EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate D - Food Safety: Production and distribution chain
Unit D.3 - Chemicals, contaminants and pesticides

Clothianidin

SANCO/10533/05 - Final

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COMMISSION WORKING DOCUMENT - DOES NOT NECESSARILY REPRESENT THE VIEWS OF THE COMMISSION SERVICES

Review report for the active substance **clothianidin**

Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 27 January 2006 in view of the inclusion of clothianidin in Annex I of Directive 91/414/EEC.

1. Procedure followed for the evaluation process

This review report has been established as a result of the evaluation of the new active substance clothianidin, made in the context of the work provided for in Articles 5 and 6 of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

In accordance with the provisions of Article 6(2) of Directive 91/414/EEC, the Belgian authorities received on 26 September 2001 an application from Sumitomo Chemical Takeda Agro Company Ltd. London, hereafter referred to as the applicant, for the inclusion of the active substance clothianidin in Annex I to the Directive. The Belgian authorities indicated to the Commission on 16 October 2001 the results of a first examination of the completeness of the dossier, with regard to the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive. Subsequently, and in accordance with the requirements of Article 6(2), a dossier on clothianidin was distributed to the Member States and the Commission.

The Commission referred the dossier to the Standing Committee on the Food Chain and Animal Health in the meeting of the working group 'legislation' thereof on 27 November 2001, during which the Member States confirmed the receipt of the dossier.

In accordance with the provisions of Article 6(3), which requires the confirmation at Community level that the dossier is to be considered as satisfying, in principle, the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive and in accordance with the procedure laid down in Article 20 of the Directive, the Commission confirmed in its Decision 2002/305/EC [1] of 19 April 2002 that these requirements were satisfied.

Within the framework of that decision and with a view to the further organisation of the works related to the detailed examination of the dossier provided for in Article 6(2) and (4) of Directive 91/414/EEC, it was agreed between the Member States and the Commission that Belgium, as rapporteur Member State, would carry out the detailed examination of the dossier and report the conclusions of the examination accompanied by any recommendations on the inclusion or non-inclusion and any conditions relating thereto, to the Commission as soon as possible and at the latest within a period of one year.

Belgium submitted to the Commission on 04 June 2003 the report of its detailed scientific examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of clothianidin in Annex I to the Directive.

On receipt of the draft assessment report, the Commission forwarded it for consultation to all the Member States as well as to Sumitomo Chemical Takeda Agro Company Ltd. London being the sole applicant on 12 June 2003.

The active substance was evaluated in the Co-rapporteur System, with the United Kingdom acting as Co-Rapporteur Member State. Further discussions between the Rapporteur Member State and the Co-rapporteur Member State were organised , to review the draft assessment report and the comments received thereon in particular on each of the following disciplines :

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions.

The evaluation between the Rapporteur Member State and the Co-rapporteur Member State took place from October 2003 to February 2004.

The report of the peer review (in this case the final reporting table) was circulated, for further consultation, to Member States and the sole applicant on 25 May 2004.

The dossier, revised draft assessment report and the peer review report including in particular an outline resumé of the remaining technical questions, were referred to the Standing Committee on

[1] OJ L 104, 20.4.2002, p.42.

the Food Chain and Animal Health, and specialised working groups of this Committee, for final examination, with participation of experts from all Member States. This final examination took place from May 2004 to September 2005, and was finalised in the meeting of the Standing Committee on 27 January 2006.

The present review report contains the conclusions of this final examination; given the importance of the revised draft assessment report, the peer review report and the comments and clarifications submitted after the revision of the draft assessment report as basic information for the final examination process, these documents are considered respectively as background documents A, B and C to this review report and are part of it.

The review of clothianidin did not reveal any open questions or concerns, which would have required a consultation of the Scientific Committee on Plants or of the European Food Safety Authority which has taken over the role of that Committee.

2. Purposes of this review report

This review report, including the background documents and appendices thereto, have been developed and finalised in support of the Directive 2006/41/EC[2] concerning the inclusion of clothianidin in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing clothianidin they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In parallel with the provisions of Article 7(6) of Regulation 3600/92 for existing active substances, the Commission and the Member States will keep available or make available this review report for consultation by any interested parties or will make it available to them on their specific request. Moreover the Commission will send a copy of this review report (not including the background documents) to the applicant.

The information in this review report is, at least partly, based on information which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated possession of regulatory access to the information on which this review report is based.

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[2] OJ L 187, 18.7.2006, p. 24.

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing clothianidin will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each clothianidin containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the uses which were proposed and supported by the sole data submitter and mentioned in the list of uses supported by available data (attached as Appendix IV to this Review Report).

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC. This may in particular be the case for the risk to honeybees and non-target arthropods for uses of clothianidin other than as a seed dressing as set out in Appendix IV to this Review Report.

4. Specific conclusions which are highlighted in this evaluation

4.1 Residues of clothianidin in foodstuffs

The review has established that the residues arising from the proposed uses, consequent on application consistent with good plant protection practice, have no harmful effects on human or animal health. The Theoretical Maximum Daily Intake (TMDI) for a 60 kg adult is 0.00206 % of the Acceptable Daily Intake (ADI), based on the FAO/WHO European Diet (1998). This low intake value reflects the current limited use pattern for this active substance. The acute intake calculation was performed based on the ARfD value of 0.10 mg/kg bw/day. The national estimated short term intake (NESTI) for maize is 0.0417 % and 0.083 % of the ARfD respectively for adults and toddlers; and for sugar beet: 0.046 % and 2.58 % of the ARfD respectively for adults and toddlers.

