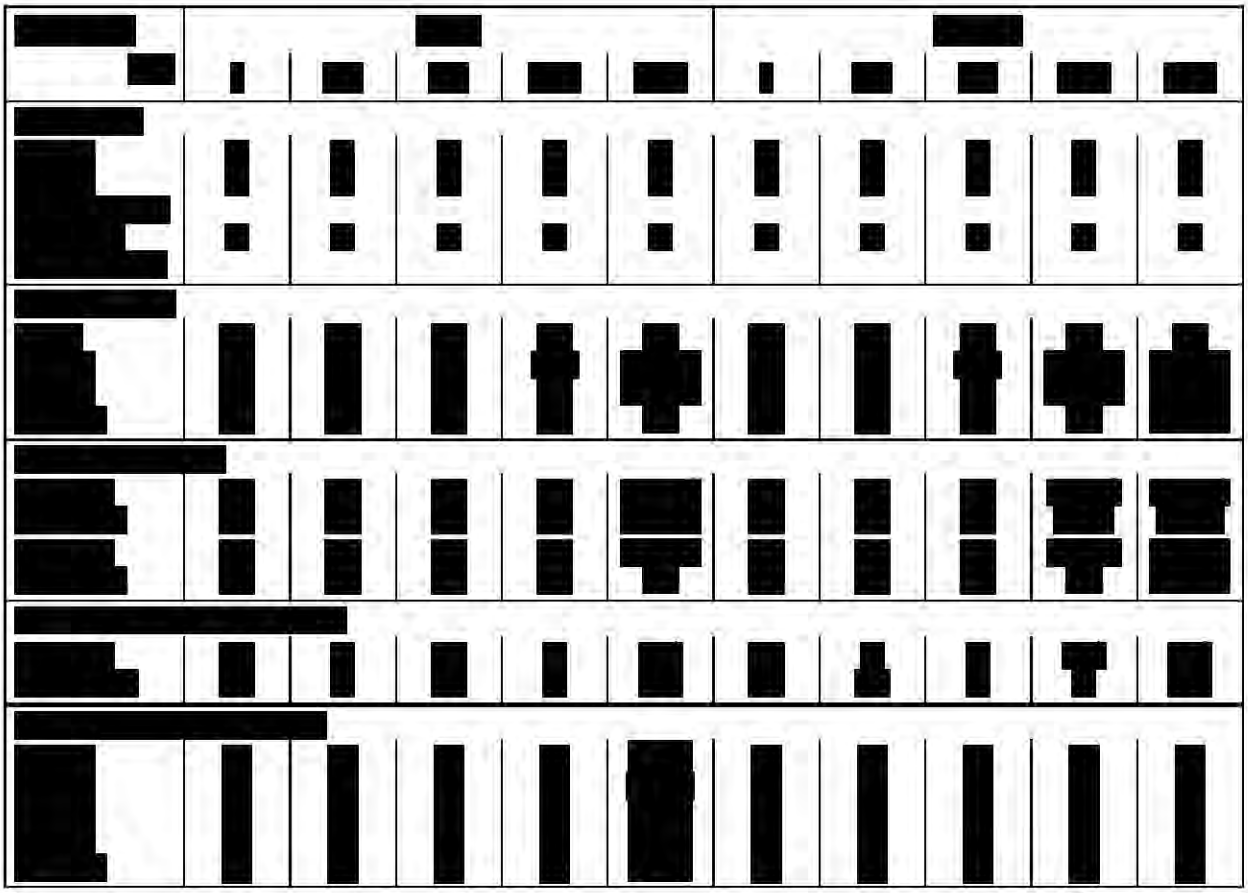
Section A6.5/6.7	Carcinogenicity study (2-year) Rat
Annex Point IIA VI.6.5 and 6.7/01	2-year dietary chronic toxicity/carcinogenicity study in rats
5.3.4 Reliability	1
5.3.5 Deficiencies	No

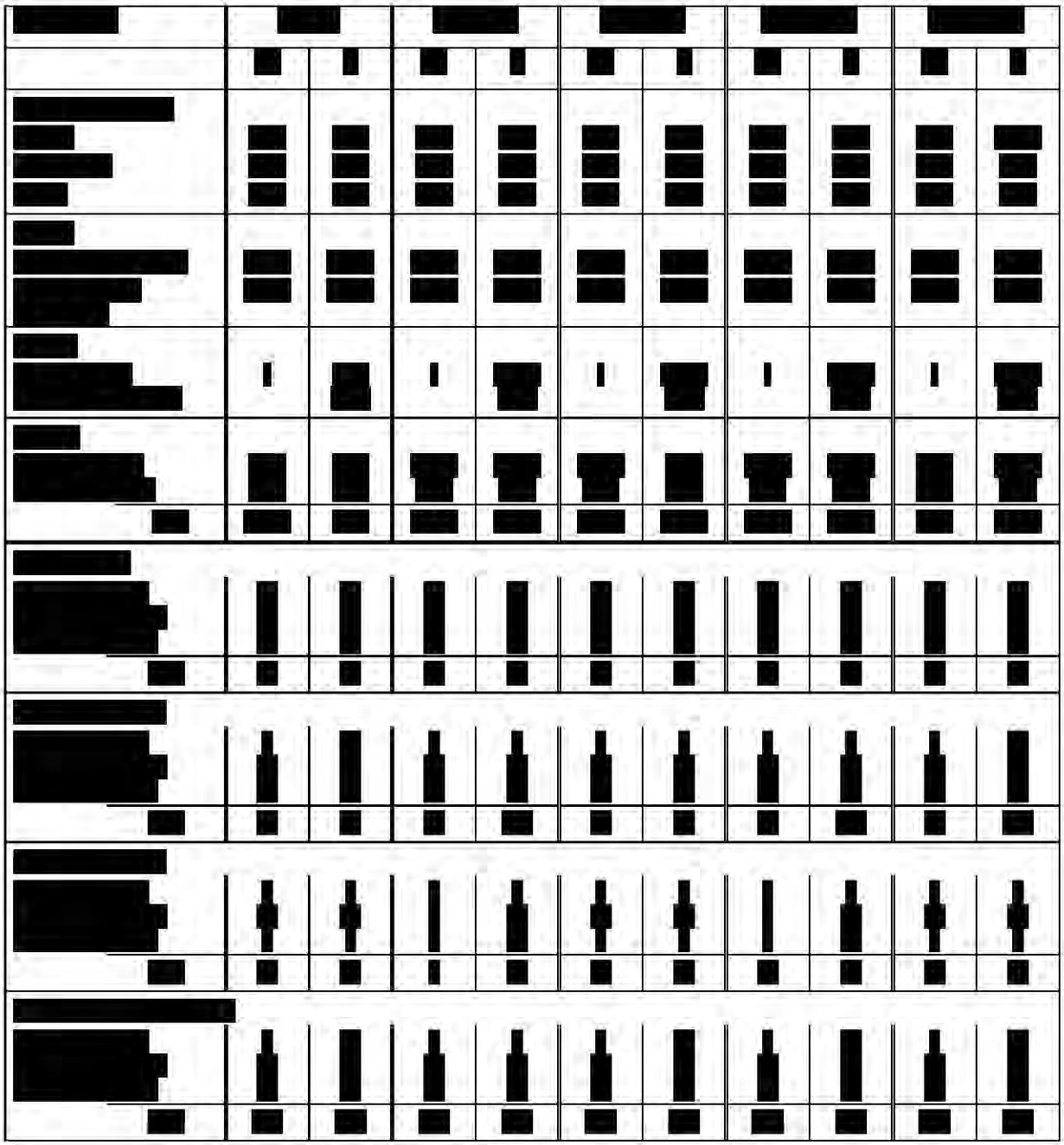
Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability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

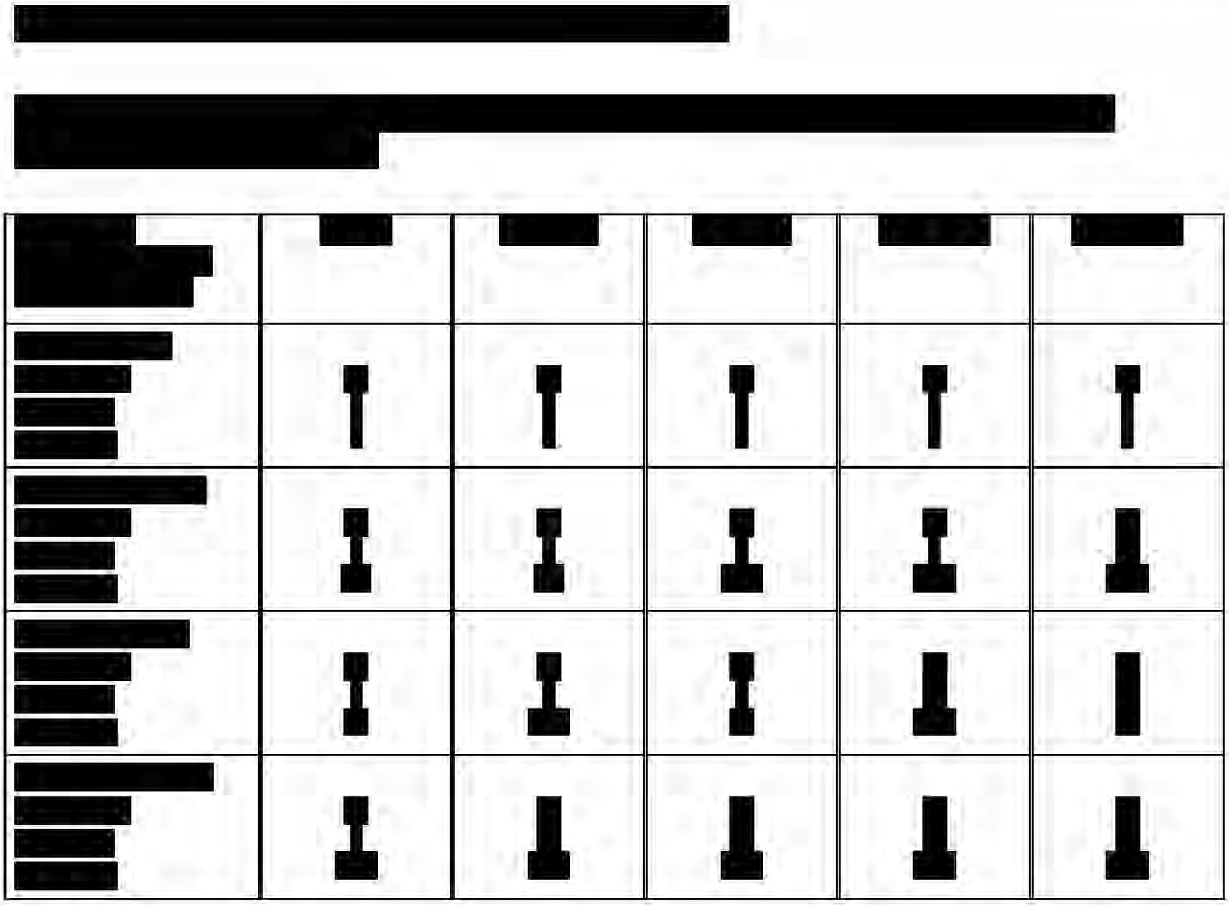


[redacted]

[redacted]



[redacted]



Section A6.7 Carcinogenicity study (18-month) Mouse

Annex Point IIA VI.6.7/02 18-month dietary carcinogenicity study in mice

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000b); [redacted], 27.03.2000
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	Data submitted on existing a.s. for the purpose of its first entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC (May 1988); Japan MAFF (59 NohSan no. 4200, 1985); EPA-FIFRA section 83-2; OECD no. 451 (1981), EPA-OPPTS 870.4200 (June 1996)
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 (stability of the compound and its homogeneity and stability in food were tested).
3.2	**Test Animals**	[redacted] male and [redacted] female 5 week old albino mice per group [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	18 month (at least 78 weeks)
3.3.2	Interim sacrifice(s)	-
3.3.3	Final sacrifice	after 78 weeks
3.3.4	Frequency of exposure	Daily
3.3.5	Postexposure period	None

