Section A4.1 (01)
Annex Point IIA4.1

Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of the active substance and additives (e.g. stabilisers)
TI-435 technical grade active ingredient (TGAI)

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]. (2001): [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data on existing a.s. submitted for the first time for entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes OPPTS 830.1800
2.2	**GLP**	No
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	[redacted]
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	[redacted]
3.2.4	Interfering substance(s)	[redacted]
3.3	**Linearity**	
3.3.1	Calibration range	[redacted]
3.3.2	Number of measurements	[redacted]
3.3.3	Linearity	[redacted]
3.4	**Specificity: interfering substances**	[redacted]
3.5	**Recovery rates at different levels**	[redacted]

Section A4.1 (01)
Annex Point IIA4.1

Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of the active substance and additives (e.g. stabilisers)
TI-435 technical grade active ingredient (TGAI)

		[redacted]
3.5.1	Relative standard deviation	[redacted]
3.6	**Limit of determination**	[redacted]
3.7	**Precision**	
3.7.1	Repeatability	[redacted]
3.7.2	Independent laboratory validation	[redacted]

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

An analytical method for the analysis of TI-435 technical grade active ingredient (TGAI) was validated according to OPPTS 830.1800. TI-435 was diluted in methanol and analysed directly by liquid chromatography (HPLC) using reversed phase conditions and UV detection. An internal standard (3-nitrophenol) was used for identification of TI-435.

Linearity, specificity, accuracy (recovery rates) and repeatability of the analytical method were determined.

4.2 Conclusion

Validity criteria of the analytical method presented can be considered as fulfilled. Linearity, specificity, accuracy and repeatability of the analytical method have been demonstrated.

4.2.1 Reliability: 2

4.2.2 Deficiencies: GLP compliance not stated

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*

Section A4.1 (01) **Annex Point IIA4.1**	**Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of the active substance and additives (e.g. stabilisers)** **TI-435 technical grade active ingredient (TGAI)**

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 A4.1/02
Annex Point IIA4.1

Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of the active substance and additives (e.g. stabilisers)
TI-435 technical grade active ingredient (TGAI) and impurities

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]. (2001b): [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	Sumitomo Chemical Takeda Agro Co., Ltd.
1.2.2	Companies with letter of access	None
1.2.3	Criteria for data protection	Data on existing a.s. submitted for the first time for entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes US EPA OPPTS 830.1700
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

The identity and analysis of TI-435 technical grade active ingredient and impurities are confidential information. Therefore, all information requested is filed separately. Please refer to the confidential section which can be found in Doc.-IIIA, chapter 12.

4 APPLICANT'S SUMMARY AND CONCLUSION

The identity and analysis of TI-435 technical grade active ingredient and impurities are confidential information. Therefore, all information requested is filed separately. Please refer to the confidential section which can be found in Doc.-IIIA, chapter 12.

4.1	**Conclusion**	Validity criteria of the analytical method can be considered as fulfilled.
4.1.1	Reliability	1
4.1.2	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	21.10.04
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]

Section A4.1/02 **Annex Point IIA4.1**	**Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of the active substance and additives (e.g. stabilisers)** **TI-435 technical grade active ingredient (TGAI) and impurities**

Acceptability	[redacted]
Remarks	[redacted]
	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 A4.2 (01)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(a) Soil

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted] (2000): [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No
2.2	**GLP**	Yes
2.3	**Deviations**	Not relevant
	3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	
3.1.1	Enrichment	[redacted]
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	HPLC
3.2.2	Detector	Electrospray MS/MS-detection in the Multiple Reaction Monitoring mode
3.2.3	Standard(s)	[redacted]
3.2.4	Interfering substance(s)	None
3.3	**Linearity**	

Section A4.2 (01)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(a) Soil

3.3.1	Calibration range	[redacted]
3.3.2	Number of measurements	[redacted]
3.3.3	Linearity	[redacted]
3.4	**Specifity: interfering substances**	[redacted]
3.5	**Recovery rates at different levels**	[redacted]
3.5.1	Relative standard deviation	See Table A4_2_01-1
3.6	**Limit of determination**	[redacted]
3.7	**Precision**	
3.7.1	Repeatability	[redacted]
3.7.2	Independent laboratory validation	Not relevant

Section A4.2 (01)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(a) Soil

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	A method for the residue analysis of TI-435 and the metabolites TZNG and MNG in soil was presented and validated. After extraction of fortified soil samples, TI-435, TZNG and MNG in the soil extracts were analysed directly by HPLC with Electrospray MS/MS-detection. Isotopically labelled internal standards ([redacted] were used to compensate for possible matrix effects in the MS/MS detector. Linearity, specificity, recovery rates, limit of determination and quantitation (LOD and LOQ) and repeatability of the analytical method were determined.
4.2	**Conclusion**	The analytical method presented permits the determination of residues of TI-435 and the metabolites TZNG and MNG in soil with satisfactory accuracy and precision. Therefore, the method is considered valid for the determination of residues of TI-435, TZNG and MNG in soil.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	[redacted]
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
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	

[redacted]

Section A4.2 (02)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(b) Air

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted] (2000): [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes Commission Directive 96/46EC of July 16, 1996 Directive 91/414/EEC – guideline on residue analytical method Document 8064/VI/97 rev. 4 (15/12/1998)
2.2	**GLP**	Yes
2.3	**Deviations**	No
	3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	
3.1.1	Sampling	[redacted]
3.1.2	Enrichment	[redacted]
3.1.3	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	[redacted]
3.2.4	Interfering substance(s)	[redacted]
3.3	**Linearity**	
3.3.1	Calibration range	[redacted]
3.3.2	Number of measurements	[redacted]
3.3.3	Linearity	[redacted]

Section A4.2 (02)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(b) Air

3.4	**Specifity: interfering substances**	[redacted]
3.5	**Recovery rates at different levels**	[redacted]
3.5.1	Relative standard deviation	[redacted]
3.6	**Limit of determination**	[redacted]
3.7	**Precision**	
3.7.1	Repeatability	[redacted]
3.7.2	Independent laboratory validation	[redacted]

Section A4.2 (02)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(b) Air

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	A method for residue analysis of TI-435 in air was described and validated. The required limit of quantification was defined based on toxicological parameters to be 0.081 mg/m^3. Approximately 1/10 and a 5-fold of this concentration (i.e. 0.008 mg/m^3 and 0.398 mg/m^3) were analysed. The method is based on the guidance documents Commission Directive 96/46EC and Directive 91/414/EEC – guideline on residue analytical method Document 8064/VI/97 rev. 4 (15/12/1998). Linearity, specificity, recovery rates, limit of determination and quantification (LOD and LOQ) and repeatability of the analytical method were determined.
4.2	**Conclusion**	The analytical method presented permits the determination of residues of TI-435 in air with satisfactory accuracy and precision. Therefore, the method is considered valid for the determination of residues of TI-435 in air. The results obtained by the confirmatory method (HPLC-UV using a CN phase) were in good agreement with the results obtained by the HPLC-UV method using a reversed phase.
4.2.1	Reliability	1
4.2.2	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
1. Air	
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
2. Air at workplace	
Date	[redacted]

Section A4.2 (02)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(b) Air

Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
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	

[redacted]

[redacted]

Section A4.2 (03)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(c) Water

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted]. (2000): [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	SANCO/825/00 rev. 6 of 20/06/00 of the European Commission
2.2	**GLP**	Yes
2.3	**Deviations**	No
		3 MATERIALS AND METHODS
3.1	**Preliminary treatment**	
3.1.1	Enrichment	[redacted]
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	[redacted]
3.2.4	Interfering substance(s)	[redacted]
3.3	**Linearity**	
3.3.1	Calibration range	[redacted]
3.3.2	Number of measurements	[redacted]
3.3.3	Linearity	[redacted]
3.4	**Specifity: interfering substances**	[redacted]

Section A4.2 (03)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(c) Water

3.5	**Recovery rates at different levels**	[redacted]
3.5.1	Relative standard deviation	[redacted]
3.6	**Limit of determination**	[redacted]
3.7	**Precision**	
3.7.1	Repeatability	[redacted]
3.7.2	Independent laboratory validation	[redacted]
3.8	**Confirmation analysis**	[redacted]

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	A method for residue analysis of TI-435 in drinking and surface water was presented and validated. After extraction and clean-up of fortified surface water samples, TI-435 was analysed directly by HPLC with UV detection. The method is based on guidance document SANCO/825/00 rev. 6 of 20/06/00 of the European Commission. Linearity, specificity, recovery rates, limit of determination and quantification (LOD and LOQ) and repeatability of the analytical method were determined.
4.2	**Conclusion**	The analytical method presented permits the determination of residues of TI-435 in drinking and surface water with satisfactory accuracy and precision. Therefore, the method is considered valid for the determination of residues of TI-435 in drinking and surface water.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Section A4.2 (03)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(c) Water

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2004-12-15
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	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	

[redacted]

[redacted]

Section A4.2 (05)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(a) Soil

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted]. (1999): [redacted] Bayer AG, unpublished report no. MR-343/98
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No
2.2	**GLP**	Yes
2.3	**Deviations**	Not relevant
	3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	
3.1.1	Enrichment	[redacted]
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	[redacted]
3.2.4	Interfering substance(s)	[redacted]

Section A4.2 (05)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(a) Soil

3.3 Linearity

3.3.1 Calibration range

3.3.2 Number of measurements

3.3.3 Linearity

3.4 Specifity: interfering substances

3.5 Recovery rates at different levels

3.5.1 Relative standard deviation

3.6 Limit of determination

3.7 Precision

3.7.1 Repeatability

3.7.2 Independent laboratory validation

Section A4.2 (05)
Annex Point IIA4.2

Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:

