FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

MALEIC HYDRAZIDE

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

Note: evaluation reports only

The specifications for maleic hydrazide will be published subject to AOAC/CIPAC adoption of the analytical method for determination of the content of active ingredient, and subject to AOAC/CIPAC adoption of (or submission and acceptability of peer laboratory validation data for) the analytical determination of the content of free hydrazine impurity.

FOOD AND AGRICULTURE ORGANIZATION of THE UNITED NATIONS

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MALEIC HYDRAZIDE

PART TWO

PART TWO

EVALUATION REPORTS

MALEIC HYDRAZIDE

[1] Formerly Uniroyal Chemical Company, Inc.

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

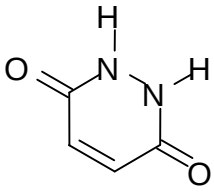
CA: 6-hydroxy-3(2H)-pyridazinone; 1,2-dihydro-3,6-pyridazinedione

Synonyms

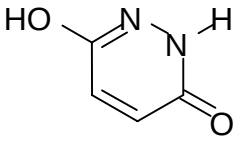
MH (WSSA, trivial)

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

Interconversion 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

EEC number

484

U.S. EPA pesticide chemical code

051501

WHO IPCS hazardous chemical number

U474 (1998)

Identity tests

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

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

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)	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 *et al.*, 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 4.35×10^{-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 *et al.*, 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 thryroid 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
Salmonella typhimurum, strains TA98, TA100, TA1535, TA1537 and TA1538.	Bacterial reverse-mutation assay (Ames assay), *in vitro*	with and without S9 metabolic activation. Tested at concentrations up to 10000 µg/plate.	negative (KMH)
E. coli, po/A$^{+/-}$	DNA repair assay, *in vitro*	0.01 to 50 µg/plate (DMSO).	negative, with and without S9 activation (KMH)
Drosophilla melanogaster	Sex-linked recessive lethal assay, *in vivo*	0.4 and 1% (w/v) in water.	negative (KMH)
Mouse lymphoma L5178Y cells	Mammalian cell gene mutation assay, *in vitro*	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, *in vivo*	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, *in vivo*	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, *in vitro*	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 (osmolarity).
Chinese hamster ovary cells	CHO sister chromatid exchange (SCE) assay, *in vitro*	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.
Bacillus subtilis, strains M45(rec-) and H17(rec+)	Recombination assay, *in vitro*	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
Daphnia magna (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)
Mysidopsis bahia (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)
Crassostrea virginica (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)
Oncorhynchus mykiss (rainbow trout)	Short-term acute toxicity	96 h. static assay, at 10°C	LC_{50} = 1435 mg/l (MH)
Lepomis macrochirus (bluegill sunfish)	Short-term acute toxicity	96 h. static assay, at 22°C	LC_{50} = 1608 mg/l (MH)
Cyprinodon variegatus (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)
Selenastrum capricornutum (green alga)	IC_{50}, effect on growth, static water	5-day at 24°C	NOEC = 8 mg/l (KMH)
Chlorella vulgaris (green alga)	IC_{50}, effect on growth, static water	96 h. at 25°C	IC_{50} >100 mg/l (MH) (highest dose tested)
Anabaena flos-aquae (bluegreen 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
Nitzschia palea (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
Skeletoma costatum (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
Lemna gibba (duckweed)	IC_{50}, effect on growth, static water	14-day, at 25°C	EC_{50} 114 mg/l (KMH) NOEC = 38.6 mg/l
Eisenia fetida (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)
Apis mellifera (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)
Apis mellifera (honey bee)	Oral toxicity (normal feeding)	Dosed and observed for 24 and 48 h at 24°C	LD_{50} >100 µg/bee (KMH)
Anas platyrhynchos (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)
Colinus virginianus (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)
Anas platyrhynchos (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)
Colinus virginianus (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 International. 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.

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 O^6-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 CO_2. 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 ingredient;

(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 hydrazine;

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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 specifications[1] 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.

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 *et al*., 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 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. (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 *et al*., 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 Melting temperature range of the "notional TC"[1]	300-302°C, with evidence of decomposition (darkening) at melting point (Crompton) 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 content.

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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 hydrazide[1] and free hydrazine[2] 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 method 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 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 he 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

[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).

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 Meting 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

Blem 2004b	FAO specification for maleic hydrazide: AOAC analytical method. E-mail from Allen Blem (Crompton Corp.) to Gero Vaagt (FAO), dated 17 September 2004.
Blem 2004a	K_by_ISE.pdf and K_test_strips.pdf. Attachments to e-mail from Allen Blem (Crompton Corp.) to Gero Vaagt (FAO), dated 14 September 2004.
Blem 2005	RE: Specification for Maleic Hydrazide. E-mail from Allen Blem (Crompton Corp.) to Gero Vaagt (FAO), dated 9 May 2005.
ICRC 2001	Report of the 2nd session of the Interim Chemical Review Committee, Rome 19-23 March, 2001. UNEP/FAO/PIC/ICRC.2/L.1.
FAO/WHO 2002	Manual on the development and use of FAO and WHO specifications for pesticides. FAO plant production and protection paper 173, FAO, Rome, 2002.