Australian Government

Australian Pesticides and Veterinary Medicines Authority

CHEMICAL REVIEW PROGRAM

REVIEW OF THE MAMMALIAN TOXICOLOGY

AND

METABOLISM/TOXICOKINETICS

OF

MOLINATE

This Report was prepared for the APVMA by

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Comments and enquiries:

The Manager, Public Affairs

Australian Pesticides and Veterinary Medicines Authority

PO Box 6182

KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4701
Email: communications@apvma.gov.au

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ABBREVIATIONS

Time		Weight	
d	Day	bw	Body weight
h	Hour	g	Gram
min	Minute	kg	Kilogram
mo	Month	µg	Microgram
wk	Week	mg	Milligram
s	Second	ng	Nanogram
yr	Year	wt	Weight

Length		**Dosing**	
cm	Centimetre	id	Intradermal
m	Metre	im	Intramuscular
µm	Micrometre	inh	Inhalation
mm	Millimetre	ip	Intraperitoneal
nm	Nanometre	iv	Intravenous
		po	Oral
		sc	Subcutaneous
		mg/kg bw/d	mg/kg bodyweight/day

Volume		Concentration	
L	Litre	M	Molar
mL	Millilitre	ppb	Parts per billion
µL	Microlitre	ppm	Parts per million

Clinical, chemistry and haematology

ALT	Alanine Aminotransferase (SGPT)
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase (SGOT)
BUN	Blood Urea Nitrogen
ChE	Cholinesterase

CPK	Creatine Phosphatase (phosphokinase)
Hb	Haemoglobin
Hct	Haematocrit
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
RBC	Red Blood Cell (erythrocyte)

Anatomy

CNS	Central nervous system
GIT	Gastro-intestinal tract

Chemistry

BP	Benzo(a)pyrene
CMC	Carboxymethyl Cellulose
CPA	Cyclophosphamide
DMSO	Dimethyl Sulfoxide
EC	Emulsifiable Concentrate
MMS	Methyl Methanesulphonate
NQO	4-Nitroquinolone-N-Oxide

Terminology

ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose
ChE	Cholinesterase Activity
CHO	Chinese Hamster Ovary
CNS	Central Nervous System
CRP	Chemical Review Program

GLP	Good Laboratory Practice
LC	Lethal Concentration
LD	Lethal Dose
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MRL	Maximum Residue Limit or Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
NZW	New Zealand White
QA	Quality Assured
SCE	Sister Chromatid Exchange
SPS	Specific Pathogen Free
TGAC	Technical Grade Active Constituent
UDS	Unscheduled DNA Synthesis

Organisations & publications

ACPH	Advisory Committee on Pesticides and Health
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATDS	Australian Total Diet Survey
CRP	Chemical Review Program
DAF	Department of Agriculture and Fisheries
DEH	Department of Environment and Heritage
DoHA	Department of Health and Ageing
EC	European Commission
FAO	Food and Agriculture Organisation of the United Nations
FAISD	First Aid Instructions & Safety Directions
FDA	Food and Drug Administration
FSANZ	Food Standards Australia New Zealand
IARC	International Agency for Research on Cancer
IPCS	International Program on Chemical Safety

JECFA	FAO/WHO Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
NDPSC	National Drugs and Poisons Scheduling Committee
NHMRC	National Health and Medical Research Council
NOHSC	National Occupational Health & Safety Commission
NRS	National Residue Survey
OCS	Office of Chemical Safety
PACC	Pesticides and Agriculture Chemicals Committee
SCOT	Standing Committee on Toxicity
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation

EXECUTIVE SUMMARY

Molinate has been used to control barnyard grass and silver top or brown beetle grass in rice cultivation in Australia for over 30 years.

Molinate was nominated for review under the Australian Pesticides and Veterinary Medicines Authority (APVMA) Chemicals Review Program (CRP) following recent reports that low doses of molinate could cause irreversible damage to nerves (neuropathy) and interfere with the development of the foetus and the young (developmental toxicity).

Molinate was last reviewed in 1986. The Acceptable Daily Intake (ADI) established at that time was based on the No Observed Effect Level (NOEL) for adverse effects on fertility in male rats. The database reviewed in 1986 did not contain any studies which indicated that molinate could cause neuropathy and developmental toxicity.

For the purposes of this review, the registrants were requested to submit all studies that had not been reviewed in 1986 or any other studies relating to neuropathy and developmental toxicity. However, the major sponsor of molinate registration in Australia, Syngenta, have recently made public their intention to voluntarily withdraw support for molinate in the USA (and probably Australia). Consequently, new unpublished data from Syngenta, which was anticipated to support molinate registration in Australia, was not submitted for review.

The other studies submitted to the OCS for evaluation were considered inadequate to address concerns relating to the potential neuropathy and developmental toxicity of molinate. Given the seriousness of these concerns, the OCS can no longer be satisfied that molinate does not pose an unacceptable risk to human health. Consequently, the OCS recommends that the APVMA consider withdrawing approval of all molinate actives and currently registered products. Further, the OCS has requested that the National Drugs and Poisons Schedule Committee (NDPSC) consider whether the current Schedule 6 entry in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) for molinate remains appropriate.

SUMMARY TOXICOLOGY REPORT

Introduction

Molinate is a thiocarbamate herbicide used for weed control in rice. It is in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) and the Australian Acceptable Daily Intake (ADI) is 0.002 mg/kg bw/d, based on a No Observed Effect Level (NOEL) of 0.2 mg/kg bw/d. Safety Directions for molinate [emulsifiable concentrate (EC) all strengths] are listed in the Handbook of First Aid and Safety Directions (FAISD). There are 3 currently approved sources of the active molinate and 4 registered products, all 960 g/L EC formulations. In drinking water, the National Health and Medical Research Council (NHMRC) Guideline Value and Health Value for molinate are 0.0005 and 0.005 mg/L, respectively.

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)

Subchronic 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, 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 LOEL was 20 ppm (~2 mg/kg bw/d). The absence of mortalities and clinical signs at the highest dose was a deficiency of the study design. (Dickhaus & Heisler 1980a & b)

Genotoxicity Studies

Molinate was not mutagenic in a forward mutation assay in mouse lymphoma L5178Y cells (Kennelly et al 1985a), it did not induce sister chromatid exchange in Chinese hamster ovary cells (Kirkland 1985a) or unscheduled DNA synthesis in HeLa cells (Kennelly et al 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

The present review was undertaken as part of the APVMA's CRP following reports that low doses of molinate could cause neuropathy and interfere with development. This concern emanated from the recent US assessment of molinate conducted as part of its re-registration process.

According to the US EPA 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 experimental animals (eg. 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 experimental species (ie. mice, rats, dogs and hens).

Several other findings of the EPA assessment are cause for concern. Low airborne concentrations of molinate impair the fertility of male rats, the EPA having assigned an inhalation LOAEL for reproductive toxicity of 0.64 mg/m^3. The 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.

Following the CRP data call-in process, a small amount of data was submitted to the OCS for evaluation. The toxicological studies submitted by Spicam Pacific Australia Pty Ltd consisted of 5 new acute studies, one short-term repeat-dose study, one subchronic 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 dramatic reduction in organ weights (males). Subchronic 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 not genotoxic.

In conclusion, the toxicological database submitted as part of the current review of molinate was considered inadequate. It 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 or interfere with development. Given the seriousness of these effects, the OCS can not be satisfied that molinate does not pose an unacceptable risk to human health. Therefore, it does not support the ongoing approval of molinate.

