.
	Honey Bees in concealed Hives	500 g/L	1.1L/100L	Spray into nests in the open and in enclosed cavities where the nest is close to the entrance used by bees.
Tobacco, Bulk, Shreds	Tobacco beetles, ants, European earwigs, fleas, moths, weevils	500 g/L	200mL/10L	Spray all surfaces. Apply 5L of prepared spray to 100 square meters.

3.2.2 Veterinary use

The majority of veterinary uses for carbaryl are for control of ectoparasites on domestic animals, including birds. The pests controlled include fleas, mites, mange and ticks. The products available for control of these pests are in the form of shampoos and dusting powders. A summary the home veterinary use patterns for carbaryl are shown in Table 5.

Table 5: Summary of home veterinary uses of carbaryl

Situation	Pests	Product description	Application instructions
Poultry and other animals, ornamental caged birds	Lice, ticks, mites, black beetle	Dusting powder containing 40-50 g/kg carbaryl	Apply directly to bird or animals and rub into coat, feathers or fur. 50g squeeze pack: Squeeze container quickly and firmly directing the resulting cloud of powder towards the bird. Liberally dust cage floor and perches.
Dogs and cats	Earmite Mild bacterial and fungal ear infections	Ear drop containing 10 mg/mL carbaryl with 20 mg/mL salicylic acid and 2 mg/mL chlorcresol	Apply several drops to both ear canals twice daily for at least 14 days
	Brown dog tick, mange mites, lice	Shampoo containing 10-40 g/L carbaryl (some products with other actives).	Wet coat and lather well with foam. Massage in and after 5 min rinse and dry thoroughly.
Dogs, cats, rabbit, mouse, guinea pig	Fleas, ticks (except paralysis tick), lice	Grooming powder containing 50 g/kg carbaryl dust (some products with other actives)	Shake powder on to animals and work in well. 0.25g carbaryl brushed into the fur of the animal and excess removed with a damp cloth Brush off excess dust. Repeat each week.
Horses and ponies	Lice, ticks and mites	Dry Shampoo, 350g block containing 37.2g/kg carbaryl	Smoothly draw block against coat of the animal, both with and against the lay of the coat. Apply freely once a day.
Horses and dogs	Mange, girth itch, Queensland itch and lice	Shampoo containing 1.0 gram carbaryl per 500ml	Shampoo coat and rinse thoroughly.
Pigs	Body louse and Sarcoptic mange	EC Insecticide containing 500g/L carbaryl	Spray pig thoroughly to wetness. Repeat application 10-14 days later.

3.2.3 Home garden use patterns

Comments received at the commencement of the review indicated that carbaryl is the insecticide of choice for the management of most chewing insect pests in gardens including leafminers, caterpillars, grubs, grasshoppers, mites, aphids and lacewings. It is selectively active and very effective against millipedes, earwigs and pear and cherry slugs. Carbaryl was also highlighted as one of the few chemical products available for the control of Lepidoptera in the home garden and also considered an extremely important chemical for control of Black Portuguese millipede (*Ommatoiulus moreletii*), found in home gardens in South Australia.

Home garden products (Table 6) are also reported as being used in nurseries mainly due to the small amount of chemical used on each occasion with the small pack size also minimising the need for storage of chemicals.

Table 6: Summary of Home Garden Uses of Carbaryl Products

Target crop	Target pest	Formulation details	Use instructions
1 FRUIT			
Apple, apricot, avocado, citrus, fruit (general), grape, nectarine, peach, pear, plum, prune, stone fruit	Codling moth, light brown apple moth, pearleaf blister mite, borer, native budworm, orinetal fruit moth, monolepta beetle, bronze orange bug, weevils, scale, grapeleaf blister mite, pear and cherry slug, green treehopper	WP 800 g/kg	Use 1g/L ai in water. Apply every 3 weeks from mid sept.
		WP 80-120 g/kg	Either packed in 60g measure packs to be diluted into 5L water or use 0.8-1g/L water
		AC 400-500 g/L	Use 1g/L ai. Spray 3 weeks after petal fall repeat every 3-4 weeks
		AC/SC. 100 g/L	Dilute to 1g/L. spray when insects first appear then every 7-10 days.
2. VEGETABLES			
Tomato, vegetable (general), broccoli, bean, brussel sprout, cabbage, carrot, cauliflower, cucurbit, leafy vegetable, potato, root vegetable, turnip,	Aphid, Caterpillar, Cutworm, Blight, Mite, Leafhopper, Thrip, Tomato grub, Ladybird, Cabbage moth, Earwig, Cabbage white butterfly, Weevil, Rutherglen bug, Green vegetable bug, Leaf spot, Russet mite, Harlequin bug, Helicoverpa, Lace bug, Potato moth, Pumpkin beetle, grasshopper	20g/kg	Dust lightly over all surfaces every 7-10 days
		WP 800 g/kg	Spray when insects first appear then every 7-10 days
		WP 80-120 g/kg	Either packed in 60g measure packs to be diluted into 5L water or use 0.8-1g/L water. Apply at 7-14 days intervals
		Ready to use liquid 0.96 g/L	Spray plants thoroughly every 7 days
		AC 400-500 g/L	Use 1g/L ai. Apply at first signs of pest activity.
		AC/SC 100 g/L	Dilute to 1g/L. spray when insects first appear then every 7-10 days.
3. ORNAMENTALS			
ornamental	Lace bug, budworm, cabbage moth, cabbage white butterfly, caterpillar, cutworm, blight, earwig, green vegetable bug, harlequin bug, helicoverpa, leafhopper, lace bug, ladybird, leafroller, potato moth, pumpkin beetle, rutherglen bug, tomato grub, grasshopper,	20g/kg ai	Dust lightly over all surfaces every 7-10 days
		WP 800 g/kg	Spray when insects first appear then every 7-10 days
		WP 80-120 g/kg	Either packed in 60g measure packs to be diluted into 5L water or use 0.8-1g/L water. Apply at 7-14 days intervals

Target crop	Target pest	Formulation details	Use instructions
		AC 400-500 g/L	Use 1g/L ai. Apply at first signs of pest activity.
		AC/SC 100 g/L	Dilute to 1g/L. spray when insects first appear then every 7-10 days.
4. OTHER HOME GARDEN USES			
Carpet, garden, general home, lawn, general non crop area, rug, animal bedding	Flea, louse, mite, millipede, grasshopper, cricket, earwig, armyworm, blackheaded pasture cockchafer, helicoverpa,	18-50 g/kg dusts	Dust area where insects seen.
		50 g/kg (animal houses, bedding, carpet)	2kg/100sq m. dust through muslin bag or by powder or hand dust. Sprinkle on floor. Sprinkle over carpet and leave for at least 1 hour then vacuum. Repeat every 14 days.
		Bait 18 g/kg	Scatter bait in garden or fill tray and place wherever pests are present.
		AC/SC 100 g/L	Turf: dilute to 2.5g/L. Spray 8L over 50 sq m.
		Ready to use liquid 60 g/L	Used with a hose-on applicator. Spray at the first signs of infestation.
5. TREES/FLOWERS			
Ornamentals including, flowers, Elm tree in non-crop situations, rose	Elf leaf beetle, aphid, azalea lace bug, cabbage moth, caterpillar, fungus, harlequin bug,, leaf spot, thrip,	20g/kg	Dust lightly thoroughly covering all surfaces at 7-10 day intervals.
		WP 800 g/kg	ELB – apply to trunk of tree in December. Repeat 4-6 weeks later. Apply in half metre wide band around trunk

4. SUMMARY OF DATA ASSESSMENT

4.1 Toxicology

4.1.1 Introduction

The toxicological assessment examined

(1) studies intended to elucidate the mechanism of tumour formation,
(2) multi-generation and reproduction and developmental studies in rats and rabbits,
(3) addenda to a previously evaluated developmental neurotoxicity study in rats,
(4) a short-term repeat-dose study and a 1-year study in dogs, and
(5) exposure studies undertaken on persons using American registered carbaryl products in simulated domestic settings.

The systemic doses likely to be delivered to users of registered carbaryl products under Australian conditions have also been estimated. These estimates have been related to toxicological benchmarks and recommendations made on the continued registration and conditions of use of carbaryl products. A summary of the toxicological profile of carbaryl is included in Appendix 2.

4.1.2 Metabolism and toxicokinetics

The absorption, excretion and toxicokinetics of carbaryl are typical of the carbamate class. Carbaryl is extensively absorbed by the oral route and excreted rapidly in the urine by humans and experimental animals except dogs, in which the faeces is also a significant route of excretion. There is little tendency for carbaryl or its metabolites to accumulate in body tissues, even after subchronic administration.

4.1.3 Cholinesterase (ChE) inhibition

Carbaryl possesses anticholinesterase activity typical of members of the carbamate class. In rats, ChE inhibition reaches its maximum between 0.5 and 1 hour following carbaryl administration by gavage. The subsequent time course of ChE inhibition is both dose- and tissue/site dependent. Recovery of plasma and RBC cholinesterase activity is rapid (within 2 hours post dosing at 10 mg/kg, and within 24 hours at 50 mg/kg). At higher doses reversibility is more prolonged.

4.1.4 Genotoxcity

No new studies were presented for the review. Previous reviews of the genotoxic potential of carbaryl have concluded that carbaryl does not damage DNA and is unlikely to be mutagenic in humans.

4.1.5 Neurotoxicity and behavioural studies

The effects of carbaryl on the nervous system of rats, chicken, monkeys and humans are primarily related to ChE inhibition and are usually transitory. In a developmental neurotoxicity study, carbaryl had no adverse effects on foetal or pup survival, growth or development at up to and including the highest dose of 10 mg/kg bw/d. In both subchronic

and developmental neurotoxicity studies, no adverse findings were made with respect to neuropathology in the adults or offspring.

4.1.6 Reproduction and development

New developmental studies in rats and rabbits were submitted for the review. Maternotoxicity was seen as cholinergic signs in rates, inhibition of plasma and red blood cell (RBC) ChE activity in rabbits, and depressed weight gain in both species. Foetal development was retarded at maternally toxic doses, but there were no treatment related visceral anomalies or malformations.

4.1.7 Carcinogenicity

In chronic rodent studies by Hamada (1993a and 1993b), carbaryl caused tumours of the thyearoid, urinary bladder and liver in rats, and kidney, liver and vascular systems in mice. However with the exception of vascular tumors, carcinogenicity did not occur below the highest doses administered (8000 and 7500 ppm in the diet to mice and rats, respectively).

Since carbaryl has not shown any convincing evidence of genotoxic activity, and because NOELs of 1000 and 1500 were demonstrated in the respective species for bladder, hepatic, thyearoid and renal tumors, these high dose tumors have not been considered a barrier to continuing registration of carbaryl, subject to adequate safeguards that would limit public exposure to the chemical.

However, the vascular system tumours are of significantly greater concern. Although these did not develop in female mice below the 8000 ppm feeding level, they occurred in males even at the lowest dose of 100 ppm. Despite the fact that carbaryl did not cause cancer to develop in a short term bioassay in genetically engineered male mice that are highly sensitive to genotoxic carcinogens, there are still limitation in the understanding of carbaryl's carcinogenic properties and its mode or mechanism of action remain uncharacterised. Under the circumstances it is considered that the use of an enhanced safety factor should be maintained and public exposure should be reduced to the lowest extent reasonably achievable. From the data assessed there is no evidence that carbaryl is carcinogenic in humans.

4.1.8 Human studies

The current submission included human exposure studies which measured the amount of carbaryl deposited on the skin and clothing of volunteers using USA carbaryl products under simulated home garden and veterinary conditions. The concentration of carbaryl in the breathing zone air was also measured. The product that had by far the greatest potential for human exposure was a 5% carbaryl veterinary dusting powder. In decreasing order of exposure potential, were 10% vegetable dusts, a 22% liquid concentrate applied to vegetables or trees by spray, and a 0.1% ready to use vegetable spray. In all cases the majority of exposure occurred via the hands. The veterinary dusting powder also caused significant exposure by inhalation whereas inhalation exposure by vegetable dusting and application of carbaryl sprays, was negligible. In general, only about 5% or less of carbaryl that became deposited on the external clothing penetrated to the skin, and comparison between gloved and un-gloved subjects showed that gloves effected a 95% reduction in exposure.

4.1.9 Exposure from home garden and home veterinary products

The APVMA "Guidelines for Pesticides used by Householders" stipulate that any domestic pesticide formulation that may be ingested should not be expected to be acutely toxic to a child at doses up to 1500 mg/kg bw and should not be acutely toxic at dermal doses up to 1000 mg/kg bw. The irritancy to skin and eye of domestic pesticide formulations should be low. Several products currently sold in home garden pack sizes are unlikely to comply with the above safety threshold. Only products containing 160 g/kg or less of carbaryl would comply with the cut-off value for acute oral toxicity.

The majority of Australian HG/HV products were found to be capable of delivering systemic doses to users in excess of the ADI for carbaryl. The only products that were not likely to deliver a toxicologically significant dose of carbaryl were, 10g/L pet shampoos, 20 g/kg garden/vegetable dusts, wettable powder, 1g/L ready to use liquid sprays and HV ear drops.

4.1.10 Conclusions

Recommendations have been formulated with a view to constraining the upper limit of carbaryl intake to the ADI and ARfD, through the use of label hazard warning statements and modifications to protective clothing and equipment. Home garden/veterinary products that have the potential to cause carbaryl intake above the ADI and ARfD under anticipated conditions of use and are not amenable to risk reduction by means of protective clothing/equipment are considered unsuitable for continued registration. Also regarded as unsuitable are products for which there are insufficient data to estimate the extent of household exposure.

The most hazardous products are veterinary dusts. Given that carbaryl shampoos are available and have a lower potential for use exposure than dusts, the most effective course of action would be to remove carbaryl based pet dusts and powders from the home veterinary market.

Although capable of delivering systemic doses 2 to 12 times higher than the ADI, carbaryl home garden vegetable dusts, wettable powders and liquids would cause much less user exposure than pet dusts. This is primarily because garden use often entails discharge at or below waist height and manual contact with treated vegetation is not required. Inhalation exposure from these products is negligible. Therefore, these products may be used safely provided appropriate warning statements and Safety Directions appear on the product labels.

Contact with carbaryl applied on turf or around the external areas of the home may result in delivery of a systemic dose above the ADI if the carbaryl was not washed off the contaminated skin within 1 hour. The appropriate risk reduction strategy here is to recommend that householders keep off treated surfaces.

It is impossible to determine the extent of householder exposure following indoor treatment with carbaryl. Label warnings are considered insufficient to ensure safety. As such it is recommended that carbaryl should not be registered for indoor use.

Insufficient information was provided to assure that the uses of carbaryl products on food producing plants in the home garden would not result in householder expose exceeding the ARfD. As such it is recommended that carbaryl should not be registered for uses on food producing plants.

Based on the information currently available to the OCS, *Joseph Lyddy Y-Itch Animal Insecticide Bactericide* contains a non-active constituent that may be carcinogenic and classifiable as a Schedule 7 (S7) chemical by the *Standard for the Uniform Scheduling of Drugs and Poisons*. Therefore, there is insufficient grounds to provide assurance that *Joseph Lyddy Y-Itch Animal Insecticide Bactericide* will not be likely to have an effect that is harmful to human beings.

4.2 Residues

4.2.1 Introduction

In 1995 the APVMA initiated a review of the use of carbaryl in cereals. The review at this time was to examine residue data and MRL related to cereals and animals that may be fed on treated cereal products. An evaluation of the human dietary exposure to carbaryl residues was also conducted.

In evaluating the human dietary exposure to carbaryl residues it was necessary to examine the intake from consumption of food commodities other than grains and animal commodities, in particular fruits and vegetables. To do this, National Estimated Daily Intake (NEDI) & National Estimated Short Term Intake (NESTI) calculations were undertaken. As a result, the residues assessment has enabled recommendations to be developed for amended MRLs to cover all food crop uses of carbaryl.

4.2.2 MRLs for cereal uses

Carbaryl is used both pre- and post-harvest on cereal grains. Maximum residues resulting from the pre-harvest only and post-harvest only uses of carbaryl were added together to derive an MRL for the combined pre- and post-harvest use. The current harvest with holding period (WHP) for cereal grains of 0-3 days was not supported by sufficient data. As 14 days after the last spray is the first time point for which an adequate number of samples were collected for the major cereal grains, the harvest WHP for cereal grains are to be extended to 14 days. Using a 14 day WHP, the residues from pre- and post-harvest use when combined suggest the MRL for cereal grains could be raised from 5 mg/kg to 15 mg/kg.

The processed cereal commodities for which residues were found to concentrate to a significant extent and for which separate MRLs are required were sorghum bran and wheat bran. To cover the maximum expected residue in wheat bran the MRL for wheat bran are to be raised from 20 mg/kg to 30 mg/kg and a separate MRL of 50 mg/kg for sorghum bran should be established.

4.2.3 Animal Feed Commodities

Carbaryl treated crops may be fed to animals leading to residues in animal tissues and milk. The current MRLs in Table 4 of the MRL Standard, (Maximum residue limits for pesticides in animal feed commodities) are Forage of cereal grains T100 mg/kg and Straw and fodder (dry) of cereal grains T100 mg/kg (where T is temporary).

These MRLs do not adequately cover the range of possible animal feed commodities for which carbaryl is currently approved for use. To remedy this situation new MRLs are recommended for a variety of animal feeds. The current Australian mammalian tissue and

milk MRLs are based on a maximum feeding level of 100 mg/kg for cereal forage or 400 mg/kg when corrected for moisture content and expressed on a dry weight basis.

The change in harvest WHP for cereal grains also requires a change in the WHP for grazing/cutting for stock food. When a 14-day grazing/cutting for stockfeed WHP is used for cereal grains an MRL of 100 mg/kg adequately cover residues in straw and fodder (dry) of cereal grains. Residues in forage crops (dry weight basis) are also covered by an MRL of 100 mg/kg for cereal forage (green) when combined with a 14 day WHP.

Pasture is grown as forage or hay for feeding to animals. An MRL of 300 mg/kg for hay or fodder (dry) of grasses is required to adequately cover natural variation in residue results when combined with an extended WHP of 7 days for cutting for stock food. An appropriate MRL for grass pasture (green) is 400 mg/kg when expressed on a dry weight basis.

Legume crops are sometimes grown as animal feeds (succulent crops) or the waste left after the harvesting of grain is fed to animals (fodder/hay). The residue data supported an MRL of 400 mg/kg for legume forage (green) and 100 mg/kg (dry weight basis) for legume fodder when combined with a 7 day WHP.

On examining the data for miscellaneous forage and fodder crops it was apparent the current grazing WHP of 3 days could lead to residues in excess of 400 mg/kg (on a dry weight basis) and therefore violations of Australian animal tissue MRLs. The grazing WHP for miscellaneous fodder and forage crops should be extended to 7 days to afford the necessary margin of safety against residue violations in animal tissues. In addition, an MRL of 300 mg/kg should apply to crops classified under the CODEX crop grouping AM 0165 miscellaneous fodder and forage crops (except leguminous and grassy plants (Gramineae), but including grasses for sugar production.

4.2.4 Animal treatments

Carbaryl is registered as a direct treatment for the food-producing animals including pigs and poultry. Literature evidence indicated that direct treatment of pigs results in negligible residues. Therefore the MRLs for mammalian commodities can be set based on estimated exposure to residues in the animal diet and from animal transfer studies that determine residues in tissues and milk after feeding at different levels. The maximum feeding level, based on the revised MRLs for animal feed commodities is estimated to be approximately 400 ppm for cattle and was used in assessing the mammalian animal MRLs.

Assuming that residues increase with dose, the maximum residue in edible offal was estimated to be 0.16 mg/kg. The current MRL for edible offal (mammalian) of T0.2 mg/kg will be adequate to cover residues in liver and kidney. Carbaryl has a log $P_{o/w}$ of 1.59 and is unlikely to partition into fat tissues. The current whole milk and meat (mammalian) MRLs of *0.05 and T0.2 mg/kg respectively are too high. These MRLs should be amended to reflect that residues are expected to be below the limit of quantitation (0.02 mg/kg) of the analytical method for both commodities.

The CODEX MRLs established for mammalian tissues and milk were based on feeding forage and fodder crops at 100 mg/kg fresh weight (400 mg/kg when expressed on a dry weight basis). As the Australian MRLs were set based on the same maximum feeding level there is minimal risk of violations of the relevant CODEX MRLs.

In the case of poultry, residues from direct treatment are much higher than those incurred from feeding treated grain. The poultry MRLs do not require amendment as part of this review.

4.2.5 Dietary Intake

The review of toxicology information, as discussed in Section 9, recommended an increase in the ADI from 0.004 mg/kg bw/day to 0.008 mg/kg bw/day. In addition an ARfD of 0.01 mg/kg bw/day was established for carbaryl. It is therefore necessary to determine that the current use patterns will not result in a dietary intake that will exceed the revised ADI for lifetime exposure (chronic dietary intake), or the ARfD for short term exposure (acute dietary intake).

Carbaryl has not been included any of the FSANZ Market Basket Surveys or Total Diet Surveys of the last decade and so there is no information on actual dietary exposure. In such cases conservative models that overestimate dietary intake are used to establish human safety. The model used in Australia and recommended by the joint consultation of the WHO and FAO on dietary exposure to pesticides is the NEDI and NESTI calculations.

In the NEDI calculation use is made of survey results for agricultural commodities, processing factors for commodities such as washing, peeling or cooking, and median or maximum residues for "worst-case" trials. If there is no data to allow any reduction in the residue level it is assumed that residues are present at levels corresponding to the MRL (worst-case).

The NEDI calculation using the recommended MRLs together with those already established accounts for approximately 89% of the ADI of 0.004 mg/kg bw/day. As the NEDI calculation is widely recognised as a gross overestimate of the likely intake and the estimated exposure is less than the ADI it is concluded that the risk to human health from exposure to carbaryl residues in the diet is minimal.

Where insufficient residue trial data were available, the highest residue (HR) from trials of a similar crop or the current MRL was used as the HR value in the NESTI calculations. A minimum of 41 consumers is required in the dietary survey results to adequately determine the 97.5^{th} percentile consumption figure. Where the number of consumers was less than 41, large portion sizes of similar commodities were used. Where the number of consumers was still <41, the consumption figure for the entire crop group was used as a conservative estimate.

Of the crops and commodities for which there were sufficient residues data available to allow the establishment of an MRL, the NESTI calculation did not exceed the ARfD for the following:

- raspberries
- beetroot, potato, sugarbeet, turnips (Swede)
- pome fruit (fruit thinning use pattern only)
- macadamia nuts, pecan nuts
- cottonseed
- cereal grains
- animal commodities

Further details can be found in Section 9.

4.2.6 Changes to MRL Standard

Sufficient data was available to allow revision of the current MRLs for a number of commodities. The details of these changes can be found in Section 6, recommendations.

4.2.7 Withholding periods

The assessment highlighted that changes were required to withholding periods on relevant labels, the details of which can be found in Section 5, recommendations.

4.2.8 Summary residue data assessed

A summary of the residue assessment for human foods, with respect to residues data and acute dietary intake, is tabulated in Table 7.

Table 7: Summary of available residues data and dietary exposure assessment

Crop group	Sufficient residues data to establish MRL	Insufficient residues data to establish MRL	Dietary exposure exceeds ARfD	Commodities with sufficient data and where exposure <ARfD
Fruit Berry	Grapes Raspberries	All other berry crops	Grapes	Raspberries
Fruit Citrus	Oranges	All other citrus	Oranges	
Fruit Pome	Whole group (fruit thinning use) Apples Pears		Apples Pears	Whole group (fruit thinning use only)
Fruit Stone	Peach Cherry Plum Apricots Nectarines		Peach Cherry Plum Apricots Nectarines	
Fruit Tropical inedible peel		All crops		
Fruit Tropical edible peel		All crops		
Seed Oil	Cotton	Sunflower Linseed		Cotton
Tree Nuts	Macadamia nuts Pecan nuts			Macadamia nuts Pecan nuts
Vegetable Bulb		All crops		
Vegetable Brassica	Cabbage Cauliflower Broccoli	All other brassica vegetables	Cabbage Cauliflower Broccoli	
Vegetable Cucurbits	Cucumber Cantaloupe Zucchini Bottle gourd	Other cucurbits including watermelon, pumpkin	Cucumber Cantaloupe Zucchini Bottle gourd	
Vegetable Leafy	Whole group		Whole group	
Vegetable	Chilli peppers	Mushrooms	Chilli peppers	

Fruiting other than cucerbits	Capsicums Eggplant Okra Sweetcorn Tomatoes	Cape gooseberry	Capsicums Eggplant Okra Sweetcorn Tomatoes	
Vegetable Pulses		All pulses		
Vegetable Legumes	Beans Peas		Beans Peas	
Vegetable Root and Tuber	Potatoes Sugarbeets Beetroot Turnip (Swede)	Carrots Parsnips		Potatoes Sugarbeets Beetroot Turnip (Swede)
Vegetable Stork and Stem	Asparagus	All other stalk and stem vegetables	Asparagus	
Grains Cereal	Cereal grains			Cereal grains

4.3 International Regulatory Status

4.3.1 JMPR activity

Carbaryl was reviewed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1963, 1965, 1966, 1967, 1969 and 1973. The original ADI of 0-0.02 mg/kg bw/d was set in 1963 on the basis of a No Observable Adverse Effect Limit (NOAEL) of 1.8 mg/kg bw/d in a 1-year dog study. This was revised to 0-0.01 mg/kg bw/d in 1969 because of concern about effects on the male reproductive system seen in a 1-year gavage study in rats with a NOAEL of 2 mg/kg bw/d, and because a dose of 0.12 mg/kg bw/d may have affected renal function in a 6-week study in humans. In 1973, the JMPR established a full ADI of 0-0.01 mg/kg bw/d.

The JMPR carried out a further toxicological review of carbaryl in 1996, and decreased the ADI to 0.003 mg/kg bw/d by application of a 5000-fold safety factor to the LOEL for vascular tumours in male mice. The JMPR again considered carbaryl in 2001. The ADI was revised upwards to 0.008 mg/kg bw/d; while the basis for the ADI was unchanged, the safety factor was relaxed to 2000. The JMPR also established an ARfD for carbaryl of 0.2 mg/kg bw, based on a NOAEL for ChE inhibition of 125 ppm (equal to 3.8 mg/kg bw/d) in a 5-week dietary study in dogs. A safety factor of 25 was applied because ChE inhibition by carbaryl [in rats] is "rapidly reversible and driven by the peak concentration in plasma."

4.3.2 United States Environmental Protection Agency (US EPA) activity

In October 1996, the US EPA imposed exposure mitigation measures on carbaryl based products. Pending the submission of user exposure studies to the Agency, dust formulations were removed from uses on trees and ornamental plants where application was intended to be higher than chest height, and some applications to pets. The conditions of use of household liquid and dust products were amended to prohibit use more than once per week, and to mandate that gloves be worn during application.

In June 2003 the US EPA release an Interim Re-registration Eligibility Decision (IRED) for carbaryl. The report identified that "although all uses of carbaryl may not meet current safety standards and some uses may pose unreasonable risks to human health and the environment these effects could be mitigated".

Outcomes
The report supported the continued registration of carbaryl products.

Dietary Risk
Both the acute and chronic risks of exposure to carbaryl from food were found to be below the US EPA's level of concern.

The US EPA ADI is 0.008 mg/kg bw/d, in accordance with the JMPR level outlined in 4.3.1 above. As is recommended in this report the ADI for Australia as set by OCS is to be revised from 0.004 mg/kg bw/d to 0.008 mg/kg bw/d in accordance with the relaxing of the safety factor to 2000.

The US EPA acute and chronic Reference Doses are both 0.01 mg/kg/d. The ARfD was based on a NOAEL of 1 mg/kg/d in a rat developmental neurotoxicity study, to which an uncertainty factor of 100 was applied. The chronic RfD was derived by applying a 300-fold uncertainty factor to a LOAEL of 3.1 mg/kg/d for inhibition of plasma and brain ChE activity in a chronic dog study.

Residential Risk
The US EPA was concerned about the exposure of householders using carbaryl lawn, garden, ornamental plant and pet flea control products as well as adults doing garden work and toddlers playing on treated lawns. As an outcome of these concerns the registrant cancelled all liquid and dust uses on pets, except flea collars. Other risks were mitigated by changes to the amount of active ingredient, packaging and size of residential products and the cancelling of liquid board casts on lawns (pending the results of data being developed).

4.3.3 United Kingdom Ministry for Agriculture, Fisheries and Forestry (*UK MAFF) report Sept 1996*

An initial review conducted in 1996 by the UK MAFF identified toxicological concerns about worker exposure to carbaryl. At this time the regulatory actions taken included:

- Revocation of use in poultry houses;
- Prohibition of application via hand held or similar equipment;
- Home garden uses of carbaryl revoked;
- Modification to application equipment; and
- Label protective equipment requirements strengthened.

In 1998 the UK MAFF commenced a review of anticholinesterase compounds that included examination of carbaryl. Registrants were not prepared to support the continued registration of carbaryl through such a review and therefore all carbaryl products were subject to phase out.

5. REVIEW RECOMMENDATIONS

On the basis of the evaluation of the submitted data and information, the following recommendations are made with regard to the continued registration of carbaryl products in Australia.

5.1 Affirm registrations with label variations

5.1.1 Label variations that do not included changes in use patterns.

The APVMA is not satisfied that the labels of the products in Table 8 contain adequate instructions pertaining to warning statements and safety directions. The APVMA is satisfied that the conditions of label approval for the products in Table 8 can be varied in such a way so that they contain adequate instructions in accordance with s. 14(3)(g) of the Agvet Codes.

Table 8: Product registration to be affirmed with label variations.

Product Number	Product name	Registrant	Label Approval Number
33575	Fido's Fre-Itch Flea Shampoo For Cats And Dogs	Mavlab Pty Ltd	33575/1002
39998	Fido's Ear Drops	Mavlab Pty Ltd	39998/0101
40143	Joseph Lyddy G-Wizz Insecticidal Dry Shampoo For Horses And Ponies	Waproo Pty Ltd	40143/0500
41250	Vetapet Coalfoam Medicated Foam With Ectoparasitic Control For Dogs And Cats	Bocko P/L & Trademarketing Solutions P/L T/As Pharmachem	41250/1101
47966	I Love My Pet Ear Drops Ear Cleaner & Treatment For Cats And Dogs	My Pet Products Australia Pty Ltd	47966/01
50741	I Love My Pet Flea Rid Shampoo For Dogs & Cats	My Pet Products Australia Pty Ltd	50741/0598

The APVMA is satisfied that the registration of the following product (Table 9) can be varied in such a way that the requirements for continued registration will be complied with and therefore will vary the formulation of the product.

Table 9: Product registration to be affirmed with minor formulation change.

