WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

CLOTHIANIDIN

(*E*)-1-[(2-chloro-1,3-thiazol-5-yl)methyl]-3-methyl-2-nitroguanidine

World Health Organization

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

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

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

INTRODUCTION

WHO establishes and publishes specifications[2] 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. evaluation reports include 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 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.

[2] Publications available on the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, https://extranet.who.int/pqweb/vector-control-products

PART ONE: SPECIFICATIONS FOR CLOTHIANIDIN

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CLOTHIANIDIN

Clothianidin Information

ISO common name

Clothianidin (ISO 1750 published)

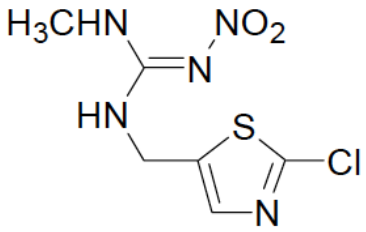
Chemical name

IUPAC (*E*)-1-[(2-chloro-1,3-thiazol-5-yl)methyl]-3-methyl-2-nitroguanidine

CA [*C*(*E*)]-*N*-[(2-chloro-5-thiazolyl)methyl]-*N′*-methyl-*N″*-nitroguanidine

Synonyms TI-435

Structural formula



Molecular formula

$C_6H_8ClN_5O_2S$

Relative molecular mass

249.7

CAS Registry number

210880-92-5

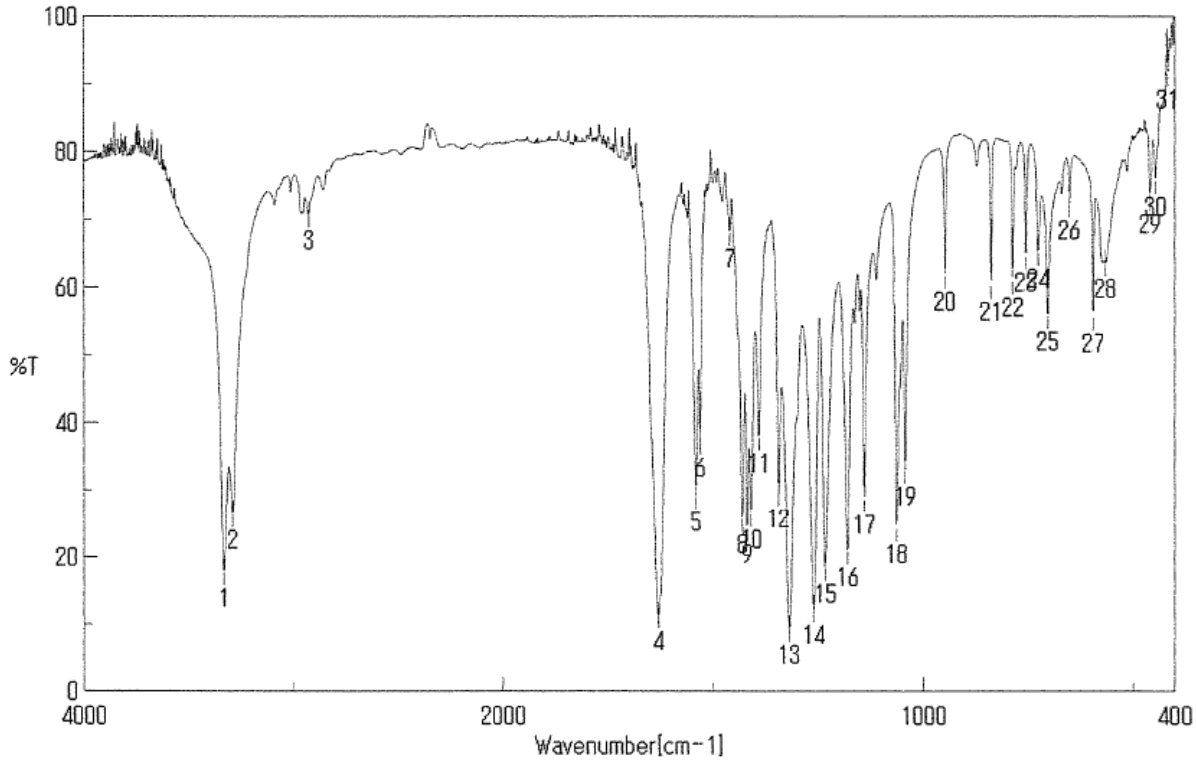
CIPAC number

738

Identity tests

Retention time in reversed phase HPLC, IR spectrum

Figure 1. IR spectrum of clothianidin



Clothianidin Technical Material - 738/TC/1 (September 2021)

WHO specification 738/TC/1 (September 2021*)

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 (738/2015.1, 738/2018.2, 738/2020.2). The specification 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 (738/2015.1, 738/2018.2, 738/2020.2), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of clothianidin together with related manufacturing impurities and shall be white to pale yellow crystalline powder free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (738/TC/M/2, CIPAC Handbook N, p.15, 2012)

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 **Clothianidin content** (738/TC/M/3, CIPAC Handbook N, p.15, 2012)

The clothianidin content shall be declared (not less than 960 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 Unit – Vector Control Product Assessment Team (PQT/VCP) website, https://extranet.who.int/pqweb/vector-control-products.

Clothianidin Technical Material - 738/TC/2 (January 2020)

WHO specification 738/TC/2 (January 2020*)

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 reports (738/2015.2, 738/2020.1, 738/2021). The specification should be applicable to TC produced by 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 TC produced by other manufacturers. The evaluation reports (738/2015.2, 738/2020.1, 738/2021), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of clothianidin together with related manufacturing impurities and shall be a white to pale yellow crystalline powder free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (738/TC/M/2, CIPAC Handbook N, p.15, 2012)

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 **Clothianidin content** (738/TC/M/3, CIPAC Handbook N, p.15, 2012)

The clothianidin content shall be declared (not less than 975 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities

3.1 By-products of manufacture or storage (Note 1)

Note 1 There are no relevant impurities to be controlled in the TC of the manufacturer identified in the evaluation reports 738/2015.2, 738/2020.1 and 738/2021,. However a compound (TI triazan, IUPAC name: (Z)-5-benzyl-1-methyl-N-nitro-1,3,5-triazinan-2-imine, CAS-Nr. 141856-57-7) may occur as a result of certain manufacturing processes. If this impurity would occur at > 3 g/kg (of clothianidin) in the products of other manufacturers, it would be designated as a relevant impurity and a clause would be required to limit its concentration.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, https://extranet.who.int/pqweb/vector-control-products

Clothianidin Water Dispersible Granules - 738/WG (September 2021*)

WHO specification 738/WG (December 2021*)

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 (738/2015.1, 738/2018.1, 738/2020.3). The specification should be applicable to relevant products of these manufacturers and those of any other formulators who use only TC from the evaluated sources. The specification is not an endorsement of those products nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (738/2015.1, 738/2018.1, 738/2020.3), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of technical clothianidin, complying with the requirements of the WHO specification 738/TC, in the form of off-white to brown granules with faint characteristic odour, together with carriers and any other necessary formulants. It shall be in the form of granules for application after disintegration and dispersion in water. The formulation shall be dry, free-flowing, nearly dust-free or essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (738/WG/M/2, CIPAC Handbook N, p.17, 2012)

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 **Clothianidin content** (738/WG/M/3, CIPAC Handbook N, p.18, 2012) (Note 1)

The clothianidin content shall be declared (500 g/kg) and, when determined, the average content measured shall not differ from that declared by more than ± 5%.

3 Physical properties

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

The formulation shall be completely wetted in 1 minute 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 the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, https://extranet.who.int/pqweb/vector-control-products.

3.3 **Dispersibility** (MT 174, CIPAC Handbook F, p.435, 1995)

Dispersibility: minimum 80% after 1 minute of stirring.

3.4 **Suspensibility** (MT 184.1, CIPAC Handbook P, p.245, 2021) (Notes 2 and 3)

Suspensibility: minimum 60% after 30 minutes in CIPAC Standard Water D at 25 ± 5°C.

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

Maximum: 70 ml after 1 minute.

3.6 **Dustiness** (MT 171.1, CIPAC Handbook P, p.235, 2021) (Note 5)

The formulation shall have a maximum collected dust of 30 mg by the gravimetric method.

3.7 **Flowability** (MT 172.2, CIPAC Handbook P, p.241, 2021)

At least 99% of the formulation 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 46.4, CIPAC Handbook P, p.22, 2021)

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

- wet sieve test (3.2)
- dispersibility (3.3)
- suspensibility (3.4)
- dustiness (3.6)
- attrition resistance (3.8).

Note 1 The sonication time may be increased, if necessary.

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 method MT 184.1.

Note 3 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method 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, chemical assay shall be the referee method.

Note 4 The mass of sample to be used in the test corresponds to a 0.5 % application rate. The test is to be conducted in CIPAC standard water D at 25 ± 5°C.

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

PART TWO: EVALUATIONS OF CLOTHIANIDIN

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FAO/WHO Evaluation Report 738/2021

Recommendations

The Meeting recommended the following:

(i) The clothianidin TC proposed by BASF and produced by a second source should be accepted as equivalent to the clothianidin reference profile of BASF.

(ii) The existing WHO specification for clothianidin TC (738/TC/2) should be extended to encompass the technical material produced by the additional source of BASF.

Appraisal

In August 2018, BASF acquired ownership of the clothianidin data package and became de facto the reference manufacturer and the owner of the clothianidin WHO specification previously owned by Bayer CropScience. The production of clothianidin TC according to the WHO specification remains at Bayer manufacturing site but is now operated under contract for BASF.

The Meeting considered data and information submitted by BASF for the determination of the equivalence for clothianidin TC in support of an extension of the existing WHO specification 738/TC/2 to the technical material produced by an additional source of BASF. The data submitted were in accordance with the requirements of the manual on development and use of FAO and WHO specifications for pesticides [FAO/WHO Manual, 2016] The draft specification and the supporting data were provided by BASF in 2021.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on clothianidin and all impurities present at or above 1g/kg, and their manufacturing limits in the TC. Mass balances ranged from 994.3 to 999.6 g/kg in the 5-batch data. The declared minimum clothianidin content (980 g/kg) was higher than that of the WHO specification 738/TC/2. The maximum limits for the impurities were supported by the 5-batch data and were statistically justified.

The confidential data submitted to WHO on the manufacturing process and purity / impurity profile of clothianidin are identical to those submitted for registration in Brasil [Bonilha, 2021].

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted in the reference profile. Manufacturing limits for impurities occurring in the material under consideration did not exceed the limits in the reference profile with more than the acceptable amounts. Four new impurities were analysed; however, these impurities were either not detected or were detected below the LOQ of 0.5 g/kg and were not considered relevant. Clothianidin TC manufactured by BASF's second source was found to not significantly differ from the impurity profile of the reference source.

The Meeting noted that an intermediate in an early step of the process had some structural similarities with a potential impurity in the clothianidin TC produced by BASF: the TI-triazan (WHO specification 738/TC/2, January 2020). The study on five batches

produced in the new source did include both intermediates in the list of impurities; however, none were detected with an LOQ of 0.5 g/kg.

The same method of analysis was used for the determination of the active substance in clothianidin TC for the alternative source as well as for the reference source BASF. The organic impurities were determined by HPLC with UV detection, and Karl Fischer coulometric titration was used to determine residual water. For the analysis of the impurities in clothianidin TC in this alternative source, the same method was used with respect to separating conditions (column, eluent, gradient); however, two additional impurities were analysed. The LOQ for the analytes in the analytical methods was 0.5 g/kg respectively; for water determination, the LOQ was 1.0 g/kg.

Data on melting point for the technical material (99.7%) were provided. Toxicity data were available for the mutagenicity profile (Ames test) derived from the technical grade active ingredient manufactured by the proposer with a purity of 98.2%. OECD test method was used. The *in vitro* reverse mutation study on the BASF' second source of clothianidin TC did not indicate a positive response.

Based on the higher purity and similarity of the impurity profiles of the second source of clothianidin TC compared to the reference source, and considering the absence of mutagenicity, the Meeting concluded that the BASF second source of clothianidin TC is equivalent to the clothianidin reference profile supporting the existing specification 738/TC/2 on basis on Tier-1.

Supporting Information for Evaluation Report 738/2021

Table 1. Chemical composition and properties of clothianidin technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.43%–99.96%
Declared minimum clothianidin content	980 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	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 and/or TK	172.7°C (decomposition starting at 195°C)	99.7	[DSC “OECD 102”]	M-471394-01-1

Annex 1: Hazard Summary Provided by the Proposer

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from Clothianidin 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 the technical clothianidin (alternative source) based on *in vitro* and *in vivo* tests

Species	Test	Purity % note	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium	Reverse mutation assay Ames test *in vitro*	98.2	Guideline OECD 471 S. typhimurium: TA98, TA100, TA102, TA 1535, TA 1537 Experiment I 0-156.25-312.5-625-1250-2500-5000 µg/plate (-/+ 5% S9 mix) Experiment II 0-51.2-128-320-800-2000-5000 µg/plate (-/+ 10% S9 mix)	Negative	481-1-06-8038

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
WHO 2018		2018	https://extranet.who.int/pqweb/sites/default/files/vcp-documents/WHOVC-SP_Clothianidin_2018.pdf
FAO/WHO Manual, 2016		2016	Manual on development and use of FAO and WHO specifications for pesticides, First edition -third revision https://extranet.who.int/pqweb/vector-control-product/document/manual-development-and-use-fao-and-who-specifications-pesticides
Bonilha, 2021		2021	e-mail from Estela Bonilha [estela.bonilha@agricultura.gov.br] to László Bura [Laszlo.bura@efsa.europa.eu] on 17. 05. 2021., 19:43
CIPAC, N	Martijn A and Dobrat W	2012	CIPAC Handbook Volume N. Analysis of Technical and Formulated Pesticides, p.18, 2012
M-471394-01-1	Winkler, S.	2013	Clothianidin (TI 435, AE 1283742), technical substance: Melting point, boiling point. Siemens AG, Germany. GLP. Unpublished.
481-1-06-8038	Nagane, R.M.	2014	Bacterial reverse mutation test of clothianidin TC using Salmonella typhimurium. JAI Research Foundation, India. GLP. Unpublished

CLOTHIANIDIN

FAO/WHO Evaluation Report 738/2020.3

Recommendations

The Meeting recommended that the existing WHO specification for clothianidin water dispersible granules (WG) should be extended to encompass the corresponding product of Tagros Chemicals India Private Limited.

Appraisal

The Meeting considered data and supporting information submitted in 2019 by Tagros Chemicals India Private Limited (Tagros) to support the equivalence of their clothianidin WG with the existing WHO specification 738/WG (WHO, 2018). The data submitted were in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (2016, third revision of the first edition). The reference specification and supporting data for clothianidin WG had been provided by Sumitomo. The clothianidin technical material of Tagros was accepted as equivalent to the reference profile of Sumitomo clothianidin TC based on Tier-1 and Tier-2 data (FAO/WHO evaluation report 738/2020.2).

Data were submitted on determination of all physical-chemical and technical properties included in the existing WG specification and all complied with the current specification. The analytical method for the active ingredient was reversed-phase HPLC with UV detection, similar to the CIPAC method 738/WG/M/3. Physical-chemical properties data were provided for appearance, wettability, wet sieve test, dispersibility, suspensibility, persistent foam, dustiness, flowability, attrition resistance and stability at elevated temperature. Quality control data were also submitted and showed that the clothianidin WG from Tagros fully comply with the requirements of the existing specification.

The Meeting recommended to extend the existing WHO specification for clothianidin WG to the WG produced by Tagros Chemicals India Private Limited.

The Meeting also recommended to editorially update the CIPAC methods for suspensibility (MT 184.1 instead of MT 184), flowability (MT 172.2 instead of MT 172.1) and stability at elevated temperature (MT 46.4 instead of MT 46.3). These updated methods published in CIPAC Handbook P are considered to provide equivalent results with the previous versions.

