

# FAO SPECIFICATIONS AND EVALUATIONS

## FOR PLANT PROTECTION PRODUCTS

### IMAZALIL

(±)-allyl-1-(2,4-dichlorophenyl)-2-imidazol-1-ylethyl ether

2001



FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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### IMAZALIL

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## Disclaimer<sup>1</sup>

FAO specifications are developed with the basic objective of ensuring that pesticides complying with them are satisfactory for the purpose for which they are intended so that they may serve as an international point of reference. The specifications do not constitute an endorsement or warranty of the use of a particular pesticide for a particular purpose. Neither do they constitute a warranty that pesticides complying with these specifications are suitable for the control of any given pest, or for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular application must be decided at the national or provincial level.

Furthermore, the preparation and use of pesticides complying with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable thereto. FAO shall not be liable for any injury, loss, damage or prejudice of any kind that may be suffered as a result of the preparation, transportation, sale or use of pesticides complying with these specifications. Additionally, FAO wishes to alert users of specifications to the fact that improper field mixing and/or application of pesticides can result in either a lowering or complete loss of efficacy. This holds true even where the pesticide complies with the specification. Accordingly, FAO can accept no responsibility for the consequences of improper field mixing and/or application.

FAO is not responsible for ensuring that any product claimed to comply with FAO specifications actually does so.

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<sup>1</sup> This disclaimer applies to all specifications published by FAO. Furthermore it does not undertake to insure anyone who utilizes these specifications against liability for infringement of any Letters Patent nor assume any such liability.

## INTRODUCTION

FAO establishes and publishes specifications\* for technical material and related formulations of plant protection products 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 5<sup>th</sup> 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 Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent.”

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 5<sup>th</sup> 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 Panel of Experts. 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 methods of synthesis. FAO has the possibility to extend the scope of the specifications to similar products, but only when the Panel of Experts has been satisfied that the additional products are equivalent to those which formed the basis of the reference specification.

\* Footnote: The publications are available on the Internet under (<http://www.fao.org/WAICENT/FAOINFO/AGRICULT/AGP/AGPP/Pesticid/>) or as hardcopy from the Plant Protection Information Officer.

**PART ONE**  
**SPECIFICATIONS**

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**IMAZALIL**

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FAO SPECIFICATIONS AND EVALUATIONS FOR  
PLANT PROTECTION PRODUCTS

**IMAZALIL**

INFORMATION

*Common name*

Imazalil (ISO)

*Chemical names*

*IUPAC*

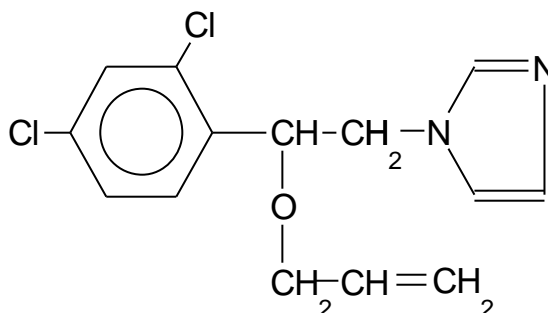
(±)-allyl-1-(2,4-dichlorophenyl)-2-imidazol-1-ylethyl ether

(±)-1-(β-allyloxy-2,4-dichlorophenylethyl) imidazole

*CA*

(±)-1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole

*Structural formula*



*Molecular formula*

C<sub>14</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O

*Relative molecular mass*

297.18

*CAS registry number*

35554-44-0 (unstated stereochemistry); 7390-28-0

*CIPAC number*

335

# IMAZALIL (FREE BASE) TECHNICAL MATERIAL

## FAO Specification 335/TC (2001)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation report (335/2001). It should be applicable to relevant products of these manufacturers 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 (335/2001) as PART TWO forms an integral part of this publication.*

### 1 Description

The material shall consist of imazalil together with related manufacturing impurities, in the form of an off white to brown crystalline mass, free from visible extraneous matter and added modifying agents.

### 2 Active Ingredient

#### 2.1 Identity tests (335/TC/M/2, CIPAC E, page 96)

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 Imazalil content (335/TC/M/3, CIPAC E, page 96)

The imazalil content shall be declared (not less than 950 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

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# IMAZALIL SULPHATE TECHNICAL MATERIAL

## FAO Specification 335.306/TC (2001)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation report (335/2001). It should be applicable to relevant products of these manufacturers 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 (335/2001) as PART TWO forms an integral part of this publication.*

### 1 Description

The material shall consist of imazalil sulphate together with related manufacturing impurities, in the form of an off white to yellow powder, free from visible extraneous matter and added modifying agents.

### 2 Active Ingredient

#### 2.1 Identity tests (335/TC/M/2, CIPAC E, page 96)(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 Imazalil content (335/TC/M/3, CIPAC E, page 96) (Note 2)

The imazalil content shall be declared (not less than 725 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

### 3 Relevant impurities

#### 3.1 Water (MT 30)

Maximum: 10g/kg

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Note 1 The identity of the active ingredient should be confirmed by comparison of GC retention time with that of an authentic standard of imazalil free base. The identity can be further confirmed by comparison of R<sub>f</sub> values in TLC. Having established the identity of the liberated free base, as above, the identity of the imazalil sulphate salt may be determined by its melting point, 128 - 134°C.

