Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

1-Methylcyclopropene

2010

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1-METHYLCYCLOPROPENE

DISCLAIMER[1]

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.

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[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.

Since 1999 the development of FAO specifications follows the **New Procedure**, described in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" (FAO Plant Production and Protection Page No. 149). 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 plant protection product in accordance with chapter 4, 5 and 6 of the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products".

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/pest-and-pesticide-management/en/

OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

SPECIFICATIONS FOR 1-METHYLCYCLOPROPENE

1-METHYLCYCLOPROPENE

INFORMATION

ISO common name

No ISO common name was allocated for 1-methylcyclopropene

Chemical name(s)

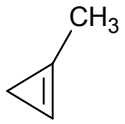
IUPAC 1-methylcyclopropene

CAS 1-methylcyclopropene

Synonyms

1-MCP

Structural formula



Molecular formula

C_4H_6

Relative molecular mass

54.091 g/mol

CAS Registry number

3100-04-7

CIPAC number

767

Identity tests

Retention time in GC, mass spectrum from GC/MS.

1-METHYLCYCLOPROPENE TECHNICAL CONCENTRATE

FAO specification 767/TK (January 2010*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (767/2008). It should be applicable to relevant products of this manufacturer 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 the products of other manufacturers. The evaluation report (767/2008) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of 1-methylcyclopropene at a concentration of 3.3% together with related manufacturing impurities, in the form of a complex with alpha-cyclodextrin, together with any other necessary co-formulants. It shall be in the form of a powder free from visible extraneous matter and added modifying agents except for the diluents.

2 Active ingredient

2.1 **Identity tests** (767/TK/ Note 1)

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 **1-methylcyclopropene content** (767/TK Note 1)

The 1-methylcyclopropene content shall be declared (g/kg) and, when determined, the average measured content shall not differ from that declared by more than the following tolerance:

Declared content, g/kg	Tolerance
up to 33 Note: the upper limit is included in the range	± 10% of the declared content

3 Relevant impurities

3.1 **By-products of manufacture (Note 2)**

Maximum 0.05% of 3-chloro-2-methylpropene of the 1- MCP content found under 2.2.

Maximum 0.05% of 1-chloro-2-methylpropene of the 1-MCP 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/pest-and-pesticide-management/en/

Note 1 Methods for the identification and determination of 1-MCP content in TK and in a VP formulation were presented at the CIPAC Meeting in 2009 and provisionally adopted as CIPAC methods. Prior to their publication in Handbook N, copies of the method may be obtained through the CIPAC website, https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 2 The independent laboratory validated capillary GC-FID method (CIPAC/4667) for the determination of the relevant impurities 3-chloro-2-methylpropene and 1-chloro-2-methylpropene in 1-MCP TK and VP formulation was adopted by CIPAC in 2009 and is available through the CIPAC website, https://www.cipac.org/index.php/methods-publications/alphabetical-search.

1-METHYLCYCLOPROPENE VAPOUR RELEASING PRODUCT

FAO specification 767/VP (January 2010*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (767/2008). It should be applicable to relevant products of this manufacturer 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 the products of other manufacturers. The evaluation report (767/2008) as PART TWO forms an integral part of this publication.

1 Description

The material is identical to 767/TK It shall be in the form of a powder to be applied as a gas of the active ingredient after dissolution in water, but which may contain insoluble inert ingredients.

2 Active ingredient

2.1 **Identity tests** (767/VP/ Note 1)

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 **1-methylcyclopropene content** (767/VP/ Note 1)

The 1-methylcyclopropene content shall be declared (g/kg) and, when determined, the average measured content shall not differ from that declared by more than the following tolerance:

Declared content, g/kg	Tolerance
up to 33 Note: the upper limit is included in the range	± 10% of the declared content

3. Relevant impurities (Note 2)

3.1 By-products of manufacture

Maximum 0.05% of 3-chloro-2-methylpropene of the 1- MCP content found under 2.2.

Maximum 0.05% of 1-chloro-2-methylpropene of the 1-MCP 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/pest-and-pesticide-management/en/

4 Storage stability

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

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage.