4.2 Exposure of operators, workers and bystanders

The review has identified acceptable exposure scenarios for operators, workers and bystanders, which require, however, confirmation for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

4.3 Ecotoxicology

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account as detailed in section 7 of this report.

5. Identity and Physical/chemical properties

The main identity and the physical/chemical properties of clothianidin are given in Appendix I.

The active substance shall have a minimum purity of 960 g/kg technical product.

The review has established that for the active substance notified by the applicant (Sumitomo Chemical Takeda Agro Company Ltd. London), none of the manufacturing impurities considered are, on the basis of information currently available, of toxicological or environmental concern.

6. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in Annex VI of that Directive, the most important endpoints as identified during the evaluation process are listed in Appendix II.

7. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing clothianidin

On the basis of the proposed and supported uses, the following particular issues have been identified as requiring particular and short term (within 12 months at the latest) attention from the Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

Member States

- must pay particular attention to the protection of groundwater, when the active substance is applied in regions with vulnerable soil and/or climate conditions;
- must pay particular attention to the risk to granivorous birds and mammals when the substance is used as a seed dressing.

Conditions of use shall include risk mitigation measures, where appropriate.

8. List of studies to be generated

No further studies were identified which were considered at this stage, and under the current inclusion conditions necessary in relation to the inclusion of clothianidin in Annex I.

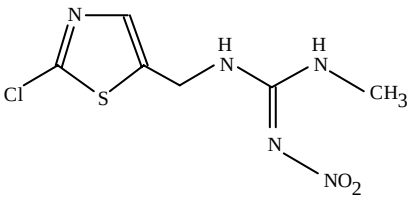
9. Updating of this review report

The technical information in this report may require periodic updating to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Such adaptations will be examined and finalised in the Standing Committee on the Food Chain and Animal Health, in connection with any amendment of the inclusion conditions for clothianidin in Annex I of the Directive.

APPENDIX I

Identity, physical and chemical properties

CLOTHIANIDIN

Common name (ISO)	Clothianidin
Development Code (for new actives only)	TI-435
Chemical name (IUPAC)	(*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine
Chemical name (CA)	[*C(E)*]-*N*-[(2-chloro-5-thiazolyl)methyl]-N'-methyl-N''-nitroguanidine
CIPAC No	738
CAS No	210880-92-5
EEC No	not allocated
FAO SPECIFICATION	not available
Minimum purity	min. 960 g/kg (full scale manufacturing)
Molecular formula	$C_6H_8ClN_5O_2S$
Molecular mass	249.7 g/mol
Structural formula	

Melting point	176.8°C (99.7%)
Boiling point	Not applicable (not a low melting substance)
Appearance	clear and colourless powder, odourless (99.7%) dim yellow powder, odourless (97.6%)
Relative density	D_4^{20} = 1.61 (99.7%)
Vapour pressure	3.8 x 10^{-11} Pa at 20°C
Henry's law constant	2.9 x 10^{-11} $Pa.m^3.mol^{-1}$ at 20°C
Solubility in water	Milli-Q water : 0.327 g/L at 20°C
	pH 4: 0.304 g/L at 20°C
	pH 10: 0.340 g/L at 20°C
Solubility in organic solvents	solubility at 25°C in heptane : < 0.00104 g/L xylene : 0.0128 g/L dichloromethane : 1.32 g/L methanol : 6.26 g/L octanol : 0.938 g/L acetone : 15.2 g/L ethylacetate : 2.03 g/L
Partition co-efficient (log P_{ow})	pH 4: 0.893 at 25°C
	pH 7: 0.905 at 25°C
	pH 10: 0.873 at 25°C
Hydrolytic stability (DT_{50})	pH 4 : stable at 50°C
	pH 7 : stable at 50°C
	pH 9 : 1401 d at 20°C
Dissociation constant	pKa = 11.09
Quantum yield of direct photo-transformation in water at λ >290 nm	0.014
Flammability	not highly flammable
Explosive properties	not explosive
UV/VIS absorption (max.)	neutral conditions : λ_{max} 265.5 nm : ε = 1.71 x 10^4 $L.mol^{-1}.cm^{-1}$ λ_{max} 214.5 nm : ε = 7.77 x 10^3 $L.mol^{-1}.cm^{-1}$ at 290 nm : ε = 5350 $L.mol^{-1}.cm^{-1}$
Photostability in water (DT_{50})	pH 7 : 3.3 hr at 25°C

APPENDIX II

END POINTS AND RELATED INFORMATION

CLOTHIANIDIN

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	-oral: rapid (24h) and efficient (89-95%) -dermal: 2.25% (monkey study)
Distribution:	Widely distributed up to 72h, slight preference for kidney, liver, urinary bladder, adrenales
Potential for accumulation:	no evidence
Rate and extent of excretion:	Rapid, within 24h: 91% (low dose), 57% (high dose) in urine; <7% in faeces; limited enterohepatic circulation
Toxicologically significant compounds:	Clothianidin[a]; MG[p,ph], TMG[p] [a]: animals, [p]: plants; [ph]: photolysis
Metabolism in animals:	Moderate metabolisation (urine, 72h, % of dose): 56-74% parent compound, 8-13% MNG, 7-11% TZNG, 9% MTCA, 1-4% NTG +9 metabolites <2% Oxydative demethylation and C-N cleavage between thiazolyl-nitroimino moiety