DOSE LEVELS RELEVANT FOR RISK ASSESSMENT

No studies in the current submission were considered suitable for establishing an Acute Reference Dose (ARfD) or refining the existing ADI for molinate.

CONSIDERATION OF PUBLIC HEALTH STANDARDS

Approval Status

Due to the absence of data to allay concerns over the potential of molinate to impair fertility and cause neuropathy, the ongoing approval of the active, molinate, sourced from the following manufacturers can no longer be supported:

Approval holder	Manufacturer
Nufarm Australia Limited	Tri-Chemical RT 1052 Budapest V Deak Ferenc U.7-9 HUNGARY
Sipcam Pacific Australia Pty Ltd	Oxon Italia S.p.A. Via Sempione 195-20016 Pero (MI) ITALY
Nufarm Australia Limited	Nufarm Australia Limited Mason Road Kwinana Western Australia 6167 AUSTRALIA

Impurity Limits

An integral part of the safety assessment of an active constituent is a consideration of the chemical composition of the material. The active constituent will contain measurable levels of impurities, which can arise during manufacture and/or from subsequent degradation during storage. The chemical identity of these impurities is generally well characterised. The impurities present in the technical-grade material are usually of no particular concern since health standards are established based on toxicology studies conducted using the mixture. However, for those which have high acute toxicity, genotoxicity or teratogenic potential, concentration limits need to be set, so that the toxicological profile of the technical-grade

active constituent does not appreciably alter in the event of slight changes in the proportions of the impurities.

The molinate technical active contains no impurities of toxicological concern.

Acceptable Daily intake (ADI)

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. It is calculated by dividing the overall NOEL from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intraspecies variation, the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

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.

Acute Reference Dose (ARfD)

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.

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

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.

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

- In rats, molinate has low to moderate oral toxicity (LD_{50} = 549 mg/kg bw) and low dermal toxicity (LD_{50} ~ 4350 mg/kg bw). Data evaluated in 1986 indicated that molinate has moderate inhalational toxicity (the LC_{50} in rats was 830 mg/m^3). Molinate was a slight skin and eye irritant in rabbits and was classified as a skin sensitiser in the guinea pig maximisation test.
- Molinate is formulated as an emulsifiable concentrate at 960 g/L, and is used solely as a herbicide in rice cultivation. It is applied as a spray, either on-ground or aerially, to dry rice bays, rice in permanent water or to inflowing water. Molinate can be used undiluted when applied to inflowing water, or diluted in water for other applications. The on-

ground use rate per hectare is 3.75 L in 200 L water for dry bays and 3.75 L in 5-10 L for permanent water. For aerial application, the use rate per hectare is 3.75 L in 10-100 L.

- Certain aspects of the reproductive toxicity of molinate were recognised when the chemical underwent a public health assessment in Australia in 1980 and 1986. The ADI established at the time (0.002 mg/kg bw/d) was based on the NOEL of 0.2 mg/kg bw/d, for testicular degeneration in male rats, and a 100-fold safety factor. Molinate was placed in Schedule 6 of the SUSDP in 1972.
- New data submitted to the US EPA, as part of their re-registration program, indicated that molinate caused neuropathy and developmental toxicity in experimental animals at low doses. The potential relevance of the neuropathy findings to humans is considered high because the lesions developed in four species and there was no evidence that they were reversible.
- The major issues raised by the EPA assessment were:

  - The high dermal absorption of molinate (40%)

  - NOAELs were not established in acute and 90-day neurotoxicity studies in rats. The Low Observable Adverse Effect Level (LOAEL) in the acute study was 25 mg/kg bw (decreased motor activity, increased time to tail flick). The LOAEL in the 90-day study was 4 mg/kg bw/d (decreased brain cholinesterase activity and neuropathy target esterase activity), while nerve fibre degeneration in the sciatic and sural nerves occurred in males at 35.5 mg/kg bw/d.

  - A NOAEL was not established in a rat developmental neurotoxicity study (LOAEL = 1.8 mg/kg bw/d; reduction in startle amplitude in pups). Reductions in morphometric measurements of certain areas of the cerebellum also occurred in pups at the maternal NOAEL (6.9 mg/kg bw/d).

  - The NOAEL for developmental toxicity (2.2 mg/kg bw/d; increased runting) was below the NOAEL for maternotoxicity in rats (35 mg/kg bw/d).

  - In a 2-generation reproduction study, a NOAEL was not determined for decreased brain weight in adults and pups of all generations (LOAEL = 0.4 mg/kg bw/d). Effects on the reproductive organs and delayed vaginal opening occurred at low doses (0.8 mg/kg bw/d).

  - The absence of NOAELs for neuropathy in chronic rat and dog studies. The LOAEL in rats was 0.4 mg/kg bw/d based on the increased incidence of degeneration or demyelination in the sciatic nerve, and muscle atrophy. In dogs, the LOAEL was 1 mg/kg bw/d based on demyelination of the sciatic nerve and in the lumbar, sacral and thoracic regions of the spinal cord.

- None of the data underpinning the EPA's assessment were submitted for evaluation as part of the current Australian review on molinate. Other studies submitted to the OCS for evaluation did not address concerns relating to the potential neuropathy and developmental toxicity of molinate. In the absence of data to address these serious toxicological concerns, the OCS recommends that the NDPSC consider whether the

current Schedule 6 entry in the SUSDP remains appropriate. The NDPSC may consider molinate appropriate for inclusion in Schedule 7 with an Appendix J entry.

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.

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.

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.

RECOMMENDATIONS

1. Approval Status

Approval of molinate active constituent is no longer supported because the requested data required to determine its neuropathy potential and developmental toxicity has not been provided.

2. Product Registration

Registration approval of all molinate products is no longer supported.

3. Poisons Schedule

Given its potential to cause neuropathy and developmental toxicity, the NDPSC may consider molinate appropriate for inclusion in Schedule 7 of the SUSDP with an Appendix J entry.

MAIN TOXICOLOGY REPORT

1. INTRODUCTION

Based on the information available, molinate was not nominated for assessment under the CRP when candidate chemicals were originally considered in 1995. Molinate was classified as an agricultural chemical of low concern by the Department of Health and Ageing (DoHA), and appears not to have been of special concern to the Department of Environment and Heritage (DEH), the National Occupational Health and Safety Commission (NOHSC), the APVMA or the public.

However, since 1995, several new studies have been completed but not submitted to the APVMA for review. These new studies were reviewed by the US EPA under their re-registration program, and highlighted several toxicological concerns. The US EPA has concluded that molinate causes neurotoxicity [including effects on the development of the foetal central nervous system (CNS)] in experimental animals following repeated exposure at low doses. The absence of a NOEL for neurotoxicity in chronically exposed rats and dogs is of special concern, as is the low inhalation LOAEL for reproductive toxicity of 0.64 mg/m^3. Developmental effects in rats included decreased brain weight, delayed vaginal opening and increased runting, and an increased incidence of lesions of the ovaries, testes and adrenals in parental animals. Because of the narrow margin between the pivotal NOEL (for reproductive effects) of 0.2 mg/kg bw/d and the LOAEL for neurotoxicity (0.3 mg/kg bw/d), there is a need to review whether the current ADI provides a sufficient margin of safety for human exposure via the diet and water.