Section A6.7	**Carcinogenicity study (18-month) Mouse**	
Annex Point IIA VI.6.7/02	18-month dietary carcinogenicity study in mice	
Oral		
3.3.6	Type	in food
3.3.7	Concentration	[redacted] o 0, 13.5, 47.2, 171.4 and 251.9 mg/kg bw/day for males and 0, 17.0, 65.1, 215.9 and 281.1 mg/kg bw/day for females food consumption per day: ad libitum
3.3.8	Vehicle	None ([redacted]
3.3.9	Concentration in vehicle	-
3.3.10	Total volume applied	-
3.3.11	Controls	plain diet
3.4	**Examinations**	
3.4.1	Body weight	yes ([redacted]
3.4.2	Food consumption	Yes ([redacted]
3.4.3	Water consumption	No
3.4.4	Clinical signs	yes (daily), [redacted]
3.4.5	Macroskopic investigations	Masses: yes (weekly)
3.4.6	Ophthalmoscopic examination	No
3.4.7	Haematology	yes, [redacted]
3.4.8	Clinical Chemisty	No
3.4.9	Urinalysis	No
3.4.10	Pathology	

Section A6.7 **Carcinogenicity study (18-month) Mouse**

Annex Point IIA VI.6.7/02 18-month dietary carcinogenicity study in mice

3.4.10.1	Organ Weights	Yes (
3.4.10.2	Gross and histopathology	Yes
3.4.11	Other examinations	-
3.5	**Statistics**	
3.6	**Further remarks**	-

4 RESULTS AND DISCUSSION

4.1	**Body weight**	
4.2	**Food consumption and compound intake**	
4.3	**Water consumption**	
4.4	**Clinical signs**	

Section A6.7 **Carcinogenicity study (18-month) Mouse**

Annex Point IIA VI.6.7/02 18-month dietary carcinogenicity study in mice

[redacted]

4.5	**Macroscopic investigations**	[redacted]
4.6	**Ophtalmoscopic examination**	[redacted]
4.7	**Haematology**	[redacted]
4.8	**Clinical Chemistry**	[redacted]
4.9	**Urinalysis**	[redacted]
4.10	**Pathology**	[redacted]
4.11	**Organ weights**	[redacted]
4.12	**Gross and histopathology**	[redacted]
4.13	**Other examinations**	-
4.14	**Time to tumours**	-
4.15	**Other**	-

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Carcinogenicity evaluation after chronic (18-month) dietary exposure of mice to TI-435; no relevant deviation from guidelines (87/302/EEC; [redacted]
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	[redacted]. Main effects of treatment were reduced bw development and food consumption, and slight to moderate hepatocellular hypertrophy

Section A6.7	Carcinogenicity study (18-month) Mouse	
Annex Point IIA VI.6.7/02	18-month dietary carcinogenicity study in mice	
	indicated the liver as a target organ. Treatment with TI-435 did not result in any indication for a carcinogenic response. LOAEL = [redacted] 171 and 216 mg/kg bw/day for males and females, respectively due to reduced bw development (females) and hepatocellular hypertrophy NOAEL = [redacted] 47.2 and 65.1 mg/kg bw/day for males and females, respectively	
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
[redacted]	
Remarks	

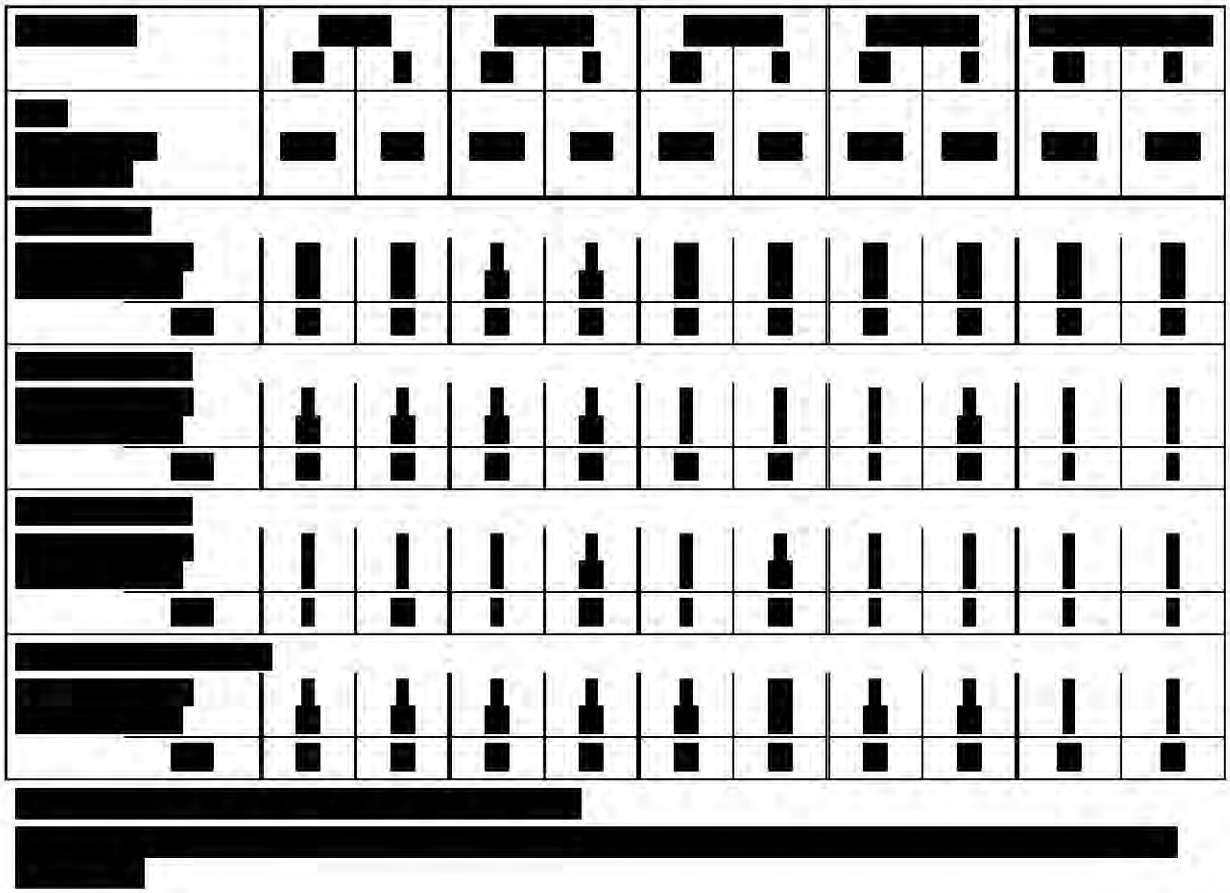
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss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

Section A6.7 **Carcinogenicity study (18-month) Mouse**

Annex Point IIA VI.6.7/02 18-month dietary carcinogenicity study in mice

[redacted]

Table A6_7/02-2 Results of carcinogenicity study (18-month mouse): histopathology and tumour incidences



Section A6.8.1 Teratogenicity Study Rat

Annex Point IIA
VI.6.8.1/01

Developmental toxicity study (gavage application) in the rat

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]1998a[redacted]14.04.1998
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 the purpose of its first entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC B.31, OECD draft guideline no. 414 (1999), US-EPA OPPTS 870.3700 (1996), Japan MAFF (59 NohSan no. 4200, 1985)
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	[redacted]
3.2	**Test Animals**	[redacted] female Sprague-Dawley rats per group (Crl:CD [BR[redacted]
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	rat day 6-19 post mating
3.3.2	Postexposure period	-

Section A6.8.1	Teratogenicity Study	Rat
Annex Point IIA VI.6.8.1/01	Developmental toxicity study (gavage application) in the rat	

		Oral
3.3.3	Type	Gavage
3.3.4	Concentration	0, 10, 40 and 125 mg/kg bw/day (food consumption per day: *ad libitum*)
3.3.5	Vehicle	[redacted]
3.3.6	Concentration in vehicle	0, 1, 4 and 12.5 mg/mL
3.3.7	Total volume applied	10 mL/kg bw
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes ([redacted]
3.4.2	Food consumption	Yes [redacted]
3.4.3	Clinical signs	Yes ([redacted]
3.4.4	Examination of uterine content	Gravid uterine weight Number of corpora lutea Number of implantations early and late resorptions
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, No. of dead Foetuses, Foetal Weight, Sex Ratio, External alternations
3.4.5.2	Skelet	Yes (about half of foetuses)
3.4.5.3	Soft tissue	Yes (about half of foetuses)
3.5	**Further remarks**	-
		4 RESULTS AND DISCUSSION
4.1	**Maternal toxic Effects**	[redacted]
4.2	**Teratogenic / embryotoxic effects**	There were no treatment-related effects at any dose level on the litter parameters ([redacted]). There were no treatment-related effects at any dose level on the nature and incidence of external, soft tissue and skeletal malformations and variations ([redacted]
4.3	**Other effects**	-

Section A6.8.1 **Teratogenicity Study** **Rat**

Annex Point IIA VI.6.8.1/01 Developmental toxicity study (gavage application) in the rat

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Evaluation of the embryotoxic and teratogenic potential after oral application to pregnant rats (on days 6-19 of gestation); no relevant deviations to guidelines 87/302/EEC B.31, OECD 414, US-EPA OPPTS 870.3700, Japan MAFF)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 did not indicate any embryotoxic or teratogenic potential in this study in rats. Reduced food consumption and bw development were seen in dams.
5.3.1	LOAEL maternal toxic effects	[redacted]
5.3.2	NO(A)EL maternal toxic effects	NOEL 10 mg/kg bw/day NOAEL 40 mg/kg bw/day
5.3.3	LO(A)EL embryotoxic / teratogenic effects	- [redacted]
5.3.4	NO(A)EL embryotoxic / teratogenic effects	>125 mg/kg bw/day
5.3.5	Reliability	1
5.3.6	Deficiencies	No

Section A6.8.1 Teratogenicity Study Rat

Annex Point IIA VI.6.8.1/01 Developmental toxicity study (gavage application) in the 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	2004-10-07
Materials and Methods	Applicants version is acceptable
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	1
Acceptability	acceptable
Remarks	CA-table 1 is added by the RMS
	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 A6.8.1 **Teratogenicity Study** **Rat**

Annex Point IIA
VI.6.8.1/01

Developmental toxicity study (gavage application) in the rat

[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]	[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 A6.8.1 Teratogenicity Study Rabbit

Annex Point IIA
VI.6.8.1/02

Developmental toxicity study (gavage application) in the rabbit

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]1998b[redacted] 16.04.1998
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 the purpose of its first entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC B.31, OECD draft guideline no. 414 (1999), US-EPA OPPTS 870.3700 (1996), Japan MAFF (59 NohSan no. 4200, 1985)
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	[redacted]
3.2	**Test Animals**	[redacted] female New Zealand White rabbits [redacted]
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	rabbit day 6-28 post mating
3.3.2	Postexposure period	- (sacrifice on day 29)
		Oral
3.3.3	Type	Gavage

Section A6.8.1 **Teratogenicity Study** **Rabbit**

Annex Point IIA VI.6.8.1/02 Developmental toxicity study (gavage application) in the rabbit

3.3.4	Concentration	0, 10, 25, 75 and 100 mg/kg bw/day [redacted]
3.3.5	Vehicle	[redacted]
3.3.6	Concentration in vehicle	[redacted]
3.3.7	Total volume applied	10 mL/kg bw
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes (on day 0 of gestation, daily during the treatment period and on the day of sacrifice)
3.4.2	Food consumption	Yes (daily)
3.4.3	Clinical signs	Yes (before and about one hour after dosing on days 6 to 28, and on day 29); mortality (twice daily)
3.4.4	Examination of uterine content	Gravid uterine weight Number of corpora lutea Number of implantations early and late resorptions
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, No. of dead Foetuses, Foetal Weight, Sex Ratio, External alternations
3.4.5.2	Skelet	Yes
3.4.5.3	Soft tissue	Yes
3.5	**Further remarks**	-

4 RESULTS AND DISCUSSION

4.1 Maternal toxic Effects

[redacted]

4.2 Teratogenic / embryotoxic effects

[redacted]

Section A6.8.1 **Teratogenicity Study** **Rabbit**

Annex Point IIA VI.6.8.1/02 Developmental toxicity study (gavage application) in the rabbit

[redacted]

4.3 Other effects

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Evaluation of the embryotoxic and teratogenic potential after oral application to pregnant rabbits (on days 6-28 of gestation); no relevant deviations to guidelines (87/302/EEC B.31, OECD 414, US-EPA OPPTS 870.3700, Japan MAFF)

5.2 Results and discussion

[redacted]

5.3 Conclusion

TI-435 did not indicate a teratogenic potential in this study in rabbits. Probably related to maternal toxicity (reduced food consumption, bw development even mortality) increased post-implantation loss and lower fetal weights associated with a slight delay in ossification were seen at the highest dose level of 100 mg/kg bw/day.

