Australian Pesticides &
Veterinary Medicines Authority

The Reconsideration of Approvals and Registrations Relating to Molinate

REVIEW SCOPE DOCUMENT

MAY 2003

Australian Pesticides &
Veterinary Medicines Authority

Canberra
Australia

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

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Review Scope Document
Molinate

FOREWORD

The APVMA is the National Registration Authority for Agricultural and Veterinary Chemicals. For information regarding the APVMA, please visit www.apvma.gov.au.

SUMMARY

The APVMA has initiated its reconsideration of the approvals of the active constituent molinate, the registrations of products containing molinate and the approvals of associated labels. This document defines the scope of the matters of concern to the APVMA, outlines the kind of information the APVMA requires to conduct a comprehensive scientific assessment of molinate and invites submissions from the public.

Approvals of the active constituent molinate are being reconsidered because of toxicological concerns. Products containing molinate and all associated labels are being reviewed because of toxicological, environmental and occupational health and safety concerns.

The reconsiderations will be made after the APVMA assesses 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 APVMA's review will be available for public comment early-2005.

The APVMA will review the following aspects of active constituent approvals, product registrations and label approvals for molinate:

- Toxicology, including:
    - the potential for impaired fertility and neuropathy in humans which might pose an undue hazard to human health; and
    - potential for toxicological exposure to humans via the oral, dermal and inhalation routes.

- Environmental, including:
    - the potential for contamination of waterways indicated by varying levels of molinate recorded in drainage water from rice fields; and
    - potential hazard to non-target fauna and flora

- Occupational Health and Safety, including:
    - possible risks to workers health associated with short and intermediate term occupational exposure; and
    - the potential for hazards to worker safety

- The adequacy of instructions and warnings on product labels.

A decision on the reconsideration will be made after the APVMA has reviewed all the data and other information provided to it for this purpose

1 INTRODUCTION

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

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

The APVMA has decided to reconsider the approvals of the active constituent molinate, the registrations of products containing molinate and the approvals of associated labels, based on concerns related to toxicology, environment and occupational health and safety.

2 REASONS FOR REVIEW

Molinate (ethyl N, N'-hexamethylenethiolocarbamate) is a post-emergent, systemic thiocarbamate herbicide used exclusively in rice growing for the control of barnyard grasses (*Echinochloa* spp.) and silver top or brown beetle grass (*Diplachne fusca*).

Molinate was originally nominated for review following to concerns identified in the recent assessment conducted by the US EPA as a part of its re-registration process, particularly those results suggesting that at low dose levels molinate could impair fertility and cause neuropathy in experimental animals. The details of the concerns that have been raised can be found in Sections 5 -7 of this report.

3 SCOPE OF THE REVIEW

The scope of the review has been defined taking into consideration the reasons for the nomination of molinate, 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:

- Therapeutic Goods Administration (TGA), Office of Chemical Safety, as detailed in Section 5;
- Environment Australia (EA) as detailed in Section 6; and
- National Occupational Health and Safety Commission (NOHSC) as detailed in Section 7

it appears that the APVMA might not be able to maintain its satisfaction that continued approvals of the active constituent molinate and registration of products containing molinate:

- would not be an undue hazard to the safety of people exposed to it during its handling; and/or
- would not be likely to have an effect that is harmful to human beings; and /or
- would not be likely have an unintended effect that is harmful to animals, plants or things or to the environment.

It also appears that the APVMA might not be able to maintain its satisfaction that labels for products containing molinate contain adequate instructions.

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

The APVMA will therefore review the following aspects of active constituent approvals, product registrations and label approvals for molinate:

- Toxicology, including:
    - the potential for impaired fertility and neuropathy in humans which might pose an undue hazard to human health; and
    - potential for toxicological exposure to humans via the oral, dermal and inhalation routes.

- Environmental, including:
    - the potential for contamination of waterways indicated by varying levels of molinate recorded in drainage water from rice fields; and
    - potential hazard to non-target fauna and flora

- Occupational health and safety, including:
    - possible risks to workers health associated with short and intermediate term occupational exposure; and
    - the potential for hazards to worker safety

- The adequacy of instructions and warnings on product labels

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

4 REGULATORY STATUS AND USE PATTERNS OF MOLINATE IN AUSTRALIA

4.1 Active Constituent and Products

At the commencement of the review, there were four (4) approvals of molinate active constituent and one (1) manufacturing concentrate (Attachment 1, Table 1) and four (4) registered products containing the active constituent molinate with four (4) registrants (Attachment 1, Table 2). All four products are emulsifiable concentrates (EC) with a molinate concentration of 960 g/L. The products are registered in New South Wales and Victoria only. These active constituent approvals and product registrations are subject to this review. It should be noted that any active constituent approvals and product registrations that occur after the commencement of the review would be made subject to the outcomes of the review.

