Section A1 Applicant

Annex Point IIA1

1.1 Applicant	Name: Bayer Environmental Science SAS Address: 16 rue Jean-Marie Leclair CP 106 69266 Lyon Cedex 09 France Main Contact: [redacted] Telephone: Fax number: E-mail address: Second contact: [redacted] Telephone: Fax number: E-mail address:
1.2 Manufacturer of Active Substance (if different)	Current production site Name: Bayer CropScience AG Address: Industiral Operations Alfred Nobel-Strasse 50 D-40789 Monheim am Rhein Contact: [redacted] Telephone: Fax number: E-mail address: Location of manufacturing plant: [redacted]
1.3 Manufacturer of Product(s) (if different) 1) Product 1 2) Product 2	**1. Imidacloprid GR 0.5 (Quick Bayt®)** Name: Bayer Environmental Science SAS Address: 16 rue Jean-Marie Leclair CP 106 69266 Lyon Cedex 09 France Contact: [redacted] Telephone: Fax number: E-mail address: Location of formulating plant: [redacted] **2. Imidacloprid GL 2.15 (Maxforce® White IC)** Name: Bayer Environmental Science SAS Address: 16 rue Jean-Marie Leclair CP 106 69266 Lyon Cedex 09 France Contact person (1): [redacted] Telephone: Fax number: E-mail address: Location of formulating plant: [redacted]

Section A1 Applicant

Annex Point IIA1

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/06/28
Materials and methods	The applicant's version is acceptable.
Conclusion	Applicant's version is adopted
Reliability	4
Acceptability	acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*

2.10 Exposure data in conformity with Annex VIIA to Council Directive 92/32 EEC (OJ No L 154, 5.6.1992, p.1) amending Council Directive 67/548/EEC

Subsection			**Official use only**
2.10.1	**Human exposure towards active substance**		
2.10.1.1	**Production**		
	i) Description of process	**Active substance:** Technical imidacloprid is produced at an industrial production plant [redacted], by trained professionals using a [redacted] described in Document IIIA Confidential Appendix. The active ingredient is then formulated to end products for the crop and biocide marketplace.	
	ii) Workplace description	**Active substance:** Technical imidacloprid is produced [redacted]. The [redacted] has an area of about 350 ha whereas BCS is located on a limited area of about 14.2 ha. The number of employees at the [redacted] site is at 1050. The [redacted] site is Seveso II classified. The amount of highly dangerous substances is in all plants above the limits given by German legislation (Bundesimmissionsschutz-Gesetz / Störfallverordnung). The BCS-site is certified according to DIN ISO 9001 (quality management) and DIN ISO 14001 (environmental management). The site has been audited and been shown to be working according to BCS production guidelines. It is one of BCS principles, that BCS conduct its business with respect and care for the environment and without compromising the health and safety of people, whether employees, customers, or citizens around the world. The production lines are dedicated to imidacloprid, and the product line is cleaned only for maintenance purposes, any effluent from cleaning the production line is incinerated. There are no direct releases to water or soil.	

ii) Workplace description	The production line operates as a closed system, with the whole process fully automated by an electronic process control system located in a control room. The equipment consists of reactors, distillation columns, filters, centrifuges, dryers, vacuum pumps, absorptions columns and filling machines. Weighing ingredients, charging equipment and packaging are carried out by employees in a ventilated semi-open area with contaminated air being filtered before leaving the building. Air flow exchange represents > 5 changes per hour. The manufacture line is operated by 5 staff who works in a five shift pattern of 8 hours (Sundays 12 hours). 330 days and 60 people a year are assigned to imidacloprid production; this constitutes approximately 40% of the production workers time (rotation between different lines). During the production of imidacloprid charging ingredients, filling and packaging, the following personal safety measures are required: dust masks (ABEK P3 - dust filter), protective impermeable one-way clothing, protective rubber or butyl gloves, safety glasses and helmets. For cleaning, depending on the type, circumstances and extent of the cleaning process and also with regard to the estimated hazards, the employees at the Imidacloprid plant will use their personal protection clothing in a graduated way. - while cleaning the imidacloprid filling station, employees will use their dusk mask, one-way protecting clothing and rubber gloves - on opening a pipe filled with hazardous substances (e.g. chlorine) the employee has to wear a mask (charcoal, rubber made) or maybe he has to use a breathing apparatus together with full protection clothing (rubber made) and rubber gloves. Occupational medical surveillance (see Point 6.12.1/01, Document M-245951-01-1) has been performed every two years on a routine basis since 1993 at [redacted]. 65 workers were assessed as having been exposed to ingredients and imidacloprid technical during its production. The surveillance did not reveal any unwanted effects in the workers. The examinations included the following laboratory parameters , medical and technical examinations:	

	<table><tr><td>Laboratory examinations</td><td>BSR, Full blood count, AST, ALT, y-GT, Glucose Creatinine Cholesterol Urine status</td></tr><tr><td>Medical examinations</td><td>History, Full physical examination with orientating neurological status (reflexes, sensitivity coordination) Skin status. Examinations based on the German rules G25 (driving/steering), G26.2/3 (breathing protection), G37 (VDU work), B04 (BAPRO)</td></tr><tr><td>Technical examinations</td><td>Lung function ECG, Ergometry Vision testing Audiometry Chest X-Ray Sonography (if necessary)</td></tr></table> Since 1993 no accidents with imidacloprid occurred in the workers and no consultations of the Medical Department due to work or contact with Imidacloprid were required. No imidacloprid-related allergenicity observations could be determined since 1993.	
iii) Inhalation exposure	**Active substance:** Technical imidacloprid is produced at [redacted]. Therefore assessment of inhalation exposure is necessary. Due to i) Production operating as an automated closed system, with the whole process fully automated by an electronic process control system located in a control room ii) Local extraction ventilation of 5 changes of air per hour (~100 000m^3/hr) throughout site. iii) Maximum work place limits of 0,7 mg/m3 imidacloprid (regularly monitored) iv) PPE equipment including a ABEK P3 - dust filter Inhalation exposure is not expected / negligable for the people involved in the production of imidacloprid. Since 1993 no accidents with Imidacloprid occurred in the workers and no consultations of the Medical Department due to work or contact with imidacloprid were required. In the instance when an accidental exposure may occur, the procedures in the active MSDS would be followed (Document: M-246172-02-1).	

	iv) Dermal exposure	**Active substance:** Technical imidacloprid is produced at [redacted]. Therefore assessment of dermal exposure is necessary. Due to production operating as an automated closed system, with the whole process fully automated by an electronic process control system located in a control, and the effective personal protective measures worn when charging ingredients, filling and packaging: goggles, rubber gloves, ABEK P3 - dust filter, impermeable one-way clothing based on coated paper (for example "Tyvec" from Dupont) Dermal exposure is not expected for the people involved in the production of imidacloprid. Since 1993 no accidents with Imidacloprid occurred in the workers and no consultations of the Medical Department due to work or contact with imidacloprid were required. No imidacloprid-related allergenicity observations could be determined since 1993. In the instance when an accidental exposure may occur, the procedures in the active MSDS would be followed (Document: M-246172-02-1).
2.10.1.2	**Intended use(s)**	
1.Professional Uses		
	i) Description of process	Technical imidacloprid is not intended for use as a biocidal product. It is always reformulated into a biocidal product before use. See sections A2.10_02 and A2.10_03 for formulations Imidacloprid GR 0.5 and Imidacloprid GL 2.15.
	ii) Workplace description	Not applicable
	iii) Inhalation exposure	Not applicable
	iv) Dermal exposure	Not applicable
2. Non-professional Uses including the general public		Technical imidacloprid is not intended for use as a biocidal product. It is always reformulated into a biocidal product before use. See sections A2.10_02 and A2.10_03 for formulations Imidacloprid GR 0.5 and Imidacloprid GL 2.15.
	i) via inhalational contact	Not applicable
	ii) via skin contact	Not applicable
	iii) via drinking water	Not applicable
	iv) via food	Not applicable
	v) indirect via environment	Not applicable

2.10.2 Environmental exposure towards active substance		
2.10.2.1 Production		
i) Releases into water	**Active substance:** Technical imidacloprid is produced at [redacted]. Therefore assessment of release into water is necessary. Gases and liquid waste from the imidacloprid production and cleaning process are incinerated at an incineration plant. Incineration occurs at several incineration plants which are run by [redacted]. There is no solid waste to release. Hence there is no release to soil or water. In addition other waste water from the site is incinerated in two ways: a) Waste water like kitchen cleaning, toilets etc. goes untreated to the central waste water treatment, which is run by [redacted]. There it is biological degraded. b) Waste water with a very low content of chemicals, which is are known that they are sensible towards alkaline degradation, are pretreated with a sodium hydroxide solution. The sources of this waste water are scrubbers or water from cleaning the production plant itself. The resulting water is then sent to the central waste water station. Mechanical and biological treatment methods are employed. The permissible discharge level is about 6000mg/l DOC (dissolved organic carbon). In the instance when an accidental exposure may occur, the procedures in the active MSDS are followed (M-246172-02-1). The [redacted] is certified according to DIN ISO 14001 (environmental management).	
ii) Releases into air	**Active substance:** Technical imidacloprid is produced at [redacted]. Therefore assessment of release into air is necessary. Exhausted air is handled in three separate ways:	

ii) Releases into air	a) Normal air, that means "not contaminated air" or compartment air, is exhausted with a frequency of 5 air changes per hour and leaves the plant continuously without any further treatment. b) Secondly, from areas where loading chemicals or filling produced imidacloprid into packing, the dust contaminated air is locally exhausted and cleaned by a double filter system before it leaves the plant. The filters are cleaned regularly, controlled by the differential pressure at the filter medium, and disposed by incineration. The current permissible discharge level of total dust (including highly toxic substances) is at 2 mg/m³ and is monitored on a yearly basis. These controls have shown levels of about 1 mg/m³. c) Waste air (or more accurately waste gas) from closed systems (vessels) is collected and transferred to a central incineration plant here at the Dormagen site. It is incinerated together with the waste gases of more then 10 other plants. The emissions are controlled continuously and deviations from permitted values are reported to the German authorities. Imidacloprid has a working place limit of about 0, 7 mg /m³ air. The [redacted] is certified according to DIN ISO 14001 (environmental management).	
iii) Waste disposal	**Active substance:** Technical imidacloprid is produced at [redacted]. Therefore assessment of waste disposal is necessary. Gases and liquid waste from the imidacloprid production and cleaning process are incinerated at an incineration plant. Incineration occurs at several incineration plants which are run by Bayer Industry Services. There is no solid waste to release. Incineration occurs at several incineration plants which are run by [redacted]. The [redacted] is certified according to DIN ISO 14001 (environmental management).	

2.10.2.2 Intended use(s)	Technical imidacloprid is not intended for use as a biocidal product. It is always reformulated into a biocidal product before use. See Document II-B Imidacloprid GR 0.5 and Imidacloprid GL 2.15 for exposure form intended uses from formulations.	
Affected compartment(s):		
Water	Not applicable	
Sediment	Not applicable	
Air	Not applicable	
Soil	Not applicable	
Predicted concentrations in the affected compartment(s)		
Water	Not applicable	
Sediment	Not applicable	
Air	Not applicable	
Soil	Not applicable	

Confidential Imidacloprid	Information considered as confidential, therefore located in A12 section.	

A2.10/01 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/05/03 - human health
Materials and methods	acceptable
Conclusion	Imidacloprid is produced [redacted]. The exposure during the production of the active substance is not assessed by the rapporteur under the requirements of the BPD. However, the rapporteur assumes that the production is performed in conformity with national and European occupational safety and health regulations.
Reliability	Not applicable, because given information are not based on standard tests.
Acceptability	acceptable
Remarks	No remarks
Date	2007/04/12 - environmental
Materials and methods	The applicant's version is acceptable
Conclusion	not applicable
Reliability	not applicable
Acceptability	acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

2.10 Exposure data in conformity with Annex VIIA to Council Directive 92/32 EEC (OJ No L 154, 5.6.1992, p.1) amending Council Directive 67/548/EEC

Subsection		Official use only
2.10.1 Human exposure towards active substance		
2.10.1.1 Production		
i) Description of process	**Formulation: Imidacloprid GR 0.5** Imidacloprid GR 0.5 is manufactured at an industrial production plant [redacted]) by trained professionals using a 3-step process described in Document IIIB Confidential Appendix.	
ii) Workplace description	**Formulation: Imidacloprid GR 0.5** Imidacloprid technical is formulated into Imidacloprid GR 0.5 at [redacted]. The site covers 1.5 hectares and employs 50 people. Dimensions of the Imidacloprid GR 0.5 production area is 186 m2 (130 m3), whilst the packing department are 91.6 m2 (274.8 m3). [redacted] is GMP certified, and works according the legislation of the Netherlands BRZO (Decision Risk Heavy Accidents), which is a derived legislation of the Seveso II. Additionally it works according the Dutch Environment Legislation.	

