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Australian Pesticides and Veterinary Medicines Authority

APRIL 2016

Chemistry report

For the review of maldison

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EXECUTIVE SUMMARY

Maldison (also known as malathion) is a non-systemic, broad spectrum organophosphorus (OP) insecticide and acaricide used in agricultural and veterinary products.

Approvals of the active constituent maldison, registered products containing maldison, and all associated labels are being reconsidered by the APVMA because of concerns that they may be:

- an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
- likely to have an effect that is harmful to human beings.

This report covers the chemistry aspects of the maldison review, with a focus on the stability of the maldison active constituent and potential formation of toxicologically significant impurities.

The APVMA has an established Standard for maldison active constituents which specifies minimum purity requirements and maximum limits for the following toxicologically significant impurities:

- isomalathion
- malaoxon
- the trialkyl phosphorothioates
    - O,O,S-trimethylphosphorothioate (MeOOSPO)
    - O,S,S–trimethylphosphorodithioate (MeOSSPO).

As an outcome of the chemistry assessment, it is recommended that the APVMA Standard for maldison active constituents is amended to more closely align with the Food and Agriculture Organisation of the United Nations (FAO) specifications and evaluations for maldison (2013).

APVMA specifications for assessing the chemical stability of maldison active constituents and products have been developed based on the proposed APVMA Standard for active constituents, and relevant parts of the FAO specifications and evaluations for maldison (2013).

As an outcome of this assessment, the following recommendations are made:

- it is recommended that the Australian pesticides common name for maldison is changed to malathion to harmonise with the International Organization for Standardization (ISO) common name
- approved maldison active constituents and registered products must comply with the APVMA specifications for maldison active constituents and products outlined in this report. Active constituents and/or products that do not comply with the APVMA specifications should be suspended or cancelled, unless steps are taken to address APVMA concerns
- it is recommended that maldison products be made date-controlled products, with a shelf life of no more than two years after manufacture, to avoid public health risks from potential formation of isomalathion over time
- the APVMA Standard for maldison active constituent should be amended to reflect the APVMA specifications outlined in Table 5

- it is recommended that an APVMA product standard be established to reflect the APVMA specifications outlined in Table 5
- for all future approvals and registrations of maldison active constituents and products, it is recommended that storage stability tests include isomalathion measurements, which must not exceed the relevant revised APVMA Standard for maldison active constituents and proposed product standard.

1 INTRODUCTION

1.1 Scope of maldison review

The review of maldison commenced in 2003 due to human health concerns. Of particular concern is the potential formation of toxicologically significant impurities, metabolites and degradants in active constituents and products, after opening and during storage, and the potential adverse effects of these on human health. The scope of the review includes the following assessments:

- toxicology of active constituents and products containing maldison, including four[1] impurities specified in the APVMA Standard for maldison active constituent
- chemical stability of approved maldison active constituents and registered products
- occupational health and safety including:
  - risk to people mixing, loading and applying maldison
  - risk to worker/public on re-entry to treated areas
  - adequacy and suitability of first aid and safety directions on product labels.

During the assessment phase, data for storage stability of approved maldison active constituents and registered maldison-containing products were received from holders.

This chemistry component assessment considers and includes the following:

- the assessment of the submitted storage stability data
- determination of whether current approved active constituents and registered products comply with safety standards
- recommended regulatory measures.

1.2 Maldison product registrations and associated use-patterns

Maldison-containing products are registered for use in a variety of agricultural and veterinary situations, for both domestic and commercial applications.

Domestic uses include as home garden sprays for control of various insects and for use on pets and pet facilities for the control of fleas, lice and mange.

Commercial products are used to control insects in horticultural areas such as fruit and vegetable crops, field crops, pastures and stored cereal grains. They are also used to control pests on native eucalyptus vegetation and

[1] The impurities in the APVMA Standard for maldison: ie iso-malathion (ISOM), malaoxon, O,S,S–trimethylphosphorodithioate (MeOSSPO) and O,O,S–trimethylphosphorothioate (MeOOSPO)