Only limited new toxicological data were submitted by industry as part of the current review. Three public submissions were also received and these are described in Appendix 2

1.1 History of Committee Considerations of molinate in Australia

National Drugs and Poisons Schedule Committee (NDPSC)

Molinate was placed in Schedule 6 of the SUSDP as a new entry at the March 1972 meeting of NDPSC, based on a consideration of unspecified "tabulated" toxicity data on a number of Ag/Vet chemicals. It was considered at three subsequent meetings of the NDPSC. A negative Ames test was noted in November 1980. The issue of toxicological equivalence of a new TGAC source was considered in August 1984. Molinate was presented to the NDPSC "for information" at the February 1987 meeting, but no further details were recorded in the Minutes and there was no change to the schedule status of molinate. [It is possible that the committee considered information on reproductive toxicity referred by the (then) Pesticides and Agricultural Chemicals Committee (PACC); see below].

Advisory Committee on Pesticides and Health (ACPH, formerly the PACC)

Molinate was considered several times by the Pesticides and Agricultural Chemicals Committee (PACC). A toxicology evaluation was considered at the November 1980 meeting, the data having been submitted by ICI and Stauffer in support of a MRL in rice. The Minutes remark that the sponsor should be advised that the data were "extremely poor". The main target organ identified was the rat testis, with irreversible testicular degeneration, decreased fertility and declining sperm motility occurring in subchronic and reproduction studies (the testes [and probably nervous system] were not examined in the submitted 2-yr rat study). These effects were not noted in a 2-yr mouse study but the study was described as being poorly conducted. There appears not to have been any chronic dog study. The lowest NOEL was 0.2 mg/kg bw/d in a 3-generation rat reproductive study, to which a 2000-fold safety

factor was applied, yielding an ADI of 0.0001 mg/kg bw/d. The enhanced safety factor was chosen because of the inadequacy of the available chronic studies. A provisional MRL was set in rice.

The next consideration of molinate occurred in February 1981, when the PACC noted information supplied by the sponsor to assist in identifying 4 compounds whose product codes had been mentioned in toxicology reports considered at the previous meeting. In May 1981, the PACC confirmed the MRL for rice after receiving advice from ICI that no further chronic rat studies were available and none were proposed.

In November 1984, the PACC deferred setting a MRL for molinate in potable water, due to the lack of adequate chronic toxicity data. PACC confirmed this decision at its December 1985 meeting, but recommended a provisional MRL of 0.001 mg/L in June 1986 following receipt of additional chronic toxicity and other studies. The final PACC consideration of molinate occurred in November 1986. The additional data confirmed the most sensitive species was the rat with the target organ being the testes, with the pivotal NOEL remaining at 0.2 mg/kg bw/d. The effect did not occur in other species. The safety factor was reduced to 100, yielding a revised ADI of 0.002 mg/kg bw/d. The provisional MRL for molinate in water was confirmed at 0.001 mg/L. PACC further recommended that because of concerns over the potential reproductive toxicity arising from occupational exposure to molinate, the matter should be referred to the [N]DPSC.

NHMRC Standing Committee On Toxicity (SCOT)

Molinate was never considered by SCOT.

1.2 Australian Toxicology Evaluations

As discussed above, a toxicology data assessment on molinate was considered by the PACC in 1980.

A subsequent toxicology data submission was reviewed in 1986. It comprised metabolism and toxicokinetics studies in mice, rats and carp; acute toxicity, irritancy and dermal sensitisation studies; short-term repeat-dose studies in rats (oral) and rabbits (via the oral and dermal routes, respectively); subchronic studies in dogs (oral) and rats (1 oral and 2 inhalational [the second inhalation study concentrated on reproductive effects]); chronic toxicity studies in rats and mice (the mouse study incorporated a group for study of reproductive effects); a 3-generation reproduction study in rats; special fertility studies in mice, rats, rabbits and primates; developmental toxicity studies in mice and rabbits; genotoxicity studies; and exposure studies in humans during aerial application.

The predominant toxicological effect discussed is degeneration of the seminiferous tubules with consequent suppression of sperm production and impaired fertility. These effects were even seen following acute oral or inhalation exposure, albeit at near-lethal doses; both mice and rats were affected. The evaluation report does not mention neurotoxicity but hind limb weakness was observed in a 21-day rat study. It is unclear whether the studies included investigations that would have revealed neurotoxicity.

A submission from another sponsor seeking approval of molinate was reviewed in 1993 but it contained no toxicology data.

ADI and ARfD

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 (a 10-fold factor to cover intraspecies variation and a 10-fold factor to cover interspecies variation).

There is no Australian ARfD for molinate.

Poisons Scheduling

At present, molinate is listed in Schedule 6 of SUSDP.

MRLs in drinking water

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 a Guideline Value and a Health Value 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. The current Guideline Value for molinate is 0.0005 mg/L. Health Values are intended for use by authorities in managing the public health risks associated with inadvertent exposure due to a spill or the misuse of a pesticide. Health Values are based on 10% of the ADI, assuming a daily water consumption of 2 L for a 70 kg adult. The current Health Value for molinate is 0.005 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).

1.3 International Toxicology Assessments

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.

European Union

Molinate was recently re-registered in Europe following amendment to the European Commission (EC) Council Directive 91/414/EEC to include molinate, on the 5th 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. While the original assessment report is not available on the EC's website, it was reported that the review was finalised on the 4th July 2003 and that there were no "open questions or concerns" and that products containing molinate satisfy the necessary legislative requirements.

US EPA

The US EPA has recently performed a toxicological evaluation of molinate, which has been summarised in a Re-registration Eligibility Decision (RED) document. At this stage it has not been possible to undertake a detailed comparison of the databases evaluated by the US EPA and by DoHA, but it appears that the EPA database includes numerous studies that have never been evaluated by this Department. These comprise (at least) a chronic study in dogs, rat 2-

generation reproduction and rat developmental studies, and acute neurotoxicity studies in hens and rats, a 90-day rat neurotoxicity study and a rat developmental neurotoxicity study.

The US EPA's assessment of effects on the male reproductive system is broadly consistent with the findings of the two DoHA evaluations. The NOAEL for decreased male fertility was 0.2 mg/kg bw/d, established in a reproduction study in rats (LOAEL = 4 mg/kg bw/d). It is noteworthy that in the various reproduction studies, there was disruption of spermatogenesis at oral doses ranging down to 0.5 mg/kg bw/d. Furthermore, in a 4-week inhalation study, the NOAEL for effects on male fertility was 0.30 mg/m^3 and the LOAEL was 0.64 mg/m^3. The anti-fertility effects proved to be reversible after treatment was withdrawn and animals were allowed a 3-month recovery period. Adverse effects also occurred on the female reproductive organs: ovarian vacuolation and hypertrophy were noted in rats in reproduction studies at and above 2.9 mg/kg bw/d.

In developmental and reproductive studies performed in rats, a number of toxicological effects were observed which had not previously been described. Increased runting occurred below the NOAEL for maternotoxicity. No NOAEL was established for decreased brain weight in parental rats and pups (LOAEL = 0.4 mg/kg bw/d), with the EPA concluding that this was both a developmental and a systemic effect. Delayed vaginal opening occurred in female rats exposed *in utero* and during lactation to low doses of molinate (0.8 mg/kg bw/d), while microscopic lesions of the ovaries, testes and adrenals were observed in parental animals at this same dose.