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
WHO 2018		2018	WHO specifications for clothianidin https://extranet.who.int/pqweb/vector-control-product/document/clothianidin-2018
FAO/WHO Manual, 2016		2016	Manual on development and use of FAO and WHO specifications for pesticides, First edition - third revision https://extranet.who.int/pqweb/vector-control-products/manual-amendments
CIPAC N	Martijn A and Dobrat W	2012	CIPAC Handbook Volume N. Analysis of Technical and Formulated Pesticides, p.18, 2012.
CIPAC F	Martijn A and Dobrat W	1995	CIPAC Handbook Volume F. Physico-chemical Methods for Technical and Formulated Pesticides.
CIPAC J	Martijn A and Dobrat W	2000	CIPAC Handbook Volume J. 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 O	Cardeal de Oliveira MC and Garvey J	2017	CIPAC Handbook Volume O. Analysis of Technical and Formulated Pesticides.
RCC 9146	Uma Ganesh	2019	Determination of Color, Odor and Physical Sate for Clothianidin 50% WG. Study Number 9146, RCC Laboratories India Private Limited, GLP, Unpublished.
RCC 9147	Uma Ganesh	2019	Determination of Wettability for Clothianidin 50% WG. Study Number 9147, RCC Laboratories India Private Limited, GLP, Unpublished.
RCC 9148	Uma Ganesh	2019	Determination of Foam Persistence for Clothianidin 50% WG. Study Number 9148, RCC Laboratories India Private Limited, GLP, Unpublished.
RCC 9149	Uma Ganesh	2019	Determination of Flowability for Clothianidin 50% WG. Study Number 9149, RCC Laboratories India Private Limited, GLP, Unpublished.
9150	Uma Ganesh	2019	Accelerated Storage Stability and Corrosion Characteristics of Clothianidin 50% WG. Study Number 9150, RCC Laboratories India Private Limited, GLP, Unpublished.

CLOTHIANIDIN

FAO/WHO Evaluation Report 738/2020.2

Recommendations

The Meeting recommended the following:

(i) The clothianidin TC proposed by Tagros Chemicals India Private Limited should be accepted as equivalent to the clothianidin reference profile of Sumitomo.

(ii) The existing FAO specification 738/TC/1 for clothianidin TC should be extended to the technical material produced by Tagros Chemicals India Private Limited.

(iii) The existing WHO specification 738/TC/1 for clothianidin TC should be extended to the technical material produced by Tagros Chemicals India Private Limited.

Appraisal

The Meeting considered data and supporting information submitted in 2019 by Tagros Chemicals India Private Limited (Tagros) for the determination of the equivalence of their clothianidin TC with the Sumitomo reference profile (FAO/WHO specification 738/TC/1) (WHO, 2018). The data submitted were in accordance with the requirements of the manual on development and use of FAO and WHO specifications for pesticides (2016, third revision of the first edition). The reference specification and supporting data for clothianidin TC had been provided by Sumitomo.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on clothianidin and all impurities present at or above 1 g/kg and their manufacturing limits in the TC.

The confidential information (manufacturing process, purity and impurity profile) submitted to FAO/WHO was confirmed by the Australian authorities (APVMA) as being identical to that submitted for registration in Australia (Margerison, 2020).

The manufacturing process, impurity profile and five batch analyses were compared with the data of the reference profile of Sumitomo. The manufacturing process of Tagros is different than that used by the first source of Sumitomo, considered as the reference source. However, it is somewhat similar to the process of the second source of Sumitomo, considered equivalent to the first one. The Tagros process leads to a reduced amount of impurities and higher purity of the technical clothianidin produced. The proposer declared the minimum active ingredient content of their clothianidin TC as 980 g/kg, which is higher than the purity of the existing FAO/WHO specification 738/TC/1 for the clothianidin TC from Sumitomo (960 g/kg). Mass balances ranged from 992.0 to 995.2 g/kg in the five batch data. The maximum limits for the impurities were supported by the five batch data and were statistically justified.

The analytical method for the active ingredient content was reversed-phase HPLC with UV detection, similar to CIPAC method 738/TC/M/3. The organic impurities were determined by HPLC with UV detection and GC-MS, and Karl Fischer coulometric titration was used to determine residual water.

The impurity profiles of the clothianidin TC of Tagros and Sumitomo are different, with Tagros containing less impurities. Comparing the Tagros profile with the Sumitomo

reference profile, there is one common impurity and two new impurities, one being a residual solvent.

The Meeting considered the possible relevance of these two new impurities.

- The QSAR analysis of impurities provided by Tagros showed that the toxicity of impurities is comparable with this of the active ingredient. The *in-vitro* reverse mutation study with clothianidin TC did not indicate a positive response. A dermal sensitization study (Local Lymph Node Assay) done with one of the technical materials from the five batch analysis was also provided. The study was conducted in compliance with GLP and according to OECD Test Guideline 429. Clothianidin TC did not demonstrate dermal sensitization potential in the mouse LLNA.
- Tagros had initially specified a manufacturing limit of 2 g/kg for the residual solvent. A maximum acceptable concentration of 2 g/kg was calculated by the Meeting taking into account the worst-case-possible hazard, which in the present case is acute oral toxicity, the reference dose for oral exposure derived by the US EPA, and the hazard classification by ECHA and UN GHS for this residual solvent. At the request of the Meeting, the proposer provided additional quality control data showing that the content of this potentially relevant impurity was lower than 1 g/kg in their clothianidin TC. The Meeting therefore concluded that this impurity was not relevant in the technical material of Tagros.

The Meeting concluded that the clothianidin TC of Tagros Chemicals India Private Limited should be accepted as equivalent to the reference profile of Sumitomo clothianidin TC based on Tier-1 and Tier-2 data.

Supporting Information
for
Evaluation Report 738/2020.2

Physico-chemical properties of clothianidin

Table 1. Chemical composition and properties of clothianidin 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 99.20-99.52% and percentages of unknowns were 0.48-0.80%.			
Declared minimum clothianidin content	980 g/kg			
Relevant impurities ≥ 1 g/kg and maximum limits for them	None			
Relevant impurities < 1 g/kg and maximum limits for them	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	174 - 176°C	98.62	-	-

Formulations and co-formulated active ingredients

The present application is for determination of equivalence of clothianidin technical.

Methods of analysis and testing

The analytical method for the active ingredient was reversed-phase HPLC with UV detection, similar to CIPAC method 738/TC/M/3.

The methods for determination of organic impurities are based on analysis by reverse phase liquid chromatography using UV detection and quantification by external standard calibration and gas chromatography with mass spectrometry detection (GC-MS).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as clothianidin.

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 clothianidin 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 clothianidin technical material based on *in vitro* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Results	References
Salmonella typhimurium TA1535, TA98, TA100 and TA1537 *Escherichia coli* WP2uvrA (pKM101)	Bacterial reverse mutation test	98.40	OECD 471 The bacterial tester strains were exposed to clothianidin technical in triplicate at 50, 158, 500, 1581 and 5000 µg/plate using the direct plate incorporation mode of exposure in the initial mutation assay and using the pre-incubation mode of exposure in the confirmatory mutation assay in the presence and absence of metabolic activation system (S9 fraction prepared from Aroclor 1254 induced rat liver).	Negative Clothianidin technical was not mutagenic in this Bacterial Reverse Mutation Assay up to the highest OECD 471 recommended dose of 5000 µg/plate, under the conditions of testing employed.	G18447

Table 3. *In vivo* Local Lymph Node Assay (LLNA, OECD Guideline 429) sensitization test data of clothianidin technical material

Species	Test	Purity %	Guideline, duration, doses and conditions	Results	References
Local lymph node assay (LLNA) in CBA/Ca mice	Dermal sensitization study	98.62	OECD Guideline for Testing of Chemicals, Test Guideline No. 429, Skin Sensitization: Local Lymph Node Assay. 22 July 2010	The test item clothianidin technical did not demonstrate dermal sensitization potential in the mouse LLNA, as the lymph nodes draining the area of topical application did not elicit a proliferative response greater than the 3X threshold.	G19423

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
WHO 2018		2018	WHO specifications for clothianidin https://extranet.who.int/pqweb/vector-control-product/document/clothianidin-2018
FAO/WHO Manual, 2016		2016	Manual on development and use of FAO and WHO specifications for pesticides, First edition - third revision https://extranet.who.int/pqweb/vector-control-products/manual-amendments
Margerison, 2020		2020	Notice of approval of an active constituent, Agricultural and Veterinary Chemicals Code (Agvet Code), as set out in the Schedule to the Agricultural and Veterinary Chemicals Code Act 1994, No. 122206.
ECHA			https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/37212
CIPAC N	Martijn A and Dobrat W	2012	CIPAC Handbook Volume N. Analysis of Technical and Formulated Pesticides, p.18, 2012.
G18231	Ravikanth Gogineni	2019	Five Batch Analysis of Clothianidin Technical. Study Number G18231, Eurofins Advinus Limited, GLP, Unpublished.
G18447	Divyashree K	2019	Clothianidin Technical: Bacterial Reverse Mutation Test. Study Number G18447, Eurofins Advinus Limited, GLP, Unpublished.
G19423	Kammar, Umesh	2020	Clothianidin Technical: local lymph node assay (LLNA) in CBA/Ca mice, OECD Guideline for Testing of Chemicals, Test Guideline No. 429 (2010): Skin Sensitization: Local Lymph Node Assay, GLP, Unpublished.

CLOTHIANIDIN

CLOTHIANIDIN + DELTAMETHRIN

FAO/WHO Evaluation Report 738/2020.1

Recommendations

The Meeting recommended the following:

(i) The change of manufacturer of the FAO reference specifications for clothianidin TC and FS from Bayer CropScience to BASF SE should be noted by FAO.

(ii) The editorially updated specifications for clothianidin TC and FS should be adopted by FAO.

(iii) The change of manufacturer of the WHO reference specification for clothianidin TC from Bayer CropScience to BASF SE should be noted by WHO.

(iv) The editorially updated specifications for clothianidin TC and clothianidin + deltamethrin WP-SB should be adopted by WHO.

Appraisal

The Meeting noted that in a press release dated on April 26, 2018[1], BASF SE, Germany (BASF) announced the acquisition of clothianidin TC and certain formulated products from Bayer CropScience (BCS). Before this, BCS was the holder of one of the reference FAO and WHO specification for clothianidin TC and of the FAO specification for clothianidin FS (FAO/WHO evaluation reports 738/2015).

Later on, FAO and WHO were contacted by BCS in an official letter dated October 31, 2019, and in an e-mail dated December 10, 2019, stating the following:

- The intellectual property rights for clothianidin TC and certain formulations used in agriculture from BCS had been acquired by BASF.
- The manufacturing of clothianidin TC and certain formulations used in agriculture which are now under control of BASF continue to comply with all specifications clauses and limits as per the data package in support of clothianidin that had been evaluated by JMPS in 2015.
- BASF assures the continued support and stewardship for clothianidin TC and certain formulations acquired from BCS.
- The clothianidin + deltamethrin WP-SB formulation used in public health remains the property of BCS.

The Meeting therefore concluded that both the manufacturing sites and processes for manufacturing clothianidin TC and certain formulated products used in agriculture were not affected by the transition from BCS to BASF.

The Meeting also noted that the specifications for clothianidin FS and clothianidin + deltamethrin WP-SB needed some editorial updates to reflect the latest versions of certain physical-chemical test methods (suspensibility: MT 184.1 instead of MT 184,

[1] https://www.basf.com/global/en/media/news-releases/2018/04/p-18-182.html

stability at elevated temperature: MT 46.4 instead of MT 46.3, both considered to provide equivalent results with the previous versions).

For these reasons, the Meeting recommended that BASF should be noted as the new holder of the reference specifications for clothianidin TC previously owned by BCS and formulated products used in agriculture and that these specifications should be considered as the new reference specifications.

CLOTHIANIDIN

FAO/WHO Evaluation Report 738/2018.2

Recommendations

The Meeting recommended the following.

(i) The clothianidin TC proposed by Sumitomo Chemical Co., Ltd. and produced by a second source should be accepted as equivalent to the clothianidin reference profile.

(ii) The existing WHO specification for clothianidin TC should be extended to the technical material produced by the additional source of Sumitomo Chemical Co., Ltd.

Appraisal

The Meeting considered data and supporting information submitted in 2017 by Sumitomo Chemical Co., Ltd. (Sumitomo) for the determination of the equivalence for clothianidin TC (WHO specification 521/TC, September 2017). The data submitted were in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (2016, 3rd revision of the First Edition). Sumitomo wanted to add an additional site for the manufacturing of their clothianidin TC on their behalf and to their specification. The reference specification and supporting data for clothianidin had been provided by Sumitomo.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1g/kg, and their manufacturing limits in the TC. The manufacturing process of the second source is somewhat different than that used by the first one. Both processes are based on a 3 step reaction, with the new process leading to reduced amount of impurities and higher purity of the technical clothianidin produced [Sumitomo, 101].

Mass balances ranged from 998.4 - 1002.8 g/kg in the 5-batch data. The maximum limits for the impurities were supported by the 5-batch data and were statistically justified. The proposer declared the minimum purity of the clothianidin TC produced by the new source as 980 g/kg - somewhat higher than the existing clothianidin Sumitomo FAO and WHO specifications (960 g/kg). The organic impurities were determined by HPLC with UV detection and Karl Fischer coulometric titration was used to determine residual water.

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted in the reference profile. Clothianidin TC manufactured by Sumitomo's second source was found to not significantly differ from the impurity profile of the reference first source: it showed a similar impurity profile with lower limits for all impurities. The study on *in-vitro* reverse mutation with clothianidin TC from the second source did not indicate a positive response.

However the Meeting noted that an intermediate in an early step of the process had some structural similarities with a potential impurity in the clothianidin TC produced by

Bayer CropScience - the TI-triazan (FAO specification 738/TC, October 2016 and WHO specification 738/TC, July 2018).

The first study on 5 typical batches produced in the new source did not include this intermediate in the list of impurities identified and quantified at or above 1 g/kg [Sumitomo, 101]. The Meeting therefore concluded that levels of this suspected potential impurity could by slightly below 1 g/kg at maximum. Later on, a second study was submitted where the same batches had been reanalyzed for possible presence of low concentrations of this compound. The triazan could not be detected with a quantification limit of 0.24 g/kg [Sumitomo, THP-0131].

Initially, when this triazan intermediate was toxicologically screened using the structure-activity relationships (SAR) software Derek Nexus (Derek Nexus: 6.0.0, Nexus: 2.2.0), it predicted a skin sensitization effect. The same prediction resulted from screening the structurally similar Bayer's TI-triazan (see FAO/WHO evaluation report 738/2015) when analyzed with Derek Nexus. This TI-triazan was tested positive for skin sensitization in the guinea pig maximization test according to Magnusson and Kligman.

The Meeting therefore requested Sumitomo to provide futher studies to elucidate the sensitization alert on the triazan intermediate by the SAR software.

Sumitomo later on provided three different Local Lymph Node Assays (LLNA) with clothianidin TC from the second source to inform on its skin sensitizing potential. The study THT-0365 was conducted in compliance with GLP and according to OECD Test Guideline 429, while studies THT-0369 and G2170 did not conform to neither and were therefore considered as supporting information. All three studies were negative for skin sensitization. However, whereas study THT-0365, a reduced LLNA (rLLNA) test, using 25 % clothianidin and study G2170 had both some experimental shortcomings, the third study [THT-0369], a rLLNA with 25 % clothianidin TC from the second source spiked with 0.2 % (relative to clothianidin) triazan intermediate, was found to conclusively demonstrate that clothianidin TC from the second source is devoid of skin sensitizing potential

For these reasons, the Meeting concluded that even an improbable worst case presence of the triazan intermediate in the TC would not elicit a sensitizing reaction and therefore the clothianidin TC produced in the second source should be accepted as equivalent to the reference TC by Tier-1 and Tier-2.

The Meeting also noted the Sumitomo's intention to have the equivalence for the WHO specification only.