Note 1 Methods for the identification and determination of 1-MCP content in TK and in a VP formulation were presented at the CIPAC Meeting in 2009 and provisionally adopted as CIPAC methods. Prior to their publication in Handbook N, copies of the method may be obtained through the CIPAC website, https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 2 The independent laboratory validated capillary GC-FID method (CIPAC/4667) for the determination of the relevant impurities 3-chloro-2-methylpropene and 1-chloro-2-methylpropene in 1-MCP TK and VP formulation was adopted by CIPAC in 2009 and is available through the CIPAC website, https://www.cipac.org/index.php/methods-publications

PART TWO

EVALUATION REPORTS

1-METHYLCYCLOPROPENE

FAO/WHO EVALUATION REPORTS 767/2008

Recommendations

The Meeting recommended that:

(i) the specifications for 1-methylcyclopropene (1-MCP), TK and VP proposed by Rohm and Haas, as amended, should be adopted by FAO

Appraisal

1-MCP is an active ingredient that is under patent and has not previously been the subject of FAO specifications. The proposer stated that 1-MCP is prepared and traded only as the TK which is also the end use product, the VP. 1-MCP is used at ppm levels in storage rooms mainly for apples to control ethylene-induced ripening processes and is therefore considered as a plant growth regulator.
1-MCP is a gas at room temperature and standard pressure. The solubility in water is 137 mg/L at 20 ˚C. 1-MCP is slightly fat soluble (log P_{ow} = 2.4) and is soluble in some organic solvents. The auto flammability was in the range of 188-191°C and the lower flammability level around 1.25-1.60 %. The in-use concentration range will therefore never exceed levels of concern with regard to flammability.

1-MCP is commercialised as an inclusion complex with alpha-cyclodextrin, which has been shown not to be highly flammable. The active substance cannot be isolated in a purified form as it rapidly self-reacts resulting in a violent exothermic reaction.

Confidential information on the manufacturing process, on impurities at or above 1 g/kg in 1-MCP, and on toxicological relevant impurities, was provided by the proposer. On the basis of the information provided impurities 3-chloro-2-methylpropene and 1-chloro-2-methylpropene have to be regarded as relevant impurities. The limits proposed, 0.05%, were below the classification and labelling limits of GHS for carcinogenic and mutagenic impurities (0.1%), and thus in line with earlier JMPS recommendations. The limits for the impurities were supported by 5 batch analyses. Mass balances were high (99-100%). Confirmation was received from the UK Pesticides Safety Directorate that the information on the batch analysis and manufacturing process were the same as those submitted for registration in the UK. The data supplied supports the minimum specification for the active ingredient.

The analytical method for determination of 1-MCP in the formulation is based on capillary GC with FID on a Porabond column providing sufficient retention of the target compound, similar to those for the relevant impurities 1- and 2-chloromethylcyclopropene.

There is a reduced data set available for this active because of the nature of the compound, its indoor use and exposure routes connected to that specific use. There is limited ecotoxicity data as there will be very limited exposure. This reduced data set

was accepted by the EU. A reasoned case for the non-submission of this data was also provided by the data holder.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 767/2008

Uses

1-MCP is a plant growth regulator for food storage, predominantly for apples. It blocks the ethylene receptors, preventing normal fruit responses to ethylene. The product is manufactured as a TK, which is also the end use product. The 1-MCP gas is released from the TK into the controlled atmosphere by dissolving it in water: The water molecules displace the 1-MCP in the alpha-cyclodextrin inclusion complex.

Identity of the active ingredient

ISO common name

No ISO common name was allocated for 1-methylcyclopropene

Chemical name(s)

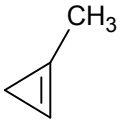
IUPAC 1-methylcyclopropene

CAS 1-methylcyclopropene

Synonyms

1-MCP

Structural formula



Molecular formula

C_4H_6

Relative molecular mass

54.091 g/mol

CAS Registry number

3100-04-7

CIPAC number

767

Identity tests

Retention time in GC, mass spectrum from GC/MS.