In addition to reproductive/developmental effects, neuropathy was seen in mice, rats, dogs and hens, but the US EPA did not comment on whether the nerve lesions were reversible. NOAELs were not established in acute and 90-day neurotoxicity studies in rats. The LOAEL in the acute study was 25 mg/kg bw (decreased motor activity and increased time to tail flick), while the LOAEL in the 90-day study was 4 mg/kg bw/d (decreased brain cholinesterase and neuropathy target esterase activities). In the 90-day study, degeneration of the sciatic and sural nerves occurred in males at 35.5 mg/kg bw/d. A NOAEL was not established in a rat developmental neurotoxicity study, with a reduction in startle amplitude in pups seen at the lowest dose of 1.8 mg/kg bw/d. Reductions in morphometric measurements of certain areas of the cerebellum also occurred in pups at the maternal NOAEL (6.9 mg/kg bw/d). The chronic dog study did not demonstrate a NOAEL, with demyelination of the sciatic nerve and spinal cord occurring at the lowest dose of 1 mg/kg bw/d. Similarly, degeneration and demyelination of the sciatic nerve (combined with muscle atrophy) occurred in the rat chronic study at the lowest dose of 0.3 mg/kg bw/d. When molinate was administered to rats via the dermal route for 21 days, erythrocyte ChE activity was inhibited at the lowest dose of 10 mg/kg bw/d, and so a NOAEL was not established.

A study conducted in rats indicated that the level of dermal absorption ranged from 17-47%. The US EPA considered that a 40% dermal absorption factor is therefore appropriate.

The main regulatory end points of the US EPA toxicology assessment were:

- An ARfD of 0.0006 mg/kg was set, based on a LOAEL of 1.8 mg/kg bw/d in the acute neurotoxicity study in rats and applying a 3000-fold safety factor.
- A chronic RfD of 0.0001 mg/kg bw/d was set, based on a LOAEL of 0.3 mg/kg bw/d in the chronic rat study and applying a 3000-fold safety factor.

- Molinate was classified as a Group C (possible) human carcinogen, based on kidney tumours in male rats at the high dose of 13 mg/kg bw/d in the chronic study.

On the 17th September 2003, Syngenta Crop Protection Inc. announced the phase-out of molinate in the USA 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".

1.4 Chemistry of the active constituent molinate

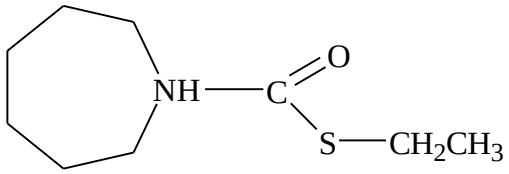
Approved common name: molinate (ISO)

Chemical name: ethyl N, N'-hexamethylenethiolocarbamate

CAS Registry number: 2212-67-1

Empirical formula: $C_9H_{17}NOS$

Molecular weight: 187.3



Chemical structure:

Chemical class: Thiocarbamate

Structural analogues: None

Chemical and physical properties

Colour:	Clear (technical material is amber)
Odour:	Aromatic odour
Physical state:	Liquid
Boiling point:	136.5°C
Density (20°C):	1.063
n-Octanol/water partition coefficient (log K_{ow}) :	2.88
Vapour pressure at 25°C:	746 mPa
Solubility:	
in water:	88 mg/L (20°C)
in organic solvents:	Miscible with most common organic solvents
Stability:	Stable at room temperature for 2 years and at least 1 month at 120°C

Impurities of Toxicological Concern

The active constituent molinate contains no impurities of toxicological concern.

1.5 Products

At the time of this review, there were 4 approved molinate products in Australia, all 960 g/L EC formulations.

2. METABOLISM AND TOXICOKINETICS

2.1 Metabolism and Toxicokinetics

No metabolism or toxicokinetic data were submitted for evaluation

2.2 Percutaneous absorption

No percutaneous absorption data were submitted for evaluation.

3. ACUTE STUDIES

3.1 Active Constituent

Summary of acute toxicity of molinate

Study	Species	Results	Reference
Oral	Rats	549 (14 days postdose)	Heisler (1979)
Dermal	Rabbits	4.35 mL/kg	Dickhaus & Heisler (1985)
Inhalation (4-h)	Rats	No data	
Skin irritation	Rabbits	Slight	Dickhaus & Heisler (1980a)
Eye irritation	Rabbits	Slight	Dickhaus & Heisler (1990b)
Skin sensitisation	Guinea pigs	Sensitiser	Allen (1995)

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. Report date: December 1979.

Test Compound: Molinate (Oxon-Italia, Pero/Milano; purity unspecified)

Batch: Not specified

Test Species: Wistar rats, 5/sex/dose, 120-140 g bw, sourced from Winkelmann, Paderborn, Germany

Study Duration: 14 days

Laboratory: Phamatox Forshung and Beratung GmbG, Hannover, Germany.

GLP& QA: None

Guidelines: FDA guidelines (1959)

Dosing method	Vehicle	Observation Period	Dose tested (mg/kg bw)	Oral LD_{50} (mg/kg bw)
Oral gavage	Distilled water and Tween 20	14 days	400, 504, 635, 800 & 1008	972 (24 h) 689 (7 d) 549 (14 d)

Clinical signs: Apathy (every dose), reduced respiration (every dose), diminished reflexing (at 800 and 1008 mg/kg bw) and doughy faeces (at and above 504 mg/kg bw) occurred at 2-5 hours post-administration and reportedly lasted for up to 72 hours. The severity of these signs appeared to increase with dose and at the highest dose of 1008 mg/kg bw, clinical signs were evident at 2-5 minutes postdose. Rough hair coats were noted in surviving rats, while bw gain was reduced at and above 635 mg/kg bw.

Necropsy findings: Hyperaemia was reported in the gastro-intestinal tract (GIT) of dead rats. Autopsy of surviving rats revealed no abnormalities.

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. Report date: March 1985.

Test Compound: Molinate Technical (Oxon-Italia, Pero/Milano) (96.4% purity)

Batch: Not specified

Test Species: Wistar rats, 5/sex/dose, 200 g bw, sourced from Winkelmann, Paderborn, Germany

Study Duration: 14 days

Laboratory: Phamatox Forshung and Beratung GmbG, Hannover, Germany.

GLP& QA: None

Guidelines: FDA guidelines (1959); OECD guidelines (1981)

Dosing method	Vehicle	Observation Period	Doses tested (mL/kg bw)	Dermal LD_{50} (mL/kg bw)*
Dermal application to clipped intact occluded skin. Dressing and residue removed at 24 h	None	14 days	2.5, 4.0, 5.0 & 6.5	5.15 (48 h) (range 4.55-5.82) 4.35 (14 d) (range 3.88-4.87)

* Equivalent to g/kg bw given that the specific gravity density of molinate is 1.063

Clinical signs: All rats were reportedly subdued following dosing, which the authors attributed to the occlusive dressing. There were no treatment-related clinical signs. There was a dose-related loss of bodyweight at and above 4.0 mL/kg bw in males and at every dose in females. Decreased food and water consumption were reported at and above 4 mL/kg bw.

Necropsy findings: There were no treatment-related abnormalities.

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. Report date: August 1980.

Test Compound: Molinate Technical (Oxon-Italia, Pero/Milano; 96.4% purity)

Batch: Not specified

Test Species: 8 NZW rabbits, aged 6-8 months, 2.5-3.5 kg bw, unspecified source

Study Duration: 14 days

Laboratory: Phamatox Forshung and Beratung GmbG, Hannover, Germany.

