

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

MALEIC HYDRAZIDE

6-hydroxy-2H-pyridazin-3-one;
1,2-dihydroxypyridazine-3,6-dione



FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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DISCLAIMER¹

FAO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

Additionally, FAO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

¹ This disclaimer applies to all specifications published by FAO.

INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of agricultural pesticides, with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 1999, the development of FAO specifications has followed the **New Procedure**, described in the 1st edition of “Manual for Development and Use of FAO and WHO Specifications for Pesticides” (2002) and amended with the supplement of this manual (2006), which is available only on the internet through the FAO and WHO web sites. This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPS, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the “Manual on development and use of FAO and WHO specifications for pesticides”.

Part Two: The Evaluation Report(s) of the plant protection product reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, annex 1 or 2 of the “Manual on the development and use of FAO specifications for plant protection products” and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT
<http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/>

PART ONE

SPECIFICATIONS

MALEIC HYDRAZIDE

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MALEIC HYDRAZIDE

INFORMATION

ISO common names

maleic hydrazide (E-ISO); hydrazide maléique (F-ISO); both accepted in lieu of common names

Chemical name(s)

IUPAC: 6-hydroxy-2H-pyridazin-3-one; 1,2-dihydropyridazine-3,6-dione

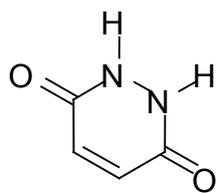
CA: 6-hydroxy-3(2H)-pyridazinone; 1,2-dihydro-3,6-pyridazinedione

Synonyms

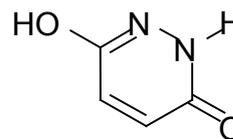
MH (WSSA, trivial)

Structural formulae

Maleic hydrazide is often named and drawn as two isomeric structures:



1,2-dihydro-3,6-pyridazinone



6-hydroxy-2H-pyridazin-3-one

Inter-conversion of the tautomers occurs readily in aqueous solution

Molecular formulae

maleic hydrazide (MH): $C_4H_4N_2O_2$

maleic hydrazide potassium salt (KMH): $C_4H_3KN_2O_2$

Relative molecular mass

maleic hydrazide (MH), 112.1

maleic hydrazide potassium salt (KMH), 150.2

CAS Registry numbers

123-33-1, maleic hydrazide pyridazinedione tautomer (MH)

10071-13-3, maleic hydrazide hydroxypyridazinone tautomer (MH)

51542-52-0, maleic hydrazide potassium salt (KMH)

CIPAC numbers

maleic hydrazide (MH): 310

maleic hydrazide potassium salt (KMH): 310.019

Identity tests

maleic hydrazide: HPLC retention time (detection at 302 nm), UV and IR spectra (reference IR spectrum provided to FAO).

potassium salt: flame test (qualitative) ion-selective electrode,
potassium-selective test strips (semi-quantitative).
diethanolamine salt: fishy odour (a qualitative test for the absence of
the diethanolamine salt)

MALEIC HYDRAZIDE TECHNICAL MATERIAL (Note 1)

FAO Specification 310/TC (June 2008*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (310/2001, 310/2003, 310/2004) (Note 1). It should be applicable to TC produced by these manufacturers (Note 1) but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (310/2001, 310/2003, 310/2004), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of maleic hydrazide together with related manufacturing impurities and shall be a white crystalline powder, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 Identity tests (Note 2)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 Maleic hydrazide content (Note 2)

The maleic hydrazide content shall be declared (not less than 970 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities

3.1 Hydrazine (Note 3)

Maximum: 0.001 g/kg (1 mg/kg).

Note 1 This specification is applicable to maleic hydrazide TC prepared by manufacturers identified in the evaluation reports listed, with the exception of Fair Products Inc, as this company does not isolate technical grade maleic hydrazide. Accordingly, this specification cannot be applied to any form of technical grade maleic hydrazide that may be produced by Fair Products Inc. The formulations of this manufacturer have been evaluated through a process of determining equivalence with the TC represented by the reference profile of impurities. See also Note 1 in the formulation specifications.

Note 2 The analytical method for identification and determination of maleic hydrazide content in technical and formulated maleic hydrazide is described in the following paper. Mertz J.L., Lau D.Y. and Borth D.M. Liquid chromatographic determination of maleic hydrazide in

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/>

technical and formulated products: collaborative study. *J. AOAC International*, **89**(4), 929-936, 2006.

Note 3 The analytical method for identification and determination of hydrazine content in technical and formulated maleic hydrazide is described in the following paper. Riggs A.S., Borth D.M., Tutty D.G. and Yu W.S. Determination of hydrazine in maleic hydrazide technical and pesticide formulations by gas chromatography: collaborative study. *J. AOAC International* **91**(1), 5-12, 2008.

MALEIC HYDRAZIDE SOLUBLE CONCENTRATE

FAO Specification 310.019/SL (June 2008*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (310/2001, 310/2003, 310/2004). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated sources (Note 1). The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (310/2001, 310/2003, 310/2004), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of technical maleic hydrazide, complying with the requirements of FAO specification 310/TC (June 2008) (Note 1), in the form of maleic hydrazide potassium salt, dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a clear or opalescent liquid, free from visible suspended matter and sediment, to be applied as a true solution of the active ingredient in water.

2 Active ingredient

2.1 Identity tests (Note 2)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 Maleic hydrazide content (Note 2)

The maleic hydrazide content shall be declared (g/kg or g/l at $20 \pm 2^\circ\text{C}$, Note 3) and, when determined, the content measured shall not differ from that declared by more than the following tolerances.

Declared content, g/kg or g/l	Permitted tolerance
above 100 up to 250	$\pm 6\%$ of the declared content
above 250 up to 500	$\pm 5\%$ of the declared content
Note: in each range the upper limit is included	

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/>

3 Relevant impurities

3.1 Hydrazine (Note 4)

Maximum: 0.001 g/kg (1 mg/kg) of the maleic hydrazide content found under 2.2.

4 Physical properties

4.1 Solution stability (MT 41, CIPAC Handbook F, p.131, 1995)

The formulation, after the stability test at 54°C (clause 5.2) and following dilution (Note 5) with CIPAC standard water D and standing at $30 \pm 2^\circ\text{C}$ for 18 h, shall give a clear or opalescent solution, free from more than a trace of sediment and visible solid particles. No separated material shall be observable.

4.2 Persistent foam (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 6)

Maximum: 50 ml after 1 min.

5 Storage stability

5.1 Stability at 0°C (MT 39.3, CIPAC Handbook J, p.126, 2000)

After storage at $0 \pm 2^\circ\text{C}$ for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

5.2 Stability at elevated temperature (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active ingredient content must not be lower than 97% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:

- hydrazine (3.1);
- solution stability (4.1).

Note 1 The maleic hydrazide present in the formulation is expected to comply with the requirements of FAO specification 310/TC (June 2008). However, the TC may be either isolated prior to formulation or formed notionally, in an integrated process of synthesis and formulation. In the latter case, compliance with specification 310/TC (June 2008) has been evaluated indirectly through a determination of equivalence but it cannot be tested directly.

Note 2 The analytical method for identification and determination of maleic hydrazide content in technical and formulated maleic hydrazide is described in the following paper. Mertz J.L., Lau D.Y. and Borth D.M. Liquid chromatographic determination of maleic hydrazide in technical and formulated products: collaborative study. *J. AOAC International*, **89**(4), 929-936, 2006.

The analytical method for identification of potassium, in maleic hydrazide formulated in the form of its potassium salt can be [downloaded here](#).

Note 3 If the buyer requires both g/kg and g/l at 20°C, then in cases of dispute the analytical results shall be calculated as g/kg.

Note 4 The analytical method for identification and determination of hydrazine content in technical and formulated maleic hydrazide is described in the following paper. Riggs A.S., Borth D.M.,

Tutty D.G. and Yu W.S. Determination of hydrazine in maleic hydrazide technical and pesticide formulations by gas chromatography: collaborative study. *J. AOAC International* **91**(1), 5-12, 2008.

Note 5 The concentration used for the test should not be higher than the highest concentration recommended in the instructions for use.

Note 6 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 7 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

MALEIC HYDRAZIDE WATER SOLUBLE GRANULES

FAO Specification 310.019/SG (June 2008*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (310/2001, 310/2003, 310/2004). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated sources (Note 1). The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (310/2001, 310/2003, 310/2004), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of granules containing technical maleic hydrazide complying with the requirements of the FAO specification 310/TC (June 2008) (Note 1), in the form of maleic hydrazide potassium salt, and suitable carriers and/or necessary formulants. It shall be homogeneous, free from visible extraneous matter and/or hard lumps, free flowing, and essentially non-dusty. The active ingredient shall be soluble in water. Insoluble carriers and formulants shall not interfere with compliance with clause 4.1.

2 Active ingredient

2.1 Identity tests (Note 2)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 Maleic hydrazide content (Note 2)

The maleic hydrazide content shall be declared (g/kg) and, when determined, the content measured shall not differ from that declared by more than the following tolerance.

Declared content, g/kg	Permitted tolerance
above 500	± 25 g/kg

3 Relevant impurities

3.1 Hydrazine (Note 3)

Maximum: 0.001 g/kg (1 mg/kg) of the maleic hydrazide content found under 2.2.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/>

3.2 **Water** (MT 30.5, CIPAC Handbook J, p.120, 2000)

Maximum: 70 g/kg.

4 **Physical properties**

4.1 **Degree of dissolution and solution stability** (MT 179, CIPAC Handbook H, p.307, 1998)

Residue of formulation noted after dissolution in CIPAC Standard Water D at $30 \pm 2^\circ\text{C}$.