Acute toxicity

Rat LD_{50} oral:	500 mg/kg bw < LD50 < 2000 mg/kg bw
Rat LD_{50} dermal:	No data Rabbit LD_{50} dermal: >2000 mg/kg b.w./d
Rat LC_{50} inhalation:	>5.54 mg/l air
Skin irritation:	not irritant
Eye irritation:	not irritant
Skin sensitization (test method used and result):	not sensitizing

Short term toxicity

Target / critical effect:	haematopoietic organs (rat, dog); kidney (mouse)
Lowest relevant oral NOAEL / NOEL:	10 mg/kg bw/d (developmental toxicity rat: body weight gain decrease; developmental toxicity rabbit: clinical signs)
Lowest relevant dermal NOAEL / NOEL:	systemic NOAEL: 300 mg/kg bw/d (21 d rat: bw effects) local NOAEL >1000 mg/kg bw/d (21 d rat)
Lowest relevant inhalation NOAEL / NOEL:	not determined

Genotoxicity

In-vitro: pve in TK and CHL: clastogenic at cytotoxic doses; nve in Ames, HPRT *In-vivo*: nve in mouse bone marrow and liver UDS

Long term toxicity and carcinogenicity

Target / critical effect:	interstitial ovarial gland hyperplasia, bw effects, feed consumption (2 yr rat)
Lowest relevant NOAEL:	9.7 mg/kg bw/d
Carcinogenicity:	none

Reproductive toxicity

Target / critical effect - Reproduction:	2G rat: slight stillborn pup incidence; slight sperm motility / morphology
Lowest relevant reproductive NOAEL / NOEL:	NOAEL parental/pup toxicity: 10 mg/kg bw/d (bw, thymus weight, preputial separation / vaginal patency) NOAEL reproduction: 32.7 mg/kg bw/d
Target / critical effect - Developmental toxicity:	Rabbit: absence intermediate lung lobe, ossification sternal centers
Lowest relevant developmental NOAEL / NOEL:	NOAEL maternal: 10 mg/kg bw/d (mortality, clinical signs) NOAEL foetal: 25 mg/kg bw/d (abortions, premature deliveries, foetal weight) NOAEL reproduction: 25 mg/kg bw/d

Delayed neurotoxicity

-Delayed neurotoxicity not required

-Acute neurotoxicity: 60 mg/kg bw/d (locomotor activity, hypothermia)

-Short-term neurotoxicity NOAEL: 177 mg/kg bw/d

-neurodevelopmental toxicity NOAEL:

43 mg/kg bw/d (startle habituation, motor activity, surface righting, brain histometry findings)

Other toxicological studies

Metabolite data:

Livestock/plant/environmental metabolites more toxic than Clothianidin, but occur at very low residue levels or present in the rat, thus toxicologically covered.

Investigation on enzyme induction:

Slight enzymatic induction potential in the liver; no influence on thyroid hormone activity (T_3, T_4, TSH) in 90d rat study.

Pharmacological studies:

Effects consistent with nicotinoic CNS-stimulation and depression

(impaired pupillar function, deep respiration, hypothermia, increased heart rate, hypotension)

Medical data

No data: new compound

Summary

	Value	Study	Safety factor
ADI:	0.097 mg/kg bw/d	2 yr rat, oral	100
AOEL systemic:	0.10 mg/kg bw/d	developmental toxicity rat and rabbit	100
AOEL inhalation:	Not relevant		
AOEL dermal:	Not relevant		
ARfD (acute reference dose):	0.10 mg/kg bw/d	developmental toxicity rat and rabbit	100

Dermal absorption

2.25% (in-vivo monkey study)

2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:	1.5-11.2 % after 120 days (10 soils)
Non-extractable residues after 100 days:	1.9-9.9 % after 120 days (10 soils)
Major metabolites above 10 % of applied active substance: name and/or code % of applied rate (range and maximum)	TZNG : 9.1% after 120 days (4 soils) MNG : 10.7% after 120 days (4 soils)

Supplemental studies

Anaerobic:	water/sediment system : no mineralisation : < 0.1% max. level bound residues : 82.6% at day 182 each individual metabolite < 5%
Soil photolysis:	Mineralisation : 4.5 % at day 17 Max level bound residues : 36.8% at day 17 Each individual metabolite (TZNG, TZMU, MNG, U1-U6) < 4.4% DT_{50lab} (20°C, irradiation) : 8.2 days equivalent to 34 days, June natural summer sunlight at 40°N. (R^2 = 0.9729) DT_{50lab} (20°C, dark condition) : 183 days (R^2 = 0.8315) DT_{90lab} (20°C, irradiation) : 27 days DT_{90lab} (20°C, dark condition) : > 1 year
Remarks:	none