The Meeting also proposed to update the CIPAC method for suspensibility in the WG specification (MT 184.1 instead of MT 184, which are considered as equivalent), but Sumitomo replied that they prefer to get some experience with their WG formulation to be sure that the specification limit is still valid using MT 184.1.

Supporting Information
for
Evaluation Report 738/2018.2

Physico-chemical properties of clothianidin

Table 1. Chemical composition and properties of clothianidin technical material (TC) from second source

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.84 – 100.28 % and percentage of unknows were less than 0.1% each.			
Declared minimum clothianidin content	980 g/kg			
Relevant impurities ≥ 1 g/kg and maximum limits for them	None			
Relevant impurities **<** 1 g/kg and maximum limits for them	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	172.2ºC - 174.2ºC	100.06%	OECD 102 (TG-DTA)	SCC Report No. THP-0111, Reference No.103

Annex 1: Hazard Summary Provided by the Proposer

Notes.

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

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

Table 2. *In vitro* mutagenicity test data of clothianidin TC from second source

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium / Escherichia coli	Reverse mutation assay 'Ames test' *in vitro*	99.0%	JMAFF 12 - Nousan 8147; OECD 471; US EPA OPPTS 870.5100 *S. typhimurium*: TA 98, TA 100, TA 1535, TA 1537 *E. coli*: WP2uvrA$^-$313-625-1250-2500-5000 µg/plate (+/-S9 mix)	Negative	[105]

Table 3. *In vivo* Local Lymph Node Assay (LLNA, OECD Guideline 429) sensitization test data of clothianidin TC from second source

Study	GLP	Dosage	Result	Study number
Reduced LLNA	Yes	25 % clothianidin TC (only dose tested)	Negative	THT-0365
LLNA	No	5, 10, 25 and 50% clothianidin TC	Negative	G2170
Reduced LLNA	No	25 % clothianidin TC spiked with 0.2% Triazan (only dose tested)	Negative	THT-0369 (G2178)

Annex 2: References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
2989W Reference No.101	Harris Shen, and Lisa Mannella	2017	5-Batch Analysis for Clothianidin Technical Grade. SCC report No. THP-0105, GLP. EAG Laboratories-Hercules, USA, unpublished.
Reference No.102	Keisuke Ozaki	2017	Information on the Batches Used in the study of Five Batch Analysis of Clothianidin Technical Grade. SCC report No. THP-0106, Sumitomo Chemical Co., Ltd., 2017, unpublished.
Reference No.103	Yu Yanagisawa	2017	Melting point/Melting range of Clothianidin technical grade. SCC report No. THP-0111, Sumitomo Chemical Co., Ltd., unpublished.
Reference No.104	Mika Koga and Fumio Nishioka	2017	Physico-chemical properties of Clothianidin water dispersible granules. SCC report No.THF-0070, Sumitomo Chemical Co., Ltd., unpublished.
B170681, Reference No 105	Munehiro Nakagawa	2017	Bacterial Reverse Mutation Study of Clothianidin Technical Material. SCC report No. THT-0339, GLP, LSI Medience Corporation, Japan. unpublished.
THP-0131	Yu Yanagisawa	2018	Batch Analysis of Clothianidin Technical Grade for M-Triazan. Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Japan. Non-GLP, unpublished.
THT-0365		2018	Clothianidin technical material: Skin Sensitization Study in Mice - Local Lymph Node Assay, GLP, unpublished.
THT-0369		2018	Skin sensitization test of Clothianidin spiked with an impurity (Triazan) in mice (Local Lymph Node Assay). Non-GLP, unpublished.
G2170		2018	Skin sensitization test of Clothianidin technical material in mice (Local Lymph Node Assay). Non-GLP, unpublished.

CLOTHIANIDIN

FAO/WHO Evaluation Report 738/2018.1

Recommendations

The Meeting recommended that the revised specification for clothianidin WG proposed by Sumitomo Chemical Co., Ltd., and as amended, should be adopted by WHO.

Appraisal

The Meeting considered data submitted by Sumitomo Chemical Co., Ltd. on the generation of persistent foam of the clothianidin 50 WG formulation. The WHO specifications for clothianidin TC and WG were published in September 2017. The test method for persistent foam was the new CIPAC method MT 47.3 with a limit of 70 ml after 1 minute.

The Meeting was requested by the company to reconsider the use of the CIPAC method MT 47.3 at the maximum use rate based on the following reasons:

- The generation of persistent foam using MT 47.3 is susceptible to a considerable variability due to some differences in headspace dimensions in the cylinder used compliant with the requirements of MT 47.3.
- The use rate of the product is clearly higher than for agricultural products.

The company provided data (Nishioka F. and Kozuki Y., 2018) showing that the foam produced and remaining after 1 minute is dependent on the headspace dimensions and the use rate. Briefly, the higher the use rate is and the larger the distance from the liquid to the stopper is, the higher is the volume of foam remaining.

The company therefore requested the Meeting to reconsider the use concentration of MT 47.3 for the clothianidin 50 WG and proposed to deviate from the maximum use rate of typically 1.5 to 2.0 % while maintaining the limit of 70 ml after 1 minute. By fixing the use rate at 0.5 %, the inherent variability of foam produced by the WG and using MT 47.3 can be clearly reduced (Nishioka F., 2018).

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	Nishioka F. and Kozuki Y.	2018	Persistent foam of clothianidin 50 WG. Draft revised specification and supporting data for clothianidin water dispersible granules. Sumitomo Chemical Company, Japan, March 2018, not published.
	Nishioka F.	2018	Persistent foam of clothianidin water dispersible granules, Sumitomo Chemical Company, Japan, April 2018, not GLP and not published.

CLOTHIANIDIN

FAO/WHO Evaluation Report 738/2015.2

Recommendations

The Meeting recommended that the specifications for clothianidin TC and FS proposed by Bayer CropScience, as amended, should be adopted by FAO.

Appraisal

The Meeting considered data on clothianidin submitted by Bayer CropScience (BCS) in support of FAO specifications for the technical material and a FS formulation.

The insecticide clothianidin was developed by Takeda Chemical Industries in Japan in the 1990. This also explains the code number allocated to that compound - TI-435 - , with "TI" standing for Takeda Industries. Takeda was later incorporated into Sumitomo, and clothianidin was further developed jointly by Sumitomo Chemical Company (SCC) and Bayer CropScience (BCS). Therefore, some of the nonpublished studies referenced in the hazard summary are owned by Sumitomo, some by Bayer. This may explain the unusual situation, that two reference specifications for the same compound were developed and published - the first one for Sumitomo in 2009, and the second for Bayer in 2015 due to the fact that two slightly different specifications each with supporting data were evaluated and adopted by FAO and WHO (see below).

Clothianidin is a neonicotinoid insecticide that controls insects by acting as an agonist at the nicotinic acetylcholine receptor, affecting the synapses in the insect central nervous system. Clothianidin is not under patent.

Clothianidin was evaluated by the FAO/WHO JMPR in 2010 [JMPR, 2010] and JMPR agreed to re-evaluate the clothianidin residue definition in 2011.

It was evaluated by US EPA, the results were published in the US Federal Register [EPA, 2011]. Clothianidin 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 2006. It was included in Annex I with a minimum purity of 960 g/kg [CR, 2011].

The data for clothianidin were evaluated in support of FAO specifications based on the draft specifications and the supporting data provided by Bayer CropScience in 2008 and a revised submission was received in November 2011 and April 2015. The FAO specifications for clothianidin were first published in 2011 and last modified in 2015 for TC, SC, GR, SG, FS and WG based on submission of data by Sumitomo Chemical Co., Ltd. [FAO, 2015].

The supporting data on clothianidin TC, WS and FS formulations were in accordance with the requirements of the second revision of the first edition of the Manual on development and use of FAO and WHO specifications for pesticides [FAO/WHO Manual] and supported the proposed specifications. In the updated submission BCS no longer supported the WS specification [Bascou, 2012].

A statement was provided by the German pesticides regulatory authority confirming that the confidential data on the manufacturing process and declaration of composition

submitted to the FAO were the same as those submitted to the national regulatory authority [Hänel, 2015].

Clothianidin is a white to cream coloured crystalline powder. It is not volatile and has a melting point of 176.8 °C. It is slightly soluble in water at 0.33 g/l at 20°C. It is not fat soluble and is not likely to bioaccumulate with a log P_{ow} of circa 0.9. It is considered to be stable to hydrolysis at all environmentally relevant pHs. It undergoes rapid photolysis with a half lifehalf-life of 3.3 hours at pH 7 at 25°C. Clothianidin is a strong base with a pK_a of 11.

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present below or above 1 g/kg and their manufacturing limits in the TC. Mass balances were 99.57-100.24% in the 5-batch data.

At the 2009 JMPS Meeting it was discussed whether or not there are two reference sources of clothianidin or if Sumitomo is the reference source and Bayer should be considered equivalent on the basis of the additional toxicological data on their impurities. As Sumitomo and BCS utilize different manufacturing processes leading to different minimum content of the active ingredient, and, more importantly, the two TC have entirely different impurity profiles, the Meeting considered that two separate specifications should therefore be developed for the TC produced by Sumitomo and BCS. The minimum content of the TC produced by BCS is 975 g/kg, however based on the submitted data an even higher minimal purity could have been specified.

In the submission Bayer CropScience proposed that there are no impurities of toxicological relevance. The impurity TI-435-triazan was reported to be sensitizing [M-020895-01-1] and according to the criteria defined in the FAO/WHO Manual, (Determination of the relevance or non-relevance of impurities and Appendix J) it would be relevant. The 2009 JMPS meeting considered that the impurities, with the exception of TI-435-triazan are not relevant. To decide on the relevance of this impurity a study using OECD 406 (Directive 92/69/EC, Method B.6) on the Bayer technical material was requested. The Meeting noted that BCS had tested the impurity only, however a test is needed on the TC with a representative content of the impurity. In order to demonstrate the non-relevance of the impurity TI-435-triazan contained in the clothianidin batches at the specified maximum concentration of 0.3%, BCS conducted a skin sensitization study, that has proved that under the conditions of the maximization test, clothianidin TC is not a sensitizer [M-424556-01-2]. As a consequence there is no need to consider TI-435-triazan as a relevant impurity. Nevertheless this impurity may be potentially relevant in other products where the concentration would be higher. The Meeting agreed to add a footnote in the specification to reflect that and a method should be available for the determination of the impurity. The HPLC method for the determination of the impurity was submitted in May 2015 [AM025915MP1].

The recent submission of April 2015 contained one new impurity in comparison to the data submitted in 2011. Additional data were requested about the relevance of this impurity.

BCS confirmed that the new impurity identified was present in BCS clothianidin TC in batches used in nontoxicity studies, in batches used in genotoxicity studies as well as in skin sensitization study. It has been identified only recently due to the improvement

of the analytical method. Quantification of this formerly unspecified impurity with reference standard resulted in its specification as significant impurity.

The extension of the scope of the HPLC method for the determination of clothianidin in TC and FS formulations was accepted as a full CIPAC method in 2011. [CIPAC Handbook N].

The proposed specifications for TC and FS were essentially in accordance with the requirements of the FAO/WHO Manual. If the FS formulation is to be used diluted, the clause for persistent foam is given on the basis of a 30% w/v concentration which may be the used concentration and it was already agreed in the published specification, too. The clause for suspensibility is given on basis on the highest and lowest concentration of use which means that the reference to the CIPAC method in the specification may exceed the upper range of concentration which is broadly speaking about 10 %. The test for suspensibility is based on the sedimentation of formulation particles in a water column and determination of a possible accumulation of particles in the lowest 10 % after a given time. Any use concentration that is near or greater than the lower 10 % is not within the scope of the method.

The Meeting considered the differences in the descriptions and in the clauses of the previously published specifications for clothianidin FS proposed by Sumitomo and BCS. The Meeting concluded that the description clauses and limits in the clauses for ‘Persistent foam’, ‘Suspensibility’ and ‘Adhesion to seeds’ in the published and proposed specifications justify two different FS specifications.

Supporting Information
for
Evaluation Report 738/2015.2

Uses

Clothianidin is a systemic insecticide which acts as acute contact and stomach poison. Clothianidin belongs to the chemical class of neonicotinoid insecticides. The mode of action is by agonizing the insect nicotinic acetylcholine receptors in the nervous system of pest insects.

Clothianidin has a broad spectrum of activity, particularly against sucking insects such as aphids, leaf hoppers, thrips and white flies. Furthermore, various species of beetles (e.g. *Atomaria* spp., *Agriotes lineatus*, *Diabrotica* spp.) and some species of flies (e.g. *Oscinella* frit and *Pegomyia* spp.) and cut worm (e.g. *Agrotis* spp.) are effectively controlled. Clothianidin formulations are used in seed treatments as well as for foliar spray applications. BCS clothianidin is currently registered in the Europe, Northern and Southern America and Africa.

Identity of the active ingredient

ISO common name (ISO 1750, published)

Clothianidin

Chemical name(s)
IUPAC

(*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine

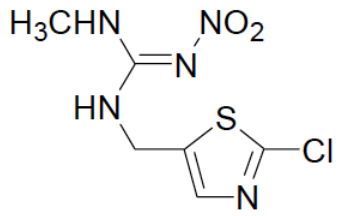
CA

[*C*(*E*)-*N*-[(2-chloro-5-thiazolyl)methyl]-*N*'-methyl-*N*''-nitroguanidine

Synonyms

TI-435

Structural formula



Molecular formula

$C_6H_8ClN_5O_2S$

Molar mass

249.7 g/mol

CAS Registry number

210880-92-5

CIPAC number

738

Identity tests

HPLC UV-detection and IR

Note: Sumitomo Chemical Company is the owner of the initial data package for clothianidin. Bayer CropScience has a commercial arrangement with Sumitomo and has a letter of access to the initial data package.

Physico-chemical properties of clothianidin

Table 1. Physico-chemical properties of pure clothianidin

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study reference
Vapour pressure	1.3×10^{-10} Pa at 25°C 3.8×10^{-11} Pa at 20°C (extrapolated)	99.7	OECD 104 EC A.4	M-026219-03-2
Melting point, boiling point and/or temperature of decomposition	Melting point: 176.8°C Boiling point: decomposes before boiling Decomposition temperature: 242°C	99.7	OECD 102 EC A.1 (DSC)	M-025309-02-1
Solubility in water	pH 7: 0.327 g/L at 20°C determined in Milli-Q water (resistivity at least 17 megaohms)	99.7	OECD 105 (equivalent to EEC A.6, flask method)	M-026209-04-1
Octanol/water partition coefficient	pH 4 log P_{OW} = 0.89 at 25 °C pH 7 log P_{OW} = 0.91 at 25 °C pH 10 log P_{OW} = 0.87 at 25 °C	99.7	EEC A8	M-041740-01-1
Hydrolysis characteristics	Half-life = 14.4 days at 50°C at pH 9 Half-life = 3.7 days at 62°C at pH 9 Half-life = 0.7 days at 74°C at pH 9 Stable at 50°C at pH 4 and 7 (<10% degradation after 5 days) Stable at 25°C at pH 5, 7 and 9 (<5% degradation after 33 days)	>98.0	EPA Series 161-1 EEC method C.7	M-048047-01-1

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study reference
Photolysis characteristics	Half-life 3.3 hours in sterile buffer pH 7 at 25°C Equivalent to 0.6 days of summer solar exposure at Pheonix, Arizona, US (40° latitude) Equipment: Suntest® Light source: Xenon lamp with UV cut-off filter at 290 nm. Intensity (300-800 nm) = 1027 W/m^2 by radiometry. Photonflow density = 125.86 X 1014 s^{-1} cm^{-2}. Quantum yield (Φ) = 0.014	>99.0	EPA Series 161-2 SETAC	M-023549-02-1 M-010153-02-1
Dissociation characteristics	pK_a = 11.09 (at 20°C)	99.7	OECD 112 (spectrophoto-metric method)	M-026209-04-1
Solubility in organic solvents	< 0.00104 g/l *n*-heptane at 25°C 1.32 g/l dichloromethane at 25°C 0.0128 g/l xylene at 25°C 0.938 g/l *n*-octanol at 25°C 15.2 g/l acetone at 25°C 2.03 g/l ethyl acetate at 25°C 6.26 g/l methanol at 25°C	99.7	OECD 105 (equivalent to EEC A.6, flask method)	M-026209-04-1

Table 2. Chemical composition and properties of clothianidin 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 99.57 - 100.24 % and percentages of unknowns were <0.2 %.
Declared minimum clothianidin 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
Melting temperature range of the TC	172 - 174°C (98.0%) [M-427760-01-1]

Methods of analysis and testing

The analytical method for the active ingredient in TC is HPLC using UV detection at 225 nm and internal standardization. The clothianidin content of the TC and FS formulations is determined by the CIPAC method 783/TC/M/3 and 783/FS/M/3.