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

	The production line is dedicated to imidacloprid. The floor of the production area is cleaned daily. Besides that the department is cleaned with water on a monthly base. At the end of a production run the whole installation is empty and the palletiser is cleaned at the end of the day. All waste water is incinerated. Wipe tests are also conducted. The production line is an open system and dust is exhausted by means of exhaust points. By means of directed exhaustion the 'contaminated' air is exhausted from the working area. The contamination in the air comprises of small dust particles. These particles are filtered from the air by means of a filter system. Dust emission is subject to the local (Barneveld) environmental license and is fixed on 5 mg/m3. The production line is operated by 6-8 staff (2 staff load the mixer and press the granules and four to six pack the granules).. Production and packaging into final sizes packs all occur on one site. With respect to personal protective equipment, in the production line safety glasses, safety shoes, equipped with steel noses and certified permeable pharmaceutical clothes are worn. Additionally during weighing of the active ingredients P2-duskmasks and long protective gloves are worn. All production people wear hearing protection, tested in compliance with EN 253-2. For cleaning, water resistant impermeable clothing is worn in addition to other safety measure already described.	

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

	[redacted]V provided the following statement with respect to occupational surveillance. To whom it may concern: I, B.R. Woudstra, MD, PhD, medical doctor and occupational health specialist, employed by ArboExtra, Herenwal 124, 8841 BE Heerenveen, the Netherlands, declare that after careful examination of the report "Onderzoek naar de blootstelling aan gevaarlijke stoffen bij [redacted], and after examining all medical reports of employees [redacted] in our possession; that no groups or individuals were identified with health problems connected to the production or handling of Quickbait* or Flybait. The company [redacted] produces these products since almost 5 years, during which, to my knowledge, no related employee health incidents were reported or recognized. March 6 2006, Heerenveen, the Netherlands Bouke Woudstra, MD, PhD, # Translation: "Investigation into the exposure to dangerous chemicals at [redacted], by ing R.H. Bouius RAH (registered occupational hygienist) Cyclus Arboprojecten Amsterdam, 26-8-2005" * Quickbait = Imidacloprid GR 0.5 Hence, [redacted] has been producing Imidacloprid GR 0.5 for 5 years. Since this time no related employee health problems were reported or recognised.	

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

iii) Inhalation exposure	**Formulation: Imidacloprid GR 0.5** Due to i) PPE equipment (including a P2 dust mask during loading ingredients) ii) The ventilation in the open area 11000m^3/hr (8.4 air changes/hr) iii) The low vapour pressure of imidacloprid iv) The Imidacloprid GR 0.5 formulation, has less than 1% of its particles with a size less than 75µm (see Imidacloprid Document III-B 3.II, M-257402-01-1). Thus Imidacloprid GR 0.5 is not considered to be a powder formulation containing a significant proportion (e.g. > 1% on a weight basis) of particles with particle size MMAD < 50 µm. Inhalation exposure is not expected for the people involved in the production/packaging of Imidacloprid GR 0.5. [redacted] has been producing Imidacloprid GR 0.5 for 5 years. Since this time no related employee health problems were reported or recognised. In the instance when an accidental exposure may occur, the procedures in the active and formulation MSDS would be followed (Documents: M-246172-02-1 & M-266496-01-1).If hazardous material is released on a larger scale the [redacted] emergency plan is followed.	
iv) Dermal exposure	**Formulation: Imidacloprid GR 0.5** With respect to personal protective equipment, in the production line safety glasses, safety shoes, equipped with steel noses and certified permeable pharmaceutical clothes are worn. Additionally during weighing of the active ingredients P2-duskmasks and long protective gloves are worn. Dermal exposure is not expected for the people involved in the production/packaging of Imidacloprid GR 0.5. Since initial production of Imidacloprid GR 0.5 at [redacted] 5 years ago, no related employee health incidents were reported to the Medical department, or accidents. In the instance when an accidental exposure may occur, the procedures in the active and formulation MSDS would be followed (Documents: M-246172-02-1 & M-266496-01-1). If hazardous material is released on a larger scale the [redacted] emergency plan is followed.	
2.10.1.2 Intended use(s) **1.Professional Uses**		

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

i) Description of process	Imidacloprid GR 0.5 is a granule bait formulation insecticide which contains the active substance imidacloprid at a concentration of 0.5 % w/w. The product is used for fly control in commercial animal housings. Imidacloprid GR 0.5 can be applied in two ways: • As a granule placed in small baiting points, (free, small vessels or suitable proprietary fly bait stations) on dry level surfaces. Not for use on pathways or manure • As a paint on application to suitable fly resting sites (e.g. walls, joists, window ledges and suitable fittings). Additionally it can be painted onto discrete areas, e.g. sheets of cardboard which are then hung in areas frequented by flies. Cards are removed when no longer effective and disposed of as contaminated waste. The quantity of Imidacloprid GR 0.5 applied in animal housings is dependent on the floor area. The application rate is 2 g of formulated product per square metre of floor area, giving a target application rate of 0.01 g active ingredient per 1 m^2 of total floor area. The product may be applied up to eight times per year (April – October), with a minimum interval of 21 days between applications. Operators may be exposed when applying the granule directly or during mixing and application of the paint. Post-application exposure occurs on disposal of granules, and cleaning painting apparatus.	
ii) Workplace description	For both application of the granule in small baiting points and as a paint on product 500 m^2 floor area/day is considered to be the treated area. Personal protective equipment worn by professional contractors and framers includes gloves.	
iii) Inhalation exposure	Estimation of exposure are given in Document II-B_Imidacloprid GR 0.5 of the dossier	
iv) Dermal exposure	Estimation of exposure are given in See Document II-B_Imidacloprid GR 0.5 of the dossier	
2. Non-professional Uses including the general public	The product is for professional use only. Secondary exposure as a consequence of professional use of the product is discussed in Document II-B_IMIDACLOPRID GR 0.5 of the dossier	
i) via inhalational contact	Non-professional use is not considered	
ii) via skin contact	Non-professional use is not considered	
iii) via drinking water	Non-professional use is not considered	
iv) via food	Non-professional use is not considered	

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

v) indirect via environment	Non-professional use is not considered	
2.10.2 Environmental exposure towards active substance		
2.10.2.1 Production		
i) Releases into water	**Formulation: Imidacloprid GR 0.5** No release, the solid and fluid waste is collected and transported to an authorized waste disposal company, which is licensed to eliminate waste by incineration. Waste water from cleaning is also incinerated. In the instance when an accidental exposure may occur, the procedures in the active and formulation MSDSs are followed (Documents: M-246172-02-1 & M-266496-01-1). If hazardous material is released on a larger scale the [redacted] emergency plan is followed. [redacted] works according the Dutch Environment Legislation.	
ii) Releases into air	**Formulation: Imidacloprid GR 0.5** Current permissible discharge levels exist at 5 mg/m^3 total dust, and are subject to the local environmental license (Barneveld). Ventilation of outlet air in the Imidacloprid GR 0.5 production area is generated by two filter systems. The total filter capacity is together 11000m³/h. When the capacity of the filters is going down (measured on a regular base) the filters are cleaned, and the solid waste is transported to the AVR for incineration. If hazardous material is released on a larger scale the [redacted] emergency plan is followed. [redacted] works according the Dutch Environment Legislation.	
iii) Waste disposal	**Formulation: Imidacloprid GR 0.5** The solid and fluid waste is collected and transported to an authorized waste disposal company, where it is eliminated in incineration facilities. Waste water from cleaning is also incinerated. [redacted] works according the Dutch Environment Legislation.	

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

2.10.2.2 Intended use(s)		
Affected compartment(s):		
Water	See Document II-B_Imidacloprid GR 0.5 of the dossier	
Sediment	See Document II-B_Imidacloprid GR 0.5 of the dossier	
Air	See Document II-B_Imidacloprid GR 0.5 of the dossier	
Soil	See Document II-B_Imidacloprid GR 0.5 of the dossier	
Predicted concentrations in the affected compartment(s)		
Water	See Document II-B_Imidacloprid GR 0.5 of the dossier	
Sediment	See Document II-B_Imidacloprid GR 0.5 of the dossier	
Air	See Document II-B_Imidacloprid GR 0.5 of the dossier	
Soil	See Document II-B_Imidacloprid GR 0.5 of the dossier	

A2.10/02 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/05/03 - human health
Materials and methods	Acceptable
Conclusion	Imidacloprid GR 0.5 is produced in the EU. The exposure during the formulation of the biocidal product is not assessed by the rapporteur under the requirements of the BPD. However, the rapporteur assumes that the formulation is performed in conformity with national and European occupational safety and health regulations.
Reliability	Not applicable, because given information are not based on standard tests.
Acceptability	acceptable
Remarks	No remarks
Date	2007/04/12 - environmental
Materials and methods	The applicant´s version is acceptable.
Conclusion	not applicable.
Reliability	not applicable.
Acceptability	acceptable.
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

A2.10/03 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

2.10 Exposure data in conformity with Annex VIIA to Council Directive 92/32 EEC (OJ No L 154, 5.6.1992, p.1) amending Council Directive 67/548/EEC

Subsection		Official use only
2.10.1	**Human exposure towards active substance**	
2.10.1.1	**Production**	
i) Description of process	**Formulation: Imidacloprid GL 2.15** Imidacloprid GL 2.15 is manufactured at an industrial production plant inside the EU ([redacted] by trained professionals using a [redacted] process scribed in Document IIIB Confidential Appendix.	
ii) Workplace description	**Formulation: Imidacloprid GL 2.15** Imidacloprid technical is formulated into Imidacloprid GL 2.15 at [redacted] The site covers .9.7 hectares and employs 420 people. This site is Seveso II classified (high threshold) which is within the Störfall Verordnung ([redacted] classification. It has the GMP/FDA certificate from the Pharmaceutical industry. Additionally the area for Formulation and Filling of Imidacloprid GL 2.15 is legislated by "4.BimSchV Nr. 4.2 Spalte 2" (Bundes Immissions Schutz Verordnung). The production line is not dedicated to any single product (multi-purpose equipment), with the exception of the filling apparatus, which is dedicated equipment. After each campaign the production lines are cleaned down and the waste water recycled by an external company which is a specialist in waste disposal. The production line is a closed system (mixing vessel and filling apparatus). Weighing of ingredients occurs in a ventilated weighing cabin with an air renewal of greater than 20 times per hour (air flow is > 6900m^3/hr, with 80% representing HEPA filtered air and 20% fresh air. In the formulation area air renewal is greater than 10 times per hour (air flow is > 3900m^3/hr.). Additionally the formulation area pressure is higher than the surrounding area. Filling and packaging occurs under normal air pressure.	

A2.10/03 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

The production line is operated by 7 staff. Formulation workers are dedicated to one task within the process, whilst filling/packaging employees rotate between roles. Production and packaging into the final product (30g cartridges) all occur on the one site.

During the production of Imidacloprid GL 2.15 the following personal safety measures are required:

Formulation: cap, safety goggles, certified permeable pharmaceutical clothes, safety shoes.
In addition if handling ingredients and open product: mask (3M, 9332), gloves (UVEX Rubifix S or UVEX S6 Profabutyl).