Rate of degradation

Laboratory studies

	First order kinetics (lab and field studies)
DT_{50}lab (20 °C, aerobic):	DT_{50lab} (a.s., 20°C, aerobic): 143-1001 days, median = 545 days (10 soils, R^2 = 0.7176-0.9987) DT_{50lab} (MNG, 20°C, aerobic): 82.4-108 days, median = 86.4 days (3 soils, R^2 = 0.865-975) DT_{50lab} (TZNG, 20°C, aerobic): 62.1-111 days, median = 89.8 days (3 soils, R^2 = 0.913-0.957) DT_{50lab} (NTG, 20°C, aerobic): 57-95 days, median = 59 days (3 soils)
DT_{90}lab (20 °C, aerobic):	DT_{90lab} (a.s., 20°C, aerobic): > 1000 days (10 soils) DT_{90lab} (MNG, 20°C, aerobic): 274-359 days, median = 287 days (3 soils) DT_{90lab} (TZNG, 20°C, aerobic): 206-368 days, median = 298 days (3 soils) DT_{90lab} (NTG, 20°C, aerobic): 188-315 days, median = 196 days (3 soils)
DT_{50}lab (10 °C, aerobic):	DT_{50lab} (10°C, aerobic): not required, field studies at relevant temperatures are available
DT_{50}lab (20 °C, anaerobic):	DT_{50lab} (20°C, anaerobic, water/sediment): 21 days
	degradation in the saturated zone: not required, anaerobic degradation data available

Field studies (country or region)

DT_{50f} from soil dissipation studies:	DT_{50f} converted to 20°C, 8 locations in Germany, Great Britain, France, Spain, 6 bare soils and 2 cropped areas : 13.3-305.4 days, median = 156 days, geo. mean =120.1 days
DT_{90f} from soil dissipation studies:	DT_{90f} converted to 20°C, 8 locations in Germany, Great Britain, France, Spain, 6 bare soils and 2 cropped areas : 44.2-1017.9 days, median = 517 days
Soil accumulation studies:	4 field trials in Southern France, Germany and Great Britain, a.s. applied as seed dressing at 0.15 kg a.s./ha/year. Maximum concentrations in soil on a period of 1.5 –2.5 years (depending on the fields): Burscheid (GE), 34.8 µg a.s./kg soil at day 882, 10-20 cm depth St Etienne du Gres (FR), 40.8 µg a.s./kg soil at day 120, 0-10 cm depth Wellesbourne (UK), 37.0 µg a.s./kg soil at day 547, 0-10 cm depth MNG and TMG < 5 µg/kg soil

Soil residue studies:	Not required
Remarks: e.g. effect of soil pH on degradation rate	Not relevant

Adsorption/desorption

K_f / K_{oc}:	Koc (a.s.) : 84-345 (mean = 160, median = 123, 1/n = 0.8088-0.8648, 5 soils) Koc (MNG) : 5.2-34.3 (mean = 20.5, 1/n = 0.7017-1.1012, 5 soils) Koc (TZNG) : 204.5-432.5 (mean = 275.4, 1/n = 0.7832-0.9010, 5 soils) Koc (TZMU) : 46.4-95.8 (mean = 61.8, 1/n = 0.8430-0.9276, 5 soils) Koc (TMG) : 525-3620 (mean = 2459, 1/n = 0.7297-0.8493, 5 soils) Koc (TNG) : 13.8-17.3 (mean = 16.0, 1/n = 0.87-0.88, 3 soils)
K_d:	
pH dependence:	no

Mobility

Laboratory studies:

Column leaching:	Not required
Aged residue leaching:	Not required

Field studies:

Lysimeter/Field leaching studies:	- 1 lysimeter, Germany, seed treatment application of 100 g a.s./ha on winter barley and 137 g a.s./ha on winter wheat, 860-912 mm annual rainfall annual average concentration in the leachate: 0.013, 0.062 and 0.104 µg a.s. equivalent/l respectively for the 1st, 2nd and 3rd years a.s. not detected in the leachates. - 2 lysimeters, Germany, foliar application of 160 g a.s./ha on grass during 2 consecutive years, summer applications, 847-930 mm annual rainfall. annual average concentration in the leachate: in the range 0.080-0.417 µg a.s. equivalent/l depending on year and lysimeter a.s. not detected in the leachates. MNG at maximum level of 0.068 µg/l, NTG at maximum level of 0.037 µg/l.
Remarks:	none

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:	pH 4, 50°C: hydrolytically stable
	pH 7, 50°C: hydrolytically stable
	pH 9, 50°C: DT_{50} = 14.4 d pH 9, 20°C: DT_{50} = 1401 d
Major metabolites:	No degradates at temperature of environmental concern (20°C)
Photolytic degradation:	xenon light with UV filter (cut off λ < 290 nm) ,at 25°C, phosphate buffer pH 7 (sterile conditions, cosolvent acetonitrile < 1%), continuous irradiation for 18 d: DT_{50} = 3.3 h (mean of 2 labels)
Major metabolites:	*photolysis products > 10% of applied radioactivity:* TZMU : *N*-(2-chlorothiazol-5-ylmethyl)-*N'*-methylurea (35% after 24 h; 23% after 18 d) MG : methylguanidine (35% after 18 d) HMIO : 4-hydroxy-2-methylamino-2-imidazolin-5-one (27% after 24 h; 7% after 18 d) FA : formamide (16% after 5 d, 14% after 18 d) MU : methylurea (11% after 18 d) CO_2 (34% after 18 d in thiazolyl study)

Biological degradation

Readily biodegradable:	Not readily biodegradable
Water/sediment study:	
DT_{50} water: DT_{90} water:	30.8-49.8 days not determined
DT_{50} whole system: DT_{90} whole system:	48.0-64.8 days not determined
Distribution in water / sediment systems (active substance)	Water : max. level of 92.3% at day 0, Sediment : max. level of 37.3% at day 7
Distribution in water / sediment systems (metabolites)	Water : No metabolite detected Sediment : TMG at max. level of 22.9% at day 58
Accumulation in water and/or sediment:	No accumulation