The method(s) for determination of impurities are based on a HPLC method using UV detection and internal standardisation.

There are no relevant impurities in clothianidin technical material.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EPA, and/or EC while those for the formulations were for example, CIPAC, as indicated in the specifications.

Formulations and co-formulated active ingredients

The main formulation types available are FS and WS.
Clothianidin can be co-formulated with other insecticides or fungicides like *beta*-cyfluthrin, fluoxastrobin, imidacloprid, methiocarb, prothioconazole, tebuconazole, thiodicarb, thiram or triazoxide.

These formulations are registered and sold in Europe, Northern and Southern America, Africa.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed and quantified as clothianidin.

Annex 1: Hazard Summary Provided by the Proposer

Note:

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

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

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

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Rat male/female	Oral	96.0	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 401; Directive 92/69/EC Method B.I.; Directive 92/18/EEC, L97; US-EPA Section 81-1; OPPTS 870. 1100	LD_{50} = > 5000 mg/kg bw	M-027393-01-1
Rat male/female	Acute neurotoxicity gavage	95.2-96.0	US-EPA-FIFRA, Guideline 81-8(SS); US-EPA OPPTS 870.6200 0-100-200-400 mg/kg bw/d	NOELs (male / female) Overall = > 60 / 100 mg/kg bw Neurotoxicity = > 400 mg/kg bw/d not neurotoxic	M-027750-03-1
Mouse male/female	Oral	96.0	OECD 401; Directive 92/69/EC, Method B. 1.; Directive 92/18/EEC, L97; US-EPA Section 81-1; US-EPA OPPTS 870.1100	LD_{50} = 389 mg/kg bw (m) 465 mg/kg bw (f)	M-027394-01-1
Rat male/female	Dermal	96.0	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 402; Directive 92/69/EC, Method B.3.; Directive 92/18/EEC, L97; US-EPA Section 81-2; US-EPA OPPTS 870.1200 24 h semi-occlusive conditions	LD_{50} = > 2000 mg/kg bw	M-027396-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Rat male/female	Inhalation	96.0	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 403; Directive 92/69/EC, Method B.2.; Directive 92/18/EEC, OJEC, L97; USA-EPA Section 81-3; US-EPA OPPTS 870.1330 4.5 h exposure	LC_{50} = > 6.141 mg/L	M-027390-01-1
Rabbit male/female	Skin irritation	96.0	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 404; Directive 92/69/EC, Method B.4.; Directive 92/18/EEC L97; US-EPA Section 81-5; US-EPA OPPTS 870.2500 4 h exposure	Non-irritating	M-027402-01-1
Rabbit male	Eye irritation	96.0	OECD 405; Directive 92/69/EC, Method B.5.; Directive 92/18/EEC L97; US-EPA Section 81-4; US-EPA OPPTS 870.2400 24 h exposure	Non-irritating	M-027400-01-1
Guinea pig	Skin sensitization	96.0	OECD 406; Directive 92/69/EC, Method B.6.; Directive 92/18/EEC L97; US-EPA Section 81-6; US-EPA OPPTS 870.2600	Non-sensitizing	M-027406-01-1

Table 4. Toxicology profile of technical clothianidin based on repeated administration (sub-acute to chronic)

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Rat male/female	Sub-acute feeding	97.5	OECD 407; Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.7.; EPA Guideline in Subdivision F. Hazard Evaluation: Human and Domestic Animals, November 1984; JMAFF 59 Nohsan No. 4200 4 weeks 0-1250-2500-5000-7500 ppm (equivalent to: 0-120-249-475-602 mg/kg bw/d (male), 0-137-228-454-689 mg/kg bw/d (female))	NOAEL = 120 / 137 mg/kg bw/d LOEL = 249 / 228 mg/kg bw/d	M-027408-01-1
Mouse male/female	Sub-acute feeding	97.5	OECD 407; Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.7.: EPA Guideline in Subdivision F. Hazard Evaluation: Human and Domestic Animals; JMAFF Nohsan No. 4200 deviation: duration 4 weeks 0-500-1000-2000-4000 ppm (equivalent to: 0-90-190-383-683 mg/kg bw/d (male) 0-122-248-491-619 mg/kg bw/d (female))	NOAEL = 190 / 248 mg/kg bw/d LOEL = 383 / 491 mg/kg bw/d	M-027413-01-1
Dog female	Dose-range finding (palatability) feeding	95.2	Exposure to increasing dose levels 0 (for 11 days) - 3000 / 4000 / 5000 ppm (days 1-3 / 4-8 / 9-11) (equivalent to: 0- 51.1/50.8/51.8 mg/kg bw/d)	NOEL = 51.8 mg/kg bw/d	M-027385-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Dog male/female	Dose-range finding feeding	95.2	Directive 88/302/EEC, Method B.27; US-EPA FIFRA Subdivision F, Section 82-1; US-EPA 870.3150; JMAFF 59 Nohsan No. 4200; mainly in accordance to OECD 409 4 weeks, 3 animals/sex/group 0-1250-2500-5000 ppm (equivalent to: 0-36.3-35.8-62.4 mg/kg bw/d (male) 0-35.6-52.3-57.4 mg/kg bw/d (female))	NOAEL = 36.3 / 35.6 mg/kg bw/d LOEL = 35.8 / 52.3 mg/kg bw/d	M-027342-01-1
Rat male/female	Sub-acute dermal	95.2	US-EPA OPPTS 870.3200; JMAFF 59 Nohsan No. 4200; Directive 88/302/EEC (OJEC No. L 133/27) Part B; OECD 410 6 hrs/day, 28 days 0-100-300-1000 mg/kg bw/d	NOEL = > 1000 mg/kg bw/d	M-027480-01-1
Rat male/female	Sub-chronic feeding	95.3	FIFRA 82-1; TSCA 798.2650; US-EPA OPPTS 870.3100, OECD 408; JMAFF 59 NohSan No. 4200; Directive 87/302/EEC, part B 97 days 0-150-500-3000 ppm (equivalent to: 0-9.0-27.9-202 mg/kg bw/d (male) 0-10.9-34.0-254 mg/kg bw/d (female))	NOAEL = 27.9 / 34.0 mg/kg bw/d LOEL = 202 / 254 mg/kg bw/d	M-027268-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Dog male/female	Sub-chronic feeding	95.2	US-EPA-FTFRA Section. 82-1; US-EPA-OPPTS OPPTS 870.3150; OECD 409; JMAFF 59 Nohsan No. 4200; Directive 88/302/EEC (OJEC No. L 133/12), Part B 13 weeks 0-325-650-1500-2250 ppm (equivalent to: 0-9.2-19.3-40.9-58.2 mg/kg bw/d (male) 0-9.6-21.2- 42.1-61.8 mg/kg bw/d (female))	NOAEL = 19.3 / 21.2 mg/kg bw/d LOEL = 40.9 / 42.1 mg/kg bw/d	M-036499-02-1
Dog male/female	Sub-chronic feeding	95.2	EPA-FIFRA Guideline 83-1; EPA-OPPTS Guideline Section 870.4100; OECD 452; JMAFF 59 Nohsan No. 4200, Directive 88/302/EEC, Part B 52 weeks 0-325-650-1500-2000ppm (equivalent to: 0-7.8-16.6-36.3-46.4 mg/kg bw/d (male) 0-8.5-15.0-40.1-52.9 mg/kg bw/d (female))	NOAEL = 36.3 / 40.1 mg/kg bw/d LOEL = 46.4 / 52.9 mg/kg bw/d	M-036542-01-1
Rat male/female	Chronic oncogenicity feeding	95.2-95.5	JMAFF 59 NohSan No. 4200; OECD 453; EEC 88/302/EEC; FIFRA F, 83-5; OPPTS 870.4300 104 weeks 0-150-500-1500-3000 ppm (equivalent to: 0-8.1-27.4-82-157 mg/kg bw/d (male) 0-9.7-32.5-97.8-193 mg/kg bw/d (female))	NOAEL = 27.4 / 9.7 mg/kg bw/d LOEL = 82 / 32.5 mg/kg bw/d not carcinogenic	M-031986-02-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Mouse male/female	Oncogenicity feeding	95.2	JMAFF 59 NohSan No. 4200; OECD 451; EEC 88/302/EEC; FIFRA F, 83-2; OPPTS 870.4200 78 weeks 0-100-350-700/2000/2500/2000/1800 (week 1-4/ 5-10/ 11-34/ 35-termination 2000 ppm (m)/ 1800 ppm (f)) -1250 ppm (equivalent to: 0-13.5-47.2-171.4-251.9 mg/kg bw/d (male) 0-17.0-65.1-215.9-281.1 mg/kg bw/d (female))	NOAEL = 47.2 / 65.1 mg/kg bw/d LOEL = 171.4 / 215.9 mg/kg bw/d not carcinogenic	M-032363-02-1
Rat male/female	Pilot reproduction one generation	95.2-96.0	US-EPA-FIFRA, Section 158.340, No. 83-4: US-EPA-TSCA, 40 CFR Section 798.4700: Guideline 87/302/EEC; OECD 416; J MAFF, 59 NohSan No. 4200 pre-mating 8 weeks 0-50-100-500-1000 ppm (equivalent during pre-mating to: 3.2-3.5 / 5.9-6.8 / 31.7-36.4 / 66.6 - 70.8 mg/kg bw/d)	NOEL repro. = > 66.6 mg/kg bw/d	M-027255-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Rat male/female	Reproduction 2-generation	95.3-96.0	US-EPA, OPPTS 870.3800; Directive 91/414/EEC; OECD 416; JMAFF, 59 NohSan No. 4200 0-150-500-2500 ppm (equivalent to both generations combined: 0-10.2-32.7-179.6 mg/kg bw/d (male) 0-11.8-37.9-212.9 mg/kg bw/d (female)	Parental NOEL = 32.7/11.8 mg/kg bw/d LOEL = 179.6/37.9 mg/kg bw/d Reproductive NOEL = >179.6/ >212.9 mg/kg bw/d Offspring NOEL = 10.2/11.8 mg/kg bw/d LOEL = 32.7/37.9 mg/kg bw/d	M-031280-02-1
Rat female	Dose-range finding developmental toxicity	96.0	US-EPA OPPTS 870.3700 gestation days 6-19 0-125-250-500-1000 mg/kg bw/d	Maternal NOAEL = not established LOEL = 125 mg/kg bw/d Developmental NOAEL = 125 mg/kg bw/d LOEL = 250 mg/kg bw/d	M-027430-02-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Rat female	Developmental toxicity	95.2	Guideline 88/302/EEC; OECD 414; US-EPA OPPTS 870.3700; JMAFF 59 NohSan no. 4200 gestation days 6-19 0-10-40-125 mg/kg bw/d	Maternal NOEL = 10 mg/kg bw/d LOEL = 40 mg/kg bw/d Developmental NOAEL = 125 mg/kg bw/d LOEL = > 125 mg/kg bw/d not teratogenic	M-027416-01-1
Rabbit female	Dose-range finding developmental toxicity	96.0	US-EPA OPPTS 870.3700 gestation days 6-28 0-62.5-125-250-500 mg/kg bw/d	Maternal NOAEL = 62.5 mg/kg bw/d MTD < 125 mg/kg bw/d Developmental NOAEL > 62.5 mg/kg bw/d	M-027436-02-1
Rabbit female	Developmental toxicity	95.2-95.5	Guideline 88/302/EEC, OECD 414; US-EPA OPPTS 870.3700; JMAFF 59 NohSan no. 4200 gestation days 6-28 0-10-25-75-100 mg/kg bw/d	Maternal NOEL = 10 mg/kg bw/d LOEL = 25 mg/kg bw/d Developmental NOAEL = 75 mg/kg bw/d LOEL = 100 mg/kg bw/d not teratogenic	M-027442-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Rat male/female	Sub-chronic neurotoxicity feeding	95.3-96.0	US-EPA-FIFRA, Guideline 82-5(b); US-EPA OPPTS 870.6200 0-150-1000-3000 ppm equivalent to: 0-9.2-60-177 mg/kg bw/d (male) 0-10.6-71-200 mg/kg bw/d (female)	NOELs (male / female) Overall = 60 / 71 mg/kg bw d Neurotoxicity = >177 / >200 mg/kg bw/d not neurotoxic	M-027986-01-1
Rat male/female	Developmental neurotoxicity feeding	95.5-95.9	US-EPA OPPTS 870.6300; US-EPA Guideline 83-3; US-EPA Pesticide Assessment Guidelines, Subdivision F, addendum 10, neurotoxicity day 0 of gestation until 22 days post partum 0-150-500-1750 ppm (equivalent to: 0-12.9-42.9-142 mg/kg bw/d (gestation) 0-27.3-90.0-299 mg/kg bw/d (lactation)	NOELs (gestation / lactation) Maternal = 42.9 / 90.0 mg/kg bw/d Developmental = 12.9 / 27.3 mg/kg bw/d Developmental neurobehavioral effects > 142 / > 299 mg/kg bw/d	M-027178-02-1