Note 2 The CIPAC method for TC/TK is intended for the free base, not the sulphate salt. The CIPAC method may be applied to the sulphate salt TC if the free base is first liberated and extracted, in a manner analogous to that indicated in the CIPAC method for the SL. Weigh accurately sufficient material to contain 50mg imazalil free base into a 40 ml clear vial, liberate the free base by adding 1 ml of 25% aqueous ammonium hydroxide solution. Allow to stand for a minimum 2 hours (do not shake) before continuing with the extraction of the imazalil (free base). Note that this is a longer period than given for liberation of the free base in the CIPAC method for SL. It is possible to use either dichloromethane or toluene for the extraction of the free base, retaining the lower or upper layer, respectively.



# IMAZALIL SOLUBLE CONCENTRATE

## FAO Specification 335.306/SL (2001)

*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 (335/2001). 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 (335/2001) as PART TWO forms an integral part of this publication.*

### 1 Description

The material shall consist of imazalil technical material, complying with the requirements of FAO specification 335.306/TC, in the form of imazalil sulfate dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a clear or opalescent liquid, free from visible suspended matter and sediment, to be applied as a true solution of the active ingredient in water.

### 2 Active ingredient

#### 2.1 Identity tests (CIPAC 335/SL/M/-, CIPAC E, page 99) (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 (Note 2).

#### 2.2 Imazalil content (Note 3)

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

Declared content, g/kg	Permitted tolerance
up to 25 g/l	$\pm 15\%$
above 25 up to 100 g/l	$\pm 10\%$
above 100 up to 250 g/l	$\pm 6\%$
above 250 up to 500 g/l	$\pm 5\%$
Note: in each range the upper limit is included	

### 3 Physical properties

#### 3.1 Solution stability (MT 41)

The formulation, after the stability test at  $54^\circ\text{C}$  (see 4.2) and following dilution (Note 4) with CIPAC standard water D and standing at  $30 \pm 2^\circ\text{C}$  for 18 h, shall give a clear or opalescent solution, free from more than a trace of sediment and visible solid particles. Any visible sediment of particle produced shall pass through a  $45\mu\text{m}$  sieve (Note 5).

### 3.2 Persistent foam (MT 47.2)(Note 6)

Maximum: 60 ml after 1 minute.

## 4 Storage stability

### 4.1 Stability at 0°C (MT 39.3)

(Note 7)

### 4.2 Stability at elevated temperature (MT 46.3)

After storage at  $54 \pm 2^\circ\text{C}$  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 8).

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**Note 1** The identity of the active ingredient shall be confirmed by comparison of GC retention times of imazalil with that of an internal standard. The identity of the active ingredient can be further confirmed by TLC. The identity of the imazalil sulphate salt may be determined by its melting point in the range 128 - 134°C.

**Note 2** Extraction details SL formulations CIPAC Handbook E p 95 - 99. The following extraction step is required for the sulphate salt.

Weigh accurately sufficient material to contain 50mg imazalil free base into a 40 ml clear vial, liberate the free base by adding 1 ml of 25% aqueous ammonium hydroxide solution. Allow to stand for a minimum 2 hours (do not shake) before continuing with the extraction of the imazalil (free base). Note that this is a longer period than given for liberation of the free base in the CIPAC method for SL. It is possible to use either dichloromethane or toluene for the extraction of the free base, retaining the lower or upper layer, respectively.

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

**Note 4** The concentration used for the test should not be higher than the highest concentration recommended in the instructions for use.

**Note 5** Precipitation may occur if the buffering capacity of the system is exceeded. It is recommended that water of  $\text{pH} \leq 7$  is used.

**Note 6** The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier.

**Note 7** Where relevant to the local conditions of transport, storage or use of the SL, the product must be labelled protect from frost.

**Note 8** Samples of the formulation taken before and after the storage stability test should be analysed concurrently after the test in order to reduce the analytical error.

# IMAZALIL SOLUTION FOR SEED TREATMENT

## FAO Specification 335/LS (2001)

*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 (335/2001). 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 (335/2001) as PART TWO forms an integral part of this publication.*

### 1 Description

The material shall consist of imazalil technical material, complying with the requirements of FAO specification [335/TC], in the form of imazalil free base, dissolved in suitable solvents, together with any other necessary formulants, including colouring matter (Note 1). It shall be in the form of a clear or opalescent liquid, free from visible suspended matter and sediment.

### 2 Active ingredient

#### 2.1 Identity tests (CIPAC 335/SL/M/-) CIPAC Handbook E page 99 (Note 2)

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

#### 2.2 Imazalil content (Note 3)

The imazalil content shall be declared (g/l at  $20 \pm 2^{\circ}\text{C}$ ) and, when determined, the content measured shall not differ from that declared by more than tolerance given in the following table.

Declared content, g/kg	Permitted tolerance
up to 25 g/l	$\pm 15\%$
above 25 up to 100 g/l	$\pm 10\%$
above 100 up to 250 g/l	$\pm 6\%$
Note: in each range the upper limit is included	

### 3 Physical properties

(Note 4)

## 4 Storage stability

### 4.1 Stability at 0°C (MT 39.3)

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

### 4.2 Stability at elevated temperature (MT 46.3)

After storage at  $54 \pm 2^\circ\text{C}$  for 14 days (Note 5 and 6) the determined average active ingredient content must not be lower than 95% relative to the determined average content found before.

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Note 1 The formulation shall contain a dye that permanently colours the seed after treatment (red is recommended) and cannot be removed by washing with water. In some countries, there may be a legal requirement that a specific colour shall be used. The same colour must not be used for denaturing seeds intended for use as livestock feeding stuffs.

