WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

IMIDACLOPRID

(*E*)-1-(6-chloro-3-pyridylmethyl)-*N*-nitroimidazolidin-2-ylideneamine

World Health Organization

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Disclaimer[1]

WHO 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.

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

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

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

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[1] This disclaimer applies to all specifications published by WHO.

INTRODUCTION

WHO establishes and publishes specifications* for technical material and related formulations of public health 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 2002, the development of WHO specifications follows the **New Procedure**, described in the Manual for Development and Use of FAO and WHO Specifications for Pesticides. This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the "FAO/WHO Joint Meeting on Pesticide Specifications" (JMPS).

WHO specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO 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 above-mentioned manual.

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the above-mentioned manual 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.

WHO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO 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. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* Footnote: The publications are available on the Internet under the WHO Prequalification Team - Vector control products (PQT-VC) website.

PART ONE

SPECIFICATIONS

IMIDACLOPRID

INFORMATION

ISO common name

Imidacloprid (BSI, E-ISO 1750, published)

Synonyms

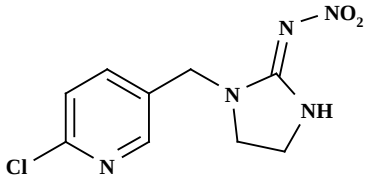
BAY NTN 33 893

Chemical names

IUPAC (*E*)-1-(6-chloro-3-pyridylmethyl)-*N*-nitroimidazolidin-2-ylideneamine

CA (2*E*)-1-[(6-chloro-3-pyridinyl)methyl]-*N*-nitro-2-imidazolidinimine

Structural formula



Empirical formula

$C_9H_{10}ClN_5O_2$

Relative molecular mass

255.7

CAS Registry number

138261-41-3

CIPAC number

582

Identity tests

Retention time in HPLC with UV-detection, IR, NMR

IMIDACLOPRID TECHNICAL MATERIAL

WHO specification 582/TC (February 2019*)

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 (582/2004, 582/2012 & 582/2017.1). It should be applicable to TC produced by these manufacturers 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 TC produced by other manufacturers. The evaluation reports (582/2004 582/2012 & 582/2017.1), as PART TWO, form an integral part of this publication.

1 Description

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

2 Active ingredient

2.1 **Identity tests** (582/TC/M2/2, CIPAC Handbook K, p.70, 2003)

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 **Imidacloprid content** (582/TC/M2/3, CIPAC Handbook K, p.70, 2003)

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

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

PART TWO

EVALUATION REPORTS

IMIDACLOPRID

IMIDACLOPRID

FAO/WHO EVALUATION REPORT 582/2017.1

Recommendations

The Meeting recommended:

(i) that the imidacloprid TC, proposed by UPL Limited, be accepted as equivalent to the imidacloprid reference profile.

(ii) to extend the existing FAO specification for imidacloprid TC to the technical material produced by UPL Limited.

(iii) the specification for imidacloprid TC, including the extension to the technical material produced by UPL Limited, should be adopted by WHO.

(iv) the specification for imidacloprid UL (in combination with prallethrin), proposed by Clarke Mosquito Control Products, Inc., and as amended, should be adopted by WHO, subject to the adoption of the extensions of the analytical methods for imidacloprid and prallethrin to UL formulations by CIPAC.

Appraisal

The data for imidacloprid were evaluated in support of new FAO specifications based on the draft specifications and the supporting data provided by Bayer CropScience AG in 2003, by Cheminova A/S for extension of GR specification in 2007 and by Cheminova A/S for extension of TC, WG, SL, SC, WS and FS formulations in 2012. The FAO specifications for imidacloprid were published in 2006, 2008 and 2013 [FAO, 2013].

Supporting data on imidacloprid TC were provided by UPL Limited (UPL) in support of an equivalence determination with the reference profile that supports the existing imidacloprid FAO specifications 582/TC (May 2013) and to extend it also as WHO specification.

The data submitted were in accordance with the requirements of the FAO/WHO Manual [FAO/WHO 2016], and supported the existing specifications.

UPL's imidacloprid is currently registered in Argentina, Australia, China, Costa Rica, Mexico, South Korea and United States of America.

The confidential data provided on the manufacturing process of imidacloprid are the same as those submitted for registration in the United States of America. The 5-batch analysis results submitted to FAO are the same as those provided to the US-EPA for registration purposes. The impurities and QC limits for imidacloprid TC produced by UPL agree exactly between the information submitted to FAO and to the US [EPA].

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data. Mass balances were 99.8 – 99.9 % in the 5-batch data.
The declared minimum active ingredient content in the TC (975 g/kg) is slightly higher than that of the existing FAO specification (970 g/kg).

Manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile with more than the acceptable values, except for one impurity considered of no significance.

The analytical method for the imidacloprid content was reversed-phase HPLC with UV detection, based on the CIPAC method 582/TC/M2/3 [CIPAC K]. Impurities were also determined by HPLC-UV. Validation data were provided for imidacloprid and the impurities. Methods for the impurities were validated with LOQs of 0.2 - 2.07 g/kg in the TC.

The manufacturing pathway of this technical material is different from that of the product with the reference profile, however the impurity profiles are similar. Tier-1 information was sufficient to decide on the equivalence of UPL's imidacloprid TC with the reference profile of Bayer.

In addition to the *in-vitro* mutagenicity required in Tier-1 of the equivalence determination, additional studies on toxicology were available for rat acute oral, rat acute dermal, rat acute inhalation, rabbit eye irritation, rabbit skin irritation and Guinea pig skin sensitization and also for a rat pre-natal developmental toxicity. These studies were not taken into consideration during the evaluation of the equivalence of the technical materials.

The Meeting concluded that the UPL imidacloprid TC was equivalent to the imidacloprid reference TC based on Tier-1 evaluation.

The Meeting noted that imidacloprid currently has a TC specification for FAO, but does not have a WHO specification. Since a second manufacturer wanted to extend the FAO equivalence but also requested a WHO specification, the Meeting recommended that the holder of the reference TC specification (Bayer) should be contacted and asked for agreement with the extension of the TC specification to WHO. This was done in the meantime and a written agreement by Bayer was received, stating that there would be no objection from their side to extend the imidacloprid FAO TC specification to WHO as well.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 582/2017.1

Physico-chemical properties of imidacloprid

Table 1. Chemical composition and properties of imidacloprid 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 and WHO. Mass balances were 99.8 – 99.9 % and percentages of unknowns were 0.1 – 0.18 %.
Declared minimum imidacloprid content	975 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

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	145.3 ± 0.15°C at normal atmospheric pressure (760 mm Hg)	98	OECD 102 and OCSPP 830.7200	202-2-11-14433
Solubility in organic solvents	57.8 g/l in acetone at 20°C 71.9 g/l in dichloromethane at 20°C 18.2 g/l in methanol at 20°C 4.4 g/l in hexane at 20°C	95	a.i. concentration determined by HPLC	3841

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is a HPLC method using a reversed phase column based on CIPAC method 582/TC/M2/3 [JRF-5551]. The methods for determination of impurities are based on analysis by reverse phase liquid chromatography using a C_8 column, UV detection and quantification by external standard, and additional methods by ion chromatography and titration [JRF-5551].

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD and CIPAC.

Formulations and co-formulated active ingredients

The main formulation types available are GR, WG, WS, SC, SL, OD and FS (agricultural formulations).

Up to now, imidacloprid does not have any approved public health uses with the exception of some approvals for use against bed bugs.

Imidacloprid may be co-formulated with other insecticides or fungicides.

