Australian Government

Australian Pesticides and Veterinary Medicines Authority

MOLINATE

PRELIMINARY REVIEW FINDINGS

The reconsideration of the active constituent molinate, registration of products containing molinate and approvals of their associated labels.

JANUARY 2014

ISBN: 978-1-922188-53-3 (electronic)

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FOREWORD

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

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

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

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

In undertaking reconsiderations (hereafter referred to as reviews), the APVMA works in close cooperation with advisory agencies including the Office of Chemical Safety within the Department of Health, the Department of Sustainability, Environment, Water, Population and Communities, and the state departments of agriculture, as well as other expert advisers as appropriate.

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

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

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

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

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

This review summary should be read in conjunction with the Toxicological Assessment (www.apvma.gov.au/products/review/docs/molinate_toxicology.pdf) and Occupational Health and Safety Assessment (www.apvma.gov.au/products/review/docs/molinate_riskassesment.pdf).

SUBMISSIONS FROM THE PUBLIC ARE INVITED

This Preliminary Review Findings report:

- outlines the APVMA review process
- advises interested parties how to respond to the review
- summarises the technical assessments from the reviewing agencies
- outlines the proposed regulatory action to be taken in relation to the continued approval and registration of molinate in Australia.

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

Comments on this report will be assessed by the APVMA (and partner agencies where required) prior to finalisation of the review and publication of the Final Review report.

Preparing your comments for submission

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

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

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

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

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

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

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

The closing date for submissions is 6 **April 2014**.

Submissions can be sent to:

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CONTENTS

ABBREVIATIONS

µg	microgram
AAA	Aerial Agricultural Association of Australia
ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake
ANZECC	Australian and New Zealand Environment Conservation Council
ARMCANZ	Agriculture and Resource Management Council of Australia and New Zealand
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
bw	bodyweight
d	day
DSEWPaC	Department of Sustainability, Environment, Water, Population and Communities (Australian Government)
EC	emulsifiable concentrate
FAISD	Handbook of first aid instructions, safety directions and warning statements for agricultural and veterinary chemicals
FAO	Food and Agriculture Organization of the United Nations
h	hour
ha	hectare
IARC	International Agency for Research on Cancer
IPCS	International Program on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	kilogram
L	litre
LD50	Median Lethal Dose
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
m	metre
mg	milligram
mg/kg bw/day	mg/kg bodyweight/day
mL	millilitre
MOE	Margin Of Exposure
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
NHMRC	National Health and Medical Research Council.
NSW EPA	NSW Environment Protection Authority
OCS	Office of Chemical Safety
OHS	Occupational Health and Safety
PHED	Pesticide Handler Exposure Database
PMRA	Pest Management Regulatory Agency (within Health Canada)
PPE	Personal Protective Equipment
ppm	parts per million
PRF	Preliminary Review Findings
RED	US EPA Re-registration Eligibility Decision (RED)
RGA	Rice Growers' Association of Australia
RIRDC	Rural Industries Research and Development Corporation
SCWIIRT	Soluble Chemical Water Injection In Rice Technique
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
USA	United States of America
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

EXECUTIVE SUMMARY

Molinate is used in Australia as a pre- and post-emergent herbicide to control barnyard grass and silver top or brown beetle grass in the cultivation of rice.

A review of the active constituent molinate, all products containing molinate, and their associated labels commenced in 2003 because of data indicating that molinate could cause irreversible damage to nerves (neuropathy) and interfere with development in laboratory animals.

As at June 2013, there were three molinate active constituent approvals and two registered products containing molinate. The two registered products are Emulsifiable Concentrate (EC) formulations containing 960 g/L molinate.

Preliminary review findings

Toxicological Assessment

The toxicological assessment for the review of molinate was undertaken by the Office of Chemical Safety (OCS) in January 2004. The studies submitted to the OCS for evaluation were considered inadequate to address concerns relating to the potential neuropathy and developmental toxicity of molinate. Given these concerns, the OCS recommended that the APVMA consider withdrawing approval of all molinate active constituents and currently registered products. The toxicology assessment was published in June 2013 (www.apvma.gov.au/products/review/docs/molinate_toxicology.pdf).