(a) Soil

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	A method for the residue analysis of TI-435 and the metabolites TZNG, TZMU, MNG and TMG in soil was presented and validated. After extraction of fortified soil samples, TI-435, TZNG, TZMU, MNG and TMG in the soil extracts were analysed directly by HPLC with Electrospray MS/MS-detection. Isotopically labelled internal standards ([redacted]) were used to compensate for possible matrix effects in the MS/MS detector. Linearity, specificity, recovery rates, limit of determination and quantitation (LOD and LOQ) and repeatability of the analytical method were determined.
4.2	**Conclusion**	The analytical method presented permits the determination of residues of TI-435 and the metabolites TZNG, TZMU, MNG and TMG in soil with satisfactory accuracy and precision. Therefore, the method is considered valid for the determination of residues of TI-435, TZNG, TZMU, MNG and TMG in soil.
4.2.1	Reliability	1
4.2.2	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	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Table A4_2_05-1: **Recovery in %**

Fortification level		**0.005 mg/kg wet soil**			**0.05 mg/kg wet soil**			
	n	mean	range	rel. SD	mean	range	rel. SD	overall rel. SD
TI-435								
Watsonville	5	92	87 - 99	6.1	99	95 -106	4.6	
Howe	5	102	93 -110	6.9	101	93 -107	5.0	
Hoefchen	5	97	91 -106	6.5	100	96 -101	2.3	
mean		97		7.4	100		4.0	6.0
TZNG								
Watsonville	5	92	87 - 97	5.3	96	91 -105	5.7	
Howe	5	94	88 -100	4.5	96	90 -108	7.7	
Hoefchen	5	92	87 - 97	5.0	92	86 - 99	5.0	
mean		92		4.6	95		6.1	5.5
TZMU								
Watsonville	5	97	86 -107	9.3	87	79 - 93	6.8	
Howe	5	92	79 -105	10.4	95	88 -101	5.5	
Hoefchen	5	97	91 -103	5.4	93	84 -101	6.8	
mean		95		8.4	92		7.0	7.9
MNG								
Watsonville	5	73	67 - 81	7.7	96	79 -111	12.0	
Howe	5	81	75 - 96	10.4	98	91 -104	5.3	
Hoefchen	5	80	69 - 89	10.0	96	90 -109	7.9	
mean		78		10.0	97		8.2	13.9
TMG								
Watsonville	5	97	88-112	10.0	97	88-110	8.7	
Howe	5	107	92-134	14.8	107	101-114	4.8	
Hoefchen	5	93	88- 99	4.7	100	92-126	14.3	
mean		99		11.8	101		10.1	10.9

Section A4.3/01
Annex Point IIIA IV.1

Analytical methods including recovery rates and the limits of determination for residues in/on food or feedstuffs and other products where relevant

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000c): [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes SANCO/825/00 rev. 6 of 20/06/00 of the European Commission and BBA Guideline: Residue Analytical Methods for Post-Registration Control Purposes of July 21, 1998
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	[redacted]
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Column	[redacted]
3.2.4	Standard(s)	[redacted]
3.2.5	Interfering substance(s)	[redacted]

Section A4.3/01
Annex Point IIIA IV.1

Analytical methods including recovery rates and the limits of determination for residues in/on food or feedstuffs and other products where relevant

3.3	**Linearity**	
3.3.1	Calibration range	[redacted]
3.3.2	Number of measurements	[redacted]
3.3.3	Linearity	[redacted]
3.4	**Specifity: interfering substances**	[redacted]
3.5	**Recovery rates at different levels**	[redacted]
3.5.1	Relative standard deviation	[redacted]
3.6	**Limit of determination**	[redacted]
3.7	**Precision**	
3.7.1	Repeatability	[redacted]
3.7.2	Independent laboratory validation	[redacted]
3.8	**Confirmation analysis**	[redacted]

Section A4.3/01
Annex Point IIIA IV.1

Analytical methods including recovery rates and the limits of determination for residues in/on food or feedstuffs and other products where relevant

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	A method for the determination of the residue of TI-435 in plant material is presented and validated. Specimens of apple, wheat, sugar-beet and oil seed rape were extracted with acetone / water (3:1, v/v). After cleanup of the extract, the samples were analysed by HPLC. The method is based on SANCO/825/00 rev. 6 of 20/06/00 of the European Commission. Linearity, specificity, recovery rates, limit of determination and quantitation (LOD and LOQ) and repeatability of the analytical method were determined.
4.2	**Conclusion**	The analytical method presented permits the determination of residues of TI-435 in tested matrices with satisfactory accuracy and precision. Therefore, the method is considered valid for the determination of residues of TI-435 in plant material.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	[redacted]
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
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*

Section A4.3/01
Annex Point IIIA IV.1

Analytical methods including recovery rates and the limits of determination for residues in/on food or feedstuffs and other products where relevant

Remarks

Table [redacted]

[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

[redacted]

[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Section A4.3/02
Annex Point IIIA IV.1

Analytical methods including recovery rates and the limits of determination for residues in/on food or feedstuffs and other products where relevant

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2001): [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted]
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

[redacted]

3.1	**Preliminary treatment**	
3.1.1	Enrichment	[redacted]
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]

Section A4.3/02
Annex Point IIIA IV.1

Analytical methods including recovery rates and the limits of determination for residues in/on food or feedstuffs and other products where relevant

3.2.3	Column	[redacted]
3.2.4	Standard(s)	[redacted]
3.2.5	Interfering substance(s)	[redacted]
3.3	**Linearity**	
3.3.1	Calibration range	[redacted]
3.3.2	Number of measurements	[redacted]
3.3.3	Linearity	[redacted]
3.4	**Specifity: interfering substances**	[redacted]
3.5	**Recovery rates at different levels**	[redacted]
3.5.1	Relative standard deviation	[redacted]
3.6	**Limit of determination**	[redacted]
3.7	**Precision**	
3.7.1	Repeatability	[redacted]
3.7.2	Independent laboratory validation	[redacted]
3.8	**Confirmation analysis**	[redacted]

Section A4.3/02
Annex Point IIIA IV.1

Analytical methods including recovery rates and the limits of determination for residues in/on food or feedstuffs and other products where relevant

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	An analytical method is presented that describes the additional validation of method 00657 (summarised in Section A4.3/01) at a limit of quantitation of 0.01 mg/kg for determination of the active substance in plant material. The method is based on SANCO/825/00 rev. 6 of 20/06/00 of the European Commission. Linearity, specificity, recovery rates, limit of determination and quantitation (LOD and LOQ) and repeatability of the analytical method were determined.
4.2	**Conclusion**	The analytical method presented permits the determination of residues of TI-435 in tested matrices with satisfactory accuracy and precision down to a limit of quantitation of 0.01 mg/kg. Therefore, the method is considered valid for the determination of residues of TI-435 in plant material.
4.2.1	Reliability	1
4.2.2	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	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
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	

[redacted]

[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
					[redacted]	
					[redacted]	

[redacted]

[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Section A5 Effectiveness against target organisms and intended uses

Subsection (Annex Point)			Official use only
5.1	**Function (IIA5.1)**	insecticide	
5.2	**Organism(s) to be controlled and products, organisms or objects to be protected (IIA5.2)**		
5.2.1	**Organism(s) to be controlled (IIA5.2)**	Efficacy against all major wood destroying insects, e.g. larvae of house longhorn beetle (*Hylotrupes bajulus*) and termites such as *Reticulitermes santonensis.* Organisms to be controlled exist in all parts of the Community with the exeption of termites missing in wide areas of middle and northern Europe.	
5.2.2	**Products, organisms or objects to be protected (IIA5.2)**	All kinds of construction wood, partical board and ply wood.	
5.3	**Effects on target organisms, and likely concentration at which the active substance will be used (IIA5.3)**		
5.3.1	**Effects on target organisms (IIA5.3)**	insecticidal, with contact and stomach action For results of efficacy tests with TI-435 refer to the summary table on the last page of this section.	
5.3.2	**Likely concentrations at which the A.S. will be used (IIA5.3)**	A: [redacted]	
	PT 08	The present dossier is to support product type PT 08.	
	PTn	Not yet relevant in the context of this dossier.	
5.4	**Mode of action (including time delay) (IIA5.4)**		
5.4.1	**Mode of action**	TI-435 belongs to the chemical class of insecticides known as neonicotinoids or chloronicotinyls and especially active against homopteran and coleopteran pest species. The compound acts agonistically on insect nicotinic acetylcholine receptors located in the central nervous system (Nauen *et al.*, 2001). TI-435 has excellent systemic properties as indicated by its physicochemical characteristics.	

Section A5 Effectiveness against target organisms and intended uses

5.4.2	**Time delay**	not applicable; TI-435 is active *per se*
5.5	**Field of use envisaged (IIA5.5)**	
	MG01: Disinfectants, general biocidal products	currently not relevant
	MG02: Preservatives	[redacted]
	MG03: Pest control	currently not relevant
	MG04: Other biocidal products	currently not relevant
	Further specification	none
5.6	**User (IIA5.6)**	
	Industrial	Industrial users are manufacturers of products for wood protection and applicators of those products to wood (e.g. saw-mills and impregnation plants) by pre-treatment in industrial premises (protective treatment): dipping treatment (use classes 1-3) and vacuum pressure treatment (use classes 1-4a).
	Professional	Professional users are special trained staff of service companies specialised in wood preservation performing curative (remedial) treatment by brushing or spraying of indoor wood under roof (using full protective equipment incl. respiratory protection).
	General public	Non-professional uses not envisaged.
5.7	**Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (IIA5.7)**	
5.7.1	**Development of resistance**	Because of the wide alternation of generations (e.g. house longhorn beetle), no formation of resistance has to be expected. Moreover, application of wood preservatives generally takes place above the lethal level. Therefore no formation of resistance within the

Section A5 **Effectiveness against target organisms and intended uses**

alternation of generations is possible.

However, TI-435 belongs to the chemical class of chloronicotinyls/ neonicotinoids like many other insecticides which might promote the development of resistance.

5.7.2 Management strategies

Active substances of different chemical classes should be used in rotation. This is to avoid a selection of the pest when the next generation has to be treated.

The product should be used as recommended in terms of dose to be applied and treatment intervals. The effective dose must be applied and no higher or lower doses.

