Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

INDOXACARB

**(S)-7-chloro-2-[methoxycarbonyl-(4-trifluoromethoxyphenyl)
-carbamoyl]-2,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylic acid,
methyl ester**

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INDOXACARB

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

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

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

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

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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.

From 1999, the development of FAO specifications follows the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) - currently available as 3rd revision of the 1st edition (2016) - , which is available only on the internet through the FAO and WHO web sites.

This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPM, rather than the JMPS.]

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

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

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" 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 developed 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.

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

PART ONE

SPECIFICATIONS

INDOXACARB

INDOXACARB

INFORMATION

ISO common name

Indoxacarb (ISO 1750 published)

Synonyms

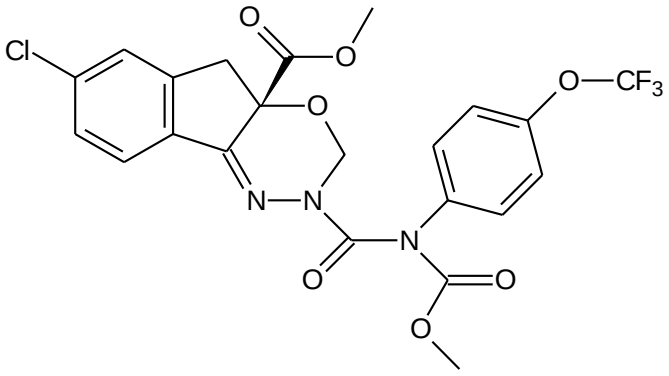
none

Chemical name(s)

IUPAC (S)-7-chloro-2-[methoxycarbonyl-(4-trifluoromethoxyphenyl)-carbamoyl]-2,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylic acid, methyl ester

CA (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate

Structural formula



Molecular formula

$C_{22}H_{17}ClF_3N_3O_7$

Relative molecular mass

527.8

CAS Registry number

173584-44-6

144171-61-9 (R/S- ratio 50/50; DPX-JW062)

CIPAC number

612

Identity tests

HPLC retention time, UV and IR spectra

INDOXACARB TECHNICAL MATERIAL

FAO Specification 612 / TC (December 2018)*

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose name are listed in the evaluation reports (612/2009 & 612/2018.1). It should be applicable to relevant technical materials of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the technical materials of other manufacturers. The evaluation reports (612/2009 & 612/2018.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of indoxacarb together with related manufacturing impurities, in the form of a tan to light brown amorphous solid, and shall be free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (612/TC/M/2, CIPAC Handbook N, p. 74, 2011)

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 **Indoxacarb content** (612/TC/M/3, CIPAC Handbook N, p. 74, 2011)

The indoxacarb content shall be declared (not less than 900 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

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

INDOXACARB TECHNICAL CONCENTRATE

FAO Specification 612 / TK (December 2018)*

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (612/2009 & 612/2018.1). It should be applicable to relevant technical concentrates of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the technical concentrates of other manufacturers. The evaluation reports (612/2009 & 612/2018.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of indoxacarb together with related manufacturing impurities and shall be a white powdered solid free from visible extraneous matter and added modifying agents except for the diluent.

2 Active ingredient

2.1 **Identity tests** (612/TK/M/2, CIPAC Handbook N, p. 77, 2011)

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 **Indoxacarb content** (612/TK/M/3, CIPAC Handbook N, p. 77, 2011)

The indoxacarb content shall be declared (not less than 467 g/kg) and, when determined, the average measured content shall not differ from that declared by more than the following tolerances:

Declared content in g/kg	Tolerance
above 250 up to 500	± 5% of the declared content
above 500	±25 g/kg of the declared content
Note: In each range the upper limit is included	

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

INDOXACARB EMULSIFIABLE CONCENTRATE

FAO Specification 612 / EC (December 2018)*

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose name are listed in the evaluation reports (612/2009 & 612/2018.1). 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 reports (612/2009 & 612/2018.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of technical indoxacarb, complying with the requirements of FAO specification 612/TC (December 2018), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 **Identity tests** (612/EC/M/2, CIPAC Handbook N, p. 79, 2011)

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 **Indoxacarb content** (612/EC/M/3, CIPAC Handbook N, p. 79, 2011).

The indoxacarb content shall be declared (g/kg or g/l at 20 ± 2° C, Note 1) and, when determined, the content measured shall not differ from that declared by more than the following tolerance:

Declared content g/kg or g/l at 20 ± 2° C	**Tolerance**
Above 100 up to 250	± 6% of the declared content

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

3 Physical properties

3.1 Emulsion stability and re-emulsification (MT 36.3, CIPAC Handbook K, p. 137, 2003)

The formulation, when diluted at 30 ± 2ºC with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of Stability
0 h	Initial emulsion complete
0.5 h	"Cream", maximum: 0 ml
2.0 h	"Cream", maximum: 1 ml "Free oil": maximum: 0 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 1 ml "Free oil": maximum: 0 ml
Note: In applying MT 36.3, tests after 24 h are required only where results at 2 h are in doubt.	

3.2 Persistent foam (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 2)

Maximum: 10 mL after 1 minute

4 Storage stability

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

After storage at 0 ±2°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, 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 3) and the formulation shall continue to comply with the clause for:
- emulsion stability and re-emulsification (3.1)

Note 1 If the buyer requires both g/kg and g/l at 20ºC, then in case of dispute the analytical results shall be calculated as g/kg.

Note 2 The mass of sample to be used in the test should be specified at the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 3 Analysis of the formulation, before and after the storage stability test, may be carried out concurrently (i.e. after storage) to reduce analytical error.

INDOXACARB WATER DISPERSIBLE GRANULES

FAO Specification 612 / WG (December 2018*)

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 (612/2009 & 612/2018.1). 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 reports (612/2009 & 612/2018.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of technical indoxacarb complying with the requirements of FAO specification 612/TK (December 2018), together with carriers and any other necessary formulants. The product shall be in the form of roughly spherical granules with a nominal size range of 0.15 to 1.4 mm and an average of approximately 0.5 to 0.7 mm, for application after disintegration and dispersion in water. The product shall be dry, free flowing, essentially non-dusty and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (612/WG/M/2, CIPAC Handbook N, p. 77, 2011)

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 **Indoxacarb content** (612/WG/M/3, CIPAC Handbook N, p. 77, 2011).

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

Declared content g/kg	**Tolerance**
Above 250 up to 500	± 5% of the declared content

3 Physical properties

3.1 **Wettability** (MT 53.3.1, CIPAC Handbook F, p. 165, 1995)

The formulation shall be completely wetted in 60 seconds, without swirling.

3.2 **Wet sieve test** (MT 185, CIPAC Handbook K, p. 149, 2003)

Maximum: 2 % retained on a 75 µm test sieve.

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

3.3 **Spontaneity of dispersion** (MT 174, CIPAC Handbook F, p. 435, 1995)

A dispersibility of 80 % minimum shall be obtained after 1 minute of stirring.

3.4 **Suspensibility** (MT 184.1) (Notes 1, 2 & 3)

A minimum of 60% of the indoxacarb content found under 2.2 shall be in suspension after 30 minutes in CIPAC standard water D at 25 ± 5º C

3.5 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 4).

Maximum: 10 ml after 1 minute.

3.6 **Dustiness** (MT 171.1) (Notes 5 & 6).

Nearly dust free.

3.7 **Flowability** (MT 172.1, CIPAC Handbook O, p. 187, 2017)

A minimum of 99% of the product shall pass through a 5 mm test sieve after 20 drops of the sieve.

3.8 **Attrition resistance** (MT 178.2, CIPAC Handbook K, p .140, 2003)

Minimum: 98% attrition resistance.

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 7) and the formulation shall continue to comply with the clauses for:

- wet sieve test (3.2);
- spontaneity of dispersion (3.3);
- suspensibility (3.4);
- dustiness (3.6),
- attrition resistance (3.8)

Note 1 MT 184.1 is the revised version of MT 184 and was adopted at the 2018 CIPAC Meeting in Panama. Prior to its publiction in an next Handbook, copies of the method can be obtained through https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 2 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in the method.

Note 3 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric method, MT 168, may be used on a routine basis, provided that it has been shown to give equal results to those of chemical assay. In case of dispute, the chemical method shall be the “referee method”.

Note 4 The mass of the sample to be used in the test should be specified at the highest rate recommended by the supplier.

Note 5 Measurement of dustiness must be carried out on the sample “as received” and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical method of MT 171.1, usually shows good correlation with the gravimetric method and can, therefore, be used as an alternative where the equipment is available. Where correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute, the gravimetric method shall be used.

Note 6 MT 171.1 is a revised version of MT 171. This new method was accepted as a provisional CIPAC method in 2015. Prior to publication of the method in a Handbook, copies of the method may be obtained through the CIPAC website, https://www.cipac.org/index.php/methods-publications/errata

Note 7 Analysis of the formulation before and after storage stability test may be carried out concurrently (i.e. after storage) to minimize the analytical error.

INDOXACARB OIL DISPERSION

FAO Specification 612 / OD (December 2018) *

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose name are listed in the evaluation reports (612/2009 & 612/2018.1). 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 (612/2009 & 612/2018.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of a stable suspension of fine particles of technical indoxacarb complying with the requirements of FAO specification 612/TK (December 2018) in the form of a white to off-white viscous liquid with a faint sweet odour, in a non-aqueous fluid together with suitable formulants. After shaking or stirring of the sample, the material shall be homogeneous (Note 1).