Physico-chemical properties of 1-MCP

Table1. Physical-chemical properties of 1-MCP[1]

Parameter	Value(s) and conditions	Method	References
Vapour pressure	$2x10^{5}$ Pa at 20 °C of 1-MCP gas	Modified Watson correlation	AF-01-190 ER 7.21
Melting point	Not relevant as 1-MCP is a gas	OECD 102	AF-01-155 ER 7.15
Boiling point	Not relevant as 1-MCP will instantly polymerise	OECD 103 Meissner's calculation	AF-01-156 ER 7.16
Temperature of decomposition	The formulated product was stable up to 150 ^{o}C	1-MCP could not be tested due to the extreme hazards associated with handling neat 1-MCP OECD 113	
Solubility in water	solubility at 20°C was 137 mg/L No pH effect	Moderately soluble. The method involved the production of gas from the product which was then bubbled through water until saturation was reached. OECD 105 and EEC A.6.	AF-01-191 ER 8.5
Solubility in organic solvents	solvent solubility (mg/L) n-heptane 2450 xylene 2250 ethyl acetate 12500 methanol 11000 acetone 2400 dichloromethane 2000	Moderately soluble. The method involved the production of gas from the product which was then bubbled through each solvent until saturation was reached.	AF-01-189 ER 8.3
Octanol/water partition coefficient	log P_{ow} = 2.4	EEC method A 8 HPLC OECD 107 and 117	APR-01-014 ER 7.8

Hydrolysis (DT_{50}) characteristics	Not relevant. 1-MCP will not hydrolyse.	OECD 111	AF-01-188 ER 8.2
Flammability	LFL: 1.25-1.60 % The in use concentration will never exceed levels of concern. Auto flammability: 188-191 °C	ASTM method E681, 1985 ASTM method E659, 1984 (1)	AF-01-153 ER 7.13
Photolysis characteristics	Not required since no absorption max in aqueous solution > 240 nm		
Other degradation characteristics Stability in air, photochemical oxidative degradation.	Reaction with hydroxyl radical measured to give a calculated half life of 4.4 hours in the atmosphere.	Laser induced	00RC-1033 ER 6.2 APR-01-054 ER 6.11 AF-01-160 ER 7.19
Dissociation characteristics	Not applicable. 1-MCP is an unsaturated aliphatic hydrocarbon and it does not contain functional groups capable of dissociation in water		

[1] All tests were conducted on 1-MCP gas evolved from the inclusion complex with alpha-cyclodextrin

Table 2. **Chemical composition and properties of 1-MCP technical material (TK)**

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99 %
Declared minimum 1-MCP content	960 g/kg based on evolved gas
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	3-chloro-2-methylpropene ≤0.05 % of the evolved gas 1-chloro-2-methylpropene ≤0.05 % of the evolved gas
Stabilisers or other additives and maximum limits for them:	Alpha-cyclodextrin encapsulation agent and dextrose. The dextrose is used as a diluent to adjust the content of 1-MCP in the TK to 3.3%.
Melting or boiling temperature range of the TK	Not applicable as the TK is an alpha-cyclodextrin complex.

Background information on toxicology / ecotoxicology

1-MCP has been reviewed for classification by European Chemicals Bureau (ECB) on November, 2006 and January, 2007. ECB has concluded that no health classification is needed for 1-MCP up to a maximum concentration of 5.0% in alpha-cyclodextrin. Also, ECB concluded no classification would be required for environmental effects. A minimum data set on ecotoxicity is necessary for this compound as it is only used indoors and environmental exposure is very low.

Formulations and co-formulated active ingredients

1-MCP is manufactured and encapsulated into alpha-cyclodextrin as an inclusion complex in a single manufacturing process. The resulting material is then filtered, washed and dried to a powder and the concentration of 1-MCP is adjusted to 3.3 % by the addition of dextrose. 1-MCP is not co-formulated with any other pesticide. The only formulation type is the VP.

Methods of analysis and testing

1-MCP is determined by gas chromatography (GC), using a surrogate calibration standard, cis-2-butene and FID detection. Identification is by means of GC retention time. Validation included running specially isolated pure 1-methylcyclopropene against

cis-2-butene demonstrating that the detector response was within 5 % and the test method corrects for the difference. A batch was also analysed by GC-MS, which supported the structural identity of 1-MCP. The method of the relevant impurities is by GC-FID. The calibration is against analytical standards of each compound. Structural identity of impurities was confirmed by GC-MS. As the TK and formulated product are the same, no additional method was provided. These methods were adopted by CIPAC in 2009.

