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

3.5.2	Gross and histopathology	Yes [redacted]
3.5.3	Other examinations	-
3.5.4	Statistics	Where appropriate: Bartlett's test for heterogeneity of variance between groups followed by one-way analysis of variance on homogeneous or transformed data followed by Dunnetts' t-test for multiple comparisons between treated and control groups at 1% and 5% probability

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]

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

[redacted]

4.4 Ophtalmoscopic examination [redacted]

4.5 Blood analysis [redacted]

4.5.1 Haematology [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]

4.7 Other -

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods Toxicity evaluation after short-term (28 day) dietary exposure of dogs to TI-435; no relevant deviation from guidelines (88/302/EEC B27, EPA

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

FIFRA 82-1)

5.2	Results and discussion	[redacted]
5.3	Conclusion	Dose levels of 2500 and 5000 ppm exceeded the maximum tolerated dose level. Effects of treatment comprised clinical signs of toxicity, weight loss, haematological and blood biochemistry perturbations, and histomorphological lesions in haematopoietic/lymphoid tissues and duodenum.
5.3.1	[redacted]	[redacted]
5.3.2	NO(A)EL	NOAEL = 1250 ppm corresponding to 34.3 and 35.8 mg/kg bw/day for males and females, respectively
5.3.3	Other	Remark: For males the NOAEL expressed in mg/kg bw/day is only slightly lower than the LOAEL. The latter is due to the markedly reduced food consumption at the LOAEL (2500 ppm) leading to an in total only slightly higher test article intake than at the NOAEL with normal food consumption at 1250 ppm. Nevertheless the NOAEL at 34.3/35.8 mg/kg bw/day for males/females is considered valid.
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]

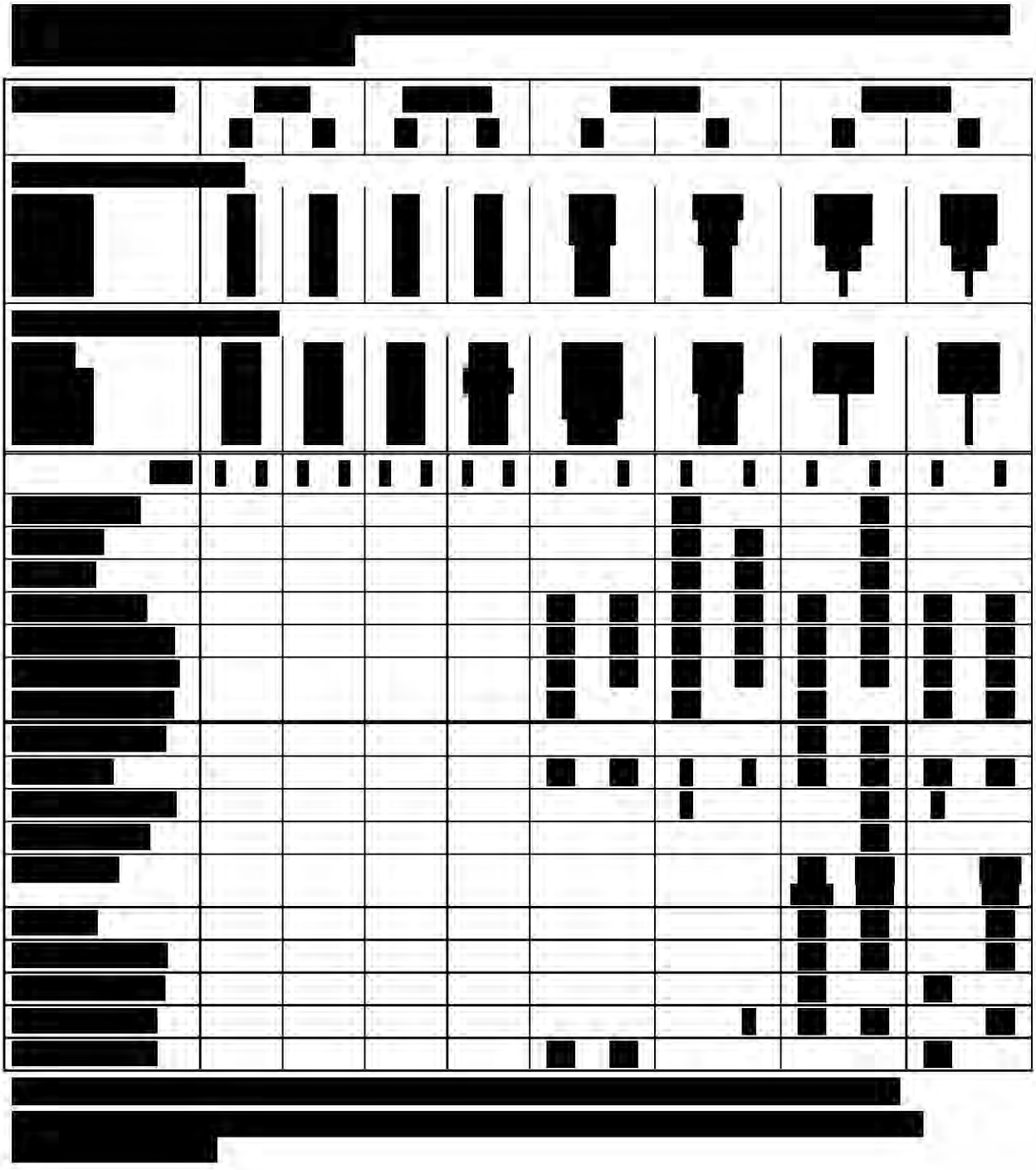
Section A6.3.1 Short-term repeated dose toxicity (28 days) Oral

Annex Point IIA VI.6.3.1/02

28-day dietary toxicity study in dogs

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]	[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 A6.3.2 **Subchronic dermal toxicity** **Rat**

Annex Point IIA
VI.6.3.2/01

28-day dermal toxicity study in rats

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000); [redacted] 13.10.2000
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 92/69/EEC (method B9), OECD no. 410 (1981), US EPA-OPPTS [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 (prepared daily)
3.2	**Test Animals**	[redacted] male and [redacted] female 8 week old rats per group ([redacted]
3.3	**Administration/ Exposure**	dermal
3.3.1	Duration of treatment	28 days
3.3.2	Frequency of exposure	daily
3.3.3	Postexposure period	none

Section A6.3.2	Subchronic dermal toxicity	Rat
Annex Point IIA VI.6.3.2/01	28-day dermal toxicity study in rats	

3.3.4	**Dermal**	
3.3.4.1	Area covered	10% of body surface (5 x 5 cm^2)
3.3.4.2	Occlusion	occlusive
3.3.4.3	Vehicle	deionised water (reverse osmosis water)
3.3.4.4	Concentration in vehicle	Application site was wetted with deionised water before the solid test material was applied and covered with a gauze pad moistened with another 1.0 mL of deionised water
3.3.4.5	Total volume applied	See 3.3.4.4 Dose levels: 0, 100, 300 and 1000 mg/kg bw/day
3.3.4.6	Duration of exposure	6 h per day
3.3.4.7	Removal of test substance	Water-moistened tissue
3.3.4.8	Controls	deionised water
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	yes (daily), thorough clinical examination was performed weekly
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	No
3.4.5	Ophthalmoscopic examination	Yes (all animals at pre-test and during week 4)
3.4.6	Haematology	yes, [redacted]
3.4.7	Clinical Chemistry	yes, [redacted]
3.4.8	Urinalysis	no
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	yes [redacted]
3.5.2	Gross and	yes

	histopathology	gross pathology: all dose groups [redacted]
3.5.3	Other examinations	[redacted]
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	[redacted]
4.2	**Body weight gain**	[redacted]
4.3	**Food consumption and compound intake**	[redacted]
4.4	**Ophtalmoscopic examination**	[redacted]
4.5	**Blood analysis**	[redacted]

Section A6.3.2	Subchronic dermal toxicity	Rat
Annex Point IIA VI.6.3.2/01	28-day dermal toxicity study in rats	

4.6	**Sacrifice and pathology**	[redacted]
4.7	**Other**	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Toxicity evaluation after 28-day dermal exposure of rats to TI-435; no relevant deviation from guidelines (92/69/EEC B9, OECD 410, US EPA-OPPTS 870.3200, Japan MAFF)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	[redacted] was well-tolerated upon dermal application for 28 days. There were no infications for skin irritation.
5.3.1	LO(A)EL	-
5.3.2	NO(A)EL	1000 mg/kg bw/day as discussed above, in absence of a similar effect in females and as bw development was normal for weeks 2-4, the lower bw gain in the 1st week of treatment in males was considered to be unrelated to treatment
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
Date	2004-10-07
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]