Product Number	Product Name	Registrant	Label Approval Number
40145	Joseph Lyddy Y-Itch Animal Insecticide Bactericide	Waproo Pty Ltd	Label yet to be approved

5.1.2 Label variations that include deletion of use patterns.

The following variations to approved labels are proposed:

a. Delete use on berry fruits except raspberries
b. Delete use on citrus fruits
c. Delete use on stone fruit
d. Delete use on pome fruit, except for fruit thinning
e. Delete use on tropical fruit
f. Delete use on sunflower and linseed crops
g. Delete use on vegetable crops except, potatoes, sugarbeets, beetroot and turnip (swede)
h. Delete use on poultry
i. Delete use of veterinary dusts for the treatment of animals and birds
j. Delete use of dust formulations for indoor use on domestic premises
k. Delete use of dust formulations for treatment of carpets, rugs and animal bedding

Withholding Periods

Cereal grains

Insert: **DO NOT** harvest for 14 days after application

Insert: **DO NOT** graze or cut for stock food for 14 days after application

Insert: Cereal grain treated with 16 ml of this preparation must be held in storage and not be used for processing for human consumption or for stock food within 90 days of treatment.

Pasture and Lucerne

Insert: **DO NOT** graze or cut for stock food for 7 days after application

Cotton

Insert: **DO NOT** harvest for 3 days after application

Raspberries, Beetroot, Potato, Sugar beet, Turnips (Swede)

Insert: **DO NOT** harvest for 3 days after application

Macadamia nuts, pecan nuts

No withholding period required when used as directed

Pome fruit (fruit thinning use pattern)

No withholding period required when used as directed (when applied once at 7-28 days after full bloom).

Changes to Label Instructions

Cotton

Insert: This Product Must Not Be Used On Cotton That Will Or May Be Fed To Livestock.

Summary

A summary of the above label changes by crop and pest is listed in Table 10.

Table 10: Summary of label changes by situation and pest

Situation	Pest	Recommendations
Home veterinary dusts for the treatment of animals and birds	Fleas, mites, ticks. lice	User exposure is likely to exceed the ADI and recommended ARfD. **Delete from labels**
Dust formulations for treatment of carpets, rugs and animal bedding	Fleas, mites, ticks. lice	Insufficient data was received to enable the assessment to estimate householder exposure and assure an adequate margin of safety. **Delete from labels**
Poultry	mites, ticks, lice	Insufficient data was available to assess residues in poultry from direct animal treatment. **Delete from labels**
Pigs	Body Louse, Sarcoptic mange	Sufficient data was available to assess residues in poultry from direct animal treatment. No concerns– **Retain use**
Avocados	Redshouldered leaf beetle	Insufficient data to establish MRL **Delete from labels**
Blueberries	Grasshoppers	Insufficient data to establish MRL. **Delete from labels**
Cape gooseberry	Threelined potato beetle	Insufficient data to establish MRL. **Delete from labels**
Citrus	Lightbrown apple moth, yellow peach moth, fruit piercing moth, citrus leaf-eating caterpillar, Fuller's rose weevil	Insufficient data to establish MRL. For oranges dietary exposure exceeds ARfD. **Delete from labels**
Feijoa, guavas	Orange fruit borer	Insufficient data to establish MRL. **Delete from labels**
Fruit – general	Wingless grasshopper	Insufficient data to establish MRL **Delete from labels**
Grapes	Grapeleaf blister mite, grapevine hawk moth, grapevine moth, lightbrown apple moth, cutworms, mealybugs	Dietary exposure exceeds ARfD. **Delete from labels**
Jaboticaba, Jackfruit	Swarming leaf beetle	Insufficient data to establish MRL. **Delete from labels**
Kiwi fruit	Lightbrown apple moth	Insufficient data to establish MRL. **Delete from labels**
Loquats	Light brown apple moth	Insufficient data to establish MRL. **Delete from labels**
Lychees	Caster oil looper, leaf eating looper, macadamia nutborer, redshouldered leaf beetle, swarming leaf beetle	Insufficient data to establish MRL. **Delete from labels**
Macadamias	Macadamia nutborer, macadamia twig-girdler, reshouldered leaf beetle, cornelian (butterfly), macadamia cup moth, macadamia nut moth, yellow peach moth	Exposure< ARfD. No concerns associated with use – **Retain use**
Mangoes	Fig leafhoppers	Insufficient data to establish MRL. **Delete from labels**
Pecans	Orange fruitborer, yellow peach moth	No concerns associated with use – **Retain use**
Pome fruit Apples, pears	Early fruit caterpillars, codling moth, lightbrown apple moth, pear leaf blister mite, fruit thinning	Dietary exposure exceeds ARfD. **Delete from labels**

Pears	Pear and cherry slug	Dietary exposure exceeds ARfD. **Delete from labels**
Rambutans	Caster oil looper,. Redshouldered leaf beetle, swarming leaf beetle	Insufficient data to establish MRL. **Delete from labels**
Raspberries	Grasshoppers, lightbrown apple moth, raspberry fruit caterpillar	Exposure< ARfD. No concerns associated with use – **Retain use**
Strawberry	Grasshoppers	Insufficient data to establish MRL. **Delete from labels**
Stone fruit Apricots, nectarines, peaches, plums, prunes	Green treehopper, lightbrown apple moth, oriental fruit moth, pear and cherry slug, redshouldered leaf beetle, orange fruit borer, heliothis (budworms), European earwig	Dietary exposure exceeds ARfD. **Delete from labels**
Beans, cucurbits	Heliothis (budworms), pumpkin beetle, 28-spotted ladybird	Dietary exposure exceeds ARfD. **Delete from labels**
Capsicum	Beetles, weevils	Dietary exposure exceeds ARfD. **Delete from labels**
Carrots	Vegetable weevil	Insufficient data to establish MRL. **Delete from labels**
Cucurbits	Cucurbit stemborer	Dietary exposure exceeds ARfD. Insufficient data to establish MRL. **Delete from labels**
Leafy vegetables	Vegetable weevil	Dietary exposure exceeds ARfD. **Delete from labels**
Sweet corn	Red-shouldered leaf beetle	Dietary exposure exceeds ARfD. **Delete from labels**
Vegetables – general	Vegetable weevil	Dietary exposure exceeds ARfD. **Delete from labels**
Potatoes	Potato moth	Exposure< ARfD. No concerns associated with use – **Retain use**
Tomatoes	Leafminer caterpillars	Dietary exposure exceeds ARfD. **Delete from labels**
Cereals	Armyworms, cutworms, heliothis (budworms), Rutherglen bug, Wingless grasshopper, Australian plague locust, migratory locust, yellow winged locust	Exposure< ARfD. No concerns associated with use – **Retain use**
Cereals stored grain	Lesser grain borer	Exposure< ARfD. No concerns associated with use – **Retain use**
for disinfestation of grain storage buildings	Lesser grain borer	No concerns associated with use – **Retain use**
Pasture	Wingless grasshopper, Australian plague locust, migratory locust, yellow winged locust	No concerns associated with use – **Retain use**
Cotton	Rough bollworm	Exposure< ARfD. No concerns associated with use – **Retain use**
Linseed	Heliothis (budworm)	Insufficient data to establish MRL. **Delete from labels**
Lucerne	Heliothis (budworms), leafhoppers (Jassids)	No concerns associated with use – **Retain use**
Pastures, pasture seed crops	Lucerne leafroller	No concerns associated with use – **Retain use**
Rice	Brown planthopper	No concerns associated with use – **Retain use**
Sorghum	Sorghum midge, heliothis (budworms)	No concerns associated with use – **Retain use**
Sunflower	Black sunflower scarab Armyworms, cutworms, heliothis (budworms), Rutherglen bug	Insufficient data to establish MRL. **Delete from labels**

commercial, industrial and domestic areas, tobacco storage sheds and rights of way, in non-crop areas in general,	European Earwig, Plague locust, Wingless grasshopper, ants, moths, fleas and weevils, wasps, honey bees	No concerns associated with use – **Retain use**
ornamentals, lawns, elm trees (in non-crop areas), kenaf, Duboisia and rosella,	Variety of Leaf eating insects	No concerns associated with use – **Retain use**

It is then recommended that these variations to label instructions would satisfy the requirements for continued registration of products.

5.1.3 Label amendments.

The APVMA is not satisfied that the labels of the products in Table 11 contain adequate instructions pertaining to warning statements and safety directions. The APVMA is satisfied that the conditions of label approval for the products in Table 11 can be varied in such a way so that they contain adequate instructions in accordance with s. 14(3)(g) of the Agvet Codes.

Table 11: The following registered products and label approval numbers are affected by the proposed label changes describe in 5.1.2.

Product Number	Product Name	Registrant	Label Approval Number
31995	CRG Liquid Carbaryl Insect Spray	Chemical Recovery Co Pty Ltd	31995/0798
32002	Yates Carbaryl Caterpillar & Grasshopper Insect Spray	Arthur Yates & Co Limited	32002/0202
32009	Nufarm Flowable Carbaryl 500 Insecticide	Nufarm Australia Limited	32009/0603^
39082	Hortico Hose-On Lawn Grub Killer	Orica Australia Pty Ltd	39082/0700
39876	Yates Garden Spray Insecticide Fungicide	Arthur Yates & Co Limited	39876/0998
40146	Bugmaster Flowable Insecticide	Bayer Cropscience Pty Ltd	40146/0603^
42029	David Grays Flower Dust	David Gray & Co. Pty Limited	42029/0702
42041	David Grays Rose Dust	David Gray & Co. Pty Limited	42041/02
42261	David Grays Cricket & Grasshopper Killer Bait	David Gray & Co. Pty Limited	42261/1202
45944	Garden King Multipest SCC general purpose insecticide-fungicide-miticide	Envirogreen Pty Ltd	45944/0503^
49326	Kendon Carbaryl Wettable Powder Insecticide	Kendon Chemicals & Mnfg Co Pty Ltd	49326/0400
52213	David Grays Carbaryl 500 Flowable Insecticide	David Gray & Co. Pty Limited	52213/0100
52472	Garden King Tomato & Vegetable Dust Insecticide & Fungicide	Envirogreen Pty Ltd	52475/0702
52493	Richgro Garden Products Carbaryl Caterpillar & Grasshopper Insecticide	A Richards Pty Ltd T/A Richgro Garden Products	52493/0300
54634	Richgro Garden Products Armyworms, Cockchafers & Lawn Grub Killer"	A Richards Pty Ltd T/A Richgro Garden Products	54634/0603^

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

5.1.4 Changes to Registration of Home Garden Products

A maximum carbaryl concentration of 160 g/kg (or g/L) is recommended for home garden products, as less concentrated preparations are expected to have acute oral LD_{50} above 1500 mg/kg bw and therefore exceed the safety threshold for registration of home garden products. Products affected by the discussed changes are listed in Table 12.

It is recommended that the label of home garden products be varied to ensure uses of the product comply with registration restrictions of carbaryl products. The following label statement is to be added to all home garden products.

Insert: **DO NOT** Apply To Food Producing Plants.

The following warning statement is to be added to products applied on and around the exterior of domestic premises**:**

Insert: Avoid Bare Skin Contact With Treated Surfaces.

5.1.5 Changes to Registered Products For Use on Pigs.

One carbaryl product is registered for use on pigs. From the data submitted it was determined that residues in pig tissues following treatment at the Australian label rate (0.5% solution) at 7 day WHP would comply with the mammalian tissue MRL. Therefore the APVMA is satisfied that the use of the registered carbaryl product on pigs in accordance with the instructions for use would not be likely to be an undue hazard to the safety of people using anything containing its residue.

It is recommended that the label be varied so that the veterinary use pattern for pigs be placed in a separate table on the label to distinguish it from the registered agricultural uses of the product and the following label statement remain on the label:

Retain: **DO NOT** use less that 7 days before slaughter for human consumption

5.2 Cancellations of Registrations and Label Approvals

The APVMA cannot be satisfied that continued registration of products in Table 12 would not be an undue hazard to the safety of people exposed to it during its handling or people using any thing containing its residues and would not be likely to have an effect that is harmful to human beings. Therefore, the APVMA is not satisfied that the conditions of registration of these products can be varied in such a way that the requirements for continued registration will be complied with and proposes the products in Table 12 be cancelled.

Table 12: Products proposed to be cancelled.

Product Number	Products Registrations To Be Cancelled	Registrant	Label Approval Number
Reason: Continued registration would be likely to have an effect that is harmful to human beings. The concentration of carbaryl in these products exceeds the safety threshold for registration of home garden products (>160g/kg or 160 g/L).			
31997	Chemspray Carbaryl Insecticide	Envirogreen Pty Ltd	31997/0802 31997/0903^
49325	Kendon Carbaryl Liquid Insecticide	Kendon Chemicals & Mnfg Co Pty Ltd	49325/1098 49325/0400

Product Number	Products Registrations To Be Cancelled	Registrant	Label Approval Number
49937	Garden King Carbaryl Liquid Insecticide	Envirogreen Pty Ltd	49937/0802 49937/1097
54949	David Grays Carbaryl Liquid Insecticide	David Gray & Co. Pty Limited	54949/0102
Reason: Insufficient data exists to allow an evaluation of the potential hazard to human beings from the use of these products.			
50102	Friskies Kill Flea Carpet Deodoriser	Go-Pet Petcare Solutions, a div of Nestle Australia Ltd	50102/0798
57952*	Go-Pet Kill Flea Carpet Deodoriser	Go-Pet Petcare Solutions, a div of Nestle Australia ltd	57952/0903
Reason: There is an unacceptable risk of user exposure from home veterinary dusts for the treatment of animals and birds that is likely to exceed the ADI and recommended ARfD and that revised warning statements and enhanced personal protective equipment are not likely to be effective in protecting users from absorbing toxicologically significant systemic doses of carbaryl.			
33576	Saint Bemard Flea Powder For Dogs And Cats	Saint Bernard Pet Care Pty Ltd	33576/01 33576/0402 33576/0801
36387	Watch Cat Flea Powder For Cats	Go-Pet Petcare Solutions A Div Of Nestle Australia Ltd	36387/0299 36387/1198
36388	Watch Dog Flea Powder For Dogs	Go-Pet Petcare Solutions A Div Of Nestle Australia Ltd	36388/0299 36388/1198
37434	Fido's Free-Itch CPP Flea Powder For Cats And Dogs	Mavlab Pty Ltd	37434/0101
40080	Fido's Free Itch Flea Powder	Mavlab Pty Ltd	40080/0402
41244	David Skatta-7 Tick Flea Louse Powder	Bocko P/L & Trademarketing Solutions P/L T/A Pharmachem	41244/0901
46303	Masterpet Flea Powder For All Dogs And Cats 100gm	Masterpet Australia Pty Limited	46303/001
46851	Keydust Dusting Powder	International Animal Health Products Pty Ltd	46851/0100
47855	I Love My Pet Flea Powder For Cats And Dogs	My Pet Products Australia Pty Ltd	47855/01
50664	I Love My Pet Flea Rid Powder For Cats And Dogs	My Pet Products Australia Pty Ltd	50664/0598
51206	Family Pets Flea And Tick Pet Grooming Powder For Dogs, Cats Puppies And Kittens	Aristopet Pty Ltd T/As Family Companion Pet Products	51206/0998
Reason: Dietary intake exceeds the acute reference dose.			
39864	Yates Lanosan Tomato Spray Insecticides And Fungicide	Arthur Yates & Co Limited	39864/0500 39864/0598
42055	David Grays Vegetable Dust	David Gray & Co. Pty Limited	42055/02
48753	Tomato Dust Insecticides And Fungicide	Crop Care Australasia Pty Ltd	48753/01
51625	Richgro Garden Products Ready To Use Pest-Stop Tomato	A Richards Pty Ltd T/A Richgro Garden Products	51625/0499
53260	Hortico Tomato Dust	Orica Australia Pty Ltd	53260/0700
53912	Yates Ready To Use Tomato Gun Pest & Disease Spray	Arthur Yates & Co Limited	53912/0702
58127*	Yates Insect & Disease Control Blitzem Tomato Gun	Orica Australia Pty Ltd	58127/0903^
58135*	Yates Insect & Disease Control Blitzem Tomato Dust	Orica Australia Pty Ltd	58135/0903^
Reason: Insuficent data is available to ensure dietary intake would not exceed the acute reference dose.			
53231	Hortico Cabbage Dust	Orica Australia Pty Ltd	53234/0700

*Products registered after the commencement of the extended scope of the review, that are subject to the outcomes of the review.

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

Table 13: Carbaryl Products included in the review that have been withdrawn prior to the completion of the review.

Product Number	Product Name	Registrant	Label Approval Number/s
32000	Defender Home Garden Grasshopper Caterp illar Carbaryl Insecticide	Scotts Australia Pty Ltd	?
33194	Hortico Carbaryl Cabbage Dust	Orica Australia Pty Ltd	?
33957	Hortico Carbaryl Tomato	Orica Australia Pty Ltd	?
39879	Yates Carbaryl Cabbage Dust	Arthur Yates & Co Limitied	39879/0802
40754	Defender home garden grasshopper caterpillar carbaryl insecticide	Scotts Australia Pty Ltd	?
42054	David Grays Tomato Dust	David Gray & Co. Pty Limited	42054/02
47108	Chemspray Carbaryl Flowable Insecticide	Envirogreen Pty Ltd	47108/0599 47108/0998 47108/3260
49133	Defender Trouble Shooter Tomato Spray	Scotts Australia Pty Ltd	49133/01
49870	Defender Tomato Doctor Insecticide/Fungicide	Scotts Australia Pty Ltd	49870/01

? Labels transitioned from the states and not having and approval number.

Old approved labels are deemed not to contain adequate instructions and are to be cancelled. Products with old labels that to be cancelled are listed in Table 14.

Table 14: The following label approvals are deemed not to contain adequate instructions and thus are to be cancelled.

Product Number	Label approval numbers
32002	32002/0301 32002/0498 32002/1001
32009	32009/0801 32009/0902 32009/0300
33575	33575/1200
40146	40146/01 40146/02 40146/0500 40146/1197 40146/4535
45944	?
49326	49326/1098
52472	52472/0100
54634	54634/0402

? Labels transitioned from the states and not having and approval number.

6. AMENDMENTS TO STANDARDS

As an outcome of the review of carbaryl, and based on the advice of the 20th and 23rd meetings of the Advisory Committee on Pesticides and Health (ACPH) and consideration of the expanded toxicological database on carbaryl, the following recommendations are made by the Office of Chemical Safety and APVMA Chemistry and Residues section:

6.1 Public Health Standards

6.1.1 Acceptable Daily Intake

The current ADI for carbaryl is 0.004 mg/kg bw/d, derived by applying a 4000-fold safety factor to a LOEL of 100 ppm (16 mg/kg bw/d) for vascular tumours occurring in male mice in a 2-year dietary study. The review recommends that the ADI be revised to 0.008 mg/kg bw/d derived by applying a 2000-fold safety factor to the same LOEL of 100 ppm for vascular tumour formation.

6.1.2 Acute Reference Dose

An ARfD of 0.01 mg/kg bw is recommended, applying a 100-fold safety factor to NOELs of 1 mg/kg bw/d, established in rat 13-week subchronic and developmental neurotoxicity studies, based on behavioural indications of autonomic neurotoxicity and brain, plasma and erythrocyte ChE depression (LOEL=10 mg/kg bw/d).

6.1.3 Water Quality Guidelines

The current Health Value for Carbaryl of 0.03mg/L in drinking water remains unchanged.

6.1.4 Poisons Scheduling

Carbaryl is classified as a Schedule 6 poison in the Standard of the Uniform Scheduling of Drugs and Poisons (SUSDP), with Schedule 5 entries for preparations containing 10 per cent or less of carbaryl, or when impregnated into plastic resin material containing 20 per cent or less of carbaryl. Carbaryl preparations for human therapeutic use are listed in Schedule 4, but none are currently on the Australian market. Based on the decisions of the National Drugs and Poisons Schedule Committee at its 36th meeting, no changes are recommended to the Poisons Schedule status of carbaryl.

6.1.5 Safety Directions

The required Safety Directions for carbaryl products are as listed in Table 15.

Table 15: Safety Directions for carbaryl products First Aid Instruction and Safety Directions (FAISD) 31 December 2003.

Formulation	Safety Directions	Statement
DU 50 g/kg or less in 500g pack or less	210, 211	Avoid contact with eyes and skin.
	220, 221	Do not inhale dust.
	351	Wash hands after use.
HG AC 60 g/L or less in hose-end sprayers	120, 130, 131, 132, 133	Product is poisonous if absorbed by skin contact or inhaled or swallowed.
	160, 162	May irritate the eyes.
	210, 211,	Avoid contact with eyes and skin.
	220, 223	Do not inhale spray mist.

	279, 283, 290, 292b, 312	When using the product wear rubber apron and rubber gloves.
	340, 341, 342	If product or spray on skin, immediately wash with soap and water.
	350	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
	360, 361, 366-	After each day's use, wash gloves and contaminated clothing.
HG BA 18 g/kg or less	120, 130, 131, 132, 133,	Product is poisonous if absorbed by skin contact or inhaled or swallowed.
	210, 211	Avoid contact with eyes and skin.
	220, 221,	Do not inhale dust.
	351	Wash hands after use.
HG DU 20 g/kg or less with maldison 10 g/kg or less and mancozeb 40 g/kg or less and sulfur 300 g/kg or less	120, 130, 131, 132, 133	Product is poisonous if absorbed by skin contact or inhaled or swallowed.
	160, 162, 163, 164,	May irritate the eyes and nose and throat and skin.
	180, 181	Repeated exposure may cause allergic disorders sensitive workers should use protective clothing.
	210, 211	Avoid contact with eyes and skin.
	220, 221	Do not inhale dust
	279, 280, 283, 290, 292b, 312	When opening the container and using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing)
	350,	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
	360, 361, 366	After each day's use, wash gloves and contaminated clothing.
HG SC 100 g/L or less	120, 130, 131, 133	Product is poisonous if absorbed by skin contact or inhaled or swallowed.
	210, 211	Avoid contact with eyes and skin.
	220, 223	Do not inhale spray mist
	279, 280, 283, 290, 312	When opening the container and using the product rubber gloves.
	350	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
	360, 361	After each day's use, wash gloves
HV Shampoo 10 g/L or less	120, 130, 131, 133	Product is poisonous if absorbed by skin contact or swallowed.
	161, 162, 164	May irritate the eyes and skin.
	210, 211	Avoid contact with eyes and skin.
	279, 280, 283, 290, 312	When opening the container and using the product wear rubber gloves.
	340, 342	If product on skin, immediately wash area with soap and water.
	340, 343	If product in eyes, wash it out immediately with water.
	350	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
	360, 361, 366	After each day's use, wash gloves and contaminated clothing.
HV Foam 10 g/L or less with pyearethrins 1.0 g/L or less and piperonyl butoxide 10 g/L or less and coal tar 10 g/L or less with	120, 130, 131, 133	Product is poisonous if absorbed by skin contact or swallowed.
	161, 162, 163, 164	May irritate the eyes and nose and throat and skin
	210, 211	Avoid contact with eyes and skin.

quaternary ammonium compounds 100 g/L or more	279, 280, 283, 290, 312	When opening the container and using the product wear rubber gloves.
	340, 342	If product on skin, immediately wash area with soap and water.
	340, 343	If product in eyes, wash it out immediately with water.
	350	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
	360, 361, 366	After each day's use, wash gloves and contaminated clothing.
HV Ear drops 10 g/L or less	120, 130, 131, 133	Product is poisonous if absorbed by skin contact or swallowed.
	161, 162, 164	May irritate the eyes and skin.
	210, 211	Avoid contact with eyes and skin.
	340, 342	If product on skin, immediately wash area with soap and water.
	340, 343	If product in eyes, wash it out immediately with water.
	351	Wash hands after use
WP LD SC all strengths	120, 130, 131, 133	Product is poisonous if absorbed by skin contact or swallowed.
	210, 211	Avoid contact with eyes and skin.
	220, (221WP), 223	Do not inhale (dust) spray mist
	279, 281, 290, 294,	When preparing spray wear elbow length PVC gloves.
	340, 342	If product on skin, immediately wash area with soap and water.
	350	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
	360, 361	After each day's use, wash gloves
**SR Pet Collar	Delete entry	

SR pet collars: There are currently no registered, carbaryl-based pet collars in Australia.

New entries:

Office of Chemical Safety had recommended that the following entries be added.

Formulation	Safety Directions	Statement
Bar 40g/kg or less	120 130 131 132 133	Product is poisonous if absorbed by skin contact or swallowed.
	160 162 164	May irritate the eyes and skin
	210 211	Avoid contact with eyes and skin
	220 221	Do not inhale dust
	350	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
Lotion 2g/L or less with sulfur 20g/L or less and zinc oxide 50 g/L or less	120 130 131 132 133	Product is poisonous if absorbed by skin contact or swallowed.
	160 162 164	May irritate the eyes and skin
	180	Repeated exposure may cause allergic disorders
	210 211	Avoid contact with eyes and skin
	220 222	Do not inhale vapor
	272	Ensure adequate ventilation during use
	340 342	If product on skin, immediately wash area with soap and water.
	340 343	If product in eyes, wash it out immediately with water.
	350	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.

6.1.5 First Aid Instructions

No changes are recommended to the current First Aid Instructions for carbaryl.

The following standard statements for carbaryl (Table 16) are currently specified in the *Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals* (OCS, 2002), http://www.health.gov.au/ocs/docs/pdf/faisd.pdf. These instructions are considered appropriate for a carbamate pesticide of moderate acute toxicity, and no revisions are proposed.

Table 16: Current First Aid Instructions for carbaryl.

Concentration	Code	First Aid Instruction
More than 1 per cent	a, h	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 03 4747000. If swallowed, give one atropine tablet every 5 minutes until dryness of the mouth occurs – if poisoned by skin absorption or through lungs, remove any contaminated clothing, wash skin thoroughly and give atropine tablets as above. Get to a doctor or hospital quickly.
1 per cent or less In plastic resin strips 5 per cent or less dust	a	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 03 4747000
In pressurised spray packs	o	If sprayed on skin, wash thoroughly. If sprayed in mouth, rinse mouth with water.

6.1.6 Warning Statements.

Any product applied on and around the exterior of domestic premises: The label should bear an additional warning statement: “Avoid bare skin contact with treated surfaces”.

6.2 MRL Standards

The following changes to the *MRL Standard* are required as an outcome of the review of carbaryl.

Table 1 *MRL Standard* entries

Compound		Food	MRL (mg/kg)
Carbaryl			
DELETE:	FS 0240	Apricot	10
	VS 0621	Asparagus	10
	FI 0326	Avocado	10
	FI 0327	Banana [in the pulp]	5
	FB 0264	Blackberries	10
	FB 0020	Blueberries	7
	FT 0289	Carambola	5
	GC 0080	Cereal grains	T5
	FS 0013	Cherries	5
	FC 0001	Citrus fruits	7
	SO 0691	Cotton seed	1
	FI 0332	Custard apple	5
	FB 0266	Dewberries (including Boysenberry and Loganberry)	10
	MO 0105	Edible offal (mammalian)	T0.2
	PE 0112	Eggs	T0.2
	FI 0371	Elephant apple	5
	FI 0335	Feijoa	5
	VC 0045	Fruiting vegetables, Cucurbits	3
	FI 0351	Granadilla	5
	FB 0269	Grapes	5
	FT 0298	Grumichama [Brazilian cherry]	5
	FT 0336	Guava	5
	FT 0300	Jaboticaba	5
	FI 0338	Jackfruit	5
		Jambu	5
	FI 0341	Kiwifruit	10
	VL 0053	Leafy vegetables	10
	FI 0343	Litchi	5
	FI 0342	Longan	5
	FI 0345	Mango	5
	MM 0095	Meat [mammalian]	T0.2
	ML 0106	Milks	T*0.05
	FS 0245	Nectarine	10
	VO 0442	Okra	10
	FT 0305	Olives	10
	DM 0305	Olives, processed	1
	FI 0350	Papaya [pawpaw]	5
	FI 0351	Passion fruit	5
	FS 0247	Peach	10
	FS 0014	Plums (including Prunes)	5
	FP 0009	Pome fruits	5
	VR 0589	Potato	0.2
	PO 0111	Poultry, Edible offal of	T5
	PM 0110	Poultry meat	T0.5
	FI 0358	Rambutan	5
	FB 0272	Raspberries	10
	FI 0359	Sapodilla	5

	FI 0360	Sapote, Black	5
	FI 0361	Sapote, Green	5
	FI 0362	Sapote, Mammey	5
	FI 0363	Sapote, White [casimiroa]	5
	FB 0275	Strawberry	7
	GS 0659	Sugar cane	T*0.05
	SO 0702	Sunflower seed	1
	VO 0447	Sweet corn (corn-on-the-cob)	1
	TN 0085	Tree nuts	1
	TN 0085	Tree nuts [whole in shell]	10
		Vegetables [except asparagus; fruiting vegetables, cucurbits; leafy vegetables; okra; potato; sweet corn (corn-on-the-cob)]	5
	CM 0654	Wheat bran, unprocessed	T20
ADD:	GC 0080	Cereal grains	15
	VR 0574	Beetroot	0.5
	SO 0691	Cotton seed	3
	MO 0105	Edible offal (mammalian)	0.2
	PE 0112	Eggs	*0.02
	TN 0669	Macadamia nut	2
	MM 0095	Meat [mammalian]	*0.02
	ML 0106	Milks	*0.02
	TN 0672	Pecan	2
	FP 0009	Pome fruits	*0.01
	VR 0589	Potato	0.1
	PM 0110	Poultry meat	*0.02
	PO 0111	Poultry, Edible offal of	0.2
	FB 0272	Raspberries, Red, Black	20
	VR 0596	Sugarbeet	0.5
	VR 0497	Swede	2
	CM 0654	Wheat bran, unprocessed	30

* MRL set at the "limit of quantitation", thus residues expected to be non-quantifiable

Table 4 *MRL Standard* entries

Compound		Animal feed commodity	MRL (mg/kg)
Carbaryl			
DELETE:	AF 0080	Forage of cereal grains	T100
	AS 0081	Straw and fodder (dry) of cereal grains	T100
ADD:		Cereal forage (green)	100
		Grass pastures (green)	400
	AS 0162	Hay or fodder (dry) of grasses	300
		Legume forage (green)	400
		Legume fodder	100
	AM 0165	Miscellaneous fodder and forage crops	300
		Sorghum bran	50
	AS 0081	Straw and fodder (dry) of cereal grains	100

Table 5 *MRL Standard* entries

Substance	Use
Carbaryl	• As an insecticide in non-crop areas including commercial, industrial and domestic areas, tobacco storage sheds and rights of way • As an insecticide on ornamentals and other non-food or animal feed crops and trees • For the disinfestation of grain storage buildings

7. CONCLUSION

Carbaryl products are registered for uses in home veterinary preparation of a number of uses. Based on the data provide, the APVMA is satisfied that the use of registered carbaryl products in pet shampoos, 1% ready to use liquid sprays and home veterinary ear drops would not be likely to have an effect that is harmful to human beings. Product labels for these products are considered not to contain the required warning statements and safety directions, therefore label are to be varied to meet the required standards.

The risk assessment indicates that use of dust preparations of carbaryl for home veterinary uses and for control of insect pests on carpets and rugs poses an unacceptable risk of exposure to uses. Therefore, the APVMA cannot be satisfied that home veterinary dust preparations intended for the treatment of companion animals and birds would not be an undue hazard to the safety of people exposed to it during its handling and would not have an effect that is harmful to human beings. It is recommended that the registrations and label approvals of these products be cancelled.