Maximum: 0.0% after 5 min.

Maximum: 0.0% after 18 hours.

4.2 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 4)

Maximum: 35 ml after 1 min.

4.3 **Dustiness** (MT 171.1, CIPAC Handbook F, p.425, 1995) (Note 5)

Essentially non-dusty.

4.4 **Flowability** (MT 172, CIPAC Handbook F, p.430, 1995)

At least 99% of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve.

5 **Storage stability**

5.1 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active ingredient content must not be lower than the determined average content found before storage (Note 6) and the formulation shall continue to comply with the clauses for:

- hydrazine (3.1);
- degree of dissolution and solution stability (4.1);
- dustiness (4.3);
- flowability (4.4).

Note 1 The maleic hydrazide present in the formulation is expected to comply with the requirements of FAO specification 310/TC (June 2008). However, the TC may be either isolated prior to formulation or formed notionally, in an integrated process of synthesis and formulation. In the latter case, compliance with specification 310/TC (June 2008) has been evaluated indirectly through a determination of equivalence but it cannot be tested directly.

Note 2 The analytical method for identification and determination of maleic hydrazide content in technical and formulated maleic hydrazide is described in the following paper. Mertz J.L., Lau D.Y. and Borth D.M. Liquid chromatographic determination of maleic hydrazide in technical and formulated products: collaborative study. *J. AOAC International*, **89**(4), 929-936, 2006.

The analytical method for identification of potassium, in maleic hydrazide formulated in the form of its potassium salt can be [downloaded here](#).

- Note 3 The analytical method for identification and determination of hydrazine content in technical and formulated maleic hydrazide is described in the following paper. Riggs A.S., Borth D.M., Tutty D.G. and Yu W.S. Determination of hydrazine in maleic hydrazide technical and pesticide formulations by gas chromatography: collaborative study. *J. AOAC International* **91**(1), 5-12, 2008.
- Note 4 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.
- Note 5 The optical method, MT 171.2, usually shows good correlation with the gravimetric method, MT 171.1 and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.
- Note 6 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

MALEIC HYDRAZIDE WATER SOLUBLE POWDER (Note 1)

FAO Specification 310.019/SP (June 2008*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (310/2001, 310/2003, 310/2004). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated sources (Note 2). The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (310/2001, 310/2003, 310/2004), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of an homogeneous mixture of technical maleic hydrazide, complying with the requirements of FAO specification 310/TC (June 2008) (Note 2), in the form of the potassium salt, together with any necessary formulants. It shall be in the form of a powder to be applied as a true solution of the active ingredient after solution in water, but which may contain insoluble inert ingredients. Where the material is packaged in sealed water soluble bags (Note 3), a defined quantity of the material shall be contained in the bag.

2 Active ingredient

2.1 Identity tests (Note 4)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 Maleic hydrazide content (Note 4)

The maleic hydrazide content shall be declared (g/kg) and, when determined, the content measured shall not differ from that declared by more than the following tolerance.

Declared content, g/kg	Permitted tolerance
above 500	± 25 g/kg

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/>

3 Relevant impurities

3.1 Hydrazine (Note 5)

Maximum: 0.001 g/kg (1 mg/kg) of the maleic hydrazide content found under 2.2.

3.2 Water (MT 30.5, CIPAC Handbook J, p.120, 2000)

Maximum: 20 g/kg.

4 Physical properties

4.1 Wettability (MT 53.3, CIPAC Handbook F, p.164, 1995)

The formulation shall be completely wetted in 1 min without swirling.

4.2 Degree of dissolution and solution stability (MT 179, CIPAC Handbook H, p.307, 1998)

Residue of formulation noted after dissolution in CIPAC Standard Water D at $30 \pm 2^\circ\text{C}$.

Maximum: 0.0% after 5 min.

Maximum: 0.0% after 18 hours.

4.3 Persistent foam (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 6)

Maximum: 40 ml after 1 min.

In the case of water-soluble bag packaging, the provisions of clause 6.3 should be applied.

5 Storage stability

5.1 Stability at elevated temperature (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active ingredient content must not be lower than 97% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:

- hydrazine (3.1);
- wettability (4.1);
- degree of dissolution and solution stability (4.2).

In the case of water-soluble bag packaging, the package should be enclosed in a watertight sachet, box or any other container at $50 \pm 2^\circ\text{C}$ for 14 days.

The determined average active ingredient content must not be lower than 97% relative to the determined average content found before storage (Note 7), and the formulation shall continue to comply with the clauses for:

- hydrazine (3.1);
- wettability (4.1);
- dissolution of the bag (6.1);
- degree of dissolution and solution stability (6.2).

None of the bags tested should show signs of leakage or rupture during normal handling, before and after storage.

6 Material packaged in a sealed water-soluble bag (Notes 8, 9 and 10)

6.1 Dissolution of the bag (MT 176, CIPAC Handbook F, p.440, 1995)

The dissolution of the bag shall be tested on a sample of the emptied and cleaned bag taken according to the procedure described in Note 8, together with an appropriate proportion of the SP.

Flow time of the suspension: maximum 15 sec.

6.2 Degree of dissolution and solution stability (MT 179, CIPAC Handbook H, p.307, 1998)

The degree of dissolution and solution stability shall be tested on a solution containing the SP and the bag material in the actual ratio of application, prepared according to the procedure described in Note 9.

Residue of formulation retained on a 75 µm test sieve after dissolution in CIPAC Standard Water D at 30 ± 2°C.

Maximum: 0.0% after 5 min.

Maximum: 0.0% after 18 hours.

6.3 Persistent foam (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 6)

The persistent foam shall be tested on a solution containing the SP and the bag in the actual ratio of application, prepared according to the procedure described in Note 10.

Maximum: 40 ml after 1 min.

Note 1 This specification is not applicable to “damp-SP” products, as described in evaluation 310/2004, in part 2 of this publication.

Note 2 The maleic hydrazide present in the formulation is expected to comply with the requirements of FAO specification 310/TC (June 2008). However, the TC may be either isolated prior to formulation or formed notionally, in an integrated process of synthesis and formulation. In the latter case, compliance with specification 310/TC (June 2008) has been evaluated indirectly through a determination of equivalence but it cannot be tested directly.

Note 3 For record keeping purposes, the suffix “SB” should be added to the formulation code (SP-SB).

Note 4 The analytical method for identification and determination of maleic hydrazide content in technical and formulated maleic hydrazide is described in the following paper. Mertz J.L., Lau D.Y. and Borth D.M. Liquid chromatographic determination of maleic hydrazide in technical and formulated products: collaborative study. *J. AOAC International*, **89**(4), 929-936, 2006.

The analytical method for identification of potassium, in maleic hydrazide formulated in the form of its potassium salt can be [downloaded here](#).

Note 5 The analytical method for identification and determination of hydrazine content in technical and formulated maleic hydrazide is described in the following paper. Riggs A.S., Borth D.M., Tutty D.G. and Yu W.S. Determination of hydrazine in maleic hydrazide technical and pesticide formulations by gas chromatography: collaborative study. *J. AOAC International* **91**(1), 5-12, 2008.

Note 6 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 7 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

Note 8 Sub-sampling

Lay the bag on a bench and carefully open one side of the bag with a cutter, taking care not to damage the seals.

Transfer the contents of the bag into a suitable flask. This material shall be used to carry out the tests for: active ingredient identity (2.1), active ingredient content 2.2, hydrazine content (3.1), water content (3.2), wettability (4.2), dissolution of the bag (6.1), degree of dissolution and solution stability (6.2) and persistent foam (6.3).

The bag is then opened on three sides, completely cleaned of adhering powder by brushing or suction and weighed to the nearest 10 mg. It shall be used to carry out the dissolution test (6.1). Aliquots of an aqueous solution of the bag material shall be used in the tests of degree of dissolution and solution stability (6.2) and persistent foam (6.3).

In the case of delay of the above tests, the bag shall be stored in a watertight container (glass bottle or equivalent) to avoid any change in its properties.

Note 9 The sampling of the bag for the dissolution test should be as follows:

Lay the empty cleaned bag in its original configuration (double layer). Delineate and then cut up a test sample including part of the upper seal (5 cm) and symmetrically including the vertical seal (10 cm).

If the size of the bag is less than this dimension, use the whole bag.

Carry out the dissolution test immediately to avoid any modification of the sample.

Note 10 The procedure for adding the bag material to the solution for the rate of dissolution, solution stability and the persistent foam tests should be as follows:

Prepare a stock solution of the bag material (1 mg/ml) by weighing approximately a 100 mg sample (\underline{n} mg) of the bag (excluding sealed parts) to the nearest mg. Dissolve this sample by stirring in the standard water used for the tests to give a final volume of \underline{n} ml. Store the stock solution in a stoppered bottle before use.

Calculate the volume (\underline{V} ml) of the stock solution of the bag to be added to the test suspension of the water soluble powder according to the following equation:

$$V(\text{ml}) = X \times \frac{1000B}{W}$$

where: B (g) = weight of the emptied and cleaned bag;
W (g) = nominal weight of the SP contained in the bag;
X (g) = weight of the SP sample used in the test.

PART TWO

EVALUATION REPORTS

MALEIC HYDRAZIDE

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2001 Evaluation report based on submission of data from Crompton Corporation ¹ (TC, SG, SL)	2
2003 Evaluation report based on submission of data from Drexel Corporation (TC, SP, SL) and Fair Products Inc. (SP, SL)	16
2004 Evaluation report based on submission of data from Crompton Corporation ¹ (counter-ion identification) and Fair Products Inc. (damp-SP)	24

¹ Formerly Uniroyal Chemical Company, Inc., latterly Chemtura Corporation.