Section A6.3.2	Subchronic dermal toxicity	Rat
Annex Point IIA VI.6.3.2/01	28-day dermal toxicity study in rats	

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]

Section A6.4.1 Subchronic oral toxicity test (90 days) Dog

Annex Point IIA
VI.6.4.1/01

90-day dietary toxicity study in dogs

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000a); [redacted] 14.03.2000
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	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 2001/59/EC (method B27), EPA FIFRA Subdivision F (section 82-1, 1984), OECD guideline no. 409 (1981), Japan MAFF (59 NohSan No. 4200, 1985), US EPA OPPTS 870.3150
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	Paleyellow 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**	[redacted] male and [redacted] female Beagle dogs per group ([redacted])
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	at least 13 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None

Section A6.4.1	Subchronic oral toxicity test (90 days) Dog
Annex Point IIA VI.6.4.1/01	90-day dietary toxicity study in dogs

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	[redacted] 0, 9.2, 19.3, 40.9 and 58.2 mg/kg bw/day for males and 0, 9.6, 21.2, 42.1 and 61.8 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), thorough clinical examination was performed weekly
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	No
3.4.5	Ophthalmoscopic examination	Yes (all animals at pre-test and during week 13)
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]

Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Dog**

Annex Point IIA VI.6.4.1/01 90-day dietary toxicity study in dogs

3.5.2	Gross and histopathology	Yes [redacted]
3.5.3	Other examinations	-
3.5.4	Statistics	[redacted]
3.6	**Further remarks**	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	[redacted]
4.1.2	Mortality	None
4.2	**Body weight gain**	[redacted]
4.3	**Food consumption and compound intake**	[redacted]
4.4	**Ophtalmoscopic examination**	[redacted]

Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Dog**

Annex Point IIA VI.6.4.1/01 90-day dietary toxicity study in dogs

4.5	**Blood analysis**	
4.5.1	Haematology	[redacted]
4.5.2	Clinical chemistry	[redacted]
4.5.3	Urinalysis	[redacted]
4.6	**Sacrifice and pathology**	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Toxicity evaluation after subchronic (90 day) dietary exposure of dogs to TI-435; no relevant deviation from guidelines (2001/59/EC B27, EPA FIFRA 82-1, OECD 409, Japan MAFF, US EPA OPPTS 870.3150)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	Effects of treatment comprised clinical signs of toxicity, reduced bw development, haematological and blood biochemistry perturbations but no histomorphological lesions.
5.3.1	LO(A)EL	[redacted]
5.3.2	NO(A)EL	NO(A)EL = 650 ppm corresponding to 19.3 and 21.2 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
Date	2004-10-07

Section A6.4.1 Subchronic oral toxicity test (90 days) Dog

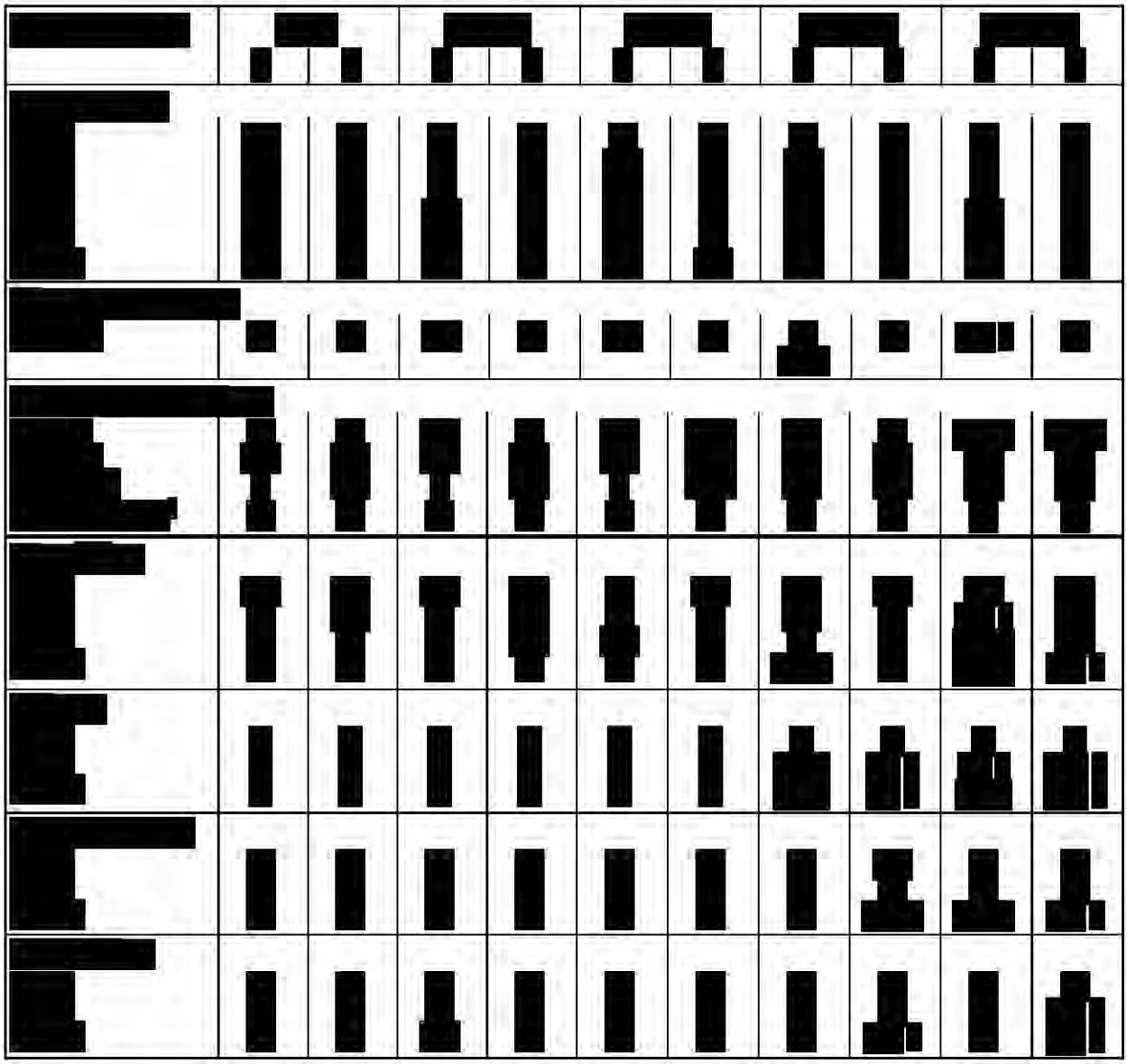
Annex Point IIA VI.6.4.1/01

90-day dietary toxicity study in dogs

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]



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Section A6.4.1 Subchronic oral toxicity test (1-year) Dog

Annex Point IIA
VI.6.4.1/02

1-year dietary toxicity study in dogs

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000b); [redacted] 22.03.2000
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	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC (method B30), EPA FIFRA Subdivision F (section 83-1, 1984), OECD guideline no. 452 (1981), Japan MAFF (59 NohSan No. 4200, 1985), US EPA OPPTS 870.4100 (1998)
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] male and [redacted] female beagle dogs per group [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	52 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None

Section A6.4.1 **Subchronic oral toxicity test (1-year)** **Dog**

Annex Point IIA VI.6.4.1/02 1-year dietary toxicity study in dogs

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	[redacted] 0, 7.8, 16.6, 36.3 and 46.4 mg/kg bw/day for males and 0, 8.5, 15.0, 40.1 and 52.9 mg/kg bw/day for females food consumption per day: ad libitum
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	plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	yes [redacted]
3.4.1.2	Mortality	yes [redacted]
3.4.2	Body weight	yes [redacted]
3.4.3	Food consumption	Yes [redacted]
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	Yes [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]

[redacted]

3.5.2	Gross and histopathology	Yes [redacted]
3.5.3	Other examinations	-
3.5.4	Statistics	Where appropriate: Levene's test for homogeneity of variance between groups followed by one-way analysis of variance on homogeneous or transformed data followed by Dunnetts' t-test for multiple comparisons between treated and control groups at 1% and 5% probability.
3.6	**Further remarks**	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	[redacted]
4.1.2	Mortality	None
4.2	**Body weight gain**	[redacted]
4.3	**Food consumption and compound intake**	[redacted]
4.4	**Ophtalmoscopic examination**	[redacted]