Insufficient data was available to assess residues in poultry from direct animal treatment. Therefore, the APVMA cannot be satisfied that the use of the product in accordance with the instructions for its use would not result in residues in poultry commodities exceeding the limits established. Therefore, the APVMA cannot be satisfied that home veterinary dust preparations intended for the treatment of companion animals and birds would not be an undue hazard to the safety of people exposed to it during its handling and would not have an effect that is harmful to human beings. Other uses of the product as companion animal dust are also not supported on toxicological grounds. It is recommended that the registrations and label approvals of these products be cancelled.

The APVMA considers that any product with an acute oral LD_{50} of 1500 mg/kg bw or less is not suitable for domestic/home garden use, because of the toxicological risk. It was found that products containing carbaryl and marketed as 800 g/kg wettable powder and liquids containing 400 and 500 g/L carbaryl are above this safety threshold. Therefore, the APVMA cannot be satisfied that domestic / home garden products with a maximum carbaryl concentration of greater than 160 g/kg (or g/L), 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. Therefore, because of the unacceptable risk the concentration of domestic/home garden products will be restricted to maximum carbaryl concentration 160 g/kg (or g/L). It is recommended that the registrations and label approvals of these products be cancelled.

The toxicological assessment concluded that there was insufficient data to determine user exposure from home garden uses of carbaryl on food producing plants. There was also insufficient data available to ensure dietary intake would not exceed the acute reference dose. Therefore, the APVMA cannot be satisfied that such uses would not be an undue hazard to the safety of people using 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. It is recommended that uses of carbaryl on food producing plants in the home garden be deleted and product labels be varied. For other products registered exclusively for these uses it is recommended that registrations be cancelled.

The toxicological assessment identified that one carbaryl product contains a non-active constituent that is potentially carcinogenic and is classifiable as Schedule 7. The registrant

has agreed to reformulate the product. It is recommended that after the product is reformulated use can continue after the label is updated to meet required standards.

Safety directions for one product have not been set. Therefore as an out come of the review the registrant will be required to provide information to allow safety directions to be set for this product.

Insufficient data were received to enable the assessment of residues in berry fruits (except raspberries and grapes), tropical fruit (both edible and inedible peel varieties), citrus fruits (except oranges), Cape gooseberry, sunflower and linseed, brassica vegetables (except cabbage, broccoli and cauliflower), cucurbit vegetables (except cucumber, cantaloupe, bottle gourd and zucchini), mushrooms, carrots and parsnips, pulses, bulb vegetables and stalk and stem vegetables (except asparagus). Therefore, the APVMA cannot be satisfied that use of carbaryl products on the above fruit and vegetable crops would not be an undue hazard to the safety of people using anything containing its residues. Thus some product labels will be varied and as all instructions or use for some products are to be deleted, these products will be cancelled.

Sufficient data was received to enable the assessment of residues in grapes, oranges, pome fruit (late pre-harvest applications only), stone fruits, cabbage, broccoli and cauliflower, cucumber, cantaloupe, bottle gourd and zucchini, leafy vegetables, fruiting vegetables (except mushrooms and Cape gooseberries), legumes and asparagus. Because of unacceptable residue and acute dietary risk the APVMA cannot be satisfied that use of carbaryl products on some horticultural and vegetable crops would be an undue hazard to the safety of people using anything containing its residues. Thus some product labels will be varied and as all instructions or use for some products are to be deleted, these products will be cancelled.

Based on the submitted data the APVMA is satisfied that continued use of registered carbaryl products on raspberries, beetroot, potato, sugarbeet, turnips (Swede), pome fruit (fruit thinning use pattern only), macadamia nuts, pecan nuts, cottonseed, cereal grains, pastures and miscellaneous other forage and fodder crops would not be an undue hazard to the safety of people using anything containing its residues. It is recommended that these use patterns remain and product labels be varied to meet required standards.

A carbaryl product is registered for use as a direct treatment to pigs. Sufficient data was available to assess residues in pigs from direct animal treatment, however, the APVMA is satisfied that the use of the product in accordance with the instructions for its use would not result in residues in pork commodities exceeding the limits established. Therefore, the APVMA is satisfied that the use of the product would have be an undue hazard to the safety of people using anything containing its residues. It is recommended that this use pattern remain and the product label be varied to meet required standards.

Livestock may be exposed to residues of carbaryl. Sufficient data were available to assess residues in animal commodities resulting from dietary exposure to feeds containing carbaryl residues, however, the APVMA is satisfied that the use of carbaryl products on potential animal feeds (except cotton) in accordance with the instructions for use would not be an undue hazard to the safely of people using anything containing its residues. Thus, the registrations of products for use for animal feeds (except cotton) remain and product labels are to be varied to meet required standards

Carbaryl products are also registered for used in various situations considered to be non-food uses (ie. not for human or livestock consumption): as an insecticide in commercial, industrial and domestic areas, tobacco storage sheds and rights of way, in non-crop areas in general, ornamentals, lawns, elm trees (in non-crop areas), kenaf, Duboisia and rosella, and for disinfestation of grain storage buildings. There are no residues issues relating to non-food uses of carbaryl products therefore the APVMA is satisfied that the use of carbaryl products in the above non-crop areas in accordance with the instructions for use would not be an undue hazard to the safely of people using anything containing its residues. It is recommended that these use patterns remain and product labels be varied to meet required standards.

8. TOXICOLOGY ASSESSMENT

8.1 Introduction

Carbaryl is a carbamate effective against a broad range of insects, mites, lice, millipedes and other pests. It is used in a diverse range of situations encompassing agricultural crops, veterinary treatment of commercial and companion animals and birds, and the home garden. Carbaryl is classified as a Schedule 6 poison in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), with Schedule 5 entries for preparations containing 10 per cent or less of carbaryl, or when impregnated into plastic resin material containing 20 per cent or less of carbaryl. Carbaryl preparations for human therapeutic use are listed in Schedule 4, an entry originating from the former use of carbaryl against head lice. No carbaryl-based products are now listed in the Australian Register of Therapeutic Goods (ARTG).

This toxicological evaluation examines (1) supplementary studies intended to elucidate the mechanism of tumour formation, (2) replacement multi-generation reproduction and developmental studies in rats and rabbits, (3) addenda to a previously evaluated developmental neurotoxicity study in rats, (4) a short-term repeat-dose study and a 1-year study in dogs, and (5) exposure studies undertaken on persons using American registered carbaryl products in domestic settings.

During the early to mid 1990s, the sponsoring company undertook a number of studies intended to modernise the toxicological database on carbaryl, which was by then approximately 30 years old. Significant concerns were raised at a national and international level by findings of the oncogenic activity in mice and rats in replacement 2-year studies performed by Hamada (1993a, 1993b) at Hazleton laboratories. These results were in contrast to the earlier carcinogenicity studies, which had proven negative.

Evaluation of the Hamada studies, other replacement data, historical control data and mechanistic toxicology and metabolism studies has been undertaken by the OCS from 1994 onwards. Consideration of these evaluations by the Advisory Committee on Pesticides and Health (ACPH) occurred in October 1998. ACPH agreed with OCS's view that there were treatment-related vascular tumours in male mice at the lowest dose tested, and reduced the Australian ADI for carbaryl from 0.01 to 0.004 mg/kg bw/d by applying a 4000-fold safety factor to the Lowest Observable Effect Limit (LOEL) of 16 mg/kg bw/d.

The OCS has also estimated the systemic doses likely to be delivered to users of Australian registered carbaryl products, under Australian conditions. These estimates have been related to toxicological benchmarks to support recommendations on the continued registration and conditions of use of carbaryl home garden and veterinary products, including safety directions.

8.1.2 Kinetics and Metabolism

Valles (1999) conducted a metabolism study in male mice which received a 50 mg/kg bw gavage dose of radiolabelled carbaryl following 14 d administration of carbaryl in the diet at 0, 10, 100, 1000 or 8000 ppm, equivalent to approximately 1.5, 15, 150 and 1200 mg/kg bw/d. Pre-treatment dose levels did not influence the excretion of radioactivity, 80% of which appeared in the urine. Up to 21 radioactive components were detected in the urine, in which the major metabolites were dihydrodihydroxy naphthyl sulfate, hydroxycarbaryl

glucuronide /dihydrodihydroxy carbaryl, alpha-naphthyl sulfate and alpha-naphthyl glucuronide. Pre-treatment at 8000 ppm elicited increases in production of dihydrodihydroxy naphthyl sulfate and hydroxycarbaryl glucuronide/dihydrodihydroxy carbaryl, which are believed to be formed via epoxide intermediates. The 8000 ppm group excreted approximately 25% of the administered radioactivity in the form of these urinary metabolites, compared to 17% by the non-pretreated animals. At 8000 ppm there was also a decline in the urinary excretion of some unidentified metabolites, possibly formed by alkyl oxidation. Pre-treatment with 10 and 100 ppm carbaryl appeared to inhibit the hydrolytic pathway of metabolism. However, levels of the major hydrolysis products alpha-naphthyl sulfate and alpha-naphthyl glucuronide in the 1000 and 8000 ppm groups' urine, were similar to values from the non-pretreated group, accounting for about 30% of administered radioactivity.

8.1.3 Short-term Repeat-dose Study

Hamada (1991) administered carbaryl technical to dogs in the diet at concentrations of 0, 20, 45 or 125 ppm for approximately 5 week. The study included measurement of plasma and Red Blood Cells (RBC) activity prior to treatment and on study days 14 and 32, and brain ChE activity at termination. A probable treatment-related depression of plasma ChE activity occurred in 125 ppm males and females, which displayed up to a 23% reduction compared with baseline activity. Statistical significance against controls was achieved on d 14 but not subsequently, due mainly to a decline in ChE activity among controls. There were no treatment-related effects on RBC or brain ChE activity, or on gross necropsy findings. Consequently, the NOEL is set at 45 ppm (equal to 1.4 mg/kg bw/d).

8.1.4 Chronic Study

Hamada (1987) administered carbaryl technical to beagle dogs in the diet at concentrations of 0, 125, 400 or 1250 ppm for 12 mo. Mean achieved doses were approximately 3.5, 11 and 34 mg/kg bw/d for males and 3.8, 11 and 36 mg/kg bw/d for females at 125, 400 and 1250 ppm, respectively. Bodyweight gain was inhibited to a biologically significant extent at 1250 ppm during the first 5 week of treatment, accompanied (in females only) by reduced feed consumption, particularly between week 1 and 5. Leucocyte and segmented neutrophil counts became statistically and biologically significantly elevated in 1250 ppm males. Carbaryl caused dose-related inhibition of ChE activity at all 3 feeding levels in females, and at 400 and 1250 ppm in males. Plasma ChE inhibition *vs* control was 47-66% at 1250 ppm ($p<0.05$ throughout the study), was 9-36% at 400 ppm ($p<0.05$ throughout the study in males and at 5, 13 and 26 week in females), and was 12-23% in 125 ppm females ($p<0.05$ at 5, 13 and 26 week). RBC ChE inhibition *vs* control was 30-56% at 1250 ppm ($p<0.05$ throughout the study) and 19-34% at 400 ppm ($p<0.05$ at 5, 13 and 26 week in females but only at 5 and 13 week in males). Brain ChE activity was depressed by 14-32% in the treated male groups but failed to attain statistical significance against control, while treated females showed 20-36% inhibition which was dose-related and significant ($p<0.05$) at all doses. The female 1250 ppm group had slight but significant ($p<0.05$) depression in albumin concentration at all measured time points, together with increased inorganic phosphorus at week 52. Absolute and relative liver weights were increased in 1250 ppm males. There were no treatment-related gross or histopathological findings. Based on statistically significant depression of plasma and brain ChE activity in females treated at the lowest dose of 125 ppm (approximately 3.8 mg/kg bw/d), the study is considered not to have demonstrated a NOEL.

8.1.5 Carcinogenicity Studies

A subchronic carcinogenicity study was performed by Chuzel (1999) in male "knockout" mice, heterozygous for the p53 tumour suppressor gene. The mouse strain (C57Bl/6 Tac fBR-[KO]Trp53N5-T) is phenotypically normal, but has enhanced susceptibility to genotoxic events. Carbaryl was administered via the diet at concentrations of 0, 10, 30, 100, 300, 1000 or 4000 ppm (equal to 1.8, 5.2, 17.5, 52, 165 and 717 mg/kg bw/d) for 180 d. Carbaryl did not induce mortality or clinical signs. Treatment-related observations were confined to the 4000 ppm group, which displayed a slight but significant ($p<0.01$ *vs.* control) deficit in food consumption, correlated with lower mean bodyweight ($p<0.05$ or 0.01 *vs.* control). At study termination the 4000 ppm group mean bw remained approximately 8% below the control value. A transient decrease in food consumption among the 1000 ppm group ($p<0.05$ *vs.* control) was not accompanied by decreased growth or bw. An increase was noted in absolute and relative liver and kidney weights at 1000 and 4000 ppm, while depression in thymus weight occurred at 4000 ppm only. Statistical significance ($p<0.05$ or 0.01 *vs.* control) was attained with respect to most of these parameters. Globular deposits in the upper (umbrella) cell layer of the urinary bladder epithelium affected many animals at 100 ppm or greater. The relative severity of accumulation was dose related, but there was no accompanying irritation or hyperplastic response. The NOEL was 30 ppm (equal to 5.2 mg/kg bw/d), based on the presence of deposits in the urinary bladder epithelium at and above the next highest dose of 100 ppm. There was no treatment-related tumourigenesis.

In a study validating use of p53 knockout mice for investigating vascular tumour development (Bigot, 1999), heterozygous (+/-) males were gavaged daily with urethane at 1, 10 or 100 mg/kg bw/d for 180 d. Seventeen/20 animals from the 100 mg/kg bw/d group died prematurely, mainly from internal haemorrhage. The entire 1 mg/kg bw/d group survived, while there were 2 intercurrent deaths at 10 mg/kg bw/d. Histopathology revealed hepatic angiectasis at 10 and 100 mg/kg bw/d, and vascular neoplasia in the livers of 18/20 mice receiving 100 mg/kg bw/d, together with single occurrences of hemangiosarcoma of the spleen and abdominal cavity and cardiac hemangioma. The 10 mg/kg bw/d group showed 1 case of multiple hepatic hemangioma. Other treatment-related tumours comprised subcutaneous sarcoma and lymphoma at 10 and 100 mg/kg bw/d, and adenoma of the lung and hepatocellular carcinoma at 100 mg/kg only. No neoplasms were present in the 1 mg/kg bw/d group. A negative control group gavaged with 250 mg/kg bw/d d-limonene displayed inappetence, mononuclear cell infiltration of the renal peripelvis and slight to moderate hyperplasia of the non-glandular stomach, but no treatment-related neoplasia. Comparison between vehicle control groups of p53 heterozygous and wild type (p53 +/+) mice showed that the genetic difference between these strains did not affect spontaneous tumour formation.

In a published review, Venkatachalam *et al.* (2001) discuss the biological and molecular mechanisms underlying enhanced cancer formation in mice heterozygous for the gene coding for the p53 protein (p53+/- mice). The p53+/- mouse strain contains one wild-type allele, together with an inactive mutant gene coding for p53. Over a half of the tumours collected from these mice retain an intact wild-type allele, while in the remainder, the wild-type allele had become completely deleted. Tumours arising at less than 18 months of age tend to have a higher frequency of complete p53 allele loss than those arising later in the mouse life span. P53 +/- tumours that retain the wild-type allele also retain sensitivity to apoptosis following irradiation, and display other markers of p53 functionality. Compared with cells from p53 +/+ animals, fibroblasts derived from p53 -/- mouse embryos show a higher growth rate, saturation density, and less cell cycle arrest response following exposure

to ionising radiation. The +/- genotype has growth characteristics and radiation response intermediate between those of the +/+ and -/- genotypes. Thus, it appears that the p53 protein is "haploinsufficient": loss of a single copy of the wild-type allele is sufficient to impair (but not prevent) the protein's tumour suppression activity. This finding is unexpected, as it has hitherto been believed that loss of *both* copies of a tumour suppressor gene are a prerequisite for tumour formation. Tumours from carcinogen-treated p53+/- mice do not reveal any consistent relationship between the carcinogen's mode of action, and whether the tumours retain or lose the remaining wild-type p53 allele. The authors suggest that the target tissue itself may have some influence over the loss or retention of the wild-type p53 allele. They conclude that carcinogenesis in the p53 +/- mouse model is likely to involve numerous carcinogen-tissue interactions that determine the likely site of tumour origin, tumour formation latency, the oncogenic lesions responsible for tumour formation, the cell-signalling pathways affected, and whether or not the wild-type p53 allele becomes inactivated.

Debruyne (1998) performed cellular proliferation studies on the kidney and liver of mice previously exposed to carbaryl for 52 weeks in a dietary study (Hamada, 1993b). Cell turnover was measured in tissue from the control and 8000 ppm interim sacrifice groups, by staining for Proliferating Cell Nuclear Antigen (PCNA). The mean number of PCNA-positive renal cortical tubular cells in 8000 ppm males (3.9/1000) was approximately 3-fold higher than in control male kidney (1.2/1000). In control females, the rate of PCNA-positive hepatocytes (mean=4.6/1000) was approximately half the mean positive staining rate among the 8000 ppm group (8.3/1000). These data suggest a higher amount of cellular replication in the kidney of male mice and the liver of females receiving 8000 ppm carbaryl, compared with controls. There is an apparent correlation between this parameter and Hamada's (1993b) finding of renal and hepatic tumours in the 8000 ppm males and females, respectively. By contrast, there was no biologically significant enhancement of cell turnover in the liver of 8000 ppm males or kidney of 8000 ppm females, which were not sites of tumour development.

Irisarri (1996) measured cellular proliferation by PCNA staining in the liver, urinary bladder and thyearoid gland of rats that had been exposed to carbaryl for 52 week in a dietary study (Hamada, 1993a). There was a small increase in cell cycling activity in the male thyearoid and female liver at 7500 ppm. Although of equivocal biological significance, this finding does correlate with elevated incidences of thyearoidal adenoma and hepatic adenoma in 7500 ppm males and females, respectively, in the chronic dietary experiment. A 10-fold increase in cell cycling in the urinary bladder epithelium of 7500 ppm males was of clear biological significance and correlates with the hyper- and neoplastic response observed by Hamada (1993a) within this group.

In a discussion paper, Cohen (1995) agrees with the registrant's position that carbaryl causes renal and urinary bladder tumours in rodents via a non-genotoxic mechanism. He considers it likely that the bladder tumours observed in rats at 7500 ppm resulted from a direct mitogenic effect by carbaryl or its metabolites on the urinary epithelium. Cohen's argument is based on his (1994) mechanistic study with another aromatic carbamate, propoxur, which has also been shown to cause urinary bladder cancer in rats at a high (8000 ppm) dietary dose. Cohen demonstrated cellular proliferation in the absence of necrotic injury, formation of calculi, amorphous precipitates, or crystals. With regard to the proliferative lesions seen in the male rat kidney at 7500 ppm, Cohen also attributes these to mitogenic stimulus. The author concludes that without knowing the exact mechanism involved in rats, or the route of carbaryl metabolism in humans, it was impossible to predict whether cancer of the urinary

tract could occur in humans. However, given that urinary tract hyperplasia/neoplasia are restricted to rats and require dietary exposure exceeding the Maximum Tolerated Dose (MTD), such lesions are unlikely at the anticipated levels of human exposure. In this respect, Dr Cohen's conclusions are consistent with the position taken by the Australian reviewing toxicologist in OCS's 1998 evaluation.

8.1.6 Reproductive Studies

In a 2-generation reproduction study (Tyl *et al.*, 2001), rats were treated with carbaryl technical in their diet at concentrations of 0, 75, 300 or 1500 ppm for a 10-week period, and throught mating, gestation and lactation of the resulting F1 litter. The procedure was repeated with the F1 pups, which were treated at the same doses until the end of lactation of the F2 litter. The NOEL for effects on the parental generations was 75 ppm, based on the following findings at and above the next highest dose: decreased bw gain, bw, feed consumption and conversion efficiency in F0 and F1 adults of both sexes, combined with depression in gestational bw and lactational bw and feed consumption in F1 females. A single 1500 ppm F0 male was found to be producing 100% non-motile sperm that had abnormal morphology. The 1500 ppm F0 group mean sperm motility was reduced and there was a small increase in the proportion of abnormal sperm at 1500 and possibly 300 ppm. However, there were no similar findings in F1 adults. Carbaryl did not affect the sex ratio, or growth or survival of F1 or F2 foetuses *in utero*, and did not cause malformations or clinical signs among pups during lactation. However, F1 and F2 pup growth was reduced and mortality was increased during lactation at 1500 ppm. F2 pup mortality was also enhanced at 300 ppm. Puberty was significantly retarded in both sexes at 1500 ppm. The NOEL for effects on pups was therefore 75 ppm (approximately 4.7 mg/kg bw/d), based on increased mortality during lactation of the F2 litters at and above 300 ppm.

8.1.7 Developmental Studies

Repetto-Larsay (1998) administered carbaryl by gavage to mated female rats at 0, 1, 4 or 30 mg/kg bw/d on d 6 – 20 inclusive of presumed gestation. No premature mortality occurred. At 30 mg/kg bw/d, most dams had at least one occurrence of increased salivation within 20 min of dosing, and this group also showed significantly ($p<0.01$) depressed food consumption, a transient loss of bw at the commencement of dosing, an 8% deficit (*vs.* control) in terminal bw, and significant ($p<0.01$) reduction in cumulative gross and net (without uterus) bw gain. Foetal survival and sex ratio were not compromised but there was evidence of foetotoxicity at 30 mg/kg bw/d, seen as a 13% reduction in gravid uterine weight, a significant ($p<0.01$) deficit in foetal bw, an increased incidence of runts, and delayed ossification of the spinal vertebrae and paw. However, there were no treatment-related visceral anomalies or malformations. The NOEL was 4 mg/kg bw/d, based on maternotoxicity (salivation and depressed food consumption and bw gain) and foetotoxicity (reduced foetal bw and delayed ossification) at the highest dose of 30 mg/kg bw/d.

In a range finding study by Tyl (1999), carbaryl was administered by gavage to mated female rabbits at 0, 3, 7.5, 20, 50 or 100 mg/kg bw/d on d 6 – 29 inclusive of presumed gestation. No treatment-related clinical signs or unscheduled deaths were observed. There was a significant ($p<0.05$) trend towards decreasing maternal bw gain over the dosing period, with group mean values being reduced by about 20% at 50 and 100 mg/kg bw/d. A parallel trend occurred in net maternal bw change when corrected for gravid uterine weight. At 100 mg/kg bw/d, ChE activity was inhibited by 20% in RBC and 59% in plasma ($p<0.05$) relative to control values. There was no effect on foetal survival or development. Although

a near significant (p=0.0506) trend towards dose related depression in foetal bw occurred, attributable to a 16% reduction (*vs.* control) at 100 mg/kg bw/d, the finding was of equivocal biological significance. As this is a range finding study employing limited group sizes and limited observations, a NOEL will not be set.

Tyl, Marr and Myers (1999) gavaged mated female rabbits with 0, 5, 50 or 150 mg/kg bw/d carbaryl on d 6 – 29 inclusive of presumed gestation. The 150 mg/kg bw/d group lost weight over gestation day (gd) 6 – 9, and displayed significantly ($p<0.01$) depressed cumulative bw gain over the dosing and entire gestation periods. When corrected for gravid uterine weight, maternal net bw loss was nearly 3-fold higher at 150 mg/kg bw/d than among controls. ChE activity was inhibited dose-relatedly at 50 and 150 mg/kg bw/d ($p<0.01$). At the mid and high doses, respectively, ChE inhibition amounted to approximately 46 and 68% in plasma and 19 and 29% in erythrocytes. Treatment did not compromise foetal survival or sex ratio, but caused significant ($p<0.01$) depression in foetal bodyweight at 150 mg/kg bw/d. However, there were no effects on foetal development. The NOEL for maternal effects was 5 mg/kg bw/d, based on plasma and RBC ChE inhibition at and above the next highest dose of 50 mg/kg bw/d. The NOEL for foetotoxicity was 50 mg/kg bw/d, based on depressed bodyweight at the highest dose of 150 mg/kg bw/d.

8.1.8 Neurotoxicity Studies

In amendments to a developmental neurotoxicity study by the same authors, which was evaluated by OCS in 1998, Robinson and Broxup (2001a & b) performed additional morphometric analyses on the forebrain and cerebellum of 11- and 70-d old offspring from the control dams and dams receiving 10 mg carbaryl/kg bw/d.by gavage from GD 6 to 10 d post-partum. The additional measurements had been recommended in a US EPA assessment which indicated a possible treatment-related decrease in the length and weight of the cerubellum in 11 d old female offspring of dams treated at 10 mg/kg bw/d, together with a bilateral increase in the width of the cerebellum in 70 d old female offspring from the same group. [The OCS assessment did not ascribe toxicological significance to these findings because of contradictory sex- and time-related changes from control.] The findings of these two supplementary studies were entirely negative with respect to all measured parameters, and do not change the OCS's original conclusion that there were no neurotoxic or developmental effects on pups at the highest dose (10 mg carbaryl/kg bw/d). The maternal NOEL remains at 1 mg/kg bw/d (based on reduced bw gain, autonomic effects, tremors and ChE depression at the highest dose).

8.1.9 Human Studies

A series of user exposure studies was performed, in which untrained volunteers applied various carbaryl based home garden/veterinary insecticides while wearing a long sleeved cotton shirt, long cotton pants and a whole body dosimeter under the outer clothing. The amount of carbaryl deposited on the clothing, inner dosimeter, hands, face and neck was measured by HPLC. Breathing zone air was also sampled and assayed for the active constituent.

During application of a 5.4% powder insecticide product to 3 dogs, volunteers were exposed dermally and inhalationally to a mean of 1111 and 7986 µg carbaryl, respectively, when wearing or not wearing gloves. When adjusted for volunteer bodyweight and the amount of active constituent used, carbaryl exposure was 4.8 and 36 µg/kg bw/g applied, under the respective conditions (Merricks, 1997a).

When ungloved volunteers applied a 22.4% liquid product to vegetables, the mean exposure to carbaryl was 836 µg and 247 µg, using hose-end and hand-held pump sprayers, respectively. When adjusted for bodyweight and the amount of active constituent used, carbaryl exposure was 0.5 and 0.4 µg/kg bw/g applied, with the respective sprayer types. If gloves were worn, total exposure was reduced to 7 µg and 5.9 µg (0.004 and 0.011 µg/kg bw/g applied), with hose-end and hand held pump sprayers, respectively (Merricks, 1997b).

Application of the 22.4% liquid product to 2 large and 2 small trees, caused volunteers to be exposed to a mean of 743 and 524 µg carbaryl when using hose-end and hand-held spray apparatus, respectively. Greater than 99% of exposure was via the ungloved hands. When normalised for bodyweight and the amount of active constituent used, carbaryl exposure was 0.6 and 0.8 µg/kg bw/g applied, with the respective sprayer types (Merricks, 1998).

Use of a 0.1% ready-to-use liquid, which was applied directly from its pump bottle package, resulted in a mean exposure to carbaryl of 87 µg. Gloves effected a 95% reduction in dermal exposure to the active constituent. When adjusted for bodyweight and the amount of active constituent used, carbaryl exposure was 1.2 µg/kg bw/g applied if gloves were not worn, and 0.06 µg/kg bw/g if applied with gloves (Merricks, 1997b).

When ungloved volunteers treated vegetables with a 9.8% dust product, the mean exposure to carbaryl was 1181 µg. When normalised for volunteer bodyweight and the amount of active constituent used, carbaryl exposure was 2.1 µg/kg bw/g applied (Merricks, 1997b).

8.2 Discussion

8.2.1 Metabolism and Toxicokinetics

The absorption, excretion and toxicokinetics of carbaryl are typical of the carbamate class. Carbaryl is extensively absorbed by the oral route and excreted rapidly in the urine by humans and experimental animals except dogs, in which the faeces is also a significant route of excretion. There is little tendency for carbaryl or its metabolites to accumulate in body tissues, even after subchronic administration. Carbaryl induces the hepatic mixed function oxidase system in mice, showing an induction profile similar to phenobarbital.

In studies previously evaluated by OCS, rats metabolised carbaryl by three main pathways: hydrolysis, alkyl oxidation and arene oxide formation. The latter pathway is believed to proceed via production of epoxide intermediates which are then conjugated by glutathione, either immediately or following the action of epoxide hydrase. There is some evidence (Totis, 1996) that in rats, activity of the arene oxide/epoxidation pathway is enhanced by prolonged dietary administration of 7500 ppm carbaryl, by comparison with the pathway's activity at lower doses. There was a concomitant decline in metabolism via hydrolysis at 7500 ppm. The sponsors suggest that generation of the putative epoxides is associated with formation of kidney, urinary bladder and thyearoid tumours in rats receiving 7500 ppm carbaryl during the 2-year study by Hamada (1993a). In a discussion paper, Cohen (1995) agrees with the registrant's position that epoxidised metabolites of carbaryl cause renal and urinary bladder tumours in rodents. He considers it likely that the bladder tumours observed in rats at 7500 ppm resulted from a direct mitogenic effect on the urinary epithelium, based on his (1994) mechanistic study with propoxur, which has also been shown to cause urinary

bladder cancer in rats. Cohen also attributes the proliferative lesions seen in the male rat kidney at 7500 ppm, to mitogenic stimulus.

In the current submission, the sponsors have directed their efforts towards finding a relationship between carbaryl metabolism and carcinogenicity in mice. In Hamada's (1993b) chronic study, vascular, renal and hepatic tumours were increased in mice treated at 8000 ppm, and vascular tumours were also elevated in 1000 and 100 ppm males. With the addition of a 10 ppm group, these same dietary carbaryl levels were administered to mice for 14 d prior to a 50 mg/kg bw oral bolus dose and subsequent quantification/identification of urinary metabolites (Valles, 1999). Consistent with results obtained in rats, pre-treatment with 8000 ppm carbaryl (but not lower doses) increased the urinary excretion of metabolites formed via epoxides, relative to products of hydrolysis and alkyl oxidation. However, the response was smaller in mice than rats. The alkyl oxidation/epoxidation pathway was not identical in the two species, giving rise to one metabolite that was unique to rats and another that was detected only in mice. This might explain the differential response of mice and rats with regard to formation of vascular or renal tumours (which were confined to mice) and neoplasms of the thyearoid or urinary bladder (which occurred only in rats).

Although 10 and 100 ppm mice showed a modest decline in the proportion of carbaryl metabolised by hydrolysis, the relative activity of the hydrolysis pathway was not reduced at higher doses. Even if the finding did not arise from experimental variation, it is difficult to conceive how it would have any bearing on tumour development.

If the entire body of knowledge about carbaryl metabolism in rats and mice is considered in relationship to tumour formation in these species, some limited conclusions may be drawn, as follows:

- Arene oxide formation/epoxidation occurs in both mice and rats at *all* the carbaryl doses tested;

- The arene oxide/epoxidation pathway becomes relatively more active at 7500 to 8000 ppm, which exceeds the maximum tolerated dose in both mice and rats;

- The hydrolysis and hydroxylation pathways of carbaryl metabolism may become saturated at dietary levels exceeding 1000 ppm;

- At 8000 ppm, the occurrence of hepatic and/or vascular tumours in female mice and increased incidence of renal and/or vascular tumours among males may indeed occur in response to enhanced epoxide formation; but

- Vascular tumours formed in male mice at 100 and 1000 ppm carbaryl cannot be explained in terms of preferential arene oxidation/epoxidation at 8000 ppm; and

- Since the arene oxide/epoxidation pathway is also active in male mice at 10 ppm (a feeding level not tested in mouse carcinogenicity studies), the findings fail to suggest any particular threshold dose below which the formation of vascular tumours would not occur.

