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For Agricultural & Veterinary Chemicals

MALDISON (MALATHION)

REVIEW SCOPE DOCUMENT

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Review Scope Document
Maldison (Malathion)

SUMMARY

Note: In this document, maldison may be read as malathion.

The NRA has initiated the reconsideration of the approvals of the active constituent maldison, registration of products containing maldison and the approval of associated labels. The purpose of this scope document is to define the scope of the matters of concern to the NRA and to outline the data necessary for the NRA to conduct a comprehensive scientific assessment of maldison.

Approvals of the active constituent maldison are being reconsidered because of concerns that the presence of certain impurities (specified in the minimum compositional standard – MCS) may be harmful to human beings.

Registrations of products containing maldison are being reconsidered because of concerns that the handling and use of maldison might be an undue hazard to the safety of workers.

All associated label approvals are being reconsidered because of concerns that label instructions may be inadequate.

The reconsiderations will be made after the NRA has assessed all the data and other information provided to it for this purpose – the assessment process is hereafter referred to as 'review'.

It is anticipated that a draft report of the NRA's review of maldison will be available for public comment in late 2004.

The NRA's review will examine the following matters:

- Toxicological effects primarily related to the four impurities specified in the minimum compositional standard (MCS) for maldison active constituent.
- Toxicological effects associated with products containing maldison. In particular, the potential for formation of toxic impurities during product storage.
- Occupational health and safety issues including:
  - Risk to workers mixing, loading and applying maldison;
  - Risk to worker on re-entry to treated areas; and
  - Adequacy and suitability of personal protective equipment (PPE) and specified re-entry intervals.
- Adequacy of instructions and warnings on product labels.

1. INTRODUCTION

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

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

The NRA has decided to reconsider all approvals of the active constituent maldison, all registrations of products containing maldison and all approvals of associated labels on the basis of concerns over both public and worker safety and the adequacy of label instructions and warnings.

Although the active constituent is known elsewhere in the world as malathion (Approved ISO common name), the Standards Australia approved name is maldison.

2. NOMINATION OF THE CHEMICAL

Maldison is an organophosphorus insecticide used to control a wide range of insect pests of agricultural crops and animals. It is also used for outdoor home use. It is a broad-spectrum, non-systemic insecticide and acaricide with contact, stomach and respiratory action.

Reasons why maldison was considered a priority for review include:

- Concern over public safety when used in fruit fly eradication programs in urban areas;
- Concerns over the adequacy of occupational health and safety assessment for products;
- Inconsistencies with safety directions on maldison product labels; and
- Concerns over re-entry intervals for workers, as identified in the assessment by relevant regulatory authorities in the USA.

The details of the concerns that have been raised can be found in Sections 5, 6 and 7 of this document.

3. SCOPE OF THE REVIEW

Taking into consideration the reasons for nomination of maldison, the information already available on this chemical and the way in which it is used in Australia, the scope of the review has been defined.

The NRA will review the following matters relevant to active constituent approvals, product registrations and label approvals for maldison (as appropriate):

- Toxicological effects primarily related to the four impurities specified in the minimum compositional standard (MCS) for maldison active constituent.
- Toxicological effects associated with products containing maldison. In particular, the potential for formation of impurities during product storage.
- Occupational health and safety issues including:
    - Risk to workers mixing, loading and applying maldison;
    - Risk to workers on re-entry to treated areas; and
    - Adequacy and suitability of PPE and specified re-entry intervals.
- Appropriateness or adequacy of label information.

Registrants and approval holders will be required to undertake certain actions aimed at securing relevant data that might address these matters. However, the public is invited to make submissions to the review regarding any of the matters raised in this scope document (see Section 8).

4. REGULATORY STATUS AND USE PATTERNS OF MALDISON IN AUSTRALIA

4.1 Products

As at January 2003 there were two (2) approvals of maldison active constituents and forty four (44) registered products containing the active constituent maldison, with 24 registrants. A range of different formulation types exists: emulsifiable concentrates, baits, aerosols, oil in water emulsions, ultra low volume (ULV), dusts, solids, shampoos and other topical solutions.

4.2 Current use patterns

Maldison is a non-systemic wide spectrum organophosphorus (OP) insecticide. Products containing maldison include agricultural or veterinary products intended for use either in commercial or domestic situations, or in some cases both. It is also used in public health applications such as the control of mosquitoes, and is frequently used in fruit fly eradication programs in urban areas.