Section A6.4.1 **Subchronic oral toxicity test (1-year)** **Dog**

Annex Point IIA VI.6.4.1/02 1-year dietary toxicity study in dogs

4.5	**Blood analysis**	
4.5.1	Haematology	[redacted]
4.5.2	Clinical chemistry	[redacted]
4.5.3	Urinalysis	[redacted]
4.6	**Sacrifice and pathology**	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Toxicity evaluation after subchronic (1-year) dietary exposure of dogs to TI-435; no relevant deviation from guidelines (87/302/EEC B30, EPA FIFRA 83-1, OECD 452, Japan MAFF, US EPA OPPTS 870.4100)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	Relevant effects of treatment comprised a reduced bw development and haematological perturbations but no histomorphological lesions.
5.3.1	LO(A)EL	[redacted]
5.3.2	NO(A)EL	NOEL = 650 ppm corresponding to 16.6 and 15.0 mg/kg bw/day for males and females, respectively NOAEL = 1500 ppm corresponding to 36.3 and 40.1 mg/kg bw/day for males and females, respectively
5.3.3	Other	-
5.3.4	Reliability	1
5.3.5	Deficiencies	No

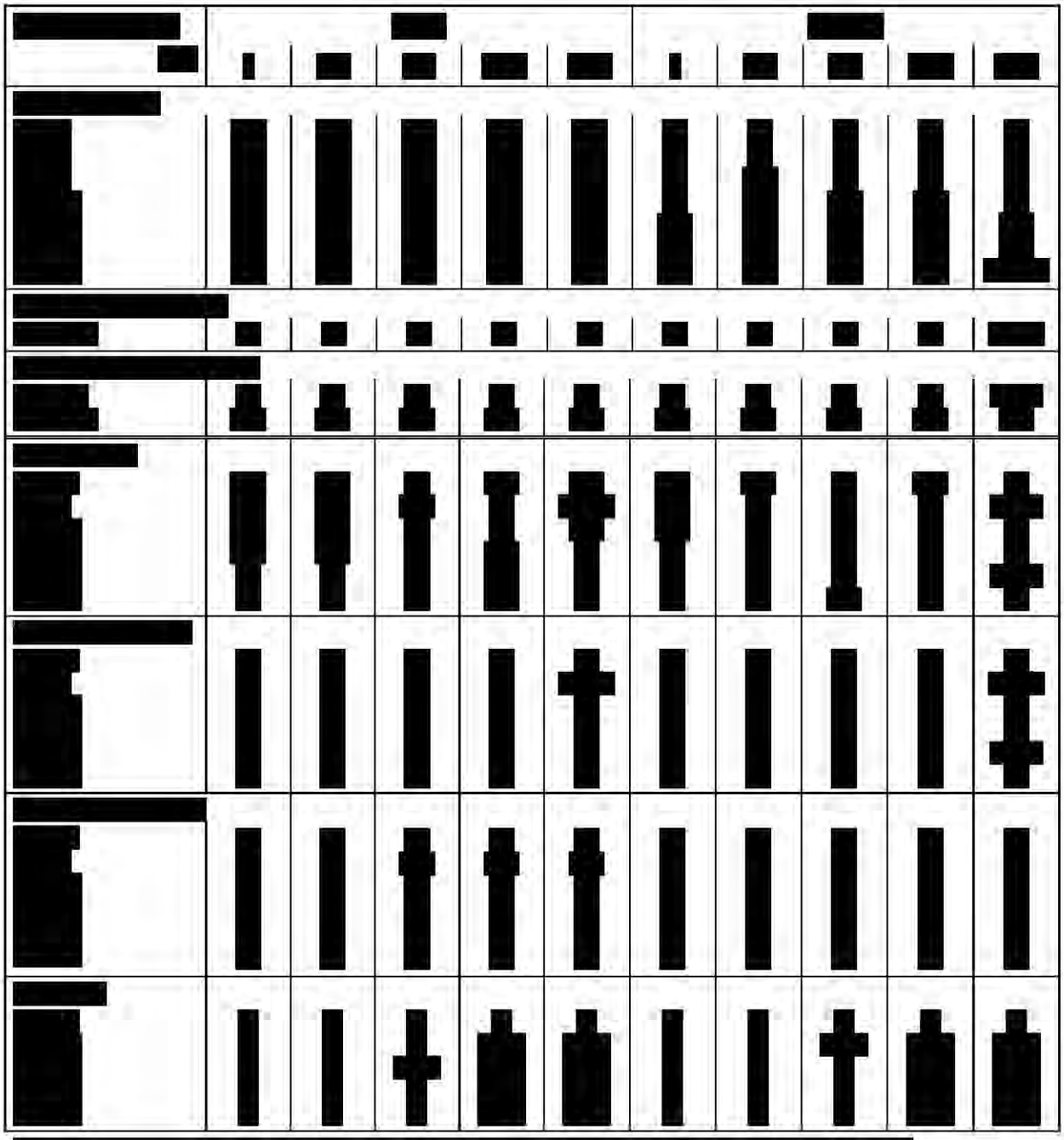
Section A6.4.1 **Subchronic oral toxicity test (1-year)** **Dog**

Annex Point IIA
VI.6.4.1/02

1-year dietary toxicity study in dogs

	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 ... *(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]



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Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Rat**

Annex Point IIA
VI.6.4.1/03

90-day dietary toxicity study in rats

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]. (2000); [redacted], 22.02.2000
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 2001/59/EC (method B26), EPA FIFRA Subdivision F (section 82-1, 1984), OECD guideline no. 408, Japan MAFF (59 NohSan No. 4200)
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 homogenicity and stability in food were tested).
3.2	**Test Animals**	[redacted] male and [redacted] female Sprague Dawley rats [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	13 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	for the control and high dose group 15 rats/sex/group were kept for a recovery period of 7 weeks

Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Rat**

Annex Point IIA
VI.6.4.1/03

90-day dietary toxicity study in rats

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	[redacted] 0, 9.0, 27.9 and 202 mg/kg bw/day for males and 0, 10.9, 34.0 and 254 mg/kg bw/day for females food consumption per day: ad libitum
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 [redacted]
3.4.1.2	Mortality	yes (daily)
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 [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]
3.5.2	Gross and histopathology	Yes [redacted]
3.5.3	Other examinations	[redacted]
3.5.4	Statistics	Where appropriate: Bartlett's test for heterogeneity of variance between groups ($p \leq 0.001$); for equal variances: one-way analysis of variance on homogeneous or transformed data followed by Dunnett's test for multiple comparisons between treated and control groups at 1% and 5% probability; for unequal variances: Kruskal-Wallis ANOVA followed by Mann-Whitney-U test. Frequency data: Chi-square and/or Fisher exact test
3.6	**Further remarks**	-

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	[redacted]
4.1.2	Mortality	[redacted]
4.2	**Body weight gain**	[redacted]
4.3	**Food consumption and compound intake**	[redacted]

Section A6.4.1 **Subchronic oral toxicity test (90 days) Rat**

Annex Point IIA
VI.6.4.1/03

90-day dietary toxicity study in rats

[redacted]

4.4 Ophtalmoscopic examination

[redacted]

4.5 Blood analysis

4.5.1 Haematology

[redacted]

4.5.2 Clinical chemistry

[redacted]

4.5.3 Urinalysis

[redacted]

4.6 Sacrifice and pathology

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Toxicity evaluation after subchronic (90 day) dietary exposure of rats to TI-435; no relevant deviation from guidelines (2001/59/EC B26, EPA FIFRA 82-1, OECD 408, Japan MAFF)

5.2 Results and discussion

[redacted]

5.3 Conclusion

Effects of treatment comprised reduced bw development, indications for an increased functional load of the liver (in absence of liver damage) and pigmentation of the spleen in males.