5.3.1	LOAEL maternal toxic effects	75 mg/kg bw/day reduced food consumption and bw gain during treatment
5.3.2	NO(A)EL maternal toxic effects	NOEL 10 mg/kg bw/day NOAEL 25 mg/kg bw/day
5.3.3	LO(A)EL embryotoxic / teratogenic effects	[redacted]
5.3.4	NO(A)EL embryotoxic / teratogenic effects	75 mg/kg bw/day
5.3.5	Reliability	1

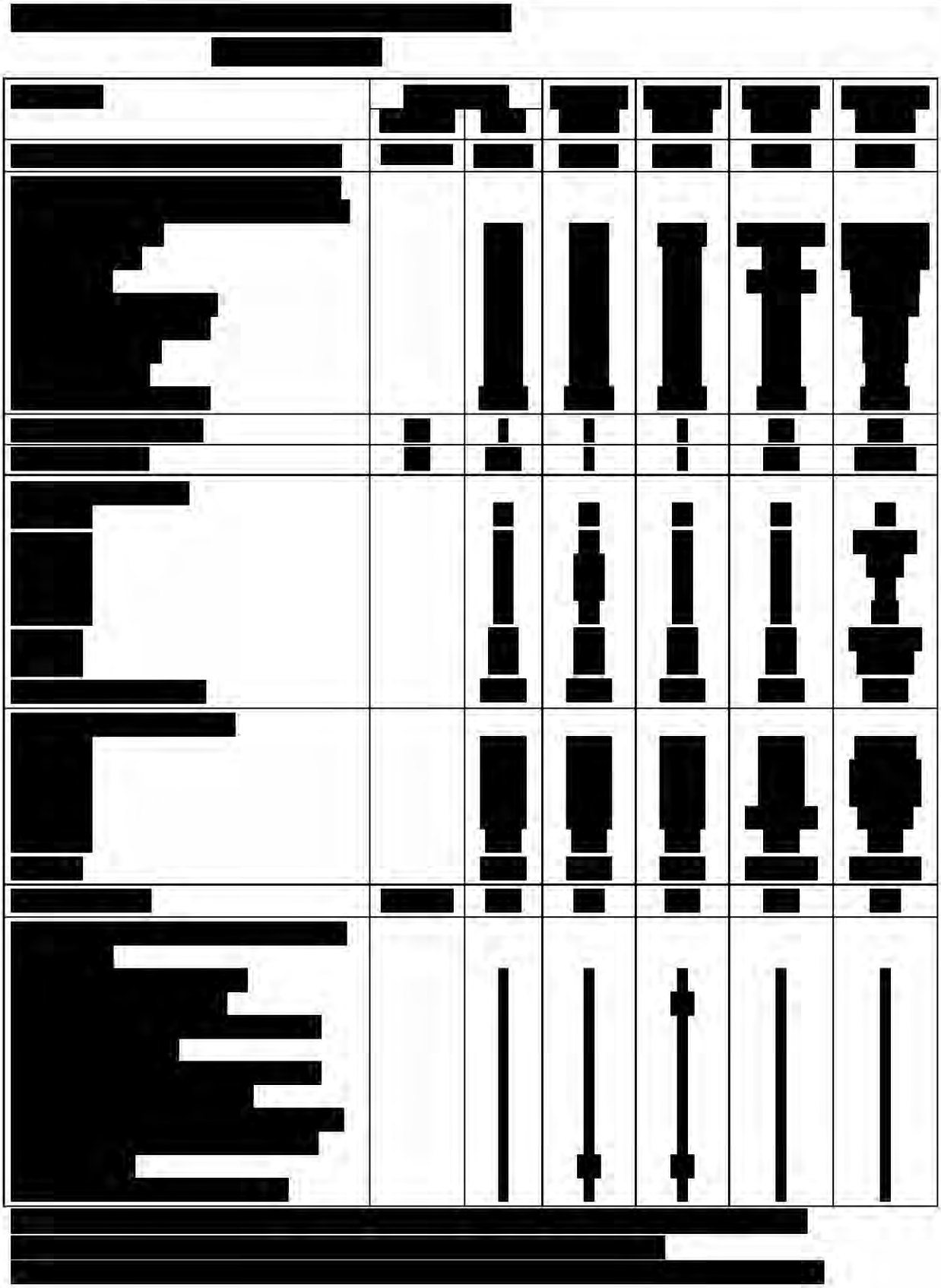
Section A6.8.1	**Teratogenicity Study**	**Rabbit**
Annex Point IIA VI.6.8.1/02	Developmental toxicity study (gavage application) in the rabbit	
5.3.6 Deficiencies	No	

	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	
	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	

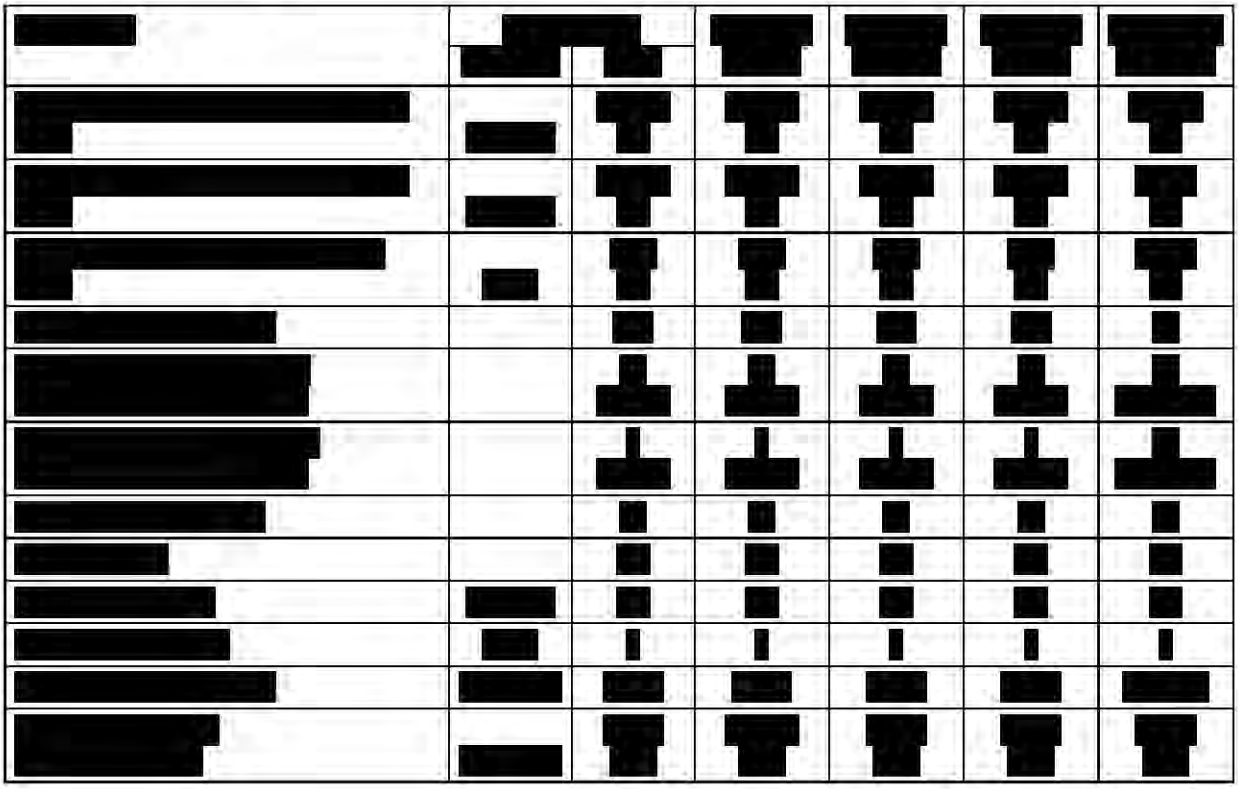
Section A6.8.1 **Teratogenicity Study** **Rabbit**

Annex Point IIA
VI.6.8.1/02

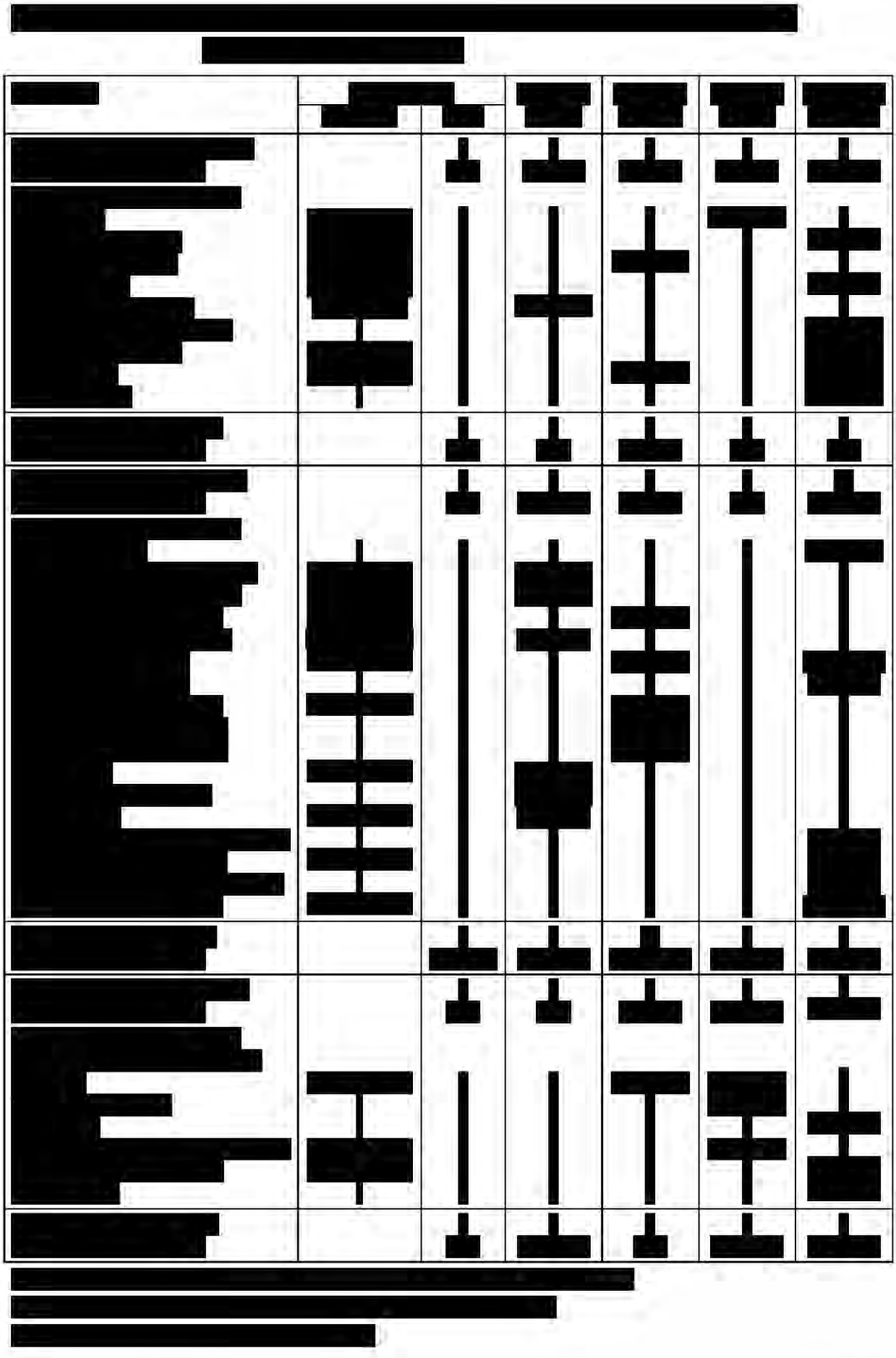
Developmental toxicity study (gavage application) in the rabbit