Registered uses

Various combinations of the following hosts and pests are indicated on currently approved labels.

Hosts: aquatic areas, flowers, fruit, vegetables, trees/forests, stored cereals, oil seed crops, ornamentals, lucerne/pasture, citrus, fruit trees, roses, grapevines, animal housing, industrial and home garden situations, non-crop and recreation areas, tobacco and on and a variety of animals including dogs, cats, rabbits, birds (including poultry), mice, pigs, horses and cattle.

Pests: aphids, beetles, borers, bugs, flies, grasshoppers, jassids, leafhoppers, locusts, thrips, weevils, worms, fleas, lice, midges, ticks, scale insects, caterpillars, sucking insects, Rutherglen bug, green vegetable bug, cabbage moth, loopers, leaf rust, powdery mildew, black spot, mealy bug, fruit fly and mange.

5. TOXICOLOGICAL ISSUES

Maldison is considered to be one of the least toxic of all the organophosphorus compounds with the oral median lethal dose (LD_{50}) being in the range of 10,700 to 12,500 mg/kg bw. This lower toxicity, relative to other organophosphorus compounds, is possibly related to its relative inefficiency in inhibiting the function of an important enzyme known as acetylcholinesterase (AChE). AChE is the enzyme primarily responsible for terminating the transmission of nerve impulses in the autonomic (involuntary) nervous system and at neuromuscular junctions.

Impurities of maldison

The toxic impurities of maldison include iso-malathion, malaoxon, and various trialkyl phosphorothioates such as O,S,S–trimethylphosphorodithioate and O,O,S–trimethylphosphorothioate. These impurities have been detected in various sources of technical maldison and may arise as impurities during the manufacturing process or may be formed on prolonged storage or storage at elevated temperatures. In the case of iso-malathion, this impurity is known to occur at high concentrations after storage of maldison products under extreme conditions. It is a direct inhibitor of maldison metabolism (by blocking the action of carboxylesterase) resulting in the prevention of maldison detoxification (TGA 2001). O,S,S–trimethylphosphorodithioate and O,O,S–trimethylphosphorothioate could contribute to the acute toxicity of maldison if present in sufficient amounts, since they appear to be slightly more acutely toxic than iso-malathion (TGA 2001).

The safety, efficacy and environmental impact of agricultural and veterinary products can be significantly dependent on the composition of the active constituent. The Minimum Compositional Standard (NRA 2002) specifies the minium purity for the active constituent (including relative amounts of isomers where relevant) and the maximum allowable levels of impurities of toxicological concern.

Table 1: Maximum impurity limits – maldison

	MCS (g/kg)	Oral LD_{50} – rat (mg/kg bw)*
maldison	940	10,700-12,500
iso-malathion	2	113
malaoxon	1	158
O,O,S – trimethylphosphorothioate	5	60
O,S,S – trimethylphosphorodithioate	0.1	27

* milligrams per kilogram bodyweight

While these impurity limits exist, ongoing quality assurance concerns warrant a review of these limits. This issue has also been of concern to many members of the public especially in the light of the numerous reports that are readily available on the internet and question the public safety of maldison when used in fruit fly eradication programs in urban areas.

In 1978 a report (Baker *et. al* (1978)) indicated that of 7,500 men spraying a maldison formulation in Pakistan, 2,800 were poisoned and 5 died. An investigation into the cause of these deaths implicated a toxic degradate, isomalathion, as the likely causative agent. Several subsequent studies reported in peer-reviewed journals have also investigated the chemistry surrounding the instability of maldison and identified other very toxic degradates, such as O,S,S–trimethylphosphorodithioate and O,O,S–trimethylphosphorothioate.

Previous reviews in the late 1980s and early 1990s indicated that maldison is not teratogenic, mutagenic or carcinogenic. However, maldison is considered a priority for review on the basis of the toxicity of its impurities, metabolites and degradates and the potential implications of these on human health. Since much of the existing information regarding the toxicity of maldison was derived from studies performed some time ago it is considered that many of these studies, which currently support existing health standards, are likely to have been replaced by contemporary Good Laboratory Practice and Test Guideline studies. The reviews completed by the JMPR in 1997 and the US EPA in 2000 confirm that there are at

least 30 new toxicological studies which have not been reviewed by Australian authorities. There is also a considerable amount of information on the internet that highlights the hazard of impure maldison that will be considered.