UPL's imidacloprid formulations are registered and sold in a range of countries including Argentina, Australia, China, Costa Rica, Mexico, South Korea, United States of America.

Physical properties

The physical properties, the methods for testing them and the limits proposed for the TC were OECD, CIPAC as appropriate.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The content of active ingredient is expressed as imidacloprid.

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 imidacloprid having impurity profiles similar to those referred to in the table above.

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

Table 2. Mutagenicity profile of imidacloprid technical material based on *in vitro* tests

Species	Test	Purity % Note[2]	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium	*In vitro* test. Reverse mutation in five strains of *Salmonella typhimurium* (TA1537, TA1535, TA98, TA100 and TA102)	98.02	OECD 471, between156.25 to 5000 µg/plate both in absence and presence of metabolic activation system for 5 strains	Negative [Non-Mutagenic] Bacterial cultures were exposed to imidacloprid technical at eight concentrations (two plates/concentration) between 1.5 and 5000 µg/plate both in the absence and presence of metabolic activation system (5% v/v S9 mix) in the initial toxicity-mutation test. Imidacloprid technical did not induce any significant increase in the number of revertants, with and without S9 mix, in any of the five tester strains. To confirm the negative results obtained in the initial toxicity mutation test, confirmatory mutation test was conducted with the concentration modification and increased S9 concentration i.e. 10 % v/v	481-1-06-14432

[2] Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

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

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result	Study number
Wistar Rat Female	oral	98.08	Guideline: EPA OPPTS 870.1100. (OECD 425). Method: Single oral dose. Doses: 260, 380, or 550 mg/kg. Duration: 14 days observation.	LD50 = 380 mg/kg bw	5702
Wistar Rat Male and Female	dermal	98.08	Guideline: EPA OPPTS 870.1200. (OECD 402). Method: Single topical application. Dose: 5000 mg/kg. Duration: 14 days observation.	LD50 = >5000 mg/kg bw	5703
Wistar Rat Male and Female	inhalation	98.08	Guideline: EPA OPPTS 870.1300 (OECD 403). Method: Four hour single exposure via inhalation (nose-only exposure). Dose: Maximum technically attainable concentration with UPL test substance by laboratory was 0.589 mg/L (dust) for 4 hours exposure in experiment. Duration: 14 days observation.	LC50 = >0.589 mg/l air	5707
New Zealand white rabbit and Female	skin irritation	98.08	Guideline: EPA OPPTS 870.2500. (OECD 404). Method: Single topical application. Dose: 500 mg. Duration: 72 hours observation.	Non Irritant	5704
New Zealand white rabbit and Male	eye irritation	98.08	Guideline: EPA OPPTS 870.2400. (OECD 405). Method: Single instillation via the ocular route. Dose: 100 mg. Duration: 72 hours observation.	Non Irritant	5705
Hartley Guinea pigs and Male and Female	skin sensitisation	98.08	Guideline: EPA OPPTS 870.2600. (OECD 429). Method: guinea pig maximisation test. Dose: 2.5% in propylene glycol intradermal injection day 0, topical application (100 mg) on Day 7.	Non Sensitizer	5706

Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Table 4. Toxicology profile of imidacloprid technical material based on repeated administration (subacute to chronic)

Species	Test	Purity, %	Guideline, duration, doses and conditions	Result	Study number
Wistar rats and Female	Pre-natal developmental toxicity	98.49	OECD 414, 50, 100, 200 mg/kg b.wt/day on gestational days 5 to 19	NOAEL = 50 mg/kg/bw/day For maternal and foetal toxicity Non-teratogenic up to dose level of 200 mg/kg bw/day	2097

Background information on toxicity and ecotoxicity

Imidacloprid was evaluated by the FAO/WHO JMPR in 2001 for toxicology and in 2002, 2006 and 2008 for residues.
The IPCS hazard classification of imidacloprid is: moderately hazardous, class II [IPCS 2009].
Classification according to Reg. 1272/2008 as amended [Reg 1272]:
Xn;R22: Harmful if swallowed.
N; R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
GHS classification according to UN edition 2005 [WHO, 2005]:
Acute oral toxicity: Category 4 (H302).
Hazards to the aquatic environment: Acute and Chronic Category 1 (H400, H410).

ANNEX 2: REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
JMPR 2001		2001	http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/Download/2001_rep/REPORT2001.pdf; p.106
JMPR 2002		2002	http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/Download/2002_rep/2002JMPRReport2.pdf; p.150
JMPR 2006		2006	http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/Download/2006_rep/Imidacloprid.pdf; p. 150
JMPR 2008		2008	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report08/Imidacloprid.pdf; p.217
EPA 1994		1994	Federal Register Vol. 59, No. 230 (1.12.1994) http://www.gpo.gov/fdsys/pkg/FR-1994-12-01/html/X94-11201.htm
EPA 1996		1996	Federal Register Vol. 61, No. 31 (14.02.1996) http://www.gpo.gov/fdsys/pkg/FR-1996-02-29/pdf/96-4392.pdf
EPA 2010		2010	Federal Register Vol. 75, No. 81 (28.04.2010) http://www.knowledgemosaic.com/gateway/FedReg/Fed.2010-9761.htm
CR, 2011		2011	Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 – OJ L 153, 11.6.2011 p. 97.
FAO, 2013		2008	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Imidacloprid_2013_01.pdf
FAO/WHO Manual, 2016		2016	Manual on development and use of FAO and WHO specifications for pesticides, First edition – third revision, FAO Plant Production and Protection Paper 228.
EPA		2017	E-mail from US-EPA, sent on 13.10.2017, [from: leifer.kerry@epa.gov mailto: to laszlo.bura@efsa.europa.eu]
CIPAC, K	Martijn A and Dobrat W	2003	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides, p.70.
202-2-11-14433		2016	Melting Point/ Melting Range of Imidacloprid technical. doc No 202-2-11-14433, GLP, Unpublished.
3841		2002	Solubility of Imidacloprid Technical in organic solvents, Doc No 3841, GLP, Unpublished.
5551		2016	Summary of UPL Analytical Method for determination of Imidacloprid in Imidacloprid TC, WHO Document 2.
IPCS 2009		2009	The WHO Recommended Classification of Pesticides by Hazard; http://www.who.int/ipcs/publications/pesticides_hazard_2009.pdf
Reg 1272		2008	Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. 31.12.2008 EN Official Journal of the European Union L 353/1.
WHO, 2005		2005	The WHO recommended classification of pesticides by hazard and guidelines to classification: 2004, WHO, Geneva.

481-1-06-14432	2016	Bacterial Reverse Mutation Test of Imidaclopriid Technical using *Salmonella Typhmurium*, Document no 481-1-06-14432, GLP, Unpublished.
5702	2006	Imidacloprid Technical: Acute ORAL Toxicity Study of Im-idacloprid Technical in Rats. Doc. No.: 5702. GLP. Un-published.
5703	2006	Acute Dermal Toxicity Study of Imidacloprid Technical in Rats. Doc. No.: 5703. GLP. Unpublished.
5707	2006	Acute Inhalation Toxicity Study of Imidacloprid Technical in Rats. Doc. No.: 5707 GLP. Unpublished.
5704	2010	Primary Skin Irritation Study of Imidacloprid Technical in Rabbits. Doc. No 5704. GLP. Unpublished.
5706	2010	Skin sensitisation Study of Imidacloprid Technical in Guinea pigs. Doc. No.: 5706. GLP. Unpublished.
2097	2011	Prenatal developmental toxicity study of Imidacloprid technical in rats, Doc no 2097, GLP, Unpublished.