Occupational health and safety assessment

The occupational health and safety (OHS) assessment for the review of molinate was undertaken by the OCS in 2006. From this initial assessment, the OCS concluded that the ground application of molinate via herbigation[1] or SCWIIRT[2] methods could no longer be supported given that it poses an unacceptable dermal and inhalation risk to workers based on default Pesticide Handler Exposure Database (PHED) database exposure figures.

In 2011, as an interim collaborative effort with the APVMA, registrants voluntarily amended product labels to specify use in closed supply and delivery systems by tractor and fixed wing or helicopter only, in order to reduce worker exposure to molinate. In 2012, summary data submitted to the APVMA was not considered adequate to address worker exposure concerns raised in the 2006 risk assessment. As a result, the OCS

[1] Herbigation involves adding molinate into the water supply as it enters the rice bay. This process involves inserting a herbigation kit into the orifice plate at the base of a 20 L drum.

[2] SCWIIRT (Soluble Chemical Water Injection In Rice Technique) method involves using a 4-wheeled agricultural motorbike, tractor, ute, helicopter or hovercraft to drag a hose across the surface of the water and essentially dribble the molinate into the water under low pressure (<200 kPa).

recommended to the APVMA that the ongoing ground or aerial application of molinate could not be supported.

The OHS assessment was published in June 2013 (www.apvma.gov.au/products/review/docs/molinate_riskassesment.pdf).

Environmental Assessment

A preliminary assessment of Australian water monitoring data on molinate was undertaken by the Department of Sustainability, Environment, Water, Population and Communities (DSEWPaC) in 2004, and further considered in 2005 following comment from industry. DSEWPaC concluded that additional molinate water monitoring data was required from non-drought seasons, including the 2004–2005 and 2005–2006 rice growing seasons, to determine changes in molinate levels in drainage water over time. At the time of this report, this additional monitoring data had not been provided to DSEWPaC, however given the human health concerns regarding molinate, further efforts will not be taken to obtain this data. However, any future registration applications for molinate would require not only the human health and OHS concerns to be addressed but also environmental data requirements to be met.

Public Submissions

Following the announcement of the review of molinate in 2003, several general submissions were received from the Ricegrowers' Association of Australia Inc. (RGA), the Aerial Agricultural Association of Australia (AAA) and Rural Industries Research and Development Corporation (RIRDC). These submissions provided background information on the current use of molinate in rice cultivation, and proposed a future direction for the use of molinate.

Proposed Review Findings

The proposed findings of the review are that, the APVMA is not satisfied that continued use of or any other dealing with the active constituent or products containing molinate;

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

Proposed Review Recommendations

After consideration of all data, including additional assessments, the APVMA molinate review recommendations are to cancel:

a) all molinate active constituent approvals (see Section 3.1, Table 2)

b) all molinate product registrations (see Section 3.2, Table 3:)

c) all molinate product label approvals (see Section 3.2, Table 3:)

1 INTRODUCTION

Molinate is a member of the thiocarbamate group of herbicides. It has been used to control barnyard grass (*Echinochloa* spp.) and silver top or brown beetle grass (*Diplachnefusca*) in rice cultivation in Australia for over 30 years. It is absorbed by plant roots with acropetal (base to apex) translocation to the leaves and inhibits lipid synthesis and seed germination.

1.1 Regulatory status of molinate in Australia

As at June 2013, there were three molinate active constituent approvals and two registered products containing molinate (Table 2 and 3 in section 3). The two registered products are EC formulations containing 960 g/L molinate.

1.2 Overseas regulatory status

United States (US)

Molinate is not registered in the US. It was voluntarily cancelled by the registrant (Syngenta Crop Protection) in 2008.

US EPA Re-registration Eligibility Decision (RED) document (2002)

In 2002, the US EPA completed a human health and environmental evaluation of molinate, summarised in a Re-registration Eligibility Decision (RED) document. Some of the pivotal toxicology studies considered in the US risk assessment were not submitted to the Australian review. These comprise (at least) a chronic dietary study in dogs, a rat 2-generation reproduction study, rat developmental studies, acute neurotoxicity studies in hens and rats, a 90-day rat neurotoxicity study and a rat developmental neurotoxicity study. In summary, the US EPA RED document determined the following:

- Molinate is neurotoxic after single and multiple doses via the oral, dermal and inhalation routes of exposure in mice, rats and dogs. In neurotoxicity studies of varying durations, clinical signs indicative of nervous system effects, cholinesterase and neurotoxic esterase inhibition and neuropathology occurred.
- Molinate was classified as ‘Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential’ using the 1999 draft Guidelines for Carcinogen Risk Assessment.
- In a developmental neurotoxicity study, pups born to molinate-treated dams exhibited treatment-related functional and anatomical nervous system effects;
- Evidence of reproductive toxicity occurred in studies conducted in rats, mice, rabbits and dogs, however, the male rat appeared to be particularly sensitive.
- The results of acute and chronic dietary assessments on molinate determined that for all population subgroups risk estimates were below the level of concern. However, the aggregate risk assessment of acute exposure to food and surface water in children exceeded the level of concern. The RED stated that this assessment may overestimate the risk and that refinement of either food or water exposure levels may bring the risks into an acceptable range.

- Short and intermediate-term dermal and inhalation risks exceeded the level of concern for pilots applying granular and liquid molinate formulations. This was also true for handlers mixing/loading liquids for ground-based application and applying liquids using ground-based equipment and when additional protective clothing/PPE were added.
- Additional toxicology, chemistry and residue data was required.

Following the release of the US EPA RED document on molinate, Syngenta Crop Protection Inc. announced the phase-out of molinate in the USA on the 17 September 2003 over the next 5 years. The reasons cited for the phase-out included the level of investment required to maintain molinate registrations, the changing rice market in California and the southern USA and 'certain regulatory challenges'. In 2008, molinate was cancelled by US EPA.

Canada

The Pest Management Regulatory Agency (PMRA), responsible for the registration and regulation of pesticides in Canada, has never registered molinate as an active consistent in any pesticide.

European Union

Molinate was re-registered in Europe following amendment to the European Commission (EC) Council Directive 91/414/EEC to include molinate, on the 5 September 2003 (new Commission Directive 2003/81/EC). This followed the initial assessment of molinate by Portugal, which was subsequently reviewed by the Standing Committee on the Food Chain and Animal Health. The review was finalised on the 4 July 2003 and concluded that there were no 'open questions or concerns' and that products containing molinate satisfy the necessary legislative requirements. Molinate products are registered for use in France, Greece, Italy, Spain and Portugal as granular formulations for use in rice/paddy fields.

World Health Organisation (WHO)

Molinate has not been reviewed by the International Program on Chemical Safety (IPCS), the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) or the International Agency for Research on Cancer (IARC). However, the WHO has assigned a drinking water quality guideline value of 6 µg /L.

1.3 Approved molinate use pattern in Australia

Application rates of 2.5 to 3.75 L/ha (2.4–3.6 kg molinate active/ha) are used either before planting to water-seeded or shallow soil-seeded rice, or as a post-flood, post-emergence application to rice (up to the 4-leaf stage of grass weeds).

Molinate may be applied by one of the following methods:

- aerial application (helicopter or fixed wing): as either a blanket spray or using the SCWIIRT technique;
- ground application: as either a blanket spray, herbigation or using the SCWIIRT technique.

A survey of registrants in 2011 indicated that approximately 90% of molinate is applied by aerial application through a Bickley boom (modified SCWIIRT system) or similar, 5% applied by a SCWIIRT-type ground system and 5% by herbigation. No conventional ground application of molinate is currently in use.

1.4 Reasons for Molinate Review

In 2003, the active constituent molinate, all products containing molinate and their associated labels were placed under review because of human health, OHS and environmental concerns. During the US EPA review of molinate in 2002, studies suggested that at low doses, molinate could cause irreversible damage to nerves (neuropathy), interfere with the development of the foetus and the young (developmental toxicity), and impair fertility in laboratory animals.

1.5 Scope of the Review

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

- be an undue hazard to the safety of people exposed to it during its handling; and
- have an effect that is harmful to human beings; and
- have an unintended effect that is harmful to animals, plants or things or to the environment.

The scope of this review was to assess the following aspects of active constituent approvals, product registrations and label approvals for molinate:

- Toxicology, including:
    - the potential for molinate to impair fertility or cause neuropathy in humans, which might pose an undue hazard to human health;
    - and the potential for toxicologically-significant exposure to humans via the oral, dermal and inhalation routes.
- Occupational Health and Safety, including:
    - the possible risks to workers health associated with short and intermediate term occupational exposure; and
- Environmental, including:
    - the potential for contamination of waterways; and
    - the potential hazard to non-target fauna and flora

The review also considered whether molinate product labels carried adequate instructions and warning statements. Such instructions should include:

- the circumstances in which the product should be used
- how the product should be used
- frequency of the use of the product
- safe handling of the product.