Note 2 The identity of the active ingredient shall be confirmed by comparison of GC retention times of imazalil with that of an internal standard. The identity of the active ingredient can be further confirmed by TLC.

Note 3 If the buyer requires both g/kg and g/l at  $20^\circ\text{C}$ , then in case of dispute the analytical results shall be calculated as g/kg.

Note 4 A test of solution stability, required for certain SL formulations, is not applicable in this case as the product is intended to be applied undiluted.

Note 5 Unless other temperatures and/or times are specified.

Note 6 Samples of the formulation taken before and after the storage stability test should be analysed concurrently after the test in order to reduce the analytical error.

# IMAZALIL EMULSIFIABLE CONCENTRATE

## FAO Specification 335/EC (2001)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation report (335/2001). It should be applicable to relevant products of these manufacturers 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 (335/2001) as PART TWO forms an integral part of this publication.*

### 1 Description

The material shall consist of technical imazalil, complying with the requirements of FAO specification 335/TC, in the form of imazalil free base, dissolved in suitable solvents, together with any other necessary formulants. It shall be free from visible suspended matter and sediment.

### 2 Active ingredient

#### 2.1 Identity tests (CIPAC 335/EC/M/-) CIPAC Handbook E page 99 (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 Imazalil content

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

Declared content, g/kg	Permitted tolerance
above 25 up to 100 g/l	$\pm 10\%$
above 100 up to 250 g/l	$\pm 6\%$
above 250 up to 500 g/l	$\pm 5\%$
Note: in each range the upper limit is included	

### 3 Physical properties

#### 3.1 Emulsion stability and re-emulsification (MT 36.1) (Note 3)

The formulation, when diluted at  $30 \pm 2^\circ\text{C}$  (Notes 4 & 5) with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.1
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 0 ml
2.0 h	"bottom cream", <1 ml "Free oil", maximum: 0 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 0 ml "Free oil", maximum: 0 ml
Note: tests after 24 h are required only where results at 2 h are in doubt	

#### 3.2 Persistent foam (MT 47.2) (Note 6)

Maximum: 60 ml after 1 min.

### 4 Storage stability

#### 4.1 Stability at $0^\circ\text{C}$ (MT 39.3)

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

#### 4.2 Stability at elevated temperature (MT 46.3)

After storage at  $54 \pm 2^\circ\text{C}$  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 7) and the formulation shall continue to comply with the clause for emulsion stability and re-emulsification (3.1).

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**Note 1** The identity of the active ingredient shall be confirmed by comparison of GC retention times of imazalil with that of an internal standard. The identity of the active ingredient can be further confirmed by TLC

**Note 2** If the buyer requires both g/kg and g/l at  $20^\circ\text{C}$ , then in case of dispute the analytical results shall be calculated as g/kg.

**Note 3** This test will normally only be carried out after the heat stability test, clause 4.2.

**Note 4** Unless another temperature is specified.

**Note 5** MT 36.1 tests the formulation at 5% dilution.

**Note 6** The test should be carried out at the highest application concentration.

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

**PART TWO**  
**EVALUATION REPORT(S)**

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**IMAZALIL**

2001	EVALUATION REPORT BASED ON SUBMISSION OF DATA FROM JANSSEN PHARMACEUTICA NV (TC, EC, SL and LS) AND MAKHTESHIM CHEMICAL WORKS LTD (TC and EC)	15
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FAO SPECIFICATIONS AND EVALUATIONS FOR  
PLANT PROTECTION PRODUCTS

**IMAZALIL**

EVALUATION REPORT 335/2001

**Explanation**

Imazalil was scheduled as an existing FAO specification to be reviewed in under the new procedure.

The existing specifications were for imazalil technical material (FAO 335/TC/S/F (1992)), imazalil technical concentrate (FAO 335/TK/S/F (1992)), emulsifiable concentrate (FAO 335/EC/S/F (1992)) and soluble concentrate (FAO 335/SL/S/F (1992)).

Imazalil has been the subject of EU review<sup>1,2,3,4</sup> and is listed in Annex 1 of the European Community Council Directive 91/414, as described in Commission Directive 97/73/EC. The expiry date of the inclusion is 31 December 2008. Imazalil is registered for use in many countries.

Imazalil was considered by the JMPR in 77, 80, 84, 85, 86T, 88R, 91T, 94R.

The draft specifications and supporting data were provided for TC, EC, SL and LS by Janssen Pharmaceutica NV in 1999-2000 and for TC and EC by Makhteshim Chemical Works Ltd in 2000. Both proposers confirmed that the information submitted was identical to that submitted to the European Commission for the purposes of the EU review.

**Uses**

Imazalil is a systemic fungicide, acting by interfering with the cellular permeability of pathogenic fungi. It belongs to the demethylation inhibitor group of fungicides, which inhibit a cytochrome P450 dependent enzyme. These enzymes demethylate ergosterol precursors.

The compound is used as an agricultural fungicide for seed dressings and pre- and post-harvest application to crops.