For cleaning and maintenance : cap, safety goggles, gloves (only for cleaning: UVEX Rubifix S or UVEX S6 Profabutyl), certified permeable pharmaceutical clothes, safety shoes,

Occupational medical surveillance (see Point A6.12.1/04, Document M-267506-01-1) has been performed on a routine basis since 1998 at [redacted] About 7 workers are exposed to imidacloprid technical and formulation during its production annually (14 in total since 1998). The surveillance did not reveal any unwanted effects in the workers. The examinations included the following laboratory parameters , medical and technical examinations:

Laboratory examinations: on initiation of employment	BSR, Full blood count, AST, ALT, y-GT, Glucose Creatinine Cholesterol Urine status
Medical Examinations: on initiation of employment and every three years	History, Full physical examination with orientating neurological status (reflexes, sensitivity coordination) Skin status. Examinations based on the German rules G25 (driving/steering), G26.2/3 (breathing protection), G37 (VDU work), B04 (BAPRO)
Technical examinations: on initiation of employment and every three years	Lung function Vision testing Audiometry

Since 1998 no accidents during Imidacloprid GL 2.15 formulation occurred in the workers and no consultations of the Medical Department due to work or contact with imidacloprid were required.

A2.10/03 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

iii) Inhalation exposure	**Formulation: Imidacloprid GL 2.5** Due to i) Weighing of ingredients in a weighing cabin with an air renewal > 20 times / hr ii) Production (vessel and filling) operating as a closed system with an air renewal > 10 times / hr under high pressure compared to the surroundings iii) PPE equipment including a 3M, 9332 mask when handling ingredients and open product. iv) The low vapour pressure of imidacloprid (vapour pressure < 1 x 10^{-2} pa at 20°C, see Imidacloprid Document III-A 3.2). Inhalation exposure is not expected for the people involved in the production of imidacloprid Since 1998 no accidents during Imidacloprid GL 2.15 formulation have occurred in the workers and no consultations of the Medical Department due to work or contact with imidacloprid were required. In the instance when an accidental exposure may occur, the procedures in the active and formulation MSDS would be followed (Documents: M-246172-02-1 & M-266764-01-1)	
iv) Dermal exposure	**Formulation: Imidacloprid GL 2.5** Due to the production line operating as a closed system (mixing vessel and filling apparatus), and the effective personal protective measures worn during the above mentioned tasks (cap, safety goggles, certified permeable pharmaceutical clothes, safety shoes, mask (3M, 9332), gloves (UVEX Rubifix S or UVEX S6 Profabutyl) dermal exposure is not expected for the people involved in the production/re-packaging of Imidacloprid GL 2.15 Since 1998 no accidents during Imidacloprid GL 2.15 formulation have occurred in the workers and no consultations of the Medical Department due to work or contact with imidacloprid were required. In the instance when an accidental exposure may occur, the procedures in the active and formulation MSDS would be followed (Documents: M-246172-02-1 & M-266764-01-1).	
2.10.1.2 Intended use(s) 1.Professional Uses		

A2.10/03 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

	i) Description of process	Imidacloprid GL 2.15 is a ready to use insecticidal gel bait for the control of cockroaches for public hygiene, nuisance control and food storage practice. The product contains 2.15 % w/w imidacloprid and is effective against German cockroaches *(Blattella germanica)*, Brown-banded cockroaches *(Supella longipalpa)*, Oriental cockroaches *(Blatta orientalis) and* American cockroaches *(Periplanata americana)* both as nymphs and adults. The product may be used to control cockroaches in: Domestic premises (including kitchens), food handling areas, continuously occupied public buildings and small scale animal housings. The application rate is adjusted to the size of the infestation and the type of cockroach found ranging between 0.1 -0.3g product / m^2. Operators may be at risk of dermal exposure when sealing partially used cartridges, with the end cap provided by the manufacturer, and/or when removing the end cap.	
	ii) Workplace description	For a usual working day it can be expected that the end cap be handled five times for sealing and opening the cartridge (e.g. due to treatment at different locations). Personal protective equipment worn by professional contractors when using Imidacloprid GL 2.15 will include gloves.	
	iii) Inhalation exposure	Estimation of exposure are given in Document II-B_Imidacloprid GL 2.15 of the dossier	
	iv) Dermal exposure	Estimation of exposure are given in See Document II-B_Imidacloprid GL 2.15 of the dossier	
2. Non-professional Uses including the general public		The product is for professional use only. Secondary exposure as a consequence of professional use of the product is discussed in Document II-B_IMIDACLOPRID GL 2.15 of the dossier	
	i) via inhalational contact	Non-professional use is not considered	
	ii) via skin contact	Non-professional use is not considered	
	iii) via drinking water	Non-professional use is not considered	
	iv) via food	Non-professional use is not considered	
	v) indirect via environment	Non-professional use is not considered	
2.10.2	**Environmental exposure towards active substance**		
2.10.2.1	**Production**		

A2.10/03 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

i) Releases into water	**Formulation: Imidacloprid GL 2.5** No release, the waste water is recycled by a company, which is a specialist in waste disposal by incineration. Discharge level for water is set at Level 0. Additionally, the area for Formulation and Filling of Imidacloprid GL 2.15 is legislated by "4.BimSchV Nr. 4.2 Spalte 2" (Bundes Immissions Schutz Verordnung) [redacted] is monitored for water leaving the site. They have a limits for MKW (Mineralkohlenwasserstoffe= mineral hydrocarbons: 10mg/liter) and LHKW (halogenierte Mineralkohlenwasserstoffe= halogenated mineral hydrocarbons 0,1mg/liter). In the instance when an accidental exposure may occur, the procedures in the active and formulation MSDSs are followed (Documents: M-246172-02-1 & M-266764-01-1).	
ii) Releases into air	**Formulation: Imidacloprid GL 2.5** Not applicable to the formulation of Imidacloprid GL 2.15, due to the ingredients low vapour pressure, and the formulation being a non-volatile gel. Imidacloprid GL 2.15 is produced in a closed system (mixing and filling). Air renewal occurs in the weighing are (>20 fold per hour), and greater than 10 fold/hour in the formulation room. Waste air in the plant is exhausted via chimney through a single filter system, and filters are incinerated twice a year. [redacted] is not subject to the TA Luft discharge regulations, so no discharge levels exist for their exhausted air. The area for Formulation and Filling of Imidacloprid GL 2.15 is legislated by "4.BimSchV Nr. 4.2 Spalte 2" (Bundes Immissions Schutz Verordnung)	
iii) Waste disposal	**Formulation: Imidacloprid GL 2.5** For [redacted] • waste water is recycled by a company, which is a specialist in waste disposal by incineration. • product contaminated packaging material is incinerated • non contaminated materials e.g. paper, packaging material, plastic is recycled. The area for Formulation and Filling of Imidacloprid GL 2.15 is legislated by "4.BimSchV Nr. 4.2 Spalte 2" (Bundes Immissions Schutz Verordnung)	

A2.10/03 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

2.10.2.2 Intended use(s)		
Affected compartment(s):		
Water	See Document II-B_Imidacloprid GL 2.15 of the dossier	
Sediment	See Document II-B_Imidacloprid GL 2.15 of the dossier	
Air	See Document II-B_Imidacloprid GL 2.15 of the dossier	
Soil	See Document II-B_Imidacloprid GL 2.15 of the dossier	
Predicted concentrations in the affected compartment(s)		
Water	See Document II-B_Imidacloprid GL 2.15 of the dossier	
Sediment	See Document II-B_Imidacloprid GL 2.15 of the dossier	
Air	See Document II-B_Imidacloprid GL 2.15 of the dossier	
Soil	See Document II-B_Imidacloprid GL 2.15 of the dossier	

A2.10/03 **Section A2.10** **Annex Point IIA2.10**	**Identity of Active Substance** A2.10 Exposure Data in Conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) Amending Council Directive 67/548/EEC

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/05/03 - human health
Materials and methods	Acceptable
Conclusion	Imidacloprid GL 2.15 is produced [redacted]. The exposure during the formulation of the biocidal product is not assessed by the rapporteur under the requirements of the BPD. However, the rapporteur assumes that the formulation is performed in conformity with national and European occupational safety and health regulations.
Reliability	Not applicable, because given information are not based on standard tests.
Acceptability	acceptable
Remarks	No remarks
Date	2007/04/12 - environmental
Materials and methods	The applicant´s version is acceptable.
Conclusion	not applicable
Reliability	not applicable
Acceptability	acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.1/01 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in rat

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monographB.6.2.1, II A, 5.2.1 /01*
	Authors (year)	[redacted] (1989a)
	Title	NTN 33893 - Study for acute oral toxicity to rats
	Company, report No.	Bayer CropScience AG, Report-No.: 18594 BES Ref. : M-025996-01-1
	Date	1989-12-15
	Testing facility	[redacted]
	Dates of work	October – November 1989
	Test substance(s)	Molecule(s): imidacloprid Substance(s) : NTN 33893 Z (Batch-No.) : 180587
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 401, FIFRA § 81-1, EEC B.1.
2.2	**GLP**	Yes (certified laboratory)
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, mixed batch 180587, purity: 94.2 %, was formulated in Cremophor® EL / demineralised water (2 % v/v).
3.1.2	Specification	Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2.1	Description	
3.1.2.2	Purity	
3.1.2.3	Stability	

Section A6.1.1/01 Oral Acute Toxicity

Annex Point IIA6.1.1 *LD50 study in rat*

3.2	**Test Animals**	The test substance was administered in a single dose by oral gavage to fasted SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]).
3.2.1	Species	
3.2.2	Strain	
3.2.3	Source	
3.2.4	Sex	
3.2.5	Age/weight at study initiation	167-187g and 7-8 wk male; 168-194 g and 10-12 wk female
3.2.6	Number of animals per group	5 male, 5 female
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	
3.3.1	Postexposure period	14 days
3.3.2	Type	Formulated in Cremophor® EL / demineralised water (2 % v/v).
3.3.3	Concentration	Application volume: 10 mL/kg bw.
3.3.4	Vehicle	
3.3.5	Concentration in vehicle	
3.3.6	Total volume applied	
3.4	**Examinations**	Clinical signs, body weight, gross necropsy
3.5	**Method of determination of LD_{50}**	Method of Bliss

X

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	See Table A6.1.1/01-1. Apathy and labored breathing were the findings observed at a dose of 100 mg/kg bw; at higher doses, clinical signs additionally included accelerated breathing, decreased motility, staggering gait, narrowed eyelids, trembling and spasms.
4.2	**Pathology**	In the animals which died during the post treatment period, the following findings were recorded: liver dark; spleen pale, slightly dark in one animal; lung dark, patchy and distended; glandular stomach mucosa slightly reddened. No test substance-related changes were noted in animals sacrificed at the end of the observation period.
4.3	**Other**	Body weight development may have been disturbed initially as documented by slight decrements in weight gain observable 4 days postdose in animals treated with 250-400 mg/kg body weight and higher.
4.4	**LD_{50}**	Males 424 mg/kg bw Females 450 mg/kg bw< LD_{50}<475 mg/kg bw

Section A6.1.1/01 Oral Acute Toxicity

Annex Point IIA6.1.1 *LD50 study in rat*

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In an acute oral toxicity study conducted according to OECD 401, FIFRA § 81-1, EEC B.1. guidelines, imidacloprid was administered in a single dose by oral gavage to fasted SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted] at dose levels ranging from 50 to 1800 mg/kg bw.
5.2	**Results and discussion**	Mortalities occurred at dose levels at and above 400 mg/kg bw in both males and females. Apathy and labored breathing were the findings observed at a dose of 100 mg/kg bw; at higher doses, clinical signs additionally included accelerated breathing, decreased motility, staggering gait, narrowed eyelids, trembling and spasms. In the animals which died during the post treatment period, the following findings were recorded: liver dark; spleen pale, slightly dark in one animal; lung dark, patchy and distended; glandular stomach mucosa slightly reddened. No test substance-related changes were noted in animals sacrificed at the end of the observation period.
5.3	**Conclusion**	Imidacloprid is moderately toxic to rats following acute oral administration.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/01/22
Materials and Methods	3.3.3: Dose levels tested: 50 (M only)-100-250-315-400-450-475 (F only)-500-1800 mg/kg bw Otherwise acceptable
Results and discussion	Acceptable
Conclusion	Applicant's version is accepted. LD_{50}, males 424 mg/kg bw LD_{50}, females 450 mg/kg bw < LD_{50} < 475 mg/kg bw
Reliability	1
Acceptability	Acceptable
Remarks	Acc. to Dir. 67/548/EEC, results call for C & L as 'harmful if swallowed' (Xn; R22).