IMIDACLOPRID

FAO/WHO EVALUATION REPORT 582/2012

Recommendations

The Meeting recommended that:

(i) the specification for imidacloprid TC proposed by Cheminova A/S be accepted as equivalent to the imidacloprid reference profile.

(ii) the existing TC specification be extended to the technical material produced by Cheminova A/S.

(iii) the existing WG, SL, SC, WS and FS specifications be extended to the materials produced by Cheminova A/S, with certain revisions, e.g. updated references to CIPAC methods.

(iv) the IUPAC name imidacloprid be amended in the existing specification to bring it in line with the latest published version.

(iv) the inclusion of the adhesion to seeds specification clause for the existing imidacloprid WS and FS specifications.

(v) the storage stability specification clause in the WG, SL and WS specifications be amended to bring it in line with the latest revision of the Specification Manual.

Appraisal

Imidacloprid is not under patent.

Imidacloprid was evaluated by the FAO/WHO JMPR in 2001 for toxicology and in 2002, 2006 and 2008 for residues [JMPR 2001, JMPR 2002, JMPR 2006, JMPR 2008].

It was evaluated by U.S. EPA, the results were published in the U.S Federal Register [EPA 1994, EPA 1996, EPA 2010]. Imidacloprid was evaluated by the European Commission as part of the EU review of existing active substances for inclusion in Annex I of the Council directive 91/414/EEC in 2009. It was included in Annex I with a minimum purity of 970 g/kg [CR, 2011].

The data for imidacloprid were evaluated in support of new FAO specifications based on the draft specifications and the supporting data provided by Bayer CropScience in 2003 and Cheminova A/S for extension of GR specification in 2007. The FAO specifications for imidacloprid were published in 2006 and 2008 [FAO, 2006].

Supporting data on imidacloprid TC, WG, SL, SC, WS and FS formulations were provided by Cheminova A/S in support of an equivalence determination with the reference profile that supports the existing imidacloprid FAO specifications 582/TC (April 2006), 582/WG (April 2006), 582/SL (April 2006), 582/SC (April 2006), 582/WS (April 2006) and 582/FS (April 2006).

The data submitted were in accordance with the requirements of the [FAO/WHO Manual, 2010] and supported the existing specifications.

Cheminova A/S imidacloprid is currently registered in Australia, Argentina, Brasil, EU, as well as several other countries.

The confidential data provided on the manufacturing processes of imidacloprid are identical to those submitted for registration in the United Kingdom. The 5-batch analysis results submitted to FAO are the same as those provided to the UK for registration purposes. The impurities and QC limits for imidacloprid TC produced by Cheminova A/S agree exactly between the information submitted to FAO and to the UK [Tessier, 2011].

The Meeting was provided with commercially confidential information on the manufacturing processes and batch analysis data. None of the impurities present in batches were above 1 g/kg and as a consequence they were not included in the specification of the TC. Mass balances were 99.8 - 100.9 % in the 5-batch data. The declared minimum active ingredient content (970 g/kg) agrees with that of the FAO specification, however based on the Cheminova's data even a higher value could have been proposed.

Manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile. Three new impurities were identified. Two of the new impurities in the Cheminova A/S imidacloprid technical are probably formed in the last reaction step before recristallyzation. These impurities were considered not relevant based on the mutagenicity test conducted using a technical material included also in the 5-batch analysis of imidacloprid with a content of these impurities similar to that of the 5-batches.

The findings in the study allowed the conclusion that the test material did not induce mutation under the conditions of the study [549 IDC]. A further Ames test on technical material containing 0.16% w/w of one of these impurities was conducted and was also negative [377 IDC]. Due to the structural similarity of these two impurities, both of them were considered not relevant.

The third impurity has a toxicity that is completely different in humans from that of the a.i. and therefore should qualify as relevant. But as it has not been detected using a method with an LOQ of 0.61 g/kg, this would mean that at an oral LD_{50} dose (450 mg/kg in the WHO classification for pesticides) of imidacloprid, the dose of this impurity would be <0.27 mg/kg, and this is below the US EPA oral reference dose to humans and thus the margin of safety should be sufficiently large. In conclusion, this third impurity is not considered relevant in the imidacloprid technical material.

The company used CIPAC method 582/TC/M2/3 [CIPAC K] for determination of the content of the active ingredient imidacloprid in TC and formulations. The impurities in the TC were determined by HPLC-UV as well. Validation data were provided for imidacloprid and the impurities. Methods for the impurities were validated to LOQs of 0.46 - 0.72 g/kg in the TC.

As the synthetic pathways of this technical material are completely different from that of the product with the reference profile, and also the impurity profiles are completely different, the equivalence cannot be decided based on Tier-1 evidence only. As a consequence, in addition to the mutagenicity required in the first tier, additional studies on toxicology are needed for equivalence determination. Toxicity data were available for reverse mutation in *Salmonella typhimurium* and *Escherichia coli,* for rat acute oral, rat acute dermal, rat acute inhalation, rabbit eye irritation, rabbit skin irritation and mice skin sensitization. The ratings were equivalent to those of the

reference material, except the rabbit eye irritation study, where imidacloprid technical was classified as minimally irritating to the eye under the classification scheme used in the study. According to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) however, this study would not trigger for eye irritation [WHO, 2009; CLP, 2009].

The Meeting concluded that the Cheminova A/S imidacloprid TC was equivalent to the imidacloprid reference TC based on Tier-1 and Tier-2 evaluation.

The ISO common name 'imidacloprid' was originally approved for a mixture of (E)- and (Z)-isomers, but in 2007 it was determined that the substance in crystalline form is comprised almost entirely of the (E)-isomer and requested that the definition be changed. The original proposer (Bayer AgroScience) approached ISO and they agreed to change what the ISO name referred to. Cheminova confirmed that their technical material also entirely consists of the (*E*)-isomer. The method Cheminova use for analysis of imidacloprid in imidacloprid technical is based on the existing CIPAC method (CIPAC MT 582/TC/M2/).

Physical property data were provided for imidacloprid SL, SC, WG, FS and WS formulations for comparison with the existing specifications. The formulations complied with all specifications before and after storage.

The Manual on development and use of FAO and WHO specifications for pesticides. (November 2010 - second revision of the First Edition) proposes the inclusion of the adhesion to seeds specification clause for the WS and FS specifications. As Cheminova's application was for equivalence, and no clause was previously included in the existing FAO specifications for imidacloprid FS and WS, a clause for attrition resistance has not been proposed by Cheminova on purpose.

However the company confirmed that the inclusion of such a clause for the WS and FS specifications with a proposed limit of minimum 98% would be acceptable.

The Meeting recommended amendment of the IUPAC name of imidacloprid in the existing FAO specifications to (*E*)-1-(6-chloro-3-pyridylmethyl)-*N*-nitroimidazolidin-2-ylideneamine.

The Meeting recommended amendment of the existing WS and FS specifications including the clause for adhesion to seeds (MT 194).

The Meeting also recommended amendment of the storage stability test specification clause:

- for imidacloprid WG by adding attrition resistance to be tested also after storage;
- for imidacloprid SL by adding solution stability to be tested also after storage;
- for imidacloprid WS and FS by adding adhesion to seeds to be tested also after storage;

as recommended by the revised (second revision November 2010) 1st edition of the Manual on development and use of FAO and WHO specifications for pesticides.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 582/2012

Uses

Imidacloprid is an insecticide belonging to the nitroguanidine subgroup of the neonicotinoids. These compounds act on the nicotinic acetylcholin receptor (nAChR) and interfere with the transmission of nerve impulses in insects. It has a broad spectrum of contact and ingestion activity against insect pests, and lacks activity against spider mites or nematodes. It is systemic in plants and has significant residual activity. It is used in agriculture against sucking insects, phytophagous coleoptera and various other pests.