5.3.1 LO(A)EL

[redacted]

5.3.2 NO(A)EL

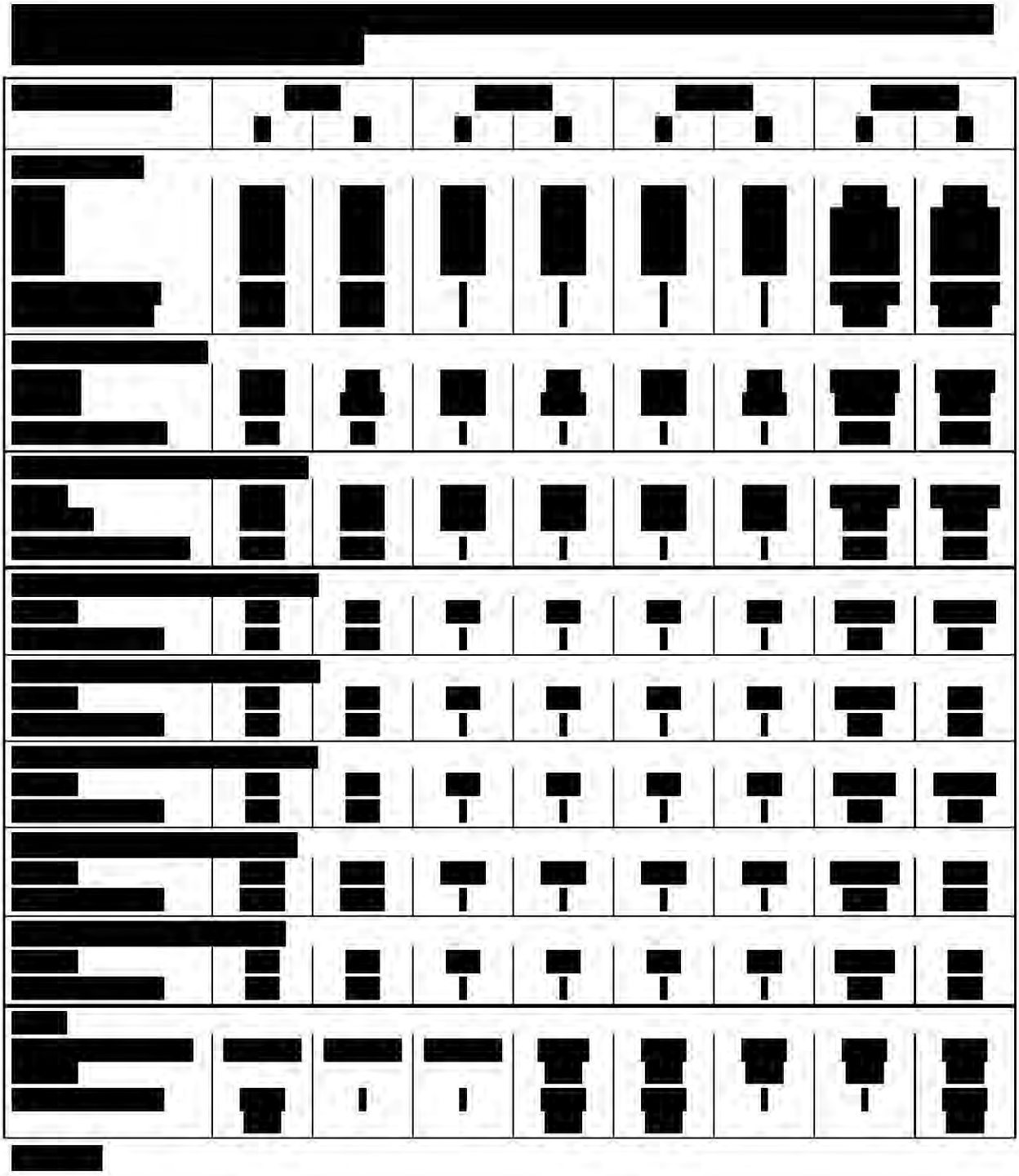
NO(A)EL = 500 ppm corresponding to 27.9 and 34.0 mg/kg bw/day for males and females, respectively

5.3.3 Other

-

Section A6.4.1	**Subchronic oral toxicity test (90 days)**	**Rat**
Annex Point IIA VI.6.4.1/03	90-day dietary toxicity 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	2004-10-07
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	



Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Mouse**
Annex Point IIA VI.6.4.1 90-day dietary toxicity study in mice

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted] (2000); [redacted] 08.12.2000
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 B.7 (predecessor of 2001/59/EC B.26), OECD 408
2.2	**GLP**	[redacted]
2.3	**Deviations**	(from 2001/59/EC B.26): no FOB and motor activity were measured, blood clotting time/potential was not investigated.
	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 (homogeneity and stability in food were tested in an earlier study in this laboratory).
3.2	**Test Animals**	[redacted] male and [redacted] female Crl: CD-1 (ICR) BR mice per [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	13 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None
3.3.4	Type	in food

Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Mouse**
Annex Point IIA VI.6.4.1 90-day dietary toxicity study in mice

3.3.5	Concentration	[redacted] 0, 16, 82, 160 and 263 mg/kg bw/day for males and 0, 22, 107, 207 and 329 mg/kg bw/day for females food consumption per day: *ad libitum*
3.3.6	Vehicle	None [redacted]
3.3.7	Concentration in vehicle	-
3.3.8	Total volume applied	-
3.3.9	Controls	plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	yes [redacted]
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	No
3.4.5	Ophthalmoscopic examination	yes [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]

Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Mouse**
Annex Point IIA VI.6.4.1 90-day dietary toxicity study in mice

3.5.2	Gross and histopathology	yes [redacted]
3.5.3	Other examinations	-
3.5.4	Statistics	Where appropriate: Bartlett's test for heterogeneity of variance between groups followed by one-way analysis of variance on homogeneous or transformed data followed by Student's t- test and Williams' test. In case of heterogeneity of variance a Kruskal-Wallis analysis was performed followed by the non-parametric equivalents of the t test and Williams' test. Macrospcopic and microscopic data were analysed by Fisher's exact test where appropriate.
3.6	**Further remarks**	-

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	[redacted]
4.1.2	Mortality	[redacted]
4.2	**Body weight gain**	[redacted]
4.3	**Food consumption and compound intake**	[redacted]

Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Mouse**

Annex Point IIA VI.6.4.1 90-day dietary toxicity study in mice

4.4 Ophtalmoscopic examination

4.5 Blood analysis

4.5.1 Haematology

4.5.2 Clinical chemistry

4.5.3 Urinalysis

4.6 Sacrifice and pathology

Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Mouse**
Annex Point IIA VI.6.4.1 90-day dietary toxicity study in mice

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Toxicity evaluation after subchronic (90 day) dietary exposure of mice to [redacted]; no relevant deviation from guidelines (88/302/EEC B.7 [predecessor of 2001/59/EC B.26], OECD 408) apparent. However the quality and validity of data was considered to be compromised due to serious GLP-problems at the test facility.

5.2 Results and discussion

[redacted]

5.3 Conclusion

Due to the GLP-problems in the laboratory, the results of this study are not considered relevant for the risk assessment of TI-435. Effects were mainly a reduced body weight development and food consumption at ≥1000 ppm accompanied by associated findings in organ weights and increased blood urea nitrogen (at 1500 ppm). For females reduced lung weights were seen at 1500 ppm. Also in high dose females there was an indication for exacerbation of normal cyclic activity. (For comparison no treatment-related changes in ovaries and uterus were detected in the 18-month mouse study up to the highest dose level of 1800 ppm.)

5.3.1 LO(A)EL

[redacted]

5.3.2 NO(A)EL

NO(A)EL = 500 ppm corresponding to 82 and 107 mg/kg bw/day for males and females, respectively

5.3.3 Other

-

5.3.4 Reliability

4

5.3.5 Deficiencies

[redacted]