2 Active Ingredient

2.1 **Identity tests** (612/OD/M/2, CIPAC Handbook N, p. 79) (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 **Indoxacarb content** (612/OD/M/3, CIPAC Handbook N, p. 80 (Note 2).

The indoxacarb content shall be declared (g/kg or g/l at 20 ± 2°C, Note 3) and, when determined, the content measured shall not differ from that declared by more than the following tolerance:

Declared content in g/kg or g/l at 20°C	**Tolerance**
above 100 up to 250	± 6% of declared content

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

3 Physical Properties

3.1 **Pourability** (MT 148.1, CIPAC Handbook J, p. 133, 2000)

Maximum “residue”: 12 % (Note 4)

3.2 **Spontaneity of dispersion** (MT 160, CIPAC Handbook F, p. 391, 1995) (Note 5)

A minimum of 80% of the active ingredient found under 2.2 shall be in the suspension after 5 minutes in CIPAC standard water D at 30 ± 2°C.

3.3 **Suspensibility** (MT 184.1) (Notes 5 & 6)

A minimum of 75% of the active ingredient found under 2.2 shall be in suspension after 30 minutes in CIPAC Standard water D at 25 ± 5°C.

3.4 **Wet sieve test** (MT 185, CIPAC Handbook K, p. 149, 2003) (Note 7)

Maximum: 1% of the formulation shall be retained on a 75 µm test sieve.

3.5 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 8).

Maximum: 20 ml after 1 minute.

4 Storage Stability

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

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with the clauses for:

- suspensibility (3.3)
- wet sieve test (3.4)

4.2 **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 10) and the formulation shall continue to comply with the clauses for:

- pourability (3.1);
- spontaneity of dispersion (3.2);
- suspensibility (3.3);
- wet sieve test (3.4).

Note 1 Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, oil dispersions (OD) usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom.
Therefore, before sampling, homogenise the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, by gently shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately. After this procedure, the container should not contain a sticky layer of non-

dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer (“cake”) is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenisation procedure.

Note 2 The method designation for the indoxacarb OD in Handbook N is erroneously "612/SC/M/-" instead of "612/OD/M/-" .The CIPAC decisions of the 2009 Meeting in El Salvador state: "The chiral normal phase HPLC method (CIPAC/4613) for the determination of indoxacarb in TC, TK, OD, WG and EC formulations was accepted as a full CIPAC method. (With note explaining why the SC formulation should be renamed as OD,...). This note is missing.

Note 3 Unless homogenisation is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre, and in the calculation of the active ingredient content (in g/l), if methods other than OECD 109 are used. If the buyer requires both g/kg and g/l at 20 ± 2 °C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 4 When performing the test in glass as required, the pourability could be higher.

Note 5 MT 184.1 is the revised version of MT 184 and was adopted at the 2018 CIPAC Meeting in Panama. Prior to its publiction in an next Handbook, copies of the method can be obtained through https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 6 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric method, MT 168, may be used on a routine basis, provided that it has been shown to give equal results to those of chemical assay. In case of dispute, the chemical method shall be the “referee method”.

Note 7: This test detects coarse particles (e.g. caused by crystal growth) or agglomerates (crust formation) or extraneous materials, which could cause blockage of spray nozzles or filters in the spray tank.

Note 8: The mass of the sample to be used in the test should be specified at the highest rate recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 9: Samples of the formulation taken before and after storage stability test may be analyzed concurrently after the test in order to minimize the analytical error.

PART TWO

EVALUATION REPORTS

INDOXACARB

INDOXACARB

FAO/WHO EVALUATION REPORT 612/2018.2

Recommendations

The Meeting recommended the following:

(i) The indoxacarb TK as proposed by Gharda Chemicals Ltd. should not be accepted as equivalent to the indoxacarb reference profile by FAO.

(ii) The FAO specifications for indoxacarb TK and OD should be not be extended to encompass the materials produced by Gharda Chemicals Ltd.

Appraisal

The Meeting considered data and supporting information submitted in December 2017 by Gharda Chemicals Ltd. (India) (Gharda) in support of extension of the existing FAO specifications for indoxacarb TK and OD and for new WHO specifications for TK and OD as well. The Meeting noted, that indoxacarb technical and/or formulated products had previously not been evaluated and for public health use by WHO and no WHO specification for indoxacarb and its formulations are published. Such an evaluation would require the intention and support of the current holder of the reference specifications (FMC Inc.). No such declaration of intention has been received from FMC. For these reasons, the request by Gharda for development of new WHO specifications for TK and OD were not further considered. .

The data submitted were broadly in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (2016, 3rd revision of the 1st edition). The reference specification and supporting data for indoxacarb were provided by DuPont and the FAO specification was published in 2009. In 2018, the transition of indoxacarb TC, TK and formulated products were noted by FAO and the specifications were editorially updated.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg, as well as any relevant impurities below 1 g/kg, and their manufacturing limits in the TK.

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted in the reference profile. Gharda utilizes a different manufacturing process as compared to that of the reference product. Indoxacarb TK produced by Gharda contains impurities not present in the reference material.

The Meeting considered the toxicological impact of these additional impurities in the Gharda source, and decided that when taken as a whole, and at the concentrations as specified in the Gharda source, a request for a 28 day toxicity study was necessary.

A mutagenicity study (OECD 471) for indoxacarb was provided as part of the Tier-1 data package. Gharda's indoxacarb TK did not induce reverse mutations in an *in vitro* bacterial assay. Gharda also presented acute toxicity, irritation and sensitization studies which strictly speaking did not give rise to any particular concern.

A 28 day study according to OECD guideline 407 was provided by Gharda on request of the Meeting. The Meeting disagreed with the conclusions of the 28 day study as presented by the study authors (Sawant, 2018). The assessment done by JMPS resulted in a lower NOAEL than that deduced by the study authors, albeit this lower NOAEL is still within the range (a factor of $10^{-0.5}$ for repeated dose studies) deemed acceptable by the revised Tier-2 equivalence process.

However, a closer examination of the raw data revealed adverse effects on the prostate and seminal vesicles with coagulating gland of the test animals (male accessory sex glands - weight decrease, atrophy). It was noted that in the original reference study the prostate was not weighed. Also, different strains of rats were used in each study so these differences could be attributed to strain specific effects. However, in the whole database for the reference source no effects on prostate were recorded. Therefore, the male accessory sex glands were considered as a new toxicity endpoint of Gharda's TK.

It was acknowledged that the reference study was not conducted according to OECD test guideline 407 and only a report could be consulted, while the study with the new source was compliant with OECD test guideline 407 and the original study could be scrutinized. This leads to some uncertainties in the comparative assessment of the studies and it cannot be entirely ruled out that the procedure followed is biased in the direction of finding new toxicity in the new study that was not reported in the old study.

However, the Meeting had assessed both Tier-1 and Tier-2 data, and concluded that the weight of evidence raised reasonable doubts that the equivalence for Gharda's indoxacarb TK could be established. Taking all information into account, the Meeting concluded that equivalence of Gharda's TK with the reference source was not demonstrated.

The Meeting also noted that Gharda provided an OD 5-batch analysis report as part of their OD formulation dossier and the results from the 5-batch study indicated that the Gharda OD complies with the reference OD FAO specification from 2009. All methods used by Gharda in their OD 5-batch analysis are the latest CIPAC methods. However, since the TK reference specification will not be extended to include the Gharda source, an extension of the existing OD reference specification is not possible.

The Meeting recommended that an evaluation report should be published.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 612/2018.2

Table 1. Chemical composition and properties of indoxacarb technical concentrate (indoxacarb *3S+1R*[1]) (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 in the range of 99.35% to 100.46% with no unknowns.	
Declared minimum indoxacarb content: Indoxacarb (S)-methyl-7-chloro-2,5-dihydro-2-[(methoxy carbonyl)[4-(trifluoromethoxy)phenyl] amino] carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(*3H*)carboxylate			467.0 g/kg min.	
Indoxacarb (chemical purity, sum of *R*- and *S*-enantiomer) (*R,S*)-methyl-7-chloro-2,5-dihydro-2-[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(*3H*)carboxylate			670.0 g/kg min.	
S : R Indoxacarb ratio			75:25 ± 5	
Relevant impurities ≥ 1 g/kg and maximum limits for them			None	
Relevant impurities <1 g/kg and maximum limits for them			None	
Stabilizers or other additives and maximum limits for them			None	
Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TK	141.33 - 141.28 ^{0}C	68.0%	OPPTS 830:7200, OECD 102, EEC.A1	2
Solubility in organic solvents	Acetone: 316.45 g/L at 20.5^{o}C Dichloromethane: 409.60 g/L at 20.5^{o}C	67.0%	CIPAC 181	8

[1] According to the ISO common name definition, indoxacarb refers to the compound with *S*-configuration only. For practical reasons however, the terms "*S*-" and "*R*-indoxacarb" respectively are used in this evaluation report, although not quite correct, to describe the enantioenriched technical concentrate and the ratio of indoxacarb to its insecticidally inactive *R*-enantiomer.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from Indoxacarb technical concentrate (TK) having impurity profiles similar to those referred to in the table above.

