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OHS Risk Assessment

of the

ground and aerial application

of molinate

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OHS Risk Assessment of the ground and aerial application of molinate

Background

Molinate is a thiocarbamate herbicide, which has been used to control barnyard grass and silver top or brown beetle grass in rice cultivation in Australia for over 30 years. Molinate may be applied aerially (aeroplane and helicopter) or via a number of ground methods [herbigation and Soluble Chemical Water Injection In Rice Technique (SCWIIRT)]. Label directions on molinate products indicate that it can be applied to both dry and wet rice bays. There are currently two registered products containing molinate, the details of which are summarised in the following Table.

APVMA product No.	Product name	Formulation type	Molinate content
49597	Ordram Herbicide	Emulsifiable concentrate	960 g/L
56744	Sirion Herbicide	Emulsifiable concentrate	960 g/L

In January 2004, the OCS completed a toxicological assessment of molinate as part of the Australian Pesticides and Veterinary Medicines Authority (APVMA) Chemical Review Program (CRP). This followed 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). When molinate was last reviewed in 1986, there were no studies in the toxicological database which indicated that molinate could cause neuropathy and developmental toxicity. New studies addressing these concerns were not submitted as part of the 2004 review. Given the seriousness of these concerns, the OCS was no longer satisfied that molinate does not pose an unacceptable risk to human health. Consequently, the OCS recommended that the APVMA consider withdrawing approval of all molinate actives and currently registered products. Further, the OCS 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 remained appropriate. Subsequent to the OCS 2004 assessment, the NDPSC rescheduled molinate into Schedule 7 with an Appendix J entry.

In the absence of toxicological data to allow the OCS to evaluate the neuropathy potential and developmental toxicity of molinate, in 2006 the APVMA requested an interim OHS risk assessment for the ground application of molinate by Herbigation and SCWIIRT. This document has been updated (in this report) to include PHED modelling of aerial application methods.

OHS Risk Assessment

Product description and use patterns

Label directions for all three molinate products indicate that they can be applied via SCWIIRT using a 4-wheeled agricultural motorbike, tractor, utility vehicle, helicopter or hovercraft. This method involves dragging a hose across the surface of the rice bay, essentially 'dribbling' the molinate into the water under low pressure (<200 kPa). There is no application of molinate by this method onto dry rice bays. Generally, the farmer would apply molinate by this method (i.e. there is limited if any application by contractors).

Label directions indicate that 3.75 L of the product (maximum quantity applied) is mixed with water to make up to 5-10 L/ha of spray solution (3.6 kg molinate/ha). Each litre of the product contains 960 g of molinate. The spray solution can be applied from pre-sowing up to the 4 leaf-stage of grass weed. The APVMA has advised that the maximum area treated is 30 ha/day. Therefore a worker will use up to 108 kg of molinate/day. If an average rice farm is 100 ha then it is conceivable that molinate would be applied over a 3-4 day period, once or twice in a season.

Label directions for Ordram Herbicide also list ground application by herbigation. In this method molinate is trickled into the supply water as it enters the rice bay. The APVMA has advised that approximately 5% of rice growers apply molinate by herbigation. This process involves inserting a herbigation kit into the orifice plate at the base of a 20 L drum. The rate for herbigation is 3.75 L/ha, so a 20 L drum would be sufficient to treat 5.3 ha. As the average rice farm is approximately 100 ha, the APVMA have indicated that a farmer would have to calibrate and use nineteen 20 L drums of molinate (380 L of the product) to treat an entire farm. In reports received by the APVMA, it was emphasised that herbigation is a "messy process" and workers tend to smell of the chemical following use. Using herbigation, molinate can be applied to up to 30 ha/day and therefore a worker could use up to 108 kg/day of molinate.

Selection of No Observed Effect Level (NOEL)

Workers may be exposed to molinate through dermal contact with any undiluted product, the spray mixture or water/vegetation. While the ground application of molinate by herbigation and SCWIIRT does not involve spraying per se, molinate is relatively volatile (vapour pressure of 746 mPa) and therefore workers are also likely to be exposed via inhalation.

Molinate is used once or twice in a 3-month season, and as mentioned above, may be applied to a farm over a 3-4 day period. Therefore short-term repeat-dose studies are appropriate for establishing NOELs for OHS risk assessment purposes. NOELs considered for OHS risk assessment are presented in Table 1 overleaf.