Overall, an association between epoxide formation and tumour development is considered biologically credible, but remains unproven. Beyond showing a difference in the epoxidised metabolites excreted by males of the two species, the metabolism studies have provided no

detailed explanation as to why epoxide generation may cause vascular tumours in mice but not rats. It also remains unknown why female mice are more resistant to vascular tumour formation than males. Comparative metabolism data in female mice would have been valuable in this regard. Given that carbaryl metabolism is qualitatively similar in laboratory animals and humans, the current findings in rodents may be relevant to man, but the metabolism data alone cannot be used to predict whether humans would be more or less sensitive to vascular tumourigenesis than mice and rats.

8.2.2 Cholinesterase Inhibition

Carbaryl possesses anticholinesterase activity typical of members of the carbamate class. In rats, ChE inhibition reaches its maximum between 0.5 and 1 h following carbaryl administration by gavage. The subsequent time course of ChE inhibition is both dose- and tissue/site-dependent. Recovery of plasma and red blood cell ChE activity is rapid (within 2 h post-dosing at 10 mg/kg bw, and within 24 h at 50 mg/kg bw). Brain ChE activity is slower to recover, taking 24 h to fully regain baseline values at 10 and 50 mg/kg bw. At higher doses, reversibility is more prolonged.

ChE inhibition was the main toxicological finding in the newly-submitted 12-month dog study by Hamada (1987), in which there was statistically and biologically significant inhibition of plasma and brain ChE activity at the lowest dietary level of 125 ppm (3.8 mg/kg bw/d). RBC ChE activity was inhibited at and above 400 ppm (11 mg/kg bw/d). Plasma ChE inhibition was present from week 5 onwards and persisted until termination, although the effect was diminished at week 26 and 52, perhaps because of a gradual reduction in achieved carbaryl dose during the study.

By contrast, when a 5-week dietary study in dogs was performed at the same laboratory 4 year later, there was no effect on brain ChE activity at the highest feeding level of 125 ppm, and the effect on plasma ChE activity, although present, probably lay near the threshold of biological significance. There were no significant methodological differences between the 5-week and 1-year studies. The delivered doses at 125 ppm in the 5-week study were very similar to those achieved during the first 5-week of the 1-year study. Blood samples for ChE assay were obtained approximately 2 hours after withdrawal of feed in both studies. It is considered that in the 5-week study, a combination of biological variation, technical variation in the ChE assay, and lack of statistical power due to small sample size (n=6/group) may have obscured inhibition of plasma ChE at 125 ppm.

Plasma and whole blood ChE have been measured in a human study following single oral doses of up to 2.0 mg/kg bw, and at weekly intervals during administration of repeated oral doses of 0.06 or 0.13 mg/kg bw/d for 6 week (Wills *et al.*, 1968). No inhibition of ChE activity was observed. However, the study is considered unreliable due to a lack of methodological detail and indications from a case report (Hayes & Laws, 1991) that acute ChE poisoning can occur in humans at 2.8 mg/kg bw.

In Table 17, NOELs are presented for plasma, erythrocyte and brain ChE activity. The data suggests that rats and dogs are more susceptible than mice to plasma ChE inhibition.

Also noteworthy is the striking disparity between NOELs demonstrated in the chronic rodent studies compared with those in the acute, 13-week and developmental neurotoxicity studies, in which the LOELs in plasma, RBC and brain were 10 mg/kg bw/d. Differences between

the dosage and sampling regimes employed in the rodent 2-year and acute and repeat-dose studies are likely to be responsible. Dietary administration was used for the 2-year experiments, and the rats were probably sampled some hours after cessation of feeding, after the time of peak effect. By contrast, rats in the acute and repeat-dose studies were gavaged and then sampled 1 hour post-treatment, at the time of maximum effect. Toxicokinetic differences between dietary and oral bolus dosing may also have contributed to the apparently greater sensitivity of rats in the 13-week and developmental neurotoxicity studies.

Tables 17: Summary of doses (mg/kg bw or mg/kg bw/d) at which no inhibition of ChE activity following carbaryl administration was seen.

Species	Duration	Plasma ChE	Erythrocyte ChE	Brain ChE
Mouse	2 year	1350	16	16
Rat	Single gavage dose	Not established#	Not established#	Not established#
Rat	13 week	1	1	1
Rat	25 d (GD 6 – LD10)	1	1	1
Rat	2 year	70	11	11
Dog	5 week	1.4	3.8	3.8
Dog	1 year	Not established*	3.8	Not established*

#ChE inhibition occurred at the lowest dose of 10 mg/kg bw.
*ChE inhibition occurred at the lowest dose of 3.8 mg/kg bw/d.
ND=no data

Note: with the exception of the two studies in dogs, the tabulated studies have been evaluated previously and do not appear in this report.

8.2.3 Neurotoxicity and behavioural studies

The effects of carbaryl on the nervous system of rats, chickens, monkeys and humans are primarily related to ChE inhibition and are usually transitory. The Environmental Health Criteria Monograph on carbaryl (WHO, 1994) notes disruption to learning in rats treated for 50 days at oral doses of 10-20 mg/kg bw/d, reversible leg weakness in chickens given high doses of carbaryl, but no evidence of demyelination in the brain, sciatic nerve or spinal cord sections in the birds or in long term rodent studies. In a 10-week study in pigs, dietary administration of carbaryl at 150 mg/kg bw/d caused progressive myasthenia, incoordination ataxia, tremor, muscular contraction, terminal paraplegia and myodegeneration of the skeletal muscle. In the myelinated tracts of the cerebellum, brain stem and upper spinal cord, moderate to severe oedema was associated with vascular degeneration, but no demyelination of nerve tissue was observed.

Few of the neurotoxicity studies on carbaryl that were available before 1995 appear to have been assessed in Australia. However, this situation was improved during the late 1990s by submission of a series of excellent modern studies in rats, which thoroughly characterised the test compound's effects on the central and peripheral nervous systems, ChE activity, behaviour and foetal development. Single gavage doses of 30-50 to 90-125 mg/kg bw caused overt signs of carbamate poisoning and functional deficits in behaviour together with brain, plasma and RBC ChE depression that reversed within 24 to 48 h. ChE depression also occurred following a 10 mg/kg bw dose, but was associated only with reduced motor activity. The NOEL in the 13-week neurotoxicity study was 1 mg/kg bw/d, based on blood and brain ChE depression and behavioural effects at higher doses. A maternal NOEL of 1 mg/kg bw/d was also established on the basis of these same effects in the developmental neurotoxicity study, but carbaryl had no adverse effects on foetal or pup survival, growth or

development at up to and including the highest dose of 10 mg/kg bw/d. In both the subchronic and developmental studies, no adverse findings were made with respect to neuropathology in the adults or offspring.

Supplementary neurotoxicity studies were submitted for inclusion in the current review. These comprised additional morphometric measurements of the brain in offspring from rat dams treated at the highest dose in the developmental neurotoxicity study discussed above. The supplementary measurements were prompted by a US EPA assessment of that study, which was considered to have demonstrated possibly treatment-related effects on brain weight and morphology at 10 mg/kg bw/d. By contrast, the OCS evaluator attributed the findings to biological variation. The supplementary studies showed no treatment-related differences between the high dose (10 mg/kg bw/d) and control groups, and have no effect on OCS's previous assessment.

8.2.4 Genotoxicity

No further genotoxicity studies have been provided since the 1998 OCS evaluation. Carbaryl has been tested *in vitro* and *in vivo* in bacterial, insect, yeast, plant and mammalian systems. Previous reviews of the genotoxic potential of carbaryl have concluded that carbaryl does not damage DNA and is unlikely to be mutagenic in humans. While carbaryl has demonstrated some clastogenic potential and activity by other endpoints *in vitro* (mitotic recombination, gene conversion, unscheduled DNA synthesis in *Haemophilus influenzae, Bacillus subtilis, Saccharomyces cerevisiae, Aspergillus nidulans,* human lymphocytes and rat hepatocytes) at high doses that produced marked cell toxicity, it is not an *in vivo* clastogen. Carbaryl has yielded negative results in all but 2 mutagenicity assays in bacteria, and although several mutagenicity assays have been conducted in cultured mammalian cells, only one equivocally positive result has been obtained.

However, it would be premature to rule out the possibility that genotoxicity can be mediated by the (hypothetical) epoxides generated during carbaryl metabolism. If these entities are indeed formed in sufficient quantities, they may react with genetic material in some or all of the target tissues, under conditions that are not duplicated by the test protocols employed so far. The question will probably remain unanswered until attempts are made to detect molecular adducts on chromosomal material or other intracellular macromolecules from within the liver, kidney, thyearoid, urinary bladder and hepatic/splenic vascular system of mice and rats receiving carbaryl.

8.2.5 Reproduction and Development

One of the most significant deficiencies in the carbaryl database has been the lack of modern reproduction and developmental studies. This limitation has now been addressed with the submission of a new 2-generation reproduction study in rats and developmental studies in rats and rabbits, which were performed in accordance with current Good Laboratory Practice (GLP) standards and Test Guidelines.

The 1996 JMPR observed that the (then) available reproduction studies with carbaryl were deficient by contemporary standards. In previous 3-generation studies in rats, fertility was impaired and post-natal survival and growth were reduced at dietary doses >2000 ppm (equal to 125 mg/kg bw/d) but a dose of 100 mg/kg bw/d did not induce maternal toxicity. When carbaryl was administered by gavage, maternal toxicity was not observed at 25 mg/kg bw/d but maternal toxicity, reduced litter size and viability were found at 100 mg/kg bw/d.

The Meeting recommended that a new 2-generation study be carried out in rats, with special attention to the male reproductive system, upon which effects had been observed in some long term toxicity studies by gavage at doses significantly lower than those evaluated in dietary studies.

OCS was highly supportive of this recommendation, having previously evaluated a published paper (Pant *et al.*, 1995) showing disrupted testicular morphology and spermatogenesis in Wistar rats gavaged for 90 d (5d/week) at 50 or 100 mg/kg bw/d. Pant *et al.* observed testicular congestion and oedema, moderate atrophy of the seminiferous tubules, an approximately 2-fold increase in the proportion of abnormal sperm and a 40% reduction in sperm count *vs.* control at 50 mg/kg bw/d. At 100 mg/kg bw/d, testicular congestion and oedema were more intense, masses were present within the seminiferous tubules, the proportion of abnormal sperm was trebled and sperm count was depressed by 60%. There were dose-related depressions in glucose 6-phosphate and sorbitol dehydrogenase activity and elevations in LDH and GGT activity. The findings of Pant *et al.* are not isolated. Vashakidze (1975; evaluated by WHO in EHC 153 [1994]) reported decreased sperm motility and increased sperm abnormalities in rats intubated orally with carbaryl for 1 mo at doses of 5 mg/kg bw/d or greater.

The current 2-generation reproduction study (Tyl *et al.*, 2001) found possible treatment-related effects on the male reproductive system at the highest dose of 1500 ppm (approximately 97 mg/kg bw/d). A single F0 adult male was found to be producing 100% non-motile sperm that lacked tails. The finding was not correlated with reproductive failure, however, as the animal had mated and conceived a litter of viable pups. Given that 3 week had elapsed between mating and sacrifice of the F0 males, complete loss of active sperm may have not developed until the post-mating period. There was also an apparent dose-related increase in percentage abnormal sperm seen in the 1500 and 300 ppm F0 males, but it was not repeated in the F1 generation.

Differences in dosing methods may explain the variation between the outcome of the studies by Tyl *et al.* and Pant *et al.* The 1500 ppm males in the study of Tyl *et al.* received carbaryl by dietary administration, whereas Pant *et al.* administered carbaryl orally in peanut oil (the exact technique was not described). Oral absorption of carbaryl is rapid, suggesting that higher peak blood and tissue levels may be attained after bolus dosing than following dietary intake of an equivalent dose over the usual 8-h rodent feeding period. There may also be genetic differences in susceptibility between the Wistar rats used by Pant *et al.* and the CD (Sprague-Dawley) strain used by Tyl *et al.* Unfortunately, there is insufficient information available on the study by Vashakidze (1975) to enable comparison between the test material, animals and methods used by that author and Tyl *et al.*

The delayed puberty in F1 pups and reduced anogenital distance at birth in F2 males at 1500 ppm raise the question as to whether carbaryl mediates a specific effect on sexual development. However, the study's findings do not support such a hypothesis. Anogenital distance was found to be dependent on pup birth weight (*ie*, smaller male pups tended to have shorter anogenital distance) and hence is unlikely to have been reduced by feminised sexual development of male foetuses. Puberty was retarded in both sexes (which provides further evidence against a gender-specific effect) and retardation occurred only in the presence of inhibited bw gain. These findings are therefore both considered to be secondary to effects on bw and bw gain.

In the developmental studies, maternotoxicity was seen as cholinergic signs in rats, inhibition of plasma and RBC ChE activity in rabbits, and depressed weight gain in both species. Foetal development was retarded at maternally toxic doses, but there were no treatment-related visceral anomalies or malformations. The results were broadly consistent with those of studies previously evaluated by the OCS and the JMPR.

8.2.6 Carcinogenicity

Carbaryl is remarkable for its carcinogenic activity in the chronic rodent studies by Hamada (1993a and 1993b), having caused tumours of the thyearoid, urinary bladder and liver in rats, and kidney, liver and vascular system in mice. In the current submission, cell cycling studies on tissue specimens from Hamada's studies (with the exception of sites of vascular tumour formation) demonstrated enhanced cellular division in target tissues. These results were in marked contrast to negative findings in a series of previous oncogenicity studies in both species, dating to the early 1960s.

However, with the exception of vascular tumours, carcinogenicity did not occur below the highest doses administered (8000 and 7500 ppm in diet to mice and rats, respectively). In many respects, the high dose tumours are suggestive of inappropriate study design. On a daily basis, the high dose groups received equivalent to or greater than the acute oral LD50, and displayed marked systemic toxicity including depressed weight gain and feed consumption, behavioural changes, cataracts and anaemia. Thus, the 7500/8000 ppm groups were treated at above the maximum tolerated dose. Since carbaryl has not shown any convincing evidence of genotoxic activity, and because NOELs of 1000 and 1500 ppm were demonstrated in the respective species for bladder, hepatic, thyearoid and renal tumours, neither OCS nor the ACPH has regarded these high dose tumours as a barrier to continuing registration of carbaryl, subject to adequate safeguards that would limit public exposure to the chemical.

From a regulatory standpoint, the vascular tumours are of significantly greater concern. Although these did not develop in female mice at below the 8000 ppm feeding level, there was no apparent NOEL in males, even at the lowest dose of 100 ppm (equivalent to approximately 16 mg/kg bw/d). In the opinion of the OCS, ACPH and JMPR, historical control data on the incidence of vascular tumours has failed to demonstrate that Hamada's findings were attributable to biological variation. Furthermore, while there are often fairly well established non-genotoxic modes of action underlying the development of liver, thyearoid, kidney and urinary bladder tumours in rodents, vascular hemangioma and hemangiosarcoma are more difficult to explain, and their human relevance cannot be dismissed.

The sponsors have now focussed on eliminating genotoxicity as a probable mode of action for carbaryl. This has been attempted by use of a novel short term carcinogenicity bioassay in male p53 "knockout" mice, which compared tumour development among animals treated with carbaryl, d-limonene (as a negative control) and urethane (as a positive control).

The function of the p53 gene is related to regulation of the cell cycle. Cellular levels of p53, a phosphoprotein transcription factor, are greatly increased by radiation and other DNA damaging agents, and this increase in p53 is accompanied by an arrest in late G1 of the cell cycle. Wild type p53 can also mediate apoptosis (Donehower, 1996). By contrast, cells in which the p53 gene is deficient may continue to replicate while incorporating genetic errors that would normally be repaired or excised. Many types of human tumours contain

mutations and loss of the p53 gene. In addition, germ line mutations in p53 have been identified in affected individuals of Li-Fraumeni syndrome families, who have a 50% likelihood of developing cancer by the age of 30 (Donehower, 1996).

The heterozygous p53-deficient mice used in the current oncogenicity study with carbaryl, are phenotypically normal but have enhanced susceptibility to genotoxic events, both spontaneous and induced. The pattern of spontaneous tumour formation among p53 heterozygous mice is of major importance to their utility in the investigation of vascular tumours. Less than 8% of these mice develop tumours before 9 months of age, but tumour incidence subsequently increases to 50% by 18 months and 90% by 2 years. The principal spontaneous neoplasia in p53 +/- animals are soft tissue sarcomas, osteosarcomas and lymphomas (approximately 30% incidence, each), with brain tumours and unspecified carcinomas accounting for the remainder (Donehower, 1996). Vascular hemangiomas and hemangiosarcomas are uncommon, which does enhance the biological significance of their formation when p53 knockout mice are treated with xenobiotics.

Donehower (1996) notes accelerated development of liver hemangiosarcoma in dimethyl nitrosamine treated p53 +/- mice, while in the current study in p53 knockout mice, vascular tumours were induced by the genotoxic carcinogen, urethane (Bigot, 1999). It is of interest that urethane is metabolised to vinyl carbamate, which is further metabolised to the ultimate carcinogen, vinyl carbamate epoxide. Vinyl carbamate epoxide reacts with DNA to form one minor and two major adducts, giving rise to an A to T transversion mutation (Bowden, 1997).

Detoxification of epoxides is essential for cell survival and depends mainly on the action of epoxide hydrase or glutathione transferase. Hayes (1994) notes the existence of two forms of epoxide hydrase, an endoplasmic reticular form highly active in adult rats (especially males), and a cell cytosol form that is more active in mice than rats. Perhaps sensitivity to vascular tumour formation can be influenced by species- and gender-specific differences in epoxide hydrase activity. Circumstances leading to glutathione depletion may also enhance the vulnerability of target cells to electrophilic injury.

No treatment-related tumourigenesis occurred in p53 heterozygous mice treated with d-limonene, a non-genotoxic renal carcinogen in male rats that acts by causing α_{2U}-globulin accumulation. Nor did carbaryl elicit tumourigenesis, at up to the highest dietary feeding level of 4000 ppm.

Taken at face value, the negative findings with carbaryl in p53-deficient mice provide support for the view that carbaryl need not be regulated as a genotoxic carcinogen. Nevertheless, any chemical metabolised via a reactive electrophile must be viewed with concern.

Despite the knowledge gained from the current studies, there are still limitations in our understanding of carbaryl's carcinogenic properties, and its mode or mechanism(s) of action remain uncharacterised. The submitted cell cycling studies did not examine vascular tissue. There is a lack of regulatory experience with p53 knockout mouse carcinogenicity studies, which is sufficient to prevent OCS from discounting the results obtained in Hamada's (1993a) conventional 2-year experiment. There is also no indication as to which of the three modern carcinogenicity bioassays with carbaryl (6-month "knockout" mouse, 2-year mouse or 2-year rat) has the most human relevance. Under the circumstances, the reviewer

considers that OCS should continue to uphold use of an enhanced safety factor and reduce public exposure to the lowest extent reasonably achievable.

8.2.7 Human Studies

So far, there is no evidence that carbaryl is carcinogenic in humans. An epidemiology study of workers employed at a US plant that produces carbaryl showed a slightly lower overall rate of mortality from cancer than expected from the general population. Although there was an excess of brain tumours, this lay well within the range of chance and cannot be attributed to exposure to carbaryl.

The current submission included human exposure studies which measured the amount of carbaryl deposited on the skin and clothing of volunteers who were using American carbaryl products in simulated home garden and home veterinary situations. The concentration of carbaryl in their breathing zone air was also measured. The studies were noteworthy for their good design and clear description of the activities performed by the volunteers, and yielded detailed data on the extent and pattern of carbaryl exposure, the amount of inter-individual variation in exposure, and the effectiveness of gloves and clothing in reducing exposure.

The product that had by far the greatest potential for human exposure was a 5% carbaryl veterinary dusting powder. Then, in decreasing order of exposure potential, were 10% vegetable dusts, a 22% liquid concentrate applied to vegetables or trees by spray, and a 0.1% ready to use vegetable spray. In all cases, the majority of exposure occurred via the hands. The veterinary dusting powder also caused significant exposure by inhalation whereas inhalation exposure by vegetable dusting and application of carbaryl sprays was negligible. In general, only about 5% or less of carbaryl that became deposited on the external clothing penetrated to the skin, and comparison between gloved and un-gloved subjects showed that gloves effected a 95% reduction in exposure to the active constituent.

There was wide inter-individual variability in the extent of exposure to carbaryl after using the same product for the same application. For example, after applying insecticidal dust to dogs, the most carbaryl found on a volunteer's internal dosimeter was 13,153 µg, compared with a minimum of 63 µg. When spraying vegetables without gloves, the lowest and highest carbaryl loads on the hands were 63 and 4,440 µg, respectively. This occurred despite all members of the study group performing standardised tasks under supervision, which would have prevented them from preparing grossly over or under strength spray mixtures, or mis-applying the various products.

8.2.8 NOEL considerations

A summary of the NOELs determined for carbaryl is shown in Table 18. Note that the Table omits studies that have not been evaluated by OCS, are unsuitable for regulatory purposes, or have been superseded by replacement data.

Table 18: Summary of the NOELs determined for carbaryl

Study	NOEL (mg/kg bw/d)	LOEL and Toxic Effects
Dogs: 5-week dietary	1.4	3.8 mg/kg bw/d: depressed plasma ChE activity
Mice: 6-month dietary	5.2	17.5 mg/kg bw/d: deposits in urinary bladder epithelium.
Mice: 2-year dietary	Not established	16 mg/kg bw/d: vascular system tumours in males.
Rats: 2-year dietary	11	70 mg/kg bw/d: depressed bw gain and brain and RBC ChE activity.
Dogs: 1-year dietary	Not established	3.8 mg/kg bw/d: depressed plasma and brain ChE activity
Rats: 2-generation dietary reproduction	4.7	19 mg/kg bw/d: decreased parental bw gain, bw, feed consumption and conversion together with increased pup mortality during lactation.
Rats (male): 90-day reproduction by gavage	Not established	50 mg/kg bw/d: lethargy, decreased bw gain and spermatogenesis, increased testicular LDH and GGT activity, testicular atrophy.
Mice: dietary developmental	No adverse effects at highest dose of 30 mg/kg bw/d	-
Rats: developmental by gavage	4.0 for both maternal and foetal effects	30 mg/kg bw/d: salivation, depressed feed consumption and bw gain in dams; reduced bw and delayed ossification in foetuses.
Guinea pigs: developmental by gavage and dietary administration	No treatment-related effects at highest doses of 200 mg/kg bw/d (gavage) or 300 mg/kg bw/d (dietary)	-
Rabbits: developmental by gavage	5.0 for maternal effects 50 for foetal effects	Does: 50 mg/kg bw/d: plasma and RBC ChE inhibition; Foetuses: 150 mg/kg bw/d: depressed bw.
Dogs: dietary developmental	3.1 for foetal effects No maternal effects at highest dose of 50 mg/kg bw/d	Pups: 6.3 mg/kg bw/d: skeletal and visceral abnormalities in the absence of maternal toxicity.
Rats: 13-week neurotoxicity by gavage	1.0	10 mg/kg bw/d: blood and brain ChE inhibition and reduced motor activity.
Rats: developmental neurotoxicity by gavage	1.0 for maternal effects No adverse effects on pups	10 mg/kg bw/d: decreased maternal bw gain, ataxia, gait disturbance, tremor, constricted pupils, inhibited plasma, RBC and whole blood ChE activity.

8.3 Committee Considerations

National Drugs and Poisons Schedule Committee (NDPSC)

The Poisons Schedule status of carbaryl was considered by the National Drugs and Poisons Schedule Committee at its 36th meeting (15th-17th October 2002). The Committee noted that removal of the Schedule 4 entry had been recommended by the CRIH on the basis that carbaryl was carcinogenic in experimental animals; the available data did not permit an adequate risk assessment to be undertaken in relation to treatment of head lice and there were no registered human therapeutic products containing carbaryl.

However, the Committee considered that:

- Removal of carbaryl from Schedule 4 would delete an important import control over therapeutic goods for human use containing carbaryl, that is, the need for a prescription and the agreement of a physician to the proposed use.

- Likewise removal from Schedule 4 would permit a pharmacist to include carbaryl in a compounded preparation for individual use.

- Under the Trans-Tasman Harmonisation guidelines agreed by the Committee where both New Zealand and Australia had no registered products the entry would be retained until the completion of retrospective harmonisation. At this time, the retention or removal of these entries would be considered on their merits.

- Inclusion in Appendix C was not supported as New Zealand had no equivalent and would still have to retain carbaryl in Schedule 4, and it was debatable whether the toxicity profile warranted inclusion in Appendix C.

- Members supported the retention of the Schedule 4 entry to foster harmonisation with New Zealand and to maintain existing controls over imports and dispensing by pharmacists.

The outcome of the Committee's consideration was that:

- The existing scheduling for agricultural and veterinary uses of carbaryl was appropriate on the basis that the toxicity profile as confirmed as appropriate for inclusion in Schedule 6, and Schedule 5 for preparations containing 10% or less of carbaryl.

- The removal of the Schedule 4 entry was not supported on the basis that a doctor's prescription should continue to be required for any human therapeutic use of carbaryl.

Advisory Committee on Pesticides and Health (ACPH)

The 20th meeting of the Advisory Committee on Pesticides and Health (19th October 2000) was invited to comment upon OCS's review of the latest data, in particular the following issues:

- The utility of short-term carcinogenicity studies in p53-deficient mice, both with respect to carbaryl and more generally;

- In light of the negative findings in the short-term carcinogenicity study with carbaryl, was there any justification for changing the 4000-fold safety factor upon which the ADI is currently based;

- The OCS's recommended ARfD for carbaryl;

- A toxicologically defensible systemic dose of carbaryl to which persons may be exposed when using carbaryl products within the home;

- The assumptions used in estimating the systemic doses of carbaryl that would be absorbed by persons using or making contact with carbaryl within the home garden/veterinary setting;

- OCS's recommendations with respect to continued registration of HG/HV products are justified;

- Whether any further exposure scenarios should be considered; and

- Whether the human exposure model developed by OCS was applicable to other HG/HV pesticides?

Carbaryl was considered again by the ACPH at its 23rd meeting (2nd May 2002).

- The OCS review of additional toxicology studies on carbaryl, which had strengthened the overall database (particularly in terms of repeat-dose and chronic toxicity in non-rodents, and reproductive toxicity) but not advanced the state of knowledge on the carcinogenicity of carbaryl in rodents and its relevance to humans.

- The JMPR had set an ARfD of 0.2 mg/kg bw for carbaryl, applying a 25-fold safety factor to a NOEL for anticholinesterase effects of 3.8 mg/kg bw/d in a 5-week dog study.

- The JMPR had reduced the safety factor applied to the 16 mg/kg bw/d LOEL for tumour formation in male mice from 5000-fold to 2000-fold, resulting in an increase in the JMPR ADI for carbaryl from 0.003 to 0.008 mg/kg bw/d. The reduction in the safety factor appeared to have been made in light of the absence of carcinogenic activity in the 6-mo carcinogenicity study with carbaryl in p53 "knockout" mice, together with other supporting evidence that carbaryl is not a genotoxic carcinogen.

OCS proposed Australian ARfD of 0.01 mg carbaryl/kg bw, based on the NOEL for ChE inhibition and behavioural disturbance of 1 mg/kg bw/d in 13-week and developmental neurotoxicity studies in rats. There is no reliable NOEL for anticholinesterase effects in humans, and that humans have shown clinical signs of anticholinesterase toxicity at carbaryl doses as low as 2.8 mg/kg bw po, which lies below the canine short-term NOEL for RBC and brain ChE inhibition. The proposed ARfD of 0.01 carbaryl/kg bw was accepted.

OCS also sought the opinion of the ACPH as to whether there was any justification for the safety factor applied to the pivotal LOEL for tumour formation in male mice to be revised from its current value of 4000.

8.4 Determination of Public Health Standards

8.4.1 Acceptable Daily Intake

In October 1998 the ACPH reconsidered the ADI for carbaryl, in light of the expanded toxicological database then available, and the draft NHMRC (1999) guidelines for derivation of modifying factors for seriousness of carcinogenic effect. The ACPH recommended that a 4000-fold safety factor be applied to the LOEL of 100 ppm (16 mg/kg bw/d) for vascular tumours in male mice in a 2-year dietary study, giving a revised ADI of 0.004 mg/kg bw/d.

At its October 2000 meeting, the ACPH re-considered the ADI for carbaryl in light of the reviewed carcinogenicity study in p53 "knockout" mice and supplementary studies on the mechanism of tumour formation. The committee confirmed that the continued use of the 4000-fold safety factor for deriving the ADI remained appropriate given the continuing limitations in understanding carbaryl's carcinogenicity in rodents. No new data relevant to the carcinogenicity of carbaryl have subsequently become available. Furthermore, none of the additional studies evaluated in this report is considered to be a more suitable basis for the ADI than the current pivotal 2-year study in mice.

However, OCS notes that following the JMPR-2001 consideration of the carcinogenicity study with carbaryl in p53 "knockout" mice, the JMPR ADI for carbaryl has been increased from 0.003 to 0.008 mg/kg bw/d. This was brought about by reducing the safety factor applied to the 100 ppm LOEL for vascular tumourigenesis, from 5000- to 2000-fold. Furthermore, comment received from Bayer CropScience (formerly Aventis) on the (June 2002) draft of the Australian review has highlighted the conservatism of Australia's 4000-fold safety factor, particularly in light of the negative result obtained with carbaryl in the study in P53-deficient mice.

Taking all relevant factors into consideration, the OCS agrees that the negative result obtained in the 6-month study in P53-deficient mice has indeed significantly increased the weight of evidence that carbaryl is not genotoxic *in vivo*, thereby reducing concern over potential effects on human health. This enables the component for "confidence that carbaryl is genotoxic" to be reduced from 2 to 1, and using the NHMRC criteria on deriving safety factors, the effect of the modification is to reduce the overall safety factor from 4000 to 2000. Application of the 2000-fold safety factor to the LOEL of 100 ppm (16 mg/kg bw/d) for vascular tumours in male mice yields a revised ADI value of 0.008 mg/kg bw/d.

This approach yields the same outcome as the conventional method of deriving safety factors for agricultural and veterinary chemicals, which would incorporate the standard 100-fold component (10 for extrapolation from animals to humans, X 10 for variation in sensitivity within the human population), together with an additional 10-fold factor for use of a LOEL instead of a NOEL, and an extra 2-fold factor allowing for the remaining uncertainty as to the mode and mechanism of vascular tumour formation and for the impossibility of discounting the relevance of vascular tumours to humans.

Given that the LOEL for vascular tumour formation is probably near the threshold dose for tumourigenesis in mice, a margin of greater than 2000-fold between the ADI and the LOEL would not be likely to increase human safety. Hence, a 2000-fold SF should be sufficient to prevent a carcinogenic hazard to humans from dietary intake.