Table 5. Mutagenicity profile of technical clothianidin based on *in vitro* and *in vivo* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Salmonella typhimurium / Escherichia coli	Reverse mutation assay 'Ames test' *in vitro*	95.2-96.0	Guideline 92/69/EEC, Method B.I4.; OECD 471, US-EPA FIFRA section 84-2; JMAFF 59 NohSan no. 4200; Japan Ministry of Labour No. 77 *S. typhimurium*: TA 98, TA 100, TA 1535, TA 1537; *E. coli*: WP2uvrA$^-$ 0-50-150-500-1500-5000 µg/plate (+/- S9 mix)	Positive (+S9 mix in TA 1535 only)	M-036520-01-1
Salmonella typhimurium / Escherichia coli	Reverse mutation assay 'Ames test' *in vitro*	≥ 99.0	Guideline 92/69/EEC, Method B.14.; JMAFF 59 NohSan no. 4200 *S. typhimurium*: TA 98, TA 100, TA 1535, TA 1537; *E. coli*: WP2uvrA$^-$ 0-313-625-1250-2500-5000 µg/plate (+/-S9 mix)	Negative	M-036420-02-1
Salmonella typhimurium	Reverse mutation assay 'Ames test' *in vitro*	95.2	Directive 92/69/EEC, Method B.14.; OECD 471; US-EPA 712-C-96-219, OPPTS 870.5265 *S. typhimurium*: TA 98, TA 100, TA 102, TA 1535, TA 1537 0-16-50-158-500-1581-5000 µg/plate/tube (+/-S9 mix) TA 102: 0-16-32-48-64-80-96-112 µg/plate (+/-S9 mix)	Negative	M-009777-02-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Salmonella typhimurium	Reverse mutation assay 'Ames test' *in vitro*	98.6 (batch NLL 6100-3), 96.2 (batch 30034708)	Directive 92/69/EEC, Method B.14.; OECD 471; US- EPA 712-C-96-219, OPPTS 870.5265 *S. typhimurium*: TA 1535 Batch NLL 6100-3: 0-1000-2000-3000-4000-5000 µg/plate, Batch 30034708: 3000-5000-7000 µg/plate, 0-1000-2000-4000-6000-8000 µg/tube each batch +/- S9 mix, pre-incubation technique	Negative	M-009769-02-1
Bacillus subtilis	DNA repair assay *in vitro*	≥ 99.0	JMAFF 59 Nohsan No. 4200 0-375-750-1500-3000-6000 µg/disc (+/- S9 mix)	Negative	M-036407-02-1
Chinese hamster lung (CHL) cells	Chromosome aberration assay in vitro	96.0	OECD 473; Directive 92/69/EEC, Annex V, Part B, Method B.10.; US-EPA FIFRA section 84-2 ; JMAFF 59 Nohsan No 4200 1st assay: 0-156.25-312.5-625-937.5-1250-1875 µg/mL 2nd assay: 0- 39 to 1875 µg/mL exposure 4 – 48 hrs, recovery 0 – 18 hrs, +/- S9 mix	Positive (+/- S9 mix)	M-036479-02-1
Chinese hamster V79 cells	Chromosome aberration assay in vitro	98.0	Directive 92/69/EEC, Method B.10.; OECD 473; US-EPA 712-C-98-223, OPPTS 870.5375 - S9 mix: 0-100-200-300-350-400-700-1000-1200-1400 µg/mL + S9 mix: 0-500-1000-1600-1800-2000 µg/mL	Weakly positive (+ S9 mix)	M-053960-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Mouse lymphoma cells	Gene mutation in mammalian cells in vitro	96.0	OECD 476; Directive 87/303/EEC no. LI 33, Method B. 14.; EPA FIFRA section 84-2; JMAFF 59 Nohsan No 4200 0-312.5-625-1250-1667-2500 µg/mL (+/-S9 mix) 0-300-600-1200-1600-2000 µg/mL (-S9 mix) 0-600-1200-1600-2000-2400 µg/mL (+S9 mix)	Positive	M-036462-02-1
Chinese hamster lung V79 cells	Gene mutation in mammalian cells in vitro	95.2	Directive 88/302/EEC; OECD 476; US-EPA712-C-96-221, OPPTS 870.5300 0-156-313-625-1250-2500-5000 µg/mL (+/-S9 mix)	Negative	M-009761-02-1
Mouse bone marrow cells	Chromosome aberration assay Micronucleus test in vivo	96.0	OECD 474; Directive 92/69/EEC, no. L383A, Method B.12.; EPA section 84-2; JMAFF 59 NohSan No. 4200 0-25-50-100 mg/kg bw (oral)	Negative	M-036435-02-1
Rat hepatocytes	Unscheduled DNA synthesis in vivo	95.2-96.2	In accordance with OECD draft guideline ‘OECD Guidelines for Testing of Chemicals, Proposal for a New Guideline, "Genetic Toxicology: DNA Damage and Repair/ Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells In Vivo’ and in addition Directive 88/302/EEC; OECD 482; US-EPA PB 84-233295 0-2500-5000 mg/kg bw (oral)	Negative	M-009751-03-1

Additional toxicity studies of technical clothianidin manufactured by Bayer CropScience

Species	Test	Purity %	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study Reference
Salmonella typhimurium	Reverse mutation assay 'Ames test' *in vitro*	99.8	OECD 471; 2000/32/EC, Annex 4D; US EPA 712-C-98-247, OPPTS 870.5100 *S. typhimurium*: TA 98, TA 100, TA 102, TA 1535, TA 1537 0-33-100-333-1000-2500-5000 µg/plate (+/- S9)	Negative	[M-103604-02-1]
Chinese hamster lung V79 cells	Chromosome aberration assay *in vitro*	99.8	OECD 473; Directive 2000/32/EC, Annex 4A; EPA 712-C-98-223, OPPTS 870.5375 0-200-400-600-750-1000-1500 µg/mL (- S9 mix) 0-500-750-1000-1500 µg/mL (+ S9 mix)	Negative	[M-103614-01-1]
Chinese hamster lung V79 cells	Gene mutation in mammalian cells *in vitro*	99.8	OECD 476; Directive 2000/32/EC, Annex 4E; US EPA 712-C-98-221, OPPTS 870.5300 0-78.1-156.3-312.5-625-1250-2500 µg/mL (+/- S9 mix)	Negative	[M-103610-01-1]
Mouse bone marrow cells	Micronucleus test *in vivo*	99.8	US-EPA 712-C-98-226, OPPTS 870.5395; OECD 474; Directive 2000/32/EC, Annex 4C 0-75-150-300 mg/kg bw (intraperitoneal)	Negative	[M-103617-01-1]
Rat hepatocytes	Unscheduled DNA synthesis *in vivo*	99.8	OECD 486, EC Directive 2000/32, B.39 0-1000-2000 mg/kg bw (oral)	Negative	[M-103622-01-1]
Guinea pig	Skin sensitization	99.3	OECD 406; Guideline 96/54/EC, Method B.6.; US-EPA 712-C-03-197, OPPTS 870.2600	Non-sensitizing	[M-424556-01-2]

Table 6. Ecotoxicology profile of technical clothianidin

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Bobwhite quail *(Colinus virginianus)*	Acute oral	96.0	14d, US EPA Subdivision E, Guideline 71-1 (1982)	LD50 > 2000 mg /kg bw	M-027064-01-1
Japanese quail *(Coturnix coturnix japonica)*	Acute oral	97.6	14d, US EPA Subdivision E, Guideline 71-1 (1982)	LD50 = 430 mg /kg bw	M-027285-01-1
Bobwhite quail *(Colinus virginianus)*	dietary	96.0	8d, OECD 205 (1984)	LC50 > 5200 mg/kg diet	M-027059-01-1
Mallard duck *(Anas platyrhynchos)*	dietary	96.0	8d, OECD 205 (1984)	LC50 > 5200 mg/kg diet	M-027068-01-1
Bobwhite quail *(Colinus virginianus)*	Reproduction	97.6	20 weeks, OECD 206	NOEC = 500 mg/kg diet	M-027293-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Mallard duck *(Anas platyrhynchos*	Reproduction	97.6	20 weeks, OECD 206	NOEC = 500 mg/kg diet	M-027289-01-1
Rainbow trout *(Oncorhynchus mykiss)*	acute	96.0	96h, static, limit test, OECD 203	LC50 > 100 mg/L	M-027029-02-1
Bluegill *(Lepomis macrochirus)*	acute	97.6	96h, static, limit test, OECD 203	LC50 > 120 mg/L	M-031285-01-1
Fathead minnow *(Pimephales promelas)*	Chronic, ELS	97.6	33d, flow-through, US EPA Subdivision E, Guideline 72-4 (1982), US EPA OPPTS draft guideline 850.1400 (1996)	NOEC = 20 mg/L	M-031516-01-1
Sheepshead minnow *(Cyprinodon variegatus)*	acute	97.6	96h, static, OECD 203	LC50 > 102.5mgLl	M-027244-01-1
water flea *(Daphnia magna*)	acute toxicity	97.6	48h, static, OECD 202	EC_{50} > 120 mg/L	M-031283-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
water flea *(Daphnia magna*)	chronic toxicity	96.0	21d, semi-static, OECD 211	NOEC = 0.120 mg/L	M-027071-02-1
Mysid shrimp (*Mysidopsis bahia*)	acute	97.6	96h, flow-through	LC50 = 0.053 mg/L	M-019551-01-1
Mysid shrimp (*Mysidopsis bahia*)	chronic, life cycle	97.6	39d, flow-though, OPPTS 850.1350	NOEC = 0.0097 mg/L	M-026384-01-1
Oyster (*Crassostrea virginica*)	acute	97.6	96h, flow-through; OPPTS 850.1025	EC50 > 129.1 mg/L	M-028515-01-1
Green alga *(Scenedesmus subspicatus)*	chronic toxicity	96.0	72h, static, OECD 201	ErC50 > 270 mg/L	M-027041-02-1
Green alga *(Selenastrum capricornutum)*	chronic toxicity	97.6	72h, static, OECD 201	ErC50 > 120 mg/L	M-026366-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Sediment dwelling invertebrates *(Chironomus riparius)*	acute	97.6	48h, static	EC50 = 0.029 mg/L	M-032142-01-1
Sediment dwelling invertebrates *(Chironomus riparius)*	chronic	96.1	28d, static, BBA	EC15 = 0.00072 mg/L	M-011874-01-1
Duckweed *(Lemna gibba)*	chronic	97.6	14d, static renewal, US EPA OPPTS guideline 850.4400 (1996)	EC50 > 121 mg/L	M-031279-01-1
Honeybee (*Apis mellifera*)	Acute oral Acute contact	96.0	48h, EPPO guideline n° 170 (1992)	Oral LD50 = 0.004 µg/bee Contact LD50 = 0.044 µg/bee	M-027051-01-1
Parasitoid (*Aphidius rhopalosiphi*)	Laboratory	50.3 (WG50)	48h, tested as formulated product WG 500 g/kg SETAC (1994)	100 % mortality at 60 g a.s./ha	M-027182-01-1
Predatory mite (*Typhlodromus pyri*)	Laboratory	50.3 (WG50)	14d, tested as formulated product WG 500 g/kg SETAC (1994)	69 % mortality at 60 g a.s./ha 97 % effect on reproduction at 60 g a.s./ha	M-027179-01-1

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study reference
Ground dwelling predatory species (*Aleochara bilineata*)	Laboratory	50.3 (WG50)	28d, tested as formulated product WG 500 g/kg SETAC (1994)	89 % corrected mortality at 75 g a.s./ha	M-027200-01-1
Foliage dwelling predatory species (*Chrysoperla carnea*)	Laboratory	50.3 (WG50)	28d, tested as formulated product WG 500 g/kg SETAC (1994)	97 % corrected mortality at 60 g a.s./ha	M-027198-01-1
Earthworm (*Eisenia fetida*)	acute	96.0	14d, OECD 207	LC50 = 13.2 mg/kg soil	M-027046-01-1
Nitrogen transformation Soil respiration		49.3 (WG50)	28d, OECD 216 and 217	No significant effects (<25%) at 750 g a.s./ha (equivalent to 1 mg a.s./kg soil)	M-027297-01-1
Terrestrial plants (10 species)	Seedling emergence	49.3 (WG50)	14d, OPPTS 850.4100 and 850.4225	NOEC = 225 g a.s./ha	M-026377-01-1
Terrestrial plants (10 species)	Vegetative vigour	49.3 (WG50)	14d, OPPTS 850.4150	NOEC = 225 g a.s./ha	M-026381-01-1

Clothianidin was evaluated by the FAO/WHO JMPR in 2010 and an acceptable daily intake (ADI) of 0–0.1 mg/kg bw per day was established and estimated the acute reference dose (ARfD) as 0.6 mg/kg bw.
Clothianidin has not been evaluated by the WHO IPCS.

In the EU the classification process is not yet finalized. In conclusion the only valid classification for the time being (September 2016) is the one proposed by the company based on the current EU regulation EC 67/548 as follows:

Pictograms:	
Signal word:	Warning
Hazard statements:	H302: Harmful if swallowed
	H400: Very toxic to aquatic life
	H410: Very toxic to aquatic life with long lasting effects
Precautionary statements:	P270: Do not eat, drink or smoke when using this product
	P301+312: IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell
	P273: Avoid release to the environment
	P501: Dispose of contents/container in accordance with local regulations

Annex 2: References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
JMPR 2010		2010	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report11/Clothianidin.pdf
EPA 2011		2011	Federal Register Vol. 76, No. 86 (4.05.2011) http://www.gpo.gov/fdsys/pkg/FR-2011-05-04/pdf/2011-10706.pdf
CR 2011		2011	Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 – OJ L 153, 11.6.2011 p. 40.
FAO 2015		2015	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Clothianidin_2015_01.pdf
FAO/WHO Manual		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/fileadmin/templates/agphome/documents/Pests_Pesticides/PestSpecsManual2010.pdf
Bascou 2012		2012	E-mail from Jean-Philippe Bascou, Product Chemistry Management, Bayer CropScience, Global Regulatory Affairs, sent on 23. March 2012, 20:40 [from: jean-philippe.bascou@bayer.com to Yang, YongZhen (AGPM)]
Hänel 2015		2015	E-mail from Ralf Hänel, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, sent on 13. May 2015, 12:51 [from: ralf.haenel@bvl.bund.de to laszlo.bura@efsa.europa.eu]
M-020895-01-1		2000	TI 435-Triazan - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman) GLP, Unpublished.
M-424556-01-2		2012	Clothianidin - Study for the skin sensitization effect in Guinea pigs (Guinea pig Maximization test according to Magnusson and Kligman), GLP, Unpublished.
M-520775-01-1		2015	Determination of TI 435-Triazane in technical grade active substance Clothianidin (TI 435) HPLC - external standard, GLP Bayer CS AG, Unpublished
CIPAC N	Martijn A and Dobrat W	2012	CIPAC Handbook Volume N. Analysis of Technical and Formulated Pesticides, p.15, 2012
M-026219-03-2		2000	Vapor Pressure of TI-435, Pure Active Ingredient GLP,Unpublished, Covance Laboratories Inc., Madison, WI, USA
M-025309-02-1	Kamiya, Y., Itoh, S.	2000	Determination of melting point/melting range of TI-435 pure active ingredient (PAI) GLP, Unpublished,
M-026209-04-1		2000	Determination of Dissociation Constant and Physical-chemical Properties of TI-435 Pure Active Ingrdient (PAI) (Density, Solubility, Octanol/Water Partition Coefficient, and Dissociation Constant), GLP,Unpublished.
M-041740-01-1		2001	TI-435 (Pure Active Ingredient, PAI): Determination of the Effect of pH on Water Solubility and Partition Coefficient GLP, Unpublished.
M-048047-01-1		2000	(^{14}C)-TI-435: Hydrolytic stability GLP, Unpublished.

M-023549-02-1		2000	Photolysis of [nitroimino-^{14}C]TI-435 and [thiazolyl-2-^{14}C]TI-435 in sterile aqueous buffer solution GLP, Unpublished.
M-010153-02-1		1999	Determination of the quantum yield and assessment of the environmental half-life of the direct photodegradation of TI-435 in water, GLP, Unpublished.
M-012345-01-1		1999	TI 435 ; Assay of technical grade active ingredient Unpublished.
M-427760-01-1	Smeykal H.	2012	Clothianidin (TI 435, AE 1283742), technical substance: Melting point, boiling point, thermal stability GLP, Unpublished.
M-027393-01-1		1997	TI-435 - Acute oral toxicity study in the rat GLP, Unpublished.
M-027750-03-1		2000	An acute oral neurotoxicity screening study with technical grade TI-435 in Fischer 344 rats GLP, Unpublished.
M-027394-01-1		1997	TI-435 - Acute oral toxicity study in the mouse GLP, Unpublished.
M-027396-01-1		1997	TI-435 - Acute dermal toxicity study in the rat GLP, Unpublished.
M-027390-01-1		1998	TI-435 - Single dose inhalation (head-only) toxicity study in the rat GLP, Unpublished.
M-027402-01-1		1997	TI-435 - Skin irritation study in the rabbit GLP, Unpublished.
M-027400-01-1		1997	TI-435 - Eye irritation study in the rabbit GLP, Unpublished.
M-027406-01-1		1997	TI-435 - Skin sensitisation study in the guinea pig GLP, Unpublished.
M-027408-01-1		1997	TI-435 - Toxicity to rats by dietary administration for 4 weeks GLP, Unpublished.
M-027413-01-1		1997	Toxicity to mice by dietary administration for 4 weeks GLP, Unpublished.
M-027385-01-1		1998	Palability pilot study for dietary concentrations of TI-435 in dogs. Unpublished.
M-027342-01-1		2000	4-week dietary toxicity study with TI-435 in dogs GLP, Unpublished.
M-027480-01-1		2000	28-day dermal toxicity study with TI-435 in rats GLP, Unpublished.
M-027268-01-1		2000	Technical grade TI 435 - A subchronic toxicity testing study in the rat GLP, Unpublished.
M-036499-02-1		2000	13-Week dietary toxicity study with TI-435 in dogs GLP, Unpublished.
M-036542-01-1		2000	52-week dietary chronic toxicity study with TI-435 in dogs GLP, Unpublished.