Table 1 – NOELs from repeat dose studies conducted using molinate

Study Duration/Species/Route of Administration	Dose (mg/kg bw/d)	NOEL (mg/kg bw/d)	LOEL and endpoint
21 day/rat/oral?	0, 5, 20, 80 or 160 (units of dose not given)	None stated	Weakness in hind limbs at 80, 160. Decreased Factor X and increased APTT at 160.
21 day/rabbit/dermal	0, 0.1 or 1 mL/kg bw/d	Not established	Moderate skin irritation at 0.1 Severe skin irritation, secondary infection, anorexia, weight loss and diarrhoea at high dose.
4 weeks/rat/diet	0, 20, 100 or 500	None stated	Significantly reduced bodyweight gain and food and water consumption at 100 and above
13 week/rat/oral?	0, 35, 70 or 140	Not established	35:atrophy of ovaries with vacuolation of stromal cells in all groups, kidney nephron degeneration and hypertrophy with albumin globules in cytoplasm of all males, increased lipid, some vacuolation, hypertrophy and foamy cytoplasm in adrenals of all groups.
13 week/rat/oral?	0, 8, 16 or32	Not established	8: vacuolation of the cortical cells
13 week/dog/oral?	0, 15, 30 or 60	30	60: increased relative and absolute thyroid weight
13 week/rat/inhalation (6h per day/ 5 days per week)	0, 2.2, 11.1 or 42 mg/m^3	Not established	Testicular degeneration and abnormal sperm in all treated groups
3 month/rat/diet	0, 2, 10 or 50	Not established	LOEL: 2 mg/kg bw/d All treated animals at 90 day had macroscopic patch patterns on the liver. Testicular atrophy at lowest dose.

Study Duration/Species/Route of Administration	Dose (mg/kg bw/d)	NOEL (mg/kg bw/d)	LOEL and endpoint
2 year/rat/dietary?	0, 8, 16 or 32 reduced to 0, 0.63, 2 or 6.32 after 18 weeks	0.63	2: Increased testicular weight
2 year (99-102 weeks)/mouse/dietary?	0, 3.6, 7.2 or 14.4	7.2	In a second phase females were fed the compound from day 10-12 gestation and offspring allocated to a treatment group (dose0, 3.6, 7.2 and 14.4) decreased survival in 14.4 mice.
3 generation/rat/diet?	0, 0.063, 0.2 or 0.63	0.2	0.63: Reduction in number of litters, reduced litter size and pup survival
Developmental/mouse/oral?	0, 8, 24	None stated	"There were no significant clinical effects or effects on fertility indices. There were no teratological effects"
Developmental/rabbit/oral?	0, 2, 20 or 200	None stated	200: maternotoxicity ("weight loss, decreased food intakes and increased and abortion")increased relative and absolute liver weight. Delayed ossification of ribs and decreased extra ribs.

? indicates that the available information is incomplete i.e. a number of studies presented in Table 1 above have poor reporting/recording of study details regarding the route of exposure.

The most appropriate NOEL from Table 1 above would be 0.2 mg/kg bw/d from a 3 generation reproduction study in rats. However, no suitable toxicity studies addressing the neuropathy and developmental toxicity potential of molinate are available in the OCS database for molinate.

In contrast, the US EPA as part of their re-registration program has evaluated a number of studies (which have not been provided to OCS for evaluation) which are critical for the purpose of this current risk assessment. In particular, the low observed effect level (LOEL) of 1.8 mg/kg bw/d for neurotoxic effects in offspring in a rat oral developmental neurotoxicity study is the most appropriate study for OHS risk assessment purposes (noting that no NOEL was established in this study). In this case, a margin of exposure (MOE) of 1000 would be considered acceptable, which takes into consideration 10-fold intra- and interspecies variability and uncertainty with the use of a LOEL rather than a NOEL. This approach (1.8

mg/kg bw/d LOEL with a 1000-fold MOE) is consistent with the interim OHS risk assessment of molinate performed in 2006.

The US EPA indicated that molinate is extensively absorbed across the skin (40% dermal absorption), and systemically bioavailable at doses (oral) associated with developmental and neurotoxic effects. The OCS has not evaluated any studies on the dermal absorption of molinate, and none has been submitted by the applicant with this application. In the absence of chemical specific dermal absorption data (consisting of *in vivo* and *in vitro* studies in rats and *in vitro* human studies, conducted according to appropriate international testing guidelines in a vehicle resembling that found in the product) it is OCS practice to apply a default value of 100% dermal absorption. According to European Commission Guidance (and also appearing in the latest OECD guidance), for some chemicals, a reduced default value of 10% dermal absorption may be appropriate based on the physicochemical properties of the compound (i.e. molecular weight >500 and a log K_{ow} <-1 or >4) (EC 2004, OECD 2010). However, molinate does not fulfil the criteria specified above and therefore a default 100% dermal absorption factor has been used for risk assessment purposes.