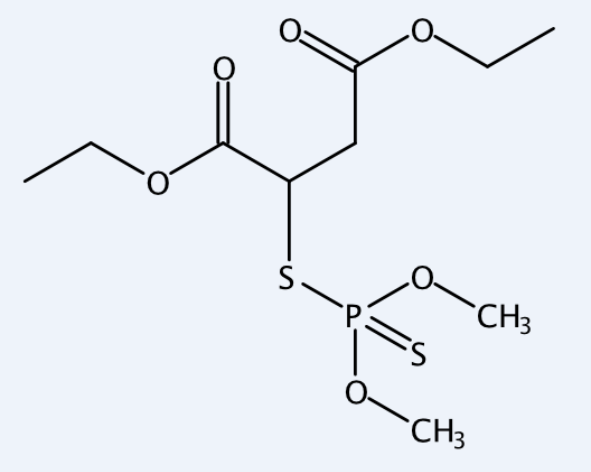
wild flowers. Other uses of maldison products are as sprays, dusts and lures for the control of pests in animal quarters, sheds, dairies, factories and stables.

Maldison-containing products are available in a variety of formulation types including emulsifiable concentrates (EC), baits (BA), aerosols (AE), oil in water emulsions (EW), ultra-low volume (UL), dustable powder (DU), solids (SO), shampoos and other topical solutions.

Some maldison-containing products are registered as fruit fly lures and baits, including enclosed, maldison-impregnated circular-wicks and small, maldison-impregnated blocks. These products contain less than 0.3 g of maldison per wick or block. These were assessed by the Office of Chemical Safety (OCS) as being of very low risk to people who prepare and use them. Hence data were not required for these five products and no chemistry assessment was conducted.

2 STRUCTURES AND PROPERTIES OF MALDISON AND ITS RELEVANT TOXICOLOGICAL IMPURITIES

2.1 Chemical identity

Common Name	malathion (ISO 1750)
Other Common Name	maldison (Australia and New Zealand Standard)[2]
IUPAC Name	diethyl(dimethoxythiophosphorylthio) succinate or S-1,2-bis(ethoxycarbonyl)ethyl O,O-dimethyl phosphorothioate
CAS Name	Diethyl [(dimethoxyphosphinothioyl)thio]butanedioate
CAS Registry Number	121–75–5
EC Number	204–497–7
Molecular Formula	$C_{10}H_{19}O_6PS_2$
Molecular Weight	330.36
Structure	
Chemical Family	Organophosphorus compound

[2] It is also known as malathion (E-ISO), mercaptothion (Republic of South Africa), carbofos (Russia), mercaptotian (Argentina) and malthon (JMAF).

2.2 Chemical and physical properties of maldison[3]

Parameters	Properties
Colour	Clear amber
Odour	Mercaptan (thiol)—like
Physical stat	Liquid
Melting point	2.85°C
Boiling Point	156–157°C at 0.7 mmHg
Density	1.23 (25°C)
Partition coefficient (log K_{ow})	2.75
Henry constant	1.21×10^{-2} Pa· m^3·mol^{-1} (calc.)
Vapour pressure	5.3 mPa (30°C)
Solubility	In water: 145 mg/L (25°C) Miscible with most organic solvents eg alcohols, esters, ketones, ether, aromatic hydrocarbons. Slightly soluble in petroleum ether and some types of mineral oil. In heptane 65–93 g/L
Stability	Relatively stable in neutral, aqueous media. Decomposed by strong acids and alkalis.

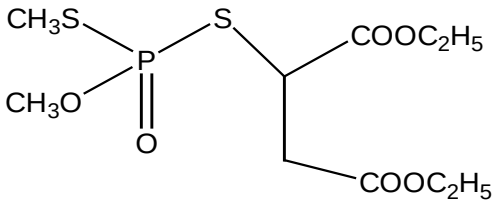
2.3 Structure of toxicologically significant impurities

The toxicologically significant impurities of maldison include:

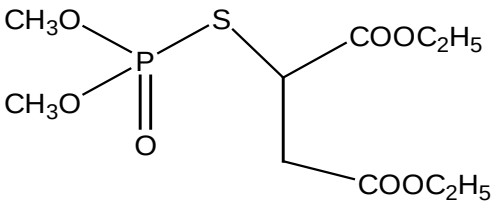
- isomalathion
- malaoxon
- various trialkyl phosphorothioates including:
  - O,S,S–trimethylphosphorodithioate (MeOSSPO)
  - O,O,S–trimethylphosphorothioate (MeOOSPO)
  - O,O,S–trimethylphosphorodithioate (MeOOSPS)
- O,O,O–trimethylphosphorothioate (MeOOOPS).