GLP& QA: None

Guidelines: FDA guidelines (1959)

Methods: 0.5 mL test compound was applied to the intact or abraded, clipped occluded dorsal skin. Skin reactions were scored according the Draize Scale at 24 and 72 hours, and 7 days, following removal of the skin wrapping.

Results: There was no mortality. Slight erythema was scored at 24 hours in 5/8 rabbits. There was no difference in the reaction between abraded and intact skin. No erythema was detected at 72 h or 7 days. No oedema was evident at any time. Molinate was classified as a slight skin irritant.

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. Report date: August 1980.

Test Compound: Molinate Technical (Oxon-Italia, Pero/Milano; 96.4% purity)

Batch: Not specified

Test Species: 6 NZW rabbits, aged 6-8 months, ~3 kg bw, unspecified source

Study Duration: 14 days

Laboratory: Phamatox Forshung and Beratung GmbG, Hannover, Germany.

GLP& QA: None

Guidelines: FDA guidelines (1959)

Methods: 0.1 mL of undiluted molinate was instilled into the conjunctival sac of one eye, with the other eye serving as an untreated control. Eye reactions were scored at 1, 2, 4, 8 and 24 hours, and at 2, 3, 4, 5, 6 and 7 days.

Results: All rabbits survived until scheduled termination. There were no signs of irritation of the cornea or iris. All rabbits exhibited erythema, chemosis and lachrymation of the conjunctivae from 1 or 2 hours, with all animals recovering 2-4 days after treatment. Molinate was classified as a slight eye irritant.

Mean eye irritancy scores in rabbits (n=6)

Lesions	Time after administration							
	1 h	2 h	4 h	8 h	24 h	2 d	4 d	5 d
Cornea	0	0	0	0	0	0	0	0
Iris	0	0	0	0	0	0	0	0
Conjunctivae								
Erythema	3	3	3	3	2.3	1.7	0.5	0
Chemosis	0	4	4	4	2.7	1.2	0	0
Lachrymation	2	2	2.8	3	1.7	0.5	0	0

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. Report date: 6th October 1995.

Test Compound: Molinate Technical (Oxon-Italia, Pero/Milano; 97.4% purity)

Batch: Q309

Test Species: Albino guinea pigs (Dunkin/Hartley strain), aged 4-5 wk, 231-303 g bw, obtained from D Hall, NewChurch, Staffordshire, England

Study Duration: 10th January to 11th February 1995

Laboratory: Huntington Research Centre Ltd, Huntington, Cambridgeshire, England

GLP& QA: Yes

Guidelines: EEC methods for the determination of toxicity, Annex of Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B6 Skin Sensitisation; Magnusson B & Kligman AM (1970) Allergic contact dermatitis in the guinea pig: Identification of Contact allergens, Thomas, CC, Springfield, Illinois, USA

Methods: The skin sensitisation potential of molinate was tested using the guinea pig maximisation test of Magnusson and Kligman. Positive control experiments were conducted periodically at the performing laboratory using hexyl cinnamic aldehyde; data provided in the study report confirmed the sensitivity of the guinea pig strain.

Doses used were determined from preliminary experiments. Ten test and five control animals were used. The induction phase consisted of 3 pairs of intradermal injections of the clipped dorsal skin on the scapular region: (1) a 1:1 mixture of Freund's complete adjuvant in water; (2) 20% v/v molinate technical in Albembicol D; and (3) 20% v/v molinate technical in a 50:50 mixture of Freund's complete adjuvant and Albembicol D. Six days later the same sites were gently rubbed with 0.2 mL of 10% w/w sodium lauryl sulphate in petrolatum. Twenty-four hours later, a filter paper containing 0.4 mL neat molinate technical was secured under an occlusive dressing for 48 hours. Control animals were treated identically to the test animals except that molinate was excluded from all solutions. After 2 weeks, a filter paper containing 0.2 mL 50% v/v molinate technical in Albembicol D was applied under an occlusive dressing to the clipped left flank of each Guinea pig.

Animals were observed daily for clinical signs. Bodyweights were recorded at induction (day 1) and at study termination (day 28). Dermal reactions were scored following topical application and challenge at 24, 48 and 72 hours, after removal of the patches.

Results: There were no mortalities or clinical signs, and the bodyweight gain appeared similar to controls. Dermal reactions after each induction were the same in control and test animals. There were no dermal reactions in controls following challenge application with molinate. Positive results for hypersensitivity occurred in 8 of the 10 test animals following challenge application at anterior (neat molinate) or posterior sites (50% v/v molinate in Albembicol D). In six of these eight animals, no dermal reaction was evident at the posterior site. Dermal reactions were graded as slight to well-defined erythema and oedema and were generally consistent across the three observation times (ie. 24, 48 and 72 h). Four of the eight animals testing positive had well defined erythema, including thickening, dryness and sloughing of the

epidermis. The other four animals were graded as having slight erythema. Oedema was graded as slight in the majority of animals (6/8), well defined in one animal and was absent in another. In the two animals that showed negative hypersensitivity (and the one without oedema but graded as positive), dryness and sloughing of the skin were noted at the anterior application site. Based on these findings, molinate was classified as a skin sensitiser.

3.2 Products/formulations

There were no acute toxicity studies conducted on any of the currently approved Australian molinate products.

SHORT-TERM REPEAT-DOSE STUDIES

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. 2-4-175-79. Lab: Phamatox Forshung and Beratung GmbG, Hannover, Germany. Sponsor: Oxon-Italia S.P.A, Pero, Milano, Italy. Report date: December 1979.

Methods: Molinate (Oxon-Italia S.P.A, Pero, Milano, Italy; unspecified batch No. & purity) was admixed in standard laboratory diet (Altromin, Lage, Germany) and fed to SPF wistar rats (5 sex/group; 100-160 g bw; age unspecified; Winklemann, Borchen, Germany) at 0, 200, 1000 or 5000 ppm for 4 weeks (equivalent to 0, 20, 100 and 500 mg/kg bw/d, respectively, using a dietary conversion factor of 10). Rats were randomly assigned to treatment groups, but it was not specified whether they had been acclimatised prior to treatment. There was no analysis of the concentration, homogeneity or stability of molinate in the diet.

Rats were observed daily. Food and water consumption were determined weekly. Rats were sacrificed after 4 weeks by an unspecified means and autopsied. Heart, liver, spleen, kidney and adrenal weights were recorded. The heart, liver, kidneys and adrenals from 5 rats/sex from the control and high-dose groups were histopathologically examined. Data were analysed using an unspecified statistical test.

Results: One high-dose male and female died during week 2, with another female dying in week 4. High-dose rats displayed dull hair coats from week 3. There were no mortalities or clinical signs in any other groups. There was a dose-related reduction in total bw gain over the 4-week treatment period, which was statistically significant ($p<0.001$) in males at every dose, and in females at 1000 and 5000 ppm (see Table below). This reduction in bodyweight gain was evident in both sexes at week 1 and continued throughout the treatment period. In fact at the highest dose, rats lost approximately 40% of their initial bodyweight. Absolute food and water consumption were significantly reduced ($p<0.001$) in males at and above 1000 ppm, and in females at 5000 ppm (see table below). This reduction occurred from the first week of dosing and continued throughout the 4-week treatment period.