Identity of the active ingredient

ISO common name

imidacloprid (E-ISO 1750, published)

Synonyms

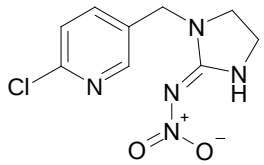
None

Chemical names

IUPAC (*E*)-1-(6-chloro-3-pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine

CA (2*E*)-1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine

Structural formula



Empirical formula

$C_9H_{10}ClN_5O_2$

Relative molecular mass

255.7

CAS Registry number

138261-41-3

CIPAC number

582

Identity tests

HPLC, UV-detection, IR, NMR

Physico-chemical properties of imidacloprid

Table 1. Chemical composition and properties of imidacloprid 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 99.8 – 100.9 % and percentages of unknowns were 0 - 02 %.
Declared minimum imidacloprid content	985 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

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	143.9 °C	98.7	OECD 102	820 IDC
Solubility in organic solvents	42.48 g/l acetone at 20 ± 0.5 °C 8.68 g/l methanol at 20 ± 0.5 °C	98.7	OECD 105	634 IDC

Formulations

The main formulation types available are GR, WG, SL, SC, WS and FS (agricultural formulations).

Imidacloprid can be co-formulated with gamma-cyhalothrin and tebuconazole.

Cheminova's imidacloprid GR, WS, WG, SC, FS and SL formulations are registered and sold in a range of countries throughout the world, including Member States of the EU, Australia, USA, Brazil and Argentina.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is an HPLC method using a reversed phase column based on CIPAC method 582/SC/M2/ [VAM 132-01]. The methods for determination of impurities are based on analysis by reverse phase liquid chromatography using RP18 column, UV detection and quantification by external standard, and an additional method by gas chromatography using a capillary column and detection by FID. Quantification is performed using external calibration.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, while those for the formulations were CIPAC, as indicated in the specifications [CIPAC Handbooks F, H, J, K and L, respectively].

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The content of active ingredient is expressed as imidacloprid.

Hazard summary

The IPCS hazard classification of imidacloprid is: moderately hazardous, class II [IPCS 2009].

Classification according to Reg. 1272/2008 as amended [Reg 1272]:
Xn;R22: Harmful if swallowed.
N; R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

GHS classification according to UN edition 2005 [WHO, 2005]:
Acute oral toxicity: Category 4.
Hazards to the aquatic environment: Acute and Chronic Category 1.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

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

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

Table 2. Mutagenicity profile of imidacloprid technical material based on *in vitro* tests

Species	Test	Purity % Note[3]	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium *Escherichia coli*	*In vitro* test. Reverse mutation in four strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535 and TA 1537) and one strain of *Escherichia coli* (WP2 uvrA).	99.0	Guideline: OECD 471, EEC B13/14 and EPA OPPTS 870.5100 Imidacloprid technical was tested in two independent experiments in the following concentrations: 31.6, 100, 316, 1000, 2500 and 5000 µg/plate in the absence and presence of S-9 in the four strains of *Salmonella typhimurium* and the one strain of *Escherichia coli*. The plates were incubated at 37 °C for 48 hrs.	The sensitivity of the assay was validated. No biological relevant increases in revertant colony numbers of any of the five tested strains were observed following treatment with imidacloprid technical at any concentration level, neither in the presence nor absence of metabolic activation. Imidacloprid technical did not cause gene mutations by base pair changes or frameshifts in the genome of the strains used. Imidacloprid TC is considered to be non-mutagenic under the condition of this bacterial reverse mutation assay.	549 IDC

[3] Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

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

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result	Study number
Eight female rats	oral	99.0	Guideline: OECD 425 and EPA OPPTS 870.1100. Method: Single oral dose with 45% imidacloprid w/w mixture in distilled water. Doses: 120, 380, 1200 or 5000 mg/kg.	LD_{50} = 2567 mg/kg bw	543 IDC
Five female and five male rats	dermal	99.0	Guideline: OECD 402 and EPA OPPTS 870.1200. Method: Single topical application for 24 hours. Dose: 5000 mg/kg.	LD_{50} > 5000 mg/kg bw	544 IDC
Five female and five male rats	inhalation	99.0	Guideline: OECD 403 and EPA OPPTS 870.1300. Method: Four hour single exposure via inhalation (nose-only exposure). Gravimetric concentration: 5.17 mg/L.	LC_{50} > 5.17 mg/L	545 IDC
Three male rabbits	skin irritation	99.0	Guideline: OECD 404 and EPA OPPTS 870.2500. Method: Single topical application for four hours. Dose: 0.5 gram (applied as a paste with distilled water)	Non-irritating to the skin	547 IDC
Three female rabbits	eye irritation	99.0	Guideline: OECD 405 and EPA OPPTS 870.2400. Method: Single instillation via the ocular route. Dose: 0.08 g of ground test substance.	Minimal irritating to the eye	546 IDC
Twenty female mice	skin sensitisation	99.0	Guideline: OECD 429 and EPA OPPTS 870.2600. Method: Daily application of 25 µl of the appropriate concentrations to the dorsal surface of each ear for three consecutive days (days 1, 2, 3). Three days following the last application of the test material all mice were injected with 20 µCi ^{3}H-methyl thymidine. The proliferation response of lymph node cells was expressed as the dpm in the lymph node and as the ratio of ^{3}H-methyl thymidine incorporation into lymph node cells of test nodes relative to that recorded for the control nodes (Stimulation Index).Concentrations: 2.5%, 5% and 10% imidacloprid in DMSO.	A stimulation index of 1.07, 0.94 and 1.23 was recorded for the three concentrations (2.5, 5 and 10%, respectively) of the test material. Imidacloprid is not a contact dermal sensitiser	548 IDC

[4] Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

ANNEX 2: REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
JMPR 2001		2001	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/REPORT2001.pdf; p. 106
JMPR 2002		2002	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/Report_2002.pdf, p. 150
JMPR 2006		2006	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/JMPRrepor2006.pdf, p. 150
JMPR 2008		2008	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report08/Imidacloprid.pdf
EPA 1994		1994	Federal Register Vol. 59, No. 230 (1.12.1994) http://www.gpo.gov/fdsys/pkg/FR-1994-12-01/html/X94-11201.htm
EPA 1996		1996	Federal Register Vol. 61, No. 31 (14.02.1996) http://www.gpo.gov/fdsys/pkg/FR-1996-02-29/pdf/96-4392.pdf
EPA 2010		2010	Federal Register Vol. 75, No. 81 (28.04.2010) http://www.knowledgemosaic.com/gateway/FedReg/Fed.2010-9761.htm
CR, 2011		2011	Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 – *OJ L 153, 11.6.2011 p. 97.*
FAO, 2006		2008	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Imidacloprid08.pdf
FAO/WHO Manual, 2010		2010	Manual on development and use of FAO and WHO specifications for pesticides, November 2010 second revision of the first edition http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/manual/en/
Tessier, 2011		2010	E-mail from Sonia Tessier, HSE, CRD, sent on 14. December 2011.
549 IDC		2010	Reverse Mutation Assay using Bacteria (Salmonella typhimurium and Escherichia coli) with Imidacloprid Technical. CHA Doc. No.: 546 IDC. 103269. GLP. Unpublished.
377 IDC		2007	Imidacloprid Technical : Reverse Mutation Assay Ames Test using *Salmonella typhimurium* and *Escherichia coli*, Unpublished report, CHA Doc. No.: 377 IDC.
CIPAC, K	Martijn A and Dobrat W Edts.	2003	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides, p.70.
WHO, 2009		2009	The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009, www.who.int/entity/ipcs/publications/pesticides_hazard_2009.pdf
CLP, 2009		2009	http://ecb.jrc.ec.europa.eu/classification-labelling/clp/ghs/index.php?indexNum=608-034-00-3&subLang=EN
820 IDC		2012	Determination of the Melting Point of Imidacloprid (technical Active Ingredient). CHA Doc. No.: 820 IDC. CHE0412-PC-059. Stähler International GmbH & Co. KG, Germany, Unpublished.
634 IDC		2011	Solubility in Water and Organic Solvents of Imidacloprid Técnico Cheminova. CHA Doc. No.: 634 IDC. RF.0265.008.1092.10. GLP. Unpublished.