It is possible that a review of these new data will suggest regulatory actions beyond the reconsideration of approvals and registrations, such as:

- determining whether the Acceptable Daily Intake (ADI) remains appropriate;
- establishing an acute reference dose (ARfD); and
- determining whether the drinking water standard remains appropriate.

6. OCCUPATIONAL HEALTH AND SAFETY ISSUES

The adequacy and suitability of the PPE and the specified re-entry intervals to ensure worker safety have not been subject to evaluation within the current regulatory framework, as noted above.

There is some evidence of label inconsistencies. There is also no entry in the First Aid Instructions and Safety Directions Handbook for the product at the highest maldison concentration (*i.e.,* 1180 g/L). No Australian labels appear to contain re-entry statements or advice.

The recent release of the US EPA re-registration eligibility decision for maldison identifies concerns for workers who mix, load and apply maldison. This assessment also points to concerns over potential worker exposure when re-entering treated areas.

7. INTERNATIONAL REGULATORY STATUS OF PRODUCTS CONTAINING MALDISON

Maldison is registered in Europe (including Finland, Denmark, Ireland, UK and Netherlands), New Zealand and the USA. It has been reviewed by Joint FAO/WHO Meeting of Experts in Pesticide Residue (JMPR), and is currently under review by the European Union. Maldison is also for the subject of a US EPA Re-registration Eligibility Decision (Nov 2000).

Maldison has been reviewed by the Joint FAO/WHO Meeting of Experts in Pesticide Residues (JMPR) in 1963, 1965, 1966, and 1997 for toxicology and in 1966, 1967, 1968, 1969, 1970, 1973, 1975, 1977, 1984, 1999, and 2000 for residues. In its 1963 toxicology evaluation, the JMPR established an ADI of 0.02 mg/kg bw/day but this was increased to 0.3 mg/kg bw/day at the 1997 meeting. The revised ADI was based on a No Observable Adverse Effect Level (NOAEL) of 29 mg/kg bw/day for reduced survival and bodyweight gain, changes in haematological parameters, inhibition of brain cholinesterase activity, increased liver, kidney and thyroid/parathyroid weights, and changes in olfactory epithelium in a 2-year rat study, and a safety factor of 100. The JMPR will consider establishing an Acute Reference Dose (ARfD) for malathion in 2003.

In its recent Re-registration Eligibility Decision (Nov 2000) the US EPA did not have major concerns with dietary exposure or exposure from drinking water. Some concerns about the use of maldison in the home garden and the potential for exposure as well as re-entry exposure into areas following maldison treatment were noted. The impurities of maldison

were also examined. Data evaluated indicated that potential impurities and degradates of maldison were present at levels which did not pose a concern for human health.

8. NEXT STAGES IN THE REVIEW

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

Interested parties are invited to provide data or information addressing the deficiencies in Section 3.1 (note that approval holders and registrants are obliged to submit specific information). These must reach the NRA by no later than **3 June 2003**. Submissions can be sent either by email to chemrev@nra.gov.au or by mail to:

Manager, Pesticides Review
National Registration Authority
P.O. Box E240
KINGSTON ACT 2604
Telephone: (02) 6272 3213
Facsimile: (02) 6272 3218

8.1 Announcement of the review

The availability of the review scope document coincides with the NRA's formal announcement of the review. Registrants will be formally advised of their responsibilities as part of this review.

8.2 Data assessment

The technical assessment of data submitted for the review of maldison will be conducted by the Therapeutic Goods Administration (TGA) and the National Occupational Health and Safety Commission (NOHSC). These agencies will advise the NRA about the concerns identified in sections 5, 6 and 7.

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

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

8.3 Consultation throughout review process

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

The draft of the review summary along with proposed recommendations will be made available to the stakeholders and public through the NRA website or direct communication. A period of at least 8 weeks will be given for these groups to comment on the draft report.

The availability of both draft and final reports will be announced extensively through the media. Major stakeholders will be approached directly and all reports will be made available on the NRA website.

Appendix 1: References

- Baker E et al., (1978). Epidemic malathion poisoning in Pakistan malaria workers. *Lancet , 1(8054), 31-34.*

- Therapeutic Goods Administration (TGA) (2001). A Review of the Regulation of Head Lice Treatments in Australia. Draft for comment July 2001. Prepared for the TGA by Dr Susan James.