(ii) The conclusions expressed in the summary below are those of Gharda Chemicals Limited with exception of the 28-day study in Table 4 below which are those of JMPS.

Table 2. **Toxicology profile of the indoxacarb technical concentrate (TK) (indoxacarb 3S+1R), based on acute toxicity, irritation and sensitization.**

Species	Test	Duration and conditions or guideline adopted*	Result	Study number
Rat, Wistar (9 females)	Acute oral	14 days OECD 423, Batch no.: IDC670T0191B (67% purity)	LD_{50} (cut off value) :500 mg /kg bw LD_{50} :>300 mg /kg bw & <2000 mg /kg bw	9 T.IXO.038
Rat, Wistar (5 males + 5 females)	Acute dermal	14 days OECD 402, Batch no.: IDC670T0191B (67% purity)	LD_{50} :>2000 mg/kg bw	10 T.IXO.039
Rat, Wistar (3 males + 3 females)	Acute Inhalation	14 days OECD 403, Batch no.: IDC670T0191B (67% purity)	LC_{50} (4 hrs) = >1.09 mg/L air (maximum attainable concentration)	11 T.IXO.042
Rabbit, New Zealand white (3 females)	Skin irritation	72 hours OECD 404, Batch no. IDC670T0191B (67% purity)	Non-irritant to rabbit skin	12 T.IXO.040
Rabbit, New Zealand white (3 males)	Eye irritation	72 hours OECD 405, Batch no.: IDC670T0191B (67% purity)	Non-irritant to rabbit eyes	13 T.IXO.041
Guinea pig, Albino Dunkin Hartley 3 males (pretest) & 15 males (main study)	Skin sensitisation	3 week in duration; 48 hour challenge OECD 406, Batch no.: IDC670T0191B (67% purity)	Weak sensitizer via method of Magnusson & Kligman	14 T.IXO.045

*) For indoxacarb 3S+R and racemic indoxacarb, the purity is the sum of the *R*- and *S*-isomer expressed as a percentage of the test material.

Table 3. **Mutagenicity profile of the Indoxacarb technical concentrate (TK) (Indoxacarb 3S+1R) material based on *in vitro* and *in vivo* tests**

Species	Test	Conditions*	Result	Study number
Salomonella typhimurium (TA1535, TA1537, TA98 TA100 and TA 102)	Bacterial Reverse Mutation Test	OECD 471 Concentrations: 0.313, 0.625, 1.25, 2.5 and 5 μg/plate (with & without metabolic activation S9) Batch no.: IDC670T0191B (67% purity)	Non-mutagenic	15 T.IXO.043
Mice, Swiss albino (30 males + 30 females)	*In vivo* micronucleus test in bone marrow cells	OECD 474 Dosages : 500, 1000, 2000 mg/kg bw Batch no.: IDC670T0191B (67% purity)	Negative	16 T.IXO.044

Table 4. **Toxicology profile of indoxacarb technical concentrate based on repeated administration**

Species	Test	Duration and conditions or guideline adopted*	Result	Study number
Rat. Sprague Dawley 10 animals per dose group	28 Day Oral	OECD 407 (2008) Batch no.: IDC67B0640 (68% purity) Dose levels: m: 0, 2.8, 8.9, 17.8 mg/kg bw/d f: 0, 0.83, 2.61, 5.3 mg/kg bw/d	NOAEL: m: 2.8 mg/kg bw/d based on weight decrease and atrophy of prostate +seminal vesicles and coagulating gland f: 2.61 mg/kg bw/d based on decreased body weight gain	Study No. 7414

***)** For indoxacarb 3S+R indoxacarb, the purity is the sum of the R- and S-isomer expressed as a percentage of the test material.

ANNEX 2

REFERENCES

Reference	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO/WHO	2016	Manual on development and use of FAO and WHO specifications for pesticides. March 2016-third revision of the First Edition. FAO Plant Production and Protection Paper. Revised. www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm
1.	K. Dattatreya Chary	2014	Determination of Vapour Pressure of Indoxacarb Technical Concentrate. Study No: 4060. Gharda Report No.: C.IXO.021. GLP. RCC Laboratories India Private Limited. Unpublished.
2.	Thiripura Sundari	2013	Indoxacarb Technical Concentrate: Melting point. Study No: 13135. Gharda Report No.: C.IXO.023. GLP. International Institute of Biotechnology & Toxicology. Unpublished.
3.	K. Dattatreya Chary	2013	Determination of Water Solubility of Indoxacarb Technical Concentrate. Study No: 4047. Gharda Report No.: C.IXO.012. GLP. RCC Laboratories India Private Limited. Unpublished.
4.	K. Dattatreya Chary	2013	Determination of Partition Coefficient of Indoxacarb Technical Concentrate. Study No: 4052. Gharda Report No.: C.IXO.016. GLP. RCC Laboratories India Private Limited. Unpublished.
5.	K. Dattatreya Chary	2014	Determination of Hydrolysis of Indoxacarb Technical Concentrate as a function of pH. Study No: 4049. Gharda Report No.: C.IXO.020. GLP. RCC Laboratories India Private Limited. Unpublished.
6.	Venkata Satish Pakki	2013	Indoxacarb Technical Concentrate: Laboratory study photolysis. Study No: 13133. Gharda Report No.: C.IXO.025. GLP. International Institute of Biotechnology & Toxicology. Unpublished.
7.	K. Dattatreya Chary	2013	Determination of Dissociation Constant Indoxacarb Technical Concentrate. Study No: 4054. Gharda Report No.: C.IXO.022. GLP. RCC Laboratories India Private Limited. Unpublished.
8.	K. Dattatreya Chary	2013	Determination of Solubility of Indoxacarb Technical Concentrate in organic solvents. Study No: 4048. Gharda Report No.: C.IXO.013. GLP. RCC Laboratories India Private Limited. Unpublished.
9.	R. D. Siva Kumar	2013	Acute oral toxicity study in rats with Indoxacarb Technical Concentrate. Study No: 4040. Gharda Report No.: T.IXO.038. GLP. RCC Laboratories India Private Limited. Unpublished.
10.		2013	Acute dermal toxicity study in rats with Indoxacarb Technical Concentrate. Study No: 4041. Gharda Report No.: T.IXO.039. GLP. Unpublished.
11.		2013	Acute inhalation toxicity study in rats with Indoxacarb Technical Concentrate. Study No: 4045. Gharda Report No.: T.IXO.042. GLP. Unpublished.

12.		2013	Acute dermal irritation/Corrosion study in rabbits with Indoxacarb Technical Concentrate. Study No: 4042. Gharda Report No.: T.IXO.040. GLP. Unpublished.
13.		2013	Acute eye irritation/Corrosion study in rabbits with Indoxacarb Technical Concentrate. Study No: 4043. Gharda Report No.: T.IXO.041. GLP. Unpublished.
14.		2013	Contact hypersensitivity in albino Guinea pigs, Maximization test (Magnusson and Kligman Method) with Indoxacarb Technical Concentrate. Study No: 4044. Gharda Report No.: T.IXO.045. GLP. Unpublished.
15.		2013	Bacterial Reverse Mutation assay with Indoxacarb Technical Concentrate. Study No: 4093. Gharda Report No.: T.IXO.043. GLP. Unpublished.
16.		2013	Micronucleus test in bone marrow cells of mouse with Indoxacarb Technical Concentrate. Study No: 4094. Gharda Report No.: T.IXO.044. GLP. Unpublished.
17		2018	Repeated dose 28 Days Oral (Dietary) Toxicity Study with Indoxacarb Technical Concentrate in Rats. Study No. 7414

INDOXACARB

FAO/WHO EVALUATION REPORT 612/2018.1

Recommendations

The Meeting recommended the following:

i) the change of manufacturer of the reference specifications for indoxacarb TC, TK, WG, EC and OD from E.I. DuPont to FMC Inc. should be noted by FAO.
ii) the editorially updated and confirmed FAO specifications for indoxacarb TC, TK, WG, EC and OD submitted by FMC Inc. should be adopted by FAO.

Appraisal

The Meeting noted that in a press release dated of March 31, 2017, FMC Inc. (FMC)[1], (USA) announced the acquisition of indoxacarb active ingredient and formulated products from E.I. Dupont. DuPont was up to then the holder of the reference FAO specifications for indoxacarb TC, TK, EC, WG and OD (FAO/WHO evaluation report 612/2009).

As such a transition may raise some concerns on the continued validity of the FAO specifications for indoxacarb technical materials and formulations (see also FAO/WHO Manual, Section 2.7 on revision of specifications), FMC was contacted by FAO and a statement on the support of the reference specifications and possible changes therein was requested.

FMC later on provided a confirmation in writing (FMC, 2018)[2] to FAO confirming the continued support for the FAO reference specifications for indoxacarb technical materials (TC, TK) and its formulated products. FMC explained that both manufacturing site and - process for indoxacarb were not affected by the transition from DuPont to their company and confirmed the continued validity of the published specifications and stewardship for them.

The Meeting also noted that the specifications needed some editorial update with regard to analytical and physical-chemical test methods. The stereospecific analytical method for determination of indoxacarb content in technical materials and formulated products is in the meantime published in Handbook O, and for several MT methods newer versions are available.