[3]The Pesticide Manual, 16th edition (November 2012), edited by C MacBean.

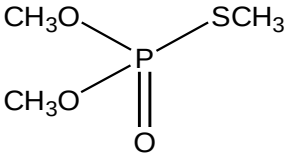
The chemical structure of the impurities are shown below.



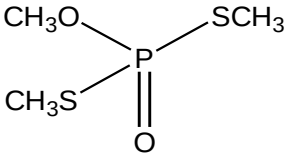
isomalathion



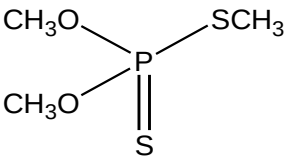
malaoxon



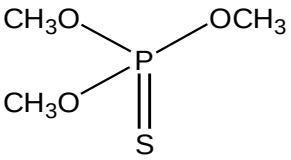
MeOOSPO



MeOSSPO



MeOOSPS



MeOOOPS

3 CURRENT STANDARDS AND SPECIFICATIONS

3.1 Australian common name for maldison

The APVMA typically adopts Australian common names for pesticides as specified in the Australian Standard number *'AS 1719–1994–Recommended common names for pesticides'* established by Standards Australia (1994).

As an outcome of the chemistry assessment, it is recommended that the Australian common name for maldison is changed to malathion to harmonize with the ISO common name as specified in the Standard '*ISO 1750:1981–Pesticides and other agrochemicals—Common names'* (ISO, 2013).

3.2 APVMA standards for maldison

Current APVMA Standard for maldison technical grade active constituent

The current APVMA Standard for maldison active constituent specifies compositional requirements for approved maldison active constituents including minimum concentration of active constituent, and the maximum allowable concentration of certain impurities. The impurity limits were set by the APVMA in 2005, following advice from the OCS.

The current APVMA Standard for maldison active constituent specifies a minimum active constituent concentration of 950 g/kg. It also specifies upper impurity limits as follows:

Current APVMA Standard for maldison active constituent

- isomalathion (CAS No. 3344-12-5): 2 g/kg (0.2%) maximum
- malaoxon (CAS No. 1634-78-2): 1 g/kg (0.1%) maximum
- MeOOSPO (CAS No. 152-20-5): 5 g/kg (0.5%) maximum
- MeOSSPO (CAS No.22608-53-3): 0.1 g/kg (0.01%) maximum

These impurities can be formed during the manufacturing process, prolonged storage or storage at elevated temperatures.

APVMA's allowable variation of active constituent concentration in products

The APVMA has prescribed standards specifying allowable variation of the active constituent concentration for agricultural chemical products as indicated in Table 1 below[4].

[4]As specified in Section 42(4) of the Agricultural and Veterinary Chemicals Code Regulations 1995.

Table 1. APVMA prescribed allowable variation of active content for chemical products

Concentration of each active constituent as specified on the product label (g/kg or g/L at 20˚C)	Standard (allowable variation)
500 or more	± 25 g/kg or g/L of the active constituent
From 250 up to but not including 500	± 5% of the content of the active constituent
From 100 up to but not including 250	± 6% of the content of the active constituent
Less than 100	± 10% of the content of the active constituent

The FAO specifications for maldison products are largely the same, with the following exceptions:

- DU above 25 up to 100 g/kg—(-10% to +25% of the active constituent)
- UL (the malathion content shall be declared (not less than 950 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content).

3.3 FAO specifications for maldison

The FAO specifications for agricultural pesticides have been established to promote the manufacture, distribution and use of pesticides that meet basic quality requirements (FAO, 2013). They are recognised by the APVMA as an authoritative reference standard, which may be applied to Australian active constituents and products where appropriate.

FAO specifications for maldison technical grade active constituent

The 2013 FAO specifications for technical maldison (active constituent) specify that the maldison concentration must not be less than 950 g/kg, which is consistent with that specified by the APVMA.

The maximum concentrations for impurities considered by the FAO to be toxicologically significant in the technical material are as follows:

- isomalathion: 4 g/kg (0.4%) maximum
- malaoxon: 1 g/kg (0.1%) maximum
- O,O,S-trimethylphosphorodithioate (MeOOSPS): 15 g/kg (1.5%) maximum
- O,O,O-trimethylphosphorothioate (MeOOOPS): 5 g/kg (0.5%) maximum

A comparison between the current APVMA and FAO standards for maldison active constituent is provided in Table 2 below.