The APVMA determined that the active constituent approvals, product registrations and label approvals for molinate be reviewed under the provisions of Part 2, Division 4 of the Agvet Codes.

1.6 Regulatory options

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

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

2 SUMMARY OF DATA ASSESSMENTS

2.1 Toxicology

The toxicological assessment for the review of molinate was undertaken by the OCS3. Of particular interest were studies submitted by registrants that had not been reviewed in 1986 (when molinate was last reviewed) or any other studies relating to neuropathy and developmental toxicity. However, in 2003 the major sponsor of molinate registration in Australia, Syngenta, announced the phase out of molinate in the USA over the next five years. Consequently, new unpublished data from Syngenta, which was anticipated to support molinate registration in Australia, was not submitted for review.

Acute Studies

In rats, the oral LD_{50} was 972, 689 and 549 mg/kg bw at 24 hours, 7 days and 14 days after dosing, respectively. Clinical signs included apathy, reduced respiration and diminished reflexing, which lasted for up to 72 hours after dosing. Gastrointestinal effects included doughy faeces and hyperaemia. (Heisler 1979)

The dermal LD_{50} in rats, under occluded conditions, was 5.15 mL/kg bw (~5150 mg/kg bw) after 48 hours and 4.35 mL/kg bw (~4350 mg/kg bw) after 14 days. There was a dose-related loss of bodyweight but no clinical signs. (Dickhaus & Heisler 1985)

Molinate was a slight skin and eye irritant in rabbits (Dickhaus & Heisler 1980a & b) and was classified as a skin sensitiser in the guinea pig maximisation test (Allen 1995).

Short-Term Repeat-Dose Studies

In a range-finding study, molinate was administered to rats via the diet for 4 weeks at 0, 200, 1000 or 5000 ppm (equivalent to 0, 20, 100 and 500 mg/kg bw/d, respectively). Mortalities occurred at 5000 ppm. Significantly reduced bodyweight gain, and food and water consumption occurred at 1000 and 5000 ppm. Absolute organ weights were significantly reduced at 5000 ppm, while relative organ weights were increased. Males appeared to be more affected than females. The possibility that these findings were due to the low palatability of the test diet can be discounted by the fact that in the acute dermal study (Dickhaus & Heisler 1985), bodyweight loss, and decreased food and water consumption occurred following a single application. Based on these findings, the authors selected doses for a future subchronic study at 20, 100 and 500 ppm. (Dickhaus & Heisler 1979)

Sub chronic Studies

Molinate was admixed in the diet and fed to rats at 0, 20, 100 or 500 ppm for 90 days (equivalent to 0, 2, 10 and 50 mg/kg bw/d, respectively). A range of organ toxicities was observed including effects on the testes,

[3]For a copy of the full toxicological assessment, refer to "Review of the mammalian toxicology and metabolism/toxicokinetics of molinate" at www.apvma.gov.au/products/review/current/molinate.php).

liver, kidneys and adrenals. Irreversible testicular degeneration occurred at and above 100 ppm (10 mg/kg bw/d). Other organ toxicities only occurred at the highest dose of 500 ppm (50 mg/kg bw/d). Liver toxicity was evidenced as hypertrophy, parenchymal degeneration, macroscopic patch patterns, increased weight and reduced serum albumin. Kidney toxicity manifested as glomerular hyalinisation and hyperplasia, reduced serum albumin and uric acid. There was an increase in the weight of the adrenals and irreversible transformation of the adrenal cortex. There was a range of significant haematology and clinical chemistry findings that collectively suggested the perturbation of the above, and possibly other, organ systems. Bodyweight gain was significantly reduced at every dose and therefore the lowest observed effect level (LOEL) was 20 ppm (2 mg/kg bw/d) (Dickhaus & Heisler 1980a & b).