VAM 132-01		2007	Determination of Imidacloprid (CAS No. 138261-41-3) in Imidacloprid technical. Cheminova A/S. Unpublished report, CHA Doc. No.: VAM 132-01.
CIPAC, F	Martijn A and Dobrat W Edts.	1995	CIPAC Handbook Volume F. Physico-chemical Methods for Technical and Formulated Pesticides.
CIPAC, H	Martijn A and Dobrat W Edts.	1998	CIPAC Handbook Volume H. Analysis of Technical and Formulated Pesticides, p.204.
CIPAC, J	Martijn A and Dobrat W Edts.	2000	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides.
CIPAC, K	Martijn A and Dobrat W	2003	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides.
CIPAC, L	Martijn A and Dobrat W	2006	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides.
IPCS 2009		2009	The WHO Recommended Classification of Pesticides by Hazard; http://www.who.int/ipcs/publications/pesticides_hazard_2009.pdf
Reg 1272		2008	Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 31.12.2008 EN Official Journal of the European Union L 353/1.
WHO, 2005		2005	The WHO recommended classification of pesticides by hazard and guidelines to classification: 2004, WHO, Geneva.
543 IDC		2011	Imidacloprid Technical : Acute Oral Toxicity Up And Down Procedure In Rats. CHA Doc. No.: 543 IDC. 30361. GLP. Unpublished.
544 IDC		2010	Imidacloprid Technical : Acute Dermal Toxicity Study in Rats. CHA Doc. No.: 544 IDC. 30362. GLP. Unpublished.
545 IDC		2010	Imidacloprid Technical : Acute Inhalation Toxicity Study in Rats. CHA Doc. No.: 545 IDC. 30363. GLP. Unpublished.
547 IDC	Lowe C	2010	Imidacloprid Technical : Primary Skin Irritation Study in Rabbits. CHA Doc. No.: 547 IDC. 30365. GLP. Unpublished.
546 IDC	Lowe C	2010	Imidacloprid Technical : Primary Eye Irritation Study in Rabbits. CHA Doc. No.: 546 IDC. 30364. GLP. Unpublished.
548 IDC		2011	Imidacloprid Technical : Local Lymph Node Assay (LLNA) in Mice. CHA Doc. No.: 548 IDC. 30366. GLP. Unpublished.

IMIDACLOPRID

FAO/WHO EVALUATION REPORT 582/2004

Recommendations

The Meeting recommended the following:

(i) The specifications for imidacloprid TC, GR, WG, WS, SC, FS, OD and SL, proposed by Bayer CropScience AG, as amended, should be adopted by FAO.

(ii) The manufacturer should resubmit a draft specification for imidacloprid DT when validated test methods and agreed guidelines become available for tablet integrity.

Appraisal

The Meeting considered data on imidacloprid, submitted by Bayer AG/Bayer CropScience AG, for the development of new FAO specifications for TC, GR, WS, WG, SC, FS, OD and SL. A draft specification for DT was also submitted but, in the absence of suitable test methods and agreed characteristics for tablet integrity, this was not considered further. The data and proposed specifications were broadly in accordance with the requirements of the FAO/WHO manual.

Imidacloprid is under patent till 2006.

Imidacloprid is an off-white powdered solid, of very low volatility. It has slight solubility in water, which is not influenced by pH, but is not fat-soluble. It is not measurably acidic or basic; it is stable at pH 4 and 7 and only very slowly hydrolyzed at pH 9. In contrast, it is subject to very rapid photolysis, which forms a major route of dissipation in the environment.

Confidential information on the method of manufacture, the technical specification and data from the analysis of production batches was presented to the meeting. Mass balances in the batch analyses were high (99.6-99.7%). The data presented were confirmed as identical to those submitted for registration in Europe (Germany is rapporteur member state for the re-evaluation and authorization of imidacloprid in the European Union under the provisions of directive 91/414/EEC).

The Meeting agreed that none of the impurities should be considered as relevant.

Analytical methods for imidacloprid (including identity tests) in TC, GR, WG, WS, SC, FS, OD, SL are full CIPAC methods. The method for GR was published in CIPAC Handbook H. The methods for TC, WG, WS, SC, FS were published in CIPAC handbook K and extensions to OD and SL were adopted by CIPAC 2004 but are not yet published. In these methods, imidacloprid is determined by reversed-phase HPLC, using external standardization and detection at 260 nm.

The method for determination of impurities was also based on reversed-phase HPLC, using isocratic elution, UV-detection and external standardization with authentic standards.

Test methods for determination of physico-chemical properties of the technical active substance were OECD, USEPA, EC, while those for the formulations were for example, CIPAC, as indicated in the specifications.

The physical properties, the methods for testing them and the limits proposed for the GR, WS, WG, SL, SC and OD specification, as amended following discussions between the Meeting and manufacturer, comply with the requirements of the FAO/WHO Manual.

The proposed specification for FS did not incorporate a clause for suspensibility, because the manufacturer explained that the product is not intended for dilution with water before use. The Meeting agreed that the clause was inappropriate in this case, that the description clause should be amended to reflect this, and that the test for persistent foam should be conducted on the undiluted product. The manufacturer noted that the red dye in the undiluted FS tends to make the exact determination of persistent foam more difficult than is usual with method MT 47.2 but stated that the product does comply with the specification.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 582/2004

Uses

Imidacloprid is a chloronicotinyl (also known as neonicotinoid) insecticide with a broad spectrum of contact and ingestion activity against insects but with no activity against spider mites or nematodes. It is used against sucking insects (such as aphids, whiteflies, leaf-hoppers, thrips, scales, mealy bugs, psyllids, phylloxera), phytophagous coleoptera (such as Colorado beetles, rice water weevils, wireworms, beetle grubs, flea beetles), and various other pests (such as lepidopterous leaf-miners, some dipterous pests, termites, locusts and fleas). It is systemic in plants, has significant residual activity, and controls pests which are resistant to other classes of insecticide.

Imidacloprid interferes with the transmission of nerve impulses in insects. As with the naturally occurring signal-transmitter acetylcholine, imidacloprid stimulates nerve cells by acting on a receptor protein. In contrast to acetylcholine, which is quickly degraded by the enzyme acetylcholine-esterase, imidacloprid is inactivated either very slowly or not at all. Pest feeding activity ceases within minutes to hours and death occurs usually within 24-48 hours but can take up to a few days.