Table 2. APVMA vs FAO specifications for maldison active constituents

Chemical	APVMA	FAO
Maldison	Min 95%	Min 95%
Malaoxon	Max 2 g/kg	Max 2 g/kg
Isomalathion	Max 2 g/kg	Max 4 g/kg
MeOOSPS	NS	Max 15 g/kg
MeOOOPS	NS	Max 5 g/kg
MeOOSPO	Max 5 g/kg	NS
MeOSSPO	Max 0.1 g/kg	NS

NS: not specified

A comparison of APVMA and FAO specifications for maldison active constituents indicates that there are two trialkyl phosphorothioate impurities, MeOOSPO and MeOSSPO, included in the APVMA Standard, but not in the FAO specifications. The APVMA Standard does not include two trialkyl phosphorothioate impurities, MeOOSPS and MeOOOPS, which are included In the FAO specifications. Further, the current upper limit for isomalathion in the APVMA Standard is half that of the FAO specifications. A reason for the differences between the APVMA and FAO active constituent standards is that they are established with consideration of analytical chemistry results and submitted data for approved active constituents, which may reflect distinct manufacturing processes and other regional factors. The APVMA Standard has been developed with consideration of advice from the OCS on human health issues, analytical chemistry results and data submitted for approved Australian active constituents, and international regulations and guidelines such as the FAO specifications. Further explanation on the development of the APVMA Standard for maldison active constituent and differences with the FAO specifications are provided in section 5.1 below.

FAO specifications for maldison products

The 2013 FAO specifications include maximum allowable impurity concentrations for toxic impurities in DU, UL, EC and EW maldison-containing product formulations (see Table 3 below). The APVMA does not currently have impurity standards for products (including maldison products), and instead rely on the Standard for active constituents used to formulate products.

Table 3. FAO specifications for maldison active constituents and product formulations

Chemical	Technical active constituent	UL	EW	EC	DU
Maldison	Min 95%	Min 95%	Active constituent content of product	Active constituent content of product	above 25 up to 100 g/kg: -10% to +25%
Malaoxon*	Max 0.1%	Max 0.1%	Max 0.8%**	Max 0.1%	Max 0.1%
Isomalathion*	Max 0.4%	Max 0.4%	Max 0.6%	Max 0.8%	Max 2.5%
MeOOSPS*	Max 1.5%	Max 1.6%	Max 1.6%	Max 1.6%	Max 1.6%
MeOOOPS*	Max 0.5%	Max 0.5%	Max 0.5%	Max 0.5%	Max 0.5%
MeOOSPO	NS	NS	NS	NS	NS
MeOSSPO	NS	NS	NS	NS	NS

**All impurity concentrations (%) are expressed as weight of impurity relative to the weight of active constituent.*

***Eg Max. 0.8% of an impurity, relative to the active constituent concentration in a product, is equivalent to 8 g of this impurity per kg of active constituent. So for a 500 g/L maldison product that contains 500 g maldison in 1 litre of the product, there should be no more than 4g of that impurity in one litre of the product.*

NS: not specified

The FAO specifications state that the storage stability results of impurities in products, after accelerated storage at 54 ± 2ºC for 14 days, should not exceed the maximum concentrations (relative to the concentration of active) as indicated in Table 3 above. In addition, the concentration of the active constituent in a maldison product should not exceed the allowable limit or ranges for the product's nominal concentration of maldison as indicated in section 3.2 above.

4 TOXICITY OF MALDISON, IMPURITIES AND EFFECTS OF STORAGE

The toxicology and human health-related aspects of maldison and associated impurities have been assessed by the OCS and will form the basis of the maldison toxicology report.

Maldison inhibits the action of acetylcholinesterase (AChE), an enzyme primarily responsible for terminating the transmission of nerve impulses in the autonomic (involuntary) nervous system, and at neuromuscular junctions. Compared to many other OPs, maldison is relatively inefficient in inhibiting the function of AChE.