Risk assessment - Estimation of exposure

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to model all potential exposure scenarios.

The following scenarios from PHED were used to estimate worker exposure to product:

> **PHED Scenario 3** - All liquids, open mixing/loading (MLOD) [High confidence data for dermal exposure (AB grade): 53 hand replicates without gloves and 59 hand replicates with gloves; High confidence data for inhalation exposure (AB grade): 85 replicates]
>
> **PHED Scenario 6** - All liquids, closed mixing/loading (MLOD) [Low- High confidence data for dermal exposure (AB grade): 0 hand replicates without gloves and 31 hand replicates with gloves; High confidence data for inhalation exposure (AB grade): 27 replicates]
>
> **PHED Scenario 7** – Aerial-fixed wing/enclosed cockpit/liquid application (APPL) eg: Low-High confidence data for dermal exposure (ABC grade): 34 hand replicates without gloves and 7 hand replicates with gloves; Medium confidence data for inhalation exposure (ABC grade): 23 replicates]
>
> **PHED Scenario 9** – Rotary (Helicopter) Application, enclosed cockpit (APPL) eg: Extremely Low confidence data for dermal exposure (C grade): 2 hand replicates without gloves and 1 hand replicate with gloves; Low confidence data for inhalation exposure (A grade): 3 replicates]

The following parameters and assumptions were used in the exposure estimates:

General:

Average worker bodyweight: 70kg

Dermal absorption factor:100%

Inhalation absorption factor:100%

For Mixing/Loading:

Maximum application rate: 3.75L/ha

Maximum area treated per day: 30ha

Maximum quantity handled per day: 108 kg a.i.

For Rotary Helicopter application:

Maximum application rate: 3.75L/ha

Maximum area treated per day: 30ha

Maximum quantity handled per day: 108 kg a.i.

For Aerial application:

Maximum application rate: 5.2L/ha

Maximum area treated per day: 100 ha

Maximum quantity handled per day: 499.2 kg a.i.

It should be noted that the applicant has also supplied closed mixing/loading data for aerial application which is based on a modification of PHED. As the suitability of the data was unable to be verified by OCS at this time (see recommendations for further data requirements), it has not been included in this risk assessment.

Table 2: Estimates of systemic exposure for molinate (mg/kg bw/day)

Estimates	Gloves	Mixer/loader dermal	Applicator dermal	Mixer/ loader Inhalation	Applicator Inhalation	Total exposure*
Estimate 1 - **Scenario 3** Open mixing/loading	N	9.7153	NA	0.0041	NA	9.7193
	Y	0.0782	NA	0.0041	NA	0.0822
	Y#	0.0284	NA	0.0001	NA	0.0284
Estimate 2 – **Scenario 6**: closed mixing/loading	N	0.0806	NA	0.0003	NA	0.0809
	Y	0.0292	NA	0.0003	NA	0.0295
Estimate 3 – **Scenario 3 and Scenario 7**: open mixing/loading and aerial application	N	44.9061	0.0787	0.0189	0.0011	45.0048
	Y	0.3613	0.0343	0.0189	0.0011	0.4155
	Y#	0.1311	0.0343	0.0004	0.0011	0.1668
Estimate 4 – **Scenario 6 and Scenario 7**: closed mixing/loading and aerial application	N	0.3726	0.0787	0.0013	0.0011	0.4537
	Y	0.1349	0.0343	0.0013	0.0011	0.1716
Estimate 5 – **Scenario 3 and Scenario 9**: open mixing/loading and helicopter application	N	9.7153	0.0066	0.0041	0.0000	9.7260
	Y	0.0782	0.0066	0.0041	0.0000	0.0889
	Y#	0.0284	0.0066	0.0001	0.0000	0.0350
Estimate 6 – **Scenario 6 and Scenario 9**: closed mixing/loading and helicopter application	N	0.0806	0.0066	0.0003	0.0000	0.0875
	Y	0.0292	0.0066	0.0003	0.0000	0.0361

*Total exposure to active. Estimates are for workers wearing long pants and long sleeved shirt (single layer of clothing). Exposure values were based on person of 70 kg bw, 100% dermal absorption factor, and a 100% default inhalational absorption factor. #Additional PPE consisting of full face piece respirator, second layer of clothing and a washable hat for mixing/loading phase only. NA – Not applicable.