Total bodyweight gain, food and water consumption

Findings	Group			
	0 ppm	200 ppm	1000 ppm	5000 ppm
Males				
bw gain (g)	115.2±14.4	85.4±9.7*	42.4±16.4*	-63±7.1*
food consump	551±47.2	553.4±42.9	445.4±29.2*	226.3±16.1*

Findings	Group			
	0 ppm	200 ppm	1000 ppm	5000 ppm
(g)				
water consump (g)	831±103	746.6±83.4	698.8±41.4*	540.3±31.2*
Females				
bw gain (g)	40.2±5.7	42.2±4.4	12.2+5.9*	-44±6.9*
food consump (g)	383.6±22.5	417±14.9*	378.4±18.5	206±12.3*
water consump (g)	661.8±121.7	622.8±57.7	684.2±120.4	495.3±25.6*

Results expressed as the mean ± 1 SD; *p<0.001

Autopsy revealed no macroscopic abnormalities. At 5000 ppm, there was a dramatic reduction in absolute heart, liver, kidney and spleen weights in males, and a similar though less marked reduction in heart, liver and spleen weights in females, relative to control weights (see Table below). Marginally lower organ weights were noted in males, but not females, at 1000 ppm. No organ weight effects were seen at 200 ppm. Relative heart (females), liver, kidney and adrenal weights were significantly elevated (p<0.01-0.001) at 5000 ppm, while relative heart, liver, and adrenal weights in males and kidney weights in females were also significantly elevated (p<0.05 or 0.001) at 1000 ppm (see Table below). These apparent increases in relative organ weights were attributable to the significantly reduced terminal bw at these doses.

Absolute organ weights

Findings	Group			
	0 ppm	200 ppm	1000 ppm	5000 ppm
Males				
Heart	0.928±0.137	0.877±0.081	0.821±0.13	0.420±0.11
Liver	11.444±0.819	10.464±0.47	9.125±0.853	5.862±0.541
Kidneys	1.962±0.315	1.842±0.203	1.487±0.163	1.178±0.109
Adrenals	0.062±0.008	0.068±0.01	0.077±0.008	0.073±0.008
Spleen	0.599±0.101	0.524±0.038	0.426±0.072	0.173±0.058
Females				
Heart	0.583±0.042	0.6±0.026	0.546±0.043	0.381±0.033
Liver	6.648±0.673	7.266±0.887	6.062±0.513	4.767±0.475
Kidneys	1.064±0.096	1.142±0.075	1.106±0.084	0.973±0.029

Findings	Group			
	0 ppm	200 ppm	1000 ppm	5000 ppm
Adrenals	0.08±0.02	0.095±0.007	0.079±0.013	0.077±0.016
Spleen	0.43±0.031	0.44±0.093	0.376±0.064	0.232±0.059

Results expressed as the mean ± 1 SD; data are bolded for ease of visual comparison

Relative organ weights

Findings	Group			
	0 ppm	200 ppm	1000 ppm	5000 ppm
Males				
Heart	0.336±0.04	0.336±0.032	0.396±0.049*	0.422±0.1
Liver	4.151±0.09	4.011±0.363	4.413±0.282*	5.943±0.695***
Kidneys	0.71±0.077	0.703±0.053	0.719±0.057	1.195±0.151***
Adrenals	0.023±0.003	0.026±0.006	0.037±0.005***	0.074±0.006***
Spleen	0.218±0.036	0.202±0.034	0.207±0.041	0.174±0.053
Females				
Heart	0.379±0.037	0.362±0.008	0.38±0.026	0.505±0.024***
Liver	4.178±0.473	4.375±.392	4.212±0.274	6.319±0.207***
Kidneys	0.689±0.035	0.691±0.064	0.769±0.045**	1.299±0.155***
Adrenals	0.052±0.016	0.057±0.004	0.055±0.009	0.102±0.012***
Spleen	0.279±0.005	0.265±0.049	0.261±0.042	0.307±0.059

Results expressed as the mean ± 1 SD; *p<0.05; **p<0.01; ***p<0.001; data are bolded for ease of visual comparison

Conclusions: Administration of molinate via the diet resulted in mortalities at 5000 ppm (~500 mg/kg bw/d), and significantly reduced bodyweight gain, and food and water consumption at 1000 and 5000 ppm (~100 and 500 mg/kg bw/d, respectively). 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.

4 SUBCHRONIC STUDIES

Dickhaus S & Heisler E (1980c) Three month subacute toxicity with molinate as feeding study in the species rat. Report No. 2-4-176-79. Lab: Phamatox Forshung and Beratung GmbG, Hannover, Germany. Sponsor: Oxon-Italia S.P.A, Pero, Milano, Italy. Report date: May 1980.

Methods: Molinate (Oxon-Italia S.P.A, Pero, Milano, Italy; unspecified batch No. & purity) was admixed in standard laboratory diet (Altromin, Lage, Germany) and fed to Wistar rats (30 sex/group; 100-115 g bw; age unspecified; Winklemann, Borchen, Germany) at 0, 20, 100 or 500 ppm for 90 days (equivalent to 0, 2, 10 and 50 mg/kg bw/d, respectively, using a dietary conversion factor of 10). The dose selection was based on the previous 4-week range-finding study by Dickhaus & Heisler (1979). After 90 days, 10 rats/sex/group were fed control diet for 30 days to determine the reversibility of any toxicity. It was not specified whether rats were acclimatised prior to treatment. There was no analysis of the concentration, homogeneity or stability of molinate in the diet.

Mortalities and clinical signs were recorded daily. Bodyweight and food consumption were recorded weekly. Food conversion efficiency was determined every 4 weeks. Haematology, clinical chemistry and urinalysis parameters were assayed at 0, 50, 90 and 120 days. The following haematology parameters were examined in all rats: leucocytes, Hct, Hb, RBC, MCV, MCH and MCHC. The following clinical chemistry parameters were assayed in all rats: potassium, phosphate, albumin, BUN, uric acid, creatinine, total bilirubin, globulin, AP, CPK, LDH, SGPT, SGOT and glucose. The following urinary parameters were analysed in 3 rats/sex/group: colour, pH, specific gravity, albumin, acetone, bilirubin, blood, sediment, urobilinogen, ketones and nitrates.

All rats were sacrificed by an unspecified means and macroscopically examined. The following organs were weighed: brain, heart, liver, kidneys, adrenal glands, spleen, ovary, testicles, uterus and prostate. These same organs, along with the following, were histopathologically examined in 5 rats/sex/dose: thyroid, stomach, duodenum, colon, pancreas, pituitary, lung urinary bladder and epididymis.

The following statistical tests were performed: 3-factorial ANOVA, where treatment, sex and time were the three factors; 3 factorial ANCOVA; and Tukey’s test.

Results

Mortalities, clinical signs, effects on bodyweight and food consumption: There were no mortalities or clinical signs. There was a dose-related reduction in bodyweight gain (see Table below), which was statistically different to the control at every dose. During the 30-day post-treatment period, female bodyweight gain remained depressed although there appeared to be some recovery. In males, only bodyweight gain at the highest dose remained significantly lower than the control after the 30-day recovery period.