**Identity**

*ISO common name*

Imazalil (E-ISO, F-ISO[m])

*Synonyms*

Imazalil (ANSI), chloramisol (Republic of South Africa), enilconazole (BAN, INN)

*Chemical names*

*IUPAC*

(±)-1-[β-(allyloxy)-2,4-dichlorophenethyl]imidazole

*CA*

(±)-1-[2-(2,4-dichlorophenyl)-2-(2-propyloxy)ethyl]-1*H*-imidazole



*CAS registry numbers*

Imazalil, 35554-44-0 (unstated stereochemistry); 73790-28-0

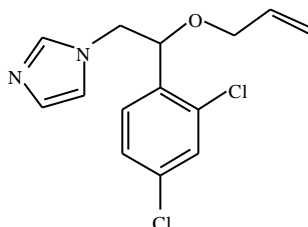
Imazalil sulphate, 58594-72-2

*CIPAC number*

Imazalil 335

Imazalil sulphate 335.306

*Structural formula*



*Molecular formula*

Imazalil, C<sub>14</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O

Imazalil sulphate, C<sub>14</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S

*Relative molecular mass*

Imazalil, 297.18

Imazalil sulphate, 395.26

*Identity tests*

Imazalil, GC by comparison of the retention time of imazalil with respect to the internal standard; TLC; UV spectrum (3 maxima 265nm, 272nm, 280nm).

Imazalil sulphate, in addition to tests for imazalil, melting point 128 to 134°C.

## Physical and chemical properties of the pure active ingredient

Test	Purity	Method	Result	Data source																
vapour pressure	99.7%	OECD 104 gas saturation method	1.58 x 10 <sup>-4</sup> Pa at 25°C	Janssen																
	97.8%	EC method A4 vapour pressure balance	2.02 x 10 <sup>-4</sup> Pa at 25°C	Makhteshim																
melting point imazalil free base	99.99 %	OECD 102 capillary with photocell	52.7°C	Janssen																
	98.96 %	OECD 102	51.5°C	Janssen																
	99.2%	OECD 102 capillary with Haake Buchler melting point apparatus	51.5 to 54°C	Makhteshim																
imazalil sulphate	not stated		128 to 134°C																	
boiling point			no data submitted but estimated by calculation to be 319°C	Janssen																
solubility in water	99.9 to 100%	OECD 105 flask method	<table border="1"> <thead> <tr> <th>pH</th> <th>g/100ml solution</th> </tr> </thead> <tbody> <tr><td>4.6</td><td>2.6</td></tr> <tr><td>4.7</td><td>1.6</td></tr> <tr><td>4.9</td><td>1.0</td></tr> <tr><td>5.4</td><td>0.29</td></tr> <tr><td>6.1</td><td>0.073</td></tr> <tr><td>8.0</td><td>0.021</td></tr> <tr><td>10.0</td><td>0.018</td></tr> </tbody> </table>	pH	g/100ml solution	4.6	2.6	4.7	1.6	4.9	1.0	5.4	0.29	6.1	0.073	8.0	0.021	10.0	0.018	Janssen
	pH	g/100ml solution																		
4.6	2.6																			
4.7	1.6																			
4.9	1.0																			
5.4	0.29																			
6.1	0.073																			
8.0	0.021																			
10.0	0.018																			
	97.8%	EPA Guidelines CG-1500 HPLC method	<table border="1"> <thead> <tr> <th>pH</th> <th>g/100ml solution</th> </tr> </thead> <tbody> <tr><td>5</td><td>0.0951</td></tr> <tr><td>7</td><td>0.0224</td></tr> <tr><td>9</td><td>0.0177</td></tr> </tbody> </table>	pH	g/100ml solution	5	0.0951	7	0.0224	9	0.0177	Makhteshim								
pH	g/100ml solution																			
5	0.0951																			
7	0.0224																			
9	0.0177																			
octanol water partition coefficient <sup>1</sup>	99.9 to 100%	OECD 107	<table border="1"> <thead> <tr> <th>pH</th> <th>P</th> </tr> </thead> <tbody> <tr><td>2.0</td><td>3.2</td></tr> <tr><td>4.1</td><td>26.0</td></tr> <tr><td>6.1</td><td>1380</td></tr> <tr><td>8.0</td><td>5900</td></tr> <tr><td>10.0</td><td>6510</td></tr> </tbody> </table>	pH	P	2.0	3.2	4.1	26.0	6.1	1380	8.0	5900	10.0	6510	Janssen				
	pH	P																		
2.0	3.2																			
4.1	26.0																			
6.1	1380																			
8.0	5900																			
10.0	6510																			
	97.8%	EPA Guidelines CG-1400 HPLC after correction for ionisation at 25°C	<table border="1"> <thead> <tr> <th>pH</th> <th>P</th> <th>log P<sub>ow</sub></th> </tr> </thead> <tbody> <tr><td>5</td><td>425</td><td>2.63</td></tr> <tr><td>7</td><td>4600</td><td>3.66</td></tr> <tr><td>9</td><td>6630</td><td>3.82</td></tr> </tbody> </table>	pH	P	log P <sub>ow</sub>	5	425	2.63	7	4600	3.66	9	6630	3.82	Makhteshim				
pH	P	log P <sub>ow</sub>																		
5	425	2.63																		
7	4600	3.66																		
9	6630	3.82																		
degradation characteristics	>97.5 %		No degradation of imazalil detected after incubation in citrate/phosphate buffers between pH 5 to 9 for up to 61 days	Janssen																
	97.8%	HPLC analysis of imazalil content in buffered solution	Imazalil did not hydrolyse to a significant extent in 35 days at 25°C and at pH values of 5 to 9	Makhteshim																
pKa	100%	OECD 112	6.53	Janssen																
	97.8%	EPA Guidelines GC-1400	5.85	Makhteshim																

<sup>1</sup> due to the basic nature of imazalil (pKa 5.85 - 6.5), values of P<sub>ow</sub> are corrected for the degree of ionisation.