Appendix 2: Active constituent approvals

Approval No.	Approval holder
44350	Cheminova Australia Pty Limited
46160	Gulmohar Pty Ltd

Appendix 3: Registered products containing maldison

Product No.	Product Name	Registrant
50333	Richgro Garden Products Malathion Insecticide	A Richards Pty Ltd T/A Richgro Garden Products
48960	Richgro Garden Products Maldison Plus Insecticide	A Richards Pty Ltd T/A Richgro Garden Products
53266	Yates Aphid & Bug Control Malathion Concentrate	Arthur Yates & Co Limited
40773	Yates Malathion Insecticide	Arthur Yates & Co Limited
35775	Richter Otitis Drops For Dogs	Ausrichter Pty Ltd
33530	E-Z-Licer Poultry Insecticide	Barry Mayer T/A Innovative Ideas
40067	Showcote Insecticidal Mala Powder	Basset (Aust) Pty Ltd
54285	Bob Martin Vetcare Malawash Insecticidal Wash	Bob Martin (Australia) Pty Ltd
33021	Pharmachemical Maldison 50 Insecticide	Bocko P/L & Trademarketing Solutions P/L T/A Pharmachem
41821	Dak Pot Lure & Insecticide Trap C165	Cedric Leathbridge T/A Bilpin Springs Orchard
41823	Q-Fly Lure & Insecticide Block	Cedric Leathbridge T/A Bilpin Springs Orchard
42657	Dak Pot Lure And Insecticide	Cedric Leathbridge T/A Bilpin Springs Orchard
41068	CRG Malathion 50% Concentrate	Chemical Recovery Co Pty Ltd
47088	CRG Malathion 500 EC Insecticide	Chemical Recovery Co Pty Ltd
49538	Fyfanon 500 EC Insecticide	Cheminova Australia Pty Limited
51150	Fyfanon 440 EW Insecticide	Cheminova Australia Pty Limited
49539	Fyfanon ULV Insecticide	Cheminova Australia Pty Limited
48992	Hy-Mal Insecticide	Crop Care Australasia Pty Ltd
50110	David Grays Malathion Grain Dust Insecticide	David Gray & Co. Pty Limited
42029	David Grays Flower Dust	David Gray & Co. Pty Limited
42041	David Grays Rose Dust	David Gray & Co. Pty Limited
42036	David Grays Malathion And White Oil	David Gray & Co. Pty Limited
42035	David Grays Malathion Garden Spray	David Gray & Co. Pty Limited
42267	David Grays Poultry Dust	David Gray & Co. Pty Limited
42289	Malathion ULV	David Gray & Co. Pty Limited
32634	Chemspray Antiscale Insecticide	Envirogreen Pty Ltd
45950	Garden King Malathion Garden Insecticide	Envirogreen Pty Ltd

Product No.	Product Name	Registrant
33006	Chemspray Malathon Insecticide	Envirogreen Pty Ltd
46042	Farmoz Maldison 500 Agricultural Insecticide	Farmoz Pty Limited
52983	Hortico Aphid Control Malathion 500 Concentrate Insecticide	Hortico (Aust) Pty Ltd
33011	Hortico Malascale Insecticide	Hortico (Aust) Pty Ltd
33013	Hortico Malathion 50 Bug-Aphis Insecticide	Hortico (Aust) Pty Ltd
37201	Inca Malaban Wash Concentrate	Inca (Flight) Company Pty Ltd
42727	Q Fly Wick	Integrated Pest Management Pty Ltd
46851	Keydust Dusting Powder	International Animal Health Products Pty Ltd
50589	Searles Fruit Fly Wick Attractant And Insecticide	J C And A T Searle Pty Ltd
46368	Di-Flea Flea And Tick Rinse And Yard Spray	Jurox Pty Limited
33018	Nufarm Maldison 500 Insecticide	Nufarm Australia Limited
33019	Nufarm Maldison ULV Insecticide	Nufarm Australia Limited
46883	RWPS Malabath Insecticidal Wash For Dogs, Cats & Birds	Rudducks Pty Ltd
40179	Pets Paradise Malabath Insecticidal Wash For Dogs, Cats & Birds	Rudducks Pty Ltd
32635	Defender Home Garden Scale Plus Insect Spray Insecticide	Scotts Australia Pty Ltd
38644	Troy Malatroy Insecticidal Wash For Dogs, Cats And Birds	Troy Laboratories Pty Ltd
46501	CPV Malarid Insecticidal Wash For Dogs, Cats And Ornamental Caged Birds	Universal Manufacturing & Laboratories Pty Ltd