5.8 Likely tonnage to be placed on the market per year (IIA5.8)

[redacted]

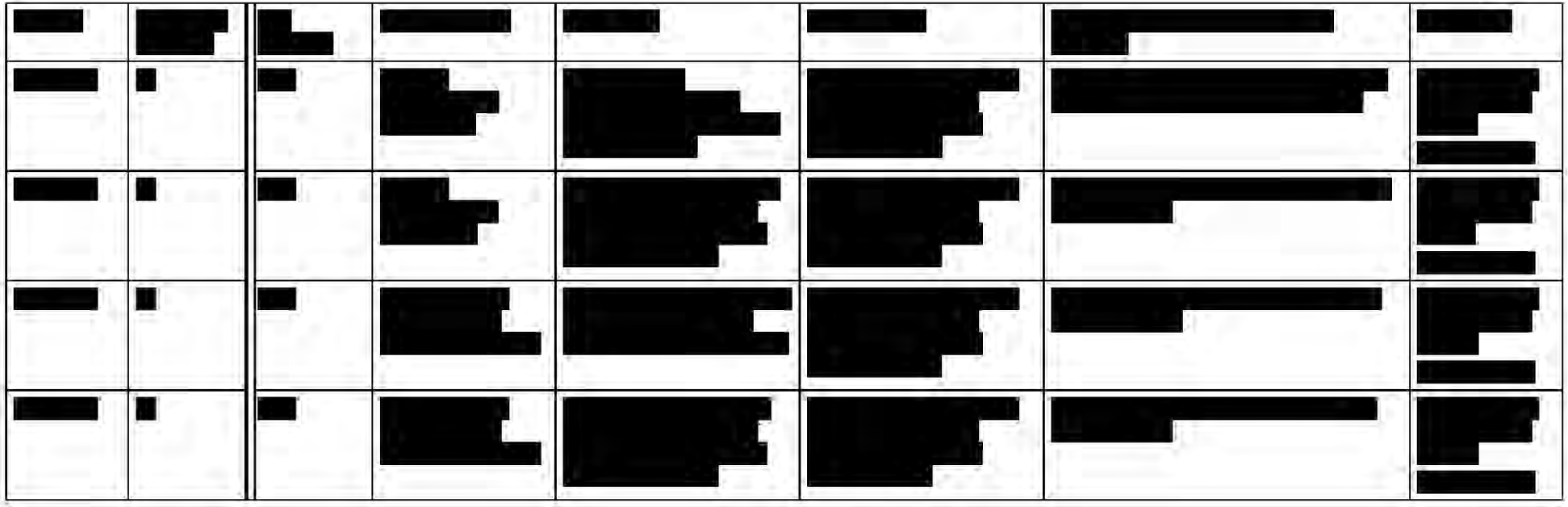
Section A5 Effectiveness against target organisms and intended uses

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2004-12-02 Human health
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...

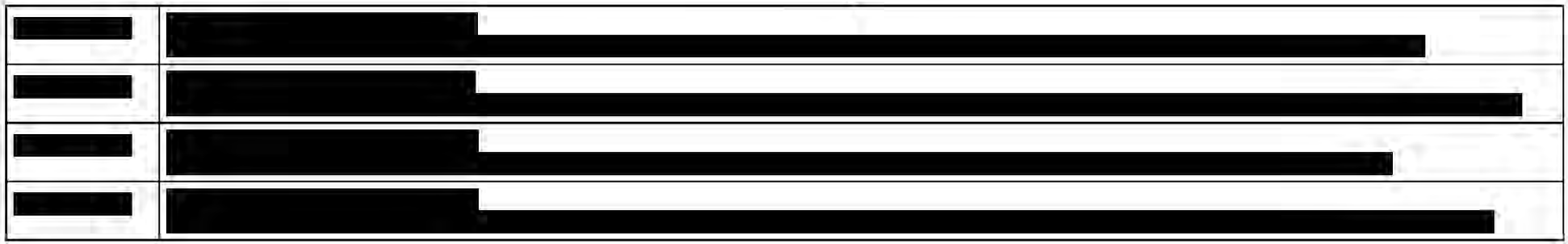
Section A5 Effectiveness against target organisms and intended uses

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	

[redacted]



[redacted]



Section A6.1.1 Acute Toxicity Oral

Annex Point IIA
VI.6.1.1/01

Acute oral toxicity study in rats (LD_{50})

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1997a); [redacted], 18.09.1997
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted on existing a.s. for its first entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [redacted] OECD No. 401 (1987)
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale, yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (test-article-vehicle formulations prepared at the day of dosing)
3.2	**Test Animals**	[redacted] rats [redacted] No control group
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days

Section A6.1.1 Acute Toxicity Oral

Annex Point IIA VI.6.1.1/01

Acute oral toxicity study in rats (LD_{50})

		Oral
3.3.2	Type	Gavage
3.3.3	Concentration	[redacted] 5000 mg/kg bw
3.3.4	Vehicle	[redacted]
3.3.5	Concentration in vehicle	Prepared according to individual bw and dosing volume
3.3.6	Total volume applied	10 mL/kg bw
3.3.7	Controls	-
3.4	**Examinations**	Clinical signs: recorded on at least 5 occasions on the day of treatment and at least once daily thereafter. Body weights were recorded pre-dose and on days 1, 4/5, 8 and 15. Decedents, animals killed in a moribund condition, and all survivors were subjected to necropsy and *post mortem* examination.
3.5	**Method of determination of LD_{50}**	Since no group showed mortality of >20%, the data were not analysed statistically.
3.6	**Further remarks**	-
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	[redacted]
4.2	**Pathology**	No gross lesions were apparent during post mortem examination of the animals.
4.3	**Other**	[redacted]
4.4	**LD_{50}**	>5000 mg/kg bw (males, females, males and females combined)
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Toxicity evaluation (bw, clinical signs, *post mortem* examination) after acute oral application to rats (gavage); no relevant deviation from guidelines (92/69/EEC method B1; EPA FIFRA 81-1, Japan MAFF, OECD 401)
5.2	**Results and discussion**	Acute oral LD_{50} in rats is >5000 mg/kg bw
5.3	**Conclusion**	No classification for oral toxicity is considered required [redacted] according to Directive 2001/59/EC (adaptation of 67/548/EEC).
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.1.1 Acute Toxicity Oral

Annex Point IIA VI.6.1.1/01

Acute oral toxicity study in rats (LD_{50})

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	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	

Section A6.1.1 **Acute Toxicity** **Oral**

Annex Point IIA
VI.6.1.1/01

Acute oral toxicity study in rats (LD_{50})

[redacted]

Section A6.1.1 Acute Toxicity Oral

Annex Point IIA
VI.6.1.1/02

Acute oral toxicity study in mice (LD_{50})

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] 18.09. 1997
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [redacted] OECD No. 401 (1987)
2.2	**GLP**	Yes
2.3	**Deviations**	None relevant for the scientific integrity or validity of the study: mice were used as they were considered the more sensitive species than rats

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale, yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (test-article-vehicle formulations prepared at the day of dosing)
3.2	**Test Animals**	[redacted] mice [redacted] No control group
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days

Section A6.1.1 Acute Toxicity Oral

Annex Point IIA VI.6.1.1/02

Acute oral toxicity study in mice (LD_{50})

		Oral
3.3.2	Type	Gavage
3.3.3	Concentration	304, 380, 475, 594 and 742 mg/kg bw
3.3.4	Vehicle	[redacted]
3.3.5	Concentration in vehicle	Prepared according to individual bw and dosing volume
3.3.6	Total volume applied	10 mL/kg bw
3.3.7	Controls	-
3.4	**Examinations**	Clinical signs: recorded on at least 5 occasions on the day of treatment and at least once daily thereafter. Body weights were recorded pre-dose and on days 1, 4, 8 and 15. Decedents, animals killed in a moribund condition, and all survivors were subjected to necropsy and *post mortem* examination.
3.5	**Method of determination of LD_{50}**	The acute median lethal dose and 95% confidence limits were estimated using moving average interpolation (C. S. Weil, 1952).
3.6	**Further remarks**	-
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	[redacted]
4.2	**Pathology**	No gross lesions were apparent during post mortem examination of the animals.
4.3	**Other**	-
4.4	**LD_{50}**	See table A6_1_1/02
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Toxicity evaluation (bw, clinical signs, *post mortem* examination) after acute oral application to mice (gavage); no relevant deviation from guidelines [redacted]
5.2	**Results and discussion**	Acute oral LD_{50} in mice (males+females combined): 425 mg/kg bw
5.3	**Conclusion**	Classification as harmful if swallowed (R22) is considered required for TI-435 according to Directive 2001/59/EC (adaptation of 67/548/EEC).
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.1.1 Acute Toxicity Oral

Annex Point IIA VI.6.1.1/02

Acute oral toxicity study in mice (LD_{50})

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	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	

Section A6.1.1 **Acute Toxicity** **Oral**

Annex Point IIA
VI.6.1.1/02

Acute oral toxicity study in mice (LD_{50})

[redacted]

Section A6.9 Neurotoxicity studies Acute study in rats

Acute oral neurotoxicity study in rats

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted] (2000); [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted on existing a.s. for its first entry into Annex I
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	[redacted]
2.2	**GLP**	Yes
2.3	**Deviations**	No
	3 MATERIALS AND METHODS	
3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (stability, homogenicity and content of test-article/vehicle formulations was analysed)
3.2	**Test Animals**	[redacted] rats [redacted]
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	4 days
3.3.2	Type	Gavage
3.3.3	Concentration	[redacted] 1000 mg/kg bw
3.3.4	Vehicle	[redacted]
3.3.5	Concentration in vehicle	Prepared according to individual bw and dosing volume
3.3.6	Total volume applied	[redacted]

Section A6.9 **Neurotoxicity studies** **Acute study in rats**

Acute oral neurotoxicity study in rats

3.3.7	Controls	-
3.4	**Examinations**	Detailed physical examination for clinical signs of toxicity, mortality: 0.5, 1, 2, 3, 4 and 24 hours after treatment, daily thereafter Body weights: prior to treatment and on day 4 or when they were found dead.
3.5	**Sacrifice and pathology**	None
3.6	**Further remarks**	-