Section A6.1.1/01 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in rat

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.1/01-1. Acute Oral Toxicity to Rat

Dose [mg/kg bw]	Toxicological results*	Duration of signs	Time of death	Mortality [%]
Males				
50	0/0/5	-	-	0
100	0/5/5	40m-1d	-	0
250	0/5/5	40m-1d	-	0
315	0/5/5	20m-1d	-	0
400	1/5/5	15m-2d	3h	20
450	4/5/5	25m-6d	2h-1d	80
500	5/5/5	20m-7h	2h-7h	100
1800	5/5/5	15m-3h	1h-3h	100
Females				
100	0/0/5	-	-	0
250	0/5/5	40m-1d	-	0
315	0/5/5	15m-2d	-	0
400	1/5/5	20m-2d	6h	20
450	0/5/5	25m-2d	-	0
475	5/5/5	30m-7h	2h-7h	100
500	5/5/5	40m-6h	2h-6h	100
1800	5/5/5	15m-1d	2h-1d	100
LD_{50} rat,	males: ~ 424 mg/kg bw females: 450 < LD_{50} < 475 mg/kg bw			

*1st figure = number of dead animals, 2nd figure = number of animals with signs, 3rd figure = number of animals in the group

Section A6.1.1/02 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in rat

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monograph B.6.2.1, II A, 5.2.1 /02*
	Authors (year)	[redacted] (1991a)
	Title	NTN 33893 AMP (proposed c.n.: Imidacloprid) - Study for acute oral toxicity to rats
	Company, report No.	Bayer CropScience AG, Report-No.: 20591 BES Ref. : M-028854-01-1
	Date	1991-08-19
	Testing facility	[redacted]
	Dates of work	October 1990 – January 1991
	Test substance(s)	Molecule(s): imidacloprid Substance: NTN 33893 AMP Z(Batch No.: 17133/90)
1.2	**Data protection**	Yes (certified laboratory)
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 401, FIFRA § 81-1, EEC B.1.
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, batch no. 17133/90, purity 96.0 %, was formulated in Cremophor EL® / demineralised water (2 % v/v).).
3.1.2	Specification	Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2.1	Description	
3.1.2.2	Purity	
3.1.2.3	Stability	

Section A6.1.1/02 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in rat

3.2	**Test Animals**	Single oral doses of the test substance were administered by stomach tube to fasted SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]).	
3.2.1	Species		
3.2.2	Strain		
3.2.3	Source		
3.2.4	Sex		
3.2.5	Age/weight at study initiation	168-184g and 7-8 wk male; 169-186 g and 10-11 wk female	
3.2.6	Number of animals per group	5 male, 5 female	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**		
3.3.1	Postexposure period	14 days	
3.3.2	Type	Formulated in Cremophor® EL / demineralised water (2 % v/v).	
3.3.3	Concentration	Application volume: 10 mL/kg bw.	X
3.3.4	Vehicle		
3.3.5	Concentration in vehicle		
3.3.6	Total volume applied		
3.4	**Examinations**	Clinical signs, body weight, gross necropsy	
3.5	**Method of determination of LD_{50}**	Method of Bliss	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	See Table A6.1.1/02-1. Apathy, staggering or spastic gait, labored breathing, transient or continuing spasms, transient tremor, decreased motility, increased water intake, diuresis, piloerection, salivation, absence of feces and transient convulsions.	
4.2	**Pathology**	The following findings were recorded in animals which died during the post-treatment observation period: lungs distended, patchy, dark; liver dark; kidney slightly pale; bladder engorged with urine; spleen slightly pale. No test substance-related changes were noted in animals sacrificed at the end of the observation period.	
4.3	**Other**	Body weight development may have been disturbed initially as documented by slight decrements in weight gain observable 4 days postdose in animals treated with 200-400 mg/kg body weight and higher.	
4.4	**LD_{50}**	Males 642 mg/kg bw Females 648 mg/kg bw	

Section A6.1.1/02 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in rat

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

In an acute oral toxicity study conducted according to OECD 401, FIFRA § 81-1, EEC B.1. guidelines, single oral doses of imidacloprid were administered by stomach tube to fasted SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]) at dose levels ranging from 50-1000 mg/kg bw.

5.2 Results and discussion

Mortalities occurred at doses at and above 350 mg/kg bw in males and at and above 450 mg/kg bw in females.

Clinical signs included apathy, staggering or spastic gait, labored breathing, transient or continuing spasms, transient tremor, decreased motility, increased water intake, diuresis, piloerection, salivation, absence of feces and transient convulsions.

The following findings were recorded in animals which died during the post-treatment observation period: lungs distended, patchy, dark; liver dark; kidney slightly pale; bladder engorged with urine; spleen slightly pale. No test substance-related changes were noted in animals sacrificed at the end of the observation period.

5.3 Conclusion

Imidacloprid is moderately toxic to rats following acute oral administration.

5.3.1 Reliability: 1

5.3.2 Deficiencies: No

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/01/22
Materials and Methods	3.3.3: Dose levels tested: Males: 50-200-350-400-500-600-750-1000 mg/kg bw; Females: 100-400-450-500-600-1000 mg/kg bw Otherwise acceptable
Results and discussion	Acceptable
Conclusion	Applicant's version is accepted. LD_{50}, males 642 mg/kg bw LD_{50}, females 648 mg/kg bw
Reliability	1
Acceptability	Acceptable
Remarks	Acc. to Dir. 67/548/EEC, results call for C & L as 'harmful if swallowed' (Xn; R22).
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.1/02-1. Acute Oral Toxicity to Rat

Dose [mg/kg bw]	Toxicological results*	Duration of signs	Time of death	Mortality [%]
Males				
50	0/0/5	-	-	0
200	0/5/5	20m-1d	-	0
350	1/5/5	55m-3d	4h	20
400	3/5/5	1h-4d	4h-1d	60
500	1/5/5	25m-4d	7h	20
600	0/5/5	15m-8d		0
750	3/5/5	15m-3d	5h-6h	60
1000	5/5/5	45m-2d	2h-2d	100
Females				
100	0/0/5	-	-	0
400	0/5/5	1h-2d	-	0
450	2/5/5	40m-4d	3h-1d	40
500	1/5/5	25m-4d	2h	20
600	2/5/5	15m-2d	6h-7h	40
1000	5/5/5	30m-6h	4h-6h	100
LD_{50} rat, males: 642 mg/kg bw females: 648 mg/kg bw				

*1st figure = number of dead animals, 2nd figure = number of animals with signs, 3rd figure = number of animals in the group

Section A6.1.1/03 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in rat

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monographB.6.2.1, II A, 5.2.1 /03*
	Authors (year)	[redacted] (1991b)
	Title	NTN 33893 CNS (c.n.: Imidacloprid (proposed) - Study for acute oral toxicity in rats
	Company, report No.	Bayer CropScience AG, Report-No.: 20637 BES Ref. : M-028901-01-1
	Date	1991-09-03
	Testing facility	[redacted]
	Dates of work	October 1990 – January 1991
	Test substance(s)	Molecule(s): imidacloprid Substance: NTN 33893 Z (Batch-no.: 180587)
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 401, FIFRA § 81-1, EEC B.1.
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, mixed batch 180587, purity: 94.3 %, was formulated in Cremophor® EL / demineralised water (2 % v/v).
3.1.2	Specification	Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2.1	Description	
3.1.2.2	Purity	

Section A6.1.1/03 Oral Acute Toxicity

Annex Point IIA6.1.1 *LD50 study in rat*

3.1.2.3 Stability

3.2	**Test Animals**	The test article was administered in a single dose by oral gavage to fasted SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]
3.2.1	Species	
3.2.2	Strain	
3.2.3	Source	
3.2.4	Sex	
3.2.5	Age/weight at study initiation	167-186g and 7-8 wk male; 170-183 g and 10-11 wk female
3.2.6	Number of animals per group	5 male, 5 female
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	
3.3.1	Postexposure period	14 days
3.3.2	Type	Formulated in Cremophor® EL / demineralised water (2 % v/v).
		Application volume: 10 mL/kg bw.

Section A6.1.1/03 Oral Acute Toxicity

Annex Point IIA6.1.1 *LD50 study in rat*

3.3.3	Concentration		X
3.3.4	Vehicle		
3.3.5	Concentration in vehicle		
3.3.6	Total volume applied		
3.4	**Examinations**	Clinical signs, body weight, gross necropsy	
3.5	**Method of determination of LD_{50}**	Method of Bliss	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	See Table A6.1.1/03-1. Apathy, staggering and spastic gait, labored breathing; at higher doses reduced motility, spasmodic state, periodic tremors, soft faeces and piloerection.	
4.2	**Pathology**	Findings in animals that died during the post-treatment observation period included: lung distended, mottled, dark; liver dark; bladder distended with clear urine. No test article-related gross pathological findings were observed in the animals sacrificed at the end of the post-treatment observation period.	
4.3	**Other**	Body weight gain: Body weight development may have been disturbed initially as documented by slight decrements in weight gain observable 4 days postdose in animals treated with 300-350 mg/kg body weight and higher.	
4.4	**LD_{50}**	Males 504 mg/kg bw Females 379 mg/kg bw	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In an acute oral toxicity study conducted according to OECD 401, FIFRA § 81-1, EEC B.1. guidelines, imidacloprid was administered in a single dose by oral gavage to fasted SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted] at dose levels ranging from 50-600 mg/kg bw.	
5.2	**Results and discussion**	Mortalities occurred at doses at and above 300 mg/kg bw in both males and females. Clinical signs included pathy, staggering and spastic gait, labored breathing; at higher doses reduced motility, spasmodic state, periodic tremors, soft faeces and piloerection. Findings in animals that died during the post-treatment observation period included: lung distended, mottled, dark; liver dark; bladder distended with clear urine. No test article-related gross pathological findings were observed in the animals sacrificed at the end of the post-treatment observation period.	
5.3	**Conclusion**	Imidacloprid is moderately toxic to rats following acute oral administration.	
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Section A6.1.1/03 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in rat

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/01/22
Materials and Methods	3.3.3: Dose levels tested: 50/100 (M/F)-200-300-350-400-500-600 (M only) mg/kg bw Otherwise acceptable
Results and discussion	Acceptable
Conclusion	Applicant's version is accepted. LD_{50}, males 504 mg/kg bw LD_{50}, females 379 mg/kg bw
Reliability	1
Acceptability	Acceptable
Remarks	Acc. to Dir. 67/548/EEC, results call for C & L as 'harmful if swallowed' (Xn; R22).
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.1/03-1. Acute Oral Toxicity to Rat

Dose [mg/kg bw]	Toxicological results*	Duration of signs	Time of death	Mortality [%]
Males				
50	0/0/5	-	-	0
200	0/5/5	20m-1d	-	0
300	1/5/5	50m-2d	5h	20
350	1/5/5	55m-3d	6h	20
400	2/5/5	55m-5d	1d	40
500	1/5/5	25m-3d	6h	20
600	4/5/5	10m-5d	2h-3h	80
Females				
100	0/0/5	-	-	0
200	0/5/5	55m-7h	-	0
300	1/5/5	50m-2d	1d	20
350	2/5/5	55m-3d	4h-6h	40
400	2/5/5	55m-3d	4h-7h	40
500	5/5/5	35m-1d	2h-1d	100

LD_{50} rat, males: 504 mg/kg bw
females: 379 mg/kg bw

*1st figure = number of dead animals, 2nd figure = number of animals with signs, 3rd figure = number of animals in the group

Section A6.1.1/04 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in mouse

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monographB.6.2.1, II A, 5.2.1 /04*
	Authors (year)	[redacted] (1989b)
	Title	NTN 33893 - Study for acute oral toxicity to mice
	Company, report No.	Bayer CropScience AG, Report-No.: 18593 BES Ref. : M-007509-01-1
	Date	1989-12-15
	Testing facility	[redacted]
	Dates of work	October – November 1989
	Test substance(s)	Molecule(s): imidacloprid Substance(s) : NTN 33893 Z (Batch-No.) : 180587
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 401, FIFRA § 81-1, EEC B.1.
2.2	**GLP**	Yes (certified laboratory)
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, mixed batch 180587, purity: 94.2 %, was formulated in Cremophor® EL / demineralised water (2 % v/v).
3.1.2	Specification	Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2.1	Description	
3.1.2.2	Purity	
3.1.2.3	Stability	