For this reasons, the Meeting recommended that FMC should be noted as new holder of the reference specifications for indoxacarb and its formulations, and that these specifications produced by FMC should be considered as the new reference specifications.

[1] https://www.prnewswire.com/news-releases/fmc-corporation-announces-acquisition-of-significant-portion-of-duponts-crop-protection-business-simultaneous-sale-of-health-and-nutrition-to-dupont-300432498.html
[2] e-mail of Mrs. R. McKenna, FMC to FAO AGP, Mrs. Yang dated 19 December 2018

INDOXACARB

FAO/WHO EVALUATION REPORT 612/2009

Recommendations

The Meeting recommended that:

(i) the specifications for indoxacarb TC, TK, WG, EC and OD proposed by Du Pont, as amended, should be adopted by FAO.

Appraisal

Data provided by Du Pont for indoxacarb in 2007 were evaluated in support of proposed new FAO specifications for TC, TK, WG, EC and OD.
Indoxacarb has been evaluated by the 2005 JMPR. Indoxacarb was registered by the US EPA on October 30, 2000 (both TC and TK) and listed in Annex 1 of Directive 91/414 in the EU in 2006 (TK).

Indoxacarb is a Lepidoptera insecticide, which also has activity on selected sucking insect pests. The mode of action of indoxacarb is on the sodium channels blocking the flow of sodium ions into certain nerve cell ion channels, resulting in paralysis and death of the pest species.

The structure of indoxacarb shows an optically active carbon atom at the bridgehead of the oxadiazine ring. The ISO common name indoxacarb refers to the S-enantiomer solely being the carrier of insecticidal activity. The R-enantiomer does not carry insecticidal activity.

The enantiomeric composition of indoxacarb has evolved over time. Whereas in the beginning of market introduction a technical material having same amount of the R and S-enantiomer, respectively, was synthesized and could, loosely termed be called “racemic indoxacarb”, later developments led to technical materials enriched in S enantiomer having ratios of *3S+1R* and higher. Currently, a TC with a minimum purity of 900 g/kg and a TK with a minimum of 467 g/kg is produced. The 5 batch data supports the specification for the technical material (TC) of minimum 900 g/kg and for the technical concentrate (TK) a minimum of 467 g/kg. The Meeting agreed that no relevant impurities were identified in the TC and TK, respectively.

Mass balances for the TC were in the range of 982.9 to 987.8 g per kg, for the TK in the range of 982.5 to 995.8 g per kg, respectively. In the case of the TK, values were corrected for the contents of residual humidity and the diluent.

The confidential data are identical to those submitted for registration in the United States.

Indoxacarb is under patent until December 2011. The manufacturing process is under patent until April 2015. The new manufacturing process is under patent until June 2022.

The Meeting agreed that, beside the higher content of indoxacarb, based on the confidential data on composition of TC and TK and hazard data these two materials are considered as equivalent.

Indoxacarb is a white powdered solid that melts at 88.1 °C. It will not ionise at environmental pH conditions. This and the low solubility of the active substance (0.2 mg/l) and octanol/water partition coefficient (log 4.65) indicate certain lipophilicity with a potential to bioaccumulation. The low vapour pressure (9.8×10^{-9} Pa) and Henry's law constant indicate that volatilisation is not a major route of degradation. Indoxacarb is expected to be hydrolytically stable in the absence of sunlight. However, a route of degradation in water is accelerated with sunlight. In soil, both indoxacarb and its antipode are expected to be moderately persistent under both anaerobic and aerobic conditions.

The analytical methods for determination of indoxacarb in TC, TK, EC, GR and OD were presented at the 52nd CIPAC Meeting in Braunschweig, Germany in 2008 and were adopted as provisional CIPAC Method. The determination of indoxacarb is by HPLC on an enantioselective Chiralcel column that allows the separation of indoxacarb from its optical antipode and was collaboratively validated for all technical materials and formulations under discussion.

The proposed specifications for TC, TK, EC, WG and OD do comply with the requirements of the FAO and WHO Specification Manual.

<u>Issues relating to TC and TK only</u>

The two indoxacarb materials produced are intended to be formulated in specific preparations. The TC is used in the EC formulation type, whereas the TK is used in the OD and WG. The process for synthesis of the TC leads to a technical material with a low water content. Limiting the water content in the TC, which may with other active ingredients be necessary either to safeguard the stability of the active ingredient or to prevent inhomogeneity in the EC was therefore not necessary. In the same sense, clauses on pH range or acidity/alkalinity were not necessary. The diluent in the TK is added in the final step of the manufacturing process to reduce electrostatic charges and hence to facilitate the handling of the TK in the formulation process.

Issues relating to OD only

This formulation was registered as a Suspension Concentrate (SC) prior to the introduction of the Oil Dispersion (OD) code into Croplife International/FAO nomenclature. The Meeting questioned the pourability of 12 % “residue” and the rather high limit was confirmed by the proposer.

Issues relating to WG and OD

The manufacturing process of the TK leads to a somewhat higher content of water in the technical material than in the TC. Again, the use of the technical material in the WG and OD formulations allows for a somewhat higher water level in the TK and does not justify a limit.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 612/2009

SECTION 2. NON-CONFIDENTIAL DATA ON INDOXACARB (CIPAC number 612)

Uses

Indoxacarb is a Lepidoptera insecticide with activity also on selected sucking insect pests. Indoxacarb can be applied as a foliar spray in field, fruit and vegetable crops. It is used primarily as a larvicide. Indoxacarb is also effective against adults and eggs of many pest species.

Identity of the active ingredient

ISO common name

Indoxacarb (ISO 1750 published)

Chemical name(s)

IUPAC

(S)-7-chloro-2-[methoxycarbonyl-(4-trifluoromethoxyphenyl)-carbamoyl]-2,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylic acid, methyl ester

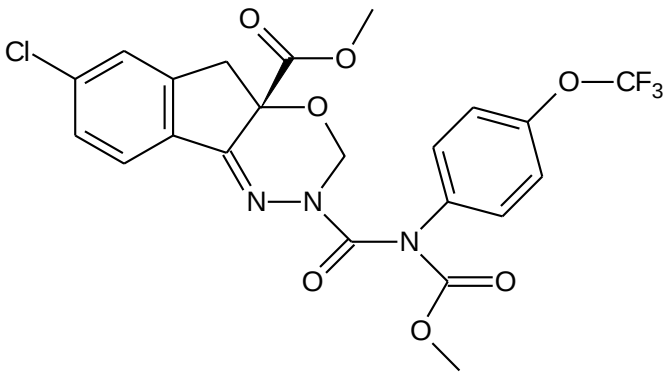
CA

(S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy) phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate

Synonyms

none

Structural formula



Molecular formula

$C_{22}H_{17}ClF_3N_3O_7$

Relative molecular mass

527.8

CAS Registry number

173584-44-6 (indoxacarb, code name DPX-KN128)

144171-61-9

CIPAC number

612

Identity tests

HPLC retention time, UV and IR Spectra

Physico-chemical properties of indoxacarb

Table 1a: Physico-chemical properties of indoxacarb

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Reference
Vapour pressure	$9.8x10^{-9}$ Pa at 20 °C $2.5x10^{-8}$ Pa at 25 °C	99.7%	Directive 97/37/EC, Annex 1, Points 2.3.1 and 2.3.2 (Effusion method: vapour pressure balance); U.S. EPA OPPTS 830.7950 (Effusion method: loss of weight)	1, AMR 4169-96
Melting point, boiling point and/or temperature of decomposition	Melting point: 88.1°C±0.4 Boiling point: Not applicable. Test material is a solid. Decomposition temperature: Not Determined	99.7%	Directive 97/37/EC, Annex 1, Points 2.2.1; EEC A.1; U.S. EPA OPPTS 830.7200(Capillary method)	2, AMR 4141-96
Relative Density	1.44 at 20°C	99.7%	Directive 94/37/EC, Annex 1, Point 2.2 EEC A.3; U.S. EPA OPPTS 830.7300 (Pycnometer method)	3, AMR 4141-96
Solubility in water	0.20 mg/l at 25°C in distilled water	99.7%	Directive 94/37/EC, Annex 1 Point 2.6; EEC A.6; U.S. EPA OPPTS 830.7860 (Column elution method)	4, AMR 4141-96
n-Octanol solubility	9.49 mg/mL at 25°C	99.7%	Directive 94/37/EC, Annex 1, Point 2.7; OECD 105; USEPA OPPTS 830-7840 (Shake flask method)	5, AMR 4141-96
Octanol/water partition coefficient	Log of K_{OW} = 4.65 at 25°C	99.7%	Directive 94/37/EC, Annex 1, Point 2.8; EEC A.8; U.S. EPA OPPTS 830-7550 (Flask method)	6, AMR 4141-96
Dissociation characteristics	Not ionized	99.7%	Directive 94/37/EC Annex 1, Points 2.9.4; OECD 112; U.S. EPA OPPTS 830.7370	9. AMR 4141-96

Table 1b: Physico-chemical properties of *indoxacarb 3S+1R* (DPX-MP062)