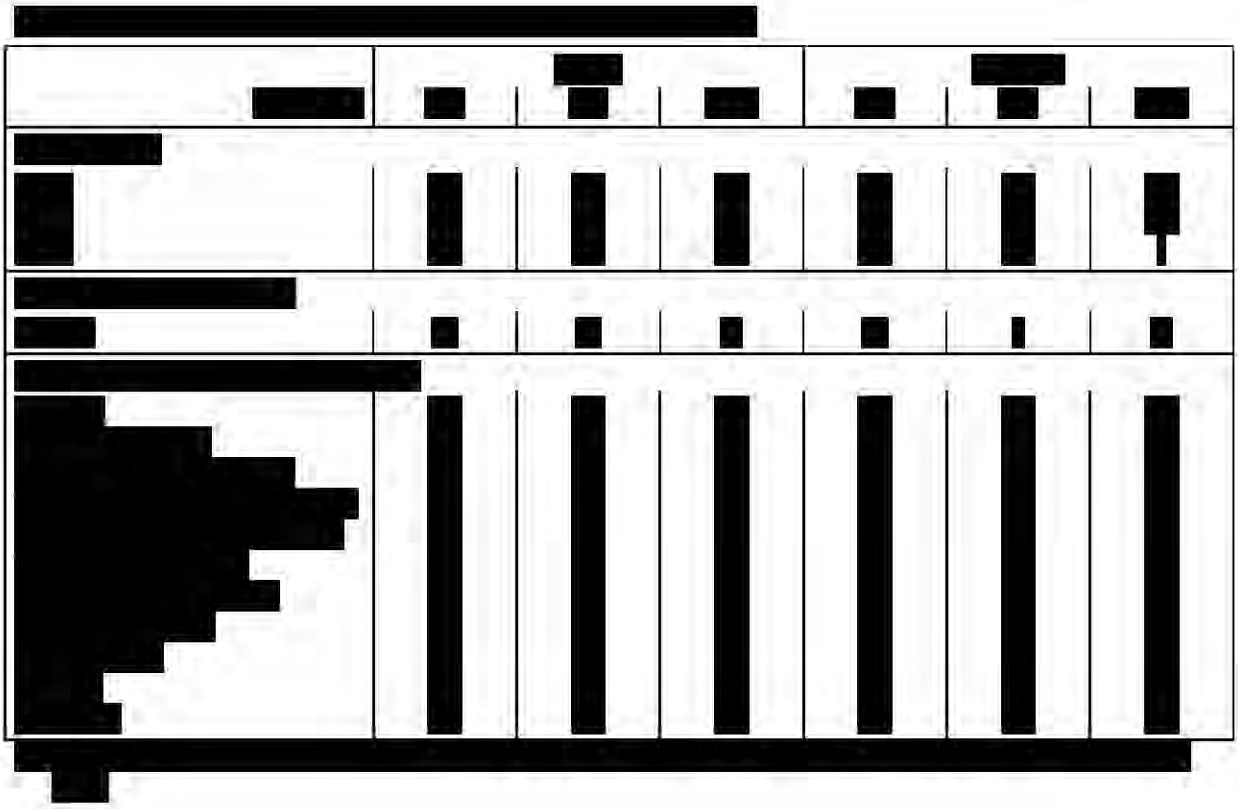
4 RESULTS AND DISCUSSION

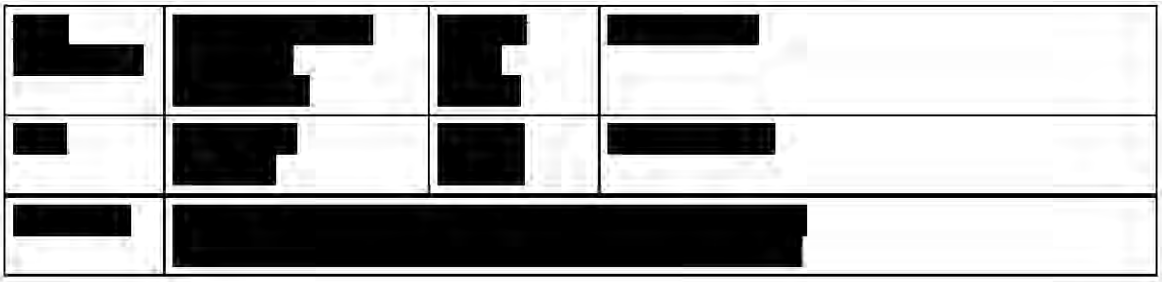
4.1	**Body weight**	The surviving males at 1000 mg/kg bw lost weight until day 4 of the study. At 500 mg/kg bw the surviving rats had a lower body weight development than at 250 mg/kg bw.
4.2	**Clinical signs**	[redacted]
4.3	**Pathology**	-

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
[redacted]		[redacted]
5.3	**Conclusion**	The time of peak effect was 4 hours after application. Dose levels selected for the main study (acute neurotoxicity study) were 100, 200 and 400 mg/kg bw.
5.3.1	[redacted]	[redacted]
5.3.2	NO(A)EL	250 mg/kg bw (for clinical signs and mortality)
5.3.3	Reliability	1
5.3.4	Deficiencies	No (study fulfilled its purpose as a range finding study)

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2005-06-06
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	2
Acceptability	Acceptable
Remarks	CA-Table 1 with the results of the study conducted with 2000 mg/kg bw is added
	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	





Section A6.1.2 Acute Toxicity Dermal

Annex Point IIA
VI.6.1.2/01

Acute dermal toxicity study in rats (Limit Test)

Official use only

1 REFERENCE

1.1	**Reference**	[redacted], 25.06.1997
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [redacted] OECD No. 402 (1987)
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale, yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (test-article-vehicle formulations prepared at the day of dosing)
3.2	**Test Animals**	[redacted] rats [redacted] No control group
3.3	**Administration/ Exposure**	
3.3.1	Postexposure period	14 days

Section A6.1.2 Acute Toxicity Dermal

Annex Point IIA VI.6.1.2/01

Acute dermal toxicity study in rats (Limit Test)

		Dermal
3.3.2	Area covered	10% of body surface (25 cm^2)
3.3.3	Occlusion	Semiocclusive
3.3.4	Vehicle	Distilled water
3.3.5	Concentration in vehicle	TI-435 (dry powder) wetted with 0.2 mL distilled water
3.3.6	Total volume applied	[redacted]: 2000 mg/kg bw)
3.3.7	Duration of exposure	24 h
3.3.8	Removal of test substance	Swabbed with moist cotton wool
3.3.9	Controls	-
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	[redacted]
4.2	**Pathology**	No gross lesions were apparent during post mortem examination of the animals.
4.3	**Other**	-
4.4	**LD_{50}**	No lethal effect at maximal dose dermal LD_{50} (males, females, males + females) >2000 mg/kg bw
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	Dermal LD_{50} in rats (males, females, males + females) >2000 mg/kg bw no mortality at limit dose
5.3	**Conclusion**	No classification required for [redacted] according to Directive 2001/59/EC (adaptation to 67/548/EEC).
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.1.2 Acute Toxicity Dermal

Annex Point IIA VI.6.1.2/01

Acute dermal toxicity study in rats (Limit Test)

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	1
Acceptability	Acceptable
Remarks	None
	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	

Section A6.1.3 Acute Toxicity Inhalation

Annex Point IIA
VI.6.1.3/01

Acute inhalation toxicity study in rats (Limit Test)

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1998); [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted on existing a.s. for its first entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [redacted], OECD No. 403 (1981)
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale, yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (4 h exposure period)
3.2	**Test Animals**	[redacted] rats per [redacted] Control group included
3.3	**Administration/ Exposure**	Inhalation
3.3.1	Postexposure period	14 days

Section A6.1.3 Acute Toxicity Inhalation

Annex Point IIA VI.6.1.3/01

Acute inhalation toxicity study in rats (Limit Test)

		Inhalation
3.3.2	Concentrations	Nominal concentration 10400 mg/m³ Gravimetrical concentration 6141 mg/m³ (concentration over the totally 4.5 h exposure period was 5538 mg/m³ including the first half hour where difficulties with the aerosol generation occurred)
3.3.3	Particle size	MMAD (mass median aerodynamic diameter) 2.78 µm ± GSD (geometric standard deviation) 2.38 µm
3.3.4	Type or preparation of particles	[redacted]
3.3.5	Type of exposure	nose/head only
3.3.6	Vehicle	-
3.3.7	Concentration in vehicle	-
3.3.8	Duration of exposure	4 h (due to technical difficulties with the aerosol generation in the first 0.5 h of exposure, the exposure period was prolonged to totally 4.5 hours to guarantee a 4 h exposure at the target concentration)
3.3.9	Controls	sham exposition
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	[redacted]
4.2	**Pathology**	There were no treatment-related gross or microscopic lesions and the lung weights of test group animals were unaffected by exposure to [redacted]
4.3	**Other**	-
4.4	**LC_{50}**	LC_{50} (male, females, males + females) >6141 mg/m³ No lethal effect at the limit dose

Section A6.1.3	Acute Toxicity Inhalation
Annex Point IIA VI.6.1.3/01	Acute inhalation toxicity study in rats (Limit Test)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Toxicity evaluation (bw, clinical signs, *post mortem* examination including signs of irritation in the inhalation tract, lung weights) after acute inhalation exposure of rats; no relevant deviation from guidelines (92/69/EEC B2, EPA FIFRA 81-3, OPPTS 870.1330, Japan MAFF, OECD 403)
5.2	**Results and discussion**	LC_{50} of [redacted] rats (male, females, males + females) >6141 mg/m^3 No lethal effect at limit dose
5.3	**Conclusion**	No classification required for [redacted] according to Directive 2001/59/EC (adaptation to 67/548/EEC)
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	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Section A6.1.3 Acute Toxicity Inhalation

Annex Point IIA VI.6.1.3/01

Acute inhalation toxicity study in rats (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	