M-031986-02-1	2000	104-week dietary combined chronic toxicity and carcinogenicity study with TI-435 in rats GLP, Unpublished.
M-032363-02-1	2000	78-week dietary carcinogenicity study with TI-435 in mice GLP, Unpublished.
M-027255-01-1	2000	A pilot reproductive toxicity study with TI-435 in the Sprague-Dawley rat. GLP, Unpublished.
M-031280-02-1	2000	A two generation reproductive toxicity study with TI-435 in the Sprague-Dawley rat. GLP, Unpublished.
M-027430-02-1	1998	Oral (gavage) dosage-range developmental toxicity study of TI-435 in rats. GLP, Unpublished.
M-027416-01-1	1998	Oral (gavage) developmental toxicity study of TI-435 in rats GLP, Unpublished.
M-027436-02-1	1998	Oral (stomach tube) dosage-range developmental toxicity study of TI-435 in rabbits. GLP, Unpublished.
M-027442-01-1	1998	Oral (stomach tube) developmental toxicity study of TI-435 in rabbits. GLP, Unpublished.
M-027986-01-1	2000	A subchronic neurotoxicity screening study with technical grade TI-435 in Fischer 344 rats. GLP, Unpublished.
M-027178-02-1	2000	Developmental neurotoxicity study of TI-435 administered orally via diet to CRL:CD BR VAF/PLUS presumed pregnant rats. GLP, Unpublished.
M-036520-01-1	2000	TI-435 - Reverse mutation assay 'Ames test' using salmonella typhimurium and escherichia coli. GLP, Unpublished.
M-036420-02-1	1990	Bacterial reverse mutation test of TI 435 GLP, Unpublished.
M-009777-02-1	1997	TI 435 - Salmonella/microsome test plate incorporation and preincubation method - revised version of Bayer report 26584, first revision. GLP, Unpublished.
M-009769-02-1	1996	Special study - TI 435 - Salmonella/microsome test using salmonella typhimurium TA 1535 plate incorporation and preincubation method - revised version of Bayer report 25739 - first revision, Unpublished
M-036407-02-1	1990	DNA repair test of TIR-435 in Bacillus subtilis GLP, Unpublished.
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M-053960-01-1	2001	TI 435 - In vitro chromosome aberration test with chinese hamster V79 cells. GLP, Unpublished.
M-036462-02-1	2000	TI-435 - L5178Y TK +/- mouse lymphoma assay GLP, Unpublished.
M-009761-02-1	1997	TI 435 - Mutagenicity study for the detection of induced forward mutations in the V79-HPRT assay in vitro - revised version of Bayer report 26437, first revision GLP, Unpublished.
M-036435-02-1	2000	TI-435 - Micronucleus test in the mouse GLP, Unpublished.
M-009751-03-1	1997	TI 435 - Test on unscheduled DNA synthesis with rat liver cells in vivo - revised version of Bayer report 26915, first revision. GLP, Unpublished.

M-103604-02-1	2003	TI-435 - *Salmonella typhimurium* reverse mutation assay GLP, Unpublished,
M-103614-01-1	2003	In vitro chromosome aberration test in Chinese hamster V79 cells with TI-435 GLP, Unpublished,
M-103610-01-1	2003	Gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) with TI-435 GLP, Unpublished,
M-103617-01-1	2003	Micronucleus assay in bone marrow cells of the mouse with TI-435* GLP, Unpublished,
M-103622-01-1	2003	In vivo/in vitro unscheduled DNA synthesis in rat hepatocytes with TI-435 GLP, Unpublished,
M-424556-01-2	2012	Clothianidin - Study for the skin sensitization effect in Guinea pigs (Guinea pig Maximization test according to Magnusson and Kligman) GLP, Unpublished,
M-027064-01-1	1998	TI-435 technical - Acute oral toxicity (LD50) to bobwhite quail GLP, Unpublished
M-027285-01-1	2000	TI-435 technical: An acute oral toxicity study with the Japanese quail. GLP, Unpublished
M-027059-01-1	1998	TI-435 technical - Dietary LC50 to the bobwhite quail GLP, Unpublished.
M-027068-01-1	1998	TI-435 technical - Dietary LC50 to the mallard duck GLP, Unpublished,
M-027293-01-1	2000	TI-435 technical: A reproduction study with the northern bobwhite (Colinus virginianus) GLP, Unpublished.
M-027289-01-1	2000	TI-435 technical: A reproduction study with the mallard (Anas platyrhynchos) GLP, Unpublished.
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M-031516-01-1	2000	TI-435 technical: An early life-stage toxicity test with the fathead minnow (Pimephales promelas) GLP, Unpublished.
M-027244-01-1	1999	TI-435 technical - Fish (Sheepshead minnow), acute toxicity test, limit test, 96 h, semi-static GLP, Unpublished.
M-031283-01-1	2000	TI-435 technical - A 48-hour static acute toxicity test with the cladoceran (Daphnia magna) GLP, Unpublished.
M-027071-02-1	1998	TI-435 technical - Daphnia magna reproduction test (21 d) GLP, Unpublished.

M-019551-01-1	2000	TI-435 technical: A 96-hour flow-through acute toxicity test with the saltwater mysid (Mysidopsis bahia) - final report GLP, Unpublished-
M-026384-01-1	2000	TI-435 technical: A flow-through life-cycle toxicity test with the salwater mysid (Mysidposis bahia) GLP, Unpublished.
M-028515-01-1	1999	TI-435 technical - Oyster, acute toxicity test (shell deposition), limit test, flow-through, 96 h GLP, Unpublished, Dr. U. Noack-Laboratorium fuer Angewandte Biologie, Sarstedt, Germany
M-027041-02-1	1998	TI-435 technical - Alga, growth inhibition test (120 (h)) (Scenedesmus subspicatus) GLP, Unpublished.
M-026366-01-1	2000	TI-435 technical - A 5-day toxicity test with the freshwater alga (Selenastrum capricornutum) GLP, Unpublished.
M-032142-01-1	2001	TI-435: Comparative acute toxicity of Chironomus riparius with TZMU, MU, TZNG and MNG GLP, Unpublished-
M-011874-01-1	1999	Infuence of TI 435 technical on development and emergence of larvae of Chironomus riparius in a water-sediment system GLP, Unpublished.
M-031279-01-1	2000	TI-435 technical - A 14-day static-renewal toxicity test with duckweed (Lemna gibba G3) GLP, Unpublished.
M-027051-01-1	1998	Final report - TI-435 technical: Acute contact and oral toxicity to honeybees GLP, Unpublished.
M-027182-01-1	1999	Final report - TI-435: Tier I standard laboratory bioassay of the effects of fresh residues on Aphidius rhopalosiphi (Hymenoptera, Braconidae) GLP, Unpublished.
M-027179-01-1	1999	Final report - TI-435: Tier I standard laboratory bioassay of the effects of fresh residues on Typhlodromus pyri (Acari, Phytoseiidae) GLP, Unpublished.
M-027200-01-1	1999	A laboratory evaluation of the effects of TI-435 50% WDG on adults of the staphylinid beetle, Aleochara bilineata GLP, Unpublished.
M-027198-01-1	1999	Final report - TI-435: Tier I standard laboratory bioassay of the effects of fresh residues on Chrysoperla carnea (Neuroptera, Chrysopidae) GLP, Unpublished.
M-027046-01-1	1998	Final report - TI-435 technical: Acute toxicity to the earthworm Eisenia foetida GLP, Unpublished.
M-027297-01-1	1999	The effect of TI-435 50 % WDG on soil microflora (OECD guidelines 216 and 217 for the testing of chemicals. Revised draft documents, January 1999) GLP, Unpublished.

M-026377-01-1		2000	TI-435 50 % WDG: A toxicity test to determine the effects of the test substance on seedling emergence of ten species of plants GLP, Unpublished.
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CIPAC J	Martijn A and Dobrat W	2000	CIPAC Handbook Volume J. Analysis of Technical and Formulated Pesticides
CIPAC K	Martijn A and Dobrat W	2003	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides

CLOTHIANIDIN

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Recommendations

The Meeting recommended that the specifications for clothianidin TC and WG proposed by Sumitomo Chemical Co., Ltd., as amended, should be adopted by WHO.

Appraisal

The Meeting considered data on clothianidin submitted by Sumitomo Chemical Co., Ltd. in 2015, in support of new WHO specifications for clothianidin TC and water dispersible granules (WG).

Up to now, clothianidin had only FAO specifications for clothianidin TC, SC, GR, SG and FS that were published in 2010 and 2011 based on a submission by Sumitomo [FAO 2011]. Sumitomo has proposed a clothianidin WG for use in indoor residual spraying with a nominal dosage of around 200 mg clothianidin / m^2. Therefore, the extension of the TC specification for clothianidin to WHO together with a WG formulation with 50 % active ingredient became necessary.

The Meeting was provided with draft specifications for clothianidin TC and WG for public health. The proposed specification for the WG was essentially in accordance with the requirements of the Manual [FAO/WHO 2010].

Clothianidin is a white to pale yellow coloured crystalline powder. It has a low volatility and has a melting point of 176.8°C. It is slightly soluble in water at 0.33 g/L at 20°C. It is not fat soluble and is not likely to bioaccumulate with a log P_{ow} of circa 0.9. It is considered to be stable to hydrolysis at all environmentally relevant pH's. It undergoes rapid photolysis with a half life of 3.3 hours at pH 7 at 25°C. Clothianidin is a strong base with a pK_a of 11.

The Meeting was provided with confidential information on the manufacturing process and limits for minimum purity and for impurities, which were supported by 5 batch analysis data. Mass balances were 99.1 - 99.5 %. The minimum purity at 960 g/kg was questioned but it was confirmed by Sumitomo that this is necessary as production is not yet stabilised. A statement was provided by the Belgian regulatory authority confirming that the confidential data on the manufacturing process and declaration of composition submitted to FAO/WHO were the same as those submitted to the national regulatory authority. The Meeting considered that none of the impurities are relevant. CIPAC methods based on reversed phase HPLC have been developed for determination of clothianidin in TC, WG, SC, GR, SG, FS and WS formulations. They were adopted as full CIPAC methods and are published in Handbook N.

Physical-chemical properties data were provided for clothianidin WG formulations for wettability, wet sieve test, degree of dispersion, suspensibility, persistent foam, dustiness, flowability and attrition resistance.

Whereas most clauses of the WG specification and their proposed limits were quite straightforward, the Meeting noted that the persistent foam of the product determined by CIPAC MT 47.3 was rather high (maximum 70 mL at 1.48% w/v and 1 minute). The company explained that, in reality, the generation of foam in the pressurized sprayers

used for IRS are of no concern. A rapid decay of the foam can be observed after initial agitation. The Meeting accepted the explanation.

The analytical method for the active ingredient in the WG formulation was reversed phase HPLC with UV detection according to CIPAC method 738/WG/M/3. [CHC 2013, CIPAC N 2012].

Supporting Information
for
Evaluation Report 738/2015.1

History

Clothianidin was developed by Takeda Chemical Industries in Japan in the 1990. This is also reflected in the development code number allocated to that compound - TI-435, with TI standing for Takeda Industries. Takeda was later incorporated into Sumitomo, and clothianidin was further developed jointly by Sumitomo Chemical Company (SCC) and Bayer CropScience (BCS). Therefore, some of the nonpublished studies referenced in the hazard summary are owned by SCC, some by BCS, and some by both companies.

Uses

Clothianidin is a systemic insecticide which acts as acute contact and stomach poison. Clothianidin belongs to the chemical class of insecticides known as neonicotinoids and is classified by the Insecticide Resistance Action Committee (IRAC) as "nicotinic Acetylcholine receptor agonist / antagonist".

Clothianidin has a broad spectrum of activity, particularly against sucking insects such as aphids, leaf hoppers, thrips and white flies. Furthermore, various species of beetles (e.g. *Atomaria* spp., *Agriotes lineatus*, *Diabrotica* spp.) and some species of flies (e.g. *Oscinella frit* and *Pegomyia* spp.) and cut worm (e.g. *Agrotis* spp.) are effectively controlled. Clothanidin shows no efficacy against spider mites and nematodes. Products containing clothianidin are used as foliar and soil applications as well as seed treatments.

Physico-chemical properties of clothianidin

Table 1. Physico-chemical properties of pure clothianidin

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one) and company report number/date
Vapour pressure	1.3×10^{-10} Pa at 25°C 3.8×10^{-11} Pa at 20°C (extrapolated)	99.7 %	OECD 104 EC A.4 [101]
Melting point, boiling point and/or temperature of decomposition	Melting point: 176.8°C Boiling point: decompose before boiling Decomposition temperature: 242 °C	99.7 %	OECD 102 EC A.1 (DSC) [102]
Solubility in water	pH 7: 0.327 g/L at 20°C determined in deionized water (resistivity > 17 MΩ)	99.7 %	OECD 105 (equivalent to EEC A.6, flask method) [103]
Octanol/water partition coefficient	pH 4 log P_{OW} = 0.893 at 25°C pH 7 log P_{OW} = 0.905 at 25°C pH 10 log P_{OW} = 0.873 at 25°C	99.7 %	EEC A8 [104]
Hydrolysis characteristics	Half-life = 14.4 days at 50 °C at pH 9 Half-life = 3.7 days at 62°C at pH 9 Half-life = 0.7 days at 74 °C at pH 9 Stable at 50 °C at pH 4 and 7 (<10% degradation after 5 days) Stable at 25°C at pH 5, 7 and 9 (<5% degradation after 33 days)	>98 %	EPA Series 161-1 EEC method C.7 [105]
Photolysis characteristics	Half-life 3.3 hours in sterile buffer pH 7 at 25°C Equivalent to 0.6 days of summer solar exposure at Phoenix, Arizona, US (40° latitude) using a Xenon lamp with UV cut-off filter at 290 nm. Intensity (300-800 nm) = 1027 W/m^2 by radiometry. Photon flow density = 125.86 X 1014 s^{-1} cm^{-2}. Quantum yield (Φ) = 0.014	>99%	EPA Series 161-2 SETAC [106] [107]
Dissociation characteristics	pK_a = 11.09 (at 20°C)	99.7%	OECD 112 (spectrophotometric method) [103]

Table 2. Chemical composition and properties of clothianidin 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 99.1 – 99.5 %.
Declared minimum clothianidin content	960 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 and/or TK	176.8°C The value given is for pure material, a measurement for the TC is not available.

Hazard summary

Clothianidin has not been evaluated by the WHO IPCS or by the FAO/WHO JMPR.

In EU the classification process is not yet finalized (but Annex I listing is already done). The classification has been discussed between the notifiers and the rapporteur member state and the proposal is reported as such in the draft assessment report:

Formulations and co-formulated active ingredients

The main formulation types available are SC, GR, SG, FS and WG.

Clothianidin is used alone or co-formulated with probenazole, cartap, validamycin, diclocymet, ferimzone, phthalide.

These formulations are registered and sold in many countries in Europe, Northern and Southern America, Africa, Asia and Australia.

Methods of analysis and testing

CIPAC methods based on reversed phase HPLC with UV detection at 269 nm and external standardization have been developed for determination of clothianidin in TC, WG, SC, GR, SG, FS and WS formulations. They were adopted as full CIPAC

The methods for determination of impurities are based on HPLC method using UV detection and internal standardization.

Test methods for determination of physical and chemical properties of the technical active ingredient were OECD, EPA, and/or EC as indicated, 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 the active ingredient

The active ingredient is expressed as clothianidin.