Physical properties

Test methods for determination of physico-chemical properties were EC, OECD, CIPAC and USEPA. The physical properties and the methods for testing them, and the limits proposed for the TK/VP, comply with the requirements of the FAO and WHO Manual (March 2006 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 1-MCP in g/kg for the VP formulation.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

The proposer confirmed the toxicological data included in the summary below were derived from 1-MCP having impurity profiles similar to those referred to in the table above.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of 1-MCP technical material, based on acute toxicity, irritation and sensitization.

Species	**Test**	**Duration and conditions or guideline adopted**	**Results and test form of 1-MCP**	References
Rat	Oral	No study	n.a.	n.a.
Rabbit	Dermal	No study	n.a.	n.a.
Rat Sprague-Dawley	Inhalation OECD 403	4 hour nose only	LC50≥2.5 mg/L concentration maximum	00R-180A ER4.1
Rabbit	Skin irritation	No study	n.a.	n.a.
Rabbit	Eye irritation	No study	n.a	n.a.
Guinea pig	Skin sensitisation	No study	n.a.	n.a.

Oral and dermal studies in rats:

Based on the physical nature of 1-MCP (i.e. a gas at room temperature), this active substance was not tested in oral or dermal toxicity studies. However, the active substance was tested via inhalation toxicity tests, inhalation being a pertinent route of potential human exposure, although virtually no exposure is expected from normal use.

No practical potential for oral exposure is expected. Using worst-case assumptions, dietary intake will be <<0.2 µg/kg bw/day. Because there is no practical exposure for operators or consumers, a limited data package was considered acceptable and hence only one species has been used in the short-term toxicity tests.

Table 4 Toxicological profile of 1-MCP based on repeated administration.

Species	**Study** **Batch**	**NOAEL** **(mg/kg bw)**	**LOAEL** **(mg/kg bw)**	**Effect at LOAEL** **(and other comments)**	**References**
Rat Sprague-Dawley	2-week inhalation toxicity study in female rats	62 average 92 a.t.d. (105 ppm)	183 average 284 a.t.d. (306 ppm)	Increased incidence of splenic extramedullary haematopoiesis (red pulp). Decreased RBC at highest dose (1000 ppm)	00R-183A ER3.2
Rat Sprague-Dawley	3-week inhalation toxicity study in male rats	42 average 68 a.t.d (107 ppm)	409 average 660 a.t.d (1039 ppm)	Increased incidence of hyaline droplets in the renal cortical tubular epithelium.	00R-183B ER4.3
Rat Sprague-Dawley	90 day inhalation toxicity study in rats	6.5 average 9.0 a.t.d. (23.5 ppm)	28 average 39 a.t.d. (107ppm)	Increased incidence of hyaline droplets in the renal cortical tubular epithelium and splenic haemosiderosis in males. Decreased RBC at highest dose (1000 ppm)	00R-183 ER5.2

Average = dose averaged over the whole study period.

a.t.d. = dose on actual treatment days.

Table 5 Summary of genotoxicity of 1-MCP vapour released from 1 MCP alpha-cyclodextrin complex.

Study	**Test system**	**Result**	**References**
Ames test	*Salmonella typimurium* strains TA98, TA100, TA1535, TA1537,	Negative	00R-193A ER 2.8

	TA102		
In Vitro Cytogenetic Assay	Chromosome aberrations in cultured human peripheral lymphocytes	Negative	00RC-194 ER 3.1
Mammalian Point Mutation	Chinese hamster ovary cells; HGPRT locus	Negative	00RC-195 ER 3.3
In vivo Cytogenetic Assay	Micronucleus assay in mice	Negative	00R-232 ER 2.2

Table 6 Summary of effects in rats administered 1-MCP via inhalation in the teratology study.