MALEIC HYDRAZIDE

FAO EVALUATION REPORT 310/2001

Explanation

The data for maleic hydrazide were evaluated in support of new FAO specifications. Maleic hydrazide is not under patent.

Maleic hydrazide was evaluated by the FAO/WHO JMPR in 1976, 1977, 1980, 1984, 1996 and 1998 and by WHO/PCS in 1999. It was evaluated/reviewed by the US EPA in 1994 and is under evaluation/review by the European Commission (Active Substance 484, List 1) under Directive 91/41/EEC. Maleic hydrazide was considered by the ICRC in 2001 in the context of the Rotterdam Convention on Prior Informed Consent, because it may contain hydrazine as an impurity.

The draft specification and supporting data were provided by Crompton Corporation (formerly Uniroyal Chemical Company, Inc.*) in 2001.

Note. Where necessary for brevity and clarity in this evaluation, KMH indicates the use of maleic hydrazide (potassium salt) and MH indicates the use of maleic hydrazide (free acid), as defined by the ISO common name, maleic hydrazide. These materials may not be present strictly as KMH or MH where, for example, they are dissolved in buffers.

Uses

Maleic hydrazide is a plant growth regulator, which inhibits plant cell division, but not enlargement of existing cells. When applied to plants, it moves through the cuticle and is actively transported to tissues where cell division is occurring. Because of its action in plants, maleic hydrazide is used by growers to control unwanted sucker (axillary bud) growth in tobacco and to control undesired sprouting of potatoes and onions in storage. Maleic hydrazide may also be used to control growth of utility turf grass along inaccessible or difficult-to-mow rights of way, and to inhibit amenity tree and shrub growth under utility lines.

Identity of the active ingredient

ISO common names

maleic hydrazide (E-ISO); hydrazide maléique (F-ISO); both accepted in lieu of common names

Chemical name(s)

IUPAC: 6-hydroxy-2H-pyridazin-3-one; 1,2-dihydropyridazine-3,6-dione

CA: 6-hydroxy-3(2H)-pyridazinone; 1,2-dihydro-3,6-pyridazinedione

* Latterly Chemtura Corporation.

Synonyms

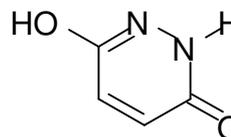
MH (WSSA, trivial)

Structural formulae

Maleic hydrazide is often named and drawn as two isomeric structures:



1,2-dihydro-3,6-pyridazinone



6-hydroxy-2H-pyridazin-3-one

Inter-conversion of the tautomers occurs readily in aqueous solution

Molecular formulae

maleic hydrazide (MH): $C_4H_4N_2O_2$

maleic hydrazide potassium salt (KMH): $C_4H_3KN_2O_2$

Relative molecular mass

maleic hydrazide (MH), 112.1

maleic hydrazide potassium salt (KMH), 150.2

CAS Registry numbers

123-33-1, maleic hydrazide pyridazinedione tautomer (MH)

10071-13-3, maleic hydrazide hydroxypyridazinone tautomer (MH)

51542-52-0, maleic hydrazide potassium salt (KMH)

CIPAC numbers

maleic hydrazide (MH): 310

maleic hydrazide potassium salt (KMH): 310.019

Identity tests

maleic hydrazide: HPLC retention time (detection at 302 nm), UV and IR spectra (reference IR spectrum provided to FAO).

potassium salt: flame test (qualitative) ion-selective electrode, potassium-selective test strips (semi-quantitative).

diethanolamine salt: fishy odour (a qualitative test for the absence of the diethanolamine salt).

Physico-chemical properties of maleic hydrazide

Table 1. Physico-chemical properties of pure maleic hydrazide

Parameter	Value(s) and conditions	Purity %	Method
Vapour pressure	<1 x 10 ⁻⁵ Pa at 25 °C	Not reported	U.S. EPA Guideline 63-9
Melting point	Melting point: 300-302 °C, with decomposition (blackening of the liquid)	Not reported	U.S. EPA Guideline 63-5
Solubility in water	144.0 g/l at 20 °C at pH 7 148.8 g/l at 20 °C at pH 9 4.4 g/l at 25 °C at pH 4.3 (MH) 4.5 g/l at 25 °C in unbuffered water (MH) 400 g/l at 25 °C (KMH)	Not reported	OECD 105, flask method Pesticide Manual, 2000 (method not reported)
Solubility in aqueous solutions	sodium hydroxide, 77.9% m/m aqueous triethanolamine, 66.8% m/m	Not reported	MT 71.1 MT 76
Solubility in organic solvents	acetone, 0.9% m/m ethanol, 15.1% m/m xylene, 0.0% m/m methanol, 4.2 g/l at 25 °C hexane, <0.001 g/l at 25 °C toluene, <0.001 g/l at 25 °C	Not reported	MT 27 MT 7.2 MT 11 Pesticide Manual 2000, method not reported
Octanol/water partition coefficient	log P _{OW} = -0.683 at pH 5 log P _{OW} = -2.01 at pH 7 log P _{OW} = -2.4182 at pH 9 (temperatures not reported) log P _{OW} = -0.56 (unionised acid, 25 °C)	Not reported	U.S. EPA Guideline 63-11 K. Chamberlain <i>et al.</i> , 1996
Hydrolysis characteristics	Maleic hydrazide is stable at 45 °C and 85 °C for 2 months in aqueous solution at pH 3, 6 and 9 (concentration not reported)	Not reported	U.S. EPA Guideline 161-1
Photolysis characteristics	Starting with MH in aqueous solution, maleic hydrazide was stable to simulated sunlight at pH 5 and 7 at 25 °C over a 30-day exposure period. It degraded slowly at pH 9 and 25 °C, with a calculated half-life of 15.9 days and rate constant of 4.35 x 10 ⁻² day ⁻¹ . At pH 7 and 9, the maleic hydrazide would be present largely as the anion. The degradation products at pH 9 were maleate and succinate. Starting with KMH, photolysis of aqueous solutions at pH 5, 7 and 9 produced calculated half-lives of 58, 58 and 34 days, respectively. The major product was maleate. KMH was found to be stable to photolysis on a sandy loam soil (conditions not reported).	Not reported	U.S. EPA Guidelines 161-2
Other degradation characteristics	Decomposed by oxidising agents and strong acids.	Not reported	Pesticide Manual, 2000, methods not reported
Dissociation characteristics	pKa = 5.62 at 20 °C pKa = 5.79 at 25 °C	Not reported	U.S. EPA Guideline 63-10 K. Chamberlain <i>et al.</i> , 1996

Table 2. Chemical composition and properties of maleic hydrazide (MH) technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 10-batch analysis data	Confidential information was supplied and is held on file by FAO. Mass balances for MH were 99.0 to 99.9%, unidentified organic impurities were individually $<0.1\%$. Total volatiles and ash, combined, were $<0.5\%$.
Declared minimum maleic hydrazide content	980 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities <1 g/kg and maximum limits for them:	hydrazine, 0.001 g/kg (1 ppm)
Stabilisers or other additives and maximum limits for them:	none
Melting temperature range of the TC	300-302°C, with evidence of decomposition (darkening) at melting point

The U.S. EPA specification for hydrazine is <15 ppm (0.015 g/kg) in technical maleic hydrazide.

Toxicological summaries

Notes.

- (i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from maleic hydrazide having impurity profiles similar to those referred to in the table above. The mammalian toxicity and mutagenicity studies were conducted with materials of various hydrazine content, all less than 2 ppm (JMPR 1996).
- (ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of maleic hydrazide technical materials, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions or guideline adopted	Result and test form of maleic hydrazide
Rat	Oral	Animals individually dosed by gavage at 5 g/kg bw. Observed for 14 d.	LD ₅₀ >5000 mg/kg bw (MH)
Rabbit	Dermal	24 h exposure. Observations for 14 d post-treatment.	LD ₅₀ >5000 mg/kg bw (MH)
Rat	Inhalation	4-hour nose-only.	LC ₅₀ >4 g/m ³ (KMH)
Rabbit	Skin irritation	24 h exposure (abraded and intact skin). Skin evaluated at 24 and 72 h post-treatment.	mildly irritating (MH)
Rabbit	Eye irritation	24 h exposure. Eyes evaluated at 1, 2, 3, 4 and 7 d.	slightly irritating (MH)
Guinea pig	Skin sensitization	3 induction exposures at 1 week intervals. Challenge treatment administered 14 d after final induction treatment. Dermal evaluations made 24 and 48 h after exposure.	not a dermal sensitizer (MH and KMH)

At the request of the U.S. EPA, technical grade KMH was used in toxicity and ecotoxicity testing conducted for the re-registration of maleic hydrazide in the USA

(USEPA 1994). Earlier work, and that conducted for regulatory actions in other countries, frequently was conducted with MH.