[redacted]



[redacted]



Section A6.8.2 Multigeneration Reproduction Toxicity Study

Annex Point IIA6.8.2/01 Two generation dietary reproduction toxicity study in rats

Official use only

~~1.~~1 REFERENCE

~~1.~~1.1	**Reference**	[redacted] (2000)
~~2.~~1.2	**Data protection**	Yes
~~1.~~1.2.1	Data owner	[redacted]
~~2.~~1.2.2	Companies with letter of access	[redacted]
~~3.~~1.2.3	Criteria for data protection	[redacted]

~~1~~2 GUIDELINES AND QUALITY ASSURANCE

~~3.~~2.1	**Guideline study**	Yes 87/302/EEC B.35, OECD guideline no. 416 (1983), EPA-OPPTS 870.3800 (1998), EPA-TSCA 798.4700; Japan MAFF (59, NohSan no.4200, 1985)
~~4.~~2.2	**GLP**	Yes
~~5.~~2.3	**Deviations**	No

~~2~~3 MATERIALS AND METHODS

~~6.~~3.1	**Test material**	[redacted]
~~1.~~3.1.1	Lot/Batch number	[redacted]
~~2.~~3.1.2	Specification	As given in section 2
~~1.~~3.1.2.1	Description	Pale yellow powder
~~2.~~3.1.2.2	Purity	[redacted]
~~3.~~3.1.2.3	Stability	[redacted]
~~7.~~3.2	**Test Animals** 3.2.1-3.2.6	[redacted] male and [redacted] female 7-8 week old Sprague-Dawley rats per [redacted]
~~1.~~3.2.7	Mating	See table A6_8_2/01-1
~~2.~~3.2.8	Duration of mating	2 weeks
~~3.~~3.2.9	Deviations from standard protocol	[redacted]
~~4.~~3.2.10	Control animals	Yes
~~8.~~3.3	**Administration/ Exposure**	Oral
~~1.~~3.3.1	Animal assignment to dosage groups	See table A6_8_2/01-1

Formatted Table
Formatted: Outline numbered + Level: 1 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm
Formatted: Highlight
Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm
Formatted: Highlight
Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm
Formatted: Highlight
Formatted … [1]
Formatted … [2]
Formatted: Highlight
Formatted … [3]
Formatted: Highlight
Formatted … [4]
Formatted … [5]
Formatted … [6]
Formatted … [7]
Formatted: Highlight
Formatted … [8]
Formatted: Highlight
Formatted … [9]
Formatted … [10]
Formatted … [11]
Formatted … [12]
Formatted: Highlight
Formatted … [13]
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted … [14]
Formatted … [15]
Formatted: Highlight
Formatted … [16]
Formatted … [17]
Formatted … [18]
Formatted … [19]

Section A6.8.2	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2/01	Two generation dietary reproduction toxicity study in rats
~~2.~~3.3.2 Duration of exposure before mating	10 weeks (70 days)
~~3.~~3.3.3 Duration of exposure in general P, F1, F2 males, females	From beginning of the study until sacrifice of parent, F1, F2-generation
	Oral
~~4.~~3.3.4 Type	in food
~~5.~~3.3.5 Concentration	[redacted] 0, 10.2, 32.7 and 179.6 mg/kg bw/day for males, and 0, 11.8, 37.9 and 212.9 mg/kg bw/day for females (pre-mating phase) [redacted]
~~6.~~3.3.6 Vehicle	[redacted]
~~7.~~3.3.7 Concentration in vehicle	-
~~8.~~3.3.8 Total volume applied	-
~~9.~~3.3.9 Controls	plain diet
~~9.~~**3.4 Examinations**	
~~1.~~3.4.1 Clinical signs	[redacted]
~~2.~~3.4.2 Body weight	[redacted]
~~3.~~3.4.3 Food/water consumption	[redacted]
~~4.~~3.4.4 Oestrus cycle	[redacted]
~~5.~~3.4.5 Sperm parameters	[redacted]
~~6.~~3.4.6 Offspring	[redacted]
~~7.~~3.4.7 Organ weights P and F1	[redacted]
~~8.~~3.4.8 Histopathology P and F1	[redacted]

Formatted Table

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, ... + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, ... + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, ... + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, ... + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Highlight

Formatted: Highlight

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, ... + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Highlight

Formatted ... [20]

Formatted ... [21]

Formatted ... [22]

Formatted ... [23]

Formatted ... [24]

Formatted: Highlight

Formatted ... [25]

Formatted: Highlight

Formatted ... [26]

Formatted: Highlight

Formatted ... [27]

Formatted: Highlight

Formatted ... [28]

Formatted: Highlight

Formatted ... [29]

Formatted: Highlight

Formatted ... [30]

Formatted: Highlight

Formatted ... [31]

Formatted: Highlight

Section A6.8.2 **Multigeneration Reproduction Toxicity Study**

Annex Point IIA6.8.2/01 Two generation dietary reproduction toxicity study in rats

~~9.~~3.4.9 Histopathology F1 not selected for mating, F2

[redacted]

~~10.~~3.5 **Further remarks**

Data were analysed statistically using ANOVA for parametric data, followed by Dunnett's test where appropriate. Non-parametric data were analysed by the Kruskal-Wallis test followed by Dunn's test.

~~3.~~ **RESULTS AND DISCUSSION**

~~11.~~4.1 **Effects**

~~1.~~4.1.1 Adults

[redacted]

Formatted Table

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Highlight

Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Formatted: Highlight

Formatted: Highlight

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Section A6.8.2 **Multigeneration Reproduction Toxicity Study**

Annex Point IIA6.8.2/01 Two generation dietary reproduction toxicity study in rats

~~2.~~4.1.2 Pups

[redacted]

~~12.~~4.2 Other

[redacted]

~~4~~5 APPLICANT'S SUMMARY AND CONCLUSION

~~13.~~5.1 **Materials and methods**

Evaluation of the potential for reproductive toxicity in a 2-generation study in rats; no relevant deviation from guidelines (87/302/EEC B.35, OECD 416, EPA-OPPTS 870.3800, EPA-TSCA 798.4700; Japan MAFF)

Formatted Table

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Highlight

Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Formatted: Highlight

Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Section A6.8.2 **Multigeneration Reproduction Toxicity Study**

Annex Point IIA6.8.2/01 Two generation dietary reproduction toxicity study in rats

~~14.~~5.2 **Results and discussion**

[redacted]

~~15.~~5.3 **Conclusion**

There was no relevant effect of treatment on reproduction at dose levels [redacted] 179.6 and 212.9 mg/kg bw/day for males and females, respectively.
Treatment-related changes comprised increases in food consumption and reductions in bw development with further findings considered to be secondary to the latter (changes in organ weight, slightly redcued sperm motility in adult males, slight delay in reaching developmental landmarks in F_1 pups).
In absence of a similar effect in F_1 females and as the final bw was comparable to controls in 500 ppm treated P females, the slightly lower bw development during pre-treatment and the lower bw at day14 of lactation are considered to be not adverse. Also in absence of a similar effect in F_2 pups and as the bw development of the F_1 generation at 500 ppm during pre-mating was comparable to controls, the marginally lower bw gain of F_1 pups at 500 ppm during day 7-14 of lactation was considered to be not adverse.
Therefore overall NOAEL of the study is considered to be 500 ppm corresponding to 32.7 and 37.9 mg/kg bw/day in males and females, respectively.

Formatted Table

Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Formatted: Highlight

Formatted: Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Section A6.8.2	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2/01	Two generation dietary reproduction toxicity study in rats
~~1.~~5.3.1 LOAEL	
~~1.~~5.3.1.1 Parent males	ppm corresponding to 163.4 mg/kg bw/day increased food consumption, reduced bw development and findings considered secondary to the latter
~~2.~~5.3.1.2 Parent females	2500 ppm corresponding to 188.8 mg/kg bw/day increased food consumption, reduced bw development and findings considered secondary to the latter; as discussed before, the marginal changes in bw in P females at 500 ppm were considered to be not adverse
~~3.~~5.3.1.3 F1 males	Adults and pups: 2500 ppm corresponding to 195.7 mg/kg bw/day reduced bw gain and related changes, increased food consumption in adults
~~4.~~5.3.1.4 F1 females	Adults and pups: 2500 ppm corresponding to 237.0 mg/kg bw/day reduced bw gain and related changes, increased food consumption in adults
~~5.~~5.3.1.5 F2 males	2500 ppm reduced bw gain
~~6.~~5.3.1.6 F2 females	2500 ppm reduced bw gain
~~2.~~5.3.2 NO(A)EL	
~~1.~~5.3.2.1 Parent males	NOEL = NOAEL = 500 ppm corresponding to 31.2 mg/kg bw/day
~~2.~~5.3.2.2 Parent females	NOEL = 150 ppm corresponding to 11.5 mg/kg bw/day NOAEL = 500 ppm corresponding to 36.8 mg/kg bw/day
~~3.~~5.3.2.3 F1 males	Pups: NOEL = 150 ppm, NOAEL = 500 ppm Adults NOEL = NOAEL = 500 ppm corresponding to 34.3 mg/kg bw/day
~~4.~~5.3.2.4 F1 females	Pups: NOEL = 150 ppm, NOAEL = 500 ppm Adults NOEL = NOAEL = 500 ppm corresponding to 39.0 mg/kg bw/day
~~5.~~5.3.2.5 F2 males	NOEL = NOAEL = 500 ppm
~~6.~~5.3.2.6 F2 females	NOEL = NOAEL = 500 ppm
~~3.~~5.3.3 Reliability	1
~~4.~~5.3.4 Deficiencies	No

Formatted Table

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Formatted: Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Formatted: Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Formatted: Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Formatted: Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Formatted: Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Formatted: Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Formatted: Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Formatted ... [32]

Formatted ... [33]

Formatted ... [34]

Formatted ... [35]

Formatted ... [36]

Formatted ... [37]

Formatted ... [38]

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]

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Conclusion	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Formatted: Highlight