However, impurities in maldison can increase (potentiate) the toxicity of maldison itself (FAO, 2013). This can occur due to increased inhibition of carboxylesterase activity, which is an important pathway for the detoxification of maldison. According to advice from the OCS, the impurities with the highest ability to cause potentiation are (in decreasing order):

1. MeOSSPO and isomalathion
2. MeOOSPO
3. MeOOOPS and MeOOSPS.

The most significant potentiators of maldison toxicity are MeOSSPO, isomalathion and MeOOSPO, all of which are included in the APVMA Standard for maldison active constituent. Other trimethyl impurities, MeOOOPS and MeOOSPS, are not considered to significantly potentiate maldison toxicity, and are not included in the APVMA Standard.

The FAO specifications and evaluations for maldison (2013) summarise oral-LD_{50} (in rats) for the impurities as shown in Table 4 below.

Table 4. Rat oral LD50s for toxicologically significant maldison impurities (FAO, 2013)

Impurity	Rat oral LD50 (mg/kg bw)	In FAO &/or APVMA Standard for active constituent?
Malaoxon	215	Both
Isomalathion *	113	Both
MeOOSPS	628	FAO only
MeOOOPS	562	FAO only
MeOOSPO *	47	APVMA only
MeOSSPO *	26	APVMA only

* A significant potentiator of maldison toxicity.

4.1 Trialkyl phosphorothioate impurities (MeOSSPO, MeOOSPO, MeOOSPS and MeOOOPS)

Two impurities, MeOSSPO and MeOOSPO are not included in the FAO specifications (2013) as they were not detected in the active constituent of the only data provider (except for one batch with a very low concentration of MeOOSPO). It was also noted that MeOSSPO, MeOOSPO and two other trialkyl phosphorothioates (MeOOOPS and MeOOSPS) were not formed after being stored for two years at 20°C, or after accelerated storage stability testing at 54°C ± 2°C for 14 days. However, both MeOSSPO and MeOOSPO have been detected in approved maldison active constituents in Australia. Hence, the FAO specifications are not appropriate for maldison active constituents approved in Australia. Consequently these additional impurities of toxicological significance are included in the APVMA Standard for maldison active constituent.

FAO (2013) reported similar results regarding the formation of trialkyl phosphorothioate impurities in maldison products, after accelerated storage stability testing, except in DU formulations. However the FAO did not consider that the increase of MeOOSPO and MeOOSPO in dust products was toxicologically significant.

4.2 Isomalathion

FAO (2013) reports that isomalathion concentrations can increase significantly during storage of products, especially at elevated temperatures. It was noted that after accelerated storage, only a small proportion (3–4 per cent) of the maldison was converted to isomalathion in EC and EW formulations, but 23 per cent and 31 per cent was converted to isomalathion in the DU and active constituent, respectively. As products cannot be purified, FAO found that the impurity limits (relative to the concentration of maldison) must be higher for the product formulations than for the active constituent.

4.3 Malaoxon

Although malaoxon is more toxic than maldison, its concentration in the active constituent is low and frequently below the limit of detection (LOD). Furthermore, its concentration does not increase significantly during storage.

There is no evidence to suggest that malaoxon is able to potentiate the maldison toxicity as the other impurities do. Hence it is unlikely that this impurity will significantly affect the overall toxicity of maldison.

5 CHEMISTRY ASSESSMENT

As part of the chemistry assessment, the APVMA re-assessed existing chemical stability data for approved active constituents and registered products containing maldison against newly developed APVMA specifications outlined in Table 5 below. Where existing data was insufficient to assess against the APVMA specifications, holders of registration were required to submit new information to support the continued registration of their products.

All data were also assessed against APVMA chemistry and manufacture data guidelines, including specifically those for generating storage stability data for agricultural and veterinary products.

5.1 APVMA specifications for assessment of storage stability results for active constituents and products containing maldison

APVMA specifications used for the assessment of maldison-containing active constituents and products were largely based on the APVMA Standard for maldison active constituent and FAO specifications for agricultural pesticides in agriculture (2013). Where appropriate, APVMA specifications were amended to reflect the compositional profile of Australian active constituents and products, while incorporating expert advice from the OCS on toxicology issues.

As an outcome of the maldison toxicology assessment conducted by the OCS, MeOOSPS and MeOOOPS are not considered to be toxicologically significant compounds and therefore are not included in the APVMA specifications. It has been determined that there are limitations for measuring MeOSSPO in EW, EC and DU formulated products. Hence, holders of EW, EC and DU products were not required to provide storage stability data for this impurity. This approach is considered reasonable, given FAO's assessment that this impurity did not increase in active constituent over prolonged real-time storage or from accelerated storage stability testing.