Effect of molinate on bodyweight gain

Findings	Group			
	0 ppm	20 ppm	100 ppm	500 ppm
Males				
Bw gain 0-7 wk (g)	167.4±20.9	156.6±18.5**	142+18****	106.7±13.6****
Bw gain 0-12 wk (g)	206.8±26.1	196.7±22.9	183.9±23.5****	137.8±16.2****
Bw gain 0-16 wk (g)	228.5±18.3	218.5±19.4	211.8±25.8*	170.1±14.7****
Females				
Bw gain 0-7 wk (g)	75.3±11.4	55.9±10.7****	46.4±8.0****	30.3±6.9****
Bw gain 0-12 wk (g)	92.6±14.6	72.6±11.7****	61±9.5****	39.5±7.2****
Bw gain 0-16 wk (g)	96.3±12.4	81±13.7****	70.3±12.9****	50.8±8.6****

Results expressed as mean ± SD (t value); *p<0.05; **p<0.02; ***p<0.005; ****p<0.0025

In females, there was a significant reduction (p<0.02-0.0025) in absolute food consumption at 100 and 500 ppm (5-8 and 11-16%, respectively, compared to the control), while in males, food consumption was only significantly lower (p<0.01-0.0025) than the control at 500 ppm (4-8%). These effects were seen over the entire study period (including the 30-d recovery period). There was a dose-related reduction in food conversion efficiency in both sexes over 0-7 and 0-12 weeks of treatment, but there was no indication of whether this finding was statistically significant.

Haematology: There was a significant dose-related increase in MCV in males at day 90 (see Table below), which was not evident at any other time or in females. The effect on MCV at 500 ppm was considered toxicologically significant as it was above (albeit slightly) the performing laboratories "normal" control range of 40-60 μ^3. There were a number of other significant haematology findings that were not toxicologically significant as they did not follow a dose-response relationship, they fell within the performing laboratories control range or were incidental in nature. These findings included:

- Reduced MCH in 500 ppm males at day 50 (20.79±1.57 μ/μg *versus* 22.42±2.07 in the control; p<0.05) (normal range of 19-25 μ/μg).
- Reduced MCHC in 500 ppm males at day 90 (37.65±6.1% *versus* 44.67±4.83% in the control; p<0.01) (normal range of 35-50%).
- Increased leucocytes in 500 ppm females at day 120 (6790±2398 versus 4520±1840 /mm^3 in the control) (normal range of 2000-10000/mm^3).

Effect of molinate on MCV in males

Findings	Group			
	0 ppm	20 ppm	100 ppm	500 ppm
Males				
MCV (μ^3) wk 13	50.77±8.92	55.93±5.94	56.56±5.21*	61.06±4.52**

Results expressed as mean ± SD; *p<0.05; **p<0.005

Clinical chemistry: There were a number of statistically-significant findings that individually were not considered treatment-related due to the lack of a dose-response effect and because they fell within the performing laboratory's normal range. However, collectively they suggest that at the highest dose of 500 ppm, there were possible treatment-related effects on the liver and/or kidneys. These findings included: increased glucose in 100 ppm females at day 50; increased α_1-globulin in 100 ppm males at day 120; decreased α_1-globulin in 500 ppm females at day 90; decreased β-globulin in 100 and 500 ppm males at day 50 and at every dose at day 120; decreased γ-globulin in 500 ppm females at day 90; decreased SGPT in 500 ppm males at day 50; increased SGPT in 100 ppm females at day 50; reduced K in 500 ppm females at day 90; reduced bilirubin in 500 ppm females at day 90; increased BUN in 500 ppm males at day 50; reduced creatinine in both sexes at 500 ppm at day 90; and increased creatinine in 500 pm males at day 120.

At 500 ppm, albumin was significantly reduced (p<0.0025) in both sexes at days 50 and 90, compared to the control (see Table below). According to the performing laboratory, the control range for albumin is 5.8-6.8 g/dL and therefore these findings are considered treatment-related and toxicologically significant. At day 120, the concentration of albumin in males was significantly higher (p<0.0025) at 500 ppm than in the control, a finding that was attributable to the decrease in control albumin. At day 120 in females, albumin had recovered to normal levels.

Effect of molinate on serum albumin levels in rats

Findings	Group			
	0 ppm	20 ppm	100 ppm	500 ppm
Males				
Albumin wk 7 (g %)	6.338±0.298	6.187±0.314	6.218±0.244	5.66±0.265****
wk 13 (g %)	6.393±0.45	6.295±0.435	6.149±0.298	5.543±0.618****
wk 17 (g %)	5.974±0.368	6.405±0.417	6.199±0.470	6.699±0.427****
Females				
Albumin wk 7 (g %)	6.370±0.266	6.270±0.303	6.236±0.24	5.716±0.334****
wk 13 (g %)	6.418±0.421	6.307±0.447	6.440±0.372	5.255±0.660****

Findings	Group			
	0 ppm	20 ppm	100 ppm	500 ppm
wk 17 (g %)	5.997±0.202	6.092±0.299	6.147±0.407	6.298+0.299

Results expressed as mean ± SD; ****p<0.0025

Uric acid was significantly reduced at 500 ppm in both males and females at day 90 only. In males, the amount of uric acid was 4.528±1.079 mg % *versus* 7.851±2.703 mg % in the controls (p<0.005). In females, the amount of uric acid was 3.100±0.807 mg % *versus* 7.344±2.176 mg % in the controls (p<0.0025). The normal range for uric acid is 4.0-9.0 mg % and therefore the effect on females was toxicologically significant.

Urinalysis: There was no treatment-related effect on any urinary parameters.

Pathology: There was a treatment-related increase in macroscopic patch patterns on the liver, which occurred in 100% of rats sacrificed at day 90 across all doses (see Table below). While there was evidence of reversal of this finding at 20 and 100 ppm, all high-dose rats remained affected at day 120. Testicular atrophy was detected in 2/10 (20%) males at 20 ppm and in 6/10 (60%) males at 500 ppm. No testicular atrophy was detected in any other group or at any other time.

Combined incidence of patch patterns on the liver

Findings	Group			
	0 ppm	20 ppm	100 ppm	500 ppm
Wk 7 (5 sex/group)	2/10 (20%)	3/10 (30%)	1/10 (10%)	1/10 (10%)
Wk 13 (15 sex/group)	4/30 (13%)	30/30 (100%)	30/30 (100%)	30/30 (100%)
Wk 17 (10 sex/group)	4/20 (20%)	10/20 (50%)	10/20 (50%)	20/20 (100%)

Results expressed as the number of rats showing the abnormality/sample size (% incidence)

Histopathological findings were reported in German and were therefore not amenable to independent evaluation. An English translation of the German summary reported a number of treatment-related abnormalities. Degeneration of the testes occurred at 500 ppm and was evident at days 50, 90 and 120. Testicular degeneration at 100 ppm could not be discounted by the authors as single rats were affected at days 50 and 120. At 500 ppm, effects on the liver (hypertrophy and parenchymal degeneration) and kidneys (glomerular hyalinisation and hyperplasia) were observed at day 50. It was reported that after the 30-day recovery period only a proportion of high-dose rats showed liver abnormalities, while kidneys were "nearly" normal. At 500 ppm, 29/30 rats were reported to have a "high-degree" of "increased transformation" of the adrenal cortex at days 50 and 90. There were a number of other histopathological findings that the authors attributed to inflammatory or immunological responses, but were similar in controls and test groups and therefore were not considered as treatment-related.