Degradation in the saturated zone	-
Remarks:	none

2.3 Fate and behaviour in air

Volatility

Vapour pressure:	3.8×10^{-11} Pa at 20°C
Henry's law constant:	2.9×10^{-11} $Pa.m^3.mol^{-1}$ at 20°C

Photolytic degradation

Direct photolysis in air:	Not required
Photochemical oxidative degradation in air DT_{50}:	DT_{50} in troposphere = 1 h, corresponding to chemical lifetime τ of 1.4 h (using a 12 h day with 1.5×10^6 OH radicals/cm^3)
Volatilisation:	from plant surfaces: not required
	from soil: not required

Remarks:	none

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:	LD_{50} (mice) = 389 mg a.s./kg bw
Acute toxicity to birds:	LD_{50} (Japanese quail) = 430 mg a.s./kg bw
Dietary toxicity to birds:	LC_{50} (mallard duck) > 752 mg a.s./kg bw
Reproductive toxicity to birds:	NOEC (bobwhite quail) = 56.8 mg a.s./kg bw
Short term oral toxicity to mammals:	NOAEL (28 d) (mice) = 190 mg a.s./kg bw

Aquatic Organisms

	Group	Test substance	Time-scale	Endpoint	Toxicity
	Laboratory tests				
Acute toxicity fish:	Oncorhynchus mykiss	clothianidin	Acute (96 h)	LC_{50}	> 104.2 mg/L
Long term toxicity fish:	Pimephales promelas	clothianidin	Long term (28 d)	NOEC	20 mg/L
Bioaccumulation fish:	Not required; log Pow < 3				
Acute toxicity invertebrate:	Daphnia magna	clothianidin	Acute (48 h)	LC_{50}	> 40 mg/L
Chronic toxicity invertebrate:	Daphnia magna	clothianidin	Long term (21 d)	NOEC	0.12 mg/L
Acute toxicity algae:	Selenastrum capricornutum	clothianidin	Acute (96 h)	E_bC_{50}	55 mg/L
Acute toxicity sediment dwelling organism:	Chironomus riparius	clothianidin	Acute (48 h)	EC_{50}	0.029 mg/L
Chronic toxicity sediment dwelling organism:	Chironomus riparius	clothianidin	Long term (28 d)	EC_{15} =	0.72×10^{-3} mg/L
	Microcosm or mesocosm tests				
	EAC = 3.1 µg a.s./L				

Honeybees

Acute oral toxicity:	LD_{50} = 0.00379 µg a.s./bee LD_{50} = 3.9 µg TZNG/bee
Acute contact toxicity:	LD_{50} = 0.04426 µg a.s./bee

Other arthropod species

Test species	Stage	Test Substance	Dose	Endpoint	% Effect
	Laboratory tests				
Aphidius rhopalosiphi	adult	clothianidin	60 g a.s./ha	Mortality	100%
Typhlodromus pyri	adult	Clothianidin 50% WDG	60 g a.s./ha	Mortality Fertility	96.7%
Aleochara bilineata	adult	Clothianidin 50% WDG	75 g a.s./ha	Mortality Fertility	99.99%
Chrysoperla carnea	adult	Clothianidin 50% WDG	60 g a.s./ha	Mortality Fertility	97%
	Extended laboratory tests				
Aphidius rhopalosiphi	adult	Clothianidin 50% WDG	0.12-10 g a.s./ha	LR_{50} NOEC	1.086 g a.s./ha 0.37 g a.s./ha
Trichogramma cacoeciae	adult	Clothianidin 50% WDG	0.05-3 g a.s./ha	LR_{50} NOER	0.36 g a.s./ha 0.14 g a.s./ha
Pardosa spp	adult	Clothianidin FS 600	166 g a.s./ha maize	Mortality Feeding	6.3%
Pardosa spp	adult	Clothianidin FS 600	65 g a.s./ha rape seed	Mortality Feeding	-1%
Pardosa spp	adult	Clothianidin FS 600	140 g a.s./ha sugar beet	Mortality Feeding	13.4%
Pardosa spp	adult	Clothianidin FS 600	70 g a.s./ha sunflower	Mortality Feeding	21%
Pardosa spp	adult	Clothianidin FS 600	167 g a.s./ha barley	Mortality Feeding	1.4%
Poecilus cupreus	adult	Clothianidin 50% WDG	15-75 g a.s./ha	LR_{50}	> 75 g as./ha
Poecilus cupreus	adult	Clothianidin FS 600	462 g a.s./ha maize	Mortality Feeding	23.3%