	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

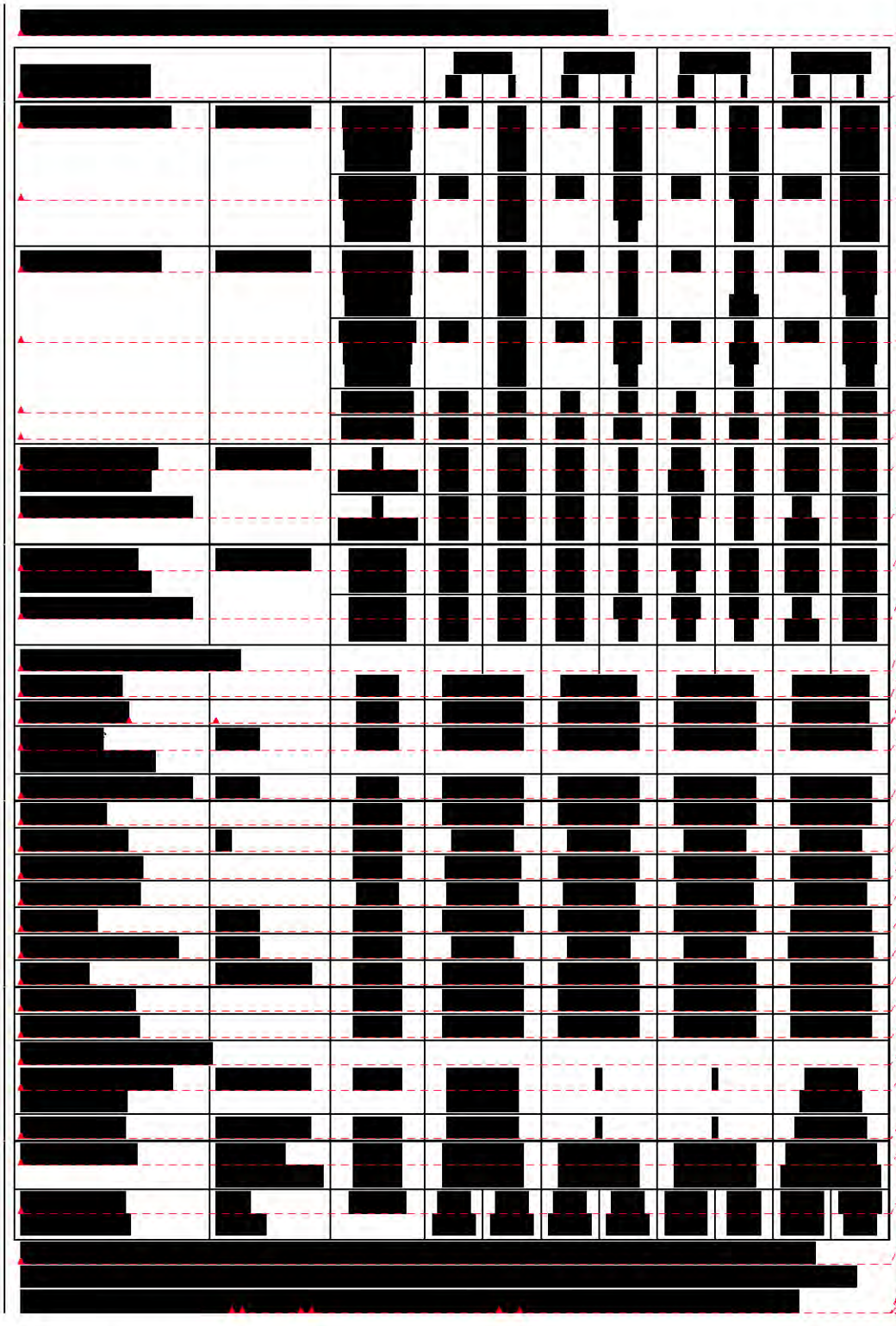
Formatted: Highlight

Formatted: Highlight

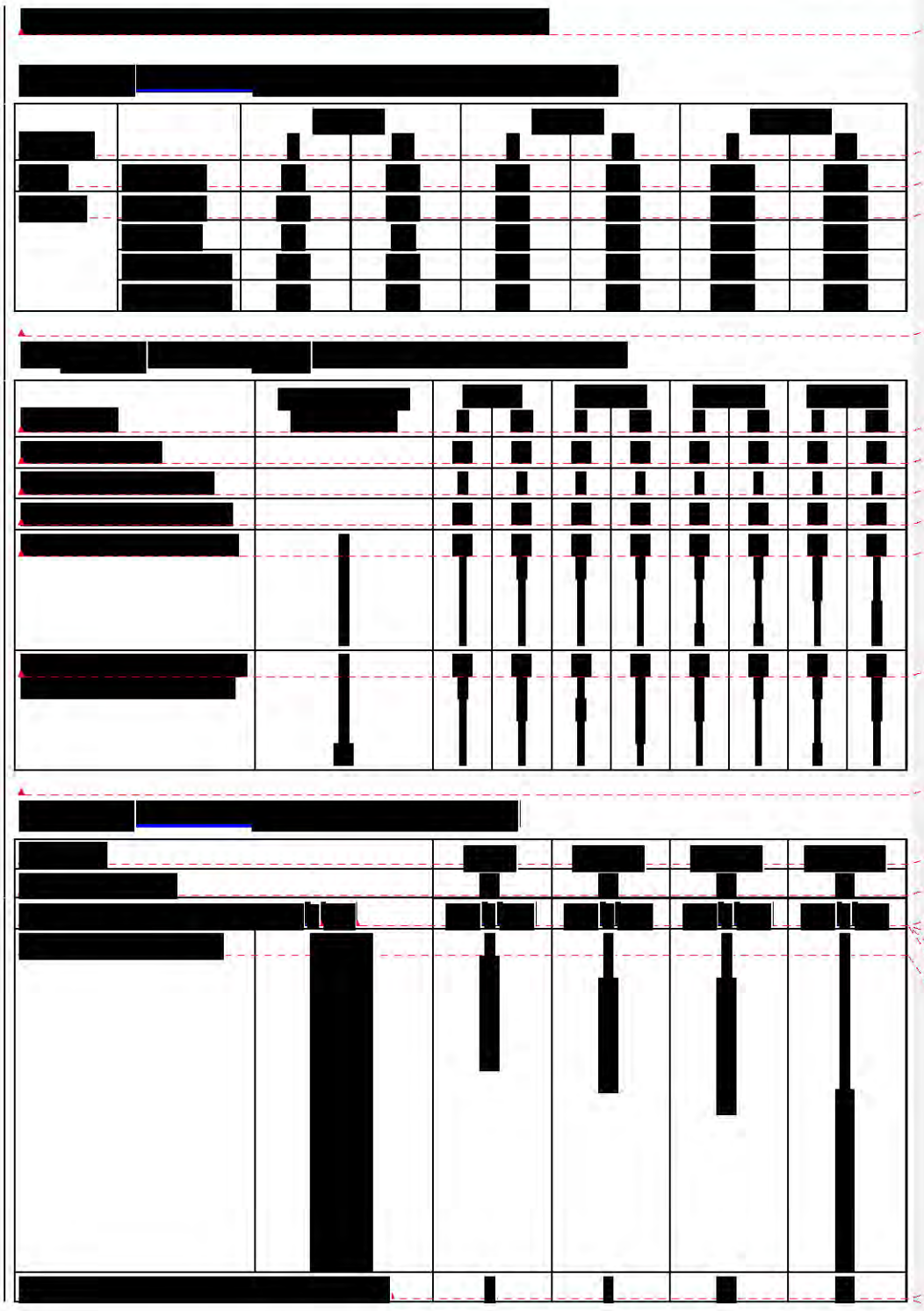
Formatted: Highlight

Formatted: Highlight

Formatted: Highlight



Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight



Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: English (U.K.), Highlight
Formatted: Highlight
Formatted: English (U.K.), Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: English (U.K.), Highlight
Formatted: Highlight

Page 1: [1] Formatted [redacted]r **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [2] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [3] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [4] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Page 1: [5] Formatted D[redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Page 1: [6] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Page 1: [7] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Page 1: [8] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [9] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [10] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 1: [11] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 1: [12] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 1: [13] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Page 1: [14] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [15] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [16] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [17] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 1: [18] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Page 1: [19] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [20] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [21] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [22] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [23] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 2 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 2.54 cm

Page 2: [24] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [25] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [26] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [27] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [28] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [29] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [30] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 2: [31] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 6: [32] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 6: [33] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 6: [34] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 6: [35] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 6: [36] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 4 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 0 cm + Indent at: 1.25 cm, Tab stops: Not at 5.08 cm

Page 6: [37] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

Page 6: [38] Formatted [redacted] **24.06.2013 14:02:00**

Outline numbered + Level: 3 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm, Tab stops: Not at 3.81 cm

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

Annex Point IIA VI.6.9/01 Acute oral neurotoxicity study in rats

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**	[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] male and [redacted] female fasted 9 week old Fischer 344 rats per group (CDF[F-344]/BR [redacted]
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days

Section A6.9 Neurotoxicity studies Acute study in rats

Annex Point IIA VI.6.9/01 Acute oral neurotoxicity study in rats

		Oral
3.3.2	Type	Gavage
3.3.3	Concentration	0, 100, 200 and 400 mg/kg bw
3.3.4	Vehicle	[redacted]
3.3.5	Concentration in vehicle	[redacted]
3.3.6	Total volume applied	[redacted]
3.3.7	Controls	vehicle
3.4	**Examinations**	[redacted]
3.5	**Sacrifice and pathology**	[redacted]
3.6	**Further remarks**	[redacted]

4 RESULTS AND DISCUSSION

4.1 Body weight

[redacted]

4.2 Clinical signs, FOB, motor activity

[redacted]

4.3 Pathology

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Neurotoxicity evaluation after acute oral application of the TI-435 to rats (gavage); no relevant deviation from guidelines (OECD 424, EPA OPPTS 870.6200)

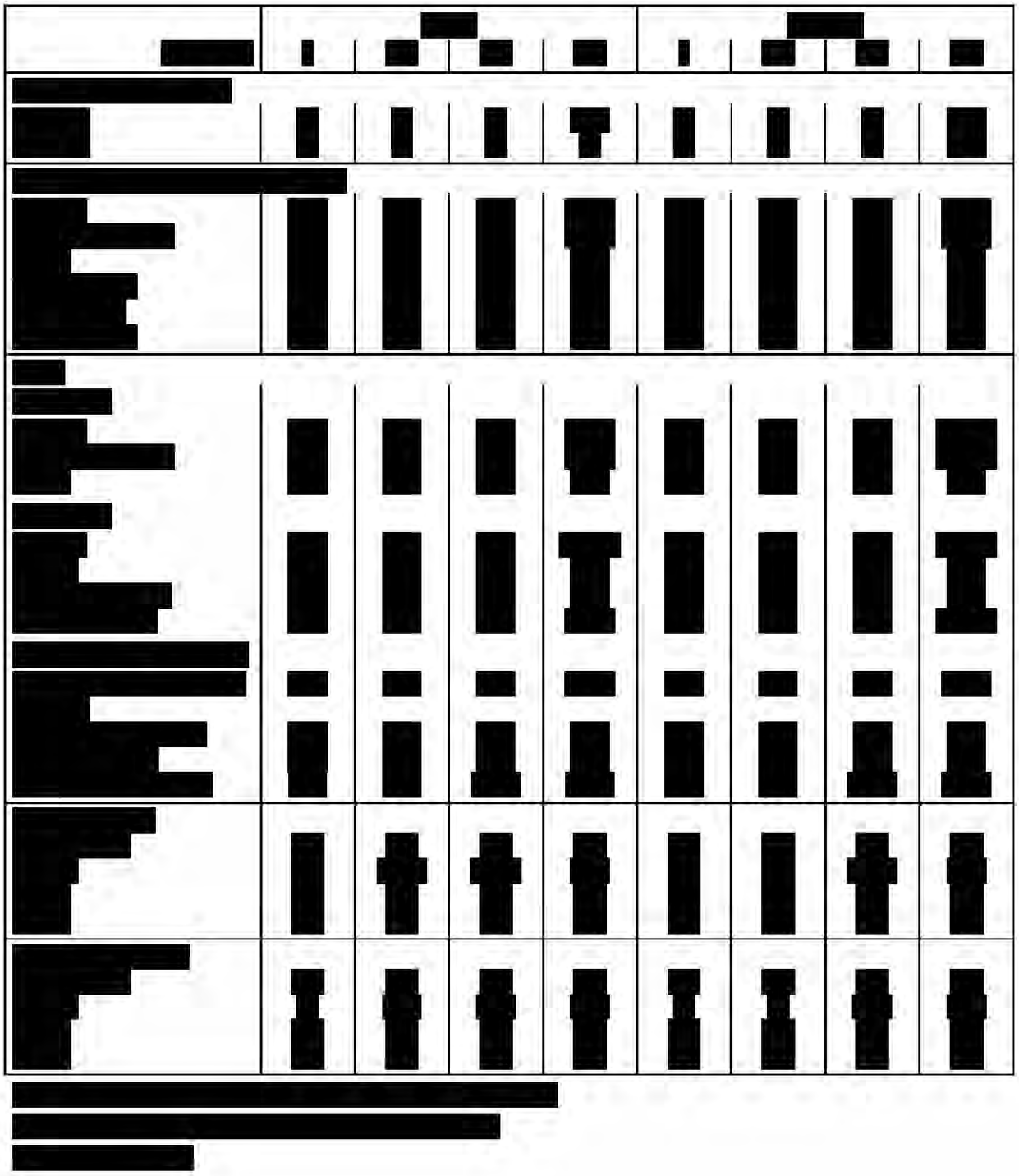
5.2 Results and discussion

[redacted]