ppm 1-MCP		0	107	329	1029
Equivalent body burden on actual days of exposure (mg/kg bw)		0	56	174	543
Number of pregnant dams		n=22	n=20	n=22	n=22
		Maternal body weight gain (g)			
Day 6 to 9		16.9	14.3	15.6	7.4*
Day 9 to 12		17.2	17.9	18.0	20.7*
Day 6 to 20		119.3	117.2	118.4	106.0
		Net maternal body weight change(= Terminal body weight minus day 6 body weight)			
Net Body Weight Change (x)		119.3	117.2	118.4	106.0
Gravid Uterine Weight (y)		75.7	78.6	72.5	72.2
Net Weight Change (x-y)		43.6	38.7	45.8	33.8 *
		Food consumption during gestation			
Day 6 to 9		22.2	23.1	21.7	17.0*
Day 6 to 20		24.1	24.1	25.0	23.1
		Maternal necropsy observations			
Number necropsied No remarkable observations	n n	22 22	22 22	22 17	22 0
Spleen					
Darkened	n %	0 0.0	0 0.0	5 22.7	22 * 100.0
Enlarged	n %	0 0.0	0 0.0	2 9.1	19+ 86.4

		Caesarean section data			
Preimplantation loss	Total	24	22	19	52
Number per animal	Mean	1.1	1.1	0.9	2.5*
% per animal	Mean	7.4	7.3	7.2	15.6a
total live litter sizes	%	12.5	12.6	11.6	12.0

[a] Excludes data from animal #00-02386 that had 'erroneous' corpora lutea counts. The number of implants in this animal (14) were excluded from preimplantation loss calculations.

- * $p < 0.05$ Fisher's exact test with Bonferroni correction. * $p<0.05$ Dunnett's test. + n=21

In an inhalation toxicokinetics study in the rat, 1-MCP appeared rapidly in the blood stream when inhaled. Following exposure, 1-MCP is cleared from the blood compartment at a modest rate. Less than 10% of available radioactivity was absorbed during 4 hours of exposure. At high dose (1000 ppm) exhalation was the main route of excretion. At low dose (100 ppm) urinary excretion and excretion via exhaled air were of equal prominence. Excretion via exhaled air is likely to be irrelevant at proposed in-use atmospheric concentrations. Fecal excretion was a minor route of excretion. Inhalation absorption (akin to oral absorption) of 1-MCP was calculated to be approximately 10%. Bioaccumulation is not expected.

With respect to acute toxicology, due to practical reasons (i.e. 1-MCP being a gas at room temperature) 1-MCP gas was only tested in an acute inhalation study. From the results of this study and from the lack of clinical signs of toxicity in this and the short-term inhalation toxicity studies (where whole body exposures were conducted), it is proposed that 1-MCP gas is unclassified with respect to acute effects.
In the short-term toxicity studies, repeated inhalation of 1-MCP resulted in decreased red blood cells, decreased red blood cell (RBC) parameters, and spleen effects. Other target organs of 1-MCP toxicity were the liver and kidneys. The overall population of white blood cells (WBCs) in males appeared to be increased in treated animals at the highest concentration used. The NOAELs were based on the kidney and RBC effects in all short-term studies.
In vitro and in vivo assays provided no evidence of mutagenic activity for vapour concentrations of 1-MCP up to 1000 ppm.
There is no expected carcinogenic risk from 1-MCP, and no effects of chronic exposure are anticipated when 1-MCP is used according to the product label. 1-MCP was not tested in chronic (long-term) and carcinogenicity studies in the rat and mouse, because there is no potential for chronic, lifetime exposure of man. The 90 day inhalation study in rats raised no alarms for potential effects upon chronic lifetime exposure. There is also no evidence for carcinogenicity or genotoxicity for 1-MCP predicted by structure activity analysis.

A two generation study in the rat was not conducted, since there is no potential for long-term exposure over a significant portion of the human lifespan. Also, in an inhalation developmental toxicity study in the rat, there

were also no adverse reproductive or developmental effects in animals when exposed to concentrations at 1000 times the level of use. Because there is no exposure for operators or consumers, a limited data package was considered acceptable and hence only 1 species has been used in the teratology studies. In the rat teratology study, a maternal NOAEL was set on darkened and enlarged spleens. No adverse fetotoxic effects were observed. The NOAEL for maternal effects for 1-MCP, when administered as a gas via whole-body inhalation over gestational day 6-19 in this developmental study was 107 ppm or 56 mg/kg/day based on darkened and enlarged spleens.

The NOEL for fetotoxicity for 1-MCP, when administered as a gas via whole-body inhalation over gestational day 6-19 in this developmental study was 1029 ppm or 543 mg/kg/day which was the highest dose tested.