The 2006 interim OHS risk assessment stated the following:

The unit exposure from 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 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 MOE for dermal and inhalation exposure was unacceptable (167) using a LOEL of 2 mg/kg bw/d. On the basis of these calculations, it is considered that the mixing and loading of molinate products poses an unacceptable risk (dermal and inhalational) to workers.

The OCS is no longer able to support the use of a reduced dermal absorption factor for molinate, this is explained in more detail under the section of this document entitled *Selection of No Observed Effect Level (NOEL).* Table 2 above shows the estimates of exposure arising from both open and closed mixing/loading as per PHED.

Margin of Exposure (MOE)

The 2006 interim OHS risk assessment contained the following information: "The combined MOE for dermal and inhalation exposure was unacceptable (167) using a LOEL of 2 mg/kg bw/d. On the basis of these calculations, it is considered that the mixing and loading of molinate products poses an unacceptable risk (dermal and inhalational) to workers…… There is no surrogate data or exposure model available for either herbigation or SCWIIRT (these methods are not used in the USA). However, given that the combined MOE for inhalational and dermal exposure is unacceptable for mixer/loaders, it is highly unlikely that exposure to molinate below 0.002 mg/kg bw/d is achievable using herbigation or SCWIIRT. On this basis, the ground application of molinate via herbigation or SCWIIRT can no longer be supported."

Table 3 below contains MOE values for both open and closed mixing/loading. As neither of these values is above the appropriate MOE (1000 as determined earlier), the mixing/loading of molinate products for ground application cannot be supported. Since values for mixing/loading are unacceptable, combined both mixing/loading will also provide unacceptable MOEs. The OCS continues to recommend that the ground application of molinate via herbigation or SCWIIRT can no longer be supported.

Table 3: MOE* for workers using molinate

Estimates	Gloves	Mixer/loader dermal	Applicator dermal	Mixer/ loader Inhalation	Applicator Inhalation	Total
Estimate 1 - Scenario 3 Open mixing/loading	N	0	NA	440	NA	0.1
	Y	23	NA	440	NA	21
	Y#	63	NA	22049	NA	63
Estimate 2 – Scenario 6: closed mixing/loading	N	22	NA	6375	NA	22
	Y	61	NA	6375	NA	61
Estimate 3 – Scenario 3 and Scenario 7: open mixing/loading and aerial application	N	0	23	95	1684	0
	Y	5	52	95	1684	4
	Y#	14	52	4770	1684	11
Estimate 4 – Scenario 6 and Scenario 7: closed mixing/loading and aerial application	N	5	23	1379	1684	4
	Y	13	52	1379	1684	10
Estimate 5 – Scenario 3 and Scenario 9: open mixing/loading and helicopter application	N	0	272	441	293998	0
	Y	23	273	441	293998	20
	Y#	63	273	22050	293998	51
Estimate 6 – Scenario 6 and Scenario 9: closed mixing/loading and helicopter application	N	22	272	6376	293998	21
	Y	62	273	6376	293998	50

Based on a NOEL of 1.8 mg/kg bw/day + a dermal absorption factor (100%) and a 100% default inhalational absorption factor.

Additional PPE consisting of full face piece respirator, second layer of clothing and a washable hat for mixing/loading phase only.

MOE values presented in Table 3 above also demonstrate that aerial application methods (such as aeroplane and rotary helicopter) are at least 20 fold lower than acceptable levels, even with additional PPE. It should be noted that additional PPE has not been applied for closed mixing/loading scenarios as this is considered inappropriate.

Recommendations

- The recommendation from the 2006 OHS risk assessment of molinate, that the OCS does NOT support the ongoing ground based application of molinate via herbigation or SCWIIRT methods on the basis of unacceptable dermal and inhalational risks to workers, remains appropriate. This recommendation was based on an updated OHS risk assessment which demonstrated that the Margin of Exposure (MOE) levels during open and closed mixing/loading are inadequate to protect the health of workers.
- There are objections on human health grounds to the use of molinate products via aerial application as the Margin of Exposure levels are inadequate to protect the health of workers using molinate. It should also be noted that the interim 2006 OHS assessment did NOT address aerial application, and that contemporary risk assessment practice would also involve the consideration of bystander exposure and spray drift.