Table 4. Toxicology profile of the maleic hydrazide technical materials, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions or guideline adopted	Result
Sprague Dawley rats, male/female	Dermal sub-chronic study	21-day. 0, 100, 500 and 1000 mg/kg/d, 5d/week (KMH, purity 97.8%)	No dermal or systemic effects observed at the highest dose. NOEL > 1000 mg/kg bw/d
Sprague Dawley rats, male/female	Sub-chronic feeding study	13-week; 0, 30, 100, 300 and 1000 mg/kg/d (KMH, purity 97.8%)	No treatment-related were seen. NOEL > 1000 mg/kg bw/d
Beagle dogs, male/female	Sub-chronic feeding study	13-week; 0, 750, 2500, 7500 and 25,000 ppm (KMH, purity 97.8%)	No treatment-related were seen. NOEL > 625 mg/kg bw/d
Beagle dogs, male/female	Feeding study	technical grade KMH (purity 99.8%, 0.04 ppm hydrazine) was fed for one year at dietary concentrations of 0, 750, 2500 and 25000 ppm.	At dosage levels of 2500 and 25000 ppm, there was a decrease in body weight gain in both sexes. Reduced heart weight was also observed in these dosage groups. There was an increased incidence of hepato-cellular inflammation and thyroid follicular cell hypertrophy in both sexes, but only at the highest dosage level. The thyrioid effect was noted only in dogs, and only at the highest dose tested. NOEL for chronic toxicity = 29 mg/kg bw/d LOEL = 87 mg/kg bw/d for males and 105 mg/kg/d for females (USEPA).
Sprague Dawley rats, male/female	Feeding study	Technical grade KMH (purity 97.8%, <0.05 ppm hydrazine) was fed to male and female rats for two years at dietary concentrations yielding intakes of 0, 25, 500 and 1000 mg/kg bw/day.	At 1000 mg/kg bw/day there was a reduction in body weight gain in both sexes and at 500 mg/kg bw/d there was a body weight reduction in males only. There were no other significant toxicological findings and no evidence of oncogenicity. NOEL for chronic toxicity = 25 mg/kg bw/d LOEL for chronic toxicity = 500 mg/kg bw/d (USEPA).
Sprague Dawley rats, male/female	Oncogenicity study	Technical grade KMH (purity 97.8%, <0.05 ppm hydrazine) was fed to male and female rats for two years at dietary concentrations yielding intakes of 0, 25, 500 and 1000 mg/kg bw/day.	At 1000 mg/kg bw/day there was a reduction in body weight gain in both sexes, and at a dose level of 500 mg/kg bw/d there was a body weight reduction in males only. There was no increase in tumour incidence as a result of KMH administration.

Species	Test	Duration and conditions or guideline adopted	Result
CD-1 mice, male/female	Oncogenicity study	A two-year oncogenicity study was conducted in mice using technical grade KMH (purity 97.6%, 1.63 ppm hydrazine) at dietary concentrations of 3, 1000, 3200 and 10000 ppm.	There was no increase in tumour incidence as a result of KMH administration.
Sprague Dawley rats, male/female	Two generation reproduction	Technical grade KMH (purity 99%, <2 ppm hydrazine) was fed to two generations of male and female rats at dietary concentrations of 0, 1000, 10000 and 30000 ppm.	At the highest dosage, there was a reduction in body weight gain in females and pups from both generations. NOEL = 500 mg/kg bw/d, for systemic adult toxicity and offspring growth. NOEL = 1500 mg/kg bw/d for reproductive effects.
Sprague Dawley rats, female	Developmental toxicity study	Technical KMH (purity 97.8%, 0.048 ppm hydrazine) was administered by oral gavage to pregnant female rats at dosage levels of 0, 30, 300 and 1000 mg/kg bw/d.	No maternal toxicity was observed, and there were no developmental or teratogenic effects. NOEL >1000 mg/kg bw/d for maternal and developmental toxicity.
Dutch Belted rabbits, female	Developmental toxicity study	Technical grade KMH (purity 99.8%, 1 ppm hydrazine) was administered by oral gavage to pregnant female rabbits at dosage levels of 0, 100, 300 and 1000 mg/kg bw/d.	Maternal toxicity, as evidenced by slightly decreased body weight, was observed at 1000 mg/kg/d. There were no developmental or teratogenic effects. NOEL = 300 mg/kg bw/d for maternal toxicity NOEL >1000 mg/kg/d for developmental toxicity.

At the request of U.S. EPA, technical grade KMH was used in toxicity and ecotoxicity testing conducted for the re-registration of maleic hydrazide in the USA (USEPA, 1994). Earlier work, and that conducted for regulatory actions in other countries, frequently was conducted with MH.

Table 5. Mutagenicity profile of maleic hydrazide technical material based on *in vitro* and *in vivo* tests

Species	Test	Conditions	Result and test form of maleic hydrazide
<i>Salmonella typhimurum</i> , strains TA98, TA100, TA1535, TA1537 and TA1538.	Bacterial reverse-mutation assay (Ames assay), <i>in vitro</i>	with and without S9 metabolic activation. Tested at concentrations up to 10000 µg/plate.	negative (KMH)
<i>E. coli</i> , po/A ^{+/−}	DNA repair assay, <i>in vitro</i>	0.01 to 50 µg/plate (DMSO).	negative, with and without S9 activation (KMH)
<i>Drosophila melanogaster</i>	Sex-linked recessive lethal assay, <i>in vivo</i>	0.4 and 1% (w/v) in water.	negative (KMH)
Mouse lymphoma L5178Y cells	Mammalian cell gene mutation assay, <i>in vitro</i>	0.625 to 10 µg/ml (water).	negative (KMH)

Species	Test	Conditions	Result and test form of maleic hydrazide
Mouse (CD-1), males and females	Micronucleus formation assay, <i>in vivo</i>	Male and female mice dosed once by oral gavage at doses equivalent to 2500 or 5000 (limit dose) mg/kg KMH. Bone marrow cells scored at 72 h for polychromatic erythrocytes with micronuclei (m-PCE).	negative (KMH). No increase in m-PCE incidence in either sex.
Mouse (B6C3F1)	Bone marrow sister chromatid exchange (SCE) assay, <i>in vivo</i>	Male and female B6C3F1 mice were given single intraperitoneal injections of KMH at dosages up to 1100 mg/kg (lethal dose). Bone marrow cells observed for SCE.	negative (KMH) No significant increases in SCE were found in any treated male or female dose group.
Chinese hamster ovary cells	CHO chromosomal aberration assay, <i>in vitro</i>	KMH assayed at 1000, 2150 or 4640 µg/ml in absence of S9 activation, and at 2150, 4640 or 10000 µg/ml (maximum conc.) in presence of S9.	equivocal (KMH) Results negative in absence of S9. In presence of S9, a statistically significant ($p < 0.01$) increase in aberration-bearing cells was observed in the 10000 µg/ml cultures at 12 h but not at 24 h. This result was considered to be equivocal because of possible confounding effect of the increased osmotic pressure (osmolality).
Chinese hamster ovary cells	CHO sister chromatid exchange (SCE) assay, <i>in vitro</i>	Tested at doses up to 10000 µg/ml, +/- S9 activation.	positive (KMH) Dose-selection testing indicated delays in cell cycling at 10000 µg/ml in absence of S9 and at 3200 and 10000 µg/ml in presence of S9. Significant increases in SCE were observed in culture treated similarly. Hence, KMH was reported to be genotoxic in this assay, but only at cytotoxic doses.
<i>Bacillus subtilis</i> , strains M45(rec-) and H17(rec+)	Recombination assay, <i>in vitro</i>	Doses up to 10000 µg/plate (DMSO). Surviving colonies of each strain were counted at 1-2 days, and the survival index (S.I., ratio of relative survival of M45:H17 strains) was determined.	positive (MH and KMH) For KMH, no differences in S.I. without S9 activation. With S9, differential toxicities (i.e., decreased S.I.) were noted, but at only 10,000 µg/plate. For MH, decreased S.I.s were observed at doses of 5000 and 10000 µg/plate, with and without S9. It was reported that both materials appear to be genotoxic at extremely high dose levels.

At the request of U.S. EPA, technical grade KMH was used in toxicity and ecotoxicity testing conducted for the reregistration of maleic hydrazide in the USA (USEPA, 1994). Earlier work, and that conducted for regulatory actions in other countries, frequently was conducted with MH.

In 1994, U.S. EPA concluded that, "Maleic hydrazide appears to be genotoxic at high doses in some of the mutagenicity tests. Since maleic hydrazide is a uracil anti-metabolite, and this is presumably its mechanism of action with respect to its plant growth/herbicidal properties, it might be expected that equivocal or positive results would be observed in some genotoxicity tests. When the totality of genotoxicity studies is considered together with the results of all the toxicological studies on maleic hydrazide and its potassium salt, including negative carcinogenicity studies in rats and mice, it was concluded that the potential human genotoxic hazard is negligible."

Table 6. Ecotoxicology profile of maleic hydrazide technical materials

Species	Test	Duration and conditions	Result and test form of maleic hydrazide
<i>Daphnia magna</i> (water flea)	Acute toxicity	48 h static bioassay, observations at 24 and 48 h.	LC ₅₀ = 108 mg/l (MH) LC ₅₀ >1000 mg/l (KMH)
<i>Mysidopsis bahia</i> (mysid shrimp)	Acute toxicity	96 h. flow-through assay at 22°C. Observations at 24, 48, 72 and 96 h.	LC ₅₀ >103 mg/l (KMH)
<i>Crassostrea virginica</i> (eastern oyster)	Shell deposition	96 h. flow-through assay at 20°C. Oysters were from a population with mean umbo to distal valve edge length of 30 mm.	EC ₅₀ >111 mg/l (KMH)
<i>Oncorhynchus mykiss</i> (rainbow trout)	Short-term acute toxicity	96 h. static assay, at 10°C	LC ₅₀ = 1435 mg/l (MH)
<i>Lepomis macrochirus</i> (bluegill sunfish)	Short-term acute toxicity	96 h. static assay, at 22°C	LC ₅₀ = 1608 mg/l (MH)
<i>Cyprinodon variegatus</i> (sheepshead minnow)	Short-term acute toxicity	96 h. flow-through assay at 22°C. Observations at 1, 2, 3 and 4 d.	LC ₅₀ = 1608 mg/l (MH)
<i>Selenastrum capricornutum</i> (green alga)	IC ₅₀ , effect on growth, static water	5-day at 24°C	NOEC = 8 mg/l (KMH)
<i>Chlorella vulgaris</i> (green alga)	IC ₅₀ , effect on growth, static water	96 h. at 25°C	IC ₅₀ >100 mg/l (MH) (highest dose tested)
<i>Anabaena flos-aquae</i> (blue-green alga)	IC ₅₀ , effect on growth, static water	5 day assay, at 24°C	EC ₅₀ >95 mg/l (KMH) NOEC = 97.8 mg/l
<i>Nitzschia palea</i> (freshwater diatom)	IC ₅₀ , effect on growth, static water	5-day, at 24°C	EC ₅₀ >97.8 mg/l (KMH) NOEC = 97.8 mg/l
<i>Skeletoma costatum</i> (saltwater diatom)	IC ₅₀ , effect on growth, static water	5-day, at 20°C	EC ₅₀ >102 mg/l (KMH) NOEC >102 mg/l