Organ weight findings were not easy to interpret. In rats sacrificed at day 50, right adrenal weights were increased by approximately 37% in 500 ppm females, a result that was

statistically significant ($p<0.025$). Spleen weights were also significantly increased ($p<0.05$-0.01) in females at every dose by approximately 25% compared to the controls. No such effects were seen in males. In rats sacrificed at day 90, there was a range of significant organ weight effects. Liver weights were increased at every dose and in both sexes by approximately 10% ($p<0.01$-0.0025). Adrenal weights were also significantly increased ($p<0.02$-0.0025) at every dose and in both sexes by approximately 10-80%. Spleen weight was significantly decreased at 100 and 500 ppm in females (~30%). There were a number of statistically significant organ weight effects in rats sacrificed following the 30-day recovery period (ie. day 120) including increased heart, liver, kidney weights in both sexes. In the absence of dose-response relationships, these findings were not considered treatment-related.

Conclusions: Dietary administration of molinate to rats for 90 days caused a range of organ toxicities including effects on the testes, 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 included 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 statistically 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 LOEL was 20 ppm (~2 mg/kg bw/d). The absence of mortalities and clinical signs at the highest dose was a deficiency of the study design.

6. CHRONIC STUDIES

No chronic toxicity studies were submitted for evaluation

7. REPRODUCTION STUDIES

No reproduction studies were submitted for evaluation.

8. DEVELOPMENTAL STUDIES

No developmental studies were submitted for evaluation.

9. GENOTOXICITY STUDIES

The following Tables summarise the findings of *in vitro* and *in vivo* genotoxicity studies submitted and evaluated as part of the current molinate review.

In vitro assays

Assay	Strain or Cell type	Concentration	Batch / Purity	Positive control	Metabolic Activation	Result	Reference
Forward mutation in mammalian cells	Mouse lymphoma L5178Y (TK +/-) (n=2)	31.3, 62.5, 125 and 250 µg/mL (-S9) 50, 100, 200 and 400 µg/mL (+S9) DMSO vehicle	Unspecified	0.19 & 0.38 µg/mL NQO (-S9) 2.0 & 3.0 µg/mL BP (+S9) DMSO vehicle	+/-	-/-	Kennelly et al (1985a) [QA]
SCE	CHO cells (n=2)	50, 100, 200 & 300 µg/mL (-S9) 125, 250, 500 & 750 µg/mL (+S9) DMSO vehicle	Unspecified	MMS: 5, 10 & 20 µg/mL (-S9) CPA: 0.625, 1.25 & 2.5 µg/mL (+S9) DMSO vehicle	+/-	-/-	Kirkland (1985a) [QA]
UDS	HeLa cells (n=6)	0.0064, 0.032, 0.16, 0.8, 4, 20, 100 & 500 µg/mL in DMSO	Unspecified	1.9 µg/mL NQO (-S9) 4.0 & 6.0 µg/mL BP (+S9) DMSO vehicle	+/-	-/-	Kennelly et al (1985b) [QA]

Results (+ = positive; - = negative or +/- = equivocal) are expressed relative to the presence (+) or absence (-) of metabolic activation; SCE = sister chromatid exchange; CHO = Chinese hamster ovary cells; S9 = rat liver post-mitochondrial fraction from Aroclor-1254 induced animals; MMS = methyl methanesulphonate; CPA = cyclophosphamide; UDS = unscheduled DNA synthesis; NQO = 4-nitroquinoline-N-oxide; BP = benzo(a)pyrene

In vivo assays

Assay	Species (Strain)	Dose or concentration	Batch / Purity	Positive control	Result	Reference
Micronucleus test	Mice (CD-1) Bone marrow	300 mg/kg bw, po (gavage) in water 0.25% CMC	Unspecified	80 mg/kg bw CPA, po in water	-	Kirkland (1985b) [QA]

SCE = sister chromatid exchange; Results (+ = positive; - = negative or +/- = equivocal); QA = quality assured study; GLP = statement of compliance with principles of good laboratory practice; CMC = carboxymethylcellulose; CPA = cyclophosphamide

10. NEUROTOXICITY STUDIES

No neurotoxicity studies were submitted for evaluation.

11. HUMAN STUDIES

No human studies were submitted for evaluation.

12. OTHER STUDIES

No other studies were submitted for evaluation.

REFERENCES

Evaluated studies

[Figures in square brackets are an Australian identification code and indicate the location of the submitted data.]

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 (1980c) Three month subacute toxicity with molinate as feeding study in the species rat. Report No. 2-4-176-79. 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 (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]

APPENDIX I: DETAILS OF TOXICOLOGICAL DATA SUBMISSIONS

Confidential Business Information

Sponsor/Provider	Submission No.	Date	Data Details
Sipcam Pacific Australia	12888	21st July 2003	4 volumes

APPENDIX 2: DETAILS OF NON-TOXICOLOGICAL DATA SUBMISSIONS

A2.1 Nufarm Australia Ltd/Crop Care Australia Pty Ltd

Submission No. 12288. Vol 5 of 6

This submission contained OHS information such as product use patterns, Material Data Safety Sheets (MSDS) and product labels for Nufarm Molinate 960 Herbicide and Ordram Herbicide. No toxicological data were provided. Other information contained in the submission included the following:

Taylor M (1993) Commercial scale field evaluation of SCHIIRT for application of molinate, bensulfuron and chlorpyrifos to aerial-sown rice in New South Wales, 1992-93 season. RIRDC Project No. AGR-1A. Agropraisals Pty Ltd, Cobram, Victoria. Report date: 9th June 1993

Taylor M (1994) Rice herbicide application in Australia. In: *Temperate rice – achievements and potential* (E Humphreys, EA Murray, WS Clampett & LG Lewin Eds). Proceedings Volume 2 of the Temperate Rice Conference, YANCO, Leeton, NSW. 21-24 February 1994.

In the absence of any toxicological data, this submission had no value in the toxicological and public health assessment of molinate.

A2.2 Public submissions

Submission No. 12288. Vol 6 of 6

Hurst P (2003) Submission on the review of molinate. Aerial Agricultural Association of Australia Ltd, Dickson, ACT.

This submission voiced interest in the retention of access to molinate for aerial applicators for weed control during rice seeding and cultivation. A variety of risk management initiatives have been instigated by the aerial agricultural industry to manage spray drift including the introduction of the "Bickley Boom", which improves the aerial application of pesticides to the target area. It was argued that molinate can be applied safely from the air and therefore its use should be maintained.

Linnegar PM (2003) APVMA molinate review. Rice Research and Development Committee, Rural Industries and Research and Development Corporation

Support for the ongoing use of molinate was the tenet of this submission based on the fact that: it has been the main herbicide used in rice production for more than 30 years; withdrawal of registration would affect the rice industry; and growers are committed to the environmentally safe use of molinate. Concern was expressed that the primary registrant of molinate, Syngenta Australia, was unlikely to provide a submission to the molinate review, which was attributed to commercial reasons. There was some discussion on the environmental considerations of the safe use of molinate, including some environmental research initiatives currently being funded by the Rural Industries Research and Development Corporation Rice Research and Development Committee.

Kerr D (2003) Australian Pesticides and Veterinary Medicines Authority: The reconsideration of approvals and registration relating to molinate. Ricegrowers' Association of Australia Inc. Leeton, NSW.

This submission voiced concern regarding the basis of the APVMA's molinate review. It was argued that changes to on-farm management practices have had a significant impact on reducing the effects of molinate on individuals and the environment. It was concluded that molinate is an important chemical in rice production and that improvements to land management practices ensure that no molinate residues enter important ecosystems.