8.4.2 Acute Reference Dose

At the commencement of the review an Australian ARfD value for carbaryl had not been set. Among the toxicological studies that would possibly be a suitable basis for an ARfD, the lowest NOEL is 0.06 mg/kg bw/d, established in a 6-week oral study performed in male prisoners (Wills *et al.*, 1968). An increased urinary amino acid:creatinine ratio was observed at the next highest dose of 0.12 mg/kg bw/d, and was interpreted by the JMPR (1970) as a slight decrease in the ability of the proximal convoluted tubule to re-absorb amino acids. Plasma and whole blood ChE activity was unaffected at either dose. Clinical signs or effects on ChE activity were not observed in a preliminary range-finding experiment, in which pairs of prisoners received single oral doses of up to 2 mg/kg bw carbaryl. However, the study

authors failed to specify the time interval elapsed between dosing and blood sampling during the main and range-finding experiments. It is therefore possible that undetected ChE inhibition occurred, given that ChE activity recovers rapidly following inhibition by carbaryl. Although the prison pharmacist checked the subjects' mouths after dosing to ensure the capsules had been swallowed, there must also be some uncertainty as to whether the carbaryl was indeed taken as intended by the study authors. Given these uncertainties, the Wills *et al.* study is considered unsuitable for regulatory purposes.

Two case studies of adverse effects in humans following carbaryl ingestion are reported in the *Handbook of Pesticide Toxicology* (Hayes & Laws, 1991). A scientist exploring the possible value of carbaryl as an anthelmintic ingested 250 mg (approximately 2.8 mg/kg bw). After 20 min, he suddenly experienced violent epigastric pain, and a little later he began to sweat profusely. A 1 mg dose of atropine produced little improvement. He gradually developed great lassitude and vomited twice. One h after taking the carbaryl, and after a total atropine dose of 3 mg, he felt better, and was completely recovered after 2 h. In the second incident, a scientist ingested (on an empty stomach) a suspension containing about 420 mg carbaryl (approximately 5.5 mg/kg bw). (He had previously taken larger doses about 1 h after a meal without any resulting illness.) After 85 min, he noted a slight change in vision and after 90 min he began to feel nauseated and lightheaded. Two mg atropine provided relief but the symptoms returned. The atropine dose was increased to 4.8 mg. Despite this, the nausea persisted and profound weakness, profuse sweating and hyperperistalsis developed. The symptoms attained maximum severity about 2 h after their onset, but definite improvement occurred within 3 h of onset and recovery was nearly complete after 4 h.

Two additional studies in humans are briefly summarised in the International Program of Chemical Safety review of carbaryl. Both studies (Hansen, 1978 and Ward *et al.*, 1988) were investigations of carbaryl metabolism and involved administration of oral doses of up to 1 mg/kg bw. No mention was made of any clinical signs or other treatment-related effects in the subjects. Although suitable data on RBC ChE activity in humans could be used for setting an ARfD for carbamates or OPs, the study of Wills *et al*. is considered unreliable, and there are no other data that would establish NOELs or LOELs for ChE inhibition by carbaryl in humans. The ARfD for carbaryl therefore has to be based upon studies in experimental animals.

A series of acute dose rangefinding studies was performed in unfasted rats gavaged with carbaryl at 10 mg/kg bw and above. The 10 mg/kg bw dose did not cause clinical signs but elicited a transient 40% decrease in motor activity (in males) at 1 h post-treatment, together with a 1 °C depression in body temperature (in females). Plasma and RBC ChE activity were depressed by up to approximately 30%. Brain ChE activity was inhibited by 30-50%.

The 1-year dog study evaluated here did not demonstrate a NOEL, due to brain and plasma ChE inhibition at the lowest dietary dose of 3.8 mg/kg bw/d. RBC ChE activity was not affected at that dose, but was inhibited at and above 11 mg/kg bw/d. Despite these findings, clinical signs did not occur even at the highest dose of 34 mg/kg bw/d. The 5-week dog study found no effect on RBC or brain ChE activity at the highest dose of 3.8 mg/kg bw/d, and formed the basis of the ARfD set by JMPR in 2001. In 1996, the JMPR summarised the Hayes and Laws case report in humans in which clinical signs were observed at 2.8 mg/kg bw. However, in the 2001 Report there was no comment about this observation. Given that overt toxicity in humans occurs *below* the NOEL for RBC and brain ChE inhibition in dogs, dogs must be significantly more resistant to the effects of carbaryl than humans. In the

absence of comparative data on the toxicokinetic and toxicodynamic behaviour of carbaryl in dogs and humans, there is no explanation for the inter-species difference in sensitivity. Hence, the OCS concluded the NOEL in the 5-week dog study can not be used as a basis for the ARfD, because it corresponds to an effect level in humans.

The lowest NOEL in repeat-dose studies in animals which is also not associated with clinical signs in humans is 1 mg/kg bw/d, established in rat 13-week subchronic and developmental neurotoxicity studies, based on behavioural indications of autonomic neurotoxicity and brain, plasma and erythrocyte ChE depression (LOEL=10 mg/kg bw/d). Application of a 100-fold safety factor to the 1 mg/kg bw/d NOEL would yield an ARfD of 0.01 mg/kg bw. This is in contrast to the ARfD set by JMPR of 0.2 mg/kg bw.

8.4.3 Intake from Drinking Water

Current registered uses of carbaryl include cotton and rice. Where a pesticide is registered for use in water or water catchment areas, the Joint Committee of the Agricultural and Resource Management Council of Australia and New Zealand and the NHMRC set Guideline and Health Values for the chemical in drinking water. A Guideline Value is generally based on the analytical limit of determination, and is set at a level consistent with good water management practice and that would not result in any significant risk to the consumer over a lifetime of consumption. Exceeding the Guideline Value indicates undesirable contamination of drinking water and should trigger action to identify the source of contamination and prevent further contamination. However, a breach of the Guideline Value does not necessarily indicate a hazard to public health. The current Guideline Value for carbaryl is 0.005 mg/L.

Health Values are intended for use by health authorities in managing the health risks associated with inadvertent exposure such as a spill or mis-use of a pesticide. The values are derived so as to limit intake *from water alone* to about 10% of the ADI, on the assumption that (based on current knowledge) there will be no significant risk to health for an adult weighing 70 kg at a daily water consumption of 2 L over a lifetime. At present, the Health Value for carbaryl is 0.03 mg/L (*Australian Drinking Water Guidelines - Summary*, NHMRC, Canberra, Australia,1996; ISBN 0 642 24462 6 or http://www.nhmrc.gov.au/publications/pdf/eh20.pdf).

Given that the ADI for carbaryl is 0.008 mg/kg bw/d, the Health Value may be calculated as:

$$\frac{0.008 \text{ mg/kg bw/d} \times 70 \text{ kg} \times 0.1}{2 \text{ L/d}}$$

$$= 0.028 \text{ mg/L}$$

Hence, the current Health Value for carbaryl of 0.03 mg/L is supported, and no revision is proposed.

8.4.4 Public exposure

Carbaryl is used for the control of a diverse range of insect pests on animals and edible and ornamental plants, and is also effective against other arthropods including millipedes when applied to and around buildings. Public exposure to carbaryl is therefore expected to occurring from:

- Consumption of residue in commercially treated fruit, vegetables and other commodities;
- Consumption of residue in home grown fruit and vegetables;
- Dermal and inhalational exposure when preparing and/or using HG and HV products;
- Dermal contact with pets, carpets, lawns and exterior surfaces treated with HG/HV products; and
- Dermal contact with surfaces treated by pest control operators.

The pattern of public exposure from domestic use is likely to be discontinuous, given seasonal variation in plant growth, fruit or vegetable production and pest activity, including fleas. However, there is scope for repeated use of carbaryl products in and around the home during the warmer months of the year. Re-treatment intervals vary between products. Pet ectoparasiticidal dusts and shampoos are applied every 1–2 week, while ear drops are administered twice daily for at least 14 d. Vegetables require treatment each 7–10 d and recommended re-treatment intervals for fruit are 2–3 week. Lawn treatments are applied monthly.

8.4.5 Acute Toxicity

The APVMA "Guidelines for pesticides used by householders" (Appendix 3-1 of the "Guidelines for registering agricultural chemicals") stipulate that any domestic pesticide formulation that may be ingested should not be expected to be acutely toxic to a child at doses up to 1500 mg/kg bw, and should not be acutely toxic at dermal doses of up to 1000 mg/kg bw. The irritancy to skin and eye of domestic pesticide formulations should be low.

During preparation of this report, it was noted that several products currently sold in HG pack sizes are unlikely to comply with the above conditions. These products are wettable powders containing 800 g/kg carbaryl, and liquids containing 400 and 500 g/L carbaryl. As none of the available OCS toxicological evaluations contain assessments of acute studies on the actual carbaryl-based products, their toxicity has to be estimated by extrapolation from the characteristics of the active constituent and excipients. Technical grade carbaryl has a worst acute oral LD50 of 246 mg/kg bw in rats, a dermal LD50 >2000 mg/kg bw in rabbits, is slightly irritating to the rabbit eye, but is not a dermal irritant or sensitiser. Whilst there appear to be no problems with excessive irritation or dermal toxicity, the acute oral LD50 of 800 g/kg WPs is estimated at 308 mg/kg bw, and the corresponding values for the 400 and 500 g/L products are predicted to be 616 and 492 mg/kg bw, respectively. Unless the acute oral hazard were influenced by other formulation constituents, only formulations containing 160 g/kg or less of carbaryl would have an oral LD50 of 1500 mg/kg bw or greater, and so comply with the cut-off value specified by the APVMA.

8.4.6 Dietary Exposure Considerations

MRLs have been set for carbaryl in approximately 70 commodities. Although many of these are minor constituents of the diet, major crops include apricot and other stone fruit, banana, cereal grains, citrus, corn, fruiting and leafy vegetables, grapes, potatoes and sugar cane.

The National Residue Survey (NRS) (1995-2000) detected carbaryl residues in a minority of samples tested. Residues were most commonly present in wheat bran (16% of samples), followed by stone fruit (10%), oats (7%), canola and sorghum (both 6%). Carbaryl was absent from all samples of nuts, tomatoes, wheat flour and pears. However, carbaryl has not been included in any of the Food Standards Australia and New Zealand (FSANZ) (formerly ANZFA) Market Basket Surveys (now termed Total Diet Surveys) of the last decade and so

there is no information on actual human dietary intake from commercially grown produce. Carbaryl based products are also registered for use on most of the fruit and vegetable species that are commonly grown in domestic premises, but the OCS lacks information on the likely dietary intake of carbaryl from home grown produce.

The interval between treatment and harvest of most commercially grown fruits and vegetables was usually 2 – 4 days, similar to the 3-day interval recommended on most HG product labels. This suggests that following spray application, carbaryl residue levels on home-grown commodities would be no less concentrated than those on commercially grown produce. Concentrations of carbaryl applied in the home garden may be higher when compared with professional users, as there is a higher probability that domestic users may deliberately or mistakenly apply excessive amounts of carbaryl, or may ignore the recommended 3-day withholding period for treated commodities. Secondly, home-grown fruits and vegetables do not have to pass through the commercial "chain of supply" to reach the consumer, thereby reducing the time interval over which carbaryl could degrade between treatment and consumption of commodities. Thirdly, there will be marked seasonal peaks in the consumption of treated garden produce, which will substitute for alternative commodities from commercial sources.

Hence, given that the high (97.5^{th} percentile) consumer exposure model would apply in the home garden setting and that carbaryl residues in home-grown produce would probably equal or exceed the levels measured under supervised trial conditions, the NESTI values are highly relevant to consumers of home-grown commodities treated with carbaryl. It is considered that there is equal or greater potential for dietary intake of carbaryl residues in home-grown commodities to exceed the ARfD, as compared with residues in commercially grown produce.

Although HG use of carbaryl on raspberries, turnip, sugarbeet, beetroot, potato, macadamias and pecans may be supportable from a toxicological standpoint, restriction of HG food uses to these particular commodities may prove ineffective because of non-compliance. It is highly probable that some users would continue to apply carbaryl to the commodities that have been shown to retain sufficient carbaryl residues to cause dietary intake exceeding the ARfD and ADI by a wide margin. Consequently, it is recommended that the HG use of carbaryl on food plants should be discontinued, as there are insufficient grounds to provide assurance that such use will not be likely to have an effect that is harmful to human beings.

8.4.7 Exposure from use of home garden and home veterinary products

OCS has estimated the systemic doses that would be absorbed by carbaryl product users under typical Australian domestic conditions. Systemic doses were usually estimated by extrapolation from the mean dermal and inhalation exposure measured in American volunteers, adjusting for dermal absorption of carbaryl. Recognising that some American product users were much more heavily exposed than average, another set of systemic dose estimates was prepared by extrapolation from the upper limit of exposure. Variation in the user's clothing was taken into account, with dose estimates being prepared for persons wearing long pants and sleeves, or short pants and sleeves. Scenarios involving either 30 min or 2 h exposure were also considered. Thus, for most of the products examined, there were 8 exposure scenarios, yielding dose estimates that ranged from a mean exposure for 30 minutes wearing long pants and sleeves, up to a worst case exposure for 2 h wearing short pants and sleeves.

Some Australian HG/HV products were found to be potentially capable of delivering systemic doses to users in excess of the ADI for carbaryl, the recommended ARfD, or both, under what are considered to be feasible exposure scenarios. However, 10 g/L pet shampoos, 20 g/kg garden/vegetable dusts, wettable powders and 1 g/L ready-to-use liquid sprays were not likely to deliver a toxicologically significant dose of carbaryl. A condensed summary of the user systemic dose estimates is presented below. For clarity, Table 19 shows only the combinations of products and exposure scenarios likely to deliver doses above the ADI and/or ARfD. Dose estimates exceeding the ARfD or ADI are highlighted.

Table 19: Exposure scenarios leading to estimated systemic carbaryl doses exceeding the ADI and/or ARfD

Exposure scenario	Duration of dermal exposure (h)	% of ARfD (10 mg/kg/d)	% of NOEL for ChE inhibition (1000 mg/kg/d)	% of ADI (8 mg/kg/d)	% of LOEL for tumours (16000 mg/kg/d)
50 g/kg pet dusts – treatment of 1 medium sized dog					
Top of range exposure, long pants & sleeves	0.5	90	0.9	117	0.058
	2.0	210	2.1	265	0.13
Top of range exposure, short pants & sleeves	0.5	200	2	253	0.13
	2.0	650	6.5	812	0.41
50 g/kg pet dusts – treatment of aviary					
Typical exposure, long pants & sleeves	2.0	82	0.82	103	0.051
Top of range exposure, long pants & sleeves	0.5	190	1.9	233	0.12
	2.0	420	4.2	525	0.26
Typical exposure, short pants & sleeves	2.0	150	1.5	188	0.094
Top of range exposure, short pants & sleeves	0.5	400	4	500	0.25
	2.0	1300	13	1625	0.81
10 g/L ear drops – accidental spill during treatment					
Typical exposure, confined to hand	2.0	125	1.25	157	0.078
50 g/kg dusts – treatment of garden and vegetables					
Top of range exposure, long pants & sleeves	2.0	93	0.93	117	0.059
Top of range exposure, short pants & sleeves	2.0	113	1.13	142	0.071
60 g/L hose on insecticide – treatment of turf					
Top of range exposure, long pants & sleeves	2.0	150	1.5	188	0.094
Top of range exposure, short pants & sleeves	0.5	120	1.2	150	0.075
	2.0	500	5	619	0.31

Before examining each group of products, it is necessary to consider the toxicological implications of the dose estimates tabulated above. The maximum dose estimate for use of one of the products (treatment of aviary with 50 g/kg bird dust) is equivalent to 13 times higher than the recommended ARfD (based on a 100-fold safety factor applied to the NOEL for ChE inhibition) and 16 times higher than the ADI (based on a 2000-fold safety factor applied to the LOEL for cancer). From a public health standpoint, this represents an unacceptable erosion of the safety margin for both endpoints, even though the use pattern for Australian carbaryl products suggests that daily exposure to such a high dose is improbable, and the APVMA Adverse Experience Reporting Program has not received any reports of toxicity in persons using carbaryl-based veterinary products.

The question arises as to whether the ARfD or the ADI is the more suitable upper dose limit for persons using HG or HV products. The ARfD for carbaryl provides a 100-fold margin of safety (MoS) for ChE inhibition and behavioural indications of neurotoxicity. However, the ARfD does not take vascular carcinogenesis into account. Because a NOEL for vascular carcinogenesis has **not** been demonstrated, it is impossible to quantify or assure the adequacy of any MoS between the ARfD and vascular cancer. Nor is it possible to dismiss the relevance of vascular cancer to humans in an acute or short term exposure scenario, especially without a defined mode of action for vascular carcinogenesis. The ADI has been set with an enhanced 2000-fold safety factor on the LOEL, in order to optimise protection against vascular cancer, and it is certain to protect against ChE inhibition (since the ADI is 80% the ARfD).

The OCS has therefore formulated its recommendations with a view to constraining the upper limit of carbaryl intake to the ADI, if this can be reasonably achieved by use of label hazard warning statements and directions to wear protective clothing and equipment. Home garden/veterinary products that have the potential to cause carbaryl intake above the ADI under anticipated conditions of use and are not amenable to risk reduction by means of protective hygiene/clothing/equipment, are considered unsuitable for continued registration. Also regarded as unsuitable, are products for which there are insufficient data to estimate the extent of householder exposure.

The most hazardous products are veterinary dusts. From the above Table 19, it is apparent that applying a 5% pet dust to one dog could deliver systemic doses up to 8-fold higher than the ADI and 6.5-fold greater than the recommended ARfD. Aviary treatment could deliver double these doses. The high level of exposure from pet dusts can be attributed to discharge of the powder into the user's breathing zone air, together with the need to touch the pet while working the powder into its feathers or fur. It is very difficult to protect product users from this combination of dermal and inhalation exposure, other than by requiring them to wear a disposable dust mask, and cover their skin with gloves and long clothing. However, this approach to risk management is unlikely to meet with success if adopted for pet grooming products, as user perception would be negative and compliance improbable. Given that carbaryl shampoos are available and have a lower potential for user exposure than dusts, the most effective course of action would be to withdraw carbaryl based pet dusts and powders from the HV market.

By comparison with pet dusts, the likely extent of user exposure from flea collars and insecticidal shampoos is an order of magnitude lower. Systemic uptake from shampooing one or two dogs is expected to lie below the ADI. Although persons treating 3 or more animals could receive systemic doses exceeding the ADI or ARfD, exposure could easily be reduced to negligible levels if users wore rubber gloves. Since pet owners are not likely to

suffer inconvenience from gloves while washing their animal(s), an appropriate new entry for carbaryl shampoos should be placed in the FAISD Handbook. Systemic exposure from flea collars is probably intermediate between exposure from dusts and shampoos. However, estimates of user exposure are hampered by a lack of data on free carbaryl levels on the surface of flea collars. OCS estimates that unwrapping and fitting a new flea collar could lead to absorption of a systemic dose equivalent to 85% of the ADI, but the delivered dose could exceed the ADI or ARfD if carbaryl accumulates on the collar's surface between manufacture and use. Gloves would provide an ideal level of protection but would impede the user unacceptably. However, exposure can be minimised by directing users to wash their hands. In any case, occasional excursions above the ADI are not necessarily of toxicological concern, and user exposure will be infrequent given that the reference product has a 4-month life. As shown in Section 10 of this report, carbaryl intake from handling a pet treated with a carbaryl shampoo or collar is unlikely to attain the ARfD or ADI.

Although capable of delivering systemic doses up to 6 times higher than the ADI and 5-fold above the recommended ARfD, carbaryl home garden vegetable dusts, wettable powders and liquids would be likely to cause much less user exposure than pet dusts. This is primarily because garden use often entails discharge at or below waist height, and manual contact with treated vegetation is not required. Based on Merricks' (1997b, 1998) evidence, inhalation exposure is negligible, even when spraying trees, and a combination of long pants, long sleeves and gloves is sufficient to limit exposure to levels well below the ADI when dusting or spraying in the home garden. Therefore, subject to the outcome of the forthcoming APVMA review of carbaryl residues in food, the current Safety Directions for carbaryl should be revised to include the appropriate statements if they are not already recommended.

8.4.8 Post-application exposure

The use of some carbaryl based home garden and professional products inside domestic homes, on lawns and as a chemical barrier on paths and walls, brings with it the question of occupants' exposure from treated surfaces. In the absence of relevant experimental data, OCS has relied upon US EPA default factors for estimating the transfer of carbaryl from turf and hard surfaces, in conjunction with the application rate per unit area calculated from the product label instructions.

Sitting or lying on treated grass or walking barefoot on treated paving, could deliver systemic doses above the ADI and ARfD if the carbaryl was not washed off the contaminated skin within an hour. Here, OCS recommends that the appropriate risk reduction strategy is to direct householders to keep off treated surfaces.

The indoor use of carbaryl is more problematic. The only indoor application of carbaryl is as an insecticide/deodorant dust for carpets, rugs and animal bedding. Label instructions specify that the dust should be sprinkled lightly and then removed by vacuuming after 1 h. It is impossible to estimate the likely extent of householder exposure because neither the application rate nor the efficiency of vacuuming are available. OCS also has no data on the persistence of carbaryl indoors. Noting that household residents (especially infants) are more likely to make contact with a treated floor than grass or pathways, and that ChE depression has been recorded in persons whose residences have been treated indoors with carbaryl (WHO, 1994), OCS believes that label warnings are insufficient to ensure safety. Consequently, it is recommending that carbaryl should not be registered for indoor use.

8.5 References

Bigot D (1999) Validation on transgenic mice – p53 knockout mice – to predict rodent carcinogenicity Study No SA 97040 Lab: Rhone-Poulenc Agro, Centre de Recherche, rue Dostoievski, Sophia Antipolis, France Sponsor: Rhone-Poulenc Agro, rue Pierre Baizet, Lyon, France Study duration: March 13, 1997 to January 6, 1999 Report date: July 21, 1999

Carmichael NG, Debruyne ELM & Bigot-Lasserre D (1999) The p53 heterozygous knockout mouse as a model for chemical carcinogenesis in vascular tissue Lab: Rhone-Poulenc Agro, Centre de Recherche, rue Dostoievski, Sophia Antipolis, France Submitted for publication [RP, sub 11859, Vol 2]

Cheng T: Dermal absorption of ^{14}C-carbaryl (80S) in male rats (preliminary and definitive phases) Study no: HWI 6224-207 Lab: Hazleton Wisconsin Inc, Madison, WISC USA Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: November 17, 1993 to January 27, 1994 Report date: July 27, 1994 [RP, sub 11697, vol 7]

Cheng T: Dermal absorption of ^{14}C-carbaryl (XLR Plus) in male rats (preliminary and definitive phases) Study no: HWI 6224-206 Lab: Hazleton Wisconsin Inc, Madison, WISC USA Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: March 22 to August 2, 1994 Report date: January 18, 1995 [RP, sub 11697, vol 7]

Chuzel F (1999) Carbaryl 6-month carcinogenicity study in p53 knockout mice by dietary administration Study No. SA 98155 Lab: Rhone-Poulenc Agro, Centre de Recherche, rue Dostoievski, Sophia Antipolis, France Sponsor: Rhone-Poulenc Agro, rue Pierre Baizet, Lyon, France Study duration: July 20, 1998 to May 6, 1999 Report date: July 08, 1999 Unpublished [RP, sub 11859, Vol 1]

Cohen SM (1995) Evaluation of the urinary bladder carcinogenicity of carbaryl in rats Unnumbered discussion paper Report date: November 2, 1995 Unpublished [RP, sub 11859, Vol 2]

Debruyne E (1998) Carbaryl 52-week toxicity study in the CD1 mouse Target organs cell cycling assessment Study No. SA 97529 Lab: Rhone-Poulenc Agro, Centre de Recherche, rue Dostoievski, Sophia Antipolis, France Sponsor: Rhone-Poulenc Agro, rue Pierre Baizet, Lyon, France Study duration: December 12 – 23, 1997 Report date: December 02, 1998 (amended report) Unpublished [RP, sub 11859, Vol 2]

Donehower, LA (1996) The p53-deficient mouse: a model for basic and applied cancer studies. Seminars in Cancer Biology 7, 269 – 278 [RP, sub 11859, Vol 2]

Hamada NN (1987) One-year oral toxicity study in beagle dogs with carbaryl technical Study No. 400-715 Lab: Hazleton Laboratories America, Vienna, VA, USA Sponsor: Union Carbide Corp, Research Triangle Park, NC USA Study duration: July 16, 1985 – July 18, 1986 Report date: March 18, 1987 Unpublished [AV, sub 12099, Vol 3, APVMA study no. 5622]

Hamada NN (1991) Subchronic toxicity study in dogs with carbaryl technical Study No. 656-152 Lab: Hazleton Laboratories America, Vienna, VA, USA Sponsor: Rhone-Poulenc Ag Co, Research Triangle Park, NC USA Study duration: November 21 – December 29, 1989 Report date: March 28, 1991 Unpublished [AV, sub 12099, Vol 1, APVMA study no. 5624]

Hamada NN (1993a) Combined chronic toxicity and oncogenicity study with carbaryl technical in Sprague-Dawley rats Study No. 656-139 Lab: Hazleton Washington Inc, USA Report date: August 06, 1993 Unpublished [RP, sub 10824]
Hamada NN (1993b) Combined chronic toxicity and oncogenicity study with carbaryl technical in CD-1 mice Study No. 656-138 Lab: Hazleton Washington Inc, USA Report date: May 20, 1993 Unpublished [RP, sub 10824]

Hardisty JF (1996) Pathology working group review report for the oncogenicity study with carbaryl technical in Sprague-Dawley rats Project No. 259-012 Lab: Experimental Pathology Laboratories Inc, Research Triangle Park, NC USA Report date: December 16, 1996 Unpublished [RP, sub 11584, Vol 6]

Irisarri E (1996) Carbaryl 52-week toxicity study in the rat and mouse Target organs cell cycling assessment Pathology report (post-mortem) Study No. SA 95493 Lab: Rhone-Poulenc Agro, Centre de Recherche, rue

Dostoievski, Sophia Antipolis, France Sponsor: Rhone-Poulenc Agro, rue Pierre Baizet, Lyon, France Study duration: November 21 - December 08, 1995 Report date: March 18, 1996 Unpublished [RP, sub 11859, Vol 4]

Merricks DL (1997a) Carbaryl applicator exposure study during application of Sevin 5 Dust to dogs by the non-professional Study Nos: 1517 (Lab) and 10565 (Sponsor) Labs: Agrisearch Inc, Frederick, MD USA; Rhone-Poulenc Ag Company, Research Triangle Park, NC USA; and Morse Laboratories Inc, Sacramento, CA USA Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: February 17 to August 22, 1997 Report date: August 22, 1997 Unpublished [RP, sub 11875, Vol 2]

Merricks DL (1997b) Carbaryl mixer/loader/applicator exposure study during application of RP-2 Liquid (21%), Sevin Ready To Use Insect Spray or Sevin 10 Dust to home garden vegetables Study Nos: 1519 (Lab) and 10564 (Sponsor) Labs: Agrisearch Inc, Frederick, MD USA; Rhone-Poulenc Ag Company, Research Triangle Park, NC USA; and Morse Laboratories Inc, Sacramento, CA USA Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: May 12 to December 15, 1997 Report date: December 15, 1997 Unpublished [RP, sub 11875, Vol 3]

Merricks DL (1998) Carbaryl mixer/loader/applicator exposure study during application of RP-2 Liquid (21%) to fruit trees and ornamental plants Study Nos: 1518 (Lab) and 10564 (Sponsor) Labs: Agrisearch Inc, Frederick, MD USA; Rhone-Poulenc Ag Company, Research Triangle Park, NC USA; and Morse Laboratories Inc, Sacramento, CA USA Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: April 7, 1997 to January 23, 1998 Report date: January 23, 1998 Unpublished [RP, sub 11875, Vol 1]

Repetto-Larsay M (1998) Carbaryl Developmental toxicology study in the rat by gavage Study No: SA 98070 Lab: Rhone-Poulenc Agro, Centre de Recherche, rue Dostoievski, Sophia Antipolis, France Sponsor: Rhone-Poulenc Agro, rue Pierre Baizet, Lyon, France Study duration: February 28 – July 24, 1998 Report date: October 21, 1998 Unpublished [RP, sub 11859, Vol 8]

Robinson K & Broxup B (2001a) A developmental neurotoxicity study of orally administered carbaryl, technical grade, in the rat. Final report amendment number 1. Study No: 97391 Lab: ClinTrials BioResearch Ltd, Senneville, Quebec, Canada. Sponsor: Aventis CropScience, Mississauga, Ontario, Canada Study duration: Not stated Report date: July 6, 2001 Unpublished [AV, sub 12099, Vol 1, APVMA Study No: 5620]

Robinson K & Broxup B (2001b) A developmental neurotoxicity study of orally administered carbaryl, technical grade, in the rat. Final report amendment number 2. Study No: 97391 Lab: ClinTrials BioResearch Ltd, Senneville, Quebec, Canada. Sponsor: Aventis CropScience, Mississauga, Ontario, Canada Study duration: Not stated Report date: July 10, 2001 Unpublished [AV, sub 12099, Vol 1, APVMA Study No: 5621]

Totis M (1996) Carbaryl Investigation of the metabolism of [^{14}C]-carbaryl in the 15 month old rat following chronic dietary administration Study No: SA 95288 Lab: Rhone-Poulenc Agro, Centre de Recherche, rue Dostoievski, Sophia Antipolis, France Sponsor: Rhone-Poulenc Agro, rue Pierre Baizet, Lyon, France Study duration: January 24 – December 13, 1996 Report date: December 19, 1996 Unpublished [RP, sub 11697, Vol 7]

Tyl RW (1999) Dose range-finding study for the developmental toxicity evaluation of carbaryl administered by gavage to New Zealand White rabbits Study No: Rb98-CAR 1 Lab: Reproductive & Developmental Toxicology Laboratory, Center for Life Sciences and Toxicology, Research Triangle Institute, Research Triangle Park, NC USA Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: September 15 – October 14, 1998 Report date: March 6, 1999 Unpublished [RP, sub 11859, Vol 9]

Tyl RW, Marr MC & Myers CB (1999) Developmental toxicity evaluation (with cholinesterase assessment) of carbaryl administered by gavage to New Zealand White rabbits Study No: 65C-7297-200/100 Lab: Reproductive & Developmental Toxicology Laboratory, Center for Life Sciences and Toxicology, Research Triangle Institute, Research Triangle Park, NC USA Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: November 17, 1998 – March 4, 1999 Report date: June 3, 1999 Unpublished [RP, sub 11859, Vol 9]

Tyl RW, Myers CB & Marr MC (2001) Two-generation reproductive toxicity evaluation of carbaryl (RPA007744) administered in the feed to CD (Sprague-Dawley) rats Study No. 65C-07407-400 Lab: Reproductive & Developmental Toxicology Laboratory, Center for Life Sciences and Toxicology, Research Triangle Institute, Research Triangle Park, NC, USA Sponsor: Aventis CropScience, Research Triangle Park, NC, USA Study duration: September 27, 1999 – November 14, 2000 Report date: May 24, 2001 Unpublished [AV, sub 12099, Vol 1 & 2, APVMA Study No. 5625]

Valles B (1999) Carbaryl: Investigation of the metabolism of [^{14}C]-carbaryl following 14 d administration to the male CD1 mouse Study No. SA 97481 Lab: Rhone-Poulenc Agro, Centre de Recherche, rue Dostoievski, Sophia Antipolis, France Sponsor: Rhone-Poulenc Ag Company, Research Triangle Park, NC USA Study duration: July 3 to November 20, 1998 Report date: June 16, 1999 Unpublished [RP, sub 11859, Vol 12]

Venkatachalam S, Tyner SD, Pickering CR, Boley S, Recio L, French JE & Donehower L (2001) Is p53 haploinsufficient for tumor suppression? Implications for the p53$^{+/-}$ mouse model in carcinogenicity testing Toxicol Pathol 29 (suppl.), 147 - 154

9. RESIDUES ASSESSMENT

9.1 Introduction

The review of carbaryl was initiated in 1995, as it was considered that the APVMA at that time did not hold sufficient residue data to support the use of carbaryl in cereals, either by field application or for use on stored grain. The scope of the review for carbaryl initially included the reconsideration of residue data and MRLs related to cereal grains and animals that may be fed on treated cereal products. The scope of the review was later extended to include home garden and home veterinary products (NRA Gazette No. 7, 6 July 1999).