Section A6.1.1/04 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in mouse

3.2	**Test Animals**	The test substance was administered in a single dose by gavage to fasted SPF-bred mice (Strain Bor: NMRI; Breeder [redacted]).	
3.2.1	Species		
3.2.2	Strain		
3.2.3	Source		
3.2.4	Sex		
3.2.5	Age/weight at study initiation	21-25 g and 4 wk male; 20-24 g and 4-5 wk female	
3.2.6	Number of animals per group	5 male, 5 female	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**		
3.3.1	Postexposure period	14 days	
3.3.2	Type	Formulated in Cremophor® EL / demineralised water (2 % v/v).	
3.3.3	Concentration	Application volume: 10 mL/kg bw.	X
3.3.4	Vehicle		
3.3.5	Concentration in vehicle		
3.3.6	Total volume applied		
3.4	**Examinations**	Clinical signs, gross necropsy, bodyweight	
3.5	**Method of determination of LD_{50}**	Method of Bliss	

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	See Table A6.1.1/04-1. Apathy, labored breathing, decreased motility, transient staggering gait, transient trembling and transient spasms.
4.2	**Pathology**	The following findings were described for animals which died during the observation period: liver pale, occasionally dark; spleen pale, occasionally dark; lung dark, patchy and distended. No test substance-related changes were noted in animals sacrificed at the end of the observation period.
4.3	**Other**	No effects were observed on the body weight development.
4.4	**LD_{50}**	Males 131 mg/kg bw Females 168 mg/kg bw< LD_{50}<475 mg/kg bw

Section A6.1.1/04 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in mouse

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In an acute oral toxicity study conducted according to OECD 401, FIFRA § 81-1, EEC B.1. guidelines, imidacloprid was administered in a single dose by gavage to fasted SPF-bred mice (Strain Bor: NMRI; Breeder [redacted]) at dose levels ranging from 10-250 mg/kg bw .
5.2	**Results and discussion**	Mortalities occurred at doses at and above 100 mg/kg bw in males and at and above 120 mg/kg bw in females. Clinical signs included apathy, labored breathing, decreased motility, transient staggering gait, transient trembling and transient spasms. The following findings were described for animals which died during the observation period: liver pale, occasionally dark; spleen pale, occasionally dark; lung dark, patchy and distended. No test substance-related changes were noted in animals sacrificed at the end of the observation period.
5.3	**Conclusion**	Following acute oral administration imidacloprid is more toxic in mice than in rats.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/08/24
Materials and Methods	3.3.3: Dose levels tested: 10-71 (M only)-100-120-140-160-250 mg/kg bw Otherwise acceptable
Results and discussion	Acceptable
Conclusion	Applicant's version is accepted. LD_{50}, males 131 mg/kg bw LD_{50}, females 168 mg/kg bw
Reliability	1
Acceptability	Acceptable
Remarks	

Section A6.1.1/04 Oral Acute Toxicity

Annex Point IIA6.1.1

LD50 study in mouse

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.1/04-1. Acute Oral Toxicity to Mouse

Dose [mg/kg bw]	Toxicological results*	Duration of signs	Time of death	Mortality [%]
Males				
10	0/0/5	-	-	0
71	0/5/5	10m-4h	-	0
100	1/5/5	5m-3h	55m	20
120	2/5/5	5m-7h	1h	40
140	2/5/5	5m-7h	10m-15m	40
160	5/5/5	5m-55m	10m-55m	100
250	5/5/5	5m-1h	20m-1h	100
Females				
10	0/0/5	-	-	0
100	0/5/5	5m-6h	-	0
120	1/5/5	5m-4h	15m	20
140	1/5/5	5m-7h	15m	20
160	2/5/5	5m-6h	25m-35m	40
250	5/5/5	5m-45m	30m-45m	100
LD_{50} mouse,	males: 131 mg/kg bw females: 168 mg/kg bw			

*1st figure = number of dead animals, 2nd figure = number of animals with signs, 3rd figure = number of animals in the group

Section A6.1.2/01 Dermal Acute Toxicity

Annex Point IIA6.1.2

LD_{50}, study in rat; limit test

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monographB.6.2.2, II A, 5.2.2/01*
	Authors (year)	[redacted] (1989)
	Title	NTN 33893 (c.n. imidacloprid (proposed) - Study for acute dermal toxicity to rats
	Company, report No.	Bayer CropScience AG, Report-No.: 18532 BES Ref. : M-025697-01-1
	Date	1989-11-15
	Testing facility	[redacted]
	Dates of work	July – August 1989
	Test substance(s)	Molecule(s): imidacloprid Substance: NTN 33893 Z (Batch no.) : 180587
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 402, FIFRA § 81-2, EEC B.3.
2.2	**GLP**	Yes (certified laboratory)
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, mixed batch 180587, purity: 94.2 % was used for testing. Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2	Specification	
3.1.2.1	Description	
3.1.2.2	Purity	
3.1.2.3	Stability	

Section A6.1.2/01 Dermal Acute Toxicity

Annex Point IIA6.1.2 *LD_{50}, study in rat; limit test*

3.2	**Test Animals**		
3.2.1	Species	SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]) male and female	
3.2.2	Strain		
3.2.3	Source		
3.2.4	Sex		
3.2.5	Age/weight at study initiation	207-234 g and 9-14 wk male; 204-214 g and 9-14 wk female	
3.2.6	Number of animals per group	5 male, 5 female	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**		
3.3.1	Postexposure period	14 days	
3.3.2	Area covered	Per OECD 402, FIFRA § 81-2, EEC B.3., no deviations noted by RMS in the December 2005 91/414 draft DAR	X
3.3.3	Occlusion	A dose of 5000 mg/kg bw of imidacloprid under 24-hour occlusive conditions	
3.3.4	Vehicle		
3.3.5	Concentration in vehicle	For each dose and animal, the solid test substance was weighed on an aluminium foil used to cover the administration site.	
3.3.6	Total volume applied	The test substance was mixed to a paste with 1.5 mL of sterile 0.9 % NaCl solution per g test substance and applied to the intact dorsal skin, shorn on the previous day	
3.3.7	Duration of exposure		
3.3.8	Removal of test substance		
3.4	**Examinations**	Clinical signs, body weight, gross necropsy	
3.5	**Method of determination of LD_{50}**	No mortalities reported, LD50 not calculated	
3.5.1	Controls	No	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	See Table A.6.1.2/01-1. A dose of 5000 mg/kg bw of imidacloprid under 24-hour occlusive conditions was tolerated by Wistar rats of both sexes without clinical signs, body weight influences or mortalities. No treatment-related findings.	
4.2	**Pathology**		
4.3	**LD_{50}**	LD_{50} rat, males and females: > 5000 mg/kg bw	

Section A6.1.2/01

Annex Point IIA6.1.2

Dermal Acute Toxicity

LD_{50}, study in rat; limit test

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In an acute dermal toxicity study conducted according to OECD 402, FIFRA § 81-2, EEC B.3. guidelines, imidacloprid was mixed to a paste with 1.5 mL of sterile 0.9 % NaCl solution per g test substance and applied to the intact dorsal skin, shorn on the previous day, of 5 SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]) per sex, respectively at a limit dose or 5000 mg/kg bw.
5.2	**Results and discussion**	A dose of 5000 mg/kg bw of imidacloprid under 24-hour occlusive conditions was tolerated by Wistar rats of both sexes without clinical signs, body weight influences or mortalities.
5.3	**Conclusion**	Imidacloprid is non-toxic to rats following dermal administration.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/01/22
Materials and Methods	3.3.2: Covered area was 6.0 cm x 6.0 cm Otherwise acceptable
Results and discussion	Acceptable
Conclusion	Applicant's version is accepted. LD_{50} > 5000 mg/kg bw (limit test)
Reliability	1
Acceptability	Acceptable
Remarks	

Section A6.1.2/01 Dermal Acute Toxicity

Annex Point IIA6.1.2

LD_{50}, study in rat; limit test

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.2/01-1: Acute dermal toxicity in rats

Dose [mg/kg bw]	Toxicological results*			Duration of signs	Time of death	Mortality [%]
Males						
5000	0	0	5	-	-	0
Females						
5000	0	0	5	-	-	0
LD_{50} rat, males and females: > 5000 mg/kg bw						

*1st figure = number of dead animals, 2nd figure = number of animals with signs, 3rd figure = number of animals in the group

Section A6.1.3/01 Inhalation Acute Toxicity

Annex Point IIA6.1.3

LC50 study in rat, dust and aerosol

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monograph B.6.2.3, II A, 5.2.3 /01*
	Authors (year)	[redacted] (1988a)
	Title	NTN 33893 - Study for acute inhalation toxicity in the rat in accordance with OECD guideline no. 403
	Company, report No.	Bayer CropScience AG, Report-No.: 16777 BES Ref. : M-027586-01-1
	Date	1988-06-06
	Testing facility	[redacted]
	Dates of work	October – November 1987
	Test substance(s)	Molecule(s): imidacloprid Substance(s) : NTN 33893 Z (Batch-No.) : 180587
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 403, FIFRA § 81-3, EEC B.2.
2.2	**GLP**	Yes (certified laboratory)
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, mixed batch 180587, purity: 95.3 % was used for testing.
3.1.2	Specification	Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2.1	Description	The test article was delivered in aerosol (nebulised with polyethylene glycol E 400 as vehicle) and dust form (undiluted).
3.1.2.2	Purity	
3.1.2.3	Stability	

Section A6.1.3/01 Inhalation Acute Toxicity

Annex Point IIA6.1.3

LC50 study in rat, dust and aerosol

3.2	**Test Animals**		
3.2.1	Species	The test article was delivered to male and female SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]) for four hours.	
3.2.2	Strain		
3.2.3	Source		
3.2.4	Sex		
3.2.5	Age/weight at study initiation	160 to 210 g meaning 8-12 wk age	
3.2.6	Number of animals per group	5 males, 5 females	X
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Inhalation	
3.3.1	Postexposure period	14 days	
3.3.2	Concentrations	Nominal concentration : 500 aerosol, [mg/m³] Analytical concentration: 69 aerosol; 1220, 2577 and 5323 dust [mg/m³]	
3.3.3	Particle size	For aerosol MMAD 1.61 [µm] ± GSD 1.44 [µm]	
3.3.4	Type or preparation of particles	The test article was delivered in aerosol (nebulised with polyethylene glycol E 400 as vehicle) and dust form (undiluted) nose only to SPF-bred Wistar rats for four hours.	
3.3.5	Type of exposure		
3.3.6	Vehicle		
3.3.7	Concentration in vehicle		
3.3.8	Duration of exposure		
3.3.9	Controls	Air and vehicle control	
3.4	**Examinations**	Clinical signs, body weight, gross necropsy	
3.5	**Method of determination of LD_{50}**	Bliss maximum likelihood method	
3.6	**Further remarks**	Subacute rangefinding was also reported; 5X6h exposure to dust ; see A6.3.3/01NK.	X

Section A6.1.3/01

Annex Point IIA6.1.3

Inhalation Acute Toxicity

LC50 study in rat, dust and aerosol

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	See Table A6.1.3/01-1. Difficult breathing, reduced motility and piloerection (group 5 and 6, dust exposed); slight tremors (group 6, dust exposed).
4.2	**Pathology**	No treatment-related findings
4.3	**Other**	Marginal decrease of body weight gains in males (group 6) and in females (group 5); statistically significant decrease of body weight gains in females (group 6) during the post-treatment observation period.
4.4	**LD_{50}**	Aerosol > 69 mg/m³, the maximum technically producible concentration Dust > 5323 mg/m³, the maximum technically producible concentration

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In an acute inhalation toxicity study conducted according to OECD 403, FIFRA § 81-3, EEC B.2. guidelines, imidacloprid was delivered to male and female SPF-bred Wistar rats (Strain Bor: WISW; Breeder [redacted]) for four hours both as an aerosol and as a dust.
5.2	**Results and discussion**	No mortalities occurred. Following exposure to dust at levels ≥ 2577 mg/m³ air, difficult breathing, reduced motility and piloerection and slight tremors were observed as well as decreased body weight gains No symptoms were observed in rats exposed to aerosol concentrations of 69 mg/m³.
5.3	**Conclusion**	Imidacloprid shows a low acute toxicity to rats following inhalation of aerosol or dust.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.1.3/01 Inhalation Acute Toxicity