## Chemical composition and properties of the technical material

Manufacturing processes for imazalil and imazalil sulphate, maximum limits for impurities <sup>3</sup> 1 g/kg, 5 batch analysis data	Confidential information was supplied and is held on file by FAO. Mass balances were high.
Declared minimum imazalil in imazalil TC (free base)	950 g/kg.
Declared minimum imazalil in imazalil sulphate TC	725 g/kg (equivalent to 964 g/kg imazalil sulphate)
Relevant impurities <sup>3</sup> 1 g/kg and maximum limits for them	none.
Relevant impurities < 1 g/kg and maximum limits for them	none.
Stabilisers or other additives, and maximum limits for them	none.

The proposers, the EU and JMPR considered that none of the impurities was relevant by the FAO definition. WHO/PCS agreed with this conclusion.

### Hazard summary

Note:

- (i) Both proposers confirmed that the toxicological data were generated using imazalil technical material (the free base) of purity consistent with that declared in the specification.

Table 1. Toxicological profile of imazalil technical material, based acute toxicity, irritation and sensitization

#### a Janssen

Species	Test	Test result
Rat	Oral LD <sub>50</sub>	Female, 227 to 309 Male, 343 to 371
Rat	Dermal LD <sub>50</sub>	>2000 mg/kg
Rat	Inhalation LC <sub>50</sub> smoke	>1.073 mg/l air
Rabbit	Skin irritancy	Non-irritant
Rabbit	Eye irritancy	Severe eye irritant
Guinea pig	Skin sensitization	Non-sensitizer

#### b Makhteshim

Species	Test	Test result
Rat	Oral LD <sub>50</sub>	Male 664 mg/kg Female 664 mg/kg
Rat	Dermal LD <sub>50</sub>	> 2000 mg/kg
Rat	Inhalation LC <sub>50</sub>	2.43 mg/l
Rabbit	Skin irritancy	Mild
Rabbit	Eye irritancy	Irritant
Guinea pig	Skin sensitization	Non-sensitizer

Table 2. Environmental fate and behaviour of imazalil

<b>Test</b>	<b>Result</b>
<b>Aerobic degradation in soil</b>	
mineralisation after 100 days	9% after 115 days
non-extractable residues after 100 days	16.6% after 115 days
relevant metabolites	none
<b>Rate of degradation</b>	
DT <sub>50</sub> lab (25°C, aerobic)	80 days
DT <sub>90</sub> lab (25°C, aerobic)	>1 year
DT <sub>50</sub> field	4 to 5 days
DT <sub>90</sub> field	54 to 68 days
<b>Adsorption/desorption</b>	
K <sub>oc</sub> /K <sub>om</sub>	K <sub>oc</sub> 2080 to 8150 mg/l
<b>Mobility</b>	
column leaching	average penetration <5cm, no residues in leachate
aged residues leaching	average penetration <2cm, no residues in leachate
<b>Fate and behaviour in water</b>	
hydrolytic degradation	No hydrolysis between pH 5 to 9
photolytic degradation	DT <sub>50</sub> in river water 18.15 hours
water/sediment study	rapid dissipation from water phase into sediment
<b>Fate and behaviour in air</b>	

Table 3. Ecotoxicological profile of imazalil

Species	Test	Result
Rat, female	Acute toxicity	LD <sub>50</sub> 227 mg as/kg bw
Japanese quail	Acute toxicity, single dose	LD <sub>50</sub> 510 mg as/kg bw
Mallard duck	5-day dietary toxicity	LD <sub>50</sub> >5620 mg/kg food
Mallard duck	Reproductive toxicity, 22-week study	NOEC 250 mg/kg food
Rat, female	Short term oral toxicity	NOAEL 11.3 mg/kg bw/day
Rainbow trout	Acute toxicity, 96-hour study	LC <sub>50</sub> 1.48 mg/l
Rainbow trout	Bioaccumulation	BCF 48.7 to 63.8
<i>Daphnia magna</i> Water flea	Acute toxicity, 48-hour study	EC <sub>50</sub> 3.5 mg/l
Algae (species not stated)	Acute toxicity	EC <sub>50</sub> 0.87 mg/l
<i>Chironomus</i> , sediment dwelling organism	Chronic toxicity	NOEC 165.4 mg/kg sediment
Honey bee	Acute oral toxicity	LD <sub>50</sub> 35.1 µg/bee 48 hours
Honey bee	Acute contact toxicity	LD <sub>50</sub> 39 µg/bee 48 hours
Coccinella (arthropod)	14 days field exposition	E (mort) 0% at 66 g as/ha
<i>Coccinella septempunctata</i>	14 days reproduction period	E (fecund) 24.4% at 66g as/ha
<i>Poecilus cupreus</i> (arthropod)	14 days field exposition	E (mort) 0% at 88 g as/ha
<i>Encarsia formosa</i>	7 days in water	E (mort) 0% 30 g as/100 l
<i>Encarsia formosa</i>	7 days in water	E (parasitisation) 0% 30 g as/100 l
Earthworm ( <i>Eisenia foetida</i> )	Acute toxicity	LC <sub>50</sub> 541 mg/kg soil
Earthworm ( <i>Eisenia foetida</i> )	Reproductive toxicity	not relevant
Soil micro-organisms, nitrogen mineralisation		no effect at 1 mg/kg soil
Soil micro-organisms, carbon mineralisation		no effect at 1 mg/kg soil

### Hazard assessments

WHO/PCS classification: Class II 'Moderately hazardous'.