Information was considered (DNA and protein sequences comparisons, and comparative ethylene binding assays) which indicated that the ethylene receptor as found in apples and many other plants and non animal kingdom organisms, does not occur in the animal kingdom. Therefore, the mechanism for the binding of ethylene in plants, which produces a sequence of biochemical events, is not relevant to man. Since 1-MCP is known to bind to the same active site in plants as does ethylene, no binding of 1-MCP to receptors in man would be expected as well.
The applicant stated that in the United States no adverse effects have been reported by manufacturing workers, applicators, retailers or the general population. No clinical signs or symptoms of poisoning are anticipated by the applicant to result from human exposure. Apart from basic supportive first aid measures, the applicant also considers that no medical treatment is required. Ultimately the applicant does not expect poisonings to occur through use of this material.

Table 7: Summary of the acute toxicity of 1-MCP cyclodextrin complex.

Route/Study	Test material	Species	Comments	Classification	References
Oral	1-MCP α-cyclodextrin complex	Rat	LD50 >5000 mg/kg bw	Not classified	00R-199 ER2.4
Dermal	1-MCP α-cyclodextrin complex	Rat	LD50 >5000 mg/kg bw	Not classified	00R-200 ER2.5
Skin irritation	1-MCP α-cyclodextrin complex	Rabbit	Not classified.	Not classified	00R-201 ER2.6
Eye irritation	1-MCP α-cyclodextrin complex	Rabbit	Not classified.	Not classified	00R-202 ER2.7
Skin sensitisation M&K method	1-MCP α-cyclodextrin complex	Guinea pig	Not classified.	Not classified	00R-203 ER2.3

No classification for the formulation was required:
No health classification for 1-MCP, up to maximum mass content of 5% encapsulated in cyclodextrin, was recommended by the Technical Committee on Classification and Labelling of ECB (Arona meeting, November 14-15, 2006). Similarly, no classification for environmental effects was recommended for 1-MCP by the Technical Committee on Classification and Labeling of ECB (Ispra meeting, January 25, 2007)

Technical specification and impurities

There are two impurities (Impurity 1, Impurity 2,) present in the technical 1-MCP which are of possible toxicological significance.

Impurity 1 and Impurity 2

Impurity 1 and Impurity 2 are monohaloalkene isomers.

Impurity 1, according to IARC monographs was positive in a heritable translocation assay in Drosophila melanogaster, a sex-linked recessive lethal mutation assay also in D. melanogaster, an in vitro mammalian cell mutation assay at the thymidine kinase locus in L5178Y mouse lymphoma cells in the absence of metabolic activation, and in an in vitro sister chromatid exchange assay in CHO cells. It was negative in 9/10 Ames tests, which were conducted. No in vivo genotoxicity assays were performed in mammals however, it was also carcinogenic in mice and rats.

Impurity 2, according to IARC Monographs was positive in 4/6 Ames assays, a ‘genetic crossing over’ or recombination assay in D. melanogaster, in an in vitro sister chromatid exchange in CHO cells, chromosomal aberration assay

also in CHO cells. Impurity 2 did not induce micronuclei in bone marrow cells in an in vivo assay in mammals (mouse micronucleus test). It was also carcinogenic in mice and rats.

The applicant states that experiments (Snyder 2001) indicate that 99.9% of Impurity 2 and Impurity 1 are released during generation of the active substance from the 3.3% alpha-cyclodextrin complex. These impurities were present at concentrations typical of commercial product in the gas phase in genotoxicity studies with 1-MCP vapour which showed no evidence for mutagenicity of 1-MCP technical.

Impurity 3, Impurity 4 and Impurity 5

These impurities appear to have no structural alerts for potential DNA reactivity according to the model of Ashby and Tennant (1988, Mutation Research 204, 17-115).

Addressing the toxicological significance of Impurity 1 and Impurity 2

The risk of mutagenicity/carcinogenicity presented by these materials was addressed by the Committee for Carcinogenicity in the UK. They concluded that the risk for carcinogenicity posed by exposure to Impurity 1 and Impurity 2 for both workers and consumers was negligible based on the upper limit set for these materials in 1-MCP. That upper limit has since been lowered by an additional 38%. This conclusion was subsequently accepted by EFSA in the EU. Upper limits for these two impurities have been included in the Annex 1 listing of 1-MCP.