Species	Test	Duration and conditions	Result and test form of maleic hydrazide
<i>Lemna gibba</i> (duckweed)	IC ₅₀ , effect on growth, static water	14-day, at 25 °C	EC ₅₀ 114 mg/l (KMH) NOEC = 38.6 mg/l
<i>Eisenia foetida</i> (earthworm)	Acute toxicity	Single soil treatment followed by 14-day exposure period, at 20-21 °C. Worms 510-556 mg at start of test.	LC ₅₀ >1000 mg/kg dry soil (KMH)
<i>Apis mellifera</i> (honey bee)	Acute contact toxicity	1.0 µl of dose solution (water) placed on ventral surface of thorax. Observed at 24 and 48h at 24 °C.	LD ₅₀ >100 µg/bee (KMH)
<i>Apis mellifera</i> (honey bee)	Oral toxicity (normal feeding)	Dosed and observed for 24 and 48 h at 24 °C	LD ₅₀ >100 µg/bee (KMH)
<i>Anas platyrhynchos</i> (Mallard duck)	Acute oral toxicity	Single dose by gavage, in corn oil. Observations for 8 d post-treatment.	LD ₅₀ > 4640 mg/kg bw (MH)
<i>Colinus virginianus</i> (Bobwhite quail)	Acute oral toxicity	Single dose administered in gelatin capsules. Observations for 14 d post treatment, 19-20 °C.	LD ₅₀ > 2000 mg/kg bw (KMH)
<i>Anas platyrhynchos</i> (Mallard duck)	Dietary toxicity	8-day (5-d exposure, 3-d observation period) sub-acute oral toxicity, rates up to 10000 mg a.i./kg diet	LD ₅₀ >10,000 mg/kg diet (MH)
<i>Colinus virginianus</i> (Bobwhite quail)	Dietary toxicity	8-day (5-d exposure, 3-d observation period), sub-acute oral toxicity, rates up to 10000 mg a.i./kg diet	LD ₅₀ >10,000 mg/kg diet (MH)

At the request of U.S. EPA, technical grade KMH was used in toxicity and ecotoxicity testing conducted for the reregistration of maleic hydrazide in the USA (USEPA, 1994). Earlier work, and that conducted for regulatory actions in other countries, frequently was conducted with MH.

The U.S. EPA (US EPA 1994) concluded that maleic hydrazide poses minimal risks to avian, mammalian and aquatic [animal] species from acute and dietary exposure and that there is minimal risk to non-target insects and non-target aquatic plants from the use of maleic hydrazide. The "levels of concern" for semi-aquatic plants were exceeded from run-off onto wet areas and those for terrestrial plants were exceeded by direct application to rights of way.

Maleic hydrazide was evaluated by the WHO IPCS in 1999 and by the FAO/WHO JMPR in 1976, 1980, 1984, 1996 and 1998.

The FAO/WHO JMPR (1998) concluded that the "International Dietary Intakes of maleic hydrazide for the five GEMS/Food regional diets, based on the STMRs for garlic, bulb onions, shallots and boiled potatoes, were in the range of 1 to 8% of the ADI. The Meeting concluded that the intake of residues of maleic hydrazide resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern" (JMPR 1998).

The IPCS hazard classification of maleic hydrazide is: "unlikely to present acute hazard in normal use", class U (WHO 1998).

The U.S. EPA considered that registered uses of maleic hydrazide will not cause unreasonable risk to humans. However, the Agency cautioned that both MH and KMH may adversely affect non-target plants and expressed particular concern about endangered plant species inhabiting rights of way or untreated areas receiving run-off from treated areas.

Maleic hydrazide and its hydrazine impurity was considered by the Interim Chemical Review Committee (ICRC, 2001) to the Rotterdam Convention on Prior Informed Consent (PIC). The committee concluded that PIC-listing is not necessary if the risks associated with the hydrazine impurity can be managed satisfactorily by means of FAO specifications for maleic hydrazide.

Formulations

The proposer stated that all manufacturers produce formulations containing maleic hydrazide in the form of the potassium salt (KMH). However, the proposer noted that choline salt formulations are listed by at least one source. Such formulations appear to be local and are not widely available in the international marketplace. The main formulation types available are water-based solution concentrates (SL) and water-soluble granules (SG). These formulations are registered and sold in many countries throughout the world. The proposer provided no information regarding co-formulation with other active ingredients.

Methods of analysis and testing

The method for determination of the active ingredient is undergoing validation by collaborative study, under the auspices of AOAC International¹. Maleic hydrazide is determined by HPLC, utilizing internal standardization (sulfanilic acid) and UV detection of sulfanilic acid at 248 nm and maleic hydrazide at 302 nm. Identification is by means of HPLC retention time and the UV spectrum. Average recovery from 4 replicate additions of technical MH to a blank formulation (concentration undefined) was 99.7%. Precision (CV), estimated from 9 replicate determinations on a TC having a mean content of 99.55% MH, was 0.43%.

For the purposes of determining free hydrazine in MH or its formulations, MH is precipitated from aqueous solution with acetic acid and removed by filtration. Hydrazine (as the salt) in the filtrate is derivatized with pentafluorobenzaldehyde, isolated by solid phase extraction, and analyzed by megabore capillary gas chromatography, using a splitless injection, a nitrogen detector and internal standardization with benzanilide. Duplicate determinations made on a sample of Royal MH7 60SG showed mean level of 0.73 mg/kg (CV 0.8%). Duplicate determinations of hydrazine added at a range of levels (0.25 to 6.2 mg/kg) showed recovery in the range 50.0 to 238%. The highest recovery was associated with the lowest levels of addition. The proposer indicated that the method is being studied under the auspices of AOAC International¹.

¹ 2008 footnote. The analytical method for determination of maleic hydrazide in technical and formulated products was adopted by AOAC International with first action status in 2004 and published in 2006. The analytical method for determination of hydrazine in technical and formulated maleic hydrazide was published in the Journal of AOAC International in 2008.

Simple flame test and odour detection methods were provided for checking that the TC and formulations are comprised essentially of the potassium salt. In combination, these methods are also capable of distinguishing a potassium-doped maleic hydrazide diethanolamine salt formulation from a true KMH formulation. Test methods for determination of physico-chemical properties of the pure and technical active ingredient were EC, OECD, CIPAC and USEPA, while those for the formulations were CIPAC, as indicated in the specifications.

Physical properties

The physical properties and the methods for testing them, and the limits proposed for the SL and SG formulations, comply with the requirements of the FAO Manual (5th edition).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient content is expressed as maleic hydrazide (free acid), in g/l for liquid formulations and g/kg for the technical material and water-soluble granule formulation, irrespective of the salt present, if any.

Appraisal

Maleic hydrazide is an active ingredient that is not under patent and has not previously been the subject of FAO specifications.

The proposer stated that maleic hydrazide, as the acid defined by the ISO name (MH), is prepared as a TC. The free acid is not used as a pesticide but is traded as a raw material. It is used only in the manufacture of formulated products that contain maleic hydrazide in the form of its potassium salt (KMH), which is prepared during the formulation process. Although the MH TC specification is therefore unlikely to be used directly for trading purposes, it forms the basis for the KMH formulation specifications and thus provides guidance to buyers and the manufacturer.

MH exhibits keto-enol tautomerization, with proton interchange occurring freely in solution, although in the IR spectrum it is evidently highly enolised. It is a fairly weak acid, of pK_a about 5.6. MH might be expected to have a second pK_a . Although not actually determined, the proposer considered on the basis of indirect evidence that the second pK_a could be in the range 8 to 9. This indicates that KMH is the monopotassium salt of maleic hydrazide, and that the hypothetical presence of K_2MH should not complicate the picture. The undissociated acid has moderate water solubility, whereas KMH is very water soluble. Neither MH nor KMH is fat soluble. MH is of very low volatility.

Maleic hydrazide is stable to hydrolysis in the range pH 3 to 9. In solution, MH is stable to photolysis at pH 5 and 7 but subject to slow photolysis at pH 9. In solution, KMH is also subject to slow photolysis at pH 9, with even slower photolysis occurring

at pH 5 and 7. KMH on a sandy loam soil was stable to photolysis. Photolysis products were identified as maleate and succinate. No information was available on the photolytic fate of the hydrazine moiety.

Confidential information on the manufacturing process, on impurities at or above 1 g/kg in MH, and on hydrazine content to the nearest 0.01 mg/kg, was provided by the proposer. Limits for the impurities were supported by 10 batch analyses, in which unidentified components (volatiles and ash) accounted for <0.46 g/kg. Mass balances were very high (99.0-99.9%). The manufacturing specification based on these batch analysis data was indicated to be identical to that submitted for registration in 40 countries. The impurity data for MH were similar to those provided to the European Commission for EU registration. Taking into account the change in molecular weight due to conversion to the potassium salt, the KMH data were broadly similar to those provided for MH and both indicated very high purity. The data for both MH and KMH indicated compliance with the specified limit for free hydrazine. The proposer stated that the impurity profiles were typical of the materials used in the toxicological and ecotoxicological testing and of the products sold.