FAO/WHO JMPR ADI: 0 to 0.03 mg/kg bw/day (1991).

EU ADI: 0 to 0.03 mg/kg bw/day.

EU AOEL: 0 - 0.05 mg/kg bw/day.

EU review summary of toxicology:

Imazalil did not show bioaccumulation, it is rapidly excreted in the urine and faeces. Extensive biotransformation of imazalil into at least 25 metabolites was observed. The pathway is essentially the same in livestock and plants.

Imazalil is classified as harmful by inhalation and via the oral route. Its percutaneous toxicity is low, it is not a skin irritant but a severe eye irritant. It is not a skin sensitizer.

After repeated oral exposure, effects were mainly seen in the liver. The effects were not considered degenerative. Imazalil is not genotoxic and it was concluded that there was no carcinogenic potential of relevance to man. There was no clear evidence of teratogenicity and no further studies were considered necessary.

However in the summary reports of the EU peer review process it was noted that the purity of the technical material differed in some of the toxicity studies. The EU report concluded that although differences in impurities were noted in the studies, it was concluded these did not give rise to any significant toxicological concerns.

#### Hazard classification following EU review:

Hazard symbol	Xn	
Indication of danger	Harmful	
Risk phrases	R 20/22	Harmful by inhalation and if swallowed
	R 41	Risk of serious damage to eyes
	R 50	Very toxic to aquatic organisms
Safety phrases	S 2	Keep out of reach of children
	S 25	Avoid contact with eyes
	S 26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice

#### Justification:

Xn R20/22	LD <sub>50</sub> oral, rat 227 to 664 mg/kg. LC <sub>50</sub> inhalation, rat 4h dust: 2.43 mg/l
Xi R 41	Imazalil is a moderate eye irritant, not completely reversible after 21 days.
R 50	EC <sub>50</sub> 72 h Selenastrum capricornutum (EC <sub>50</sub> based on growth) 0.87 mg/l

## Formulations

Janssen Pharmaceutica: EC, LS, SL, formulations are registered and sold throughout the European Union.

Makhteshim Chemical Works: the EC formulation is registered and sold in Australia, Central and South American countries, France, Greece, Netherlands, South Africa, Spain, Belgium, Italy and U.S.A.

## Methods of analysis and testing

### Methods used in the development of data

Imazalil TC and imazalil sulphate TC, determination of imazalil and impurities

#### a) Janssen

Imazalil and impurities were determined by capillary GC, using a 0.32 $\mu$ m x 25m column coated with 5% phenylmethylsiloxane stationary phase. Detection was by FID. Imazalil sulphate was used as the reference standard because this was obtainable in higher purity than imazalil free base. Imazalil free base was generated by addition of a 25% ammonium hydroxide solution followed by extraction with toluene. The method was validated satisfactorily for imazalil and all listed impurities, in respect of specificity, repeatability of injection, repeatability of analysis, accuracy, linearity, stability of solution. The limit of quantification was 0.05%w/w for all impurities.

#### b) Makhteshim

Imazalil in imazalil TC was determined by GC-FID using a 0.53 $\mu$ m capillary column (DB-17) with dibutyl phthalate as an internal standard. The method was validated for linearity, precision and the identity of the peak was confirmed by GC-MSD. Impurities in imazalil TC were also determined by GC-FID. The method was validated for precision, linearity, accuracy and the peak identities confirmed by GC-MS. Single ion monitoring was used for quantification because

of the low levels of the impurities but the ions utilised were characteristic. Imazalil in imazalil sulphate TC was determined by the CIPAC method, using ammonium hydroxide solution to liberate the free base, followed by extraction with toluene.

## Formulations

### a) Janssen

#### i) Imazalil in 50 LS (present as the free base)

Imazalil was extracted by addition of a saturated sodium chloride solution followed by partition into toluene. Imazalil was determined by capillary GC, using a 0.32 $\mu$ m x 25m column coated with 5% phenylmethylsiloxane stationary phase. Detection was by FID with quantification by external standard. The method was satisfactorily validated in respect of blank formulation analysis, specificity, repeatability of injection, repeatability of analysis, linearity, and stability in solution in the dark at ambient temperature. The effect of the matrix (bias) on the accuracy of the analysis was determined and for the LS formulation a correction factor of 0.978 (multiplication) was required.

#### ii) Imazalil in 100 SL (present as the sulphate)

Imazalil was determined by release of the imazalil free base with ammonium hydroxide followed by addition of saturated sodium chloride solution and partition of imazalil into toluene. Determination was by capillary GC using a 0.32 $\mu$ m x 25m column coated with 5% phenylmethylsiloxane stationary phase. Detection was by FID with quantification by external standard using imazalil free base. The method was satisfactorily validated in respect of blank formulation analysis, specificity, repeatability of injection, repeatability of analysis, linearity, stability in solution in the dark at ambient temperature. The effect of the matrix (bias) on the accuracy of the analysis was assessed and no matrix effect was found.

#### iii) Imazalil in 100 EC (present as the free base)

Imazalil was extracted from the formulation by addition of a saturated sodium chloride solution followed by partitioning into toluene. Imazalil was determined by capillary GC, using a 0.32 $\mu$ m x 25m column coated with 5% phenylmethylsiloxane stationary phase. Detection was by FID with quantification by external standard. The method was satisfactorily validated in respect of blank formulation analysis, specificity, repeatability of injection, repeatability of analysis, linearity, stability in solution in the dark at ambient temperature. The effect of the matrix (bias) on the accuracy of the analysis was assessed and no matrix effect was found.