In 2001 the JMPR set an ARfD for carbaryl, and the Office of Chemical Safety (OCS) recommended an ARfD in December 2002. As a consequence of the establishment of an ARfD by the OCS, the scope of the carbaryl special review was again broadened, so that the APVMA could assess the acute dietary risk of carbaryl (APVMA Gazette No. 6, 3 June 2003).

9.2 Discussion

Residue trial data was submitted by Rhône-Poulenc Rural Australia Pty Limited (now Bayer CropScience Pty Ltd) in support of the use of carbaryl in cereal grains, with additional data presented on residues in animal feed commodities and crops for human consumption. The APVMA or the Pesticides and Agricultural Chemicals Committee (PACC) had not previously evaluated most of the data presented.

Previous evaluations of the plant and animal metabolism data for carbaryl have resulted in the establishment of parent compound as the residue definition, both in Australia and internationally *via* Codex Alimentarius Commission (CODEX). The plant and animal metabolism of carbaryl, and analytical methodology, were most recently evaluated by the JMPR in 2002.

9.3 Maximum Residue Limits (MRLs)

Current Australian MRLs for carbaryl are tabulated in Table 1. Most of the Australian MRLs for carbaryl were adopted from CODEX by the Pesticide and Agricultural Chemicals Standing Committee (PACC).

Table 1 *MRL Standard* entries

Code		Food	MRL (mg/kg)
FS	0240	Apricot	10
VS	0621	Asparagus	10
FI	0326	Avocado	10
FI	0327	Banana [in the pulp]	5
FB	0264	Blackberries	10
FB	0020	Blueberries	7
FT	0289	Carambola	5
GC	0080	Cereal grains	T5
FS	0013	Cherries	5
FC	0001	Citrus fruits	7
SO	0691	Cotton seed	1

FI	0332	Custard apple	5
FB	0266	Dewberries (including Boysenberry and Loganberry)	10
MO	0105	Edible offal (mammalian)	T0.2
PE	0112	Eggs	T0.2
FI	0371	Elephant apple	5
FI	0335	Feijoa	5
VC	0045	Fruiting vegetables, Cucurbits	3
FI	0351	Granadilla	5
FB	0269	Grapes	5
FT	0298	Grumichama [Brazilian cherry]	5
FT	0336	Guava	5
FT	0300	Jaboticaba	5
FI	0338	Jackfruit	5
		Jambu	5
FI	0341	Kiwifruit	10
VL	0053	Leafy vegetables	10
FI	0343	Litchi	5
FI	0342	Longan	5
FI	0345	Mango	5
MM	0095	Meat [mammalian]	T0.2
ML	0106	Milks	T*0.05
FS	0245	Nectarine	10
VO	0442	Okra	10
FT	0305	Olives	10
DM	0305	Olives, processed	1
FI	0350	Papaya [pawpaw]	5
FI	0351	Passion fruit	5
FS	0247	Peach	10
FS	0014	Plums (including Prunes)	5
FP	0009	Pome fruits	5
VR	0589	Potato	0.2
PO	0111	Poultry, Edible offal of	T5
PM	0110	Poultry meat	T0.5
FI	0358	Rambutan	5
FB	0272	Raspberries	10
FI	0359	Sapodilla	5
FI	0360	Sapote, Black	5
FI	0361	Sapote, Green	5
FI	0362	Sapote, Mammey	5
FI	0363	Sapote, White [casimiroa]	5
FB	0275	Strawberry	7
GS	0659	Sugar cane	T*0.05
SO	0702	Sunflower seed	1
VO	0447	Sweet corn (corn-on-the-cob)	1
TN	0085	Tree nuts	1
TN	0085	Tree nuts [whole in shell]	10
		Vegetables [except asparagus; fruiting vegetables, cucurbits; leafy vegetables; okra; potato; sweet corn (corn-on-the-cob)]	5
CM	0654	Wheat bran, unprocessed	T20

Table 4 *MRL Standard* entries

Code		Animal feed commodity	MRL (mg/kg)
AF	0080	Forage of cereal grains	T100
AS	0081	Straw and fodder (dry) of cereal grains	T100

There are no current Table 5 *MRL Standard* entries for carbaryl.

9.4 Residues in cereal grain

Carbaryl is used both pre- and post-harvest on cereal grains. Residue trial data where the combined effect of pre- and post-harvest use was studied were not available, rather studies were provided for pre-harvest use only or post-harvest use only. Residues of carbaryl decline slowly with time and any Maximum Residue Limit (MRL) for the combined pre- and post-harvest use can be derived from summing residues from pre- and post-harvest application.

9.4.1 Residues of carbaryl in stored cereal grain (post-harvest)

Registered products containing carbaryl may be used on stored cereal grains, except barley. The approved rate is 5 g ai/tonne (5 mg/kg) for <3 months storage and 8 g ai/tonne (8 mg/kg) for storage periods of 3-9 months. For the latter application, treated cereal grain should be held in store and not used for processing for human consumption or for stock food within 90 days of treatment. Residues of carbaryl in stored cereal grains have been reviewed by JMPR (1976, 1977) and by Snelson (1987).

Studies measuring the activity of carbaryl on wheat by bioassay using *Rhyzopertha dominica* have been used to calculate approximate biological half-lives. For wheat treated at 5 mg/kg the half-lives were reported to be 40 weeks at 35°C, 60 weeks at 30°C, 80 weeks at 25°C and >>80 weeks at 20°C. The degradation of carbaryl stored in sealed bins at *ca.* 25°C was determined over a 39 week period (Table 19).

Table 19**:** Residues of carbaryl (mg/kg) in wheat following storage at 25°C.

Treatment	**Rate (mg carbaryl/kg)**	**Residue (mg/kg)**				
		Day 1	**Week 9**	**Week 18**	**Week 26**	**Week 39**
Carbaryl	5	3.1	2.8	-	-	1.9
Carbaryl	10	6.5	9.8	5.0	4.3	4.2
Carbaryl + pirimiphos methyl	5	3.4	3.1	-	-	2.5
Carbaryl + pirimiphos methyl	10	5.7	5.4	5.0	4.5	4.6

Degradation was reported to be more rapid in field trials in bulk wheat (12.5% moisture) held in silos. Over a 26 week period residues fell from 4.8 to 2.4 mg/kg for grain stored at 22-30°C and from 9.0 to 5.8 mg/kg for grain stored at 13-27°C. Similar results were reported for oats, malting barley, paddy rice, brown rice and white rice (Table 20).

Table 20**:** Residues of carbaryl (mg/kg) in grain following silo storage for up to 6 months.

Grain	Moisture content (%)	Application rate (mg/kg)	Residue (mg/kg)	
			3 months storage	6 months storage
Barley	13	10.6	6.5	3.5
	-	10	6.5	3.5
Oats	12	10	7.5	3.5
Rice (in husk)	13	10	7.5	3.5
	-	10	6.5	3.3
Rice (husked)	12.5	10	7.5	3.4
	-	10	6.5	3.5
Rice (polished)	12.7	10	7.5	3.5
	-	10	7.0	4.5
Wheat	12	10	7.2	6.3

Commercial scale trials have been conducted on 18 silos each holding *ca.* 2000 tons of wheat. The grain was treated with a combination of carbaryl at 6 mg/kg and pirimiphos-methyl at 4 mg/kg. The moisture content of the grain ranged from 9-11% while the average grain temperature ranged from 22-30°C over the storage period (Table 21).

Table 21**:** Ranges of carbaryl residues (mg/kg) in silo stored wheat treated at 6 mg/kg.

Bin	Residue (mg/kg)								
	Dec	Jan	Feb	Mar	Apr	May	June	Aug	Sept
1	3-5	5-6	4-6	4-6	2-4	2-4	2-4	2-4	2-4
2	1-2			1-2					
3	2-4								
4	3-5	5-6	2-4	2-4		1.5-3	1-2		
5		8-10		6-8			6-8		
6	3-5	3-5	3-5		2-4	1-2		1.5-3	
7	3-5	3-5	3-5		2-4	1-2	1-2	1.5-3	
8		2-4	3-5		2-4	2-4	2-3	2-4	
9			6-8	4-6		4-6	4-6	4-6	4-6
10			5-7	5-7		4-6	3-5	4-6	3-5
11			4-6	4-6		4-6	3-5	2-4	2-4
12				4-6		2-4	2-4	1.5-3	1.5-3
13				5-7		3-5		4-6	
14				5-7		4-6	3-5	2-4	2-4
15						4-6	2-4	1.5-3	
16						4-6	2-4	2-4	2-4
17						4-6	4-6	2-4	2-4
18					1-2, 2-4, 4-6, 5-7, 5-7		4-6		
Average	3.4	5.2	4.8	5.0	3.0	3.8	3.6	3.3	3.5

Residues in sorghum grain (12.4% moisture) treated at 8.7 mg/kg and stored in bulk silos at *ca.* 26°C were 6-8 mg/kg at week 1 declining to 2-4 mg/kg at 12 weeks and 0.6-0.8 mg/kg at 24 weeks storage. For sorghum grain (12.2% moisture) treated at 7.8 mg/kg and stored at 27°C the residues were 2-4 mg/kg at week 1 and declined to 1.5-3 mg/kg at 12 weeks and 0.4-0.6 mg/kg at 24 weeks storage.

The above results indicate that the decline of carbaryl residues in stored grain is variable. During the 3-month storage interval for the higher application rate the decline in residues ranged from nil to 65%. Another factor leading to variability is the method of sampling. Any MRL to cover residues in stored grain only should therefore be set at the maximum application rate of 8 mg/kg.

Any MRL for cereal grain must be able to cover the combined pre- and post-harvest use of carbaryl allowed on the currently approved Australian labels, i.e. the residues arising from post-harvest use should be added to those resulting from pre-harvest use.

9.4.2 Residues of carbaryl in cereal grain from in-field use (pre-harvest)

A large number of residue trials were submitted in support of a group MRL for cereal grains. Of the submitted trials barley (38), corn (3), oats (7), rice (17), rye (5), sorghum (9) and wheat (43) approximated the Australian use-pattern (1.1 kg ai/ha, harvest WHP 0-3 days). In the trials, a variety of formulations and application methods were used (ground rig and aerial application). As there was no significant difference in residues arising from different formulations or application methods, the data from the various trials were pooled and are summarised in Table 22.

Table 22**:** Summary of residues in cereal grains following foliar application of carbaryl.

Crop	Rate (kg ai/ha)	Number sprays	Interval (days)	PHI (days)	Residue (mg/kg)	
					Mean	Range
Barley	1.12 (1×)	1	-	0-1	-	6.96
	1.68 (1.5×)	1	-	14 21		0.99, 1.25 0.13, 0.38
	1.68 (1.5×)	2	7-32	7 14 21	10.9 (n=12) 6.12 (n=13) 3.46 (n=20)	1.61-26.7 0.55-17.9 0.1-20.2
	1.68 (1.5×)	4	10-14	14 21	3.02 (n=5) 1.13 (n=5)	0.15-10.6 0.1-3.94
	2-2.63 (1.8-2.4×)	2-4	7-10	7 14	 8.04 (n=4)	1.0 0.99-19.0
Corn	1.68-2.24 (1.5-2×)	2-3	11	21	-	0.07, 0.08
Oats	1.12-1.4 (1-1.25×)	1	-	0 3		0.44-49.5 4.8
	1.79 (1.6×)	1	-	21		0.32
	2.24-2.63 (2-2.4×)	1-3	10-19	0 3 7 14	 0.24 (n=4)	3.46 1.77 0.59, 0.68 <LOQ-0.44
Rice	0.56 (0.5×)	1	-	0 14		4.06 0.65
	1.12 (1×)	1	-	0 7 14		6.0, 8.65 3 1.4, 1.61
	1.68 (1.5×)	1	-	0 21		14.2 3.6
	2.24 (2×)	1-2	7	0 3 14 21	 6.49 (n=10)*	12.6, 0.46 1.4, 8.5 0.55-11.8 2.1
Rye	1.68 (1.5×)	2	14	7 14 21	6.01 (n=5) 1.40 (n=3) 1.23 (n=3)	0.90-12.96 0.42-2.74 0.40-2.07
Sorghum	2.24 (2×)	3	5-8	14	4.00 (n=9)	<0.02-9.91
Wheat	1.12 (1×)	1-5	7	0 7 14 21	 0.29 (n=4)	0.98 0.1 0.1 0.17-0.53

	1.68 (1.5×)	1-2	7-21	7 14 21	0.45 (n=11) 0.54 (n=13) 0.18 (n=17)	0.06-0.84 <0.02-3.39 <0.02-1.59
	2-2.63 (1.8-2.4×)	1-5	7-29	0 7 14 21	 0.85 (n=6)	1.7 0.06, 0.60 0.12-1.65 0.03

*a maximum residue value of 52.8 mg/kg was considered an outlier. Inclusion of this value would result in a mean carbaryl residue of 10.7 mg/kg

The current harvest WHP for cereal grains is 0-3 days. For each of the cereal crops listed the number of trials where sampling occurred at 0-3 days is insufficient to support the current cereal grain MRL and harvest WHPs, hence the cereal grain WHP requires reassessment. As fourteen days after the last spray is the first time point for which an adequate number of samples were collected for the major cereal grains, the harvest WHP should be extended to 14 days.

At 14±1 days after the last of 2-4 sprays at 1.5× the Australian label rate, carbaryl residues in barley grain ranged from 0.15 to 17.9 mg/kg. Residues of carbaryl in rice treated with 1-2 sprays at 0.5-2× the Australian rate were 0.55-11.8 mg/kg at 14 days after the last spray. In rye treated at 1.5× the Australian rate residues in grain were 0.42-2.74 mg/kg at 14 days after the last of 2 sprays. At 2× the Australian rate for sorghum, residues in grain were <0.02-9.91 mg/kg. Residues detected in wheat at 14 days after the last of 1-5 sprays at 1-2.4× the label rate were <0.02-3.39 mg/kg. Lower residues were obtained for maize and oats treated at 1-2.4× the label rate, being <0.02-0.44 mg/kg at 14 days after the last spray.

If pre-harvest application was the only approved use, the data would support an MRL of 15 mg/kg for cereal grains based on a maximum residue in barley grain of 17.9 mg/kg in a trial conducted at 1.5× the label rate. For the combined pre- and post-harvest use of carbaryl, the residues should be added. As the post-harvest use of carbaryl is not permitted on barley, the grain with the next highest pre-harvest residue was rice at 11.8 mg/kg for grain treated at 2× the label rate and harvested at 14 days after the last spray. The maximum residue in rice (worst case cereal grain) would be 11.8 ÷ 2 + 8 mg/kg = 13.9 mg/kg. The MRL for cereal grains should be raised from 5 mg/kg to 15 mg/kg and the WHP for pre-harvest use extended to 14 days.

9.4.3 Residues in processed grain commodities

In cases where residues in processed commodities are higher than in the raw agricultural commodity it is necessary to set MRLs for the processed commodity. An example relevant to cereal grains is bran. Several processing studies were available for cereal grains enabling processing factors to be determined. A processing factor is the ratio of residue in the processed commodity to residue in the grain or raw agricultural commodity (RAC). Processing factors greater than 1 indicate residues concentrate in that fraction. Table 23, shows the relevant processed commodities for cereal grain and Table 24 shows their processing factors.

Residues of carbaryl are mostly confined to the surface of grain. The processed commodities for which residues were found to concentrate to a significant extent were corn flour, corn meal and wheat bran with processing factors of 1.7, 1.3 and 2.4, respectively.

The maximum residue observed in wheat from pre-harvest treatment at a rate scaled to the Australian label rate was 2.26 mg/kg (3.39 mg/kg ÷ 1.5 = 2.26 mg/kg). The maximum

residue from post-harvest use is estimated to be 8 mg/kg. Combining the maximum pre- and post-harvest residues expected for wheat gives a maximum residue of 10.3 mg/kg. Applying an average processing factor of 2.4 for wheat bran (post-harvest) to the maximum expected residue in wheat of 10.3 mg/kg gives a maximum residue of 24.6 mg/kg for wheat bran. To cover the maximum expected residue in wheat bran the MRL for wheat bran should be raised from 20 mg/kg to 30 mg/kg.

Maximum residues in corn from in-field use of carbaryl were <0.1 mg/kg and when combined with residues expected from post-harvest use give a maximum anticipated residue of <8.1 mg/kg. Applying the experimentally derived processing factors of 1.8, 1.3 and 1.7 for corn germ, flour and meal respectively gives estimated residues for corn germ, flour and meal that are less than the proposed cereal grain MRL. Separate MRLs for processed corn (maize) commodities are therefore not required.

The maximum residue observed in the trials on rye from pre-harvest use of carbaryl was 2.74 mg/kg for crops treated at 1.5× the Australian label rate or 1.83 mg/kg when scaled for application rate. The maximum expected residue from the combined pre- and post-harvest use on rye is 1.83 + 8 = 9.83 mg/kg. Applying processing factors of 1.4 and 1.6 for bran and shorts results in maximum anticipated residues of 13.7 and 15.7 mg/kg respectively. Although the maximum anticipated residues in rye shorts is slightly higher than the proposed cereal grain MRL, bulking and blending of grain should ensure that the residue levels are adequately covered by the proposed cereal grain MRL of 15 mg/kg. Therefore, separate MRLs for processed rye commodities are not required.

Table 23: Processing factors for cereal grains treated with pre-harvest sprays of carbaryl.

Crop	Processed commodity	Processing factor (PF)
Barley	Flour	0.8, 1, 0.2, 0.2, 0.2
	Bran	1, 0.6, 0.4, 0.4, 0.4
	Red dog	0.8
	Shorts	0.7
Corn (maize)	Starch	0
	Germ	1.8
	Meal	1.3
	Grits	0.3
	Flour	1.7
	Refined oil	0.2
Rice	Polished rice	0.01
	Bran	0.9
Rye	Flour	1.1
	Bran	1.4
	Shorts	1.6
Sorghum	Flour	0.3
	Shorts	0.7
	Bran	2.4
	Grits	0.2
	Starch	0
Wheat	Flour	5*, 0.06, 0.4, 4*, 0.5, 0.1
	Bran	3.7*, 0.3, 0.6, 2*, 0.7, 1
	Shorts	3.7*, 0.1, 0.8
	Germ	0.7

*the residues in the grain were too low to generate reliable processing factors.

Table 24: Processing factors for cereal grains treated in storage (post-harvest) with carbaryl*.

Crop	Processed commodity	Processing factor (PF)
Barley	Primitive malt Commercial malt	0.2, 0.3 0.03, 0.07
Rice	Husked Milled Polished	0.1 0.02, 0.1 0.02
Wheat	Wholemeal flour Wholemeal bread Bran Shorts White flour White bread	0.4, 0.4, 0.4, 0.5, 0.5 0.2, 0.3, 0.2-0.3, 0.2-0.3 2.3, 2.3, 2.4, 2.3-2.4, 2.4-2.7 0.5, 0.5 0.02, 0.03, 0.02-0.03, 0.02-0.03 <0.02, 0.01, 0.01-0.01, 0.02

*data from Snelson 1987

In the case of sorghum there is significant concentration of the residue in the bran (PF = 2.4). Maximum anticipated residues are 4.96 + 8 mg/kg = 12.96 mg/kg for sorghum grain. Maximum residues in bran would be 31.1 mg/kg. A separate MRL of 50 mg/kg for sorghum bran should cover any residues in this commodity. Sorghum bran is not considered to be a human food therefore this MRL relates to the animal feed commodity and should appear in Table 4 of the *MRL Standard*.

9.5 Residues in fruits and vegetables

Residues trial data were provided for a wide variety of fruit and vegetable crops. The data was presented as either full studies, brief trial reports or summary tables of results. Results from all of the trial information provided to the APVMA were used to determine the levels of residues expected to occur in commodities treated according to Australian good agricultural practice (GAP) and, where required, results were scaled down to reflect the maximum approved Australian application rates. The trials available for review are included in the Appendices to this report and results are summarised in Table 25.

Table 25: Summary of trials considered as part of the review of carbaryl.

crop group	crop	PHI	application rate	highest residue	median residue	number of trials for crop	number of trials for whole group
FB	blackberries	2 to 3	0.1 kg ai/hL	4.4	NA	3	
FB	blueberries	3	0.1 kg ai/hL	1.02	NA	1	
FB	cranberries	3	0.1 kg ai/hL	1.01	NA	2	
FB	grapes	3 to 4	0.1 kg ai/hL	5.1	1.275	16	
FB	raspberries	2 to 4	0.1 kg ai/hL	14.6	4.34	9	
FB	strawberries	3 to 4	0.1 kg ai/hL	1.88	NA	2	33
FC	grapefruit	5	0.48 kg ai/hL	6.8	NA	1	
FC	lemon	5	0.48 kg ai/hL	5.1	1.94	3	
FC	orange	2 to 5	0.48 kg ai/hL	8.1	3.8	9	13
FI	avocado	3	0.1 kg ai/hL	0.57	NA	1	
FI	persimmon	3 to 4	0.1 kg ai/hL	2.3	NA	3	4
FP	apple (fruit thinning use)	78 to 82	0.1 kg ai/hL	0	0	5	

FP	apple (late pre-harvest appl)	2 to 4	0.1 kg ai/hL	5.75	0.605	16	
FP	pear	2 to 3	0.1 kg ai/hL	1.84	0.25	5	26
FS	apricot	3	0.1 kg ai/hL	1.77	NA	2	
FS	cherry	3	0.1 kg ai/hL	4.6	1.725	8	
FS	peach	3	0.1 kg ai/hL	2.14	0.86	13	
FS	plum	3	0.1 kg ai/hL	0.61	0.275	6	29
FT	olives	0	0.1 kg ai/hL	0.89	NA	2	2
SO	cotton	0 to 3	1.1 kg ai/ha	0.87	0.485	5	5
TN	almonds	0	0.1 kg ai/hL, 1.1 kg ai/ha	0.88	0.52	7	7
VA	onion	3	1.1 kg ai/ha	1.19	NA	1	1
VB	broccoli	3 to 4	1.1 kg ai/ha	3.96	1.93	13	
VB	Brussels sprouts	3 to 4	1.1 kg ai/ha	2.01	NA	2	
VB	cabbage	2 to 4	0.1 kg ai/hL, 1.1 kg ai/ha	15.8	0.925	44	
VB	cauliflower	3 to 4	0.1 kg ai/hL, 1.1 kg ai/ha	26.59	7.6	15	
VB	kohlrabi	3 to 4	1.1 kg ai/ha	10	NA	2	76
VC	cantaloupe	3	1.1 kg ai/ha	1.49	0.69	5	
VC	Cucumber	2 to 3	1.1 kg ai/ha	1.9	0.8	5	
VC	gourds (ridge, sponge, bottle)	2 to 3	0.1 kg ai/hL, 1.1 kg ai/ha	14.85	0.06	8	
VC	long melon	3	0.1 kg ai/hL	6	NA	1	
VC	pumpkin (winter squash)	3	1.1 kg ai/ha	0.39	NA	2	
VC	zucchini (summer squash)	2 to 3	1.1 kg ai/ha	1.29	0.27	9	38
VD	blackeyed bean	3	1.1 kg ai/ha	2.21	NA	1	
VD	cowpea	3	1.1 kg ai/ha	0.75	0.27	4	5
VL	beet tops	2 to 3	1.1 kg ai/ha	7	NA	2	
VL	Chinese cabbage	3 to 4	1.1 kg ai/ha	19.2	2.7	6	
VL	Collards (kale)	2 to 3	1.1 kg ai/ha	21.5	1.87	10	
VL	endive	2 to 3	1.1 kg ai/ha	15.5	10.1	7	
VL	lettuce, head	2 to 4	1.1 kg ai/ha	7.17	1.87	14	
VL	lettuce, leaf	2 to 3	1.1 kg ai/ha	27	NA	2	
VL	mustard greens	2 to 3	1.1 kg ai/ha	31.2	20	3	
VL	spinach	2 to 4	0.1 kg ai/hL, 1.1 kg ai/ha	24.5	8.855	8	
VL	Swiss chard	2 to 3	1.1 kg ai/ha	30.1	6	3	
VL	turnip tops	2 to 3	1.1 kg ai/ha	21	NA	3	58
VO	capsicums	3	0.1 kg ai/hL, 1.1 kg ai/ha	1.93	0.8	17	
VO	chilli	2 to 3	1.1 kg ai/ha	19	6.17	10	
VO	eggplant	2 to 4	0.1 kg ai/hL, 1.1 kg ai/ha	9	0.575	33	
VO	okra	2 to 4	0.1 kg ai/hL, 1.1 kg ai/ha	9.6	0.72	32	
VO	sweetcorn	2 to 4	1.1 kg ai/ha	3.04	0.2	23	
VO	tomato	2 to 4	0.1 kg ai/hL, 1.1 kg ai/ha	16.3	0.5	56	171
VP	beans (green, succulent)	2 to 4	1.1 kg ai/ha	4	1.06	17	
VP	pea (garden, field, succulent)	2 to 4	1.1 kg ai/ha	4.24	0.79	23	42

VR	carrots	4	1.1 kg ai/ha	0.06	NA	1	
VR	garden beet	3	1.1 kg ai/ha	0.14	NA	1	
VR	potato	2 to 4	1.1 kg ai/ha	0.06	0.01	9	
VR	sugarbeet	3 to 4	1.1 kg ai/ha	0.24	0	8	
VR	turnip	3	1.1 kg ai/ha	0.65	0.45	5	24
VS	asparagus	2 to 3	1.1 kg ai/ha	3.4	0.475	6	
VS	celery	3	1.1 kg ai/ha	5.1	2.3	3	9

9.5.1 Residues in berry fruit

Various Berry Crops - 33 residues trials where the use patterns were considered relevant to the approved Australian uses (PHI 3±1 days) were available for review.

Grapes - 17 trials on gave highest residues of 5.1 mg/kg with median residues of 1.275 mg/kg. The data support an MRL of 7 mg/kg for grapes.

Raspberries - 9 trials were available. Highest residues in the trials were 14.6 mg/kg, with median residues of 4.34 mg/kg. The data support an MRL of 20 mg/kg for raspberries.

Blackberries - 3 trials were available, where highest residues were 4.4 mg/kg. Relevant data were limited for other berry crops. Only a single residues trial was available for blueberries, while two trials were available for cranberries and strawberries. Insufficient residues data are available to establish an MRL for blackberries, cranberries, strawberries or blueberries.

9.5.2 Residues in citrus fruit

Citrus crops - 13 residues trials were provide. Where the use patterns were considered relevant to the approved Australian uses (PHI 2-5 days), were available for review.

Oranges - 9 relevant trials were provided. Highest residues in the trials were 8.1 mg/kg, with a median residue of 3.8 mg/kg. The data support an MRL of 10 mg/kg for oranges.

There were limited data available for other citrus fruits. A single trial was provided for grapefruit (HR 6.8 mg/kg) and three trials on lemons (HR 5.1 mg/kg). No relevant data were available for other citrus fruits.

There were insufficient data provided to support separate MRLs for grapefruit, lemons or other citrus fruits, and there are insufficient residues data available to establish a group MRL for citrus fruits.

9.5.3 Residues in pome fruit

Registered products containing carbaryl may be used on pome fruit as a foliar spray for control of insect pests, and as a foliar spray several months before harvest to aid fruit thinning. The fruit thinning use pattern involves a single application between 7-28 days after full bloom. The current Withholding Period (WHP) for this use is 3 days, however the actual time between application and harvest would be much longer. The period between the end of flowering and harvest for most apple varieties in Australia is approximately 4 months, therefore it is estimated that application 7-28 days after full bloom would be at least 3 months before harvest.

A total of 26 relevant trials were available for pome fruit, 16 for the use involving a late pre-harvest application and 5 for the fruit thinning use pattern, where application occurs several months before harvest.

Apples - 16 trials gave maximum residues of 5.75 mg/kg and a median residue of 0.605 mg/kg (PHI 3±1 days). Five (5) relevant trials were provided for pears. Maximum residues in these trials were 1.84 mg/kg with a median residue of 0.25 mg/kg (PHI 3±1 days). The data on apples and pears support a group MRL of 10 mg/kg for pome fruit for the late pre-harvest use pattern.

In 5 trials on apples, application almost 3 months before harvest resulted in residues in fruit of less than 0.01 mg/kg. In 2 trials on pears approximately 2 months before harvest, residues in fruit at harvest were non-detectable. At a WHP of approximately 90 days residues in fruit are expected to be low. The data support an MRL of 0.01 mg/kg for pome fruit for use of carbaryl as an aid to fruit thinning.

9.5.4 Residues in stone fruit

Stone fruit - 29 residues trials on, where the use patterns were considered relevant to the approved Australian uses (PHI 3 days), were provided for review.

Peaches - 13 trials on gave highest residues of 2.14 mg/kg with a median residue of 0.86 mg/kg (PHI 3 days). The data support an MRL for peaches of 5 mg/kg.

Cherries - 8 trials on gave highest residues of 4.6 mg/kg and a median residue of 1.725 mg/kg (PHI 3 days). The data support an MRL for cherries of 10 mg/kg.

Plums - 6 trials gave highest residues of 0.61 mg/kg and a median residue of 0.275 mg/kg (PHI 3 days). The data support an MRL for plums of 3 mg/kg.

Apricots - Only 2 relevant trials were available and no data were available for nectarines. The data on apricots are insufficient to establish an appropriate MRL for this commodity. However, based on the similar size and skin texture of apricots and nectarines to plums, the data on plums could be used to set MRLs for apricots and nectarines. MRLs of 3 mg/kg for apricots and nectarines are appropriate.

9.5.5 Residues in tropical fruit

Tropical fruit - 6 relevant trials where provide, where the use patterns were considered similar to the approved Australian uses, were available for review. Three (3) trials on persimmons gave maximum residues of 2.3 mg/kg while a single trial on avocado gave residues of 0.57 mg/kg (PHI 3-4 days). Two (2) trials on olives gave maximum residues of 0.89 mg/kg (PHI 0 days).

There are insufficient residues data available to support MRLs for individual tropical fruits or a group MRL.

9.5.6 Residues in bulb vegetables

Only a single relevant residues trial was available for bulb vegetables. In that trial, residues of 1.19 mg/kg occurred in onions (PHI 3 days).