Test species	Stage	Test Substance	Dose	Endpoint	% Effect
Poecilus cupreus	adult	Clothianidin FS 600	59 g a.s./ha rape seed	Mortality Feeding	33.83%
Poecilus cupreus	adult	Clothianidin FS 600	488 g a.s./ha sugar beet	Mortality Feeding	-14%
Poecilus cupreus	adult	Clothianidin FS 600	269 g a.s./ha sunflower	Mortality Feeding	29%
Poecilus cupreus	adult	Clothianidin FS 600	149 g a.s./ha barley	Mortality Feeding	16.19%
Poecilus cupreus	larvae	Clothianidin FS 600	467 g a.s./ha maize	Mortality	100%
Poecilus cupreus	larvae	Clothianidin FS 600	96 g a.s./ha rape seed	Mortality	97%
Poecilus cupreus	larvae	Clothianidin FS 600	162 g a.s./ha sugar beet	Mortality	65%
Poecilus cupreus	larvae	Clothianidin FS 600	488 g a.s./ha sugar beet	Mortality	47%
Poecilus cupreus	larvae	Clothianidin FS 600	269 g a.s./ha sunflower	Mortality	93%
Poecilus cupreus	larvae	Clothianidin FS 600	181 g a.s./ha barley	Mortality	97%
Poecilus cupreus	larvae (aged residue)	Clothianidin FS 600	73.8 µg a.s./kg dry soil	Mortality	13%
Aleochara bilineata	adult	Clothianidin FS 600	467 g a.s./ha maize	Mortality Fecundity	72%
Aleochara bilineata	adult	Clothianidin FS 600	105 g a.s./ha rape seed	Mortality Fecundity	92%
Aleochara bilineata	adult	Clothianidin FS 600	157 g a.s./ha sugar beet	Mortality Fecundity	18%

Test species	Stage	Test Substance	Dose	Endpoint	% Effect
Aleochara bilineata	adult	Clothianidin FS 600	488 g a.s./ha sugar beet	Mortality Fecundity	77%
Aleochara bilineata	adult	Clothianidin FS 600	269 g a.s./ha sunflower	Mortality Fecundity	29%
Aleochara bilineata	adult	Clothianidin FS 600	130 g a.s./ha barley	Mortality Fecundity	89.45%
Aleochara bilineata	adult	Clothianidin	100-250 µg a.s./kg dry soil	LR_{50} NOEC	> 250 µg a.s./kg = 150 µg a.s./kg
P. cupreus	larvae	Clothianidin	0.02-0.08 mg a.s./kg dry soil	LR_{50} NOEC	= 0.046 µg a.s./kg = 0.02 µg a.s./kg
	Semifield tests				
Typhlodromus pyri	adult	Clothianidin 50% WDG	9-150 g a.s./ha	LR_{50}	125.99 g a.s./ha
Aleochara bilineata	adult	Clothianidin FS 600	168 g a.s./ha barley	Mortality Fecundity	-22%
P. cupreus	larvae	Clothianidin FS 600	25 g a.s./unit, 100000 seeds/ha or 2 units/ha)	Reduction of survival rate	20%
	Field or semi-field tests Two field tests in winter wheat are available.				

Earthworms

Acute toxicity:	LC_{50} = 13.21 mg a.s./kg soil LC_{50} = 970 mg TZNG/kg soil
Reproductive toxicity:	Study is not acceptable. Not required as a field study is available (no treatment-related effects up to 225 g a.s./ha)

Soil micro-organisms

Nitrogen mineralization:	No effects up to 750 g a.s./ha
Carbon mineralization:	No effects up to 750 g a.s./ha

APPENDIX III

CLOTHIANIDIN

List of studies which were submitted during the evaluation process and were not cited in the draft assessment report:

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA, 1.11/08 (**Doc. J**)	Beeck, S.	2004a	Material accountability of TI 435 A techn./clothianidin - Analytical profile of process samples. Bayer CropScience AG, report no. 15-920-2215 March 10, 2004 GLP, unpublished
IIA, 1.11/09 IIA, 1.8/01 IIA, 1.9/02 IIA, 1.10/03 (**Doc. J**)	Riegner, K.	2004	Impurity profiles of clothianidin technical. Bayer CropScience AG September 8, 2004 non GLP, unpublished
IIA, 1.11/10 (**Doc. J**)	Kramer, H.T.	2004a	Five lot analysis of TI-435 technical. Covance, USA, report no. 6155-139 SumiTake, report no. DPCI087 September 30, 2004 GLP, unpublished
IIA, 1.11/11 IIA, 4.1.2/ 07 (**Doc. J**)	Kramer, H.T.	2004b	Method validation for the determination of "TAK 13" in TI-435 technical. Covance, USA, report no. 6155-140 SumiTake, report no. DPCI088 September 30, 2004 GLP, unpublished
IIA, 1.11/12 (**Doc. J**)	Kramer, H.T.	2004c	Nitrosamine analysis of five lots of TI-435 technical. Covance, USA, report no. 6155-142 SumiTake, report no. DPCI089 September 30, 2004 GLP, unpublished
IIA, 1.11/13 IIA, 1.9/01 IIA, 1.10/02 (**Doc. J**)	Akayama, A.	2005	New specification for clothianidin technical material. Sumitomo Chemical Takeda Agro January 6, 2005 Non-GLP, unpublished