Genotoxicity Studies

Molinate was not mutagenic in a forward mutation assay in mouse lymphoma L5178Y cells (Kennelly 1985a), it did not induce sister chromatid exchanges in Chinese hamster ovary cells (Kirkland 1985a) or unscheduled DNA synthesis in HeLa cells (Kennelly 1985b) either in the presence or absence of exogenous metabolic activation. Molinate did not induce micronuclei in mouse bone marrow erythrocytes (Kirkland 1985b).

Hazard Assessment

According to the US EPA molinate review, neurotoxicity occurred at the lowest administered doses in several short-term repeat-dose and chronic exposure studies, and a No Observable Adverse Effect Level (NOAEL) for injury to the nervous system was not demonstrated. Effects were seen on the development and/or structure and function of the nervous system of both adult and juvenile laboratory animals (e.g. inhibition of brain cholinesterase and neuropathy target esterase activities, degeneration or demyelination of the sciatic nerve or spinal cord, reduced brain weights and decreased motor activity). There appears to be no evidence that these effects are reversible; in general, degenerative lesions within the mammalian central and peripheral nervous system are likely to be irreversible. Moreover, the potential relevance to humans of the nervous system lesions is considered high because the lesions developed in four different laboratory species (i.e. mice, rats, dogs and hens). Several other findings of the US EPA assessment are cause for concern. Low airborne concentrations of molinate impair the fertility of male rats, the US EPA having assigned an inhalation low observed adverse effect concentration (LOAEC) for reproductive toxicity of 0.64 mg/m^3.

The US EPA report indicated that molinate is extensively absorbed across the skin (40% dermal absorption), and is hence potentially able to cause reproductive and neurotoxic effects at doses similar to those at which those effects occurred following oral administration. These findings have implications for occupational health and safety. A range of developmental effects was reported in rats including delayed vaginal opening, increased runting in the absence of maternotoxicity and decreased brain weights. Parental animals showed an increased incidence of lesions of the reproductive organs.

A small amount of data was submitted to the OCS for evaluation as part of the molinate review. The toxicological studies submitted by Sipcam Pacific Australia Pty Ltd consisted of 5 new acute studies, one short-term repeat-dose study, one sub chronic study and 4 genotoxicity studies. A submission received from Nufarm Australia Ltd/Crop Care Australia Pty Ltd contained OHS information only, and three public submissions were received from various professional/commercial bodies. Only data received from Sipcam was considered relevant to the toxicological and public health assessment of molinate.

Molinate has low acute oral and dermal toxicity in rats (LD_{50} values of 549 and 4350 mg/kg bw, respectively). No acute inhalational data was provided. Molinate was a slight skin and eye irritant, and a skin sensitiser. Short-term dietary administration to rats up to approximately 500 mg/kg bw/d resulted in reduced bodyweight gain, reduced food and water consumption and a reduction in organ weights (males). Sub chronic dietary administration in rats at lower doses (up to approximately 50 mg/kg bw/d) resulted in a suite of organ toxicities including effects on the testes, liver, kidneys and adrenals. These organ toxicities were evidenced as abnormal clinical chemistry, haematology, histopathology and organ weights. Of particular concerns was the occurrence of irreversible testicular degeneration at and above 10 mg/kg bw/d and irreversible transformation of the adrenals. A limited number of genotoxicity assays indicated that molinate was unlikely to be genotoxic.

In conclusion, the toxicological database submitted as part of the current review of molinate contained insufficient data to allow the OCS to perform a complete hazard assessment and, in particular, no information to assess the potential of molinate to cause neuropathy, interfere with development or impair fertility. Given the seriousness of these potential effects, the OCS cannot be satisfied that molinate does not pose an unacceptable risk to human health. Therefore, it does not support the ongoing approval of molinate.

Recommendations

Approval Status

Due to the absence of data to allay concerns over the potential of molinate to cause neuropathy, interfere with development or impair fertility, the ongoing approval of the active, molinate, can no longer be supported.

Impurity Limits

The molinate technical active contains no impurities of toxicological concern.

Acceptable Daily intake (ADI)[4]

The current Australian ADI for molinate is 0.002 mg/kg bw/d, based on the NOEL of 0.2 mg/kg bw/d (testicular degeneration in a rat 3-generation reproduction study) and using a 100-fold safety factor (10-fold factor to cover intraspecies variation and a 10-fold factor to cover interspecies variation). There was no new data submitted as part of the current review to allow the refinement of this value.