Identity of the active ingredient

ISO common names

Imidacloprid (BSI, E-ISO), imidaclopride ((m) draft F-ISO)

Synonyms

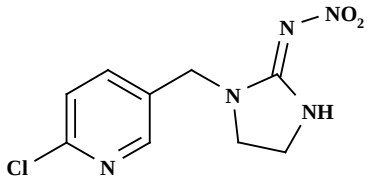
BAY NTN 33 893

Chemical names

IUPAC 1-(6-chloro-3-pyridinylmethyl)-*N*-nitroimidazolidin-2-ylideneamine

CA 1-[(6-chloro-3-pyridinyl)methyl]-*N*-nitro-2-imidazolidinimine

Structural formula



Empirical formula

$C_9H_{10}ClN_5O_2$

Relative molecular mass

255.7

CAS Registry number

138261-41-3

CIPAC number

582

Identity tests

HPLC retention time, IR and ^{1}H-NMR spectra.

Physico-chemical properties of imidacloprid

Table 1. Physico-chemical properties of pure imidacloprid

Characteristic	Value	Purity, %	Method	Reference
Vapour pressure	4×10^{-10} Pa at 20ºC 9×10^{-10} Pa at 25ºC	99.9	OECD 104, by extrapolation	PC313
Melting point	144ºC	99.9	OECD 102	PC312
Boiling point	Not measurable	-	-	PC14376
Decomposition temperature	DTA-measurement: No exothermic decomposition occurred below 150°C. TGA-measurement: Above 230 °C, a weight loss was observed both under air and under a nitrogen atmosphere. Imidacloprid is thermally stable at room temperature.	99.5	OECD 113	PC339
Solubility in water	0.61 g/l at 20°C Solubility is not influenced by pH in the range pH 4 to 9.	97.2	EEC A6 OECD 105	PC320
Octanol:water partition coefficient	P_{OW} = 3.7 Log P_{OW} = 0.57 at 21°C Effect of pH not investigated because pH (4-9) does not influence water solubility.	99.8	EEC A8 OECD 107	PC337
Hydrolysis	Imidacloprid was found to be stable with a half-life > 1 year at pH 5 and 7. Slow hydrolysis with a half-life of approx. 1 year occurred at pH 9.	>99.8	EPA 161-1	NR1276
Photolysis	Half-life = 57 min. at 5.4 mg/l, 23 to 24.5°C, sterile conditions, irradiated with xenon lamp and UV-glass filter (cut-off 290 nm). The corresponding rate constant was 0.012 min^{-1}. Environmental half-life in surface water calculated as 4.2 h, at 50° latitude (e.g. N. Germany) and at the equinox.	>99.8	EPA 161-2	PF3517
Dissociation characteristics	Imidacloprid shows very weakly basic properties. Complete protonation can be achieved only in non-aqueous solutions in presence of very strong acids. It is not possible to determine a pK value in pure aqueous systems.	99.8	OECD 112	PC317

Table 2. Chemical composition and properties of imidacloprid 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 99.6 – 99.7%.
Declared minimum imidacloprid content	970 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 temperature range (TC)	142-144 °C

Background information on toxicology/ecotoxicology

Bayer CropScience confirmed that the toxicological and ecotoxicological data included in Annex 1, below, were derived from imidacloprid having impurity profiles similar to those referred to in Table 2, above.

Imidacloprid was evaluated for toxicology by the FAO/WHO JMPR in 2001, which set the reference doses: ADI: 0.06 mg/kg bw/day; acute RfD: 0.4 mg/kg bw. Imidacloprid was evaluated for residues by the FAO/WHO JMPR in 2002, which recommended MRLs for 51 food commodities and assessed the dietary risks from long- and short-term intake of residues as "unlikely to present a public health concern".

Imidacloprid was evaluated by the U.S. EPA in 1992/93 and the results (imidacloprid compound (BAY NTN 33893 Techn.) – Registry No. EPA 3125-414, approval March 18, 1994) were published in the U.S. Federal Register in 1994. Residue tolerances were established (USEPA 1996).

The Bayer CropScience hazard phrases and classification are:

Harmful if swallowed
Harmful to aquatic organisms
Do not breathe dust
Classification: Xn: harmful
Harmful to honeybees by direct contact, but no problems expected when not sprayed into flowering crop or when used as seed treatment.

The WHO hazard classification of imidacloprid is Class II, moderately hazardous (WHO 2002).

Formulations

Imidacloprid is registered and marketed world-wide for use in more than 120 countries and on over 160 crops. The main formulation types are SL, SC, WG, WS and FS.

Methods of analysis and testing

The analytical methods for imidacloprid (including identity tests) in TC, GR, WG, WS, SC, FS, OD, SL are full CIPAC methods. The method for GR was published in CIPAC Handbook H. The methods for TC, WG, WS, SC, FS were published in CIPAC handbook K; extensions to OD and SL were adopted by CIPAC 2004 but are not yet published. In these methods, imidacloprid is determined by reversed-phase HPLC, using external standardization and detection at 260 nm.

The analytical method for determination of impurities (Bayer method 2201-0308702-98) is also based on reversed-phase HPLC, using isocratic elution and UV-detection with certified reference substances for external standard calibration. Validation reports were provided.

Test methods for determination of physico-chemical properties of the technical active substance were OECD, USEPA or EC, while those for the formulations were CIPAC, as indicated in the specifications.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of active ingredient

The active ingredient is expressed as imidacloprid, in g/kg in solid formulations, and in g/kg or g/l at 20 ± 2C in liquid formulations.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from imidacloprid having impurity profiles similar to those referred to in Table 2, above.

Table A. Toxicology profile of imidacloprid technical material, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions	Result	Reference
Rat (m,f)	oral	single application; OECD 401, purity: 94.2%	LD_{50} = 424 mg/kg bw (m) 450 mg/kg bw (f)	18594
Rat	dermal	single application 24 h; OECD 402, purity: 94.2%	LD_{50} >5000 mg/kg bw	18594
Rat	inhalation	dust, 4 h exposure; OECD 403, purity: 95.3%	LC_{50} >5323 mg/m^3	16777
Rabbit	skin irritation	OECD 404, duration of exposure: 4 hours, purity: 94.2%	non-irritating	16455
Rabbit	eye irritation	OECD 405, duration of exposure: 24 hours, purity: 94.2%	non-irritating	16456
Guinea pig	skin sensitization	Maximization test, purity: 94.2%	non-sensitizing	16533

Table B. Toxicology profile of imidacloprid technical material based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions	Result	Reference
Rabbit	sub-acute, dermal	OECD 410, purity: 95.0%	NOAEL = 1000 mg/kg bw/day	19152
Rat	sub-acute, inhalation	OECD 412, purity: 95.2%	NOAEC = 5.5 mg/m^3 air	18199
Dog	sub-acute, feeding	OECD 409, 4 weeks, purity: 92.8%	NOAEL = 7.3 mg/kg bw/day	R4196
Rat	sub-chronic, feeding	OECD 408, 13 weeks, purity: 92.8%	NOAEL = 11 mg/kg bw/day	17279
Rat	sub-chronic, feeding	OECD 408, 13 weeks, purity: 95.3%	NOAEL = 14 mg/kg bw/day	18187
Mouse	sub-chronic, feeding	OECD 408, 13 weeks, purity: 92.8%	NOAEL = 17 mg/kg bw/day	17280
Dog	sub-chronic, feeding	OECD 409, 13 weeks, purity: 95.3%	NOAEL = 7.8 mg/kg bw/day	18732
Rat	chronic/oncogenicity, feeding	OECD 453, 24 months, purity: 94.3-95.3%	NOAEL = 5.7 mg/kg bw/day Not carcinogenic	19925
Mouse	oncogenicity, feeding	OECD 451, 24 months, purity: 95.3%	NOAEL = 65.5 mg/kg bw/day Not carcinogenic	19931; 20769
Dog	chronic, feeding	OECD 452, 52 weeks, purity: 94.9%	NOAEL = 15 mg/kg bw/day	R4856
Rat	2-generation reproduction toxicity	OECD 416, purity: 94.4-95.3%	NOAEL parents = 6.7 mg/kg bw/day, NOAEL developmental = 12.5 mg/kg bw/day	R5097
Rat (f)	developmental toxicity	OECD 414, purity: 94.2%	NOAEL maternal = 10 mg/kg bw/day, NOAEL developmental = 30 mg/kg bw/day, Not teratogenic	R5442