Annex 1: Hazard Summary Provided by the Proposer

Note:

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

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

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat male/female	Oral	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 401; Directive 92/69/EC Method B.I.; Directive 92/18/EEC, L97; US-EPA Section 81-1; OPPTS 870. 1100 Purity: 96.0%	LD_{50} = > 5000 mg/kg bw	[201]
Rat male/female	Acute neurotoxicity gavage	US-EPA-FIFRA, Guideline 81-8(SS); US-EPA OPPTS 870.6200 0-100-200-400 mg/kg bw/d Purity: 95.2-96.0%	NOELs (male / female) Overall = > 60 / 100 mg/kg bw Neurotoxicity = > 400 mg/kg bw/d not neurotoxic	[202]
Mouse male/female	Oral	OECD 401; Directive 92/69/EC, Method B. 1.; Directive 92/18/EEC, L97; US-EPA Section 81-1; US-EPA OPPTS 870.1100 Purity: 96.0%	LD_{50} = 389 mg/kg bw (m) 465 mg/kg bw (f)	[203]
Rat male/female	Dermal	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 402; Directive 92/69/EC, Method B.3.; Directive 92/18/EEC, L97; US-EPA Section 81-2; US-EPA OPPTS 870.1200 24 h semi-occlusive conditions Purity: 96.0%	LD_{50} = > 2000 mg/kg bw	[204]
Rat male/female	Inhalation	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 403; Directive 92/69/EC, Method B.2.; Directive 92/18/EEC, OJEC, L97; USA-EPA Section 81-3; US-EPA OPPTS 870.1330 4.5 h exposure Purity: 96.0%	LC_{50} = > 6.141 mg/L	[205]
Rabbit male/female	Skin irritation	JMAFF 59 NohSan No 4200; JMAFF 63-44; OECD 404; Directive 92/69/EC, Method B.4.; Directive 92/18/EEC L97; US-EPA Section 81-5; US-EPA OPPTS 870.2500 4 h exposure Purity: 96.0%	Non-irritating	[206]

Rabbit male	Eye irritation	OECD 405; Directive 92/69/EC, Method B.5.; Directive 92/18/EEC L97; US-EPA Section 81-4; US-EPA OPPTS 870.2400 24 h exposure Purity: 96.0%	Non-irritating	[207]
Guinea pig	Skin sensitization	OECD 406; Directive 92/69/EC, Method B.6.; Directive 92/18/EEC L97; US-EPA Section 81-6; US-EPA OPPTS 870.2600 Purity: 96.0%	Non-sensitizing	[208]

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat male/female	Sub-acute feeding	OECD 407; Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.7.; EPA Guideline in Subdivision F. Hazard Evaluation: Human and Domestic Animals, JANUARY 1984; JMAFF 59 Nohsan No. 4200 4 weeks 0-1250-2500-5000-7500 ppm (equivalent to: 0-120-249-475-602 mg/kg bw/d (male), 0-137-228-454-689 mg/kg bw/d (female)) Purity: 97.5%	NOAEL = 120 / 137 mg/kg bw/d LOEL = 249 / 228 mg/kg bw/d	[209]
Mouse male/female	Sub-acute feeding	OECD 407; Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.7.: EPA Guideline in Subdivision F. Hazard Evaluation: Human and Domestic Animals; JMAFF Nohsan No. 4200 deviation: duration 4 weeks 0-500-1000-2000-4000 ppm (equivalent to: 0-90-190-383-683 mg/kg bw/d (male) 0-122-248-491-619 mg/kg bw/d (female)) Purity: 97.5%	NOAEL = 190 / 248 mg/kg bw/d LOEL = 383 / 491 mg/kg bw/d	[210]
Dog female	Dose-range finding (palatability) feeding	Exposure to increasing dose levels 0 (for 11 days) - 3000 / 4000 / 5000 ppm (days 1-3 / 4-8 / 9-11) (equivalent to: 0- 51.1/50.8/51.8 mg/kg bw/d) Purity: 95.2%	NOEL = 51.8 mg/kg bw/d	[211]
Dog male/female	Dose-range finding feeding	Directive 88/302/EEC, Method B.27; US-EPA FIFRA Subdivision F, Section 82-1; US-EPA 870.3150; JMAFF 59 Nohsan No. 4200; mainly in accordance to OECD 409 4 weeks, 3 animals/sex/group 0-1250-2500-5000 ppm (equivalent to: 0-36.3-35.8-62.4 mg/kg bw/d (male) 0-35.6-52.3-57.4 mg/kg bw/d (female)) Purity: 95.2%	NOAEL = 36.3 / 35.6 mg/kg bw/d LOEL = 35.8 / 52.3 mg/kg bw/d	[212]

Rat male/female	Sub-acute dermal	US-EPA OPPTS 870.3200; JMAFF 59 Nohsan No. 4200; Directive 88/302/EEC (OJEC No. L 133/27) Part B; OECD 410 6 hrs/day, 28 days 0-100-300-1000 mg/kg bw/d Purity: 95.2%	NOEL = > 1000 mg/kg bw/d	[213]
Rat male/female	Sub-chronic feeding	FIFRA 82-1; TSCA 798.2650; US-EPA OPPTS 870.3100, OECD 408; JMAFF 59 NohSan No. 4200; Directive 87/302/EEC, part B 97 days 0-150-500-3000 ppm (equivalent to: 0-9.0-27.9-202 mg/kg bw/d (male) 0-10.9-34.0-254 mg/kg bw/d (female)) Purity: 95.3%	NOAEL = 27.9 / 34.0 mg/kg bw/d LOEL = 202 / 254 mg/kg bw/d	[214]
Dog male/female	Sub-chronic feeding	US-EPA-FTFRA Section. 82-1; US-EPA-OPPTS OPPTS 870.3150; OECD 409; JMAFF 59 Nohsan No. 4200; Directive 88/302/EEC (OJEC No. L 133/12), Part B 13 weeks 0-325-650-1500-2250 ppm (equivalent to: 0-9.2-19.3-40.9-58.2 mg/kg bw/d (male) 0-9.6-21.2- 42.1-61.8 mg/kg bw/d (female)) Purity: 95.2%	NOAEL = 19.3 / 21.2 mg/kg bw/d LOEL = 40.9 / 42.1 mg/kg bw/d	[215]
Dog male/female	Sub-chronic feeding	EPA-FIFRA Guideline 83-1; EPA-OPPTS Guideline Section 870.4100; OECD 452; JMAFF 59 Nohsan No. 4200, Directive 88/302/EEC, Part B 52 weeks 0-325-650-1500-2000ppm (equivalent to: 0-7.8-16.6-36.3-46.4 mg/kg bw/d (male) 0-8.5-15.0-40.1-52.9 mg/kg bw/d (female)) Purity: 95.2%	NOAEL = 36.3 / 40.1 mg/kg bw/d LOEL = 46.4 / 52.9 mg/kg bw/d	[216]

Rat male/female	Chronic oncogenicity feeding	JMAFF 59 NohSan No. 4200; OECD 453; EEC 88/302/EEC; FIFRA F, 83-5; OPPTS 870.4300 104 weeks 0-150-500-1500-3000 ppm (equivalent to: 0-8.1-27.4-82-157 mg/kg bw/d (male) 0-9.7-32.5-97.8-193 mg/kg bw/d (female)) Purity: 95.2-95.5%	NOAEL = 27.4 / 9.7 mg/kg bw/d LOEL = 82 / 32.5 mg/kg bw/d not carcinogenic	[217]
Mouse male/female	Oncogenicity feeding	JMAFF 59 NohSan No. 4200; OECD 451; EEC 88/302/EEC; FIFRA F, 83-2; OPPTS 870.4200 78 weeks 0-100-350-700/2000/2500/2000/1800 (week 1-4/ 5-10/ 11-34/ 35-termination 2000 ppm (m)/ 1800 ppm (f)) -1250 ppm (equivalent to: 0-13.5-47.2-171.4-251.9 mg/kg bw/d (male) 0-17.0-65.1-215.9-281.1 mg/kg bw/d (female)) Purity: 95.2%	NOAEL = 47.2 / 65.1 mg/kg bw/d LOEL = 171.4 / 215.9 mg/kg bw/d not carcinogenic	[218]
Rat male/female	Pilot reproduction one generation	US-EPA-FIFRA, Section 158.340, No. 83-4: US-EPA-TSCA, 40 CFR Section 798.4700: Guideline 87/302/EEC; OECD 416; J MAFF, 59 NohSan No. 4200 pre-mating 8 weeks 0-50-100-500-1000 ppm (equivalent during pre-mating to: 3.2-3.5 / 5.9-6.8 / 31.7-36.4 / 66.6 - 70.8 mg/kg bw/d) Purity: 95.2-96.0%	NOEL repro. = > 66.6 mg/kg bw/d	[219]
Rat male/female	Reproduction 2-generation	US-EPA, OPPTS 870.3800; Directive 91/414/EEC; OECD 416; JMAFF, 59 NohSan No. 4200 0-150-500-2500 ppm (equivalent to both generations combined: 0-10.2-32.7-179.6 mg/kg bw/d (male) 0-11.8-37.9-212.9 mg/kg bw/d (female) Purity: 95.3-96.0%	Parental NOEL = 32.7/11.8 mg/kg bw/d LOEL = 179.6/37.9 mg/kg bw/d Reproductive NOEL = >179.6/ >212.9 mg/kg bw/d Offspring NOEL = 10.2/11.8 mg/kg bw/d LOEL = 32.7/37.9 mg/kg bw/d	[220]

Rat female	Dose-range finding developmental toxicity	US-EPA OPPTS 870.3700 gestation days 6-19 0-125-250-500-1000 mg/kg bw/d Purity: 96.0%	Maternal NOAEL = not established LOEL = 125 mg/kg bw/d Developmental NOAEL = 125 mg/kg bw/d LOEL = 250 mg/kg bw/d	[221]
Rat female	Developmental toxicity	Guideline 88/302/EEC; OECD 414; US-EPA OPPTS 870.3700; JMAFF 59 NohSan no. 4200 gestation days 6-19 0-10-40-125 mg/kg bw/d Purity: 95.2%	Maternal NOEL = 10 mg/kg bw/d LOEL = 40 mg/kg bw/d Developmental NOAEL = 125 mg/kg bw/d LOEL = > 125 mg/kg bw/d not teratogenic	[222]
Rabbit female	Dose-range finding developmental toxicity	US-EPA OPPTS 870.3700 gestation days 6-28 0-62.5-125-250-500 mg/kg bw/d Purity: 96.0%	Maternal NOAEL = 62.5 mg/kg bw/d MTD < 125 mg/kg bw/d Developmental NOAEL > 62.5 mg/kg bw/d	[223]
Rabbit female	Developmental toxicity	Guideline 88/302/EEC, OECD 414; US-EPA OPPTS 870.3700; JMAFF 59 NohSan no. 4200 gestation days 6-28 0-10-25-75-100 mg/kg bw/d Purity: 95.2-95.5%	Maternal NOEL = 10 mg/kg bw/d LOEL = 25 mg/kg bw/d Developmental NOAEL = 75 mg/kg bw/d LOEL = 100 mg/kg bw/d not teratogenic	[224]
Rat male/female	Sub-chronic neurotoxicity feeding	US-EPA-FIFRA, Guideline 82-5(b); US-EPA OPPTS 870.6200 0-150-1000-3000 ppm equivalent to: 0-9.2-60-177 mg/kg bw/d (male) 0-10.6-71-200 mg/kg bw/d (female) Purity: 95.3-96.0%	NOELs (male / female) Overall = 60 / 71 mg/kg bw d Neurotoxicity = >177 / >200 mg/kg bw/d not neurotoxic	[225]

Rat male/female	Developmental neurotoxicity feeding	US-EPA OPPTS 870.6300; US-EPA Guideline 83-3; US-EPA Pesticide Assessment Guidelines, Subdivision F, addendum 10, neurotoxicity day 0 of gestation until 22 days post partum 0-150-500-1750 ppm (equivalent to: 0-12.9-42.9-142 mg/kg bw/d (gestation) 0-27.3-90.0-299 mg/kg bw/d (lactation) Purity: 95.5-95.9%	NOELs (gestation / lactation) Maternal = 42.9 / 90.0 mg/kg bw/d Developmental = 12.9 / 27.3 mg/kg bw/d Developmental neurobehavioral effects > 142 / > 299 mg/kg bw/d	[226]

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

Species	Test	Duration and Conditions	Result	Reference
Salmonella typhimurium / *Escherichia coli*	Reverse mutation assay 'Ames test' in vitro	Guideline 92/69/EEC, Method B.I4.; OECD 471, US-EPA FIFRA section 84-2; JMAFF 59 NohSan no. 4200; Japan Ministry of Labour No. 77 S. typhimurium: TA 98, TA 100, TA 1535, TA 1537; E. coli: WP2uvrA$^-$ 0-50-150-500-1500-5000 µg/plate (+/- S9 mix) Purity: 95.2-96.0%	Positive (+S9 mix in TA 1535 only)	[227]
Salmonella typhimurium / *Escherichia coli*	Reverse mutation assay 'Ames test' in vitro	Guideline 92/69/EEC, Method B.14.; JMAFF 59 NohSan no. 4200 S. typhimurium: TA 98, TA 100, TA 1535, TA 1537; E. coli: WP2uvrA$^-$ 0-313-625-1250-2500-5000 µg/plate (+/-S9 mix) Purity: ≥ 99%	Negative	[228]
Salmonella typhimurium	Reverse mutation assay 'Ames test' in vitro	Directive 92/69/EEC, Method B.14.; OECD 471; US-EPA 712-C-96-219, OPPTS 870.5265 S. typhimurium: TA 98, TA 100, TA 102, TA 1535, TA 1537 0-16-50-158-500-1581-5000 µg/plate/tube (+/-S9 mix) TA 102: 0-16-32-48-64-80-96-112 µg/plate (+/-S9 mix) Purity: 95.2%	Negative	[229]
Salmonella typhimurium	Reverse mutation assay 'Ames test' in vitro	Directive 92/69/EEC, Method B.14.; OECD 471; US- EPA 712-C-96-219, OPPTS 870.5265 S. typhimurium: TA 1535 Batch NLL 6100-3: 0-1000-2000-3000-4000-5000 µg/plate, Batch 30034708: 3000-5000-7000 µg/plate, 0-1000-2000-4000-6000-8000 µg/tube each batch +/- S9 mix, pre-incubation technique Purity: 98.6% (batch NLL 6100-3), 96.2% (batch 30034708)	Negative	[230]
Bacillus subtilis	DNA repair assay in vitro	JMAFF 59 Nohsan No. 4200 0-375-750-1500-3000-6000 µg/disc (+/- S9 mix) Purity: ≥ 99%	Negative	[231]

Chinese hamster lung (CHL) cells	Chromosome aberration assay in vitro	OECD 473; Directive 92/69/EEC, Annex V, Part B, Method B.10.; US-EPA FIFRA section 84-2 ; JMAFF 59 Nohsan No 4200 1st assay: 0-156.25-312.5-625-937.5-1250-1875 µg/mL 2nd assay: 0- 39 to 1875 µg/mL exposure 4 – 48 hrs, recovery 0 – 18 hrs, +/- S9 mix Purity: 96.0%	Positive (+/- S9 mix)	[232]
Mouse lymphoma cells	Gene mutation in mammalian cells in vitro	OECD 476; Directive 87/303/EEC no. LI 33, Method B. 14.; EPA FIFRA section 84-2; JMAFF 59 Nohsan No 4200 0-312.5-625-1250-1667-2500 µg/mL (+/-S9 mix) 0-300-600-1200-1600-2000 µg/mL (-S9 mix) 0-600-1200-1600-2000-2400 µg/mL (+S9 mix) Purity: 96.0%	Positive	[233]
Chinese hamster lung V79 cells	Gene mutation in mammalian cells in vitro	Directive 88/302/EEC; OECD 476; US-EPA712-C-96-221, OPPTS 870.5300 0-156-313-625-1250-2500-5000 µg/mL (+/- S9 mix) Purity: 95.2%	Negative	[234]
Mouse bone marrow cells	Chromosome aberration assay Micronucleus test in vivo	OECD 474; Directive 92/69/EEC, no. L383A, Method B.12.; EPA section 84-2; JMAFF 59 NohSan No. 4200 0-25-50-100 mg/kg bw (oral) Purity: 96.0%	Negative	[235]
Rat hepatocytes	Unscheduled DNA synthesis in vivo	In accordance with OECD draft guideline ‘OECD Guidelines for Testing of Chemicals, Proposal for a New Guideline, "Genetic Toxicology: DNA Damage and Repair/ Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells In Vivo’ and in addition Directive 88/302/EEC; OECD 482; US-EPA PB 84-233295 0-2500-5000 mg/kg bw (oral) Purity: 95.2-96.2%	Negative	[236]