### b) Makhteshim

#### Imazalil 50 EC (present as the free base)

The proposer stated that the CIPAC method 335/EC was used.

The methods of analysis used to generate the data submitted by Janssen are compared with those of CIPAC in the tables below:

## Imazalil TC

Method component	Proposer's method CKC 99-005	CIPAC E p95
Extraction/solution	toluene	methanol
Column	capillary CPSil 8	packed OV-105
Temp/gradient	25°C/min; max 260°C	isothermal 240 °C
Carrier Gas	helium	nitrogen 30 ml/min
Injector	splitter; split insert: mixing chamber (glasswool)	direct on column 280°C
Detector temp (FID)	300°C	280°C
Detector Gas (air)	450 ml/min	250 ml/min
Detector (H <sub>2</sub> )	40 ml/min	25 ml/min
Detector Gas (make-up)	helium 45 ml/min	none
Calibration/Calculation	external standard	internal standard

## Imazalil sulphate TC

Method component	Proposer's method CKC 98-005	CIPAC E p95
Extraction/solution	ammonium hydroxide/toluene	methanol
Column	capillary CPSil 8	packed OV-105
Temp/gradient	25°C/min; max 260°C	isothermal 240 °C
Carrier Gas	helium	nitrogen 30 ml/min
Injector	splitter; split insert: mixing chamber (glasswool)	direct on column 280°C
Detector temp (FID)	300°C	280°C
Detector Gas (air)	450 ml/min	250 ml/min
Detector (H <sub>2</sub> )	40 ml/min	25 ml/min
Detector Gas (make-up)	helium 45 ml/min	none
Calibration/Calculation	no internal standard	internal standard

## Soluble liquids (including soluble concentrate and solution for seed treatment)

Method component	Proposer's methods CKC-GC 99-011 and CKC-GC 99-013	CIPAC
Extraction/solution	ammonium hydroxide/sodium chloride/toluene	ammonium hydroxide/dichloromethane
Column	capillary CPSil 8	packed OV-105
Temp/gradient	25°C/min; max 260°C	isothermal 240 °C
Carrier Gas	helium	nitrogen 30 ml/min
Injector	splitter; split insert: mixing chamber (glasswool)	direct on column 280°C
Detector temp (FID)	300°C	280°C
Detector Gas (air)	450 ml/min	250 ml/min
Detector (H <sub>2</sub> )	40 ml/min	25 ml/min
Detector Gas (make-up)	helium 45 ml/min	none
Calibration/Calculation	no internal standard	internal standard



## Emulsifiable concentrate

Method component	Proposer's method CKC-GC99-010	CIPAC
Extraction/solution	sodium chloride/toluene	methanol
Column	capillary CPSil 8	packed OV-105
Temp/gradient	25°C/min; max 260°C	isothermal 240 °C
Carrier Gas	helium	nitrogen 30 ml/min
Injector	splitter; split insert: mixing chamber (glasswool)	direct on column 280°C
Detector temp (FID)	300°C	280°C
Detector Gas (air)	450 ml/min	250 ml/min
Detector (H <sub>2</sub> )	40 ml/min	25 ml/min
Detector Gas (make-up)	helium 45 ml/min	none
Calibration/Calculation	no internal standard	internal standard

The methods differ in the sample preparation steps and in changing from packed to capillary column. It is not considered that the use of an external standard would significantly affect the results. However, the sample preparation step may be of greater significance especially in achieving satisfactory gas chromatography of the free base from injection of imazalil sulphate. There was no evidence to indicate a typographical error in the CIPAC method using methanol and, as it was subject to collaborative study and the results were acceptable, it appears that the use of methanol as a solvent in sample preparation is acceptable.

### Analytical methods to check compliance with specifications

Imazalil TC, CIPAC 335/TC/M/, CIPAC E p96

The CIPAC method (reference 335/TC/M3) determines imazalil by GC-FID after dissolution of imazalil and the internal standard ( $\pm$ )-1-[2-(2,4-dichlorophenyl)heptyl]-1*H*-imidazole.mononitrate in methanol. Analysis is by packed column.

Imazalil sulphate TC, CIPAC 335/TC/M/, CIPAC E p96

The CIPAC method as published omits the ammonium hydroxide addition step required to liberate imazalil free base and both proposers confirmed that this is required.

Formulations

CIPAC methods: for the EC, 335/EC/M/-; for the SL and LS 335/SL/M/-.

### Test methods for physico-chemical properties of formulations

All methods used were the appropriate CIPAC methods for each formulation type.

### Containers and packaging

It is recommended that metal containers are not used for imazalil sulphate.

## Appraisal

Imazalil is a systemic fungicide with foliar, post-harvest and seed treatment uses. It is a relatively low melting point solid of low to moderate volatility. Because imazalil is a weak base, solubility in water is pH-dependent, with highest solubility at lowest pH. Imazalil is manufactured as the free base and as the imazalil sulphate salt. The salt is used in the preparation of SL, SG and SP, whereas the free base is used in EC and LS formulations.

Imazalil is included in Annex 1 of EC Council Directive 91/414, and an agreed evaluation monograph including review report and conditions of Annex 1 listing was available for the present evaluation. Among the conditions of the EU review of imazalil the conditions to be fulfilled is that the purity of the active substance as manufactured shall satisfy the specification established by the FAO for this active substance.