As UL products are generally composed mostly (if not entirely) of maldison active constituent, storage stability data was required for this formulation type.

A maximum level of 0.2 per cent (2 g/kg) for isomalathion, (the same as in the current APVMA Standard for maldison active constituent), was applied to newly manufactured technical active constituent (eg storage at room temperature within one month of production), but a maximum level of 0.4 per cent (4 g/kg) was applied to aged technical active constituent (i.e. after two years storage at ambient temperature or two weeks at 54°C).

To be supported from a chemistry perspective, storage stability results for active constituents and products must comply with the APVMA specifications outlined in Table 5 below. The FAO approved use of accelerated storage data to simulate real time storage conditions of up to two years is supported by analytical testing of Australian active constituents and products.

Table 5. APVMA specifications for assessment of storage stability results of active constituents and products containing maldison

Chemical	Active constituent†	Products^			
		UL	EW	EC	DU
Maldison*	Min 95%	active constituent concentration	active constituent concentration	active constituent concentration	active constituent concentration
Malaoxon	Max 0.1%	Max. 0.1%	Max. 0.8%	Max 0.1%	Max 0.1%
Isomalathion	Max. 0.2% (fresh batch) Max. 0.4% (aged batch)	Max. 0.4%	Max. 0.6%	Max 0.8%	Max. 2.5%
MeOOSPS	NR	NR	NR	NR	NR
MeOOOPS	NR	NR	NR	NR	NR
MeOOSPO	Max 0.5%	Max. 0.5%	Max. 0.5%	Max. 0.5%	Max. 0.5%
MeOSSPO	Max 0.01%	Max. 0.01%	NR	NR	NR

† Allowable concentrations for maldison active constituent are based on the APVMA Standard for maldison active constituent, with the exception of the maximum allowable isomalathion concentration (aged batch) which has been increased to 0.4% in line with FAO specifications for maldison (2013).

^ Allowable concentrations for maldison products are based on FAO product specifications (2013), with the exception of MeOOSPS and MeOOOPS which are not required due to their low toxicological significance. The maximum allowable concentrations of MeOOSPO and MeOSSPO are the same as those for the maldison active constituent as concentrations of these chemicals do not increase over extended storage.

Because of analytical limitations, data for MeOSSPO was not required/assessed for EW, EC and DU products.

Concentration percentages for all impurities in products are relative to the weight of active in the product.

* Allowable ranges of maldison concentrations in products are as specified in the Agricultural and Veterinary Chemicals Code Regulations 1995, with the exception of UL and DU products as outlined in point 5 of section 5.2 below.

NR Not required.

5.2 Justification for APVMA specifications

As mentioned previously, for the APVMA product specifications, all impurity concentrations are expressed relative to the amount of maldison in that product, not the total product weight or volume.

With this in mind, the justifications for the final specifications used for the APVMA assessment of chemical stability results in Table 5 are as follows:

1. Given their low toxicological significance, maximum allowable concentrations for MeOOSPS and MeOOOPS are not specified in the current APVMA Standard for maldison active constituents. Hence analyses of these impurities were not required.

2. Maximum allowable concentrations of MeOOSPO and MeOSSPO for active constituents are 0.5 per cent (5 g/kg) and 0.01 per cent (0.1 g/kg) respectively.

   As these impurities are unlikely to increase significantly during storage, the same maximum concentration limits should apply for active constituents and products containing maldison. As mentioned above, because of analytical limitations, stability data for MeOSSPO was not required for EW, EC or DU products, but was required for active constituents and UL product formulations.

3. The maximum allowable concentration for malaoxon in products containing maldison is the same as the FAO specifications (2013), as supported by analytical testing results for Australian products.

4. The APVMA Standard for maldison active constituent currently specifies a maximum concentration of 2 g/kg (0.2%) for isomalathion. Since the amount of isomalathion is known to increase during storage, it is recommended that the maximum concentration of isomalathion should be increased to 4 g/kg (0.4%) after long term or accelerated storage. This is supported by the FAO (2013) who accepted advice from the World Health Organisation (WHO) and International Programme on Chemical Safety (IPCS) that an isomalathion concentration of 0.4 per cent in active constituent is acceptable.