[4] The acceptable daily intake (ADI) for humans is considered as the level of intake of a chemical that can be ingested daily over an entire lifetime without any appreciable risk to health.

Acute Reference Dose (ARfD)[5]

There is no Australian ARfD for molinate and there were no studies submitted as part of the review that would allow one to be set.

Water Quality Guidelines[6]

In light of the absence of new data to allow any refinement to the current ADI, no change is recommended to the current health value of 0.005 mg/L for molinate in drinking water.

Poisons Scheduling

Given its potential to cause neuropathy and developmental toxicity, the OCS recommended in 2004 that the Advisory Committee on Chemicals Scheduling (ACCS) consider whether the Schedule 6 entry in the SUSMP remained appropriate. In 2004, the ACCS included molinate in Schedule 7 of the SUSMP.

First-Aid Instructions

Existing first aid instructions for molinate as they appear in the First Aid Instruction and Safety Directions (FAISDs) Handbook are as follows:

Molinate	**a**

Where 'a' is "If poisoning occurs contact a doctor or Poisons Information Centre. *Phone Australia* 131126. *Phone New Zealand* 03 4747000.

There is no new data to allow any change to the existing first aid instruction for molinate.

[5] The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

[6] The NHMRC's Health Guideline Values for drinking water are intended for use by health authorities in managing the health risks associated with inadvertent exposure to pesticide residues resulting from incidents such as a spill or the misuse of a pesticide. The values are derived so as to limit intake from water alone to approximately 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 and having a daily water consumption of 2 L over a lifetime.

Safety Directions

The current hazard-based safety directions for Australian products containing molinate, as recommended in the FAISD Handbook, are shown in the Table below.

TABLE 1 EXISTING SAFETY DIRECTIONS

EC all strengths

160 162 164	May irritate the eyes and skin
210 211	Avoid contact with the eyes and skin
220 223	Do not inhale spray mist
279 281 290 294	When preparing the spray wear elbow length PVC gloves
340 342	If product on skin, immediately wash area with soap and water
350 360 361 366	After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves and contaminated clothing.

There is no new data to allow any change to the existing safety directions for molinate.

2.2 Occupational health and safety (OHS)

In 2006, an interim OHS assessment undertaken by the OCS was submitted to the APVMA. From this initial assessment, the OCS concluded that the ground application of molinate via herbigation/SCWIIRT methods could no longer be supported given that it poses an unacceptable dermal and inhalation risk to workers. In 2011, as an interim collaborative effort with the APVMA, registrants voluntarily amended product labels for use in closed supply and delivery systems by tractor or helicopter only, to reduce worker exposure to molinate. This interim measure was implemented whilst the OCS completed its assessment of additional OHS summary data submitted by the registrant.

In October 2012, the OCS concluded that the additional OHS studies were unlikely to address worker exposure concerns raised in the 2006 risk assessment. The OCS confirmed that the unit exposure from the Pesticide Handler Exposure Database (PHED) was 0.0189 mg/kg active handled for dermal exposure and 0.000183 mg/kg active handled (closed mixing/loading) for inhalation exposure. The calculated dermal exposure is 0.0117 mg/kg bw/d and inhalational exposure 0.0028 mg/kg bw/d, for a worker using 108 kg of molinate on 30 ha (3.6 kg molinate/ha), having a body weight of 70 kg, using a 40% dermal absorption factor (US EPA value), and 100% inhalation absorption factor (default value). The combined Margin of Exposure (MOE) for dermal and inhalation exposure was unacceptable (167) using a LOEL of 2 mg/kg bw/d.

On the basis of these calculations, the OCS concluded that the mixing and loading of molinate products poses an unacceptable risk (dermal and inhalational) to workers. For a copy of the full OHS assessment, refer to 'OHS risk assessment of the ground and aerial application of molinate' at www.apvma.gov.au/products/review/current/molinate.php).

As a result:

- The OCS could NOT support the ongoing ground-based application of molinate via herbigation or SCWIIRT methods due to unacceptable dermal and inhalational risks to workers because the MOE achieved during open and closed mixing/loading was unacceptable.

- The OCS could NOT support the ongoing aerial application of molinate as the MOE was unacceptable.