[redacted]

[redacted]

Section A6.1.4 **Acute Toxicity** **Skin irritation**

Annex Point IIA
VI.6.1.4/01

Acute skin irritation study in rabbits

Official use only

1 REFERENCE

1.1	**Reference**	[redacted], 25.06.1997
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [redacted] OECD No. 404 (1992)
2.2	**GLP**	Yes
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale, yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study
3.2	**Test Animals**	[redacted] New Zealand White rabbits No control group
3.3	**Administration/ Exposure**	Dermal
3.3.1	Application	
3.3.1.1	Preparation of test substance	[redacted]
3.3.1.2	Test site and Preparation of Test Site	Dorsal area of the trunk (6 cm^2) Shaved skin (clipped)
3.3.2	Occlusion	Semiocclusive

Section A6.1.4	**Acute Toxicity** **Skin irritation**
Annex Point IIA VI.6.1.4/01	Acute skin irritation study in rabbits

3.3.3	Vehicle	Distilled water
3.3.4	Concentration in vehicle	See 3.3.1.1
3.3.5	Total volume applied	See 3.3.1.1
3.3.6	Removal of test substance	Swabbed with moist cotton wool
3.3.7	Duration of exposure	4 h
3.3.8	Postexposure period	3 days
3.3.9	Controls	-
3.4	**Examinations**	
3.4.1	Clinical signs	Yes
3.4.2	Dermal examination	Yes
3.4.2.1	scoring system	Erythema and Eschar: no erythema 0 very slight erythema (barely perceptible) 1 well-defined erythema 2 moderate to severe erythema 3 severe erythema (beet redness) or eschar preventing reading of erythema 4 Oedema: no oedema 0 very slight oedema (barely perceptible) 1 slight oedema (edges of area well-defined by definite raising) 2 moderate oedema (edges raised approximately 1 mm) 3 severe oedema (raised >1 mm and expanding beyond area of exposure) 4
3.4.2.2	Examination time points	60 min, 24 h, 48 h, 72 h
3.4.3	Other examinations	-
3.5	**Further remarks**	-

4 RESULTS AND DISCUSSION

4.1	**Average score**	
4.1.1	Erythema	There were no skin reactions in any rabbit at any of the observation points (see also table A6_1-4S/01)
4.1.2	Edema	There were no skin reactions in any rabbit at any of the observation points.
4.2	**Reversibility**	Not relevant
4.3	**Other examinations**	-

[redacted] [redacted]

Section A6.1.4 **Acute Toxicity** **Skin irritation**

Annex Point IIA
VI.6.1.4/01

Acute skin irritation study in rabbits

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		
[redacted]	[redacted]		
	[redacted]		
	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]			
[redacted]			
[redacted]			

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Evaluation of skin reactions in rabbits after 4 hour dermal exposure; no relevant deviation from guidelines [redacted]
5.2	**Results and discussion**	TI-435 did not induce any skin reaction at all after dermal exposure for 4 hours.
5.3	**Conclusion**	No classification for skin irritation is considered required for [redacted] according to Directive 2001/59/EC (adaptation of 67/548/EEC).
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	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	Acceptable
Remarks	None

Section A6.1.4 Acute Toxicity Skin irritation

Annex Point IIA
VI.6.1.4/01

Acute skin irritation study in rabbits

	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	

Section 6.1.4 Acute Toxicity Eye Irritation

Annex Point IIA
VI.6.1.4/02

Acute eye irritation study in rabbits

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] 30.07.1997
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted on existing a.s. for its first entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted] OECD No. 405 (1987)
2.2	**GLP**	Yes
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale, yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study
3.2	**Test Animals**	[redacted] New Zealand White rabbits [redacted]
		No control group
3.3	**Administration/ Exposure**	
3.3.1	Preparation of test substance	Test substance was used as delivered
3.3.2	Amount of active substance instilled	66 mg corresponding to 0.1mL
3.3.3	Exposure period	The eyes remained unwashed
3.3.4	Postexposure period	3 days

Section 6.1.4 Acute Toxicity Eye Irritation

Annex Point IIA
VI.6.1.4/02

Acute eye irritation study in rabbits

3.4	**Examinations**	
3.4.1	Ophthalmoscopic examination	yes
3.4.1.1	Scoring system	Cornea (degree of opacity: area most dense assessed): no ulceration or opacity 0 scattered or diffuse areas of opacity other than slight dulling of normal lustre, details of iris clearly visible 1 easily discernible translucent area, details of iris slightly obscured 2 nacreous area, no details of iris visible but size of pupil barely discernible 3 opaque cornea, iris not discernible through opacity 4 Cornea (area of corneal opacity): total area of opacity amounts to <25% of corneal area 1 area of opacity amounts to 25 - <50% of corneal area 2 area of opacity amounts to 50 - <75% of corneal area 3 area of opacity amounts to 75 or more of corneal area 4 Iris: no reaction 0 markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia or injection, any of these or any combination thereof; iris still reacting to light 1 no iridial reflex to light, haemorrhage or gross destruction (any or all of these) 2 Conjunctivae, redness: blood vessels normal 0 some blood vessels definitely hyperaemic (injected) 1 diffuse, crimson colour, individual vessels not easily discernible 2 diffuse beefy red appearance 3 Conjunctivae, chemosis: no swelling 0 any swelling above normal 1 obvious swelling with partial eversion of lids 2 swelling with lids about half-closed 3 swelling with lids more than half-closed 4
3.4.1.2	Examination time points	0, 30 min, 60 min, 4 h, 24 h, 48 h, 72 h
[redacted]		[redacted]
3.5	**Further remarks**	As requested by the US-EPA-guideline, conjunctival discharge was also assessed.

Section 6.1.4 **Acute Toxicity Eye Irritation**

Annex Point IIA
VI.6.1.4/02

Acute eye irritation study in rabbits

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	No effects
4.2	**Average score**	(24-72 hours)
4.2.1	Cornea	0
4.2.2	Iris	0
4.2.3	Conjunctiva	
4.2.3.1	Redness	0
4.2.3.2	Chemosis	0
4.3	**Reversibility**	Yes Conjunctival redness: 24 h Conjuntival chemosis: 1 h
4.4	**Other**	[redacted]
4.5	**Overall result**	Cornea and iris were unaffected by treatment. Slight conjunctival redness was recorded up to 4 hours and slight chemosis up to 0.5 hours after treatment. [redacted] is considered to be practically non-irritant to the eye.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Evaluation of eye reactions in rabbits after instillation into the eye; no relevant deviation from guidelines ([redacted]
5.2	**Results and discussion**	Cornea and iris were unaffected by treatment. Slight conjunctival redness was recorded up to 4 hours and slight chemosis up to 0.5 hours after treatment.
5.3	**Conclusion**	No classification for eye irritation is considered required for [redacted] according to Directive 2001/59/EC (adaptation of 67/548/EEC).
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	[redacted]

Section 6.1.4 **Acute Toxicity Eye Irritation**

Annex Point IIA
VI.6.1.4/02

Acute eye irritation study in rabbits

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	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	

Section 6.1.4 **Acute Toxicity** **Eye Irritation**

Annex Point IIA
VI.6.1.4/02

Acute eye irritation study in rabbits

[redacted]

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Section A6.1.5 Acute Toxicity Skin sensitisation

Annex Point IIA
VI.6.1.5/01

Guinea pig maximisation test (GPMT)

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] 23.10.1997
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted] [redacted] OECD No. 406 (1992)
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale, yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (test-article-vehicle formulations prepared at the day of application)
3.1.2.4	Preparation of test substance for application	for induction: intradermal: 1% w/v [redacted] in Alembicol D topical: 55% w/w [redacted] in Alembicol D for challenge: 10% and 20% w/w [redacted] in Alembicol D
3.1.2.5	Pretest performed on irritant effects	Yes [redacted]

Section A6.1.5 Acute Toxicity Skin sensitisation

Annex Point IIA
VI.6.1.5/01

Guinea pig maximisation test (GPMT)

3.2	**Test Animals**	[redacted] Guinea pigs [redacted] In a [redacted]
3.3	**Administration/ Exposure**	Adjuvant
3.3.1	Induction schedule	day 1 (intradermal induction) – day 8 (topical induction) – day 21 (topical challenge) see table in appendix
3.3.2	Way of Induction	Intradermal and topical Occlusive (topical)
3.3.3	Concentrations used for induction	Intradermal: 1% w/v [redacted] (causing mild to moderate irritation)
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	50% FCA in water (1:1 v/v)
3.3.5	Challenge schedule	see table A6_1_5/01-1 in appendix
3.3.6	Concentrations used for challenge	10% and 20% w/w [redacted] (usually maximum non-irritant concentration)
3.3.7	Rechallenge	No
3.3.8	Scoring schedule	24h, 48h after challenge
3.3.9	Removal of the test substance	24 hours after challenge application treated skin areas were washed with arachis oil
3.3.10	Positive control substance	Concurrent positive control: 2,4-dinitrochlorobenzene (DNCB): Intradermal induction: 0.1% w/v in corn oil (and/or adjuvant) Topical induction: 0.5% w/v in corn oil Topical challenge: 0.2% and 0.05% w/v in corn oil Biannual positive control studies: 2-mercaptobenzothiazole Intradermal induction: 2.5% w/w in Alembicol D (and/or adjuvant) Topical induction: 60% w/w in Alembicol D Topical challenge: 15% and 30% w/w in Alembicol D
3.4	**Examinations**	
3.4.1	Pilot study	Yes
3.5	**Further remarks**	-

Section A6.1.5 **Acute Toxicity** **Skin sensitisation**

Annex Point IIA
VI.6.1.5/01

Guinea pig maximisation test (GPMT)

4 RESULTS AND DISCUSSION

4.1 Results of pilot studies

[redacted]

4.2 Results of test

See also table A6_1_5/01-2 in Appendix

4.2.1 24h after challenge

Treated: 2/20 and 3/20 at 10% and 20% [redacted], respectively
Negative controls: 1/20 and 0/20 at 10% and 20% [redacted], respectively
All skin reactions were grade 1 (slight erythema)

4.2.2 48h after challenge

Treated: 0/20 at 10% and 20% [redacted]
Negative controls: 1/20 and 0/20 at 10% and 20% [redacted], respectively
All skin reactions were grade 1 (slight erythema)

4.2.3 Other findings

[redacted]

4.3 Overall result

The study director considered the results being negative for skin sensitisation in 19/20 treated animals and inconclusive for 1/20 treated Guinea pig. Therefore the positive sensitisation incidence was 0%. (The net sensitisation rate calculated as the % of animals with any skin reactions in the treated minus controls groups would have been 5% and 15% at 10% and 20% [redacted], respectively; both values would have been below the threshold for classification according to Directive 2001/59/EC.)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted] OECD 406)

5.2 Results and discussion

The study director considered the results being negative for skin sensitisation in 19/20 treated animals and inconclusive for 1/20 treated Guinea pig. Therefore the positive sensitisation incidence was 0%.