   Consequently, the maximum concentration of isomalathion specified in the FAO specifications for product formulations, is also appropriate to assess the storage stability of Australian products containing maldison.

5. The potential for decline in maldison concentration during accelerated storage is dependent on the formulation type. According to results reported in the FAO specifications (2013), the greatest decline observed was in the DU (5.9%), and the least in active constituent (0.7%). For the EC and EW formulations, the decline was 2.6% and 2.8%, respectively.

   The maldison concentration in products should comply with the allowable range for active constituent contents specified in *Regulation 42—Prescribed standards for chemical products* as outlined in the *Agricultural and Veterinary Chemicals Code Regulations 1995* with the exception of UL and DU formulations as outlined below:

   - for a DU formulation, the tolerance range for declared contents up to 100 g/kg is -10% to +25%, instead of the usual ±10%. The +25% tolerance used in this assessment reflects an allowable variation required to offset a significant degradation that may occur in freshly formulated material after storage.
   - in the UL specification, maldison content is expressed as a minimum (950 g/kg) only, instead of the standard expression (>500 ± 25 g/kg). This is because the UL formulation consists of only, or mainly, active constituent.

5.3 Criteria for assessing active constituents and products

Storage stability data on the concentration of maldison and toxicologically significant impurities were assessed during the maldison review, for both active constituents and most of the products containing maldison. Some products such as fruit fly baits were not assessed as part of the chemistry assessment as they were deemed to be low risk.

Most of the stability data were generated under accelerated storage conditions (2 weeks at 54 °C). The submitted storage stability data were assessed against the specifications in Table 5. The analytical method and data for method validation were also evaluated against APVMA data guidelines for chemistry and manufacture.

The criteria for determining whether active constituents and products are compliant with APVMA specifications are:

- the measured concentration of active constituent and toxicologically significant impurities should be at an acceptable concentration as outlined in APVMA specifications
- there should be sufficient data for the APVMA to undertake a full assessment which meets general APVMA chemistry and manufacture data guidelines, including specifically those for generating storage stability data and validating analytical methods.

6 RECOMMENDATIONS

6.1 Amendment of Australian common name for maldison

It is recommended that the Australian pesticides common name for maldison is changed to malathion to harmonise with the ISO common name.

This may involve the implementation of regulatory measures such as amendment to relevant APVMA Standards and product labels as required. It is recommended that these amendments are phased over a suitable period of time, to allow practical implementation, while minimising unnecessary burden on Government and industry.

6.2 Approval and registration status

From a chemistry perspective, the approval of active constituents and registration of products which do not comply with APVMA specifications, or have insufficient data, are not supported.

Unless new information becomes available to the APVMA which demonstrates that these products can comply with the APVMA specifications used in this assessment (eg via re-formulation), then it is recommended that they be cancelled.

6.3 Date controlled status for maldison products

The storage stability data provided for products supports a two year shelf life only.

Prolonged storage may increase the concentration of impurities (especially isomalathion), to concentrations that do not comply with the APVMA specifications outlined in Table 5.

Therefore it is recommended that maldison products be made date-controlled products, with a shelf life of no more than two years after manufacture. This may be reconsidered if future stability data supports further amendment to these conditions.

6.4 Amendment to the APVMA Standard for maldison active constituents

It is recommended that the APVMA Standard for impurities in maldison active constituent be amended, as shown below, with the amendments in bolded italics:

- isomalathion (CAS no. 3344-12-5):
  - 2 g/kg maximum within 30 days of manufacture
  - 4 g/kg maximum (as measured after accelerated storage, or after 2 years storage at ambient temperature)
- malaoxon (CAS no. 1634-78-2): 1 g/kg maximum
- O,O,S-trimethylphosphorothioate (MeOOSPO) (CAS no. 152-20-5): 5 g/kg maximum
- O,S,S-trimethylphosphorodithoate (MeOSSPO) (CAS no. 22608-53-3): 0.1 g/kg maximum
- ***O,O,S-trimethylphosphorodithioate (MeOOSPS)*** **(CAS no. 2953-29-9)*****: 15 g/kg maximum***

- ***O,O,O-trimethylphosphorothioate (MeOOOPS)* (CAS no. 152-18-1)*: 5 g/kg maximum***