4.2 Current use patterns

Products containing molinate are used exclusively for the control of barnyard and silver top or brown beetle grasses during rice production. Molinate acts through inhibition of mitosis. Rice production in Australia is limited to parts of southern New South Wales and Northern Victoria within the Murrumbidgee and Coleambally Irrigation areas (MIA and CIA, respectively) and the Murray Valley. In the MIA during the 1999/2000 growing season molinate was the most widely used herbicide with 81 000 kg of molinate active constituent applied. Molinate is applied early in the rice-growing season, between October and December. A range of application methods are used including, direct feeding to the rice paddy water (the Soluble Chemical Water Injection in Rice Technique, or SCWIIRT) from a

tractor, 4WD farm bike and more commonly by aircraft using a continuous stream application boom (the Bickley boom).

Application of molinate can be to either aerially sown (flooded rice bays) or to sod/combine sown rice (commonly dry rice bays). The most common label rate of application of molinate is 3.75 L product (3.6 kg active) per hectare for the 1-4 leaf stage.

5 TOXICOLOGICAL ISSUES

The TGA raised concerns relating to the outcomes of the United States Environmental Protection Agency (US EPA) assessment of mammalian toxicity and metabolism of molinate[1]. The principal findings of the US EPA assessment of molinate[2] were that at low doses, molinate could cause neuropathy and impaired fertility in experimental animals.

The TGA observed that, according to the US EPA, neurotoxicity occurred at the lowest doses administered in several repeat-dose and chronic-exposure studies. TGA also noted that a No Observed Effect Level (NOEL) for injury to the nervous system has not been demonstrated. Further concerns included the low airborne concentration at which molinate impaired fertility in male rats and the findings that molinate is extensively absorbed across the skin.

In the studies assessed by the US EPA, acute and delayed neurotoxicity was seen in mice, rats, dogs and hens. In a rat 90-day neurotoxicity study, inhibition of neuropathy target esterase and brain cholinesterase (ChE) was observed at all doses, while in the rat developmental neurotoxicity study, startle response inhibition and reduced brain size was observed in pups at all doses.

The Pesticides and Agricultural Chemicals Committee (PACC), the forerunner of the current Advisory Committee on Pesticides and Health (ACPH) considered molinate on a number of occasions, between November 1980 and November 1986. Reproductive effects were noted in rat studies, with irreversible testicular degeneration, decreased fertility and declining sperm motility being observed. An Acceptable Daily Intake (ADI) 0.002 mg/kg bw/day was set based on an NOEL of 0.2 mg/kg bw/day from a 3-generation rat study and a 100-fold safety factor. An Acute Reference Dose (ARfD) has not currently been determined.

Having regard to these matters the APVMA is concerned that molinate might pose an undue hazard to human health.

6 ENVIRONMENTAL ISSUES

The US EPA review of molinate showed reproductive toxicity to mammals with a chronic No Observed Adverse Effect Level (NOAEL) of 5 mg/kg for ecologically relevant effects and may be an endocrine disrupter. Molinate exhibits moderate to high toxicity to aquatic invertebrates. However, it does not seem to be particularly toxic to aquatic plants or algae. The US report concluded that molinate is practically non-toxic to birds and slightly toxic to fish and to mammals**.**

A monitoring study by CSIRO Land and Water[3] during the period 1990-1995, found that samples from drainage channels often contained levels of molinate that exceeded guidelines for both drinking water and for the protection of aquatic environments. Levels of up to 700 µg/L were measured in drainage water as it left individual farms during October-December 1992/1993. Detected levels of molinate were lower during the remainder of the growing season as molinate applications were complete.

The Coleambally Irrigation Environmental Report 2002[4] states that the percentage of samples with molinate levels below the Environmental Guideline has increased from 31 percent in 1995 to 78 percent in 2001. It also notes that only 1 percent of recorded samples exceeded the NSW Environmental Protection Agency Action Level of 25 µg/L in 2001, compared with 36 percent in 1995. Much of this improvement has apparently come about because of changed and improved rice growing practices. Changes in water management since 1995 have resulted in rice growers being required to retain drainage water in on-farm storage ponds for 28 days after application of pesticides before water can be release into drainage channels. Similarly water availability has been restricted and as such growers more commonly recycle water on farm.