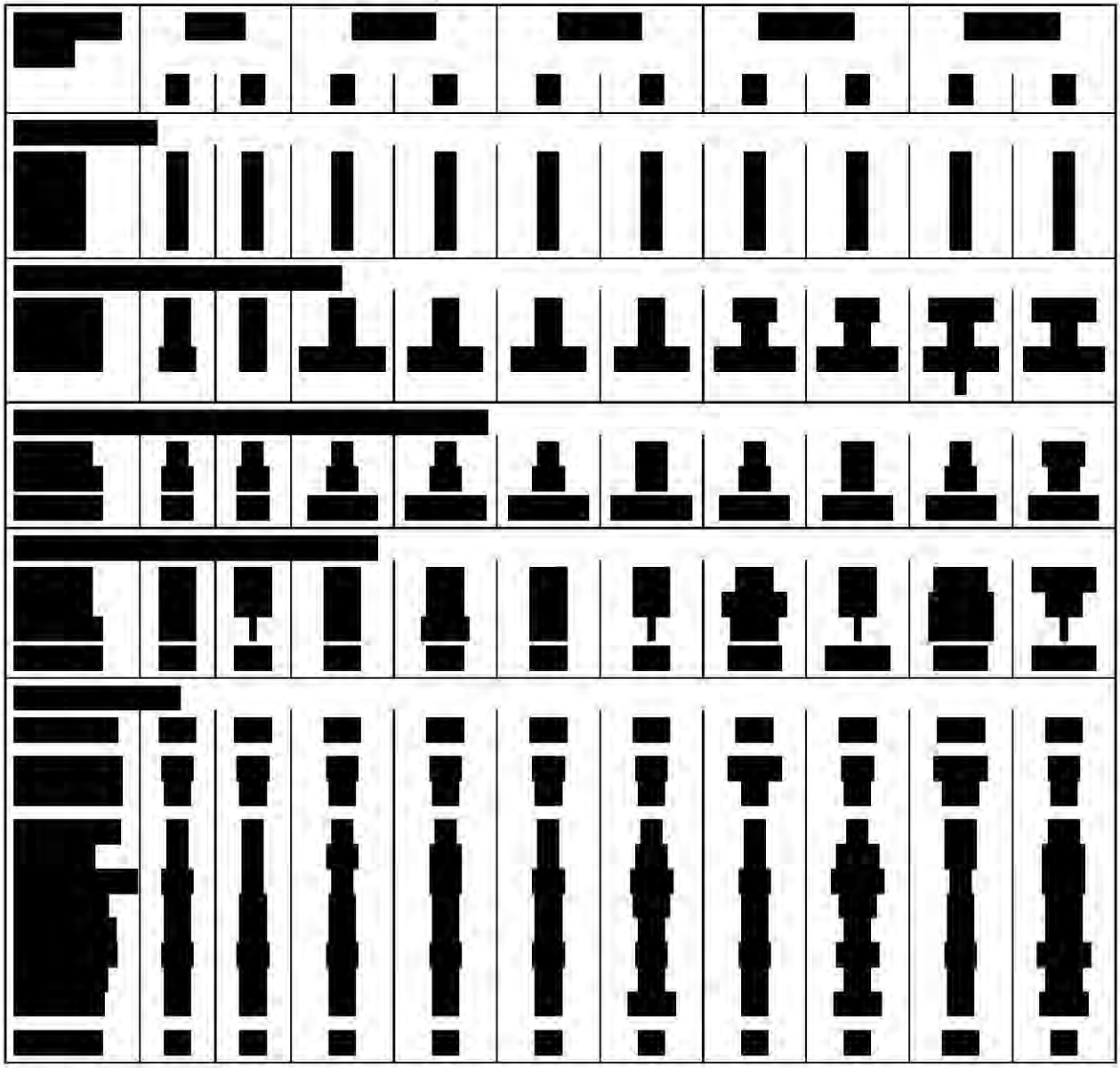
Section A6.4.1 **Subchronic oral toxicity test (90 days)** **Mouse**
Annex Point IIA VI.6.4.1 90-day dietary toxicity study in mice

	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*

Section A6.4.1	**Subchronic oral toxicity test (90 days)**	**Mouse**
Annex Point IIA VI.6.4.1	90-day dietary toxicity study in mice	

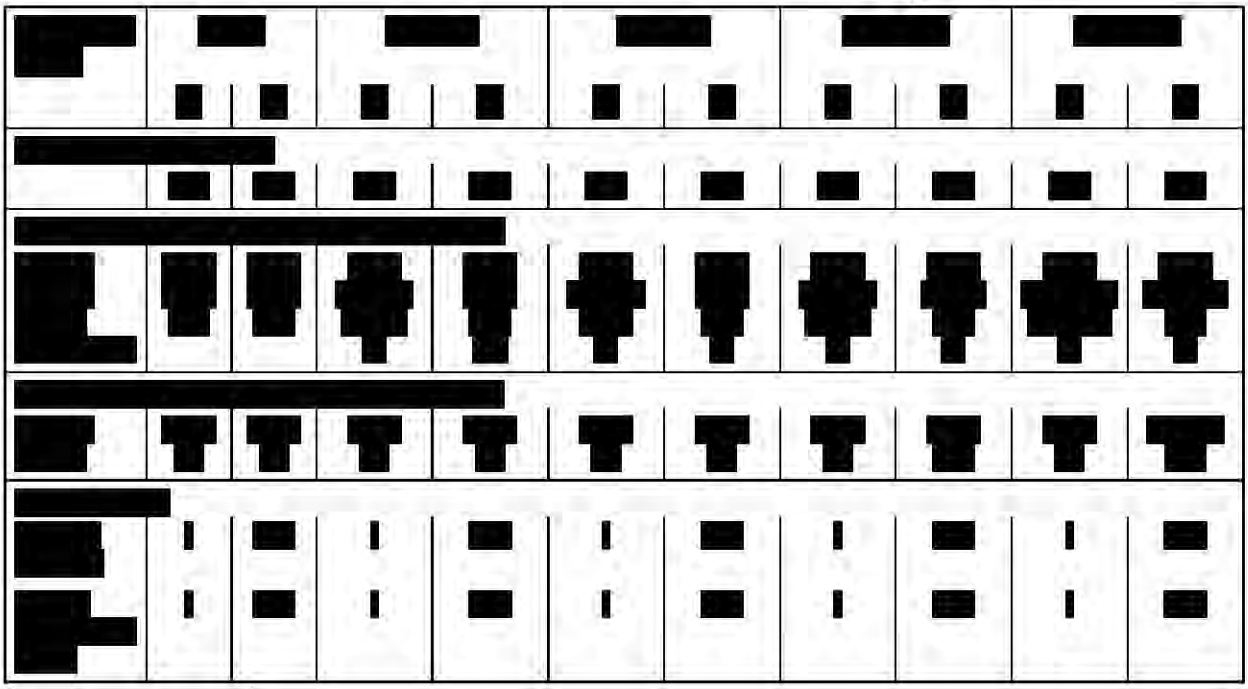
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

[redacted]



[redacted]

[redacted]



[redacted]

Section A6.5/6.7 **Carcinogenicity study (2-year)** **Rat**

Annex Point IIA VI.6.5 and 6.7/01 2-year dietary chronic toxicity/carcinogenicity study in rats

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1 REFERENCE

1.1	**Reference**	[redacted] (2000a); [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 the purpose of its first entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC B.33 (May 1988); Japan MAFF (59 NohSan no. 4200, 1985); EPA-FIFRA section 83-5; OECD no. 453 (1981) and EPA-OPPTS 870.4300 (June 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	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 albino rats per group [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	104 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None

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	

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	0 [redacted] 0, 8.1, 27.4, 82 and 157 mg/kg bw/day for males and 0, 9.7, 32.5, 97.8 and 193 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), [redacted]
3.4.1.2	Mortality	yes (twice daily)
3.4.2	Body weight	yes (weekly for the first 14 weeks, every 4 weeks thereafter)
3.4.3	Food consumption	yes (weekly for the first 13 weeks, every 4 weeks thereafter)
3.4.4	Water consumption	yes (interim sacrifice groups at weeks 12, 25 and 51)
3.4.5	Ophthalmoscopic examination	yes (all surviving animals at pre-test, prior to the interim and terminal sacrifice)
3.4.6	Haematology	yes, [redacted]
3.4.7	Clinical Chemisty	yes, [redacted]
3.4.8	Urinalysis	Yes [redacted]
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes ([redacted]

[redacted]

3.5.2 Gross and histopathology: Yes

[redacted]

3.5.3 Other examinations: -

3.5.4 Statistics

[redacted]

3.6 Further remarks

[redacted]

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs

[redacted]

4.1.2 Mortality

[redacted]

4.2 Body weight gain

[redacted]

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

[redacted]

4.3 Food/water consumption and compound intake

[redacted]

4.4 Ophtalmoscopic examination See 4.1.1

4.5 Blood analysis

4.5.1 Haematology [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 A6.5/6.7 **Carcinogenicity study (2-year)** **Rat**

Annex Point IIA VI.6.5 and 6.7/01 2-year dietary chronic toxicity/carcinogenicity study in rats

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Toxicity evaluation after chronic (2-year) dietary exposure of rats to TI-435; no relevant deviation from guidelines (87/302/EEC; Japan MAFF; EPA-FIFRA 83-5; OECD 453 and EPA-OPPTS 870.4300)

5.2 Results and discussion

[redacted]

5.3 Conclusion

Chronic treatment with up to 3000 ppm TI-435 for two years was tolerated well in rats and the high dose represented the MTD. Main effects of treatment were reduced food consumption and bw development leading to a better survival, and some histopathological changes in the stomach (slight irritation), kidney and ovaries (age-related, of dubious toxicological relevance).
Treatment with TI-435 did not result in any indication for a carcinogenic response.