Parameter	Value(s) and conditions	Purity %*	Method reference (and technique if the reference gives more than one)	Reference
Melting point, boiling point and/or temperature of decomposition	Melting point: 87.1-141.5°C (note: two separated peaks at 88 and 141°C) Boiling point: Not applicable. Test material is a solid. Decomposition temperature: 208 ± 7.0°C	99.4% 99.4%	OECD Guideline 102 (DSC and capillary method); U.S. EPA 830.7200; EEC A.1	2, DuPont-7557 RV1
Solubility in water	22.5 ±3.6 µg/L at 20°C in unbuffered water	99.4%	U.S. EPA OPPTS 830.7840; OECD, Method 105 (Water Solubility: Column Elution Method)	5, DuPont-7497
Hydrolysis characteristics	at 25 ± 1°C and pH 5 no significant degradation (less than 5%) was observed after 30 days. Half-life = 22 days at 25 ± 1 °C at pH 7 Half-life = 0.3 hours at 25 ± 1°C at pH 9	[indanone-1-14C]]DPX-MP062 – 98.4% [trifluoromethoxyphenyl(U)-14C]DPX-MP062 - 99.1%	U.S. EPA Subdivision N Chemistry, Section 161-1; OECD, Section 1, Method 111; SETAC	7, DuPont-9800
Photolysis characteristics	<u>Simulated sunlight:</u> Half-life = 4.5 days in pH 5 at 25°C	[indanone-1-14C]]DPX-MP062 - 98.4% [trifluoromethoxyphenyl(U)-14C]DPX-MP062 - 99.1%	U.S. EPA Subdivision N, Series 161-2; SETAC	8, DuPont-9801

***) For indoxacarb 3S+R and racemic indoxacarb, the purity is the sum of the R- and S-isomer expressed as a percentage of the test material.**

Table 2a: Chemical composition and properties of indoxacarb technical concentrate (TK) (*indoxacarb 3S+1R*)

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 in the range of 982.5 to 995.8 g per kg, *.
Declared minimum [a.i.] content	467 g/kg (indoxacarb)
Relevant impurities ≥ 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
Melting temperature range of the TK	87.1-141 °C
pH	4.2 (1% solution in deionized water) DPX-MP062-91 (53.55% purity**) U.S. EPA OPPTS 830.7000 (See Reference 10, AMR 4822-97)
Density	0.7 g/mL DPX-MP062-91 (53.55% purity**) U.S. EPA OPPTS 830.7300 (See Reference 3, AMR 4822-97)

***** Values were corrected for the contents of residual humidity and the diluent.

Table 2b: Chemical composition and properties of indoxacarb technical material (TC)

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 982.9 to 987.8 g per kg.
Declared minimum [a.i.] content	900 g/kg
Relevant impurities ≥ 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
Melting or boiling temperature range of the TC	Melting point 88.1°C±0.4
Relative density	1.418 (19.6**°**C) indoxacarb (95.0% purity) OECD 109; OJEC A.3; U.S. EPA OPPTS 830.7300 (See Reference 3, DuPont-14115)

HAZARD SUMMARY

Indoxacarb has been evaluated by the FAO/WHO JMPR in 2005. The JMPR established the ADI as 0-0.01 mg/kg bw, and the ARfD was established as 0.1 mg/kg bw. It should be recognized that the ADI and ARfD applies to indoxacarb (S-enantiomer) and its R-enantiomer. The EU classification categories for Indoxacarb are:

With regard to toxicological data:

Xn = Harmful

R22 = Harmful if swallowed

R43 = May cause sensitization by skin contact

With regard to fate and behaviour:

No classification required.

With regard to ecological data:

N = Dangerous to the environment

R50/53= Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

According to the WHO IPCS hazard classification system, both *indoxacarb 3S+1R* Technical Material and indoxacarb Technical Material fall into Class II (moderately hazardous) for solids.

Formulations

The main formulation types available are a water dispersible granule (WG), an oil based dispersion (OD) initially registered as a suspension concentrate (SC) and an emulsifiable concentrate (EC). These formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

A normal-phase enantioselective HPLC method with UV detection which is capable to separate indoxacarb from its optical antipode and to determine the amount of the R-enantiomer beside the active ingredient in TC, TK, WG, OD and EC was successfully validated under the auspices of CIPAC, presented at the 2008 CIPAC Meeting in Braunschweig and adopted as provisional CIPAC Method.

The method for determination of impurities in both *indoxacarb 3S+1R* Technical Material and indoxacarb Technical Material is based on reversed-phase liquid chromatography (RPLC), using UV detection at 230, 210, 254 and 290 nm and external standardisation.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EEC, EPA, CIPAC, SETAC and ASTM while those for the formulations were CIPAC, as indicated in the specifications.

Physical properties

With the exception of the pourability of the suspension concentrate, which does not present a problem in the commercial container, the physical properties, the methods for testing them and the limits proposed for the WG, OD and EC formulations, comply with the requirements of the FAO/WHO Manual (1st edition).

Containers and packaging

No extraordinary container or package issues need be considered.

Expression of the active ingredient

The active ingredient is expressed as indoxacarb.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from indoxacarb having impurity profiles similar to those referred to in the tables above.

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

Table 1A: Toxicology profile of the indoxacarb technical concentrate (TK, *indoxacarb 3S+1R* or *DPX-MP062*), based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions or guideline adopted*	Result	Reference
Male and Female Rats	Acute oral	14 days (up to 24 days) DPX-MP062 (94.5% purity) EEC 92/69, Method B.1; U.S. EPA Subdivision F, 81-1; OECD, Part 401; MAFF Japan, 59 NohSan No. 4200	LD_{50} = 1730 mg/kg bw; male 268 mg/kg bw; female	11, HLR 910-96
Male and Female Rats	Acute oral	14 days DPX-MP062-89 (MUP) (67.8% purity) EEC 92/69, Method B.1; U.S. EPA Subdivision F, 81-1; OECD, Part 401; MAFF Japan, 59 NohSan No. 4200	LD_{50} = 1070 mg/kg bw; male 407 mg/kg bw; female	11, HLO 1997-00477
Male and Female Rats	Acute dermal	14 days DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.3; U.S. EPA Subdivision F, 81-2; OECD, Part 402; MAFF Japan, 59 NohSan No. 4200	LD_{50} = >5000mg/kg bw; male and female	12, HLR 798-96 RV1
Male and Female Rats	Acute inhalation	14 days DPX-MP062-89A MUP(70.7% purity) Directive 92/69/EEC Method B.2; USEPA Subdivision F, 81-3; 59 NohSan No. 4200; OECD 403	LC_{50} = >5500 mg/m^3 (5.5 mg/L), male and female	13, HL 1997-00445
Male Rabbit (New Zealand white)	Acute skin irritation	72 hours DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.4; U.S. EPA Subdivision F, 81-5; 59 NohSan No. 4200; OECD 404	Non-irritant	14, HLO 598-96 RV1
Female Rabbit (New Zealand white)	Acute eye irritation	72 hours DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.5; U.S. EPA Subdivision F, 81-4; OECD 405; 59 NohSan No. 4200	Non-irritant	15, HLR 588-96 RV1
Male and Female Rabbit (New Zealand white)	Acute eye irritation	14 days DPX-MP062-89B MUP (67.8% purity) Directive 92/69/EEC Method B.5; U.S. EPA Subdivision F, 81-4; OECD 405; 59 NohSan No. 4200	Non-irritant	15, HLO 1997-00478
Male Guinea Pigs	Acute skin sensitisation	3 week in duration; 48 hour challenge DPX-MP062 (94.5% purity)	Dermal sensitizer via method of Magnusson & Kligman	16, HLO 388-96 RV3

Species	Test	Duration and conditions or guideline adopted*	Result	Reference
(Dunkin Hartley)		Directive 92/69/EEC Method B.6; U.S. EPA Subdivision F, 81-6; OECD 406; 59 NohSan No. 4200		

***) For indoxacarb 3S+R and racemic indoxacarb, the purity is the sum of the R- and S-isomer expressed as a percentage of the test material.**

Table 1B:Toxicology profile of the indoxacarb technical material (TC or *DPX-KN128*), based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Male and Female Rats	Acute oral	14 days DPX-KN128 (99.7% purity)* EEC 92/69, Method B.1; U.S. EPA Subdivision F, 81-1; OECD, Part 401; MAFF Japan, 59 NohSan No. 4200	LD_{50} = 843 mg/kg bw; male 179 mg/kg bw; female	11, HLR 1997-00055
Female Rodents (Mice)	Acute oral	14 days DPX-KN128 (95.5% purity) U.S. EPA OPPTS 870.1100; OECD, Part 425	LD_{50} = >2000 mg/kg bw	17, DuPont-14496
Male and Female Rats	Acute dermal	14 days DPX-KN128 (95.5% purity) Directive 92/69/EEC Method B3; U.S. EPA OPPTS 870.1200; OECD, Part 402; MAFF Japan, 59 NohSan No. 4200	LD_{50} = >5000mg/kg bw; male and female	18, DuPont-13019
Male Rabbit (New Zealand white)	Acute skin irritation	72 hours DPX-KN128 (95.5% purity) Directive 92/69/EEC Method B.4; U.S. EPA OPPTS 870.2500; 59 NohSan No. 4200; OECD 404	Non-irritant	19, DuPont-13164
Female Rabbit (New Zealand white)	Acute eye irritation	72 hours DPX-KN128 (95.5% purity) Directive 92/69/EEC Method B.5; U.S. EPA OPPTS 870.2400; OECD 405; 59 NohSan No. 4200	Non-irritant	20, DuPont-13020
Male Guinea Pigs (Dunkin Hartley)	Acute skin sensitization	3 week in duration; 48 hour challenge DPX-KN128 (95.5% purity) U.S. EPA OPPTS 870.2600; 59 NohSan No. 4200	Dermal sensitizer via method of Magnusson & Kligman	21, Dupont-13018