Species	Test	Duration and conditions	Result	Reference
Rabbit (f)	developmental toxicity	OECD 414, purity: 94.2%	NOAEL maternal = 8 mg/kg bw/day, NOAEL developmental = 24 mg/kg bw/day, Not teratogenic	R5443

Table C. Mutagenicity profile of imidacloprid technical material based on *in vitro* and *in vivo* tests

Species	Test	Conditions	Result	Reference
Salmonella microsome	Reverse mutation, *in vitro*	OECD 471, doses: 0-20-100-500-2500-12500 µg/plate, purity: 95.0%	negative	17577
Salmonella microsome	Reverse mutation, *in vitro*	OECD 471, doses: 0-8-40-200-1000-5000 µg/plate, purity: 96.0-96.3%	negative	20090
Salmonella microsome	Reverse mutation, *in vitro*	OECD 471, doses: 0-8-40-200-1000-5000 µg/plate, purity: 97.4%	negative	21775
Salmonella microsome	Reverse mutation, *in vitro*	OECD 471, doses: 0-312.5-625-1250-2500-5000 µg/plate, purity: 93.7%	negative	RA91002
Bacillus subtilis	Recombinant assay, *in vitro*	in compliance with MAFF (59 Nousan No. 4200), doses: 0-312.5-625-1250-2500-5000 µg/plate, purity: 94.7%	negative	RA90016
CHO-HGPRT	*in vitro*	OECD 476, doses: up to 125 µg/ml with S-9 mix and 1222 µg/ml without S-9 mix, purity: 95.2%	negative	17578
Saccharomyces cerevisiae	Mitotic recombination, *in vitro*	OECD 480, doses: 0-625-1250-2500-5000-10000 µg/ml, purity: 95.3%	negative	16832
Rat primary hepatocytes	UDS test, *in vitro*	OECD 482, doses: 750 µg/ml to 5.00 µg/ml, purity: 95.2%	negative	R4631
Chinese hamster ovary cells	Sister chromatid exchange, *in vitro*	OECD 473, doses: up to and including 5000µg/ml, purity: 95.2%	weakly positive	R4407
Chinese hamster ovary cells	Sister chromatid exchange, *in vitro*	OECD 473, doses: up to 400 µg/ml without S-9 mix and up to 1250 µg/ml with S-9 mix, purity: 95.2%	negative	BC1149
Human lymphocyte	Cytogenetic study, *in vitro*	OECD 473, up to 5200 µg/ml, purity: 95.2%	positive	18092
Chinese hamster bone marrow	Cytogenetic study, *in vivo*	OECD 475, dose: 2000 mg/kg, purity: 94.6%	negative	18557
Mouse bone marrow	Micronucleus test, *in vivo*	OECD 474, dose: 80 mg/kg, purity: 95.3%	negative	16837
Chinese hamster bone marrow	Sister chromatid exchange, *in vivo*	OPPTS 8705915, doses: 500-1000-2000 mg/kg, purity: 95.0%	negative	18093
Mouse germ-cell	Cytogenetic study, *in vivo*	OECD 483, dose: 80 mg/kg	negative	R5063

Table D. Ecotoxicology profile of imidacloprid technical material

Species	Test	Duration and conditions	Result	Reference
Leuciscus idus melanotus (golden orfe)	acute	96h, 21°C, purity: 95.3%	LC_{50} = 237 mg a.s./l	FO-1042
Oncorhynchus mykiss (rainbow trout)	acute	96h, 21°C, purity: 95.3%	LC_{50} = 211 mg a.s./l	FF-210
Daphnia magna (water flea)	acute	48h, 20°C static, purity: 95.4%	EC_{50} = 85 mg/l	100245
Daphnia magna (water flea)	chronic	21 d, 20°C static renewal, purity: 95.4%	NOEC = 1.8 mg/l	100247
Chironomus riparius (midge larvae)	chronic	28 d, 20°C static, purity: 98.4%	EC_{15} = 0.00225 mg/l	DOM 21035
Selenastrum capricornutum (green alga)	chronic	72h, 23°C, static, purity: 98.6%	ErC_{50} >100 mg/l LOEC <100 mg/l	DOM 20018
Earthworm	acute toxicity	14d, 22°C, purity: 92.8%	LC_{50} = 10.7 mg/kg dry soil	HBF/RG 63
Earthworm	chronic toxicity	reproduction, 8 wks, purity: 98.6%	NOEC ≥ 0.178 mg/kg (5 % O.M.)	HBF/RG 301
Apis mellifera (honey bee)	acute oral toxicity	48h, purity: 98.6% 48h and 96h, purity: 99.4% 48h, purity: 99.8%	LD_{50} >21 ng/bee LD_{50} = 40.9 ng/bee LD_{50} = 3.7 ng/bee	AH99.4.22.4 6400036 BAY 158/901384
Apis mellifera (honey bee)	acute contact toxicity	72h, purity: 98.6% 48h, 99.8%	LD_{50} = 129 ng/bee LD_{50} = 81 ng/bee	AH99.4.22.3 BAY 158/901384
Bobwhite quail	acute toxicity	14d, single dose, purity: 97.4%	LD_{50} = 152 mg a.s./kg bw	100059
Bobwhite quail	sub-acute toxicity	5d, purity: 98.4%	LC_{50} = 2225 ppm feed (14d) LC_{50} >5000 ppm feed (adult)	SXR/VB 57
Bobwhite quail	sub-chronic toxicity	20 wks, reproduction, purity: 94.8%	NOEC = 126 ppm feed	101203
Mallard duck	acute oral toxicity	14d, single dose, purity: 96.6%	LD_{50} = 283 mg a.s./kg b.w.	107354
Mallard duck	sub-acute toxicity	5d, purity: 97.4%	LC_{50} >4797 ppm feed	100238
Mallard duck	sub-chronic toxicity	20 wks, reproduction, purity: 95.8%.	NOEC = 128 ppm feed	103813-1
Japanese quail	acute oral toxicity	14d, single dose, purity: 95.3%	LD_{50} = 31 mg a.s./kg b.w.	VW-123
Japanese quail	sub-acute toxicity	5d, purity: 97.2%	LC_{50} = 392 ppm feed	GMU/VW-177