5.3.1 LO(A)EL

[redacted]

5.3.2 NO(A)EL

NOAEL = 500 and 150 ppm for males and females, respectively, corresponding to 27.4 and 9.7 mg/kg bw/day for males and females, respectively

5.3.3 Other

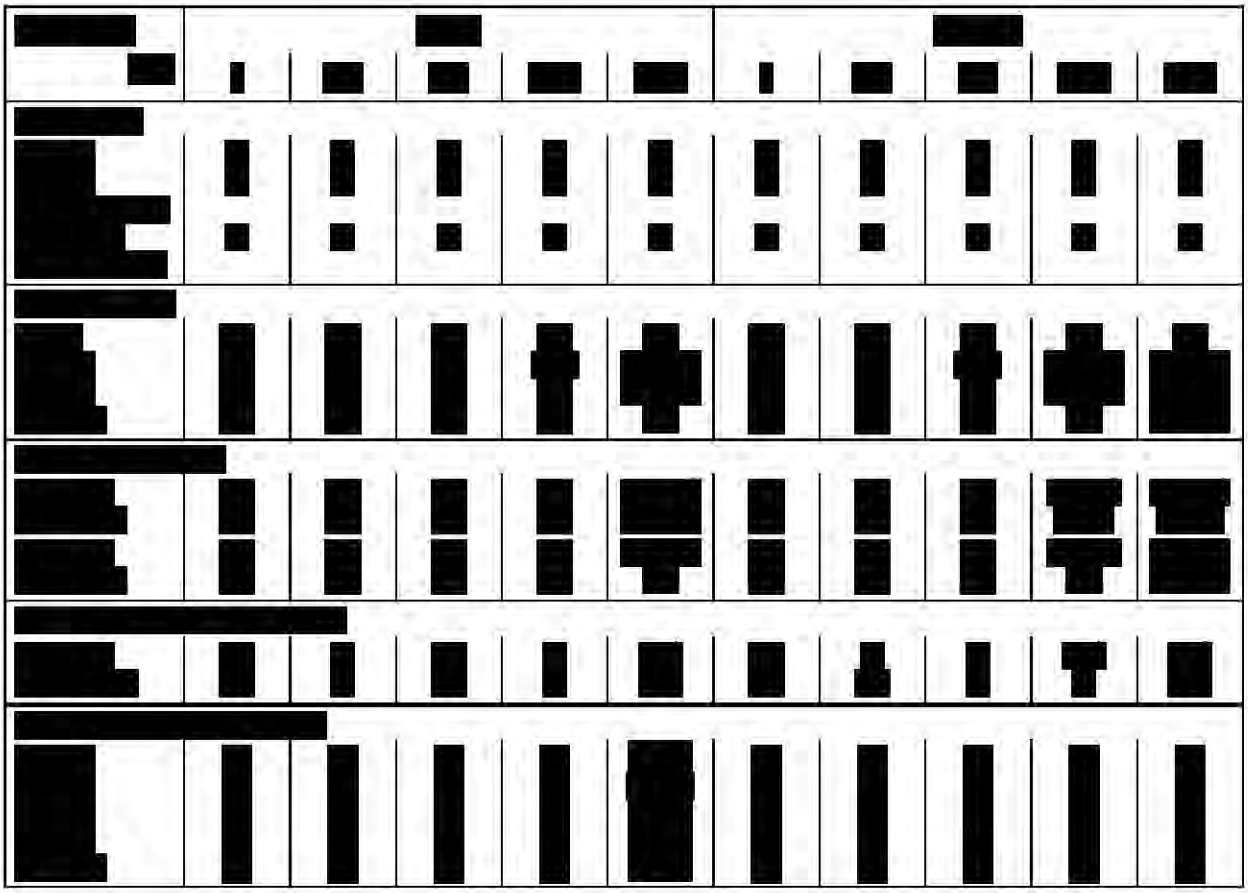
-

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

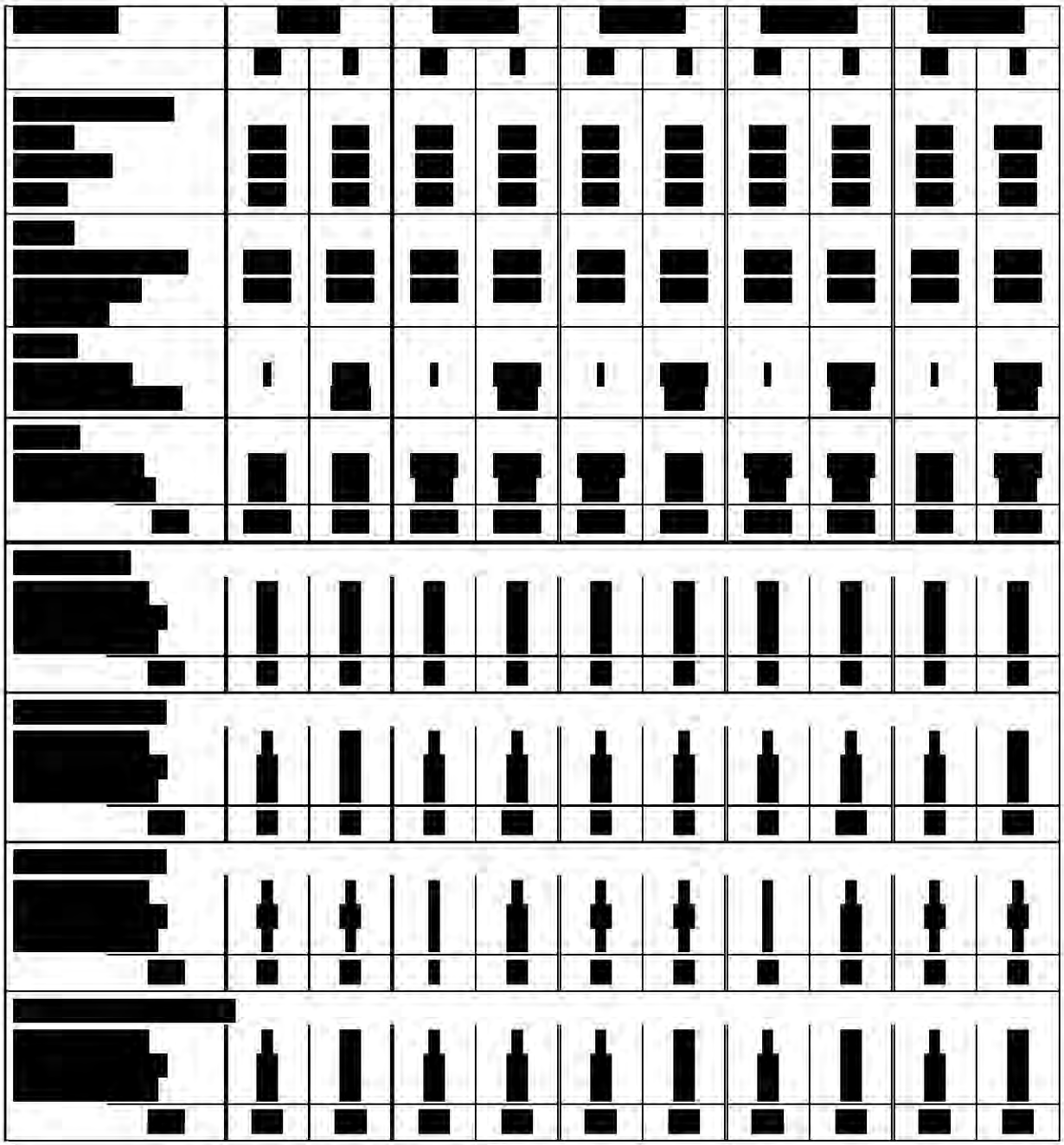
Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	[redacted]
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
	[redacted]
Reliability	[redacted]
Acceptability	[redacted]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