***) For *indoxacarb* (DPX-KN128), the purity is the S-isomer expressed as a percentage of the test material.**

Table 2: Toxicology profile of *indoxacarb 3S+1R* (*DPX-MP062*)Technical concentrate and indoxacarb (*DPX-KN128)* Technical Material (unless otherwise noted) based on repeated administration (subacute to chronic)

Species	Test	Duration and conditions or guideline adopted*	Result	Reference
Male and Female Rats (Cr1:CD)	Feeding	90 days DPX-MP062 (94.5% purity) Dose levels: 0, 10, 25, 50, 100 or 200 ppm Directive 87/302/EEC; U.S. EPA Subdivision F, 82-1; 59 Nohsan No. 4200; OECD 408	NOAEL: Male: 100 ppm (6.01 mg/kg bw/day) Female: 25 ppm (2.13 mg/kg bw/day)	22, HL 1997-00056 RV1, VO1&2, SU1
Male and Female Rats	Dermal	28-day DPX-MP062 (95.8% purity) Dose levels: 50, 500, 1000 or 2000 mg/kg bw/day Directive 92/69/EEC; U.S. EPA OPPTS 870.3200; OECD 410; 59 Nohsan No. 4200	NOAEL: Male: 1000 mg/kg bw/day Female: 50 mg/kg bw/day	23, DuPont-2813 VO1&2
Male and Female Rats	Inhalation	28-day DPX-MP062-89A MUP (70.0% purity) Dose levels: 0, 4.6, 23 or 290 mg/m^3 U.S. EPA OPPTS 870.3465; OECD 412	NOAEL: 4.6 mg/m^3 based on slight on irritant effects of silicon dioxide carrier NOAEL: 23 mg/m^3 for effects referable to DPX-MP062	24, DuPont-10222
Male and Female Rats (Cr1:CD)	Feeding	28 days DPX-JW062 (94.7% purity) Dose levels: 0, 12, 29, 59, 118 or 235 ppm Essentially meets the requirements of OECD 407	NOAEL: Male: 118 ppm (8.85 mg/kg bw/day) Female: 29 ppm (2.61 mg/kg bw/day)	HLR 403-93
Male and Female Mice (Cr1:CD)	Feeding	28 days DPX-JW062 (94.7% purity) Dose levels: 0, 12, 29, 59, 118, 235, 400, 1225 or 2450 ppm Essentially meets the requirements of OECD 407	NOAEL: Male: 59 ppm (10.8 mg/kg bw/day) Female: 118 ppm (21.5 mg/kg bw/day)	HLR 406-93 RV1
Male and Female Rats (Cr1:CD)	Feeding	90 days DPX-JW062-34 (50% DPX-KN128, 50% DPX-KN127) (94.7% purity) Dose levels: 0, 15, 30, 60, 125 or 250 ppm	NOAEL = 60 ppm (3.9 and 4.6 mg/kg bw/day for males and females, respectively)	22, HLR 751-93 RV2, VO1, SU1

Species	Test	Duration and conditions or guideline adopted*	Result	Reference
		Directive 87/302/EEC; USEPA Subdivision F, 82-1; OECD 408; 59 Nohsan No. 4200		
Male and Female Mice (Cr1:CD)	Feeding	90 days DPX-JW062-34 (50% DPX-KN128, 50% DPX-KN127) (94.7% purity) Dose levels: 0, 10, 35, 75, 150 or 300 ppm Directive 87/302/EEC; U.S. EPA Subdivision F, 82-1; OECD 408; 59 Nohsan No. 4200	NOAEL: Male: 150 ppm (23 mg/kg bw/day) Female: 75 ppm (16 mg/kg bw/day)	22, HLR 750-93 SU1, RV1, VO1&2
Male and Female Dogs (Beagle)	Feeding	90 days DPX-JW062-106 (50% DPX-KN128, 50% DPX-KN127) (95.03% purity) Dose levels: 40, 80, 160 or 640 ppm Directive 87/302/EEC; USEPA Subdivision F, 82-1; OECD 409; 59 Nohsan No. 4200	NOAEL: Male: 80 ppm (2 mg/kg bw/day) Female: 160 ppm (5 mg/kg bw/day)	17, HLO 494-95 RV3, VO1-3
Male and Female Mice	Feeding	18 month DPX-JW062-106 (50% DPX-KN128, 50% DPX-KN127) (95.0% purity) Dose levels: 0, 20, 100, 125, 150 or 200 ppm Directive 87/302/EEC; U.S. EPA Subdivision F, 83-2; OECD 451; 59 Nohsan No. 4200 (See Reference 25)	NOAEL: 20 ppm (2.63 and 3.99 mg/kg bw/day for males and females, respectively) There were no treatment-related neoplastic changes in any dose group	25, HLR 799-96 SU1, VO1-4
Male and female Rats	Feeding	2 years DPX-JW062-106 (50% DPX-KN128, 50% DPX-KN127) (95.0% purity) Dose levels: 0, 10, 20, 40, 60, 125 or 250 ppm Directive 87/302/EEC; USEPA Subdivision F, 83-5; OECD 453; 59 Nohsan No. 4200	NOAEL: Male: 60 ppm (2.40 mg/kg bw/day) Female: 40 ppm (2.13 mg/kg bw/day) There were no treatment-related neoplastic changes in any dose group	26, HLR 1174-96 RV1, SU1, VO1-9
Male and Female Dogs (Beagle)	Feeding	1 year DPX-JW062-106 (50% DPX-KN128, 50% DPX-KN127) (95.03% purity) Dose levels: 40, 80, 640 or 1280 ppm Directive 87/302/EEC; U.S. EPA Subdivision F, 83-1; OECD 452; 59 Nohsan No. 4200	NOAEL: 40 ppm (1.1 and 1.3 mg/kg bw/day for males and females, respectively)	27, HLO 885-96 RV1, SU1, VO1-4

Species	Test	Duration and conditions or guideline adopted*	Result	Reference
Rat	Acute neurotoxicity, gavage	15 days DPX-MP062 (94.5% purity) Dose levels: 0, 12.5, 25, 50, 100 or 200 mg/kg bw/day U.S. EPA Subdivision F, 81-8	NOAEL: Neuro- Male: 100 mg/kg bw/day Female: 50 mg/kg bw/day Systemic- Male: 100 mg/kg bw/day Female: 12.5 mg/kg bw/day	28, HLR 1117-96 RV2, VO1&28
Rat	Developmental neurotoxicity, gavage	Through postnatal day 60 DPX-KN128 (95.5% purity) Dose levels: 0, 0.5, 1.0, 1.5, 3.0 mg/kg bw/day U.S. EPA OPPTS 870.6300	NOAEL: Maternal: 1.5 mg/kg/day Offspring: Male: 1.5 mg/kg/day Female: 3.0 mg/kg/day	29, DuPont-15150 SU1, VO1-7
Male and Female Rats	Subchronic neurotoxicity, feeding	90 days DPX-MP062 (94.5% purity) Dose levels: 0, 10, 50, 100 or 200 ppm Directive 92/69/EEC; U.S. EPA Subdivision F, 82-7	NOAEL: Neuro- Male: 200 ppm (11.9 mg/kg bw/day) Female: 100 ppm (6.09 mg/kg bw/day) Systemic- Male: 10 ppm (0.57 mg/kg bw/day) Female: 10 ppm (0.68 mg/kg bw/day)	30, HLR 1116-96 RV1, VO1&2
Male and Female Rats	Subchronic feeding	90 days DPX-JW062-69 (91.5% purity of which 99.7% is KN128) Dose levels: 0, 3, 8, 20, 50 or 100 ppm Directive 87/302/EEC; U.S. EPA Subdivision F, 82-1; OECD 408; 59 Nohsan No. 4200	NOAEL: Male: 50 ppm (3.2 mg/kg bw/day) Female: 20 ppm (1.7 mg/kg bw/day)	22, HLR 301-94 RV2, VO1&2

***) For *indoxacarb 3S+R* (DPX-MP062) and *racemic indoxacarb* (DPX-JW069), the purity is the sum of the R- and S-isomer expressed as a percentage of the test material. For *indoxacarb* (DPX-KN128), the purity is the S-isomer expressed as a percentage of the test material.**

Table C. Developmental/ reproduction profile of *indoxacarb 3S+1R* (DPX-MP062) Technical concentrate and indoxacarb (DPX-KN128) Technical Material (unless otherwise noted) based on repeated administration