Annex Point IIA6.1.3

LC50 study in rat, dust and aerosol

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/08/24
Materials and Methods	3.2.6 Air control: 10 animals/sex/group, vehicle control: 5 animals/sex/group 3.6 In the subacute experiment, 10 test animals/sex/group were exposed to 0, 20, 100, or 500 mg imidacloprid dust/m^3 air (nominal concentrations, corresponding to analytical concentrations of 0, 20, 109, and 505 mg/m^3) for 6 h on 5 consecutive days.
Results and discussion	Acute part Applicant's summary is acceptable. Subacute part (for details cf. CA-Tables at the end of this section) 109 mg/m^3: ▪ Slight mean body weight depression on study day 4 in females (but not at 505 mg/m^3) ▪ Statistically significant induction of hepatic metabolising enzymes (N-, O-demethylases) (not recorded at 505 mg/m^3) 505 mg/m^3: ▪ Slight decrease of triglycerides (statistically significant in females only)
Conclusion	Acute inhalation, 4h, head/nose only, aerosol: LC_{50} > 0.069 g/m^3 (maximum attainable concentration) Acute inhalation, 4h, head/nose only, dust: LC_{50} > 5.323 g/m^3 Subacute inhalation, 5 x 6 h, dust: No mortality or clinical signs up to 0.505 g/m^3, body weight depression (slight, transient) as well as induction of hepatic enzymes at 109 mg/m^3.
Reliability	Acute section: 1 Subacute section: 2
Acceptability	Acute section: Acceptable Subacute section: Acceptable with restrictions, as only a limited spectrum of parameters was examined.
Remarks	

Section A6.1.3/01 Inhalation Acute Toxicity

Annex Point IIA6.1.3

LC50 study in rat, dust and aerosol

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.3/01-1. Acute inhalation toxicity in rats

Group	Concentration (nominal/analytical) (mg/m³ air)	Toxicological results#	Duration of signs	Time of death
Males				
1	Air control	0/0/10	-	-
2	vehicle control	0/0/5	-	-
3	500/69	0/0/5	-	-
4	--/1220	0/0/5	-	-
5	--/2577	0/5/5	4h-6h	-
6	--/5323	0/5/5	4h-6h	-
Females				
1	Air control	0/0/5	-	-
2	vehicle control	0/0/5	-	-
3	500/69	0/0/5	-	-
4	--/1220	0/0/5	-	-
5	--/2577	0/5/5	4h-6h	-
6	--/5323	0/5/5	4h-6h	-
LC_{50} rat males and females		(aerosol): > 69 mg/m³ air* (dust): > 5323 mg/m³ air*		

Group 1: 10 L air/minute; Group 2: 20000 µL vehicle/m³ air (nominal) – 10 L air/minute; Group 3: Nebulisation of a 2.5 % solution (g/v) – aerosol; Group 4-6: Dust dispersion

1st figure = number of dead animals; 2nd figure = number of animals with signs; 3rd figure = number of animals in the group; * max. technically producible concentration

CA-Table A6.1.3/01-1. Subacute inhalation toxicity of imidacloprid in rats (dust, exposure: 5 x 6 h): mortality and clinical signs

N	Concentration nomin.	analyt. mg/m³ air	Toxicol. result	Duration of sign	Time of death	particle ≤ 5 µm (%)
			rat - male			
1	air control		0/ 0/10	--	--	--
2	20	20	0/ 0/10	--	--	54
3	100	109	0/ 0/10	--	--	57
4	500	505	0/ 0/10	--	--	18
			rat - female			
1	air control		0/ 0/10	--	--	--
2	20	20	0/ 0/10	--	--	54
3	100	109	0/ 0/10	--	--	57
4	500	505	0/ 0/10	--	--	18

The values in the column "toxicol. result" mean:

1st figure = number of mortalities
2nd figure = number of animals with signs
3rd figure = number of animals used.

CA-Table A6.1.3/01-2. Subacute inhalation toxicity of imidacloprid in rats (dust, exposure: 5 x 6 h): mean body weight data

Tiergewichte / body weights
Mittelwerte / means (g)

	Tag relativ / day relative				
	0	4	8	15	22
air control					
m	193	195	210	239	264
w	182	181	185	188	195
20 mg/m3 air					
m	195	200	217	248	277
w	182	182	180	188	189
100 mg/m3 air					
m	195	189	211	245	273
w	180	170++	179	185	194
500 mg/m3 air					
m	196	189	208	237	268
w	185	181	180	188	195

m = maennlich/male; w = weiblich/female
++ = p smaller than 0.01 (U-Test)

CA-Table A6.1.3/01-3. Subacute inhalation toxicity of imidacloprid in rats (dust, exposure: 5 x 6 h): clinical chemistry related to liver function

KLINISCHE CHEMIE / CLINICAL CHEMISTRY LEBERGEWEBE / LIVER TISSUE					
Konz./ conc. (mg/m3)	Woche/ week	N-DEM mU/g	O-DEM mU/g	P450 nmol/g	TRIGL mcmol/g
MAENNCHEN/MALES					
air	1	156.1	9.9	28.8	5.21
20	1	160.9	9.4	24.4	5.36
100	1	200.6++	11.6	29.6	5.20
500	1				4.21
WEIBLICH/FEMALES					
air	1	58.1	8.0	26.7	5.38
20	1	67.7	7.8	24.3	5.02
100	1	140.7++	10.8++	24.5	5.26
500	1				4.48+

(N-DEM/O-DEM = N-/O-demethylase, P450 = cytochrome P450, TRIGL = triglycerides; N-DEM, O-DEm and P450 reportedly have not been measured in the groups nominally receiving 500 mg/m^3 due to an oversight)

Section A6.1.4./01 Acute Dermal Irritation

Annex Point IIA6.1.4

Rabbit Skin Irritation

			Official use only
		1 REFERENCE	
1.1	**Reference**	*PPP monograph B.6.2.4, II A, 5.2.4 /01*	
	Authors (year)	[redacted] (1988b)	
	Title	NTN 33893 - Study for irritant/corrosive potential on the skin (rabbit) according to OECD guideline no. 404	
	Company, report No.	Bayer CropScience AG, Report-No.: 16455 BES Ref. : M-028272-01-1	
	Date	1988-02-25	
	Testing facility	[redacted]	
	Dates of work	May 1987	
	Test substance(s)	Molecule(s): imidacloprid Substance(s): Imidacloprid techn, (Batch-No.: 17001/87)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s.for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	OECD 404, FIFRA § 81-4, EEC B.4.	
2.2	**GLP**	Yes (certified laboratory)	
2.3	**Deviations**	None	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2	
3.1.1	Lot/Batch number	Imidacloprid, batch no. 17001/87, purity: 94.2 % was used for testing. Specification as given in section 2; stability guaranteed for the duration of the study.	
3.1.2	Specification		
3.1.2.1	Description	500 mg of the undiluted test substance, mixed to a paste with water, was applied to the shorn skin of three rabbits (Strain HC:NZW; Breeder [redacted])	
3.1.2.2	Purity		
3.1.2.3	Stability		
3.2	**Test Animals**		
3.2.1	Species		
3.2.2	Strain		
3.2.3	Source		
3.2.4	Sex		X
3.2.5	Age/weight at study initiation	2800 to 3400 g	

Section A6.1.4./01 Acute Dermal Irritation

Annex Point IIA6.1.4 *Rabbit Skin Irritation*

3.2.6	Number of animals per group	3	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Application	Per OECD 404, FIFRA § 81-4, EEC B.4., no deviations noted by RMS in the December 2005 91/414 draft DAR	
3.3.1.1	Preparation of test substance	500 mg of the undiluted test substance, mixed to a paste with water, was applied to the shorn skin of three rabbits under semi-occlusive exposure conditions. Dressings and tape were removed after 4 hours and exposed skin areas cleaned with water.	X
3.3.1.2	Test site and Preparation of Test Site		
3.3.2	Occlusion		
3.3.3	Vehicle		
3.3.4	Concentration in vehicle		
3.3.5	Total volume applied		
3.3.6	Removal of test substance		
3.3.7	Duration of exposure		
3.3.8	Postexposure period	14 days	
3.3.9	Controls	Untreated flank	
3.4	**Examinations**	Per OECD 404, FIFRA § 81-4, EEC B.4., no deviations noted by RMS in the December 2005 91/414 draft DAR Draize grading	
		4 RESULTS AND DISCUSSION	
4.1	**Average score**		
4.1.1	Erythema	See Table A.6.1.4/01-1	
4.1.2	Edema		
4.2	**Reversibility**	No serious effect to reverse	
4.3	**Other examinations**	None	
4.4	**Overall result**	No irritation	

Section A6.1.4./01 Acute Dermal Irritation

Annex Point IIA6.1.4 *Rabbit Skin Irritation*

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In an acute dermal irritation study conducted according to OECD 404, FIFRA § 81-4, EEC B.4. guidelines, 500 mg of undiluted imidacloprid, mixed to a paste with water, was applied to the shorn skin of three rabbits under semi-occlusive exposure conditions. Dressings and tape were removed after 4 hours and exposed skin areas cleaned with water. Skin irritation was graded through 14 days post exposure according to the method of Draize.
5.2	**Results and discussion**	The results of the study show that the test substance does not possess a local irritant potential to the skin.
5.3	**Conclusion**	Imidacloprid has no irritant effect to the skin.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/01/23
Materials and Methods	3.2.4 Male animals were used. 3.3.1.2 Size of treated area: ca. 6 cm^2 Otherwise, applicant's summary is acceptable.
Results and discussion	Applicant's summary is acceptable.
Conclusion	Non-irritant (applicant's version is accepted)
Reliability	1
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.4/01-1: Rabbit skin irritation study – Skin irritation grading

Animal no.	Draize grade after												Irrit.	
	1h		24h		48h		72h		7d		14d		Index	
	E	*O*	*E*	*O*	*E*	*O*	*E*	*O*	*E*	*O*	*E*	*O*	*E*	*O*
W1	1	0	0	0	0	0	0	0	0	0	-	-	0.0	0.0
W13	0	0	0	0	0	0	0	0	0	0	-	-	0.0	0.0
V25	0	0	0	0	0	0	0	0	0	0	-	-	0.0	0.0

- = not examined; d = day; E = erythema and eschar formation; h = hour; O = oedema formation

Section 6.1.4/02 Acute Eye Irritation

Annex Point IIA6.1.4

Rabbit Eye Irritation

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monograph B.6.2.5, II A, 5.2.5 /01*
	Authors (year)	[redacted] (1988c)
	Title	NTN 33893 - Study for irritant/corrosive potential on the eye (rabbit) according to OECD guideline no. 405
	Company, report No.	Bayer CropScience AG, Report-No.: 16456 BES Ref. : M-028278-01-1
	Date	1988-02-25
	Testing facility	[redacted]
	Dates of work	May 1987
	Test substance(s)	Molecule(s): imidacloprid Substance(s): Imidacloprid techn, (Batch-No.: 17001/87)
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s.for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 405, FIFRA § 81-5, EEC B.5.
2.2	**GLP**	Yes (certified laboratory)
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, batch no. 17001/87, purity 94.2 % was used for testing.
3.1.2	Specification	Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2.1	Description	Undiluted test substance was applied to one eye of three rabbits (Strain HC:NZW; Breeder [redacted]
3.1.2.2	Purity	
3.1.2.3	Stability	

Section 6.1.4/02 Acute Eye Irritation

Annex Point IIA6.1.4 *Rabbit Eye Irritation*

3.2	**Test Animals**	
3.2.1	Species	
3.2.2	Strain	
3.2.3	Source	
3.2.4	Sex	
3.2.5	Age/weight at study initiation	3100 to 3300 g
3.2.6	Number of animals per group	3
3.2.7	Control animals	untreated eye
3.3	**Administration/ Exposure**	
3.3.1	Preparation of test substance	100 µL (appr. 60 mg) test article was administered into the conjunctival sac of three rabbits
3.3.2	Amount of active substance instilled	
3.3.3	Exposure period	24h
3.3.4	Postexposure period	21 days
3.4	**Examinations**	Per OECD 405, FIFRA § 81-5, EEC B.5., no deviations noted by RMS in the December 2005 91/414 draft DAR

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	None noted
4.2	**Average score**	
4.2.1	Cornea	See Table 6.1.4/02-1
4.2.2	Iris	
4.2.3	Conjunctiva	
4.2.3.1	Redness	
4.2.3.2	Chemosis	
4.3	**Reversibility**	Nothing significant to reverse, all clear by 24 hours
4.4	**Overall result**	The results of the study show that the test substance does not possess a local irritant potential to the eye.