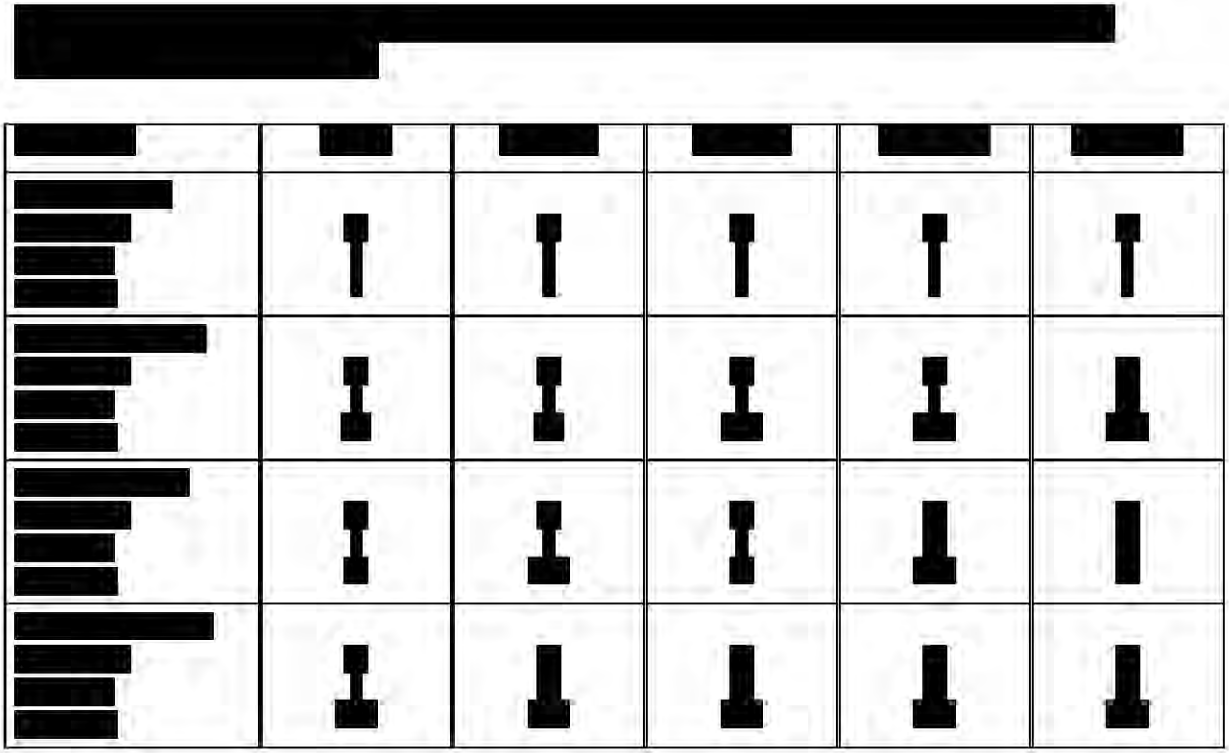
[redacted]

[redacted]



[redacted]

Evaluation by Rapporteur Member State, CA-Table



Section A6.6.1 Genotoxicity *In vitro* gene mutation in bacteria

Annex Point IIA VI.6.6.1/01

Ames test (+/- S9) using *S. typhimurium* and *E. coli*

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]. (2000); [redacted] 08.03.2000
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
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 (study was performed previous to current EU-guideline but was checked for compliance with the above)

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	Stable under conditions of this study (storage for 24 hours at RT)
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	*S. typhimurium*: TA 1535, TA 1537, TA 98, TA 100 *E. coli*: WP2 uvr A
3.2.2	Deficiencies / Proficiencies	Histidine deficient (*S. typhimurium*) Tryptophan deficient (*E. coli*)
3.2.3	Metabolic activation system	S9 mix Prepared from livers of male Sprague Dawley rats (bw about 200 g) treated with a single i.p. injection of 500 mg/kg bw Arochlor 1254 5 days prior to sacrifice.

Section A6.6.1 Genotoxicity *In vitro* gene mutation in bacteria

Annex Point IIA VI.6.6.1/01

Ames test (+/- S9) using *S. typhimurium* and *E. coli*

3.2.4	Positive control	In absence of S9: N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) at 2 µg/plate for WP2uvrA 3 µg/plate for TA 100 5 µg/plate for TA 1535 9-Aminoacridine (9AA) at 80 µg/plate for TA 1537 4-Nitroquinoline-1-oxide (4NQO) at 0.2 µg/plate for TA 98 In presence of S9: 2-Aminoantracene (2AA)at 1 µg/plate for TA 100 2 µg/plate for TA 1535 and TA 1537 10 µg/plate for WP2uvrA 0.5 µg/plate for TA 98
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	0, 50, 150, 500, 1500, 5000 µg/plate
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	None (plate incorporation assay)
3.3.4	Other modifications	-
3.4	**Examinations**	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	Non-entry field
4.1.1	without metabolic activation	[redacted]

Section A6.6.1	**Genotoxicity *In vitro* gene mutation in bacteria**
Annex Point IIA VI.6.6.1/01	Ames test (+/- S9) using *S. typhimurium* and *E. coli*

4.1.2	with metabolic activation	[redacted]
4.2	**Cytotoxicity**	No (no indications for growth inhibition)
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Evaluation of the in vitro gene mutation potential in *S. typhimurium* and *E. coli* strains; no relevant deviation from guidelines (2000/32/EC B13/14, OECD 471, EPA FIFRA 84-2, Japan Maff)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	Due to the (barely) positive response in TA 1535, a mutagenic potential might not be excluded for TI-435.
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	

Section A6.6.1 Genotoxicity *In vitro* gene mutation in bacteria

Annex Point IIA VI.6.6.1/01

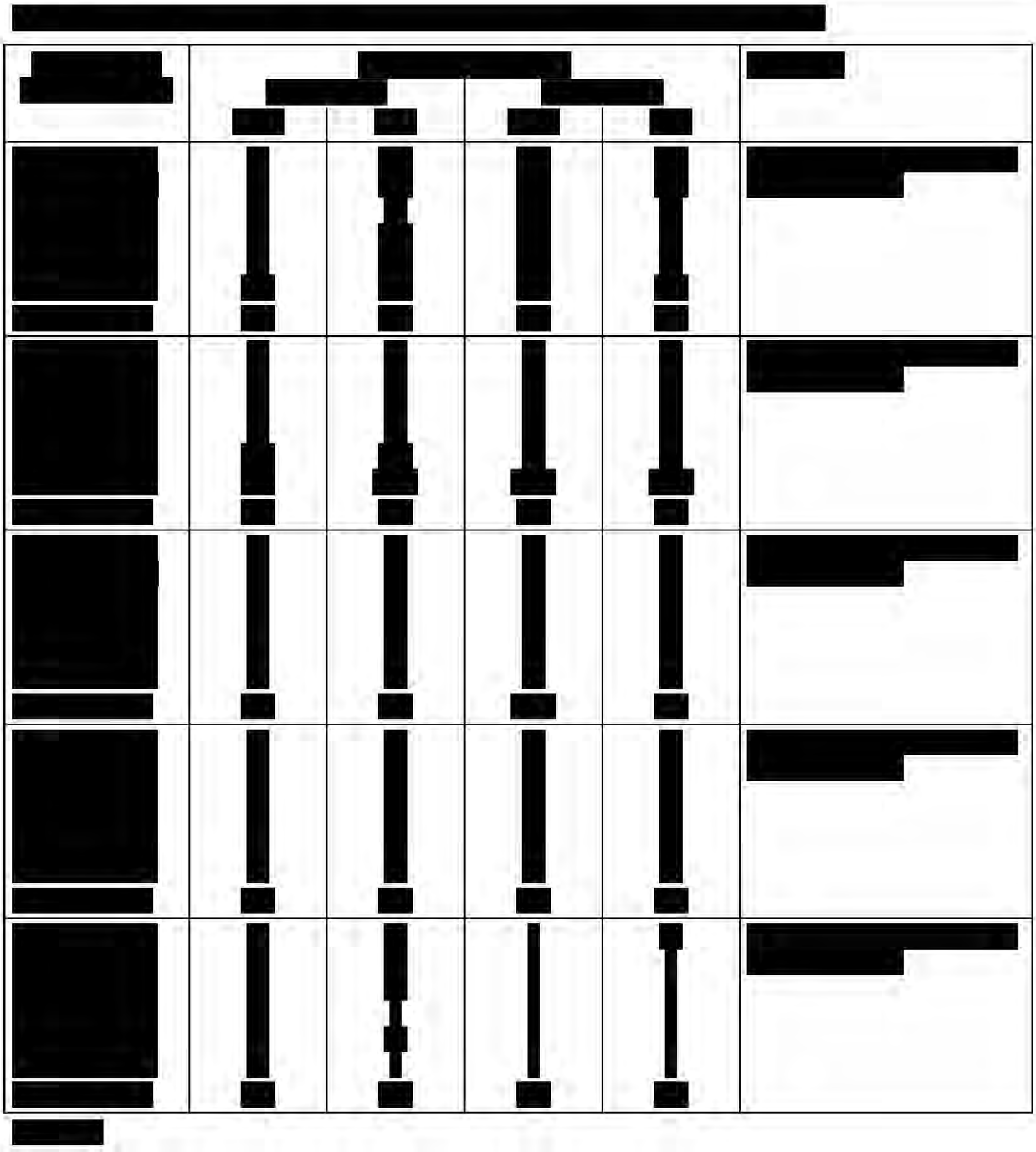
Ames test (+/- S9) using *S. typhimurium* and *E. coli*

	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 A6.6.1 **Genotoxicity *In vitro* gene mutation in bacteria**

Annex Point IIA
VI.6.6.1/01

Ames test (+/- S9) using *S. typhimurium* and *E. coli*



Section A6.6.1 Genotoxicity *In vitro* gene mutation in bacteria

Annex Point IIA VI.6.6.1/02

Ames test (+/- S9) using *S. typhimurium* and *E. coli*

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1990b [redacted], 23.04.1990
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**	[redacted]
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	White crystall
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stable under conditions of this study (tested; storage at RT in the dark)
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	*S. typhimurium*: TA 1535, TA 1537, TA 98, TA 100 *E. coli*: WP2 uvr A
3.2.2	Deficiencies / Proficiencies	Histidine deficient (*S. typhimurium*) Tryptophan deficient (*E. coli*)
3.2.3	Metabolic activation system	S9 mix Prepared from livers of 7 week old male Sprague Dawley, which were induced once with 30 mg/kg bw phenobarbital, three times with 60 mg/kg bw phenobarbital and once with 80 mg/kg bw 5,6-benzo-flavone by i.p. injection.