The specified minimum content of MH in the TC is high (980 g/kg). Free hydrazine was proposed as a relevant impurity, with a maximum content of 1 mg/kg of MH. WHO/PCS noted that hydrazine induced gene mutations in bacteria, yeasts, and *Drosophila*. *In vivo* treatment of mice, rats, and Syrian hamsters resulted in the formation of N7-methyl- and O⁶-methylguanine in liver DNA. Hydrazine produced lung, liver, nasal and a few colon tumours in rats, after inhalation or ingestion exposure, and liver and thyroid tumours in hamsters (IARC, 1999). On this basis, WHO/PCS considered hydrazine to be a relevant impurity.

Of the long-term toxicology studies available (JMPR, 1997), the studies in CD-1 and C57Bl/B6 mice are informative with respect to the assessment of the acceptable concentration of hydrazine in maleic hydrazide. For the studies on rats, the hydrazine content is identified only as <0.05 or <1.5 mg/kg. This is not useful in making a corresponding assessment for rats, as the concentration of hydrazine could, perhaps, have been exceptionally low in these cases. In the mouse studies, the content of hydrazine was 1.63 ppm and 0.6 mg/kg, and neither showed a clear carcinogenic response. WHO/PCS considered that a NOAEL for a carcinogenic response to hydrazine in maleic hydrazide in mice would be in the order of 1 mg/kg (approximating to the highest concentration tested) and that it was therefore reasonable to set the specification limit at 1 mg/kg, as proposed. Nonetheless, WHO/PCS identified the need for caution in assessing an appropriate limit, because the mouse may be less sensitive to hydrazine-induced carcinogenesis than other mammals, including the rat. WHO/PCS opinion was that the proposed specification limit for hydrazine should be reviewed if and when data on other species (e.g. rats) become available.

Physical test methods are full CIPAC methods.

The analytical method for the determination of maleic hydrazide is under collaborative study by AOAC International. Subject to adoption by AOAC and CIPAC, it can be expected to be suitable for use in support of the specifications. Identity tests for maleic hydrazide are based on HPLC retention time, UV and IR spectra.

An analytical method for the determination of free hydrazine as an impurity is in development and will be collaboratively studied under the aegis of AOAC International.

The ICRC concluded that the KMH is stable and does not degrade to produce additional free hydrazine, whereas this may not be true of some salts (e.g. diethanolamine). The proposer stated that there was no known report of degradation of MH (free acid) to produce hydrazine during storage. The proposer's tests of stability of KMH in SG and SL formulations showed no increase in hydrazine in 14 days at 55 °C. The ICRC accepted that trade in KMH should not be subject to the PIC procedure, so long as the hydrazine content is satisfactorily controlled by FAO specifications. The flame identity test provided distinguishes the presence of the stable potassium salt. The diethanolamine salt will give a negative result in this test. If potassium ions were to be added in an attempt to disguise a diethanolamine salt formulation, the distinctive odour would distinguish it from a true KMH formulation.

The JMPR allocated an ADI of 0-0.3 mg/kg bodyweight for maleic hydrazide, based on decreased weight gain and clinical chemical changes in chronic testing on rats and dogs. The purity of the technical material used in these studies was similar to that of commercial products and mostly within the TC specification, although certain studies were conducted with slightly higher hydrazine contents. The U.S. EPA allocated a Reference Dose (RfD) of 0-0.25 mg/kg bodyweight. WHO/PCS concluded that maleic hydrazide is unlikely to present acute hazard in normal use.

WHO/PCS noted that maleic hydrazide has low toxicity to aquatic organisms, earth worms, honey bees, and birds; and is unlikely to bioaccumulate. The US EPA registration data (US EPA 1994) indicate that maleic hydrazide is rapidly metabolised in soil under aerobic conditions. Half-lives of 30-60 days were observed under anaerobic conditions and the product of metabolism is CO₂. Thus WHO/PCS concluded that the environmental fate or effects of maleic hydrazide are not an impediment to its use or the specification.

Recommendations

The meeting recommended that the specifications for maleic hydrazide be adopted subject to the following:

(i) AOAC/CIPAC adoption of the analytical method for determination of the content of active ingredient¹;

(iii) AOAC/CIPAC adoption of, or submission and acceptability of peer laboratory validation data for, the analytical method for determination of the content of free hydrazine¹.

¹ 2008 footnote. The analytical method for determination of maleic hydrazide in technical and formulated products was adopted by AOAC International with first action status in 2004 and published in 2006. The analytical method for determination of hydrazine in technical and formulated maleic hydrazide was published in the Journal of AOAC International in 2008.

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MALEIC HYDRAZIDE

FAO/WHO EVALUATION REPORT 310/2003

Explanation

The Meeting evaluated data for maleic hydrazide in support of the extension of existing FAO specifications¹² to two additional manufacturers and an additional formulation (SP).

Maleic hydrazide is not under patent.

Maleic hydrazide was evaluated by the FAO/WHO JMPR in 1976, 1977, 1980, 1984, 1996 and 1998 and by WHO/PCS in 1999. It was evaluated/reviewed by the US EPA in 1994 and is under evaluation/review by the European Commission (Active Substance 484, List 1) under Directive 91/41/EEC. Maleic hydrazide was considered by the ICRC (ICRC, 2001) in the context of the Rotterdam Convention on Prior Informed Consent (PIC), because it may contain hydrazine as an impurity. The ICRC provided a timetable by which maleic hydrazide products could avoid being subject to the PIC procedure if the manufacturers developed and adhered to FAO specifications which limit the content of hydrazine.

Draft specifications and supporting data were provided by Drexel Chemical Company and Fair Products Inc. in 2002. The existing FAO specifications were developed from data provided by Crompton Corporation (formerly known as Uniroyal*) in 2001. Most of the data provided by the current proposers, in support of the extension of the specifications, were the same as those provided by Crompton Corporation in 2001 and the majority of the toxicological and ecotoxicological data submitted by Crompton were said by the manufacturers to have been generated by a consortium of the three companies (MH Task Force II). Data which are common to all three proposals are not repeated here but are accessible in FAO evaluation report 310/2001. Where different data were provided for physical and chemical properties, those originally provided by Crompton are repeated in this evaluation for comparison.

¹ Existing specifications for maleic hydrazide, based on an evaluation of Crompton data, await publication by FAO, pending validation of the analytical methods for active ingredient and hydrazine impurity.

² 2008 footnote. The analytical method for determination of maleic hydrazide in technical and formulated products was adopted by AOAC International with first action status in 2004 and published in 2006. The analytical method for determination of hydrazine in technical and formulated maleic hydrazide was published in the Journal of AOAC International in 2008.

* 2008 footnote. Latterly Chemtura Corporation.

Physico-chemical properties of maleic hydrazide

Table 1. Additional information on physico-chemical properties of pure maleic hydrazide

Parameter	Value(s) and conditions	Purity %	Method
Solubility in water	144.0 g/l at 20 °C at pH 7 148.8 g/l at 20 °C at pH 9 4.4 g/l at 25 °C at pH 4.3 (MH) 4.5 g/l at 25 °C in unbuffered water (MH) 400 g/l at 25 °C (KMH) (Crompton)	Not reported	OECD 105, flask method Pesticide Manual, 2000 (method not reported)
	4.68 g/l at 20 ± 0.5 °C at pH 5 113 g/l at 20 ± 0.5 °C at pH 7 (MH) (Drexel)	Not reported	Flask method (Method A6, Directive 92/69/EEC)
	4.0 g/l at 25 °C at pH 4.3 (MH) (Fair Products)	Not reported	Pesticide Manual, 2000 (method not reported)
Octanol/water partition coefficient	log P K_{OW} = -0.683 at pH 5 log P K_{OW} = -2.01 at pH 7 log P K_{OW} = -2.4182 at pH 9 (temperatures not reported) (Crompton) (MH Task Force II) log P K_{OW} = -0.56 (unionised acid, 25 °C) (Crompton)	Not reported	U.S. EPA Guideline 63-11 K. Chamberlain <i>et al.</i> , 1996
	log P K_{OW} = -0.327 at pH 5 and 23 °C log P K_{OW} = -1.671 at pH 7 and 23 °C log P K_{OW} = -1.413 at pH 9 and 23 °C (Drexel)	95	US EPA Guideline 63-11
Hydrolysis characteristics	Maleic hydrazide is stable at 45 °C and 85 °C for 2 months in aqueous solution at pH 3, 6 and 9 (concentration not reported) (Crompton) (MH Task Force II)	Not reported	U.S. EPA Guideline 161-1
	Stable to hydrolysis (Drexel)	Not reported	Pesticide Manual, 1994 (method not reported)
Photolysis characteristics	Starting with MH in aqueous solution, maleic hydrazide was stable to simulated sunlight at pH 5 and 7 at 25 °C over 30 d exposure. It degraded slowly at pH 9 and 25 °C, with a calculated half-life of 15.9 days and a rate constant of $4.35 \times 10^{-2} \text{ day}^{-1}$. At pH 7 and 9, the maleic hydrazide would be present largely as the anion. The degradation products at pH 9 were maleate and succinate. Starting with KMH, photolysis of aqueous solutions at pH 5, 7 and 9 produced calculated half-lives of 58, 58 and 34 days, respectively. The major product was maleate. (Crompton) (MH Task Force II). KMH was found to be stable to photolysis on a sandy loam soil (conditions not reported). (Crompton)	Not reported	U.S. EPA Guideline 161-2
Dissociation characteristics	pKa = 5.62 at 20 °C (Crompton) (MH Task Force II) pKa = 5.79 at 25 °C	Not reported	U.S. EPA Guideline 63-10 K. Chamberlain <i>et al.</i> , 1996