ANNEX 2: REFERENCES

Bayer CropScience document number	Year and title of report or publication details
100059	1990. Technical NTN 33893: An acute oral LD_{50} with Bobwhite quail.
100238	1990. Technical NTN 33893: A subacute dietary LC_{50} with Mallard ducks.
100245	1990. Acute Toxicity of NTN 33893 to *Daphnia magna.*
100247	1990. 21-Day Chronic Static Renewal Toxicity of NTN 33893 to *Daphnia magna.*
101203	1991. Technical NTN 33893: A One Generation Reproduction Study with Bobwhite Quail.
103813-1	1993. Technical NTN 33893: A One Generation Reproduction Study With Mallard Ducks.
107354	1996. NTN 33893 Technical: An acute oral LD_{50} with Mallards.
16455	1988. NTN 33893 - Study for irritant/corrosive potential on the skin (rabbit) according to OECD guideline no. 404.
16456	1988. NTN 33893 - Study for irritant/corrosive potential on the eye (rabbit) according to OECD guideline no. 405.
16533	1988. NTN 33893 technical - Study for skin sensitising effect on guinea pigs (maximisation test).
16777	1988. NTN 33893 - Study for acute inhalation toxicity in the rat in accordance with OECD guideline no. 403.
16832	1988. NTN 33893 - Test on S. cerevisiae D7 to evaluate for induction of mitotic recombination..
16837	1988. NTN 33893 - Micronucleus-test on the mouse to evaluate for clastogenic effects.
17279	1988. NTN 33893 - Pilot range-finding study for a chronic toxicity study on Wistar rats (ninety-eight day feeding study).
17280	1988. NTN 33893 - Pilot range-finding study for a cancerogenesis study on B6C3F1 mice (one hundred seven day feeding study).
17577	1989. NTN 33893 - Salmonella/microsome test to evaluate for point mutagenic effects.
17578	1989. NTN 33893 - Mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay in vitro.
18092	1989b. NTN 33893 - In vitro cytogenetic study with human lymphocytes for the detection of induced clastogenic effects.
18093	1989. NTN 33893 - Sister chromatid exchange in bone marrow of chinese hamsters in vivo.
18187	1989. NTN 33893 - Subchronic toxicity study on wistar rats (administration in the feed for 96 days).
18199	1989. NTN 33893 (proposed common name: Imidacloprid) - Subacute inhalation toxicity study on the rat according to OECD guideline no. 412.
18557	1989. NTN 33893 - In vivo cytogenetic study of the bone marrow in chinese hamster to evaluate for induced clastogenic effects.
18594	1989. NTN 33893 - Study for acute oral toxicity to rats.
18732	1990. NTN 33893 technical - Subchronic toxicity study on dogs in oral administration (thirteen-week feeding study).

Bayer CropScience document number	Year and title of report or publication details
19152	1990. NTN 33893 techn. - Study for subacute dermal toxicity in the rabbit.
19925	1991. NTN 33893 (proposed c.n.: Imidacloprid) - Chronic toxicity and cancerogenicity studies on Wistar rats (administration in food over 24 months).
19931	1991. NTN 33893 (proposed common name Imidacloprid) - Carcinogenicity study on B6C3F1 mice (administration in the food for 24 months).
20090	1991. NTN 33893 AMP - Salmonella/microsome test.
20769	1991. NTN 33893 (proposed common name: Imidacloprid) - Carcinogenicity study in B6C3F1 mice (supplementary MTD testing for study T5025710 with administration in diet over a 24-month period).
21775	1992. NTN 33893 AMP W - Salmonella/microsome test.
6400036	1999. Laboratory Testing for Toxicity (Acute Oral LD50) of NTN 33893 on Honey Bees *(Apis mellifera* L.) (Hymenoptera, Apidae).
AH99.4.22.3	1999. Honeybee *(Apis mellifera L.*) Contact Toxicity Study in the Laboratory with Imidacloprid techn.
AH99.4.22.4	1999. Honeybee *(Apis mellifera L.*) Oral Toxicity Study in the Laboratory with Imidacloprid techn.
BAY 158/901384	1990. The Acute Oral and Contact Toxicity to Honey Bees of Compound NTN 33893 Technical.
BC1149	1989. BAY NTN 33893 - Sister chromatid exchange assay in chinese hamster ovary cells.
CIPAC H	Dobrat, W. and Martijn, A. Eds. (1998): CIPAC Handbook volume H, Analysis of technical and formulated pesticides. Collaborative International Pesticides Analytical Council, Harpenden, U.K.
CIPAC K	Dobrat, W. and Martijn, A. Eds. (2003). CIPAC Handbook volume K, Analysis of technical and formulated pesticides. Collaborative International Pesticides Analytical Council, Harpenden, U.K.
DOM 20018	2000. Imidacloprid - Influence on the Growth of the Green Alga, *Selenastrum capricornutum*.
DOM 21035	2001. Influence of Imidacloprid (tech.) on Development and Emergence of Larvae of *Chironomus riparius* in a Water-Sediment System.
FAO/WHO 2002	Manual of the development and use of FAO and WHO specifications for pesticides. FAO plant production and protection paper 173. FAO, Rome, 2002.
FF-210	1988b. The acute toxicity of NTN 33893 techn. to Rainbow trout (*Salmo gairdneri*) in a static test.
FO-1042	1987. The Acute Toxicity of NTN 33893 techn. to Golden Orfe (*Leuciscus idus melanotus*) in a Static Test.
GMU/VW-177	1996. NTN 33893 techn.: 5-Day Dietary LC50 to Japanese quail.
HBF/Rg 301	1999. Influence of Low Concentrations of Imidacloprid (tech.) on the Reproduction of Earthworms (*Eisenia fetida)*.
HBF/Rg 63	1986. Acute toxicity of NTN 33893 (tech.) to earthworms.
NR1276	1989. Hydrolysis of NTN 33893.
PC1437	1996. Boiling Point of Imidacloprid (NTN 33893).
PC312	1993. Melting Point of Imidacloprid

Bayer CropScience document number	Year and title of report or publication details
PC313	1993. Vapour Pressure Curve of Imidacloprid.
PC317	1990. Dissociation constant of NTN 33893.
PC320	1993. Water solubility of Imidacloprid.
PC337	1989. Octanol/Water partition coefficient of NTN 33893.
PC339	1998. Thermal stability of the active ingredient NTN 33893.
PF3517	1988. Photodegradation of NTN 33893 in water.
R4196	1987. 28-day oral range-finding toxicity (feeding) study with NTN 33893 tech. in the dog.
R4407	1988. Clastogenic evaluation of NTN 33893 in an in vitro cytogenetic assay measuring sister chromatid exchange in chinese hamster ovary (CHO) cells.
R4631	1988. Mutagenicity test on NTN 33893 in the rat primary hepatocyte unscheduled DNA synthesis assay.
R4856	1989. 52-week oral toxicity (feeding) study with NTN 33893 technical in the dog.
R5063	1990. Mouse germ-cell cytogenetic assay with NTN 33893.
R5097	1990. Multiple generation reproduction study with NTN 33893 technical in rats.
R5442	1998. Embryotoxicity study (including teratogenicity) with NTN 33893 technical in the rat.
R5443	1988. Embryotoxicity study (including teratogenicity) with NTN 33893 technical in the rabbit.
RA90016	1990. NTN 33893 - Rec-assay with spores in the bacterial System.
RA91002	1991. NTN 33893 - Reverse mutation assay (Salmonella typhimurium and Escherichia coli).
SXR/VB 57	1996. Age-related five day dietary toxicity of imidacloprid to Bobwhite quail.
USEPA 1996	Pesticide tolerances. Imidacloprid. Federal Register, February 14, 1996, Vol. 61, No. 31 [Rules and Regulations], pages 5711 ff.
VW-123	1988. Acute oral LD_{50} of NTN 33893 to Japanese quail.
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification 2000-2002. WHO, Geneva, 2002.