- The OCS concluded that the additional toxicity data submitted by registrants to support ongoing molinate registration did not adequately address concerns about worker exposure. The OCS recommended that the APVMA should not be satisfied that the use of molinate will not be an undue health hazard to humans according to the criteria stipulated in Section 14 of the Ag/Vet Code Act of 1994.

2.3 Environment

The Department of Sustainability, Environment, Water, Populations and Communities (DSEWPaC) undertook the environmental risk assessment for the review of molinate, and in 2004, a preliminary environment report from DSEWPaC was submitted to the APVMA, which considered water monitoring data on molinate provided by NSW EPA.

Following a submission from the Ricegrowers' Association of Australia Inc. (RGA) and the NSW Department of Industry and Investment, DSEWPaC completed a revised environmental assessment in November 2005 (refer to 2.4 Summary of Public Submissions for further detail) and recommended to:

- Continue the collection of molinate monitoring data from non-drought seasons, including data from creeks/rivers into which drains flow. This data should be sought from the 2004–2005 and 2005–2006 rice growing seasons and sent to DSEWPaC for the environment risk assessment;

- Postpone the decision of a full data call in until a proper assessment of the trends in environmental molinate levels from non-drought seasons has been made;

- Maintain the established Australian and New Zealand Environment Conservation Council and Agriculture and Resource Management Council of Australia and New Zealand (ANZECC/ARMCANZ) water quality guideline values for molinate.

2.4 Summary of Public Submissions

Following the announcement of the review of molinate in 2003, submissions were received from the RGA, the Aerial Agricultural Association of Australia (AAA) and Rural Industries Research and Development Corporation (RIRDC). These submissions provided background information on the current use and application of molinate, current molinate research projects and proposed a future direction for the use of molinate in rice. The AAA submission provided information on the technology to minimise drift during application of molinate, including use of the 'Bickley boom', comprehensive job planning, interpretation of weather conditions, GPS use during application, Spraysafe accreditation of pilots/loaders/mixers/operators and rigorous aircraft testing.

Additional submissions were received from the RGA and NSW EPA. The RGA submission suggested there were numerous shortcomings in the assessment of molinate by DSEWPaC including that updated farm irrigation techniques had not been considered, unreliable results from water sampling and a lack of consideration of Australian scientific studies into molinate. Additional data was supplied from the NSW EPA demonstrating declining molinate levels in irrigation waters from three NSW rice growing districts.

Following consideration of the RGA submission, the DSEWPaC provided a revised environmental assessment report on molinate. This assessment confirmed that molinate levels leaving rice paddies showed no real trend over time and concluded that further data be supplied from non-drought seasons (at least during the 2004–2005 and 2005–2006 rice growing seasons) to clarify whether this decline in molinate levels is due to the drought or improved farm practices. In addition, DSEWPaC postponed any decision of a full data call in until a proper assessment of the trends in environmental molinate levels from non-drought seasons had been made. This is not expected to occur as both the toxicological and OHS assessments do not support use.

3 PRELIMINARY REVIEW FINDINGS AND REGULATORY ACTION

On the basis of the evaluation of the submitted data and information, the APVMA makes the following recommendations with regard to the continued approval of the active constituent molinate, registration of molinate products and label approvals in Australia:

- On the basis of the OCS toxicological assessment, the APVMA is not satisfied that the requirements for approval of active constituents continue to be met, that continued approval would not be likely to have an effect harmful to human beings.
- On the basis of the OHS assessment, the APVMA is not satisfied that the use of, or any other dealing with, the products molinate/L in accordance with instructions for use would not be likely to have an effect that is not harmful to people or would not be an undue hazard to the safety of people exposed to it during handling.

The APVMA considers that the product labels cannot be modified to carry adequate instructions or warning statements to mitigate these concerns.

3.1 Cancel approvals of the active constituent

The APVMA proposes to cancel the approval of all molinate active constituents as listed in Table 2.

Table 2: Active constituent approvals to be cancelled

APPROVAL NUMBER	APPROVAL HOLDER
44008	Nufarm Australia Limited
44458	Nufarm Australia Limited
52439	Sipcam Pacific Australia Pty Ltd

3.2 Cancel registration of products and label approvals

The APVMA proposes to cancel the registration and label approvals for these products as listed in Table 3.