Specifications were proposed by Janssen Pharmaceutica NV and Makhteshim Chemical Works Ltd. Confidential information on the method of manufacture, the technical specification and data from the analysis of production batches was presented to the meeting. Makhteshim sought specifications on the basis of equivalence of technical materials with the Janssen source. Data on relevant physical properties of the active ingredient were submitted by Janssen Pharmaceutica and Makhteshim. On the basis of the breadth of toxicological and ecotoxicological data supported by the Janssen data on impurities, the meeting agreed that the reference profile of impurities should be that of Janssen, for the purpose of determination of equivalence.

Although technical grade active ingredients of different purity were produced by the proposers, no significant differences were determined in their physical and chemical properties. The Meeting considered it unlikely that the active ingredient produced by Makhteshim would differ from that of Janssen such that relevant impurities will be present in the Makhteshim source of technical material. This was also the opinion of the EU review. The impurity profile of the Makhteshim technical material was determined for be equivalent to that of Janssen, according to the criteria provided in the FAO Manual and therefore the two sources are considered equivalent.

The EU review also considered the comparability of the Janssen and Makhteshim sources. Janssen was identified in the EU review as the main data submitter. The EU review concluded that none of the manufacturing impurities in the imazalil notified by Janssen Pharmaceutica was of toxicological or environmental concern and that the imazalil notified by Makhteshim Agan did not, in the meaning of Article 13(2) and (5) of Directive 91/414/EEC, differ significantly in degree of purity and nature of impurities from the composition registered by Janssen.

Both proposers produce imazalil sulphate; the materials differ in purity but they were considered equivalent, as discussed above. The conclusions of the EU review were that the salt may be considered as a technical concentrate (TK) but, as the salt is isolated, under existing definitions it was considered by the meeting to be a technical material (TC). The classification as TK or TC does not materially affect the conclusions of the appraisal. The sulphate salt is produced from the crude free base by further purification steps, although batch analytical data were not available it is considered by the evaluator that no additional impurities are likely to have been produced in this process and the limits for batch analysis data provided for the free base are unlikely to be exceeded in the sulphate salt.

Imazalil may be used in formulated products as the free base or as imazalil sulphate salt and therefore specifications must declare which form is used.

The CIPAC methods for the analysis of imazalil TC and TK are not applicable to the determination of imazalil in imazalil sulphate TC. The method used in the generation of data for imazalil sulphate TC by Janssen and Makhteshim included a sample preparation step, in which the free base was liberated by the addition of ammonium hydroxide. This step is analogous to that given in the CIPAC method for imazalil SL formulations and must be used for the analysis of imazalil sulphate TK.

The current CIPAC method does not provide an identity test for imazalil sulphate. For the purposes of the specification, such a test is required and both proposers agreed that, in addition to confirmation of the active ingredient as imazalil, the melting point of imazalil sulphate provided an acceptable identity test. This was accepted by the Meeting. The proposers agreed to forward the identity test to the CIPAC secretariat, for publication.

The proposers were asked to comment on the effect of pH on the formulations and whether the pH range should be included in the specifications for the formulated products. Precipitation from solution might occur if pH was such as to change the free base into the salt or vice versa. Janssen stated that the EC is normally in the range  $\geq 5$ ; the SL is normally in the range  $\leq 7$ ; and that a test of pH is not appropriate for the ready-to-use LS formulation. Janssen confirmed that, under normal use conditions and water hardness, there are generally no problems encountered because the pH of the system is usually satisfactory. The meeting agreed that a clause for pH was not required for specifications produced by either proposer.

The specifications adopted meet the requirements of the 5<sup>th</sup> edition of the FAO Manual.

A clause to limit the water content of imazalil sulphate TC is required to ensure that the material does not "cake" and the limit agreed by both proposers was adopted by the Meeting.

A clause for low temperature stability of the SL is not included in the specification because the proposer recommends that the product is not stored below 4°C. This constraint was considered acceptable by the Meeting, subject to inclusion of a note to this effect in the specification. The proposer also stated that precipitation could occur if the buffering capacity was exceeded on dilution with water. The meeting agreed that a note should be added to the specification that water at pH  $\leq 7$  should be used.

A clause for acidity/alkalinity is not included in the LS specification. The proposer confirmed the formulation is buffered and that, should the pH change from acceptable levels then any crystallisation would be detected in the appropriate dilution tests. Although the LS is prepared from imazalil free base, the CIPAC method for the SL is required for the determination of imazalil content, to ensure that the free base is regenerated from the buffered system.

## **Recommendations**

The Meeting recommended that the CIPAC secretariat should be asked to confirm that the published method of analysis is correct (or to amend it in line with the recommendations of the proposers) with respect to the sample preparation step for the imazalil sulphate TC.

The meeting recommended adoption of the specifications.

## References

- 1 Imazalil: Monograph prepared in the context of the inclusion of the active substance in Annex 1 of the Council Directive 91/414 July 1996.
- 2 European Commission Peer Review Programme; ECCO Meetings, Full report on imazalil.
- 3 Review report for the active substance imazalil. European Commission, Directorate General for Agriculture, DG VI-B.II Imazalil; Document 1688/VI/97-Rev. 8.4A 11 July 1997.
- 4 Commission Directive 97/73/EC, 15 December 1997. Including an active substance (imazalil) in Annex I to Council Directive 91/414/EEC, concerning the placing of plant protection products on the market (Text with EEA relevance). Official journal NO. L 353 , 24/12/1997 P. 0026 – 0028.