The rationale behind the suggested amendments is as follows:

- data evaluated indicates increased isomalathion concentration in active constituent after storage, from 2 g/kg to 4 g/kg for fresh *versus* aged, which is considered to be acceptable from a human health perspective by OCS or the FAO; and
- OCS have advised that two trimethyl impurities in the FAO standard (MeOOSPS & MeOOOPS) are less toxic than the two (MeOOSPO and MeOSSPO) in the current APVMA Standard for maldison active constituent. However, it is concluded that they should be retained in the APVMA active constituent Standard to ensure that that Australian active constituents continue to be manufactured in accordance with FAO established specifications.

The proposed amendments would more closely harmonise the APVMA active constituent standard with internationally accepted FAO specifications.

6.5 Proposed APVMA standard for maldison products

It is recommended that an APVMA product standard be established for maldison products based on the APVMA product specifications for the assessment of storage stability data as indicated in Table 6 below.

Table 6. Compositional requirements of proposed APVMA standard for products containing maldison

Chemical	Formulation type			
	UL	EW	EC	DU
Maldison*	active constituent concentration^	active constituent concentration	active constituent concentration	active constituent concentration^
Malaoxon	Max. 0.1%	Max. 0.8%	Max 0.1%	Max 0.1%
Isomalathion	Max. 0.4%	Max. 0.6%	Max 0.8%	Max. 2.5%
MeOOSPO	Max. 0.5%	Max. 0.5%	Max. 0.5%	Max. 0.5%
MeOSSPO	Max. 0.01%	NR	NR	NR

Concentration percentages for all impurities in products are relative to the weight of active in the product.

Because of analytical limitations, data for MeOSSPO is not required for EW, EC and DU products.

* Allowable ranges of maldison concentrations in products are as specified in the Agricultural and Veterinary Chemicals Code Regulations 1995, with the exception of UL and DU products as outlined below.

^ For a DU formulation, a tolerance range for declared contents up to 100 g/kg is -10% to +25%, instead of the usual ±10%. The +25% tolerance used in this assessment reflects an allowable variation required to offset a significant degradation that may occur in freshly formulated material after storage.

In the UL specification, maldison content is expressed as a minimum (950 g/kg) only, instead of the standard expression (>500 ± 25 g/kg). This is because the UL formulation consists of only, or mainly, an active constituent.

NR Not required.

The submitted data and supporting FAO (2013) information for isomalathion in products containing maldison indicate that isomalathion has the potential to exceed acceptable concentrations, after prolonged storage or storage at elevated temperatures. Hence the APVMA considers that all future registrations of maldison products require storage stability data for isomalathion.

It is recommended that storage stability data for other impurities (malaoxon, MeOOSPO and MeOSSPO) is not automatically required for future registrations unless otherwise specified. This is because the data provided to the review, and FAO data, clearly indicated that these are unlikely to increase significantly during storage. It is however recommended that they are included in the proposed APVMA standard for maldison products to ensure Australian registered products continue to be manufactured in accordance with FAO established specifications.

ABBREVIATIONS

General chemistry and science terminology

AC	Active Constituent
AChE	Acetylcholinesterase
AE	Aerosol formulation
BA	Bait formulation
CAS	Chemical Abstracts Service
DU	Dustable powder
EC	Emulsifiable concentrate formulation
EW	Emulsion, oil in water formulation
ISOM	Isomalathion
LD	Liquid formulation
LD_{50}	Median lethal dose
LOQ	Limit of quantitation
MCS	Minimum Compositional Standard (for technical grade active constituent)
MeOOOPS	O,O,O-trimethylphosphorothioate
MeOOSPO	O,O,S–trimethylphosphorothioate
MeOOSPS	O,O,S-trimethylphosphorodithioate
MeOSSPO	O,S,S–trimethylphosphorodithioate
OP	Organophosphorus pesticide
SO	Solid formulation
UL	Ultra low volume formulation

Organisations and publications

APVMA	Australian Pesticides and Veterinary Medicines Authority
FAO	Food and Agriculture Organization of the United Nations
ISO	International Organisation for Standardization
OCS	Office of Chemical Safety
WHO	World Health Organization
WHO/IPCS	World Health Organisation / (International) Program on Chemical Safety

REFERENCES

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