5.3 Conclusion

No classification for skin sensitisation is required for [redacted] according to Directive 2001/59/EC (adaptation of 67/548/EEC), as the positive skin reactions were below the threshold for classification (30%) defined in the Directive.

5.3.1 Reliability

1

5.3.2 Deficiencies

No

Section A6.1.5 Acute Toxicity Skin sensitisation

Annex Point IIA
VI.6.1.5/01

Guinea pig maximisation test (GPMT)

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted

EVALUATION BY RAPPORTEUR MEMBER STATE

Date 2004-10-07

Section A6.1.5 **Acute Toxicity** **Skin sensitisation**

Annex Point IIA
VI.6.1.5/01

Guinea pig maximisation test (GPMT)

[redacted]

[redacted]

[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]		

[redacted]

	[redacted]						
[redacted]	[redacted]		[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Section A6.2 Percutaneous absorption (*in vivo*) Rhesus monkeys

Annex Point IIA VI.6.2

Official use only

1 REFERENCE

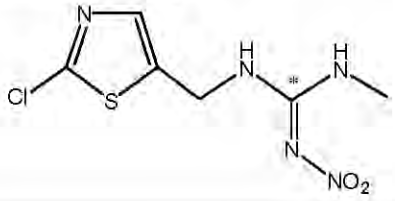
1.1	**Reference**	[redacted], 27.02.2003
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [redacted] OECD 427
2.2	**GLP**	Yes
2.3	**Deviations**	[redacted] Monkeys [redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	
3.1.2.1	Description	Red liquid (suspension)
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.1.2.4	Radiolabelling	[redacted]



[redacted]

3.2	**Test Animals**	
3.2.1	Species	Rhesus monkeys
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	[redacted]

Section A6.2 **Percutaneous absorption (*in vivo*)** **Rhesus monkeys**
Annex Point IIA VI.6.2

3.2.5	Age/weight at study initiation	3.3-5.5 kg
3.2.6	Number of animals per group	[redacted]
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Dermal
3.3.1	Preparation of test site	shaved skin
3.3.2	Concentration of test substance	5.70 µg/cm² (target 6.13 µg/cm²) [redacted]
3.3.3	Specific activity of test substance	[redacted]
3.3.4	Volume applied	100 µL
3.3.5	Size of test site	24 cm²
3.3.6	Exposure period	8 hours
3.3.7	Sampling time	4, 8, 12, 24, 48, 72, 96 and 120 hours after dermal treatment.
3.3.8	Samples	Urine, faeces, skin wash, chair wipe, pan wash, cage wash

4 RESULTS AND DISCUSSION

4.1	**Toxic effects, clinical signs**	[redacted]
4.2	**Dermal irritation**	None reported
4.3	**Recovery of labelled compound**	[redacted]
4.4	**Percutaneous absorption**	[redacted] a normalized dermal absorption of 0.245%.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted] OPPTS 870.7600, OECD 427).
5.2	**Results and discussion**	Percutaneous absorption of TI-435 in Rhesus monkeys was (normalized) 0.245% of applied dose. [redacted]

Section A6.2 **Percutaneous absorption (*in vivo*)** **Rhesus monkeys**
Annex Point IIA VI.6.2

5.3	**Conclusion**	(Normalized) dermal absorption of [redacted] at a concentration corresponding well its use as wood preservative was 0.245% of applied dose in Rhesus monkeys. The same value can be considered for human risk assessment.
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	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	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	

[redacted]

	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Section A6.2 Metabolism studies in mammals

Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]. (2000); [redacted] 11.10.2000
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Tr[redacted], OECD guideline no. 417, [redacted]
2.2	**GLP**	Yes
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	Highly pure batches as required for metabolism studies
3.1.2.1	Description	Powder
3.1.2.2	Purity	See 3.1.1
3.1.2.3	Stability	Considered stable under conditions of this study (test-article-vehicle formulations prepared at the day of dosing)
3.1.2.4	Radiolabelling	^{14}C, details see 3.1.1

Section A6.2 Metabolism studies in mammals

Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*

3.2 Test Animals

[redacted]

3.3 Administration/ Exposure

[redacted]

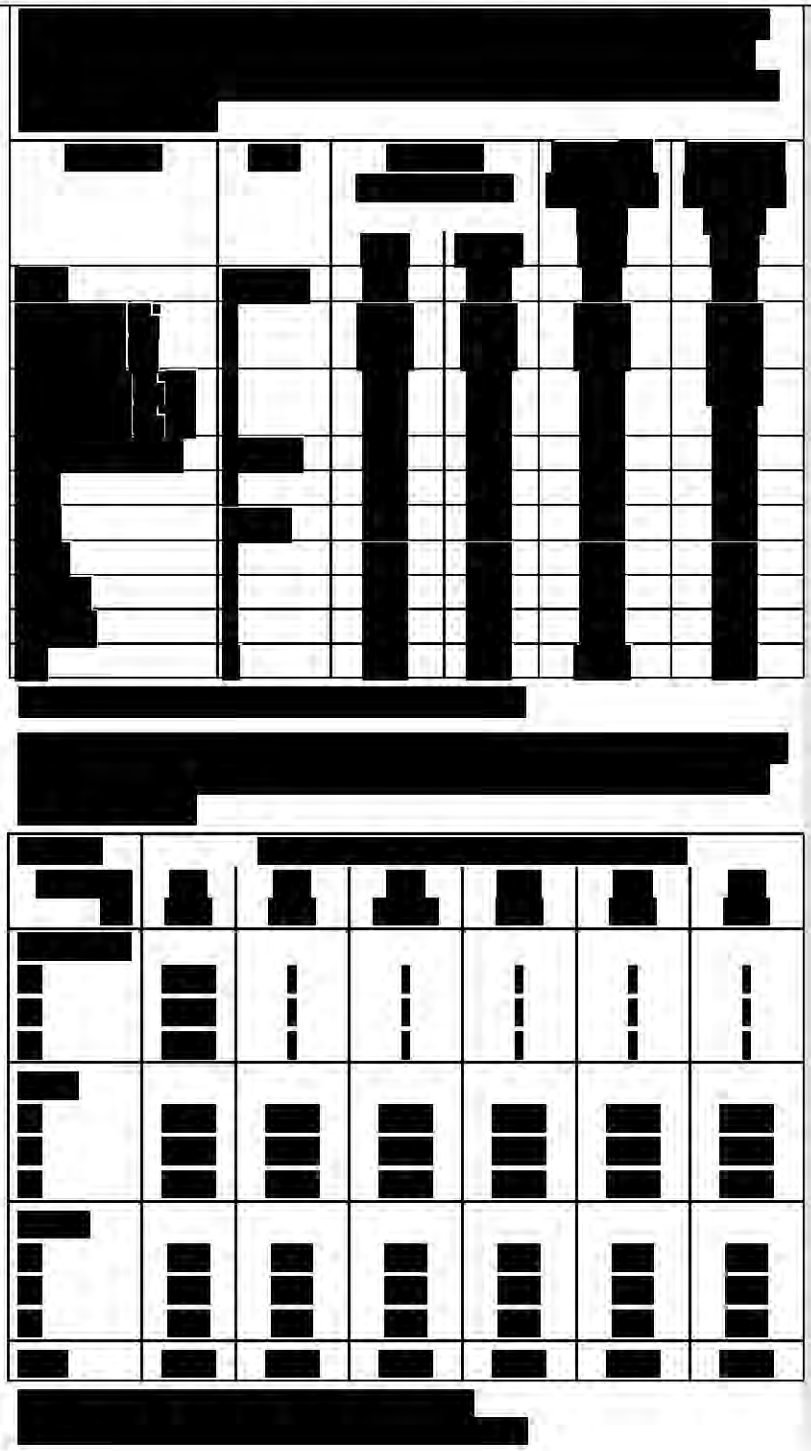
[redacted] **Toxic effects, clinical signs**

[redacted]

Section A6.2 **Metabolism studies in mammals**

Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*

[redacted]



[redacted]