There are insufficient residues data available to establish an MRL for bulb vegetables.

9.5.7 Residues in brassica vegetables

Brassica Vegetables - 76 relevant residues trials were available.

Forty-four (44) trials were available for cabbage, where highest residues of 15.8 mg/kg and median residues of 0.925 mg/kg occurred in treated crops (PHI 2-4 days). Only 4 of the trials gave residues in cabbage above 10 mg/kg. The data support an MRL of 15 mg/kg for cabbage.

Cauliflower - 15 trials were available, where highest residues of 26.6 mg/kg and median residues of 7.6 mg/kg occurred in treated crops (PHI 3-4 days). Only a single trial gave residues in cauliflower above 20 mg/kg. The next highest residue in cauliflower was 18.4 mg/kg. The data support an MRL of 20 mg/kg for cauliflower.

Broccoli - 13 trials available for gave highest residues of 3.96 mg/kg and median residues of 1.93 mg/kg in treated crops (PHI 3-4 days). The data support an MRL of 7 mg/kg for broccoli.

Brussels Sprouts - 2 trials on (HR 2.01 mg/kg, PHI 3-4 days) and two trials on kohlrabi (HR 10 mg/kg, PHI 3-4 days) were available. The data are insufficient to establish separate MRLs for these commodities. No relevant trials were available for other brassica vegetables.

9.5.8 Residues in cucurbit vegetables

Cucurbit Vegetables - 38 relevant trials were available.

Cucumber - 5 trials gave highest residues of 1.9 mg/kg and median residues of 0.8 mg/kg (PHI 2-3 days). The data support an MRL of 5 mg/kg for cucumber.

Cantaloupe (rock melon) - 5 trials gave highest residues of 1.9 mg/kg and median residues of 0.69 mg/kg. The data support an MRL of 3 mg/kg for cantaloupe.

Summer squash (zucchini) - 9 trials gave highest residues of 1.29 mg/kg and median residues of 0.27 mg/kg. The data support an MRL for summer squash of 3 mg/kg.

Residues trials were available for several types of gourd: Six (6) trials on bottle gourd (HR 0.09 mg/kg), 1 trial on ridge gourd (HR 8.02 mg/kg) and 1 trial on sponge gourd (14.85 mg/kg) (PHI 2-3 days). The data support an MRL of 0.2 mg/kg for bottle gourd but are insufficient to allow the establishment of MRLs for other gourds.

Only 2 trials on winter squash (pumpkin) and one trial on long melon were available. The data are insufficient to allow the establishment of a separate MRL for pumpkins or long melons.

9.5.9 Residues in leafy vegetables

Leafy vegetables - 58 relevant residues trials were available.

Highest residues occurring in various leafy crops were similar. Highest residues ranged from 15.5 mg/kg up to 31.2 mg/kg in trials on Chinese cabbage (6 trials), collards/kale (10 trials), endive (7 trials), leaf lettuce (2 trials), mustard greens (3 trials), spinach (8 trials), turnip tops (3 trials) and Swiss chard (3 trials). Median residues in these trials were 9.075 mg/kg (PHI 2-4 days). Only 2 samples contained residues exceeding 30 mg/kg, one in Swiss chard and one in mustard greens.

Residues occurring in head lettuce and beet tops were lower than other leafy vegetables, with highest residues of 7.17 mg/kg and median residues of 1.87 mg/kg occurring in 14 trials on head lettuce (PHI 2-4 days) and maximum residues in beet tops from 2 trials of 7.0 mg/kg.

The data support a group MRL of 30 mg/kg for leafy vegetables (except head lettuce) and an MRL of 10 mg/kg for head lettuce.

9.5.10 Residues in fruiting vegetables

Results from a total of 171 relevant residues trials were available for fruiting vegetables (non-cucurbits).

Chilli – 10 trials gave highest residues of 19 mg/kg with a median residue of 6.17 mg/kg. The next highest result was 12.9 mg/kg. The data support an MRL of 20 mg/kg for chilli peppers.

Capsicums - 17 trials gave highest residues of 1.93 mg/kg with a median residue of 0.8 mg/kg. The data support an MRL of 3 mg/kg for capsicums.

Eggplant - 33 trials gave highest residues of 9 mg/kg with a median residue of 0.575 mg/kg. The next highest result was 5.29 mg/kg, and residues in eggplant exceeded 3 mg/kg in only four samples. The sample containing residues of 9 mg/kg may be considered an outlier. The data support an MRL of 7 mg/kg for eggplant.

Okra - 32 trials gave highest residues of 9.6 mg/kg with a median residue of 0.72 mg/kg. Of the 32 samples, 30 contained residues below 3.2 mg/kg. The remaining 2 samples contained residues of 9.2 and 9.6 mg/kg. Given the large number of trials, the 2 results above 9 mg/kg may be considered outliers. The data support an MRL of 5 mg/kg for okra.

Sweet corn - 23 trials gave highest residues of 3.04 mg/kg with a median residue of 0.2 mg/kg. The next highest residue in the trials was 1.34 mg/kg. The sample containing residues of 3.04 mg/kg may be considered an outlier. The data support an MRL of 3 mg/kg for sweet corn.

Tomatoes - 56 trials gave a highest residue of 16.3 mg/kg, with a median residue of 0.535 mg/kg. Two (2) samples contained residues of 13.6 and 16.3 mg/kg, while the remainder of the samples in the trials contained residues of less than 8.9 mg/kg. Given the large number of trials for tomatoes, the two samples containing highest residues may be considered to be outliers. The data support an MRL of 10 mg/kg for tomatoes.

No relevant residues data were available for mushrooms or Cape gooseberries to allow the establishment of suitable MRLs.

9.5.11 Residues in pulses

Four relevant residues trials were available for pulses: three (3) trials on cowpeas gave highest residues of 0.75 mg/kg and 1 trial on black eyed bean gave residues of 2.21 mg/kg (PHI 3 days). The data are insufficient to allow the establishment of suitable MRLs for pulses.

9.5.12 Residues in legumes

Legume vegetables - 42 relevant residues trials were available.

Green beans - 17 trials were available, highest residues of 4 mg/kg occurred in treated produce, with a median residue of 1.06 mg/kg (PHI 2-4 days). Twenty-three (23) trials on peas gave highest residues of 4.24 mg/kg, with a median residue of 0.79 mg/kg. The data available for peas and beans support a group MRL of 7 mg/kg for legume vegetables.

9.5.13 Residues in root and tuber vegetables

Root and tuber vegetables - 24 relevant residues trials were available, where the use patterns were considered similar to Australian uses.

Potatoes - 9 trials gave highest residues of 0.06 mg/kg, with a median residue of 0.01 mg/kg (PHI 2-4 days). The data support an MRL of 0.1 mg/kg for potatoes.

Sugar beets - 8 trials gave a highest residue of 0.24 mg/kg, with a median residue of <0.02 mg/kg (PHI 3-4 days). A single trial on garden beet gave a residue of 0.14 mg/kg (PHI 3 days). The data support an MRL of 0.5 mg/kg for sugar beet. Sugar beets may be considered similar to beetroot therefore extrapolation of these data allows the establishment of an MRL of 0.5 mg/kg for beetroot.

Turnips (Swede) - 5 trials gave a highest residue of 0.65 mg/kg, and a median residue of 0.45 mg/kg. The data support an MRL of 2 mg/kg for Swede.

There were no suitable residues data available for carrots and parsnips to allow the establishment of a suitable MRL for these commodities.

9.5.14 Residues in stalk and stem vegetables

Stalk and stem vegetables - 9 relevant residues trials were available.

Asparagus - 6 trials resulted in highest residues of 3.4 mg/kg, with a median residue of 0.475 mg/kg. The data support an MRL of 5 mg/kg for asparagus.

Celery - 3 trials resulted in a highest residue of 5.1 mg/kg. The data are insufficient to allow the establishment of an MRL for celery. There are insufficient data available to establish an MRL for other stalk and stem vegetables.

9.6 Residues in oilseeds

Registered carbaryl products may be used on cotton, sunflower and linseed crops.

Oilseeds - 5 residues trials, where the use patterns were considered relevant to the approved Australian uses, were available for review.

Cottonseed - 5 trials were available where treatment occurred 0-3 days before harvest. Highest residues of 0.87 mg/kg occurred in seed, with a median residue of 0.485 mg/kg. The data support an MRL for cottonseed of 3 mg/kg.

There were no relevant residues trial data for other oilseed crops therefore no MRLs can be established for sunflower or linseed.

9.7 Residues in tree nuts

Registered carbaryl products may be used on macadamia nuts and pecan nuts. Seven (7) residues trials on almonds, where the use patterns were considered relevant to the approved Australian uses, were available for review.

In the 7 trials on almonds highest residues of 0.88 mg/kg occurred in nuts, with median residues of 0.52 mg/kg (PHI 0 days). No suitable residues data were available for macadamia or pecan nuts. The data on almonds may be used to establish an MRL for macadamia nuts and pecan nuts and 2 mg/kg.

9.8 Effect of washing and cooking on residues in fruits and vegetables

The effect of washing and cooking on residue levels in various commodities was examined in some studies. The level of carbaryl residues was found to decrease by an average of approximately 80% after washing and 80% after cooking. Between 84-100% of residues in cowpea whole pods were removed by cooking.

In several trials on citrus fruits residues were determined separately in skin and pulp, with residues in the whole fruit calculated from these values. The majority of residues were found to be present in peel, and on average residues in the citrus pulp were 0.05 times the level in the whole fruit.

In trials on bananas treated with carbaryl, residues were determined separately in peel and pulp. Residues in pulp and peel were found to be similar in magnitude, with the average ratio of residues in pulp to peel of 0.92 from 17 samples.

9.9 Residues in animal feeds

Carbaryl treated crops and crop by-products may be fed to animals. The current MRLs in Table 4 of the *MRL Standard*, (Maximum residue limits for pesticides in animal feed commodities) are AF 0080 Forage of cereal grains T100 mg/kg and AS 0081 Straw and fodder (dry) of cereal grains T100 mg/kg. These MRLs do not cover the range of possible animal feed commodities for which carbaryl is approved for use. Residue data for individual animal feed commodities are listed in the tables below and will be used to propose, where appropriate, revised or new MRLs and associated WHPs for carbaryl in the relevant animal feeds.

9.9.1 Cereals (barley, oats, rye, wheat, maize, rice, sorghum etc –1.1 kg ai/ha, pre-harvest application)

Cereal grains can be grown as a forage crop with immature plants fed to animals as succulent forage or as silage (esp. corn). The waste parts after harvesting of grain (stems, stubble, stalks, leaves and empty ears) may also be used as animal feeds in the form of straw or dry fodder. Residues data for forage and fodder/hay/straw of various cereal crops are summarised in the tables below. The residue database was extensive for maize, sorghum and wheat with smaller numbers of trials available for other cereal crops. Table 26, provides a summary of residues in cereal based livestock feeds following foliar application of carbaryl.

The harvest WHP for cereal grains can be used as the WHP for grazing/cutting for stock food. In reviewing the available cereal grain data a harvest WHP of 14 days was proposed. Residues of carbaryl in straw (wet weight basis) treated at 1-2× the label rate at 13-15 days after the last spray were 0.1-125 mg/kg. Straw contains *ca.* 85-90% dry matter. When residues observed in the trials are scaled for application rate it is apparent that an MRL of 100 mg/kg would adequately cover residues in straw and fodder (dry) of cereal grains at 14 days after the last spray.

Residues in forage crops (wet weight basis) treated at 1-2× the Australian label rate ranged from 0.06 to 146 mg/kg at 0-2 days after spraying. By 12-16 days after spraying at 1-2× label rate residues were 0.02-30 mg/kg. A maximum residue of 30 mg/kg for forage (green) of cereal grains would be enough to cover for the natural variation in residues between trials when combined with a 14 day WHP. Expressing the residue on a dry weight basis (assuming 30% dry matter) would give rise to an MRL of 100 mg/kg for cereal forage (green).

Table 26: Summary of residues in cereal based livestock feeds following foliar application of carbaryl.

Crop	Feed	Rate (kg ai/ha)	Number sprays	PHI (days)	Residue (mg/kg)*	
					Mean	Range
Barley	Forage	1.12 (1×)	1-2	3-5	-	<LOQ, 2.85
				6-8	1.79 (n=3)	0.31-3.6
				12-15	2.28 (n=4)	0.66-5.6
		1.68 (1.5×)	1-4	0-2	36.0 (n=24)	2-76.5
				3-5	18.7 (n=22)	0.86-51.9
				6-8	16.1 (n=8)	2.9-33
				12-15	6.59 (n=8)	0.17-15.1
	Straw	1.68 (1.5×)	1-4	6-8	58.8 (n=13)	2.67-129
				13-15	30.0 (n=21)	0.52-125
				21-24	17.6 (n=24)	0.22-85.7
Field corn (maize)	Forage	1.12 (1×)	1-4	0-2	31 (n=15)	6.8-90
				3-5	20 (n=11)	2.6-7.6
				6-8	8.6 (n=12)	2.3-20
				13-15	6.0 (n=9)	0.94-19
		1.68 (1.5×)	1-4	0-2	16 (n=5)	2.8-33
				3-5	20 (n=4)	3.9-38
				6-8	9.7 (n=7)	1.8-25
				13-15	4.7 (n=5)	0.26-17
		2.24 (2×)	1-3	0-2	25 (n=19)	0.68-137
				3-5	12 (n=9)	0.98-28
				6-8	5.6 (n=16)	0.74-19
				13-15	6.4 (n=18)	0.32-30

	Fodder	1.12-2.24 (1-2×)	1-4	31-162	1.1 (n=66)	<0.02-19.2§
	Silage	1.12-2.24 (1-2×)	1-4	0-107	3.7 (n=78)	0.13-53¥
Millet	Forage	1.12 (1×)	1	3-5	-	2.14
				6-8	-	1.11
		2.24 (2×)	1	0-2	-	32.5, 35.5
				3-5	-	8
				6-8	-	0.94
				13-15	-	0.37
	Straw	1.68-2.24 (1.5-2×)	1	42-62	0.24 (n=4)	0.10-0.58
Oats	Forage	1.12 (1×)	1	0-2	-	0.48, 3.76
				3-5	-	1.36
				6-8	-	0.21, 1.87
				13-15	-	0.10, 0.16
	Straw	1.4-2.24 (1.3-2×)	1-3	0-2	-	24.3, 44.6
				3-5	-	11.3
				6-8	13 (n=3)	0.09-25.2
				13-15	-	0.10, 10.5¢
Rice	Forage	1.68 (1.5×)	1-2	3-5	-	12
				6-8	-	3, 2
				13-15	-	6.1
	Straw	0.84-2.24 (0.8-2×)	1-2	0-2	17 (n=4)	3.5-30.1
				6-8	14 (n=3)	1.1-34.6
				12-15	31 (n=12)	0.64-120
				20-23	2.7 (n=7)	1.6-4
Rye	Forage	1.68 (1.5×)	2	0-2	67 (n=3)	27.7-95.7
				3-5	6.3 (n=3)	0.9-16.2
	Straw	1.68 (1.5×)	2	6-8	19 (n=5)	3.8-42.1
				12-16	6.8 (n=5)	0.5-17.3
				20-23	6.4 (n=5)	0.31-15.6
		2.24 (2×)	3	0-2	-	12.8
Sorghum	Forage	1.12-2.24 (1-2×)	1-5	0-2	28 (n=13)	0.06-146
				3-5	10 (n=8)	3.5-22
				6-8	3.9 (n=8)	1.3-9.3
				12-16	4.6 (n=18)	0.16-23.5
	Fodder	1.12-2.24 (1-2×)	1-3	0-2	57 (n=3)	36-67
				6-8	39 (n=3)	1.2-62
				12-16	5.0 (n=11)	0.05-25
				20-23	1.2 (n=3)	0.31-3
	Silage	2.24 (2×)	3	12-16	4.2 (n=10)	0.6-8.5
Wheat	Forage	1.68-2.24 (1.5-2×)	1-5	0-2	31 (n=22)	0.44-78
				3-5	13 (n=19)	0.18-33
				6-8	8.9 (n=12)	0.21-26
				12-15	4.2 (n=17)	0.02-12
				20-24	-	0.32, 0.36
	Straw	1.68-2.24 (1.5-2×)	1-5	0-2	-	0.41, 35
				6-8	19 (n=10)	0.19-81
				12-15	14 (n=9)	0.51-62
				20-24	6.3 (n=13)	0.06-27

*residues reported on a wet weight basis

§19.2 mg/kg at 48 days after the last spray
¥53 mg/kg at 28 days after the last spray
¢0.57 mg/kg at 28 days after the last spray

9.9.2 Pasture (1.1 kg ai/ha)

Pasture is grown for forage or hay for feeding to livestock. Residues in grass (wet weight basis) treated at 1.5× the label rate and used to make hay ranged from 54-1178 mg/kg at 0-2 days after spraying, declining to ≤292 mg/kg by 6-8 days. Hay comprises *ca.* 88% dry matter. Scaling the maximum observed residue for application rate and correcting for dry

matter content gives a maximum residue of 221 mg/kg. An MRL of 300 mg/kg for hay or fodder (dry) of grasses would be required to adequately cover natural variation in residue results when combined with a 7 day WHP for cutting for stock food.

Residues in grass forage (wet weight basis) treated at 0.5-1.5× the Australian label rate ranged from 0.7-1062 mg/kg at 0-2 days after spraying, declining to be ≤125 mg/kg by 6-8 days after spraying or ≤83 mg/kg if scaled for application rate. A grazing WHP of 7 days should be adequate to ensure that residues in animals will be less than the proposed animal MRLs (Table 27). An appropriate MRL for grass pasture (green) would be 100 mg/kg when expressed on a wet weight basis or 400 mg/kg when expressed on a dry weight basis using the assumption that pasture contains 25% dry matter.

Table 27**:** Summary of residues in grass animal feeds following foliar application of carbaryl.

Crop	Feed	Rate (kg ai/ha)	Number sprays	PHI (days)	Residue (mg/kg)*	
					Mean	Range
Grass (pasture)	Forage	0.56-0.84 (0.5-0.8×)	1-2	0-2	51 (n=18)	0.7-258
				3-5	16 (n=6)	0.8-32
				6-8	14 (n=9)	0.6-29
				13-15	9.4 (n=7)	0.08-32
		1.12 (1×)	1-3	0-2	69 (n=32)	4.7-126
				3-5	13 (n=9)	4.5-20.5
				6-8	6.8 (n=13)	0.21-19
				13-15	4.1 (n=11)	0.4-13
		1.68 (1.5×)	1-2	0-2	266 (n=14)	19-1062
				3-5	-	2.7
				6-8	42 (n=12)	3.2-125
				13-15	5.9 (n=25)	0.08-32
		2.24 (2×)	1-3	0-2	147 (n=28)	0.46-603
				3-5	71 (n=26)	0.02-347
				6-8	-	10.4, 23.3
	Hay	1.68 (1.5×)	2	0-2	372 (n=12)	54-1178
				3-5	-	185, 189
				6-8	62 (n=18)	0.54-292
				13-15	24 (n=19)	0.05-158
		2.24 (2×)	2	0-2	407 (n=15)	9.5-1950
				3-5	290 (n=15)	14.2-1570

*residues reported on a wet weight basi

9.9.3 Legume animal feeds (1.1 kg ai/ha)

Legume crops may be grown as animal feeds (succulent crops). Crop by-products left after the harvesting of pulse grains may also be fed to livestock (fodder/hay).

Residues in legume forage treated at 0.5-2× the label rate ranged from 0.8 to 720 mg/kg (wet weight basis) at 0-2 days after the last spray, declining to 0.05-107 mg/kg at 6-8 days and 0.10-67 mg/kg at 12-15 days after the last spray. Correcting for application rate, the data support an MRL of 100 mg/kg for legume forages (wet weight basis) when combined with a 7 day WHP. Animal feed MRLs are usually expressed on a dry weight basis. Assuming legume forage comprises 25% dry matter, 100 mg/kg (wet weight basis) corresponds to a legume forage (green) MRL of 400 mg/kg.

The data set for residues in legume fodder is limited. The maximum residue (wet weight basis) in alfalfa hay after spraying at the label rate was 70.3 mg/kg at 3-5 days after spraying

with a maximum residue of 189 mg/kg observed for crop treated at 1.3-1.7× the label rate and sampled at the same time interval. Residues in alfalfa hay at 6-8 days were 0.54-97.4 mg/kg at 0.9-1.7× the label rate declining to 0.19-12.1 mg/kg at 13-15 days after the last spray. For clover sprayed at 2× the label rate residues in hay were 12.1-66 mg/kg (wet weight basis) at 6-8 days after application. Residues in hay of beans treated at 1.5-3× the label rate were 0.12-70 mg/kg at 22-70 days after the last spray with an average value of 10 mg/kg. Scaling the results for application rate, a residue limit of 100 mg/kg (dry weight basis) for legume fodder should be adequate to cover natural variation when combined with a 7 day WHP. Table 28 shows a summary of residues in legume animal feeds following foliar application of carbaryl

Table 28: Summary of residues in legume animal feeds following foliar application of carbaryl.

Crop	Feed	Rate (kg ai/ha)	Number sprays	PHI (days)	Residue (mg/kg)*	
					Mean	Range
Bean (succulent + dry)	Forage	0.51-2.24 (0.5-2×)	1-8	0-2 3-5 6-8 13-15	53 (n=31) 52 (n=24) 27 (n=21) 17 (n=17)	1-332 0.5-228 0.05-107 0.05-67
	Hay	2.24 (2×)	1-2	0-2 3-5	8.5 (n=7) -	3.4-14 1.2
		1.68-3.36 (1.5-3×)	1-4	22-70	10.5 (n=10)	0.12-70
Clover	Forage	1.68-2.24 (1.5-2×)	1-2	0-2 3-5 6-8	34 (n=4) 29 (n=3) 14 (n=11)	18-77 12-60 3.7-49
	Hay	1.12 (1×)	1	0-2	-	35.7
		2.24 (2×)	1	6-8	28 (n=8)	12.1-66
Lucerne (alfalfa)	Forage	1.03-1.12 (0.9-1×)	1-3	0-2 3-5 6-8 12-15	23.4 (n=12) 23.1 (n=6) 9.51 (n=19) 4.26 (n=8)	10-35 2.2-37 0.22-27.5 0.19-17.6
		1.4-1.79 (1.3-1.6×)	1	0-2 3-5 6-8 12-15	51.9 (n=19) 36.7 (n=24) 8.46 (n=23) 2.84 (n=6)	1.6-131 0.36-133 0.26-41.8 0.24-13.2
		2.24 (2×)	1	0-2 3-5 6-8 12-15	70.0 (n=13) 32.8 (n=6) 33.8 (n=5) 17.9 (n=3)	2.1-333 17.8-52.1 15.7-76.5 6.2-31.1
	Hay	0.95-1.12 (0.9-1×)	1-3	0-2 3-5 6-8 12-15	- - - -	30.4 23.1, 70.3 1.21, 11.3 0.19, 8.6
		1.4-1.9 (1.3-1.7×)	1	0-2 3-5 6-8 12-15	- 132 (n=3) 23.3 (n=7) 9.08 (n=4)	40.9 23.1-189 0.54-97.4 5.6-12.1
		2.24 (2×)	1	0-2 3-5 12-15	- - 20.2 (n=4)	58 25.5, 62.3 0.21-27.4
Peanut	Forage	1.12-2.24 (1-2×)	1-13	0-2 3-5 6-8 13-15	32 (n=7) - 2.8 (n=4) 15 (n=3)	3-76 4.4, 6.6 2.39-3.3 0.29-26
	Hay	1.12-1.45 (1-1.3×)-	1-2	0-2 3-5 6-8 13-15	18 (n=3) - 3.6 (n=3) -	13.6-20.2 19.3, 15.9 0.91-8.07 1.54
Pea (succulent + dry)	Forage	1.68-2.80 (1.5-2.5×)	1-4	0-2 3-5 6-8 13-15	29 (n=7) 13 (n=3) - 8.8 (n=8)	0.8-51 2.6-24.3 3.8, 19.5 0.10-43.5

	Straw	1.68 (1.5×)	4	21	12.5 (n=8)	2.45-21.8
Soybean	Forage	0.56-2.24 (0.5-2×)	1-9	0-2 3-5 6-8 12-16 20-23	104 (n=38) 31 (n=22) 9.6 (n=29) 4.0 (n=21) 0.8 (n=6)	3.3-720 1.2-166 0.26-81 0.13-22 0.23-1.7
	Hay	0.56-2.24 (0.5-2×)	1-7	0-103	3.6 (n=18)	0.09-54.3§
Trefoil	Forage	1.68-2.24 (1.5-2×)	1-2	0-2 3-5 6-8	- - -	27.9, 29.3 22.4, 23 10.9, 16.3

*residues assumed to be on a wet weight basis
§54.3 mg/kg at 0 days after the last spray

9.9.4 Miscellaneous fodder and forage crops (1.1 kg ai/ha)

The Australian MRLs for carbaryl in mammalian tissues are based on a maximum feeding level (MFL) of 400 mg/kg in the diet, feeding of the crops listed in Table 29, at the current label grazing WHP of 3 days might result in violations of the Australian MRLs for mammalian tissues. For most of the crops listed in the Table 28, carbaryl residues at 3 days after the last treatment were close to or greater than 100 mg/kg on a wet weight basis when scaled for application rates or when assuming a linear decay of residues (>400 mg/kg when expressed on a dry weight basis). The grazing WHP for miscellaneous fodder and forage crops should be extended to 7 days to afford the necessary margin of safety against residue violations in animal tissues. The maximum residue observed at 6-8 days after the last spray was for sugar beet tops sprayed at 2× the Australian label rate and was 125 mg/kg. When scaled for application rate and moisture content (23% dry matter) a maximum residue of 272 mg/kg is obtained. A MRL of 300 mg/kg should apply to crops classified under the CODEX crop grouping AM 0165 miscellaneous fodder and forage crops (except leguminous and grassy plants (Gramineae), but including grasses for sugar production).

Table 29: Summary of residues of carbaryl (mg/kg) in miscellaneous animal feeds§ following foliar application of carbaryl.

Crop	Feed	Rate (kg ai/ha)	Number sprays	PHI (days)	Residue (mg/kg)*	
					Mean	Range
Sweet corn‡	Forage	1.12-2.24 (1-2×)	1-21	0-2 3-5 6-8 11-17	192 (n=11) 34 (n=5) 22 (n=4) 60 (n=15)	11-345 2.0-77 7.2-32 1.8-178
	Cannery waste	2.24 (2×)	6	0-2 22	18 (n=4) -	16.5-21.4 4.0, 8.4
	Fodder	1.68-2.24 (1.5-2×)	1-21	0-2 3-5 6-8 12-15	123 (n=21) 22 (n=9) 12 (n=20) 19 (n=15)	4.3-385 3.6-54 0.07-58 0.09-83
Cotton	Forage	1.12-2.24 (1-2×)	1-13	0-2 3-5 6-8 13-15 19-23 24-48	212 (n=14) 42 (n=14) 19 (n=11) 4.8 (n=10) 1.9 (n=6) 0.11 (n=6)	7.0-505 2.4-196 0.22-129 0.17-22 0.05-11.2 0.05-0.16
	Straw	2.24 (2×)	6	0-2 3-5 6-8	- - -	177 4.6 3.6
Lentil	Hay	1.4-2.8 (1.3-2.5×)	1	13-28	1.2 (n=3)	0.89-1.67

Sunflower	Forage	1.68-2.24 (1.5-2×)	1-2	0-2 12-15	59 (n=5) 0.37 (n=4)	8-116 0.09-1.0
		1.12-2.24 (1-2×)	1-2	21-93	1.2 (n=25)	0.15-3.4
Sugar beet	Forage (tops)	0.56-2.24 (0.5-2×)	1-3	0-2 3-5 6-8 12-15	49 (n=13) 48 (n=8) 21 (n=5) 0.97 (n=4)	6.5-174 4.9-211 1.3-125 0.29-1.5
Turnip	Forage (tops)	2.24-2.49 (2-2.2×)	1-6	0-2 3-5 6-8 12-15	38 (n=8) 21 (n=3) 12 (n=4) -	0.61-94 1.3-34 0.88-20.5 1.8

§ animal feeds produced from sweet corn, lentils and sunflowers have not been classified by CODEX as yet and have been included with members of the group "miscellaneous fodder and forage crops" for information purposes only
*residues reported on a wet weight basis
‡ it is not normal practice to feed sweet corn crops to animals with the majority of crops ploughed in following harvest to prepare the ground for the next cropping cycle. The maximum residue at >7 days after the last spray and corrected for application rate was 106 mg/kg on a wet weight basis, PHI = 17 days. Assuming corn forage contains 40% dry matter, this residue corrected for moisture content is 265 mg/kg. Assuming a linear decay in residues and noting the residue at 0 days was 575 mg/kg (corrected for application rate and moisture content) it is estimated that the residue at 7 days would have been 447 mg/kg, corrected for moisture content.

9.10 Animal commodity MRLs

With the exception of poultry and pigs, carbaryl is not registered as a product for direct animal treatment in food producing species (horses are not considered food-producing species in Australia). Where direct animal treatment is not allowed, MRLs for animal commodities are set based on estimated exposure to residues in the animal diet and from animal transfer studies that determine residues in tissues, milk and eggs after feeding at different levels. The maximum intake for livestock varies, depending on the species and the feeds consumed. For each species, the maximum intake is determined by the combination of feeds that give rise to the highest residues (Table 30).

Table 30: Summary of maximum resides for animal feeds treated with carbaryl.

Animal feed	Maximum residue (mg/kg)‡	%dry matter	% livestock diet	Intake (ppm feed/day)	Intake (mg/ kg bw/day)*
Cereal forage	30	30	100	100	4.0
Cereal fodder (straw/hay)	100	90	100	111	4.4
Cereal grain	15	90	100	17	0.7
Legume forage♣	54	25	100	216	8.6
Legume fodder	100	90	100	111	4.4
Pulses/legumes (seeds or pods)	5	90	100	6	0.2
Hay/fodder of grasses	300	88	100	341	13.6
Grass forage†	83	25	100	332	13.3
Miscellaneous fodder/forage crops¥	62.5	23	100	271	10.8
Pome fruit pomace§	5	40	20	2.5	0.1
Citrus pulp (dry)¢	1.96	91	20	0.4	0.02
Grape marc£	25	100	20	5	0.2
Miscellaneous fruit and vegetables	5	20	<5	1.25	0.05

‡maximum residue on a wet weight basis, unless stated otherwise the MRL expressed on a wet weight basis has been used
*intake calculated for a 500 kg animal consuming 20 kg dry matter/day
♣highest residues in legume forage crops were obtained for beans (succulent + dry) with a maximum observed residue of 107 mg/kg at 7 days after the last spray, or 54 mg/kg when scaled for application rate. The average residue at 6-8 days after the last spray at 0.5-2× the label rate was 27 mg/kg.

† the maximum residue in grass forage at 7 days after the last spray was 125 mg/kg wet weight for 1.5× the Australian label rate or 83 mg/kg when scaled for application rate

¥includes cotton, sugar beet, fodder beet and turnip tops. The maximum residue at 7 days after the last spray was observed in sugar beet tops and was equivalent to 62.5 mg/kg (wet weight basis) when corrected for application rate.