ANNEX 2
REFERENCES

Rohm and Haas document number or other reference	Year and title of report or publication details
FAO/WHO 2006	Manual on development and use of FAO and WHO specifications for pesticides, March 2006 revision of the 1st edition. FAO, Rome, March 2006; WHO, Geneva, March 2006 (internet publications).
AF-01-155 ER 7.15	2002. Determination of the melting point/melting range of 1-MCP
AF-01-156 ER 7.16	2002. Determination of the boiling point/boiling range of 1-MCP
AF-01-160 ER 7.19	2002. Screening of the thermal stability in air of 1-MCP
AF-01-190 ER 7.21	2002. Determination of the vapour pressure of 1-MCP
AF-01-157 ER 7.17	2002. Determination of colour and physical state of 1-MCP
AF-01-158 ER 7.18	2002. Determination of odour of 1-MCP
AF-01-187 ER 8.1	2002. Determination of the density of 1-MCP
AF-01-191 ER 8.5	2002. Determination of the water solubility of 1-MCP
AF-01-189 ER 8.3	2002. Determination of the solubility of 1-MCP in organic solvents
APR-01-014 ER 7.8	2001. Determination of the partition coefficient (n-octanol/water) of 1-MCP formulation
AF-01-188 ER 8.2	2002. Hydrolysis determination of 1-MCP at different pH values
AF-01-153 ER 7.13	2002. Determination of the flammability of 1-MCP formulation
APR-01-054 ER 6.11	2001. Estimation of the degradation of 1-MCP by photo-oxidation in air
00RC-1033 ER 6.2	2000. Process safety test results and interpretation for 1-methylcyclopropene
APR-00-213 ER 1.7	2000. Expert statement on the oxidizing properties of 1-methylcyclopropene (1-MCP) active ingredient and 1-MCP formulation
APR-01-004 ER 6.7	2001. pH determination of an aqueous solution of 1-MCP formulation
00R-199 ER 2.4	2001. 1-Methylcyclopropene alpha-cyclodextrin complex (3.3% a.i.): acute oral toxicity study in male and female rats

00R-200 ER 2.5	2001. 1-Methylcyclopropene alpha-cyclodextrin complex (3.3% a.i.): acute dermal toxicity study in male and female rats
00R-180A ER 4.1	2001. 1-Methylcyclopropene: acute inhalation toxicity study in rats
00R-201 ER 2.6	2001. 1-Methylcyclopropene alpha-cyclodextrin complex (3.3% a.i.): skin irritation study in rabbits
00R-202 ER 2.7	2001. 1-Methylcyclopropene alpha-cyclodextrin complex (3.3% a.i.): eye irritation study in rabbits.
00R-203 ER 2.3	2001. 1-Methylcyclopropene alpha-cyclodextrin complex (3.3% a.i.): Dermal sensitization study in guinea pigs - maximization test
00R-193A ER 2.8	2001. 1- Methylcyclopropene Vapor Released from 1-Methylcyclopropene Alpha Cyclodextrin Complex (3.3% a.i): S*almonella Typhimurium* Gene Mutagenicity Assay
00RC-194 ER 3.1	2001. 1- Methylcyclopropene Vapor Released from 1-Methylcyclopropene Alpha Cyclodextrin Complex (3.3% a.i): Chromosomal aberrations in Cultured Human Peripheral Blood Lymphocytes.
00RC-195 ER 3.3	2001. 1- Methylcyclopropene Vapor Released from 1-Methylcyclopropene Alpha Cyclodextrin Complex (3.3% a.i): CHO HGPRT Forward Mutation Assay with a Confirmatory assay and Duplicate Cultures
00R-232 ER 2.2	2001. 1-Methylcyclopropene: Micronucleus Assay in CD-1 Mouse Bone Marrow Cells
00R-183A ER 3.2	2001. 1-Methylcyclopropene: Two-week inhalation range-finding study in female rats
00R-183B ER 4.3	2001. 1-Methylcyclopropene: Two-week inhalation range-finding study in male rats
00R-183 ER 5.2	2001. 1-Methycyclopropene: Three-month inhalation toxicity study in rats