Section A6.2 **Metabolism studies in mammals**

Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*

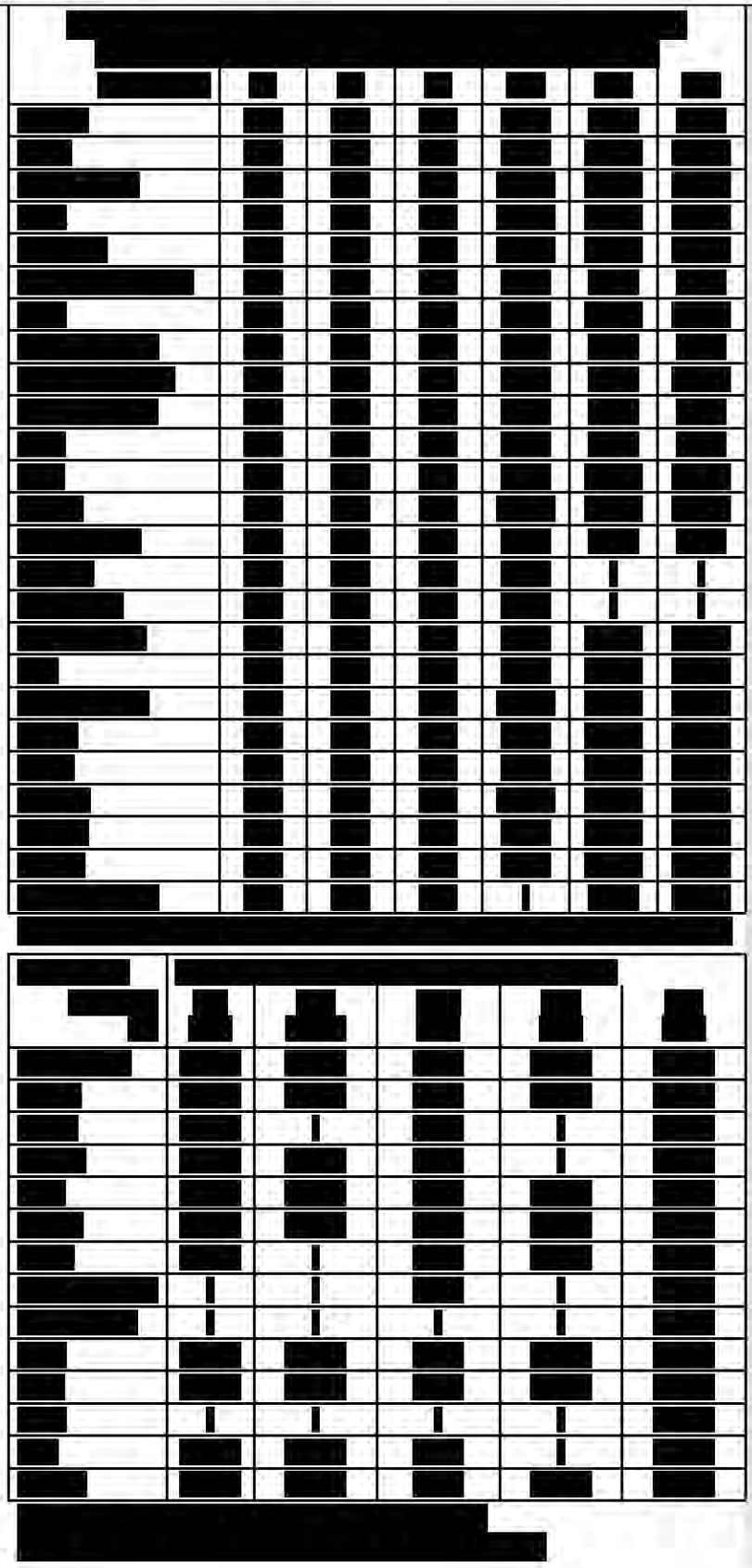
[redacted]

4.3 Distribution

[redacted]

Section A6.2 **Metabolism studies in mammals**

Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*



Section A6.2 Metabolism studies in mammals

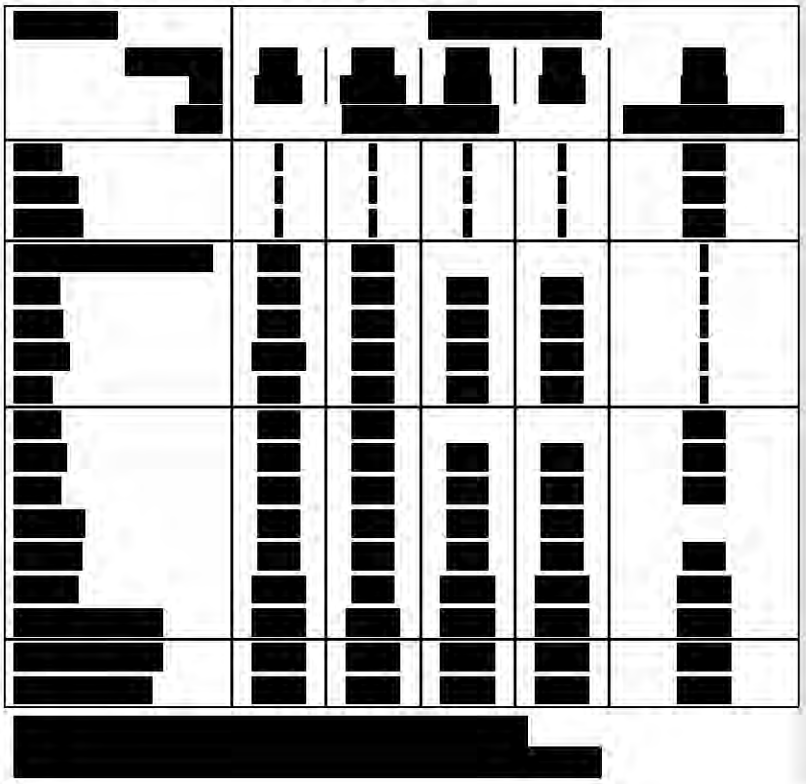
Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*

4.4 Metabolism

Identified metabolites:

ACT	5-aminomethyl-2-chlorothiazole
CTCA	2-chlorothiazole-5-carboxylic acid
MTCA	2-methylthiothiazole-5-carboxylic acid
NTG	nitroguanidine
MNG	N-methyl-N'-nitroguanidine
MG	methylguanidine
TZG	2-chlorothiazol-5-ylmethylguanidine
TMG	N-(2-chlorothiazol-5-ylmethyl)-N'-methylguanidine
TZU	2-chlorothiazol-5-ylmethylurea
THMN	N-2-chlorothiazol-5-ylmethyl-N-hydroxy-N'-methyl-N''-nitroguanidine
TZMU	N-(2-chlorothiazol-5-ylmethyl)-N'-methylurea
TZNG	N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine

The predominant component identified for all groups was the parent compound [redacted] (55-74% of applied dose, see table below). The major metabolites identified (≥10% of applied dose) were TZNG and MNG; MTCA and NTG were found at 1-10% of applied dose. These metabolites occurred predominantly in urine.
The main metabolite occurring in faeces was TMG. All other metabolites occurred at less than 2% of administered dose and together accounted for less than 11% of applied dose.



Section A6.2 **Metabolism studies in mammals**

Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

ADME evaluation in the rat (gavage application, single treatment at three dose levels, multiple treatment at one dose; absorption, distribution and elimination kinetics; identification and quantification of metabolites); no relevant deviation from guidelines [redacted]

5.2 Results and discussion

Single low and high doses (2.5–250 mg/kg bw) and repeated doses (25 mg/kg bw) of [redacted] are rapidly and extensively absorbed (~90% of applied dose) from the gastrointestinal tract and rapidly and almost completely eliminated, predominantly in the urine. High doses of [redacted] saturate the gastrointestinal absorptive mechanism and show a transient delay in excretion (at 24 h after application: 61% of applied dose at 250 mg/kg bw vs. ≥94% at 2.5/25 mg/kg bw).
[redacted] is rapidly and extensively distributed to all tissues and organs but is rapidly and almost completely eliminated from all tissues with no evidence of accumulation.
The parent [redacted] is the major fraction in excreta (55-74% of applied dose); in total 13 metabolites were identified. TZNG and MNG are the two major metabolites (≥10% of applied dose); a further metabolite is MTCA (8.5% of applied dose).
Other than saturated absorption and transiently delayed elimination of high doses, the biokinetics and metabolism of [redacted] are not markedly influenced by dose level, dose regimen and sex.

5.3 Conclusion

Rapid and almost complete absorption and excretion of [redacted] in rats after oral application essentially independent of sex, dose level, pre-treatment and label position (slight delay at high dose levels due to saturation of absorption process).
No potential for accumulation.
[redacted] (parent) was the major fraction in excreta. In total 13 metabolites were identified (TZNG and MNG ≥10%, MTCA ~8.5% of applied dose).

5.3.1 Reliability 1

5.3.2 Deficiencies No

Section A6.2 Metabolism studies in mammals

Annex Point IIA VI.6.2 *Absorption, distribution, metabolism and excretion in rats*

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	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	

Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA
VI.6.3.1/01

28-day dietary toxicity study in mice

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted] (1997a); [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes [redacted] OECD no. 407 ([redacted])
2.2	**GLP**	Yes
2.3	**Deviations**	No
	3 MATERIALS AND METHODS	
3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.2	**Test Animals**	[redacted] mice [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	28 days
3.3.2	Frequency of exposure	daily
3.3.3	Postexposure period	none

Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA VI.6.3.1/01 28-day dietary toxicity study in mice

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	[redacted] 0, 90, 190, 383 and 683 mg/kg bw/day for males and 0, 122, 248, 491 and 619 mg/kg bw/day for females food consumption per day: ad libitum
3.3.4.3	Vehicle	None ([redacted])
3.3.4.4	Concentration in vehicle	-
3.3.4.5	Total volume applied	-
3.3.4.6	Controls	plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	yes (daily)
3.4.1.2	Mortality	yes (twice daily)
3.4.2	Body weight	yes (weekly)
3.4.3	Food consumption	yes (weekly)
3.4.4	Water consumption	yes (by visual assessment)
3.4.5	Ophthalmoscopic examination	no
3.4.6	Haematology	[redacted]
3.4.7	Clinical Chemistry	[redacted]
3.4.8	Urinalysis	[redacted]
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	[redacted]
3.5.2	Gross and histopathology	[redacted]

Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA
VI.6.3.1/01

28-day dietary toxicity study in mice

[redacted]

3.5.3 Other examinations -

3.5.4 Statistics [redacted]

3.6 Further remarks

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs [redacted]

4.1.2 Mortality See 4.1.1

4.2 Body weight gain [redacted]

4.3 Food consumption and compound intake [redacted]

4.4 Ophtalmoscopic examination -

4.5 Blood analysis

4.5.1 Haematology [redacted]

Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA
VI.6.3.1/01

28-day dietary toxicity study in mice

[redacted]

4.5.2 Clinical chemistry

[redacted]

4.5.3 Urinalysis

[redacted]

4.6 Sacrifice and pathology

4.6.1 Organ weights

[redacted]

4.6.2 Gross and histopathology

[redacted]

Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA VI.6.3.1/01 28-day dietary toxicity study in mice

[redacted]

4.7 Other -

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods Toxicity evaluation after short-term (28 day) dietary exposure of mice [redacted]

5.2 Results and discussion [redacted]

5.3 Conclusion [redacted] Effects of treatment comprised clinical signs of toxicity, weight loss, haematological and blood biochemistry perturbations and histomorphological lesions in the spleen and ovaries.