Table 3: Product registrations to be cancelled

PRODUCT NUMBER	PRODUCT NAME	REGISTRANT	LABEL APPROVAL NUMBER
49597	ORDRAM HERBICIDE	CROP CARE AUSTRALASIA PTY LTD	49597/0698 49597/0800 49597/01 49597/0902 49597/0405 49597/53794
56744	SIRION HERBICIDE	SIPCAM PACIFIC AUSTRALIA PTY LTD	56744/0403 56744/0505 56744/53770 56744/56831

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Allen SA (1995) Molinate ai skin sensitisation test in the guinea pig. Report No. OXN 139a/950097/SS. Lab: Huntington Research Centre Ltd, Huntington, Cambridgeshire, England. Sponsor: Oxon-Italia S.P.A, Pero, Milano, Italy. Unpublished [SIPCAM; sub: 12288, Vol 1 of 6]

Dickhaus S & Heisler E (1979) Report on a preliminary study for 4 weeks for a 3 month subacute toxicity study in the species rat with molinate as feed admixture. Report No. No. 2-4-175-79. Lab: Phamatox Forshung and Beratung GmbG, Hannover, Germany. Sponsor: Oxon-Italia S.P.A, Pero, Milano, Italy. Unpublished [SIPCAM; sub: 12288, Vol 2 of 6]

Dickhaus S & Heisler E (1980a) Irritant effects of molinate on rabbit skin. Study No. 1-3-257-80. Lab: Phamatox Forshung and Beratung GmbG, Hannover, Germany. Sponsor: Oxon-Italia S.P.A Fine Chemicals, Pero, Milano, Italy. Unpublished [SIPCAM; sub: 12288, Vol 1 of 6]

Dickhaus S & Heisler E (1980b) Irritant effects of molinate on rabbit eye. Study No. 1-3-258-80. Lab: Phamatox Forshung and Beratung GmbG, Hannover, Germany. Sponsor: Oxon-Italia S.P.A, Pero, Milano, Italy. Unpublished [SIPCAM; sub: 12288, Vol 1 of 6]

Dickhaus S & Heisler E (1985) Acute toxicological study on compound molinate technical after dermal application to the rat. Study No. 1-4-37-88. Lab: Phamatox Forshung and Beratung GmbG, Hannover, Germany. Sponsor: Oxon Italia, S.P.A Pero/Milano. Unpublished. [SIPCAM; sub: 12288, Vol 1 of 6]

Heisler E (1979) Acute toxicological study molinate after oral application in the rat. Study No. 1-4-175-79. Lab: Phamatox Forshung and Beratung GmbG, Hannover, Germany. Sponsor: Oxon Italia, S.P.A Pero/Milano. Unpublished. [SIPCAM; sub: 12288, Vol 1 of 6]

Kennelly J (1985a) Study to determine the ability of molinate technical to induce mutations to 6-thioguanidine resistance in mouse lymphoma L5178Y cells using a fluctuation assay. Study No. OXM1/ML/KF15/ML3. Lab: Microtest Research Ltd, Heslington, York, UK. Sponsor: Oxon Italia, S.P.A Pero/Milano. [SIPCAM; sub: 12288, Vol 4 of 6]

Kennelly J (1985b) Study to determine the ability of molinate technical to induce unscheduled DNA synthesis (UDS) in HeLa cells. Study No. OXM/He/KF17/He2. Lab: Microtest Research Ltd, Heslington, York, UK. Sponsor: Oxon Italia, S.P.A Pero/Milano. [SIPCAM; sub: 12288, Vol 4 of 6]

Kirkland DJ (1985a) Study to evaluate the potential of molinate technical to induce sister chromatid exchange (SCE) in cultured hamster ovary (CHO) cells. Study No. OXN 1/SCE/KF21/SC1. Lab: Microtest Research Ltd, Heslington, York, UK. Sponsor: Oxon Italia, S.P.A Pero/Milano. [SIPCAM; sub: 12288, Vol 4 of 6]

Kirkland DJ (1985b) Study to evaluate the potential of molinate technical to induce micronuclei in the bone marrow of treated mice. Study No. OXN 1/MNT/KF18/MN1. Lab: Microtest Research Ltd, Heslington, York, UK. Sponsor: Oxon Italia, S.P.A Pero/Milano. [SIPCAM; sub: 12288, Vol 4 of 6]