Section 6.1.4/02 Acute Eye Irritation

Annex Point IIA6.1.4

Rabbit Eye Irritation

		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	In an acute eye irritation study conducted according to OECD 405, FIFRA § 81-5, EEC B.5. guidelines, 100 µL (appr. 60 mg) of imidacloprid was administered into the conjunctival sac of three rabbits (Strain HC:NZW; Breeder [redacted]). The duration of exposure was 24 hours.
5.2	**Results and discussion**	The results of the study show that the test substance does not possess a local irritant potential to the eye.
5.3	**Conclusion**	Imidacloprid has no irritant effect to the eye.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/08/24
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable.
Conclusion	Non-irritant (applicant's version is accepted)
Reliability	1
Acceptability	Acceptable without restrictions
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A.6.1.4/02-1: Rabbit eye irritation study – Eye irritation grading and symptoms

Animal no.	Organ examined	Signs	Draize grades							Irrit. grade
			1h	24h	48h	72h	7d	14d	21d	
U56 f	Cornea	o	0	0	0	0	0	-	-	0.0
		s	0	0	0	0	0	-	-	
	Iris		0	0	0	0	0	-	-	0.0
	Conjunctivae	R	2	0	0	0	0	-	-	0.0
		S	1	0	0	0	0	-	-	0.0
		T	0	0	0	0	0	-	-	
W54 m	Cornea	o	0	0	0	0	0	-	-	0.0
		s	0	0	0	0	0	-	-	
	Iris		0	0	0	0	0	-	-	0.0
	Conjunctivae	R	1	0	0	0	0	-	-	0.0
		S	0	0	0	0	0	-	-	0.0
		T	0	0	0	0	0	-	-	
N31 m	Cornea	o	0	0	0	0	0	-	-	0.0
		s	0	0	0	0	0	-	-	
	Iris		0	0	0	0	0	-	-	0.0
	Conjunctivae	R	1	0	0	0	0	-	-	0.0
		S	0	0	0	0	0	-	-	0.0
		T	0	0	0	0	0	-	-	

o: opacity; s = surface; - : not examined; m = male, f = female; R = redness, S = swelling, T = lacrimation

Section A6.1.5/01 Skin sensitisation

Annex Point IIA6.1.5

Guinea pig maximisation test (GPMT)

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monograph B.6.2.6, II A, 5.2.6 /01*
	Authors (year)	[redacted] 1988)
	Title	NTN 33893 technical - Study for skin sensitising effect on guinea pigs (maximisation test)
	Company, report No.	Bayer CropScience AG, Report-No.: 16533 BES Ref. : M-027579-01-1
	Date	1988-03-15
	Testing facility	[redacted]
	Dates of work	June 1987
	Test substance(s)	Molecule(s): imidacloprid Substance(s): Imidacloprid techn, (Batch-No.: 17001/87)
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD 406, FIFRA § 81-6, EEC B.6.
2.2	**GLP**	Yes (certified laboratory)
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	Imidacloprid, batch no. 17001/87, purity: 94.2 %. Specification as given in section 2; stability guaranteed for the duration of the study.
3.1.2	Specification	
3.1.2.1	Description	The test substance was formulated in sterile physiological saline solution containing 2 % Cremophor EL® to yield a suspension. A 1 % concentration was used for intradermal, and a 25 % concentration for topical induction. A 3 % and a 25 % concentration were used for challenge.
3.1.2.2	Purity	
3.1.2.3	Stability	
3.1.2.4	Preparation of test substance for application	
3.1.2.5	Pretest performed on irritant effects	yes

Section A6.1.5/01 Skin sensitisation

Annex Point IIA6.1.5 Guinea pig maximisation test (GPMT)

3.2	**Test Animals**	
3.2.1	Species	SPF-bred male guinea pigs (Strain DHPW; Breeder [redacted]).
3.2.2	Strain	
3.2.3	Source	
3.2.4	Sex	
3.2.5	Age/weight at study initiation	309 to 403 g corresponding to an age of between 5-8 weeks
3.2.6	Number of animals per group	20
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Per OECD 406, FIFRA § 81-6, EEC B.6., no deviations noted by the RMS in the 91/414 December 2005 draft monograph.
3.3.1	Induction schedule	See Tables A6.1.5/01-1 and A6.1.5./01-2
3.3.2	Way of Induction	
3.3.3	Concentrations used for induction	
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	
3.3.5	Challenge schedule	
3.3.6	Concentrations used for challenge	
3.3.7	Rechallenge	
3.3.8	Scoring schedule	
3.3.9	Removal of the test substance	
3.3.10	Positive control substance	formaldehyde
3.4	**Examinations**	
3.4.1	Pilot study	Yes, skin irritation examined following pre-test
		4 RESULTS AND DISCUSSION
4.1	**Results of pilot studies**	Maximum non-irritant concentrations: 1% intradermal, 25% topical
4.2	**Results of test**	See Table A6.1.5./01-2
4.2.1	24h after challenge	0/20
4.2.2	48h after challenge	0/20
4.2.3	Other findings	None for active substance; positive control resulted in skin reactions

Section A6.1.5/01 Skin sensitisation

Annex Point IIA6.1.5 Guinea pig maximisation test (GPMT)

4.3	**Overall result**	Following imidacloprid solution challenge neither the animals in the test article group, nor the animals in the control group exhibited any skin reactions.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	In a skin sensitization study (Guinea Pig Maximisation Test) conducted according to OECD 406, FIFRA § 81-6, EEC B.6. guidelines, a 1 % concentration of imidacloprid formulated in sterile physiological saline solution containing 2 % Cremophor EL® was used for intradermal induction and a 25 % concentration for topical induction. 3 % and a 25 % concentrations were used for challenge.
5.2	**Results and discussion**	Following the challenge neither the animals in the test article group, nor the animals in the control group exhibited any skin reactions.
5.3	**Conclusion**	Imidacloprid has no skin sensitising potential under the conditions of the Maximisation test.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/01/24
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable.
Conclusion	Non-sensitiser (applicant's version is acceptable)
Reliability	1
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.5/01-1. Detailed information including induction/challenge/scoring schedule for GPMT skin sensitisation test with imidacloprid

Inductions	GPMT		Observations/Remarks
	day of treatment	application	
Induction 1	0	intradermal	No irritation following 1% intradermal induction
Induction 2	5-7	topical	No skin reaction following 25% topical induction
challenge	20-22	topical	No skin reaction following 3% or 25% topical challenge
scoring 1	21-23		No reactions, scoring 0/20 both 24 and 48 h after challenge

Table A6.1.5/01-2. Result of GPMT skin sensitisation test with imidacloprid

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	**Test group**	**Positive control after 2nd challenge**
scored after 24h	0/10	0/20	7/20
scored after 48h	0/10	0/20	4/20

Section A6.2/01
Annex Point IIA.6.2

Metabolism Studies in Animals – Basic Toxicokinetics
Rat ADME Study

Official use only

1 REFERENCE

1.1	**Reference**	*PPP monographB.6.1.1, II A, 5.1.1 /01*
	Authors (year)	[redacted] (1987a)
	Title	(14C)-NTN 33893: Biokinetic part of the 'General metabolism study' in the rat
	Company, report No.	Bayer CropScience AG, Report-No.: PF2889 BES Ref. : M-024189-01-1
	Date	1987-11-09
	Testing facility	[redacted]
	Dates of work	May 6, to August 11, 1987
	Test substance(s)	Molecule(s): imidacloprid Substance(s): [pyridinyl-^{14}C-methylene] NTN 33893 labelled Specific radioactivity 5.6 MBq/mg, radiochemical purity >99% Radiochemical purity ^{13}C >99%
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	Companies with letters of access	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/ IA

2 GUIDELINES AND QUALITY ASSURANCE

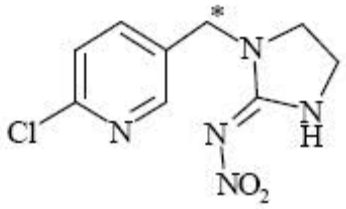
2.1	**Guideline study**	"EPA Pesticide Assessment Guidelines, Subdivision F". EPA 54019-82-025, November 1982 including the tissue-distribution study to suit the Japanese requirements
2.2	**GLP**	Yes (certified laboratory)
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	
3.1.1	Radiolabelled material	^{14}C -Labelled: [pyridinyl-14-C-methylene]-imidacloprid, radiochemical purity 99 %, chromatographic purity > 99 %. ^{13}C -Labelled: [pyridinyl-^{13}C-methylene]-imidacloprid, atom ^{13}C -purity > 99 %
3.1.2	Specification	specific radioactivity 5.6 MBq/mg
3.1.3.1	Purity	See above

Section A6.2/01 — **Metabolism Studies in Animals – Basic Toxicokinetics**

Annex Point IIA.6.2 — *Rat ADME Study*

3.1.3.2	Stability	The test compound was stable in the solution in which it was administered
3.1.3.3	Radiolabelling	
3.2	Unlabelled material	imidacloprid
3.2.1	Lot/Batch number	batch and purity not reported
3.2.2	Specification	Assumed as per section 2
3.2.2.1	Purity	Not reported, assumed in line with specification
3.2.2.2	Stability	stability guaranteed for the duration of the study
3.3	**Test Animals**	
3.3.1	Species	Wistar rats (Strain Bor:WISW (SPF Cpb); Breeder [redacted]),
3.3.2	Strain	
3.3.3	Source	
3.3.4	Sex	50 Males and 20 female
3.3.5	Weight at study initiation	Approximately 200 g at the time of dosing.
3.3.6	Number of Animals per Group	Table 6.2/01-1 provides details of the number of animals per group.
3.3.7	Control animals	No
3.4	**Administration/ Exposure**	Tables A6.2/01-1 and A6.2/01-2 provide administration details.
3.4.1	Sampling time	Plasma samples were taken at 5, 10, 20, 40 mins. and 1, 1.5, 2, 3, 4, 6, 8, 24, 32 and 48 hrs. post application. Urine was sampled in intervals of 0 – 4, 4 – 8, 8 – 24, 24 – 32 and 32 - 48 hrs. and faeces in periods of 0 - 24 and 24 – 48 hrs. after dosage.
3.5	**Samples**	
3.5.1	Blood level investigation	Blood samples taken at every sampling time were separated into plasma and erythrocytes by centrifugation
3.6.2	Tissue Concentrations	Organs and tissues collected during the experiment were weighed immediately after dissection and again following lyophilisation. Finally, they were homogenised before aliquots were taken for the determination of radioactivity by the combustion technique. For samples of organs with weights below 500 mg or residues with a low detection limit, samples were weighed and combusted in an oxygen atmosphere using an oxidiser. Radioactivity in the trapped combustion gases was measured by LSC. Fatty organs and tissues were solubilised by means of a tissue solubiliser. Radioactivity from aliquots was measured by LSC. Liquid samples were mixed with scintillation gel and measured by LSC.