Section A6.9	Neurotoxicity studies Acute study in rats	
Annex Point IIA VI.6.9/01	Acute oral neurotoxicity study in rats	
5.3	**Conclusion**	With exception of the bw development, the observed transient functional effects were considered to be neurobehavioural evidence of toxicity and/or signs of pharmacological over-stimulation but not indications for specific neurotoxicity. Therefore TI-435 is considered to be not neurotoxic in rats after acute exposure.
5.3.1	LOAEL	100 mg/kg bw for males (transient effect on motor activity) 200 mg/kg bw for females (transient effects on FOB and motor activity)
5.3.2	NO(A)EL	<100 mg/kg bw for males 100 mg/kg bw for females
5.3.3	Reliability	1
5.3.4	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	
	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_9/01-1 Table for Acute Oral Neurotoxicity (rat)



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

Annex Point IIA VI.6.9/02 Acute oral neurotoxicity study in rats

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	Data submitted on existing a.s. for its first entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes No EU guideline available, OECD 424 corresponding EPA-FIFRA Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Guideline Addendum 10, Neurotoxicity; NTIS, 1991, EPA 540/09-91-123, PB 91-154617, EPA OPPTS 870.6200 (August 1998)
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 (stability, homogeneity and content of test-article/vehicle formulations was analysed)
3.2	**Test Animals**	[redacted] male fasted 9 week old Fischer 344 rats per group (CDF[F-344]/BR strain, [redacted]
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	1-2 days

Section A6.9 Neurotoxicity studies Acute study in rats

Annex Point IIA VI.6.9/02 Acute oral neurotoxicity study in rats

		Oral
3.3.2	Type	Gavage
3.3.3	Concentration	0, 20, 40 and 60 mg/kg bw
3.3.4	Vehicle	[redacted]
3.3.5	Concentration in vehicle	[redacted]
3.3.6	Total volume applied	[redacted]
3.3.7	Controls	vehicle
3.4	**Examinations**	[redacted]
3.5	**Sacrifice and pathology**	All animals were sacrificed and discarded without necropsy and tissue preservation 1–2 days after the final assessments.
3.6	**Further remarks**	[redacted]

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

Annex Point IIA VI.6.9/02 Acute oral neurotoxicity study in rats

4 RESULTS AND DISCUSSION

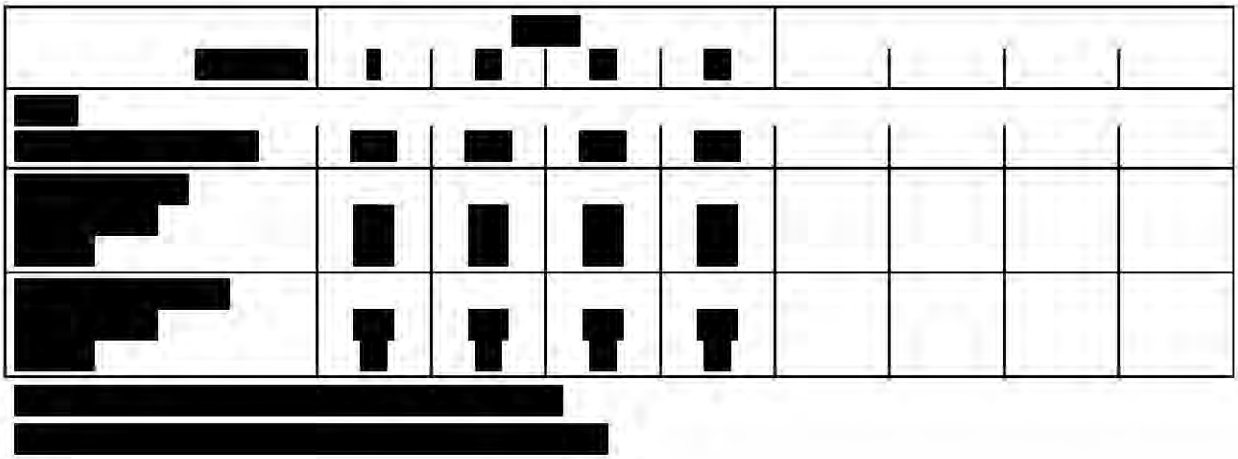
4.1	**Body weight**	No effect of treatment.
4.2	**Clinical signs, FOB, motor activity**	There were no deaths or treatment-related clinical signs. [redacted]
4.3	**Pathology**	-

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Neurotoxicity evaluation (assignment of a NOEL) after acute oral application of the TI-435 to male rats (gavage); no relevant deviation from guidelines (OECD 424, EPA OPPTS 870.6200)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	No indication for neurotoxicity or other effects of treatment were noted in this study after acute oral application of up to 60 mg/kg bw in male rats. The dose level of 60 mg/kg bw was a clear NOEL in this study.
5.3.1	LOAEL	>60 mg/kg bw (males)
5.3.2	NO(A)EL	60 mg/kg bw (males)
5.3.3	Reliability	1
5.3.4	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	
	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 A6.9 **Neurotoxicity studies** **Subchronic study in rats**

Annex Point IIA VI.6.9/03 90-day oral (feeding) neurotoxicity study in rats

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000); [redacted] 12.10.2000
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 [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 of the compound and its homogeneity and stability in food were tested)
3.2	**Test Animals**	[redacted] male and [redacted] female fasted 9 week old [redacted] rats [redacted]
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	13 weeks
3.3.2	Frequency of exposure	daily
3.3.3	Postexposure period	-

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

Annex Point IIA VI.6.9/03 90-day oral (feeding) neurotoxicity study in rats

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	[redacted] 0, 9.2, 60 and 177 mg/kg bw/day for males and 0, 10.6, 71 and 200 mg/kg bw/day for females [redacted]
3.3.4.3	Vehicle	[redacted]
3.3.4.4	Concentration in vehicle	-
3.3.4.5	Total volume applied	-
3.3.4.6	Controls	[redacted]
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	yes (daily), [redacted]
3.4.1.2	Mortality	yes [redacted]
3.4.2	Body weight	yes (weekly)
3.4.3	Food consumption	yes (weekly)
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	Yes (all animals at pre-test and during week 12)
3.4.6	Clinical pathology	No ([redacted]
3.4.7	Functional observation battery (FOB)	Yes ([redacted]
3.4.8	Motor activity	Yes [redacted]
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes; [redacted]
3.5.2	Gross and histopathology	Yes [redacted]
3.5.3	Other examinations	-

3.5.4 Statistics

[redacted]

4 RESULTS AND DISCUSSION

4.1 Observations

[redacted]

4.2 Body weight gain

[redacted]

4.3 Food consumption and compound intake

[redacted]

4.4 Ophtalmoscopic examination

[redacted]

4.5 FOB, motor activity

[redacted]

4.6 Pathology

[redacted]

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Neurotoxicity evaluation after suchronic (90-day) oral application of TI-435 to rats (feeding); no relevant deviation from guidelines (OECD 424, EPA OPPTS 870.6200)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 is considered to be not neurotoxic in rats after dietary exposure for 90 days.
5.3.1	LOAEL	[redacted] Neurotoxicity: -
5.3.2	NO(A)EL	Systemic: [redacted] 60 and 71 mg/kg bw/day for males and females, respectively Neurotoxicity: [redacted] 177 and 200 mg/kg bw/day for males and females, respectively
5.3.3	Reliability	1
5.3.4	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	
	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_9/03-1 Table for Subchronic Oral Neurotoxicity (feeding, rat)

Section A6.9 Developmental neurotoxicity study Rat

Developmental neurotoxicity study (orally via diet) in the rat

Official use only

~~1.1~~ REFERENCE

1.1	**Reference**	[redacted] (2000); [redacted], 20.10.2000
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 No applicable EU guideline; US-EPA Health Effects Test Guidelines: Developmental Neurotoxicity Study, OPPTS 870.6300 and OECD 426 (2003) (study was performed previous to the final OECD guideline but was checked for compliance)
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	[redacted]
3.2	**Test Animals**	[redacted] naturally mated female Sprague-Dawley rats per group (Crl:CD [BR] [redacted]

Formatted: Outline numbered + Level: 1 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0 cm + Tab after: 1.25 cm + Indent at: 1.25 cm

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted Table

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Section A6.9 Developmental neurotoxicity study Rat

Developmental neurotoxicity study (orally via diet) in the rat

3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	Day 0 of gestation to day 22 *post partum* (dams)
3.3.2	Postexposure period	[redacted]
3.3.3	Type	Feeding
3.3.4	Concentration	[redacted] 0, 12.9, 42.9, 142.0 mg/kg bw/day during gestation and 27.3, 90.0 and 299.0 mg/kg bw/day during lactation.
3.3.5	Vehicle	None
3.3.6	Concentration in vehicle	-
3.3.7	Total volume applied	-
3.3.8	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Body weight	Yes ([redacted]
3.4.2	Food consumption	Yes [redacted]
3.4.3	Clinical signs	Yes [redacted]
3.4.4	Physical Development	[redacted]
3.4.5	Sexual Maturation	[redacted]
3.4.6	Brain weights	[redacted]
3.4.7	Neurohistological examination	[redacted]

Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight

Section A6.9 **Developmental neurotoxicity study Rat**

Developmental neurotoxicity study (orally via diet) in the rat

3.4.8 Tests

3.4.8.1 Passive Avoidance (learning, memory)

3.4.8.2 Water maize (learning, memory)

3.4.8.3 Motor activity

3.4.8.4 Auditory startle habituation (motor/ sensory function)

3.4.9 Gross and histopathology

3.5 Further remarks Statistical evaluation of results was performed.

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs, pregnancy parameters

4.1.2 Mortality Dams: no deaths

4.2 Body weight gain

Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight

Section A6.9 Developmental neurotoxicity study Rat

Developmental neurotoxicity study (orally via diet) in the rat

[redacted]

4.3 Food consumption and compound intake

4.4 Physical development / sexual maturation

4.5 Brain weight

4.6 Neurohistology

Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight
Formatted: Font: Not Bold, Highlight
Formatted: Highlight

Section A6.9 **Developmental neurotoxicity study** **Rat**

Developmental neurotoxicity study (orally via diet) in the rat

4.7 Tests

4.7.1 Passive avoidance

4.7.2 Watermaze

4.7.3 Motor activity

4.7.4 Auditory startle

4.8 Sacrifice and pathology

Formatted: Highlight

Formatted: Highlight

Formatted: Font: Not Bold, Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Font: Not Bold, Highlight