§ In an apple processing study a processing factor of 1 was obtained for apple pomace (wet). Applying this to the Pome fruit MRL of 5 mg/kg gives a maximum estimated residue in apple pomace (wet) of 5 mg/kg.

¢ In citrus processing studies (grapefruit, lemon, orange) processing factors were 0.14-0.28 for citrus pulp (dry). Applying a processing factor of 0.28 to the Citrus fruit MRL of 7 mg/kg gives a maximum estimated residue in citrus pulp (dry) of 1.96 mg/kg.

£ No data are available for grape marc. Assuming the residue concentrates in the marc and noting grapes contain *ca.* 20% dry matter, a concentration factor of 5 is obtained. Applying this to the grape MRL of 5 gives a worst case residue in grape marc of 25 mg/kg

In the case of cattle the highest intake of carbaryl is associated with feeding grass pasture and hay at 100% of the diet. Utilising the assumptions outlined in the table footnotes above, the estimated maximum intake level in the diet is 341 mg/kg. The maximum estimated intake level is sufficiently close to 400 ppm in the diet to use this as the MFL in setting the animal tissue MRLs.

Studies reported by JMPR on residues of carbaryl in cattle tissues indicate that only low levels are expected. Residues of carbaryl in tissues of cows fed at 100 ppm in the diet for 14 days were 0.03 mg/kg for kidney, 0.04 mg/kg for liver and <0.02 mg/kg for muscle (JMPR, Dorough 1971). Carbaryl fed at up to 450 ppm in the feed for 14 days resulted in no residue (<0.01 mg/kg) in milk when analysed using a colourimetric assay (Gyearisco *et al:* 1960, JMPR 1968). No residues of carbaryl were detected in tissues of steers fed at 50 or 200 ppm in the diet for 27 days (Claborn *et al.*, 1963).

The most recent study provided as part of the carbaryl special review confirmed the residue levels of free carbaryl detected in the earlier studies reported above. Groups of 3 lactating dairy cows were fed at averages of 123, 347 and *ca.* 1437 ppm in the diet for 27 days. With the exception of two fat samples with residues of 0.03 mg/kg at the highest feeding level, residues in tissues and milk samples were <0.02 mg/kg for all feeding groups.

The metabolism of carbaryl was similar for all mammalian species studied (rats, goats, pigs, cattle, monkey, man) with similar patterns of excretion. Feeding carbaryl in the diet to other mammalian species at similar rates as for cattle should result in similar residue levels in tissues, therefore the cattle feeding studies can be used to set the mammalian tissue MRLs. Any MRL set must be able to accommodate both indirect (animal feeds) and direct (veterinary) treatment. The only mammalian food species for which direct treatment is registered in Australia is pigs, however, direct treatment of pigs does not result in significant residues. Residues in pigs one day after spraying with 1% carbaryl solution were <LOD (Claborn *et al*., 1963). As a result, only the livestock feeding aspects need be considered when assessing the adequacy of the current mammalian tissue MRLs.

Assuming that residues scale with dose, the maximum residue in edible offal is estimated to be 0.16 mg/kg based on a maximum residue of 0.04 mg/kg for liver of cows fed at 100 ppm in the diet for 14 days. The current MRL for edible offal (mammalian) of T0.2 mg/kg should be adequate to cover residues in liver and kidney. The octanol-water partition coefficient of a chemical is one of several factors that determine partitioning into fat of tissues. Carbaryl has a log $P_{o/w}$ of 1.59 and is not expected to partition into fat tissues. With the exception of the latest feeding study that detected low levels of carbaryl in fat, the body of evidence indicates that carbaryl does not preferentially partition into fat tissues. The results for the two fat samples with residues of 0.03 mg/kg appear to be anomalous and therefore should be interpreted with care. In this case the current whole milk and meat

(mammalian) MRLs of T*0.05 and T0.2 mg/kg respectively are too high. These MRLs should be amended to reflect that residues are expected to be below the limit of quantitation (0.02 mg/kg) of the analytical method for both commodities.

The CODEX MRLs for mammalian tissues were based on feeding forage and fodder crops at 100 mg/kg fresh weight (400 mg/kg when expressed on a dry weight basis). As the Australian MRLs were set based on the same maximum feeding level there is minimal risk of violations of the relevant CODEX MRLs.

The current poultry MRLs appear to have been set on recommended Codex MRLs in 1969, for direct animal treatment. Residues data for the registered use of carbaryl dust on poultry were not provided, therefore poultry MRLs must be established based on dietary exposure only. In relation to the use of registered carbaryl products as direct treatments to poultry, the APVMA is not satisfied that the use of the products would not result in residues in poultry commodities exceeding the limits established.

Feeding of laying hens at 70 ppm in the diet with carbaryl for 17 days followed by ^{14}C-carbaryl for 14 days resulted in free carbaryl residues in eggs that were <0.02 mg/kg. Total radioactive residues in tissues were 0.41±0.01 mg equiv./kg in liver, 0.031±0.003 mg equiv./kg in breast meat, 0.030±0.001 mg equiv./kg in thigh meat, 0.032±0.001 mg equiv./kg in leg meat, 0.026±0.005 mg equiv./kg in fat and 0.043±0.011 mg equiv./kg in skin. Maximum residues in eggs were 0.4 mg equiv/kg, of which only 4% was present as parent compound. The proportion of carbaryl to the total residue was not reported for tissues (Andrawes *et al*. 1972). The level of TRR in poultry tissues and eggs is likely to overestimate residues of carbaryl parent.

The estimated maximum exposure of poultry to carbaryl residues in the diet occurs from consumption of feed containing 40% sorghum bran containing residues of 50 mg/kg and 60% cereal grains containing residues of 15 mg/kg, giving a maximum feed level of 29 ppm. Maximum residues of carbaryl that should occur in tissues and eggs at 35 ppm are <0.02 mg equiv./kg for poultry meat, fat and 0.021 mg equiv/kg in skin, and *ca*. 0.2 mg equiv./kg in liver (scaled from 70 ppm feed level in the metabolism study described above). The current MRLs of T5 mg/kg for poultry edible offal and T0.5 mg/kg for poultry meat are too high and should be amended. Appropriate poultry MRLs are 0.2 mg/kg for poultry offal, *0.02 mg/kg for poultry meat and *0.02 mg/kg for eggs.

9.11 Dietary exposure

In December 2002, the Acceptable Daily Intake (ADI) for carbaryl was increased from 0.004 to 0.008 mg/kg bw/day and an acute reference dose (ARfD) was set at 0.01 mg/kg bw.[1] The APVMA was advised to assess whether the current use patterns appearing on registered product labels would result in dietary exposure that would exceed the revised ADI for lifetime exposure (chronic dietary intake) or the ARfD for short term exposure (acute dietary exposure).

9.11.1 Short term dietary exposure

Acute or short term dietary exposure to pesticide residues is estimated using procedures and methodology recommended by the joint consultation of the WHO and FAO using a National

[1] The OCS recommended a new ARfD and revised the ADI for carbaryl in its report dated December 2002.

NESTI calculation. The calculations utilise commodity unit weights (Bowles and Hamilton, 2001), 97.5th percentile dietary consumption figures (ie large portion sizes) from the 1995 Australian National Nutrition Survey (1995) and results from relevant residues trials.

Where insufficient residue trial data were available, the highest residue (HR) from trials of a similar crop or the current MRL was used as the HR value in the NESTI calculations. A minimum of 41 consumers is required in the dietary survey results to adequately determine the 97.5th percentile consumption figure. Where the number of consumers was less than 41, large portion sizes of similar commodities were used. Where the number of consumers was still <41, the consumption figure for the entire crop group was used as a conservative estimate.

The full NESTI calculations for children aged 2-6 years and for the general population aged 2 years and above are summarised in the Table 31.

Table 31: NESTIs (as % of ARfD) for children aged 2-6 years and general population aged >2 years.

Crop group	Crop	NESTI 2-6 years	NESTI >2 years	Commodities where NESTI <ARfD
FB	**berry fruits**			
	blueberries	184	33	
	blackberries	792	143	
	dewberries (incl boysen, logan)	918	166	
	gooseberry	918	166	
	grapes	2059	736	
	raspberries	37	21	raspberries
	strawberries	178	55	
FC	**citrus fruits**			
	mandarins	108	30	
	oranges	138	42	
	grapefruit	160	44	
	lemons	118	9	
FI	**tropical fruit (inedible peel)**			
	jambu	2141	531	
	avocado	296	49	
	banana (in pulp)	1159	319	
	custard apple	3562	934	
	elephant apple	2930	755	
	feijoa	2299	576	
	jackfruit	5001	1191	
	kiwifruit	4134	454	
	litchi	1667	397	
	longan	1667	397	
	mango	2960	1000	
	papaya	4438	1183	
	granadilla	1667	397	
	passionfruit	1667	196	
	rambutan	1667	397	
	sapodilla	2299	576	

	sapote	3439	899	
FP	**pome fruit**			
	apples	1929	626	
	pears	760	201	
	loquats	1005	364	
	apples (fruit thinning use)	0	0	apples (fruit thinning use)
	pears (fruit thinning use)	0	0	pears (fruit thinning use)
	loquats (fruit thinning use)	0	0	loquats (fruit thinning use)
FS	**stone fruit**			
	cherries	786	96	
	plums (including prunes)	159	58	
	apricot	491	179	
	nectarine	789	335	
	peach	649	252	
FT	**tropical fruit (edible peel)**			
	carambola	0	743	
	grumichama (Brazillian cherry)	0	515	
	jaboticaba	0	515	
	olives	0	11	olives
	guava	0	674	
MM	**animal commodities**			
	mammalian offal	2	6	mammalian offal
	meat mammalian	3	2	meat mammalian
	milks	12	3	milks
	poultry offal	4	1	poultry offal
	poultry meat	2	1	poultry meat
	eggs	1	0	eggs
TN	**tree nuts**			
	macadamias	13	1	macadamias
	pecans	10	3	pecans
SO	**oilseeds**			
	sunflower seed	4	2	sunflower seed
	cotton seed	4	2	cotton seed
	linseed	4	2	linseed
VB	**brassica vegetables**			
	cabbage	2065	1539	
	broccoli	1045	334	
	Brussels sprouts	160	70	
	cauliflower	5542	2096	
VC	**cucurbit vegetables**			
	cucumber	306	109	
	pumpkin	138	45	
	zucchini	226	58	
	watermelon	1819	1853	
	cantaloupe (rock melon)	903	257	
VL	**leafy vegetables**			
	mizuna	1759	1115	
	chard	2757	1853	
	chervil	1759	1115	
	chinese cabbage	1759	2268	

	lettuce, head	825	372	
	lettuce, leaf	3106	1801	
	rucola (rocket)	1759	1115	
	spinach	1607	1633	
VO	**fruiting vegetables**			
	Eggplant	1407	1055	
	okra	284	167	
	capsicums	183	79	
	chilli peppers	600	73	
	sweetcorn (corn on the cob)	375	102	
	tomato	3641	1236	
	mushrooms	139	83	
VR	**root vegetables**			
	potato	18	7	potato
	carrot	123	25	
	turnip	32	18	turnip
	beetroot	12	11	beetroot
VP	**legume vegetables**			
	beans	203	84	
	peas	179	101	
VD	**pulse vegetables**			
VA	**bulb vegetables**			
	onions	120	56	
	leek	504	270	
VS	**stalk and stem vegetables**			
	celery	674	202	
	asparagus	149	122	
CF	**Cereals**			
	wheat bran, unprocessed	23	39	wheat bran, unprocessed

Of the crops and commodities for which there were sufficient residues data available to allow the establishment of an MRL, the NESTI calculation did not exceed the ARfD for the following:

- raspberries
- beetroot, potato, sugarbeet, turnips (Swede)
- pome fruit (fruit thinning use pattern only)
- macadamia nuts, pecan nuts
- cottonseed
- cereal grains
- animal commodities

The above calculations and discussion on acute dietary risk has highlighted that, with the exception of the commodities listed above, the use of registered products containing carbaryl in accordance with approved labels may present an acute dietary risk to consumers of treated produce.

All uses, except those listed above and any non-food uses (including crops destined for livestock consumption), must be removed from product labels.

9.11.2 Long term dietary exposure

Carbaryl has not been included in any of the Australia and New Zealand Food Authority (ANZFA) Market Basket Surveys or Total Diet Surveys of the last decade and so there is no information on actual dietary exposure. In such cases conservative models that overestimate chronic dietary intake are used to establish human safety. The model used for chronic dietary exposure to pesticides in Australia and recommended by the joint consultation of the WHO and FAO is the National Estimated Dietary Intake (NEDI) calculation. In this calculation use is made of survey results for agricultural commodities, processing factors for commodities such as washing, peeling or cooking, and median or maximum residues for "worst-case" in available residues trials.

Survey data for carbaryl residues in different commodities were obtained from the NRS and are tabulated in Table 32.

Table 32: Residue survey data for carbaryl in raw agricultural commodities (data for 1995-1999 except apples and pears which include data from 01/1/99-25/2/2000).

Commodity	Number samples tested	Number of detections	Comment on detection residue levels
Macadamia & pecan nuts	378	0	-
Barley	1317	52	32 <0.1 mg/kg, 20<1 mg/kg
Wheat bran	209	33	18 <0.1 mg/kg, 15 <4 mg/kg
Canola	254	15	15<0.1 mg/kg
Faba beans	2	0	-
Wheat flour	209	0	-
Lupins	346	2	1<0.1 mg/kg, 1<0.2 mg/kg
Oats	116	8	5<0.1 mg/kg, 3<1 mg/kg
Peas (inc field & chick peas)	212	3	3<0.3 mg/kg
Sorghum	642	40	33<0.1 ppm, 6<1 mg/kg, 1<5 mg/kg
Triticale	1	0	-
Wheat	5800	234	186<0.1 mg/kg, 45<1 mg/kg, 3<2.5 mg/kg
Apples	205	7	5<0.05 mg/kg, 2<1 mg/kg
Pears	8	0	-
Grapes	39	1	1<2.5 mg/kg
Stone fruit	20	2	2 <5 mg/kg
Tomato	20	0	-

The NEDI calculation was based on the uses for which there were sufficient residues data to establish an MRL and where use of registered products according to label directions would not result in short term dietary exposure exceeding the acute reference dose.

The chronic dietary exposure to carbaryl is calculated at approximately 4% of the acceptable daily intake. Since the NEDI calculation is less than the ADI it is concluded that the chronic or long term dietary exposure to carbaryl residues should not present an undue risk to the health of consumers of treated produce when registered products, containing the label amendments described above, are used as directed.

9.12 Non-food uses

Registered carbaryl products may be used in a variety of non-food (human or livestock) situations: as an insecticide in commercial, industrial and domestic areas, tobacco storage sheds and rights of way, in non-crop areas in general, ornamentals, lawns, elm trees (in non-crop areas), kenaf, Duboisia and rosella, and for disinfestation of grain storage buildings.

Table 5 of the *MRL Standard* refers to uses of substances where maximum residue limits are not necessary. Specifically, these include situations where residues do not or should not occur in foods or animal feeds; or where the residues are identical to or indistinguishable from natural food components; or are otherwise of no toxicological significance.

Table 5 *MRL Standard* entries are required for non-food use patterns appearing on all registered product labels. The following Table 5 *MRL Standard* entries are recommended:

Table 5 *MRL Standard* entries

Substance	Use
Carbaryl	• As an insecticide in non-crop areas including commercial, industrial and domestic areas, lawns, tobacco storage sheds and rights of way • As an insecticide on ornamentals and other non-food or animal feed crops and trees • For the disinfestation of grain storage buildings

9.13 Other considerations

In addition to uses on registered product labels, carbaryl may be used under permit in various situations including several in-crop uses. The APVMA's powers in relation to permits are covered by Part 7, Sections 108-119 of the AgVet Chemicals Code Act. Therefore, current carbaryl permits fall outside the scope of the review.

However, some uses permitted under current permits are covered by existing MRLs. Suitable MRLs must remain in place while the permit is current. The current MRLs which cover uses approved under permit, and which are recommended for deletion or amendment as part of this review, are as follows:

Table 1 *MRL Standard* entries

Code		Food	MRL (mg/kg)
FS	0240	Apricot	10
FT	0289	Carambola	5
GC	0080	Cereal grains	T5
FS	0013	Cherries	5
FI	0343	Litchi	5
FI	0342	Longan	5
FS	0245	Nectarine	10
FS	0247	Peach	10
FS	0014	Plums (including Prunes)	5
FB	0272	Raspberries	10
GS	0659	Sugar cane	T*0.05
TN	0085	Tree nuts	1
TN	0085	Tree nuts [whole in shell]	10
		Vegetables [except asparagus; fruiting vegetables, cucurbits; leafy vegetables; okra; potato; sweet corn (corn-on-the-cob)]	5

Table 4 *MRL Standard* entries

Code		Animal feed commodity	MRL (mg/kg)
AF	0080	Forage of cereal grains	T100
AS	0081	Straw and fodder (dry) of cereal grains	T100

An increase in the current raspberry MRL from 10 to 20 mg/kg was recommended as part of this review therefore the new MRL will cover residues occurring as a result of the permit use pattern. An increase in the cereal grain MRL from 5 to 15 mg/kg, and establishment of permanent entries for cereal forage, straw and fodder in Table 4 of the *MRL Standard*, were also recommended. These new MRLs will cover residues occurring in maize treated under the current permit.

Uses of carbaryl approved under permit should be considered before any changes are made to the MRLs for the commodities listed above.

9.13.1 Trade

Use patterns appearing on approved product labels of registered carbaryl products will not change as a result of this review. As a consequence, the situation with regards to residues-in-trade issues is unchanged from the present situation.

9.14 References

Andrawes, N.R., Chancey, E.L., Crabtree, R.J., Herrett, R.A. and Weiden, M.H.J, Fate of Napthyl-1-^{14}C-Carbaryl in Laying Chickens, *J. Agr. Food Chem.*, **20**, 608-617, 1972.

Bowles, P. and Hamilton, D., Information gathered on unit weights of individual fruit and vegetable commodities, Queensland Government, Department of Primary Industries, 31 January 2001.

Claborn, H.V., Roberts, R.H., Mann, H.D., Bowman, H.C., Ivey, M.C., Weidenbach, C.P., Radeleff, R.D., Residues in body tissues of livestock sprayed with Sevin or Sevin in the diet, *J. Agr. Food Chem.* **11**, 74-76, 1963; JMPR 1966. Residues of carbaryl in pig tissues resulting from direct treatment at the maximum Australian rate of 0.5% are expected to be <LOD.

Gyearisco, G.C., Lisk, D.J., Fertig, S.N., Huddleston, E.W., Fox, F.H., Holland, R.F., Trimberger, G.W., The effects of feeding high levels of Sevin on residue, flavour and odour of the milk of dairy cattle, *J. Agric. Food Chem.* **8**, 409-410, 1960; also JMPR 1968
J. Agr. Food Chem. **11**, 74-76, 1963; JMPR 1966.

JMPR 1973; Dorough , H.W., Paper presented at the International Symposium on Pesticide Terminal Residues, Tel Aviv, Israel 17-19 February 1971

National Nutrition Survey 1995 carried out by Food Standards Australia New Zealand (formerly the Australia New Zealand Food Authority).

Snelson, J.T., Grain Protectants, ACIAR Monograph No. 3, Canberra 1987

Appendix 1:

List of products and associated label approvals, considered as part of the reconsideration of carbaryl

Product Number	Product Name	Registrant	Label approval Numbers
31995	CRG Liquid Carbaryl Insect Spray	Chemical Recovery Co Pty Ltd	31995/0798
31997	Chemspray Carbaryl Insecticide	Envirogreen Pty Ltd	31997/0802
32000	Defender Home Garden Grasshopper Caterpillar Carbaryl Insecticide	Scotts Australia Pty Ltd	?
32002	Yates Carbaryl Caterpillar & Grasshopper Insect Spray	Arthur Yates & Co Limited	32002/0202 32002/0301 32002/0498 32002/1001
32009	Nufarm Flowable Carbaryl 500 Insecticide	Nufarm Australia Limited	32009/0300 32009/0801 32009/0902
33194	Hortico Carbaryl Cabbage Dust	Orica Australia Pty Ltd	?
33575	Fido's Fre-Itch Flea Shampoo For Cats And Dogs	Mavlab Pty Ltd	33575/1002 33575/1200
33576	Saint Bernard Flea Powder For Dogs And Cats	Saint Bernard Pet Care Pty Ltd	33576/01 33576/0402 33576/0801
33957	Hortico Carbaryl Tomato Dust	Orica Australia Pty Ltd	?
36387	Watch Cat Flea Powder For Cats	Go-Pet Petcare Solutions A Div Of Nestle Australia Ltd	36387/0299 36387/1198
36388	Watch Dog Flea Powder For Dogs	Go-Pet Petcare Solutions A Div Of Nestle Australia Ltd	36388/0299 36388/1198
37434	Fido's Fre-Itch CPP Flea Powder For Cats And Dogs	Mavlab Pty Ltd	37434/0101
39082	Hortico Hose-On Lawn Grub Killer	Orica Australia Pty Ltd	39082/0700
39864	Yates Lanosan Tomato Spray Insecticide And Fungicide	Arthur Yates & Co Limited	39864/0500 39864/0598
39876	Yates Garden Spray Insecticide Fungicide	Arthur Yates & Co Limited	39876/0998
39879	Yates Carbaryl Cabbage Dust	Arthur Yates & Co Limited	39879/0802
39998	Fido's Ear Drops	Mavlab Pty Ltd	39998/0101
40080	Fido's Fre-Itch Flea Powder For Cats And Dogs	Mavlab Pty Ltd	40080/0402
40143	Joseph Lyddy G-Wizz Insecticidal Dry Shampoo For Horses And Ponies	Waproo Pty Ltd	40143/0500
40145	Joseph Lyddy Y-Itch Animal Insecticide Bactericide	Waproo Pty Ltd	?
40146	Bugmaster Flowable Insecticide	Bayer Cropscience Pty Ltd	40146/01 40146/02 40146/0500 40146/1197 40146/4535
40754	Defender Home Garden European Wasp & Garden Insect Dust	Scotts Australia Pty Ltd	?
41244	David Skatta-7 Tick Flea Louse Powder	Bocko P/L & Trademarketing Solutions P/L T/A Pharmachem	41244/0901
41250	Vetapet Coalfoam Medicated Foam With Ectoparasitic Control For Dogs And Cats	Bocko P/L & Trademarketing Solutions P/L T/As Pharmachem	41250/1101
42029	David Grays Flower Dust	David Gray & Co. Pty Limited	42029/0702
42041	David Grays Rose Dust	David Gray & Co. Pty Limited	42041/02
42054	David Grays Tomato Dust	David Gray & Co. Pty Limited	42054/02
42055	David Grays Vegetable Dust	David Gray & Co. Pty Limited	42055/02

Product Number	Product Name	Registrant	Label approval Numbers
42261	David Grays Cricket & Grasshopper Killer Bait	David Gray & Co. Pty Limited	42261/1202
45944	Garden King Multipest S-C-C General Purpose Insecticide-Fungicide-Miticide	Envirogreen Pty Ltd	?
46303	Masterpet Flea Powder For All Dogs And Cats 100gm	Masterpet Australia Pty Limited	46303/001
46851	Keydust Dusting Powder	International Animal Health Products Pty Ltd	46851/0100
47108	Chemspray Carbaryl Flowable Insecticide	Envirogreen Pty Ltd	47108/0599 47108/0998 47108/3260
47855	I Love My Pet Flea Powder For Cats And Dogs	My Pet Products Australia Pty Ltd	47855/01
47966	I Love My Pet Ear Drops Ear Cleaner & Treatment For Cats And Dogs	My Pet Products Australia Pty Ltd	47966/01
48753	Tomato Dust Insecticide & Fungicide	Crop Care Australasia Pty Ltd	48753/01
49133	Defender Trouble Shooter Tomato Spray	Scotts Australia Pty Ltd	49133/01
49325	Kendon Carbaryl Liquid Insecticide	Kendon Chemicals & Mnfg Co Pty Ltd	49325/0400 49325/1098
49326	Kendon Carbaryl Wettable Powder Insecticide	Kendon Chemicals & Mnfg Co Pty Ltd	49326/0400 49326/1098
49870	Defender Tomato Doctor Insecticide/Fungicide	Scotts Australia Pty Ltd	49870/01
49937	Garden King Carbaryl Liquid Insecticide	Envirogreen Pty Ltd	49937/0802 49937/1097
50102	Friskies Kill Flea Carpet Deodoriser	Go-Pet Petcare Solutions A Div Of Nestle Australia Ltd	50102/0798
50664	I Love My Pet Flea Rid Powder For Cats & Dogs	My Pet Products Australia Pty Ltd	50664/0598
50741	I Love My Pet Flea Rid Shampoo For Dogs & Cats	My Pet Products Australia Pty Ltd	50741/0598
51206	Family Pets Flea & Tick Pet Grooming Powder For Dogs, Cats, Puppies And Kittens	Aristopet Pty Ltd T/As Family Companion Pet Products	51206/0998
51625	Richgro Garden Products Ready To Use Pest-Stop Tomato	A Richards Pty Ltd T/A Richgro Garden Products	51625/0499
52213	David Grays Carbaryl 500 Flowable Insecticide	David Gray & Co. Pty Limited	52213/0100
52472	Garden King Tomato & Vegetable Dust Insecticide & Fungicide	Envirogreen Pty Ltd	52472/0100 52472/0702
52493	Richgro Garden Products Carbaryl Caterpillar & Grasshopper Insecticide	A Richards Pty Ltd T/A Richgro Garden Products	52493/0300
53231	Hortico Cabbage Dust	Orica Australia Pty Ltd	53231/0700
53260	Hortico Tomato Dust	Orica Australia Pty Ltd	53260/0700
53912	Yates Ready To Use Tomato Gun Pest & Disease Spray	Arthur Yates & Co Limited	53912/0702
54634	Richgro Garden Products Armyworms, Cockchafers & Lawn Grub Killer	A Richards Pty Ltd T/A Richgro Garden Products	54634/0402
54949	David Grays Carbaryl Liquid Insecticide	David Gray & Co. Pty Limited	54949/0102
57952*	Go-Pet Kill Flea Carpet Deodoriser	Go-Pet Petcare Solutions, a div of Nestle Australia ltd	57952/0903
58127*	Yates Insect & Disease Control Blitzem Tomato Gun	Orica Australia Pty Ltd	58127/0903
58135*	Yates Insect & Disease Control Blitzem Tomato Dust	Orica Australia Pty Ltd	58135/0903

? Labels transitioned from the states and not having and approval number.

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

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

Appendix 2

TOXICOLOGY HAZARD PROFILE

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption	Oral absorption is rapid and extensive in humans, rodents and other species. Dermal absorption from aqueous media is slow and saturable in rodents but enhanced in the presence of organic solvents. Pulmonary absorption is rapid.
Distribution	Small amounts in carcass, kidney and liver.
Potential for accumulation	Very low.
Rate and extent of excretion	Rapid, extensive, predominantly via urine in all species except dog.
Metabolism	Rapid. Proceeds via hydrolysis, alkyl oxidation, arene oxide formation, epoxide hydrolysis and glutathione conjugation. Pathways similar in humans, rodents and other species investigated.
Toxicologically significant compounds (animals, plants and environment)	Reactive epoxide intermediates may be formed in mice and rats.

Acute toxicity

Rat oral LD_{50} (mg/kg bw)	246
Worst oral LD_{50} in other species	150 mg/kg bw in cats
Rat dermal LD_{50} (mg/kg bw)	No data
Worst dermal LD_{50} in other species	>2000 mg/kg bw in rabbits
Rat inhalation LC_{50} (mg/m^3)	2500 (4h) as aerosol
Worst inhalation LC_{50} in other species	No data
Skin irritation	Classified as slight in rabbits
Eye irritation	Classified as not irritating in rabbits
Skin sensitization	None in guinea pigs

Metabolites of carbaryl

Rat oral LD_{50} (mg/kg bw)	
4-hydroxycarbaryl	1190
5-hydroxycarbaryl	297
7-hydroxycarbaryl	4760
hydroxymethylcarbaryl	>5000
1-naphthol	2570

Short-term toxicity

Target/critical effect	ChE depression, cholinergic symptoms
Lowest relevant oral NOEL (mg/kg bw/d)	1 in rats (13-wk neurotoxicity study by gavage)
Lowest relevant dermal NOEL (mg/kg bw/d)	No data
Lowest relevant inhalation NOEC (mg/m^3)	10 in rats (90-d study, highest dose tested)

Genotoxicity	Clastogenic *in vitro* but not *in vivo.* Interrupts spindle formation *in vitro*. Overall weight of evidence lies against mutagenicity or genotoxic activity by other mechanisms.

Long-term toxicity and carcinogenicity

Target/critical effect	Kidney: cloudy swelling of tubules
Lowest relevant NOEL (mg/kg bw/d)	1.8 in 1-yr dog study by gavage
Carcinogenicity	Vascular tumours in male mice in a 2-yr dietary study at 16 mg/kg bw/d, the lowest dose tested. At the highest dose (1350 mg/kg bw/d), there was also development of renal adenoma and carcinoma in males, while hepatic adenoma and carcinoma became elevated in females. At the high dose of 420 mg/kg bw/d in a 2-yr rat dietary study, there was treatment-related formation of urinary bladder papilloma/carcinoma in both sexes, renal carcinoma and thyroid adenoma/carcinoma in males, and hepatic adenoma in females.

Reproductive toxicity

Reproduction target/critical effect	Decreased parental bw gain, bw, feed consumption and conversion efficiency, depressed gestation and lactation bw in rat dams, and increased pup mortality.
Lowest relevant reproductive NOEL (mg/kg bw/d)	4.7 in rats

Developmental target/critical effect	Skeletal and visceral abnormalities in dogs at and above 6.3 mg/kg bw/d in the absence of maternal toxicity.
Lowest relevant developmental NOEL (mg/kg bw/d)	3.1 in dogs
Delayed neurotoxicity	No effects
Immunotoxicity	No data
Dermal absorption	In rat: Up to 2% of applied dose over 30 min, rising to a maximum of 25% at 24 h. Results obtained with formulated product applied in aqueous CMC vehicle. In humans: Up to 4.4% over 4 h and16% over 8 h, applied in acetone vehicle.

Summary

NOEL (mg/kg bw/d)	Study	Safety factor
16 mg/kg bw/d*	2-yr dietary study in mice	2000[#]
1 mg/kg bw/d	13-wk neurotoxicity and developmental neurotoxicity studies by gavage in rats	100

ADI 0.008 mg/kg bw/d, based on vascular tumour formation.
Acute RfD 0.01 mg/kg bw based on ChE inhibition, clinical signs, and reduced bw gain.

*LOEL value.
[#]The safety factor incorporates a 10-fold component for interspecies extrapolation, a 10-fold component for intraspecies variability, a 5-fold component for adequacy of the database, and a 4-fold component for seriousness of the carcinogenic response. (This 4-fold component is comprised of a 1-fold factor [low degree of confidence that carbaryl is genotoxic], a 4-factor [medium degree of confidence that carbaryl causes malignant tumours] and a further 1-fold factor [metastases not reported]).

Health Value in drinking water	Current: 0.03 mg/L