Section A6.2/01 — **Metabolism Studies in Animals – Basic Toxicokinetics**

Annex Point IIA.6.2 — *Rat ADME Study*

3.6.3	Elimination in faeces, urine and air	During excretion studies, animals were kept in special metabolism cages, which allowed separate and quantitative sampling of the excreta.
3.6.4	Elimination in Bile	During bile cannulation rats were housed under controlled temperature and humidity.
3.6.5	Quantitative evaluation	Calculation of relative concentrations: Relative concentration P = Radioactivity administered / grams of body weight Radioactivity measured/ grams of plasma or tissue Equivalent concentrations (radioactivity of metabolites calculated as equivalents of the active substance) were calculated from relative concentrations by multiplying with the dose in mg per kg. Amounts of radioactivity present in the excreta or still present at time of sacrifice in the tissues of the animal body or in the organs were calculated from measured concentrations and the weight contribution to the total body weight. Values were determined by weighing where possible. Values not accessible by weighing were estimated as follows: Plasma: 3.2 %, erythrocytes 3.2 %, dissectable fat: 5.0 %, muscle: 40.0 %
3.6.6	Determination of metabolites	This study is the biokinetic part of the general metabolism studies of imidacloprid in rats, and metabolites were not determined.
3.7	**Statistical analysis**	Evaluation of kinetics: Series of concentration-time data pairs were fitted to a sum of exponentials using the following equation: $$x_i = \mathrm{sum}_{j=1}^{N}\left[A_{(j)} \times e^{\left(-b_{(j)} \times t_{(i)}\right)}\right]$$ where A(j) = preexponential factor weighting the proportion jth exponential term in the fit function. b(j) = exponent of the jth exponential term inversely proportional to the jth half-life. N = number of exponential terms in the fit function corresponding to the number of phases in the experimental curve. (For time courses of the level of concentration or amount the time axis is shifted by the lagtime Tlag which is the interval between administration and the onset of absorption.)

4 RESULTS AND DISCUSSION

4.1 Absorption

After oral administration of both the high and low dose of [pyridinyl-^{14}C methylene] imidacloprid, the maximum dose-normalised concentration of radioactivity in the plasma was reached between 1.1 and 2.5 hours. In all cases the peak concentration was low with an average of 0.73 mg/L, compared to the equidistribution of 1. Since the majority of the administered radioactivity was excreted renally, the absorption was assumed to be high

From the experiment using bile-cannulated rats and intraduodenal administration the amount of absorbed radioactivity was calculated to be 95 % of the given dose. This is in good agreement with the estimations for the oral tests.

In all dose groups under investigation the rate of absorption can be described with an average half-life of approximately 35 minutes taking into account a lagtime of less than 2.5 minutes.

4.2 Distribution

After intravenous injection of 1 mg/kg bw, an apparent initial distribution volume (Vc) of about 84 % of the total body volume was obtained from plasma curve analysis for males and females. This result indicated that the radioactivity was readily distributed from the plasma into peripheral compartments. The distribution volume under steady-state conditions (Vss) was roughly in the same order of magnitude as the apparent initial distribution volume (Vc) after intravenous administration with the exception of male rats receiving a single oral dose of 1 mg/kg bw. This supports the assumption that the radioactivity was distributed very quickly into peripheral compartments. It also means that the parent compound and/or its labelled metabolites have a high ability to permeate the tissues.

The Mean Residence Time (MRT) of the total radioactivity in the central compartment (plasma) varied between about 9 and 17 hours indicating that the redistribution into the plasma prior to elimination, mainly via the kidney, was also a fast process.

The radioactivity remaining in the body (excluding the gastrointestinal tract) at sacrifice 48 hours after oral or intravenous administration was below 1 % of the recovered radioactivity in all dose groups. However, from the kinetics of the renal excretion and of the elimination behaviour of the total radioactivity from the plasma, it can be concluded that the remaining radioactivity in the body was subject to further elimination. At the end of the experiment (48 h post application) the average dose normalized concentration in the body (excluding gastrointestinal tract) was about 0.005 mg/L independent of the route of administration. Most of the investigated organs and tissues showed lower values. The highest value was found in the kidney and the lowest value was detected in the brain [see Table A6.2/01-3].

Identical patterns of distribution of total radioactivity were found in organs and tissues sampled at different times (40 min - 6 hours) following a single oral administration of 20 mg/kg bw. In this test maximum concentrations in all organs had been reached already 40 minutes after application [see Table A6.2/01-4].

Section A6.2/01 — Metabolism Studies in Animals – Basic Toxicokinetics

Annex Point IIA.6.2 — *Rat ADME Study*

4.3	**Elimination**	In all tests of this study the elimination of the total radioactivity from the plasma could be approximated by a combination of two exponential terms from which elimination half-lives were calculated. These half-lives varied between ca. 2.6 to 3.6 and 26 to 118 hours, respectively. The radioactivity was readily eliminated from the body. Within 48 h after administration about 92 % of an intravenous dose of 1 mg/kg bw and about 96 % of an oral dose were excreted via urine and faeces. The major part of the radioactivity was excreted via the kidneys [average ratio: 4 : 1 (urine : faeces)]. There were no differences between female and male rats. More than 90 % of the radioactivity found in urine was excreted within 24 hours after dosing, as can be expected from the fast distribution and redistribution of the radioactivity and the good water solubility of the parent compound and its metabolites. On average, the residual radioactivity in the body excluding the gastrointestinal tract at sacrifice was about 0.5 % and in the gastrointestinal tract about 0.06 % of the dose. The investigation of the expired air for radioactive CO2 over a period of 48 hours did not reveal significant amounts of radioactivity. This demonstrates that the chosen labelling position within the molecule was stable with respect to the formation of volatile C-1-fragments. The results are summarised in Table A.6.2/01-5.
4.4	**Biliary elimination**	Bile-cannulated rats excreted only 4.7 % of the dose with the faeces, 56.4 % in the urine and about 36 % with the bile. The biliary excretion was very rapid. More than 90 % of the biliary radioactivity was already excreted after 12 hours. The course of elimination can be described by two exponential terms with half-lives of 2.9 and 10.1 hours, respectively. The difference observed in renal excretion between bile-cannulated and 'intact' animals (57.5 versus 77.8 % of the recovered radioactivity) is a strong hint towards the existence of an enterohepatic circulation. A major part of the material reabsorbed from the gastrointestinal tract after biliaryexcretion appears to be eliminated via the kidney.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The biokinetic behaviour of imidacloprid was investigated according to EPA pesticide assessment guidelines including tissue distribution assessment in accordance with Japanese requirements. Wistar rats in groups of at least 5 animals per investigation received a single dose of radioactive imidacloprid:
1) orally at 20 mg/kg bw for a)excretion studies in expired air, urine and feces, b) determination of plasma levels and organ concentrations and c) a time dependent characterization study in organs and tissues) or
2) a single dose of 1 mg/kg bw orally or intravenously for a) urine and feces excretion studies and b) determination of plasma levels and organ concentrations), or
3) interduodenally at 1 mg/kg bw for an excretion study with bile, urine and feces.
In addition, a multiple dosing experiment was done where rats received 1 mg/kg bw non-radioactive doses for 14 days followed by a single radioactive dose on day 15.

During excretion studies animals were kept in cages which allowed a separate and quantitative sampling of the excreta. In all other cases animals were kept in plastic cages on wood shavings. The animals were kept at room temperature during the test period of 48 hours. In the non-radioactive pre-treatment period and during the bile cannulation the rats were housed under conditions of controlled temperature (20 °C) and humidity (40 – 80 %). Altromin 1324 standard food, 15 g per day and animal and water, ad libitum were provided.

Plasma samples were taken at 5, 10, 20, 40 mins. and 1, 1.5, 2, 3, 4, 6, 8, 24, 32 and 48 hrs. post application. The collected blood was separated into plasma and erythrocytes by centrifugation.

Urine was sampled in intervals of 0 – 4, 4 – 8, 8 – 24, 24 – 32 and 32 - 48 hrs. and faeces in periods of 0 - 24 and 24 – 48 hrs. after dosage.

The animals were sacrificed using carbon dioxide gas. Organs and tissues collected during the experiment were weighed immediately after dissection and again following lyophilisation. Finally, they were homogenised before aliquots were taken for the determination of radioactivity by the combustion technique. For samples of organs with weights below 500 mg or residues with a low detection limit, samples were weighed and combusted in an oxygen atmosphere using an oxidiser.

Radioactivity in the trapped combustion gases was measured by LSC. Radioactivity from aliquots was measured by LSC. Liquid samples were mixed with scintillation gel and measured by LSC.

5.2 Results and discussion

Absorption: After oral administration of both the high and low dose of [pyridinyl-^{14}C methylene] imidacloprid the maximum dose-normalised concentration of radioactivity in the plasma was reached between 1.1 and 2.5 hours. In all cases the peak concentration was low with an average of 0.73 mg/L, compared to the equidistribution of 1. Since the majority of the administered radioactivity was excreted renally, the absorption was assumed to be high

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In all dose groups under investigation the rate of absorption can be described with an average half-life of approximately 35 minutes taking into account a lagtime of less than 2.5 minutes.

Distribution:

After intravenous injection of 1 mg/kg bw, an apparent initial distribution volume (Vc) of about 84 % of the total body volume was obtained from plasma curve analysis for males and females. This result indicated that the radioactivity was readily distributed from the plasma into peripheral compartments. The distribution volume under steady-state conditions (Vss) was roughly in the same order of magnitude as the apparent initial distribution volume (Vc) after intravenous administration with the exception of male rats receiving a single oral dose of 1 mg/kg bw. This supports the assumption that the radioactivity was distributed very quickly into peripheral compartments. It also means that the parent compound and/or its labelled metabolites have a high ability to permeate the tissues. The Mean Residence Time (MRT) of the total radioactivity in the central compartment (plasma) varied between about 9 and 17 hours indicating that the redistribution into the plasma prior to elimination, mainly via the kidney, was also a fast process.

The radioactivity remaining in the body (excluding the gastrointestinal tract) at sacrifice 48 hours after oral or intravenous administration was below 1 % of the recovered radioactivity in all dose groups. However, from the kinetics of the renal excretion and of the elimination behavior of the total radioactivity from the plasma it can be concluded that the remaining radioactivity in the body was subject to further elimination. At the end of the experiment (48 h post application) the average dose normalized concentration in the body (excluding gastrointestinal tract) was about 0.005 mg/L independent of the route of administration. Most of the investigated organs and tissues showed lower values. The highest value was found in the kidney and the lowest value was detected in the brain.

Identical patterns of distribution of total radioactivity were found in organs and tissues sampled at different times (40 min - 6 hours) following a single oral administration of 20 mg/kg bw. In this test maximum concentrations in all organs had been reached already 40 minutes after application

Excretion

In all tests of this study the elimination of the total radioactivity from the plasma could be approximated by a combination of two exponential terms from which elimination half-lives were calculated. These half-lives varied between ca. 2.6 to 3.6 and 26 to 118 hours, respectively.

The radioactivity was readily eliminated from the body. Within 48 h after administration about 92 % of an intravenous dose of 1 mg/kg bw and about 96 % of an oral dose were excreted via urine and faeces. The major part of the radioactivity was excreted via the kidneys [average ratio: 4 : 1 (urine : faeces)]. There were no differences between female and male rats.

More than 90 % of the radioactivity found in urine was excreted within 24 hours after dosing, as can be expected from the fast distribution and redistribution of the radioactivity and the good water solubility of the parent compound and its metabolites. On average, the residual radioactivity in the body excluding the gastrointestinal tract at sacrifice was about 0.5 % and in the gastrointestinal tract about 0.06 % of the dose. The investigation of the expired air for radioactive CO2 over a period of 48 hours did not reveal significant amounts of radioactivity. This demonstrates that the chosen labelling position within the molecule was stable with respect to the formation of volatile C-1-fragments.

Biliary Excretion

Bile-cannulated rats excreted only 4.7 % of the dose with the faeces, 56.4 % in the urine and about 36 % with the bile. The biliary excretion was very rapid. More than 90 % of the biliary radioactivity was already excreted after 12 hours. The course of elimination can be described by two exponential terms with half-lives of 2.9 and 10.1 hours, respectively. The difference observed in renal excretion between bile-cannulated and 'intact' animals (57.5 versus 77.8 % of the recovered radioactivity) is a strong hint towards the existence of an enterohepatic circulation. A major part of the material reabsorbed from the gastrointestinal tract after biliary excretion appears to be eliminated via the kidney.

5.3 Conclusion

Imidacloprid is rapidly and extensively absorbed from the gastrointestinal tract following oral administration to rats. Absorbed material is distributed to all organs and tissues, with the exception of brain, in concentrations similar to or higher than the concentrations measured in plasma. The major proportion of the radioactivity is excreted renally, either directly or after enterohepatic circulation. Excretion is nearly complete after 48 hours. There was no evidence for accumulation in any of the tissues.

5.3.1 Reliability

1

5.3.2 Deficiencies

No.

Although this study reports only the biokinetic aspects and does not provide information on the metabolic reactions and identity of metabolites, these aspects were investigated and are described in detail in a separate study report (see A6.2/03)