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 1.11/14 (**Doc. J**)	Feldhues, E.	2005a	Determination of nitrosamines in TI 435 A techn./clothianidin. Amendment no. 1 Bayer AG, report no. G 05/0028/00 LEV May 23, 2005 GLP, unpublished
IIA, 1.11/15 (**Doc. J**)	Keppler, J.	2005	Ecotoxicological evaluation of clothianidin impurities "BAY 1", "BAY 3" and "BAY 4". Bayer CropScience AG March 30, 2005 Non-GLP, unpublished
IIIA, 2.5.2/ 02	Gueldner, W.	2004a	Viscosity of TI 435 FS 600 RED. Bayer CropScience AG, report no. 14 1050 5296 April 27, 2004 GLP, unpublished
IIIA, 2.7.1/ 03 IIIA, 2.7.3/ 02	Gueldner, W.	2004b	Storage stability and shelf life of TI 0435 FS 600 red. [Packaging material: HDPE] Bayer CropScience AG, report no. 06568-0249 November 11, 2004 Non-GLP, unpublished
IIA, 4.1.2/ 08 (**Doc. J**)	Krämer, F.	2002	Determination of volatile solvents in active ingredient of agrochemicals - GLC - internal standard (headspace). Bayer CropScience, report no. 2005-0013102-02 October 18, 2002 Non-GLP, unpublished
IIA, 4.1.2/ 09 (**Doc. J**)	Krämer, F.	2005	Validation of GLC-method 2005-0013102-02 - Determination of volatile solvents in active ingredient of agrochemicals, GLC - internal standard headspace - Specific solvent: "BAY 4", specific matrix: clothianidin (TI 435) Bayer CropScience, report no. VB1.8-2005-0013102 April 26, 2005 Non-GLP, unpublished
IIA, 4.1.2/ 10 (**Doc. J**)	Wanner, B.	2000	Analytical procedure for the argentometric determination of "BAY 6". Bayer AG, report no 2005-0000703-00 May 5, 2000 Non-GLP, unpublished
IIA, 4.1.2/ 11 (**Doc. J**)	Schröder, S.	2000	Validation report VB1-2005-0000703-00 E - Argentometric determination of "BAY 6". Bayer AG, report no. VB1-2005-0000703 May 9, 2000 Non-GLP, unpublished
IIA, 4.1.2/ 12 (**Doc. J**)	Beeck, S.	2003a	TI 435 A - Quantification of by-products by HPLC - internal standard. Analytical method 2005-0012602-03 E Bayer CropScience, report no. MO-03-004132 February 21, 2003 Non-GLP, unpublished
IIA, 4.1.2/13 (**Doc. J**)	Beeck, S.	2003b	Validation of HPLC-method 2005-0012602-03 - By-products of TI435 technical A, HPLC - internal standard. Bayer CropScience, report no. VB1-2005-0012602 February 18, 2003 Non-GLP, unpublished

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 4.1.2/ 14 (**Doc. J**)	Beeck, S.	2004b	TI 435 A - Quantification of by-products by HPLC - internal standard. Bayer CropScience, report no. 2005-0012603-04 June 8, 2004 Non-GLP, unpublished
IIA, 4.1.2/ 15 (**Doc. J**)	Beeck, S.	2004c	Validation of HPLC-method 2005-0012603-04 - By-products of TI435 technical A, HPLC - internal standard. Bayer CropScience, report no. VB1-2005-0012603 June 8, 2004 Non-GLP, unpublished
IIA, 4.1.2/ 16 (**Doc. J**)	Beeck, S.	2005	TI 435: HPLC-method 2005-0012603-04 - TI 435 A technical - byproducts HPLC internal standard - Separation of "BAY 2" and "BAY 3". Bayer CropScience AG April 21, 2005 Non-GLP, unpublished
IIA, 4.1.2/ 17 (**Doc. J**)	Sporenberg, W. Wilms, A.	2001	Extraction of nitrosamines, including pentane extraction in product TI-435. Bayer, report no. MO-01-022140 November 16, 2001 Non-GLP, unpublished
IIA, 4.1.2/ 18 (**Doc. J**)	Feldhues, E.	2005b	Validation of an analytical method for the determination of N-nitrosamines in TI 435 A techn. clothianidin. Bayer AG, report no. 2011-0597101-01 D May 30, 2005 Non-GLP, unpublished

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 5.1/ 02	Ohta, K.; Mikata, K.	2000	Determination of metabolites of TI-435 in major tissues of rats. Takeda Chemical Industries, Ltd., Tokyo, Japan, report no. 110286 December 20, 2000 GLP, unpublished
IIA, 5.8.1/ 18	Brown, L.D; Wheeler, C.R.; Korte, D.W.	1988	Acute oral toxicity of nitroguanidine in male and female rats. US Army Medical Research and Development Command, report no. 264 March 1988 Non-GLP, unpublished
IIA, 5.8.1/ 19	Krötlinger	1992	Nitroguanidine - summary assessment of toxicological data Bayer AG, report MO-02-013556 May 1992 Non-GLP, unpublished
IIA, 5.8.1/ 20	Coppes, V.G.; Gomez, C.L.; Magnuson, D.K.; Korte, D.W.	1988	Developmental toxicity potential of nitroguanidine in rabbits. Letterman Army Institute of Research, Presidio of San Francisco, California, USA. Institute report no. 298 September 1988 Non-GLP, published