Species	Test	Duration and conditions or guideline adopted*	Result	Reference
Rat	Teratology, gavage	DPX-MP062 (94.5% purity) Directive 87/302/EEC; U.S. EPA Subdivision F, 83-3; OECD 414; 59 Nohsan No. 4200	Maternal NOAEL = 2 mg/kg bw/day Foetal NOAEL =2 mg/kg bw/day	31, HL 1997-00202 RV2
Rat	Teratology, gavage	DPX-KN128 (95.5% purity) Directive 87/302/EEC; U.S. EPA OPPTS 870.3700; OECD 414; 59 Nohsan No. 4200	Maternal NOAEL = 2 mg/kg bw/day Foetal NOAEL =2 mg/kg bw/day	32, DuPont-12748
Rabbit	Teratology, gavage	DPX-JW062-112 (94.8% purity) Directive 87/302/EEC; U.S. EPA Subdivision F, 83-3; OECD 414; 59 Nohsan No. 4200	Maternal NOAEL = 500 mg/kg bw/day Foetal NOAEL = 500 mg/kg bw/day	31, HLR 587-95 SU1
Rat	Reproduction, Feeding	DPX-JW062-106 (95.3% purity) Dose levels: 20, 60, 100 ppm Directive 87/302/ EEC; U.S. EPA Subdivision F, 83-4	Parental NOAEL = 20 ppm (1.3 mg/kg bw/day) Offspring NOAEL = 20 ppm (1.3 mg/kg bw/day) Reproductive NOAEL =100 ppm (6.7 mg/kg bw/day)	33, HLO 115-96 RV2, VO1-46
Human and Rat	Absorption-penetration	6 hours [14C]DPX-MP062 (95.2% purity) Draft OECD guidelines (1996)	Minimal absorption for both human and rat	DuPont-3354
	Absorption-penetration	24 hours [14C]DPX-MP062 (97.2% purity) FIFRA Guideline 85-3	Very minimal absorption. Over half of what was absorbed was excreted within 24 hours.	HLO 1998-00944

***) For *indoxacarb 3S+R* (DPX-MP062) and *racemic indoxacarb* (DPX-JW069), the purity is the sum of the R- and S-isomer expressed as a percentage of the test material.**

Table D1. Mutagenicity profile of *indoxacarb 3S+1R* (DPX-MP062) Technical concentrate based on in vitro and in vivo tests

Species	Test	Conditions*	Result	Reference
Salmonella	Bacterial gene mutation	DPX-MP062 (94.5% purity)	Negative with and without activation	34, HLR 831-96

Species	Test	Conditions*	Result	Reference
typhimurium		Directive 92/69/EEC Method B.13 and Method B.14; U.S. EPA Subdivision F, 84-2; OECD 471 and 472; 59 NohSan No. 4200		
Chinese Hamster Ovary cells (HGPRT)	Mammalian cell gene mutation	DPX-MP062 (94.5% purity) Directive 87/302/EEC Part B *In vitro* Mammalian Cell Mutation Test; U.S. EPA Subdivision F, 84-2; OECD 476	Negative with and without activation	35, HLO 1997-00030
Rat hepatocytes	*In vitro* Unscheduled DNA synthesis (UDS)	DPX-MP062 (94.5% purity) Directive 87/302/EEC Part B - DNA Damage Repair - Unscheduled DNA Synthesis; U.S. EPA Subdivision F, 84-4; OECD 482; 59 NohSan No. 4200	Negative	36, HLO 1997-00033
Human lymphocytes	*In vitro* mammalian cell cytogenetics	DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.10; U.S. EPA Subdivision F, 84-2, ; OECD 473	Negative chromosome aberration with and without activation	37, HLO 979-96
Mouse bone marrow	*In vivo* micronucleus	DPX-MP062 (94.5% purity) Directive 2000/32/EEC; U.S. EPA Subdivision F, 84-2; Annex 4C-B.12.; OECD 474; 59 NohSan No. 4200	Negative	38, HLR 1046-96 RV1

***) For *indoxacarb 3S+R* (DPX-MP062), the purity is the sum of the R- and S-isomer expressed as a percentage of the test material.**

Table D2. Mutagenicity profile of indoxacarb (DPX-KN128) Technical Material based on in vitro and in vivo tests

Species	Test	Conditions	Result	Reference
Salmonella typhimurium	Bacterial gene mutation	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4D; U.S. EPA OPPTS 870.5100; OECD 471; JMAFF12 NohSan No. 8147	Negative with and without activation	34, DuPont-14332
Chinese Hamster Ovary cells (HGPRT)	Mammalian cell gene mutation	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4E; U.S. EPA OPPTS 870.5300; OECD 476; JMAFF12 NohSan No. 8147	Negative with and without activation	35, DuPont-13023
Human lymphocytes	*In vitro* mammalian cell cytogenetics	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4D; U.S. EPA OPPTS 870.5375;	Negative	37, DuPont-13022 RV1

Species	Test	Conditions	Result	Reference
		OECD 473; JMAFF12 NohSan No. 8147		
Mouse bone marrow	*In vivo* micronucleus	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4C-B.12.; U.S. EPA OPPTS 870.5395; OECD 474; 59 NohSan No. 4200	Negative	38, DuPont-13021

***) For *indoxacarb* (DPX-KN128), the purity is the S-isomer expressed as a percentage of the test material.**

Table E. Ecotoxicology profile of *indoxacarb 3S+1R* (DPX-MP062) Technical concentrate and indoxacarb (DPX-KN128) Technical Material

Species	Test	Duration and conditions*	Result	Reference
Lepomis macrochirus (bluegill sunfish)	Acute	96 hr, flow-through (unaerated) DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-1; OECD 203; EEC Method C.1.	LC_{50} = 0.90 mg/L	HLR 912-96 RV2
Oncorhynchus mykiss (rainbow trout)	Acute	96 hr, flow-through (unaerated) DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-1;OECD 203; EEC Method C.1.	LC_{50} = 0.65 mg/L	HLR 911-96 RV2
Cyprinus carpio (carp)	Acute	96 hr, static renewal (unaerated) DPX-MP062 (99.68% purity) U.S. EPA Subdivision E, 72-1; OECD 203	LC_{50} = 0.969 mg/L NOEC = 0.315 mg/L	17-4810
Ictalurus punctatus (catfish)	Acute	96 hr, flow-through (unaerated) DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-1; OECD 203; EEC Method C.1.	LC_{50} = 0.29 mg/L	HLR 866-96 RV2
Cyprinodon variegates (sheepshead minnow)	Acute	96 hr, flow-through (unaerated) DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-3	LC_{50} = >0.374 mg/L	HLO 1997-00090 RV1
Daphnia magna (water flea)	Acute toxicity	48 hr, static DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-2; OECD 202; EEC Method C.2.	EC_{50} = 0.60 mg/L	HLR 603-96 RV2
Daphnia magna (water flea)	Chronic toxicity	21 days, static renewal (unaerated) DPX-MP062 (94.5% purity)	NOEC = 0.075 mg/L MATC = 0.119 mg/L	HLR 1997-00912

Species	Test	Duration and conditions*	Result	Reference
		OECD 202; EPA-540/9-86-141; ASTM E729-88a	LOEC = 0.19 mg/L	
Oncorhynchus mykiss (rainbow trout)	Chronic toxicity: Fish early life stage toxicity test	90 days, flow-through DPX-MP062 (94.5% purity) OECD 210; U.S. EPA Subdivision E, 72-1	NOEC = 0.15 mg/L MATC = 0.20 mg/L LOEC = 0.25 mg/L	HLR 598-96 RV1
Cyprinodon variegates (sheepshead minnow)	Chronic toxicity: Fish early life stage toxicity test	35 days, flow-through DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-4	NOEC = 0.0169 mg/L MATC = 0.0265 mg/L LOEC = 0.0417 mg/	HLO 1997-00091 RV1 VOL 1-4
Chironomus riparius (midge)	Toxicity-sediment dweller	28 days, flow-through [14C]DPX-MP062 (98.4% purity) OECD 219	NOEC = 0.0262 mg/L	DuPont-4055
Mysidopsis bahia (mysid)	Acute	96 hour, flow-through DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-3	NOEC = 0.0542 mg/L	HLO 1997-00205 RV1
Mysidopsis bahia (mysid)	Chronic	28 days flow-through (unaerated) DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-4(c)	NOEC = 0.0184 mg/L MATC = 0.0274 mg/L LOEC = 0.0407 mg/	HLO 1997-00206 RV1
Mollusc	Acute	96 hour, flow-through DPX-MP062 (94.5% purity) U.S. EPA Subdivision E, 72-3(b)	EC_{50} = 0.218 mg/L	HLO 1997-00350
Lemna gibba G3 (duckweed)	Growth and reproduction	14 days DPX-MP062 (94.5% purity) U.S EPA Subdivision J, 122-2	DPX-MP062 has no inhibitory effect on the growth and reproduction of Lemna	AMR 3602-95 RV1
Skeletonema costatum (alga)	Growth and reproduction	120 hours DPX-MP062-51A (94.5% purity) Directive 96/69/EEC Method C3; U.S. EPA Subdivision J, 122-2 and 123-2	Cell Density: EC_{50} = 1215 µg/L NOEC = <107 µg/L Area Under Growth Curve: EC_{50} = 819 µg/L NOEC = <107 µg/L Growth Rate: EC_{50} = 1362 µg/L NOEC = <107 µg/	AMR 3771-96 RV2
Navicula polliculosa (alga)	Growth and reproduction	120 hours DPX-MP062-51A (94.5% purity) Directive 96/69/EEC Method C3; U.S. EPA Subdivision J, 122-2 and 123-2	Cell Density: EC_{50} = >1676 µg/L Area Under Growth Curve: EC_{50} = >1676 µg/L Growth Rate: EC_{50} = >1676 µg/L	AMR 3772-96 RV2