Having regard to the US EPA report and the history of detections of molinate in Australia, the APVMA is concerned that the use of molinate products might have unintended effects that are harmful to animals, plants or the environment.

7. OCCUPATIONAL HEALTH AND SAFETY ISSUES

The National Occupational Health and Safety Commission (NOHSC) raised concerns relating to the effects of molinate exposure, as presented in the US EPA's report. Toxic endpoint exposures are directly relevant to occupational exposure and the potential risk posed to workers using products containing molinate. NOHSC has not conducted risk assessments for any of the currently registered products and has therefore not evaluated the suitability of the personal protective equipment (PPE) to ensure worker safety. Thus, the APVMA is concerned that continued use of molinate products might present an undue hazard to workers and proposes to assess whether current occupational health & safety instructions are adequate.

8 INTERNATIONAL REGULATORY STATUS OF PRODUCTS CONTAINING MOLINATE

The European Union is reviewing molinate in its first round of reviews of pre-1993 approvals and has foreshadowed completion by July 2003.

The United States has scheduled for a re-registration eligibility decision in 2003. Health concerns (as discussed above) raised in the US EPA's preliminary risk assessment include cholinesterase inhibition in laboratory animals, delayed neurotoxicity in hens and reproductive effects in rats.

9. SUBMISSIONS FROM THE PUBLIC INVITED

Interested parties are requested to provide data addressing the issues raised in this scope document. These must reach the APVMA by no later than **18 July 2003**. Submissions can be sent either by email to chemrev@apvma.gov.au or by mail to:

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10 DATA ASSESSMENT AND POSSIBLE OUTCOMES

Environment Australia, Therapeutic Goods Administration and the National Occupational Health and Safety Commission will conduct the technical assessment of data submitted for the review of molinate. These agencies will advise the APVMA about the concerns raised in Sections 5, 6 and 7.

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

- the TGA revising the Acceptable Daily Intake (ADI);
- the NHMRC[1] revising the drinking water standard;
- the TGA establishing an acute reference dose (ARfD); and
- the NDPSC[2] revising the existing poisons schedule.

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

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

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

11 CONSULTATION THROUGHOUT THE REVIEW PROCESS

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

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

[1] National Health and Medical Research Council
[2] National Drugs and Poisons Scheduling Committee

REFERENCES

1. US EPA Toxicological Chapter, assessment of mammalian toxicity and metabolism of molinate, as part of a Re-Registration Eligibility Document for molinate
http://www.epa.gov/oppsrrd1/reregistration/molinate/Moltoxch.pdf

2. US EPA Overview Molinate Risk Assessment (2002)
http://www.epa.gov/oppsrrd1/reregistration/molinate/MolinateOverview.pdf

3. Bowmer, K.H, W. Korth, A. Scott, G. McCorkelle and M. Thomas (1998). Pesticide Monitoring in the Irrigation Areas of South-Western NSW 1990-1995, *CSIRO Land and Water Technical Report* 17/98.
http://www.clw.csiro.au/publications/technical98/tr17-98.pdf

4. Environmental Report 2002 *Coleambally Irrigation*
http://www.colyirr.com.au/documents/1921/ColyAER2002.pdf

ATTACHMENTS 1

Table 1: Active constituent approvals for molinate as at 1 April 2003

Approval Number	Name	Approval Holder
44008	Molinate manufacturing concentrate	Nufarm Australia Ltd
44276	Molinate	Syngenta Crop Protection Pty Ltd
44458	Molinate	Nufarm Australia Ltd
52439	Molinate	Sipcam Pacific Australia Pty Ltd
54519	Molinate	Syngenta Crop Protection Pty Ltd

Table 2: Registered products containing molinate as at 1 April 2003

Product Number	Product Name	Registrant	Label Approval Number(s)
31806	Nufarm Molinate 960 Herbicide	Nufarm Australia Ltd	31806/0501 31806/0600 31806/1000
45229	Farmoz Molinate 960 Selective Herbicide	Farmoz Pty Ltd	45229/0203
49597	Ordram Herbicide	Crop Care Australasia Pty Ltd	49597/01 49597/0698 49597/0800 49597/0902
54651	Synram Herbicide	Syngenta Crop Protection Pty Ltd	54651/0901