Table D. Ecotoxicology profile of technical clothianidin

Species	Test	Duration and conditions	Result	Reference
Bobwhite quail *(Colinus virginianus)*	Acute oral	14d, US EPA Subdivision E, Guideline 71-1 (1982)	LD50 > 2000 mg /kg bw	[301]
Japanese quail *(Coturnix coturnix japonica)*	Acute oral	14d, US EPA Subdivision E, Guideline 71-1 (1982)	LD50 = 430 mg /kg bw	[302]
Bobwhite quail *(Colinus virginianus)*	dietary	8d, OECD 205 (1984)	LC50 > 5200 mg/kg diet	[303]
Mallard duck *(Anas platyrhynchos)*	dietary	8d, OECD 205 (1984)	LC50 > 5200 mg/kg diet	[304]
Bobwhite quail *(Colinus virginianus)*	Reproduction	20 weeks, OECD 206	NOEC = 500 mg/kg diet	[305]
Mallard duck *(Anas platyrhynchos*	Reproduction	20 weeks, OECD 206	NOEC = 500 mg/kg diet	[306]
Rainbow trout *(Oncorhynchus mykiss)*	acute	96h, static, limit test, OECD 203	LC50 > 100 mg/l	[307]
Bluegill *(Lepomis macrochirus)*	acute	96h, static, limit test, OECD 203	LC50 > 120 mg/l	[308]
Fathead minnow *(Pimephales promelas)*	Chronic, ELS	33d, flow-through, US EPA Subdivision E, Guideline 72-4 (1982), US EPA OPPTS draft guideline 850.1400 (1996)	NOEC = 20 mg/l	[309]

Sheepshead minnow *(Cyprinodon variegatus)*	acute	96h, static, OECD 203	LC50 > 102.5mg/l	[310]
water flea *(Daphnia magna)*	acute toxicity	48h, static, OECD 202	EC_{50} > 120 mg/l	[311]
water flea *(Daphnia magna)*	Chronic toxicity	21d, semi-static, OECD 211	NOEC = 0.120 mg/l	[312]
Mysid shrimp (Mysidopsis bahia)	acute	96h, flow-through	LC50 = 0.053 mg/l	[313]
Mysid shrimp (Mysidopsis bahia)	Chronic, life cycle	39d, flow-though, OPPTS 850.1350	NOEC = 0.0097 mg/l	[314]
Oyster (*Crassostrea virginica*)	acute	96h, flow-through; OPPTS 850.1025	EC50 > 129.1 mg/l	[315]
Green alga *(Scenedesmus subspicatus)*	Chronic toxicity	72h, static, OECD 201	ErC50 > 270 mg/l	[316]
Green alga *(Selenastrum capricornutum)*	Chronic toxicity	72h, static, OECD 201	ErC50 > 120 mg/l	[317]
Sediment dwelling invertebrates *(Chironomus riparius)*	acute	48h, static	EC50 = 0.029 mg/l	[318]
Sediment dwelling invertebrates *(Chironomus riparius)*	chronic	28d, static, BBA	EC15 = 0.00072 mg/l	[319]

Duckweed *(Lemna gibba)*	chronic	14d, static renewal, US EPA OPPTS guideline 850.4400 (1996)	EC50 > 121 mg/l	[320]
Honeybee (*Apis mellifera*)	Acute oral Acute contact	48h, EPPO guideline n° 170 (1992)	Oral LD50 = 0.004 µg/bee Contact LD50 = 0.044 µg/bee	[321]
Parasitoid (*Aphidius rhopalosiphi*)	Laboratory	48h, tested as formulated product WG 500 g/kg SETAC (1994)	100 % mortality at 60 g a.s./ha	[322]
Predatory mite (*Typhlodromus pyri*)	Laboratory	14d, tested as formulated product WG 500 g/kg SETAC (1994)	69 % mortality at 60 g a.s./ha 97 % effect on reproduction at 60 g a.s./ha	[323]
Ground dwelling predatory species (*Aleochara bilineata*)	Laboratory	28d, tested as formulated product WG 500 g/kg SETAC (1994)	89 % corrected mortality at 75 g a.s./ha	[324]
Foliage dwelling predatory species (*Chrysoperla carnea*)	Laboratory	28d, tested as formulated product WG 500 g/kg SETAC (1994)	97 % corrected mortality at 60 g a.s./ha	[325]
Earthworm (*Eisenia fetida*)	acute	14d, OECD 207	LC50 = 13.2 mg/kg soil	[326]
Nitrogen transformation Soil respiration		28d, OECD 216 and 217	No significant effects (<25%) at 750 g a.s./ha (equivalent to 1 mg a.s./kg soil)	[327]
Terrestrial plants (10 species)	Seedling emergence	14d, OPPTS 850.4100 and 850.4225	NOEC = 225 g a.s./ha	[328]

Terrestrial plants (10 species)	Vegetative vigour	14d, OPPTS 850.4150	NOEC = 225 g a.s./ha	[329]

Annex 2: References

References for the TC specification and non-confidential data

Reference Number	Year Title Published / Unpublished SCC report No BCS doc. ID	Owner
[101]	Year: 2000 Title: Vapor Pressure of TI-435, Pure Active Ingredient Unpublished SCC report No: THP-0026 BCS doc ID: M-026219-03-2	SCC
[102]	Year: 2000 Title: Determination of melting point/melting range of TI-435 pure active ingredient (PAI) Unpublished SCC report No: THP-0018 BCS doc ID: M-025309-02-1	SCC
[103]	Year: 2000 Title: Determination of Dissociation Constant and Physical-chemical Properties of TI-435 Pure Active Ingredient (PAI) (Density, Solubility, Octanol/Water Partition Coefficient, and Dissociation Constant) Unpublished SCC report No: THP-0013 BCS doc ID: M-026209-04-1	SCC
[104]	Year: 2001 Title:TI-435 (Pure Active Ingredient, PAI): Determination of the Effect of pH on Water Solubility and Partition Coefficient Unpublished SCC report No:THP-0065 BCS doc ID: M-041740-01-1	SCC
[105]	Year: 2000 Title: (14C)-TI-435: Hydrolytic stability Unpublished SCC report No: THP-0024 BCS doc ID: M-048047-01-1	SCC
[106]	Year: 2000 Title: Photolysis of [nitroimino-14C]TI-435 and [thiazolyl-2-14C]TI-435 in sterile aqueous buffer solution Unpublished SCC report No: THM-0013 BCS doc ID: M-023549-02-1	SCC
[107]	Year: 1999 Title: Determination of the quantum yield and assessment of the environmental half-life of the direct photodegradation of TI-435 in water Unpublished SCC report No: THP-0023 BCS doc ID: M-010153-02-1	SCC
[108]	Year: 2001 Title: Analytical method for analysis of TI-435 technical grade active ingredient (TGAI) Unpublished SCC report No: THA-0012 BCS doc ID: not registered	SCC
[201]	Year: 1997 Title: TI-435 - Acute oral toxicity study in the rat Unpublished SCC report No: THT-0047	SCC

	BCS doc. ID: M-027393-01-1	
[202]	Year: 2000 Title: An acute oral neurotoxicity screening study with technical grade TI-435 in Fischer 344 rats Unpublished SCC report No: THT-0011 BCS doc. ID: M-027750-03-1	SCC
[203]	Year: 1997 Title: TI-435 - Acute oral toxicity study in the mouse Unpublished SCC report No: THT-0048 BCS doc. ID: M-027394-01-1	SCC
[204]	Year: 1997 Title: TI-435 - Acute dermal toxicity study in the rat Unpublished SCC report No: THT-0049 BCS doc. ID: M-027396-01-1	SCC
[205]	Year: 1998 Title: TI-435 - Single dose inhalation (head-only) toxicity study in the rat Unpublished SCC report No: THT-0070 BCS doc. M-027390-01-1	SCC
[206]	Year: 1997 Title: TI-435 - Skin irritation study in the rabbit Unpublished SCC report No: THT-0051 BCS doc. M-027402-01-1	SCC
[207]	Year: 1997 Title: TI-435 - Eye irritation study in the rabbit Unpublished SCC report No: THT-0050 BCS doc. M-027400-01-1	SCC
[208]	Year: 1997 Title: TI-435 - Skin sensitisation study in the guinea pig Unpublished SCC report No: THT-0065 BCS doc. M-027406-01-1	SCC
[209]	Year: 1997 Title: TI-435 - Toxicity to rats by dietary administration for 4 weeks Unpublished SCC report No: THT-0040 BCS doc. M-027408-01-1	SCC
[210]	Year: 1997 Title: TI-435 - Toxicity to mice by dietary administration for 4 weeks Unpublished SCC report No: THT-0041 BCS doc. M-027413-01-1	SCC
[211]	Year: 1998 Title: Palatability pilot study for dietary concentrations of TI-435 in dogs Unpublished SCC report No: THT-0078 BCS doc. M-027385-01-1	SCC
[212]	Year: 2000 Title: 4-week dietary toxicity study with TI-435 in dogs Unpublished SCC report No: THT-0069 BCS doc. M-027342-01-1	SCC
[213]	Year: 2000 Title: 28-day dermal toxicity study with TI-435 in rats	SCC

	Unpublished SCC report No: THT-0071 BCS doc. M-027480-01-1	
[214]	Year: 2000 Title: Technical grade TI 435 - A subchronic toxicity testing study in the rat Unpublished SCC report No: THT-0045 BCS doc. M-027268-01-1	SCC
[215]	Year: 2000 Title: 13-Week dietary toxicity study with TI-435 in dogs Unpublished SCC report No: THT-0003 BCS doc. M-036499-02-1	SCC
[216]	Year: 2000 Title: 52-week dietary chronic toxicity study with TI-435 in dogs Unpublished SCC report No: THT-0004 BCS doc. M-036542-01-1	SCC
[217]	Year: 2000 Title: 104-week dietary combined chronic toxicity and carcinogenicity study with TI-435 in rats Unpublished SCC report No: THT-0038 BCS doc. M-031986-02-1	SCC
[218]	Year: 2000 Title: 78-week dietary carcinogenicity study with TI-435 in mice Unpublished SCC report No: THT-0005 BCS doc. M-032363-02-1	SCC
[219]	Year: 2000 Title: A pilot reproductive toxicity study with TI-435 in the Sprague-Dawley rat Unpublished SCC report No: THT-0001 BCS doc. M-027255-01-1	SCC
[220]	Year: 2000 Title: A two generation reproductive toxicity study with TI-435 in the Sprague-Dawley rat Unpublished SCC report No: THT-0046 BCS doc. M-031280-02-1	SCC
[221]	Year: 1998 Title: Oral (gavage) dosage-range developmental toxicity study of TI-435 in rats Unpublished SCC report No: THT-0062 BCS doc. M-027430-02-1	SCC
[222]	Year: 1998 Title: Oral (gavage) developmental toxicity study of TI-435 in rats Unpublished SCC report No: THT-0061 BCS doc. M-027416-01-1	SCC
[223]	Year: 1998 Title: Oral (stomach tube) dosage-range developmental toxicity study of TI-435 in rabbits Unpublished SCC report No: THT-0060 BCS doc. M-027436-02-1	SCC
[224]	Year: 1998	SCC

	Title: Oral (stomach tube) developmental toxicity study of TI-435 in rabbits Unpublished SCC report No: THT-0059 BCS doc. M-027442-01-1	
[225]	Year: 2000 Title: A subchronic neurotoxicity screening study with technical grade TI-435 in Fischer 344 rats Unpublished SCC report No: THT-0067 BCS doc. M-027986-01-1	SCC
[226]	Year: 2000 Title: Developmental neurotoxicity study of TI-435 administered orally via diet to CRL:CD BR VAF/PLUS presumed pregnant rats Unpublished SCC report No: THT-0068 BCS doc. M-027178-02-1	SCC
[227]	Year: 2000 Title: TI-435 - Reverse mutation assay 'Ames test' using *Salmonella typhimurium* and *Escherichia coli* Unpublished SCC report No: THT-0086 BCS doc. M-036520-01-1	SCC
[228]	Year: 1990 Title: Bacterial reverse mutation test of TIR-435 Unpublished SCC report No: THT-0087 BCS doc. M-036420-02-1	SCC
[229]	Year: 1997 Title: TI 435 - Salmonella/microsome test plate incorporation and preincubation method - revised version of Bayer report 26584, first revision - Unpublished SCC report No: THT-0079 BCS doc. M-009777-02-1	SCC
[230]	Year: 1996 Title: Special study - TI 435 - Salmonella/microsome test using *Salmonella typhimurium* TA 1535 plate incorporation and preincubation method - revised version of Bayer report 25739 - first revision Unpublished SCC report No: THT-0080 BCS doc. M-009769-02-1	SCC
[231]	Year: 1990 Title: DNA repair test of TIR-435 in *Bacillus subtilis* Unpublished SCC report No: THT-0097 BCS doc. M-036407-02-1	SCC
[232]	Year: 2000 Title: TI-435 - Chromosome aberration test in CHL cells in vitro Unpublished SCC report No: THT-0096 BCS doc. M-036479-02-1	SCC
[233]	Year: 2000 Title: TI-435 - L5178Y TK +/- mouse lymphoma assay Unpublished SCC report No: THT-0099 BCS doc. M-036462-02-1	SCC
[234]	Year: 1997 Title: TI 435 - Mutagenicity study for the detection of induced forward mutations in the V79-HPRT assay in vitro - revised version of Bayer report 26437, first revision -	SCC

	Unpublished SCC report No: THT-0095 BCS doc. M-009761-02-1	
[235]	Year: 2000 Title: TI-435 - Micronucleus test in the mouse Unpublished SCC report No: THT-0098 BCS doc. M-036435-02-1	SCC
[236]	Year: 1997 Title: TI 435 - Test on unscheduled DNA synthesis with rat liver cells in vivo - revised version of Bayer report 26915, first revision - Unpublished SCC report No: THT-0100 BCS doc. M-009751-03-1	SCC
[301]	Year: 1998 Title: TI-435 technical - Acute oral toxicity (LD50) to bobwhite quail Unpublished SCC report No: THW-0119 BCS doc. M-027064-01-1	SCC
[302]	Year: 2000 Title: TI-435 technical: An acute oral toxicity study with the japanese quail Unpublished SCC report No: THW-0118 BCS doc. M-027285-01-1	SCC
[303]	Year: 1998 Title: TI-435 technical - Dietary LC50 to the bobwhite quail Unpublished SCC report No: THW-0120 BCS doc. M-027059-01-1	SCC
[304]	Year: 1998 Title: TI-435 technical - Dietary LC50 to the mallard duck Unpublished SCC report No: THW-0121 BCS doc. M-027068-01-1	SCC
[305]	Year: 2000 Title: TI-435 technical: A reproduction study with the northern bobwhite (*Colinus virginianus*) Unpublished SCC report No: THW-0116 BCS doc. M-027293-01-1	SCC
[306]	Year: 2000 Title: TI-435 technical: A reproduction study with the mallard (*Anas platyrhynchos*) Unpublished SCC report No: THW-0117 BCS doc. M-027289-01-1	SCC
[307]	Year: 1998 Title: TI-435 technical - Fish (rainbow trout), acute toxicity test, 96 h, limit test Unpublished SCC report No: THW-0029 BCS doc. M-027029-02-1	SCC
[308]	2000 Year: Title: TI-435 technical - A 96-hour static acute toxicity test with the bluegill (*Lepomis macrochirus*) Unpublished SCC report No: THW-0027 BCS doc. M-031285-01-1	BCS, SCC

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[310]	Year: 1999 Title: TI-435 technical - Fish (Sheepshead minnow), acute toxicity test, limit test, 96 h, semi-static Unpublished SCC report No: THW-0028 BCS doc. M-027244-01-1	SCC
[311]	Year: 2000 Title: TI-435 technical - A 48-hour static acute toxicity test with the cladoceran (*Daphnia magna*) Unpublished SCC report No: THW-0043 BCS doc. M-031283-01-1	BCS, SCC
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