Parameter	Value(s) and conditions	Purity %	Method
Oxidising/reducing characteristics	No temperature or visual changes observed during a 24 hr period. A temperature increase was recorded when mixed with 1% KMnO ₄ (MH Task Force II)	Not reported	U.S. EPA Guideline 63-14

Table 2. Chemical composition and properties of maleic hydrazide (MH) technical materials (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information was supplied and is held on file by FAO. Mass balances for MH were 99.0 to 99.9%, unidentified organic impurities were individually <0.1% in 10-batch data. Total volatiles and ash, combined, were <0.5% (Crompton data, evaluated 2001). Mass balances for MH were 99.7 to 100.3% and there were no unidentified impurities >0.1% (Drexel). TC (or TK) neither isolated nor sold. MH content of the "notional TC" ¹ was 96.8 to 97.2% and there were no unidentified impurities >0.1% (Fair Products).
Declared minimum maleic hydrazide content	980 g/kg (Crompton, evaluated 2001) 970 g/kg (Drexel) 960 g/kg in the "notional TC" ¹ but neither prepared nor sold as such and thus not declared (Fair Products)
Relevant impurities ≥ 1 g/kg and maximum limits for them	None (Crompton) None (Drexel) None (Fair Products)
Relevant impurities <1 g/kg and maximum limits for them:	hydrazine, 0.001 g/kg in TC and on an MH basis in formulations (Crompton) hydrazine, 0.001 g/kg in TC and on an MH basis in formulations (Drexel) hydrazine, 0.015 mg/kg in "notional TC" ¹ but 0.001 g/kg on an MH basis in formulations (Fair Products)
Stabilisers or other additives and maximum limits for them:	none (all)
Melting temperature range of the TC	300-302°C, with evidence of decomposition (darkening) at melting point (Crompton)
Melting temperature range of the "notional TC" ¹	260-266°C, with evidence of decomposition (darkening) at melting point. U.S. EPA Guideline 63-5, JIS standard (Fair Products)

The U.S. EPA specification for hydrazine is <15 ppm (0.015 g/kg) in technical maleic hydrazide.

¹ Fair Products does not isolate a TC but operates a closed loop manufacturing process in which the formulations are the only isolated products. MH synthesised by Fair Products was analyzed at a stage in the process that equates approximately to a TC but purification is incomplete at that stage. The material at this stage is termed a "notional TC" in this evaluation.

Toxicological summaries

Notes.

- (i) The proposers confirmed that the toxicological and ecotoxicological data included in the summary below were derived from maleic hydrazide having impurity profiles similar to those referred to in the table above. Fair Products stated that the toxicological data were generated, according to the direction of the USEPA, using a composite TC produced from TCs produced by Crompton, Drexel and Fair Products, hence many of the data were common to the three manufacturers of the MH Task Force II.
- (ii) The conclusions expressed in the summary below are those of the proposers, unless otherwise specified.

Table 3. Toxicology profile of maleic hydrazide technical materials, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions or guideline adopted	Result and test form of maleic hydrazide
Rat	oral	Animals individually dosed by gavage at 5 g/kg bw. Observed for 14 d. (Crompton)	LD ₅₀ >5000 mg/kg bw (MH)
Rat (m & f)	oral	OPPTS 870.1100 (Drexel)	LD ₅₀ >2000 mg/kg bw EPA MRID # 45287001
Rabbit	dermal	24 hr exposure. Observations for 14 d post-treatment. (Crompton)	LD ₅₀ >5000 mg/kg bw (MH)
Rat (m & f)	dermal	OPPTS 870.1200 (Drexel)	LD ₅₀ >2000 mg/kg bw EPA MRID # 45287002
Rat	inhalation	4-h, nose-only (Crompton)	LC ₅₀ = >4 g/m ³ (KMH)
Rat	inhalation	OPPTS 870.1300 (Drexel)	LC ₅₀ = >4000 mg/m ³ EPA MRID # 41185401
Rabbit	skin irritation	24 h exposure (abraded and intact skin). Skin evaluated at 24 and 72 h post-treatment (Crompton)	mildly irritating (MH)
Rabbit	skin irritation	OPPTS 870.2500 (Drexel)	category IV – mild or slight irritation EPA MRID # 45287004
Rabbit	eye irritation	24 h exposure. Eyes evaluated at 1, 2, 3, 4 and 7 d. (Crompton)	slightly irritating (MH)
Rabbit	eye irritation	OPPTS 870.2400 (Drexel)	category IV – minimal effects clearing in less than 24 h EPA MRID # 45287003
Guinea pig	skin sensitization	Three induction exposures at 1 week intervals. Challenge treatment administered 14 d after final induction treatment. Dermal evaluations made 24 and 48 h after exposure. (Crompton)	not a dermal sensitizer (MH and KMH)
Guinea pig	skin sensitization	OPPTS 870.2600 (Drexel)	did not cause skin sensitization EPA MRID # 45320201

No changes or new information in the evaluation of hazards and risks relating to maleic hydrazide have emerged, from national registration authorities or international organizations such as WHO/PCS and the FAO/WHO JMPR, since the evaluation of data for the existing FAO specifications in 2001.

Formulations

The main formulation types available are solution concentrates (SL), water-soluble granules (SG), water-soluble powders (SP) which may be sold in water-soluble bags (SP-SB), and damp water-soluble powders (no code). In the formulations, maleic hydrazide is present as the potassium salt. Maleic hydrazide may be co-formulated with *n*-decanol. The formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

Crompton Corporation has initiated the validation, by collaborative study, of methods for determination of maleic hydrazide and free hydrazine in technical and formulated MH, under the auspices of AOAC International. The projected date of completion of these studies were not known to the Meeting.

Physical properties

In general, the physical properties and the methods for testing them, and the limits proposed for the SL and SP formulations, comply with the requirements of the manual (FAO/WHO 2002).

However, the physical properties and methods for testing compliance with the SP specification proposed by Fair Products differed significantly from the guideline given in the manual, because the product is formulated as a damp SP. Hence, clauses for water content and wettability were omitted, because there is no need to restrict the water content to a low level and a damp powder containing a significant proportion of water should be inherently wettable. A clause for flowability was inserted, because this is a critical characteristic for a damp powder, and the storage stability at elevated temperature specifies MT 46.2 (storage in a sealed bottle), rather than MT 46.3 (storage under pressure), because of the high water content of the PD.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient content is expressed as maleic hydrazide (free acid) in g/kg.

Appraisal

The Meeting considered data submitted by Drexel Chemical Company and Fair Products Inc. for the determination of equivalence with the Crompton products, and for the development of specifications for SP formulations and a proposal to amend the existing SL specification. No proposals were made for the amendment of the existing SG specification.

Confidential information on the manufacturing process, on impurities at or above 1 g/kg in MH, and on hydrazine content to the nearest 0.01 mg/kg, was provided by Drexel. Manufacturing limits for the impurities were supported by 5 batch analyses, in which there were no unidentified components. Mass balances were high (99.7-100.3%) and the products complied with the existing specification clauses for hydrazine. The maximum water content of the Drexel TC did not comply with the usual criterion for equivalence in that the minimum content of MH was 970 g/kg,

which is slightly lower than the 980 g/kg of the existing FAO specification. Although, by this criterion, the Drexel TC did not appear to be equivalent, the meeting considered that the difference between 970 and 980 is probably not analytically significant (no data were available from the collaborative study of the method, so the judgement was based on typical method performance). In addition, the meeting agreed that, for the types of MH formulation normally prepared, it may be unnecessary for the water content of the TC to comply with a very low limit. The Meeting therefore considered the Drexel TC to be equivalent to that of Crompton and agreed that the minimum MH content of the existing FAO specification should be changed from 980 to 970 g/kg, on the basis that the change should reflect only an increase in water content.

Confidential information on the manufacturing process and on hydrazine content was provided by Fair Products, which neither sells nor produces MH in the form of a TC. The synthesis, purification and formulation processes are integrated in a closed loop and the only products isolated are the formulations. At the stage in the loop where MH synthesis is complete, the material (referred to as a “notional TC” in this evaluation) has a minimum concentration of 960 g/kg MH but it is not normally isolated as such. As a consequence of the integrated manufacture, the manufacturing specifications for MH content are applied to the formulations, not to the “notional TC”. As a consequence of further purification of the “notional TC” in the closed loop, the manufacturing specification for hydrazine falls from <15 mg/kg in the “notional TC” to the equivalent of <1 mg/kg in the MH incorporated into the formulations. The company stated that water and hydrazine are the only measurable impurities in the “notional TC”. Limits for hydrazine in the “notional TC” and formulations were supported by 5 batch analysis. At 15 mg/kg (15 ppm), the manufacturing specification for hydrazine the “notional TC” is considerably higher than the existing FAO specification but complies with the specification of US EPA. With a limit for hydrazine at 1 mg/kg of the MH present in the SL and SP, the Fair Products manufacturing specification for hydrazine is in compliance with the existing FAO specification, based upon Crompton data. The SL and SP also contain formulants and 5 batch data were provided for these. In this case, equivalence could not be determined by comparison of the TCs, because the Fair Products “notional TC” is not a TC in the normal sense. The Meeting agreed that, in this exceptional case, equivalence with respect to MH and hydrazine content could be determined at the formulation level. After reviewing the data, the Meeting considered that the MH incorporated into the Fair Products formulations is, in effect, equivalent to the TC of Crompton. However, the meeting noted that the FAO specification, encompassing TCs produced by Crompton and Drexel, must not be applied to the Fair Products “notional TC”.