Formatted: Highlight

Formatted Table

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Evaluation of the developmental neurotoxic potential in the F1 generation after oral application to pregnant rats (during gestation and lactation); no relevant deviations to guidelines OECD 426, US-EPA OPPTS 870.6300

Section A6.9 Developmental neurotoxicity study Rat

Developmental neurotoxicity study (orally via diet) in the rat

5.2	**Results and discussion**	Dams: no deaths and no clinical signs. The body weight development (gestation) and food consumption (gestation, lactation) were reduced at 1750 ppm. F1-pups: reduced body weight development in both sexes at 1750 ppm and marginally in females of the 500 ppm group. As the latter was only slight and as no toxicologically relevant effect on body weight development had been observed in the 2-generation study at the same dose level in the same strain of rats, the marginal effect at 500 ppm is considered to be not adverse. F1-young adults: There were no treatment-related clinical signs In total 5 animals of the 1750 ppm group died in the first days post-weaning, which was considered due to their low body weight development earlier. The surviving rats of those groups with a reduced body weight after lactation compensated for this after weaning resulting in similar body weights than controls at sacrifice. Reflex and physical development as well as sexual maturation were unaffected by treatment. No biologically relevant effect of treatment on learning and memory as was motor activity and motor/sensory function on all occasions except days 22/23 were recorded. At days 22/23 *post partum* the motor activity (both sexes) and the auditory startle response (females only) were slightly lower in F1 rats of the 1750 ppm group in comparison to controls. The latter was considered to be related/secondary to the reduced body weight development of these animals during lactation and therefore not to indicate developmental neurotoxicity. Brain weight, morphology and neuropathology were unaffected by treatment. At sacrifice there were no treatment related changes in dams and their offspring at any dose level.
5.3	**Conclusion**	No indication of selective developmental neurotoxicity of TI-435. Systemic toxicity was noted at 1750 ppm in dams and pups; a marginally lower body weight development was also noted in females of the 500 ppm group, which is considered to be not adverse.
5.3.1	LOAEL maternal toxic effects	[redacted]
5.3.2	NO(A)EL maternal toxic effects	500 ppm corresponding to 42.9 and 90.0 mg/kg bw/day during gestation and lactation, respectively
5.3.3	LO(A)EL developmental neurotoxicity	none
5.3.4	NO(A)EL developmental neurotoxicity	>1750 ppm
5.3.5	LOAEL developmental toxicity	[redacted]
5.3.6	NOAEL developmental toxicity	500 ppm (= NOEL for males; NOEL for females = 150 ppm)
5.3.7	Reliability	1
5.3.8	Deficiencies	No

Section A6.9 Developmental neurotoxicity study Rat

Developmental neurotoxicity study (orally via diet) in the 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	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Section A6.9 [redacted]

[redacted]

Formatted: Highlight

[redacted]

Formatted: Highlight

[redacted]

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*

Section A6.9 Developmental neurotoxicity study Rat

Developmental neurotoxicity study (orally via diet) in the rat

Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.9 Developmental neurotoxicity study Rat

Developmental neurotoxicity study (orally via diet) in the rat

[redacted]

Formatted: Highlight

Formatted: Highlight

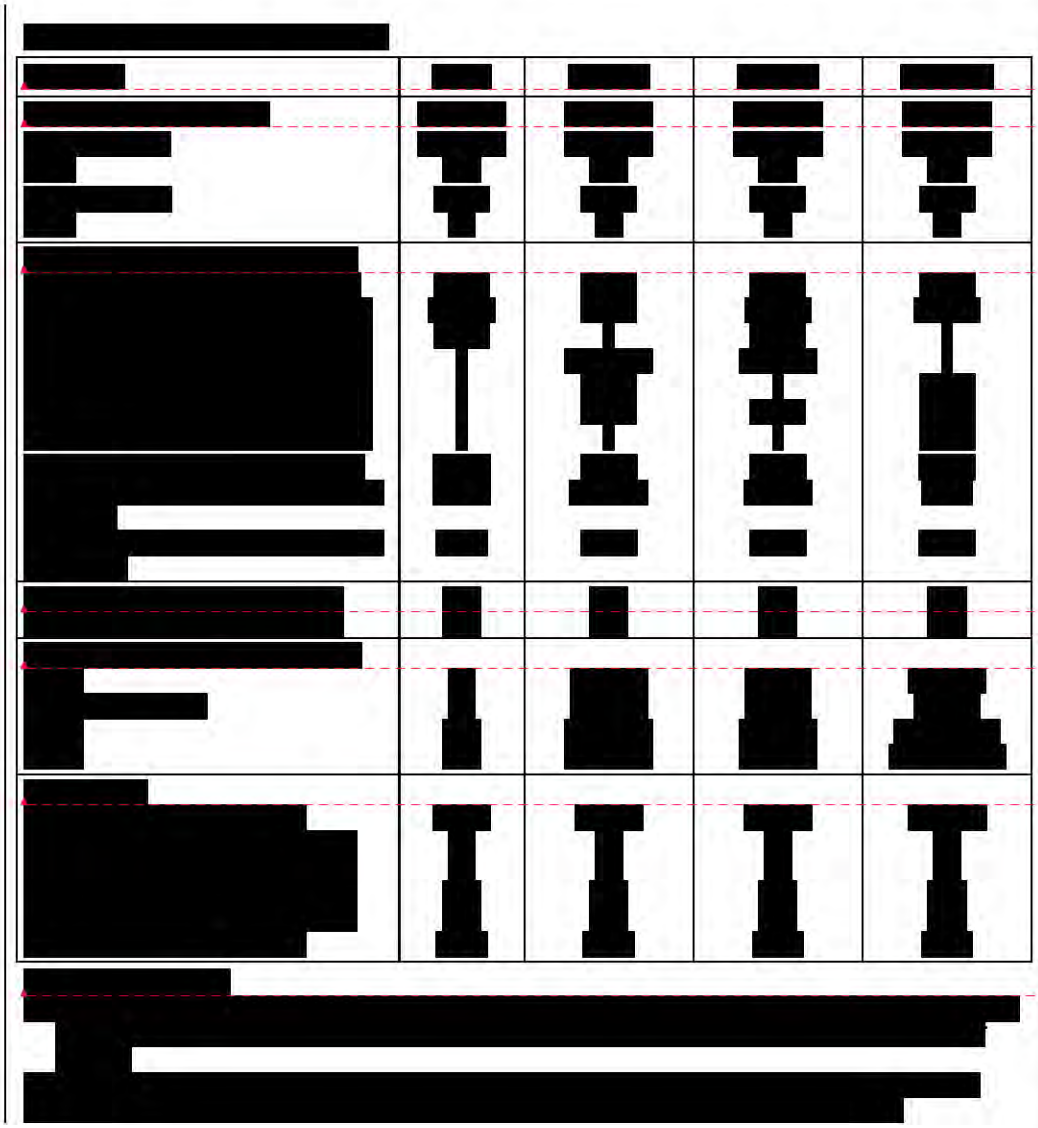
Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight



Formatted: Highlight

Formatted: Highlight

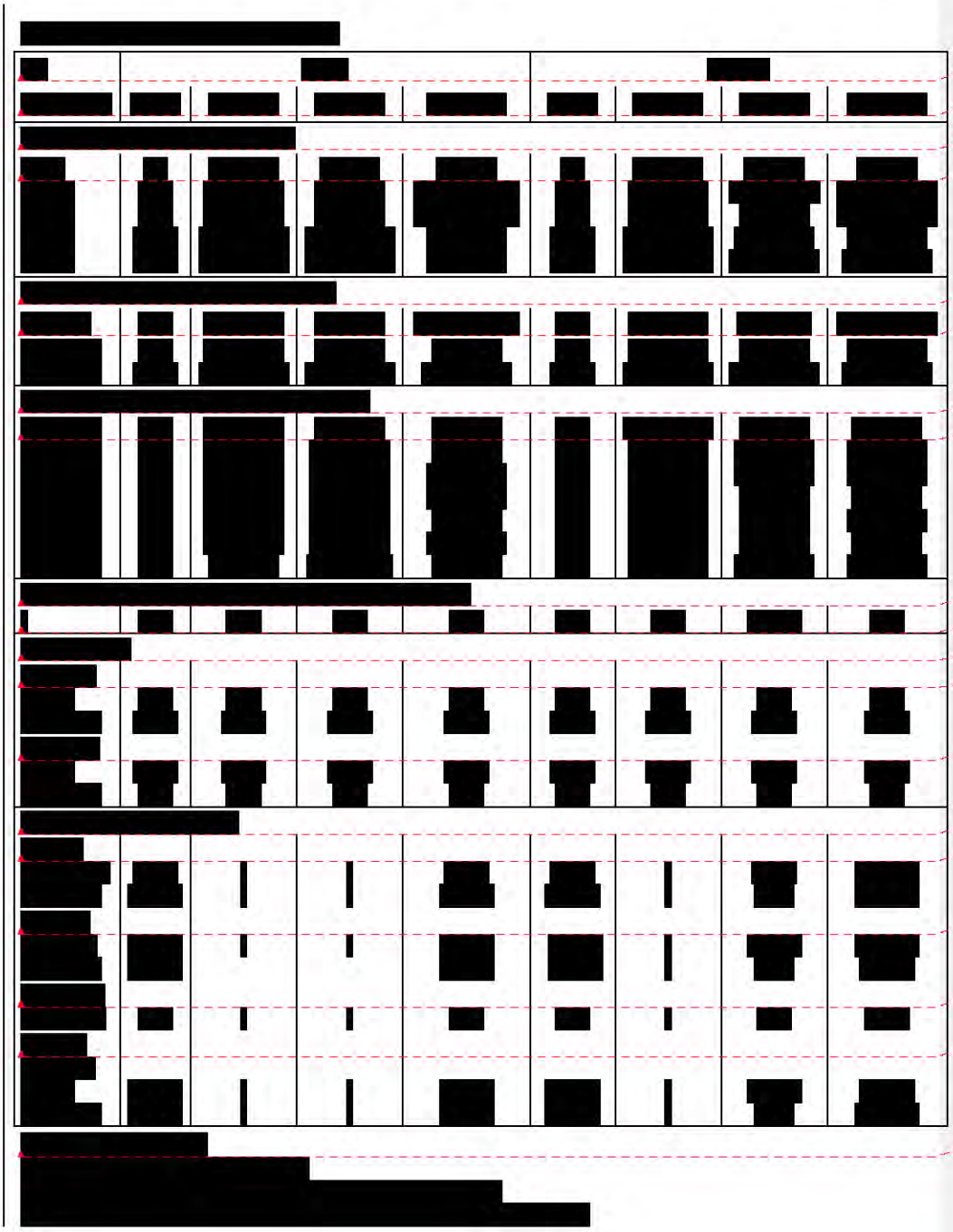
Formatted: Highlight

Formatted: Highlight

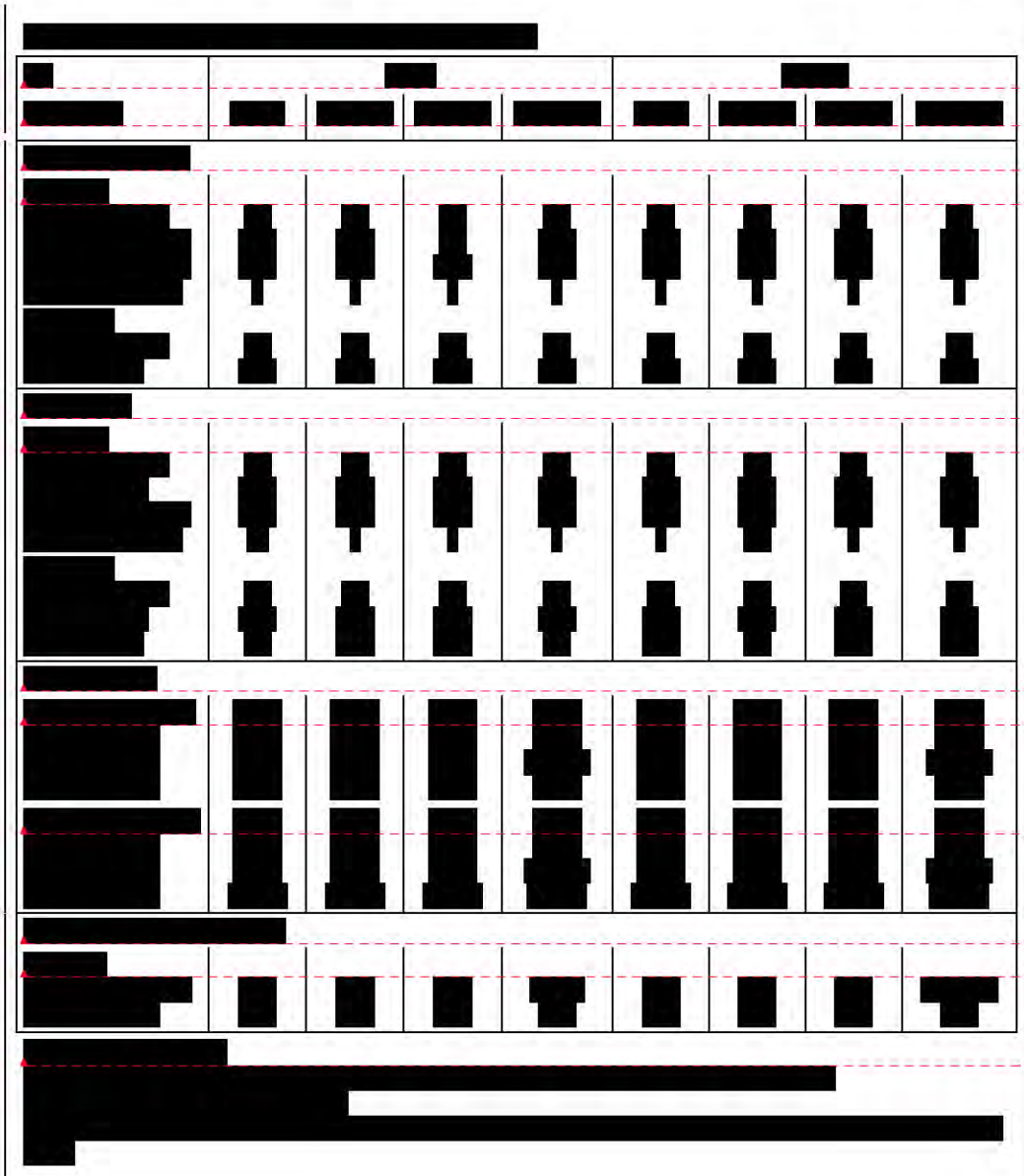
Formatted: Highlight

Formatted: Highlight

Formatted: Highlight



Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight



Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight

[redacted]

Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight

[redacted]

eld Code Changed

Section A6.10 **Toxicity studies with compounds other than the a.s.**
Annex Point IIA Ames test (+/- S9) using *S. typhimurium* with TI-435 metabolite MNG
VI.6.10.1/01

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 submitted on existing a.s. for its first entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 2000/32/EC (method B13/14), OECD no. 471 (1997), OPPTS 870.5100 (1998)
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	Not applicable
3.1.2.1	Description	White powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stable under conditions of this study (test-article/vehicle solutions were used within 4 hours after preparation)
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	*S. typhimurium*: TA 1535, TA 1537, TA 98, TA 100, TA 102
3.2.2	Deficiencies / Proficiencies	Histidine deficient
3.2.3	Metabolic activation system	S9 mix [redacted]
3.2.4	Positive control	<u>In absence of S9</u>: Nitrofurantoin (NF) at 0.2 µg/plate for TA 100 Sodium azide (NaN_3) at 10 µg/plate for TA 1535 4-nitro-1,2-phenylene diamine (4-NPDA) at 0.5 µg/plate for TA 98 10 µg/plate for TA 1537 Cumenehydroperoxide (Cumene) at 50 µg/plate for TA 102 <u>In presence of S9</u>: 2-Aminoantracene (2-AA) at 3 µg/plate for all strains

Section A6.10 **Toxicity studies with compounds other than the a.s.**

Annex Point IIA Ames test (+/- S9) using *S. typhimurium* with TI-435 metabolite MNG

VI.6.10.1/01

3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	0, 50, 158, 500, 1581, 5000 µg/plate (+/- S9) for both the plate incorporation and pre-incubation assay
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	None (plate incorporation assay) 20 min (pre-incubation assay)
3.3.4	Other modifications	-
3.4	**Examinations**	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	[redacted]
4.1.2	with metabolic activation	[redacted]
4.2	**Cytotoxicity**	[redacted]

Section A6.10 **Toxicity studies with compounds other than the a.s.**

Annex Point IIA Ames test (+/- S9) using *S. typhimurium* with TI-435 metabolite MNG

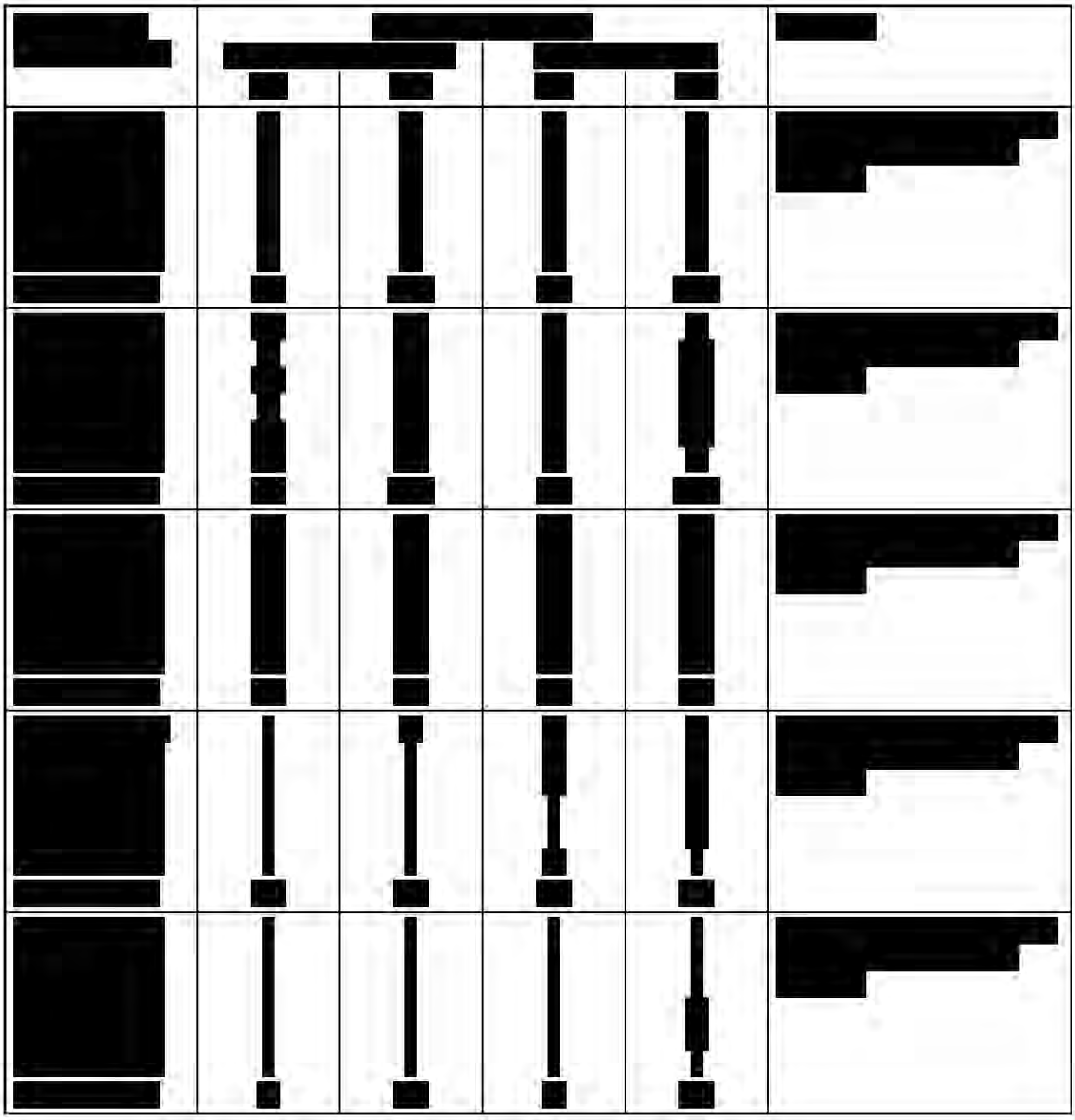
VI.6.10.1/01

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	No effect of treatment with up to 5000 µg/plate of TI-435 metabolite MNG on the number of revertant colonies on 5 *S. typhimurium* strains was seen. There were also no indications for cytotoxicity (thinning of background lawn).
5.3	**Conclusion**	MNG and/or its metabolites were considered to be not mutagenic in this *in vitro* test system.
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
[redacted]	
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	

[redacted]



Section A6.10 Toxicity studies with compounds other than the a.s.

Annex Point IIA VI.6.10.1/02 Acute oral toxicity study in rats (LD_{50}) with the TI-435 metabolite TZNG

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000c); [redacted] 20.01.2000
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 submitted on existing a.s. for its first entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [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	Not applicable
3.1.2.1	Description	White 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] female fasted rats per group ([redacted]) No control group
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days

Section A6.10		**Toxicity studies with compounds other than the a.s.**
Annex Point IIA VI.6.10.1/02		Acute oral toxicity study in rats (LD_{50}) with the TI-435 metabolite TZNG
3.3.2	Type	Gavage
3.3.3	Concentration	1125, 1350 and 1620 mg/kg bw (females) 1450 mg/kg bw (males)
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]
3.3.7	Controls	-
3.4	**Examinations**	[redacted]
3.5	**Method of determination of LD_{50}**	The acute median lethal dose and 95% confidence limits were estimated using probit analysis (Finney, D. J., 1971, Probit analysis, 3rd Ed., Cambridge University Press).
3.6	**Further remarks**	-
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	[redacted]
4.2	**Pathology**	[redacted]
4.3	**Other**	[redacted]
4.4	**LD_{50}**	1481 mg/kg bw (females) >1450 mg/kg bw (males)
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Toxicity evaluation (bw, clinical signs, *post mortem* examination) after acute oral application of the TI-435 metabolite TZNG to rats (gavage); no relevant deviation from guidelines (92/69/EEC B1; EPA OPPTS 870.1100, Japan MAFF, OECD 401)
5.2	**Results and discussion**	Acute oral LD_{50} in rats was 1481 mg/kg bw.
5.3	**Conclusion**	Classification as harmful if swallowed (R22) is considered required for TI-453 metabolite TZNG according to Directive 2001/59/EC (adaptation of 67/548/EEC). The same classification had been proposed for the parent TI-435.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.10	**Toxicity studies with compounds other than the a.s.**
Annex Point IIA VI.6.10.1/02	Acute oral toxicity study in rats (LD_{50}) with the TI-435 metabolite TZNG

	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	
	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 A6.10 **Toxicity studies with compounds other than the a.s.**

Annex Point IIA VI.6.10.1/02 Acute oral toxicity study in rats (LD_{50}) with the TI-435 metabolite TZNG

[redacted]

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