Species	Test	Duration and conditions*	Result	Reference
Pseudokirchneriella subcapitata (formerly Selenastrum capricornutum) (green alga)	Growth and reproduction	120 hours DPX-MP062 (94.5% purity) Directive 96/69/EEC Method C3; U.S. EPA Subdivision J, 122-2 and 123-2	Cell Density: EC_{50} = >110 µg/L Area Under Growth Curve: EC_{50} = >110 µg/L Growth Rate EC_{50} = >110 µg/	AMR 4273-96
Anabaena flos-aquae (Blue/green alga)	Growth and reproduction	120 hours DPX-MP062-51A (94.5% purity) Directive 96/69/EEC Method C3; U.S. EPA Subdivision J, 122-2 and 123-2	Cell Density: EC_{50} = >1931 µg/L Area Under Growth Curve: EC_{50} = >1931 µg/L Growth Rate: EC_{50} = >1931 µg/	AMR 3770-96 RV2
Eisenia foetida andrei (Earthworm)	Acute toxicity	14 days DPX-MP062-51A (94.5% purity) OECD 207; Directive 87/302/EEC	LC_{50} = >1250 mg DPX-MP062/kg soil	AMR 3968-96
Apis mellifera (honey bee)	Acute oral and contact toxicity	72 hours DPX-MP062 (99.4% purity) OECD No. 213 and No. 214	LD_{50} = Oral= 0.258 µg DPX-MP062/bee (0.194 µg DPX-KN128/bee) Contact= 0.093 µg DPX-MP062/bee (0.070 µg DPX-KN128/bee)	DuPont-3995 RV1
Soil micro-organisms		28 days DPX-MP062 (94.5% purity) Directive 91/414/EEC Annex II 8.5; SETAC- Europe Part 2:4	No effects >25% at Day 28 with 250g DPX-MP062/ha	AMR 4134-96
Colinus virginianus (Bobwhite quail)	Acute oral toxicity	21 days DPX-MP062 (94.5% purity) FIFRA Subdivision E, Section 71-1, Hazard Evaluation: Wildlife and Aquatic Organisms	LD_{50} = 98 mg/kg bw NOEL = 37.8 mg/kg bw	AMR 3940-96 RV2
Colinus virginianus (Bobwhite quail)	Dietary toxicity	5 days DPX-MP062 (94.5% purity) FIFRA Subdivision E, 71-2, Hazard Evaluation: Wildlife and Aquatic Organisms; OECD 205; ASTM Standard E857-87	LC_{50} = 808 ppm diet NOEC = 316 ppm diet	AMR 4094-96 RV1
Anas platyrhynchos (Mallard duck)	Dietary toxicity	5 days DPX-MP062 (94.5% purity) FIFRA Subdivision E, 71-2, Hazard Evaluation: Wildlife and Aquatic Organisms; OECD 205; ASTM Standard E857-87	LC_{50} = 5620 ppm diet NOEC = 562 ppm diet	AMR 4093-96 RV1

Species	Test	Duration and conditions*	Result	Reference
Colinus virginianus (Bobwhite quail)	Reproductive toxicity	21 weeks DPX-MP062 (94.5% purity) FIFRA Subdivision E, 71-4, Hazard Evaluation: Wildlife and Aquatic Organisms; OECD 206; ASTM Standard E1062-86	NOEC = Food intake = 144 ppm Ecologically relevant = 720 ppm (75.7 mg/kg bw/day)	AMR 4096-96 RV1
Anas platyrhynchos (Mallard duck)	Reproductive toxicity	21 weeks DPX-MP062 (94.5% purity) FIFRA Subdivision E, 71-4, Hazard Evaluation: Wildlife and Aquatic Organisms; OECD 206; ASTM Standard E1062-86	NOEC = 720 ppm (105.0 mg/kg bw/day)	AMR 4095-96 RV1

***) For *indoxacarb 3S+R* (DPX-MP062), the purity is the sum of the R- and S-isomer expressed as a percentage of the test material. For *indoxacarb* (DPX-KN128), the purity is the S-isomer expressed as a percentage of the test material.**

ANNEX 2. REFERENCES

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35	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 84-2, *in vitro* Mammalian Cell Gene Mutation, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA.
36	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 84-2, *in vitro* Unscheduled DNA Synthesis in Mammalian Cells in Culture, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA.
37	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 84-2, *in vitro* Mammalian Chromosomal Aberration Test, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA.
38	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 84-2, *in vivo* Micronucleus Test, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA.

Comparison of some toxicological endpoint for indoxacarb and *indoxacarb 3S+1R*

		indoxacarb 3S+1R		**indoxacarb**	
Species	**Test**	**Duration and conditions or guideline adopted***	**Result**	**Duration and conditions or guideline adopted***	**Result**
Male and Female Rats	Acute oral	14 days (up to 24 days) DPX-MP062 (94.5% purity) EEC 92/69, Method B.1; U.S. EPA Subdivision F, 81-1; OECD, Part 401; MAFF Japan, 59 NohSan No. 4200	LD_{50} = 1730 mg/kg bw; male 268 mg/kg bw; female	14 days DPX-KN128 (99.7% purity)* EEC 92/69, Method B.1; U.S. EPA Subdivision F, 81-1; OECD, Part 401; MAFF Japan, 59 NohSan No. 4200	LD_{50} = 843 mg/kg bw; male 179 mg/kg bw; female
Male and Female Rats	Acute dermal	14 days DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.3; U.S. EPA Subdivision F, 81-2; OECD, Part 402; MAFF Japan, 59 NohSan No. 4200	LD_{50} = >5000mg/kg bw; male and female	14 days DPX-KN128 (95.5% purity) Directive 92/69/EEC Method B3; U.S. EPA OPPTS 870.1200; OECD, Part 402; MAFF Japan, 59 NohSan No. 4200	LD_{50} = >5000mg/kg bw; male and female
Male Rabbit (New Zealand white)	Acute skin irritation	72 hours DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.4; U.S. EPA Subdivision F, 81-5; 59 NohSan No. 4200; OECD 404	Non-irritant	72 hours DPX-KN128 (95.5% purity) Directive 92/69/EEC Method B.4; U.S. EPA OPPTS 870.2500; 59 NohSan No. 4200; OECD 404	Non-irritant
Female Rabbit (New Zealand white)	Acute eye irritation	72 hours DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.5; U.S. EPA Subdivision F, 81-4; OECD 405; 59 NohSan No. 4200	Non-irritant	72 hours DPX-KN128 (95.5% purity) Directive 92/69/EEC Method B.5; U.S. EPA OPPTS 870.2400; OECD 405; 59 NohSan No. 4200	Non-irritant
Male Guinea Pigs	Acute skin sensitisation	3 week in duration; 48 hour challenge	Dermal sensitiser via method of Magnusson & Kligman	3 week in duration; 48 hour challenge	Dermal sensitiser via method of Magnusson & Kligman

		indoxacarb 3S+1R		**indoxacarb**	
Species	**Test**	**Duration and conditions or guideline adopted***	**Result**	**Duration and conditions or guideline adopted***	**Result**
(Dunkin Hartley)		DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.6; U.S. EPA Subdivision F, 81-6; OECD 406; 59 NohSan No. 4200		DPX-KN128 (95.5% purity) U.S. EPA OPPTS 870.2600; 59 NohSan No. 4200	

		indoxacarb 3S+1R		**indoxacarb**	
Species	**Test**	**Conditions**	**Result**	**Conditions**	**Result**
Salmonella typhimurium	Bacterial gene mutation	DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.13 and Method B.14; U.S. EPA Subdivision F, 84-2; OECD 471 and 472; 59 NohSan No. 4200	Negative with and without activation	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4D; U.S. EPA OPPTS 870.5100; OECD 471; JMAFF12 NohSan No. 8147	Negative with and without activation
Chinese Hamster Ovary cells (HGPRT)	Mammalian cell gene mutation	DPX-MP062 (94.5% purity) Directive 87/302/EEC Part B *In vitro* Mammalian Cell Mutation Test; U.S. EPA Subdivision F, 84-2; OECD 476	Negative with and without activation	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4E; U.S. EPA OPPTS 870.5300; OECD 476; JMAFF12 NohSan No. 8147	Negative with and without activation
Human lymphocytes	*In vitro* mammalian cell cytogenetics	DPX-MP062 (94.5% purity) Directive 92/69/EEC Method B.10; U.S. EPA Subdivision F, 84-2, ; OECD 473	Negative chromosome aberration with and without activation	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4D; U.S. EPA OPPTS 870.5375; OECD 473; JMAFF12 NohSan No. 8147	Negative
Mouse bone marrow	*In vivo* micronucleus	DPX-MP062 (94.5% purity)	Negative	DPX-KN128 (95.5% purity) Directive 2000/32/EEC Annex 4C-B.12.; U.S. EPA OPPTS	Negative

		indoxacarb 3S+1R		**indoxacarb**	
Species	**Test**	**Conditions**	**Result**	**Conditions**	**Result**
		Directive 2000/32/EEC; U.S. EPA Subdivision F, 84-2; Annex 4C-B.12.; OECD 474; 59 NohSan No. 4200		870.5395; OECD 474; 59 NohSan No. 4200	