The Meeting agreed that a footnote to this effect should be appended to the specification. In consequence, the formulation specifications cannot cross-reference the TC specification, if applied to Fair Products formulations, and therefore the Meeting agreed that an explanatory note should be added, to indicate that the formulations may be prepared directly from the TC or indirectly by incorporating maleic hydrazide in such a way that it effectively complies with the requirements of the TC specification. This note will appear in all of the formulation specifications when published. The Meeting also agreed that if Fair Products prepares or sells a maleic hydrazide TC in future, and wishes to claim compliance with the FAO

specification for TC, appropriate batch analysis data and manufacturing specifications would be required by FAO for the determination of equivalence.

Where data from different measurements were involved, the physico-chemical and toxicological data did not indicate any significant differences between the new and reference profiles. An exception to this was that, predictably, the melting temperature of the Fair Products "notional TC" was lower than that of the TC of Crompton. Most of the data submitted by the two new proposers were identical to those submitted by Crompton, because that company had originally submitted certain data that were generated by a consortium of the three companies (MH Task Force II) from a combined TC sample, in support of re-registration of MH with the U.S. EPA. The Meeting noted that this approach to characterization made it impossible to relate the hazard characteristics observed to the impurity profile of a particular manufacturer. Nevertheless, the synthesis of MH is expected to produce a very simple impurity profile and, because the purity of the TCs and "notional TC" was very high (disregarding water) and because differences in the hydrazine content of the traded products were minor (all complied with the 1 mg/kg limit based on maleic hydrazide content), the Meeting concluded that, in respect of the MH and related manufacturing impurities in the products sold by the three companies, significant differences in the hazards and risks presented were unlikely.

The SL specification proposed by Fair Products was in accordance with that recommended for adoption by the FAO Panel in 2001 but a revision proposed by Drexel differed in that the limit for persistent foam was 50 ml instead of 20 ml. The value of 50 ml was within the guideline given in the FAO manual and the meeting agreed that the limit should be raised to 50 ml.

A new draft specification for SP and SP-SB, proposed by Drexel, was in accordance with the requirements of the manual and was accepted by the Meeting.

A new draft specification for SP was also proposed by Fair Products, with non-standard clauses for dustiness and flowability and no clause for water content. Unlike a normal SP, which may require a low limit for water content to maintain good flowability and to avoid fusion of the powder particles, the Fair Products material is specially formulated to be a damp powder. The damp powder must possess suitable flow characteristics and produce no significant fusion of particles during storage but it has an advantage over standard SPs in that it is inherently virtually free from dust (note: the SP guideline does not incorporate a clause for dustiness, because powders are inherently dusty). The Meeting concluded that the Fair Products "SP" could not be accommodated within the SP specification agreed for the Drexel product and that it did not comply with the usual characteristics of SP. The Meeting considered that a clause for dustiness is unnecessary but that the potential for particle fusion in a damp powder made a clause for flowability essential. The Meeting also considered that a clause for wettability was unnecessary, as a damp powder containing a significant proportion of water should be inherently wettable. With no loss of water in MT 46.3, the wettability should not decrease significantly during the storage stability test.

Validation of the analytical methods for the determination of maleic hydrazide and hydrazine by AOAC International, reported in FAO evaluation 310/2001, had not been started. Drexel and Fair Products indicated that the Crompton methods are

expected to be suitable for their products but the Meeting expressed concern about the delay in validating the methods.

Recommendations

The Meeting recommended the following.

- (i) Drexel maleic hydrazide TC should be considered equivalent to that of Crompton*, with a reduction in the limit for active ingredient content changed from 980 to 970 g/kg.
- (ii) Fair Products maleic hydrazide, in the purified form in which it appears in the formulated products, should be considered equivalent to the TC of Crompton*.
- (iii) The revised specification for maleic hydrazide TC must not be applied to any Fair Products technical grade MH, unless and until data have been provided to FAO to enable the equivalence of the TCs to be proven. A note should be appended to the TC specification, to explain that the specification applies to Crompton and Drexel materials but not to Fair Products.
- (iv) A note should be appended to the formulation specifications, to explain that the cross-reference to the TC specification may indicate either direct incorporation of the TC or indirect preparation of maleic hydrazide that complies with the requirements of the TC specification.
- (v) The limit for persistent foam in the existing FAO specification for SL should be raised from 20 ml to 50 ml.
- (vi) The redrafted specification for SP and SP-SB should be adopted by FAO.
- (vii) FAO should ask industry to consider the development of a specification guideline and code for "damp SP".

The Meeting drew particular attention to the fact that the previous and present recommendations to adopt specifications remain subject to validation and adoption by AOAC/CIPAC of the analytical method for determination of active ingredient content and peer validation of the analytical method for free hydrazine content¹.

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* 2008 footnote. Latterly Chemtura Corporation.

¹ 2008 footnote. The analytical method for determination of maleic hydrazide in technical and formulated products was adopted by AOAC International with first action status in 2004 and published in 2006. The analytical method for determination of hydrazine in technical and formulated maleic hydrazide was published in the Journal of AOAC International in 2008.

MALEIC HYDRAZIDE

EVALUATION REPORT 310/2004

Explanation

In 2001, the JMPS considered data for maleic hydrazide from Crompton Corp.^{*}, in support of new FAO specifications for the TC (MH) and the SG and SL (KMH). The specifications were agreed but the recommendation for adoption was subject to satisfactory validation of the analytical methods to determine the maleic hydrazide¹ and free hydrazine²³ contents. The manufacturer provided simple qualitative tests for potassium (flame test) and diethanolamine (fishy odour) but was asked to provide a semi-quantitative test for potassium. Further information on methods was provided in 2004.

In 2003, the JMPS considered data from Drexel Corp. and Fair Products Inc. to determine equivalence with the Crompton* TC and formulations and for development of a specification for SP (KMH). The JMPS agreed that the products are equivalent (although the specification for TC should not apply to Fair Products Inc, because the company does not manufacture a TC), with exception of the SP produced by Fair Products Inc., which required further consideration as it did not comply with the guideline specification in the manual (FAO/WHO 2002).

Appraisal

Methods for identification of KMH

Crompton Corp.^{*}, provided two methods for the semi-quantitative determination of potassium as the counter-ion in KMH formulations, together with validation data (Blem 2004a). One method was based on the use of an ion-selective electrode and the other on “indicator strips”, containing dipicrylamine which forms a coloured complex with potassium ions. The Meeting agreed that the methods are acceptable for the purpose.

Specification for SP produced by Fair Products

The guideline specification for SP (FAO/WHO 2002, pp. 93-96) includes clauses limit the water content and to ensure wettability. However, the SP produced by Fair Products is intended to be damp, containing relatively high contents of both water and surfactants. Although the SP guideline does not include a clause for dustiness (powders are dusts), the manufacturer stated that the moist/damp SP presents reduced inhalation risks prior to dilution and is an inherently wettable product. On

* 2008 footnote. Latterly Chemtura Corporation.

¹ The method for determination of maleic hydrazide content was considered for adoption with First Action status by AOAC International in September 2004 (Blem 2004b) and the recommendation is being finalized (Blem 2005).

² Validation data for the method for determination of free hydrazine content were to be considered by AOAC International in late 2004 (Blem 2004b) but this is still in progress (Blem 2005).

³ 2008 footnote. The analytical method for determination of maleic hydrazide in technical and formulated products was adopted by AOAC International with first action status in 2004 and published in 2006. The analytical method for determination of hydrazine in technical and formulated maleic hydrazide was published in the Journal of AOAC International in 2008.

the other hand, flowability is a critical characteristic for a damp powder (because of the potential for cementation of particulates and crystal growth due to the presence of water), although flowability is not critical for the damp SP sold in water-soluble bags, because any potential accretion that may occur within the bags would be detected in the test for degree of dissolution (MT 179). Unlike standard SP, the test of storage stability of the damp SP at elevated temperature requires the use of method MT 46.2 (storage in a sealed bottle), rather than MT 46.3 (storage under pressure), to avoid loss of water during the test. Thus it was clear that the specification for SP based on the Drexel product (which conformed to the guideline in the manual) could not be applied to the Fair Products “damp SP”.

The problem raised general issues for specifications development. The Meeting considered the possibility of developing two different SP specifications for maleic hydrazide but this would have meant that the manufacturers would have to be named on the specifications and FAO could not accept this for legal reasons. The Meeting also considered the development of a new type of specification for the damp SP, incorporating clauses as described in the paragraph above, and a new formulation code (PD was suggested: powder, damp). The coding and general form of the specification had not been considered by industry organizations and concern was expressed that concern that the case could set a precedent for the introduction of new guidelines and codes for many minor variants of existing formulation types. However, the Meeting agreed that a critical impediment was that the CIPAC test methods for flowability (MT 45 and MT 172) have not been validated, and are probably not appropriate, for testing a damp SP.

Recommendations

The Meeting recommended the following.

- (i) The methods for semi-quantitative determination of potassium counter-ion should be made available by FAO to support the specifications.
- (ii) The specification for “damp SP” proposed by Fair Products should be reconsidered when a test for flowability of the Fair Products damp SP has been developed and validated under the auspices of CIPAC or equivalent
- (iii) Industry should consider the requirements for guideline specifications in this and other possible cases where two or more supposedly similar products cannot conform to a single specification.

References

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