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 5.8.2/ 13	Krötlinger, F.	2000b	"BAY 3" - Acute oral toxicity study in male and female Wistar rats. Bayer AG, report no. PH 30096 August 1, 2000 GLP, unpublished
IIA, 5.8.2/ 14	Herbold, B.	2000c	"BAY 3" - *Salmonella*/microsome test - Plate incorporation and preincubation method. Bayer AG, report no. PH 30172 August 23, 2000 GLP, unpublished
IIA, 5.8.2/ 15	Vohr, H.W.	2000b	"BAY 3" - Study for the skin sensitization effect in guinea pigs. Bayer AG, report no. PH 30219 September 4, 2000 GLP, unpublished
IIA, 5.8.2/ 16	Leuschner, J.	2000a	Acute eye irritation study of "BAY 3" by instillation into the conjunctival sac of rabbits. LPT Laboratory, report no. 9301/423/95 Bayer AG, report no. R 7805 May 8, 2000 GLP, unpublished
IIA, 5.8.2/ 17	Leuschner, J.	2000c	Acute skin irritation test (patch test) of "BAY 3" in rabbits. LPT Laboratory, report no. 9300/423/95 Bayer AG, report no. R 7804 April 28, 2000 GLP, unpublished
IIA, 5.8.2/ 18	Sokolowski, A.	2003	*Salmonella typhimurium* reverse mutation assay. RCC-CCR GmbH, Germany, report no. 803401 Bayer CropScience SA, report no. MO-03-015766 December 3, 2003 GLP, unpublished
IIA, 5.8.2/ 19	Poth, A.	2003	Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79/HPRT) with TI-435. RCC-CCR GmbH, Germany, report no. 803402 Bayer CropScience SA, report no. MO-03-015743 December 9, 2003 GLP, unpublished
IIA, 5.8.2/ 20	Schulz, M.	2003	*In vitro* chromosome aberration test in Chinese hamster V79 cells with TI-435. RCC-CCR GmbH, Germany, report no. 803403 Bayer CropScience SA, report no. MO-03-015744 December 9, 2003 GLP, unpublished
IIA, 5.8.2/ 21	Honarvar, N.	2003a	Micronucleus assay in bone marrow cells of the mouse with TI-435. RCC-CCR GmbH, Germany, report no. 803404 Bayer CropScience SA, report no. MO-03-015745 December 10, 2003 GLP, unpublished
IIA, 5.8.2/ 22	Honarvar, N.	2003b	*In vivo/in vitro* unscheduled DNA synthesis in rat hepatocytes with TI-435. RCC-CCR GmbH, Germany, report no. 803405 Bayer AG, report no. MO-03-015747 December 9, 2003 GLP, unpublished

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 5.8.2/ 23	Wanner, B.; Heimann, K.G.	2005	Clothianidin technical - genotoxicological testing. Bayer CropScience AG June 1, 2005 Non-GLP, unpublished

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
None			

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Repo.rt No. GLP or GEP status (where relevant) Published or not
IIA, 7.1.1.2.1/ 05	Fliege, R.	2004a	[^{14}C]-Nitroguanidine: Aerobic soil degradation in three soils. Bayer CropScience AG, report no. MEF-04/220 SumiTake, report no. DEFT045 June 28, 2004 GLP, unpublished
IIA, 7.1.1.2.2/ 05	Peters, B.	2004	Determination of the residues of TI-435 (600 FS) in/on soil and winter wheat in Germany, southern France and Great Britain. 1. Interim Report Bayer CropScience AG, report no. MEF-04/206 SumiTake, report no. DEFT047 April 30, 2004 GLP, unpublished
IIA, 7.1.2/07	Fliege, R.	2004b	[^{14}C]-Nitroguanidine: Adsorption/desorption on three soils. Bayer CropScience AG, report no. MEF-04/219 SumiTake, report no. DEFT046 June 23, 2004 GLP, unpublished
IIIA, 9.2.1/ 03	Hammel, K.; Bingemann, R.	2004a	Predicted environmental concentrations of clothianidin (TI-435) and its metabolites in ground water recharge based on calculations with FOCUS-PEARL considering kinetic sorption. Bayer CropScience AG, report no. MEF-04/338 October 5, 2004 Non-GLP, unpublished
IIIA, 9.2.3/ 02	Hammel, H.; Bingemann, R.	2004b	Predicted environmental concentrations of clothianidin (TI-435) and its metabolites in surface water and sediment. Bayer CropScience AG, report no. MEF-04/320 August 2, 2004 Non-GLP, unpublished

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIIA, 10.1.2/ 05	Wolf, Ch.	2005	Generic field monitoring of birds and mammals on maize and beet fields in Austria. Bayer CropScience AG, report no. WFC/FS017 January 20, 2005 GLP, unpublished
IIIA, 10.3/ 13	Wolf, Ch.; Fülling, O; Wilkens, S.	2003	Field monitoring of small mammals on maize fields drilled with Mesurol FS 500 dressed seeds in Germany. Bayer CropScience AG, report no. WFC/FS 06 February 6, 2003 GLP, unpublished
IIIA, 10.5.2/ 03	Maus, Ch.	2003	Evaluation of the effects of aged residues of TI 435 FS 250 on larvae of carabid beetles (*Poecilus cupreus*) under extended laboratory test conditions. Bayer CropScience AG, report no. Maus/PCL003 February 5, 2003 GLP, unpublished
IIIA, 10.5.2/ 04	Neumann, P.	2004	Evaluation of the effects on *Poecilus cupreus* larvae after the drilling of maize seeds dressed with TI-435 FS 600 in a semi-field study. Bayer CropScience AG, report no. NNP/PC022 March 16, 2004 GLP, unpublished

APPENDIX IV

List of uses supported by available data

Clothianidin

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	mg as /seed min max	kg as/ha min max		
Sugar beet / Fodder beet	EU - N EU – S	TI-435 FS 600	F	sucking and biting insects	FS	600 g/L	seed treatment	BBCH 00	1	n.a.	n.a.	0.15 – 0.6	0.0195 – 0.078	n.a.	-
Maize	EU - N EU - S	TI-435 FS 600	F	sucking and biting insects	FS	600 g/L	seed treatment	BBCH 00	1	n.a.	n.a.	0.5	0.050	n.a.	-

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

APPENDIX IV

List of uses supported by available data

08 November 2005