5.3.1 LO(A)EL [redacted]

5.3.2 NO(A)EL NOAEL = 500 ppm corresponding to 90 and 122 mg/kg bw/day for males and females, respectively

5.3.3 Other -

5.3.4 Reliability 1

5.3.5 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

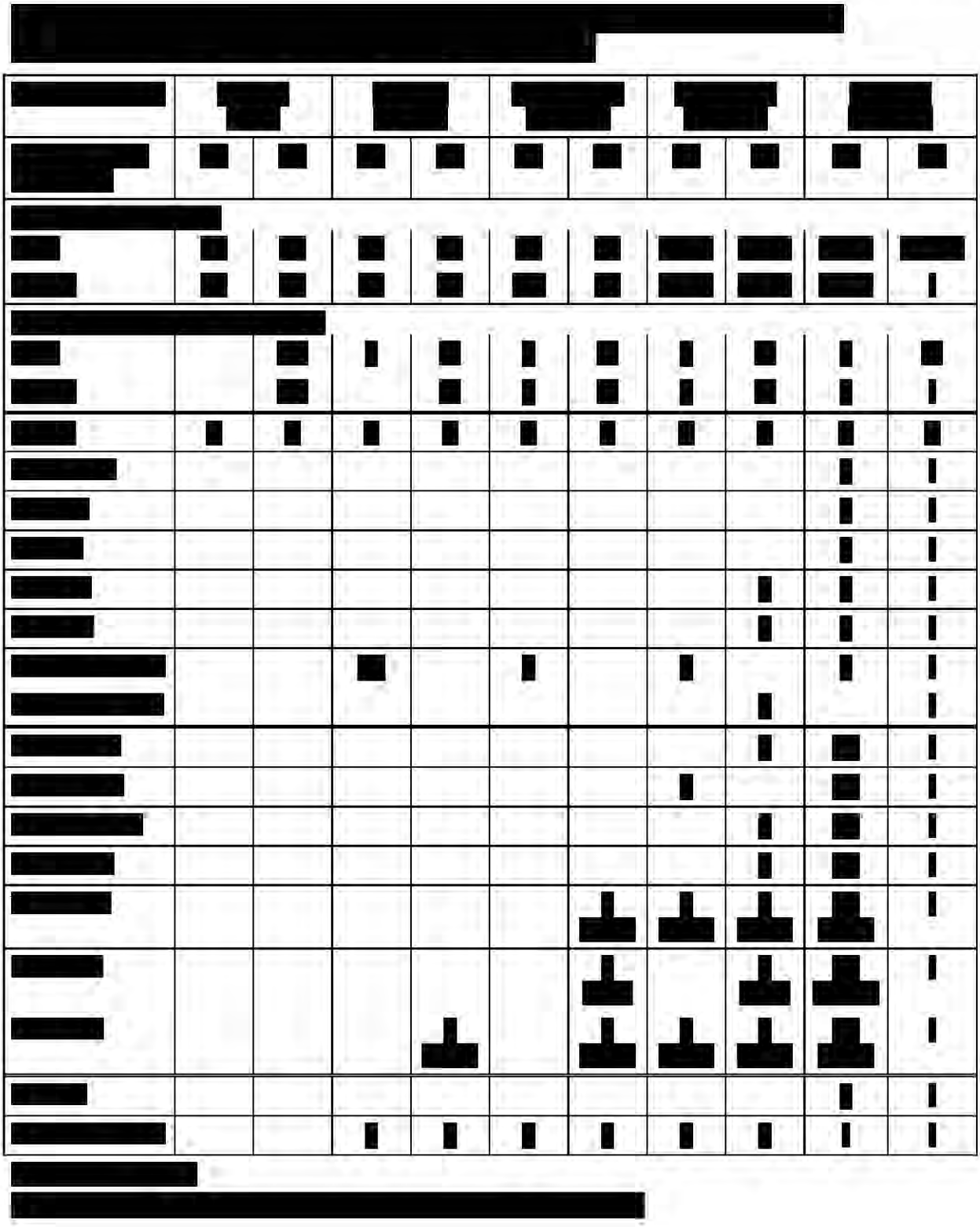
Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA
VI.6.3.1/01

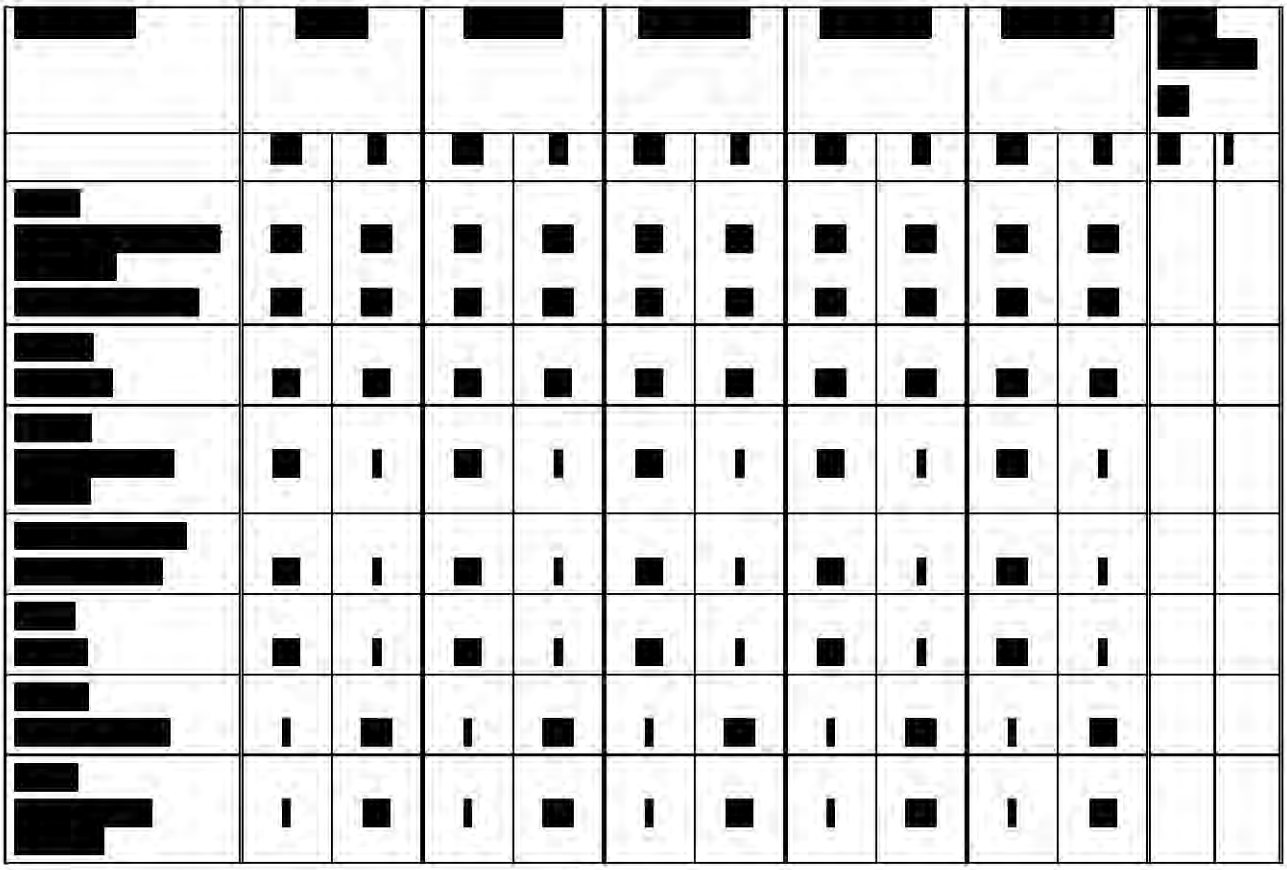
28-day dietary toxicity study in mice

Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

	COMMENTS FROM ... *(specify)*
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	



[redacted]



[redacted]

Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA
VI.6.3.1/02

28-day dietary toxicity study in dogs

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000); [redacted] 01.02.2000
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 88/302/EEC (method B27), EPA FIFRA Subdivision F, section 82-1 (1984)
2.2	**GLP**	Yes
2.3	**Deviations**	None relevant for the integrity and validity of the study: Due to the nature of the study - a dose range-finding study - its duration was 28 days (rather than 90) and there were 3 animals/sex/group (rather than 4).

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (stability of the compound and its homogenicity and stability in food were tested).
3.2	**Test Animals**	3 male and 3 female beagle dogs per group [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	At least 28 days (the surviving animals in the highest dose group were sacrificed after 3 weeks of treatment as an interim sacrifice group)
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None

Section A6.3.1 **Short-term repeated dose toxicity (28 days)** **Oral**

Annex Point IIA
VI.6.3.1/02

28-day dietary toxicity study in dogs

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	[redacted] 0, 34.3, 36.9 and 62.4 mg/kg bw/day for males and 0, 35.8, 53.5 and 57.4 mg/kg bw/day for females food consumption per day: ad libitum
3.3.4.3	Vehicle	None ([redacted])
[redacted]		[redacted]
3.3.4.5	Total volume applied	-
3.3.4.6	Controls	plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	[redacted]
3.4.1.2	Mortality	[redacted]
3.4.2	Body weight	[redacted]
3.4.3	Food consumption	[redacted]
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	[redacted]
3.4.6	Haematology	yes, [redacted]
3.4.7	Clinical Chemistry	yes, [redacted]
3.4.8	Urinalysis	yes [redacted]
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	yes [redacted]