Section A6.6.1 Genotoxicity *In vitro* gene mutation in bacteria

Annex Point IIA VI.6.6.1/02 Ames test (+/- S9) using *S. typhimurium* and *E. coli*

3.2.4	Positive control	In absence of S9: 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2) at 0.01 µg/plate for TA 100 and WP2uvrA 0.1 µg/plate for TA 98 sodium azide (NaN_3) at 0.5 µg/plate for TA 1535 2-methoxy-6-chloro-9-[3-(2-chlrorethyl)-aminopropylamino]acridine ·2 HCl (ICR-191) at 1 µg/plate for TA 1537 In presence of S9: 2-Aminoantracene (2AA) at 1 µg/plate for TA 100 2 µg/plate for TA 1535 and TA 1537 20 µg/plate for WP2uvrA 0.5 µg/plate for TA 98
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	0, 100, 500, 1000, 2000, 5000 µg/plate (1st experiment) 0, 313, 625, 1250, 2500, 5000 µg/plate (2nd experiment)
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	None (plate incorporation assay)
3.3.4	Other modifications	-
3.4	**Examinations**	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No [redacted]
4.1.2	with metabolic activation	No [redacted]
4.2	**Cytotoxicity**	No (no indications for growth inhibition)

Section A6.6.1 **Genotoxicity *In vitro* gene mutation in bacteria**

Annex Point IIA VI.6.6.1/02 Ames test (+/- S9) using *S. typhimurium* and *E. coli*

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	TI-435 did not increase the number of revertant colonies in any strain at any concentration in presence or in absence of metabolic activation.
5.3	**Conclusion**	No mutagenic potential was detected for TI-435 in this test system. The barely positive response in the study by Thompson (2000) in strain TA 1535 could not be reproduced in this study also using similar concentrations. Therefore TI-435 is considered not to have a relevant potential for bacterial gene mutation.
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

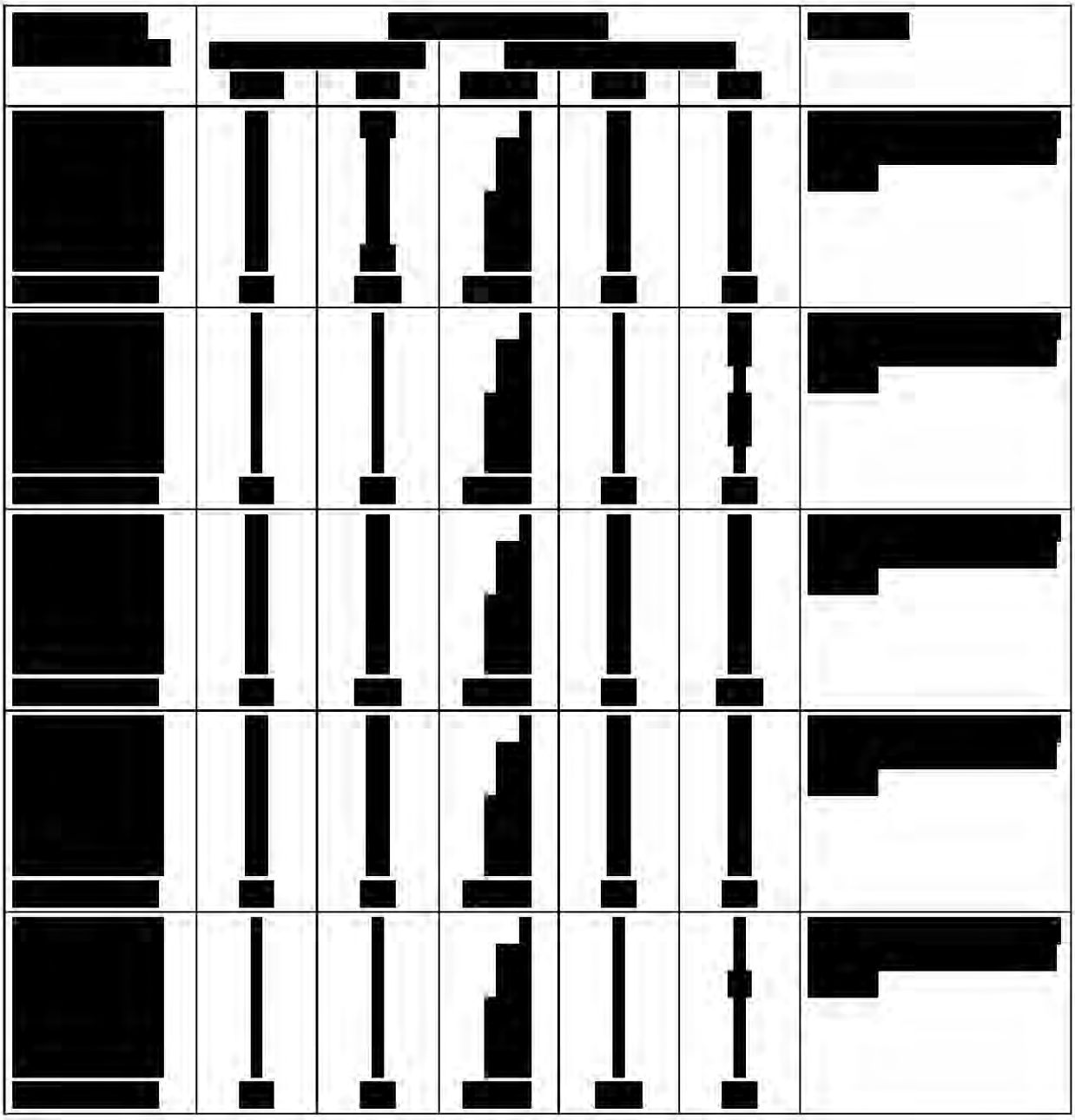
COMMENTS FROM ...

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	

Section A6.6.1 **Genotoxicity *In vitro* gene mutation in bacteria**

Annex Point IIA VI.6.6.1/02 Ames test (+/- S9) using *S. typhimurium* and *E. coli*

[redacted]



Section A6.6.1 **Genotoxicity *In vitro* gene mutation in bacteria**

Annex Point IIA VI.6.6.1/03 Ames test (+/- S9) using *S. typhimurium* and *E. coli*

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted]1999a); [redacted], 16.06.1999 ([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]
2.2	**GLP**	[redacted]
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	yellowish powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stable under conditions of this study (stability in solvent was tested)
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]

Section A6.6.1	**Genotoxicity *In vitro* gene mutation in bacteria**
Annex Point IIA VI.6.6.1/03	Ames test (+/- S9) using *S. typhimurium* and *E. coli*

3.2.4	Positive control	In absence of S9: 4-nitro-1,2-phenylenediamine (NP) at 0.5 µg/plate for TA 98 10 µg/plate for TA 1537 Nitrofurantoin (NF) at 0.2 µg/plate for TA 100 Cumene hydroperoxide (CH) at 50 µg/plate for TA 102 Sodium azide (SA) at 10 µg/plate for TA 1535 In presence of S9: 2-Aminoantracene (2AA) at 3 µg/plate for all strains
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	0, 16, 50, 158, 500, 1581 and 5000 µg/plate for experiments 1 (plate incorporation assay) and 2 (pre-incubation assay) 0, 16, 32, 48, 64, 80, 96 and 112 µg/plate for an additional 3rd experiment with TA 102 (pre-incubation assay)
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	None for the plate incorporation assay 20 min at 37°C for the 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	None of the observed results fulfilled the criteria of a positive response ([redacted]

Section A6.6.1		**Genotoxicity *In vitro* gene mutation in bacteria**
Annex Point IIA VI.6.6.1/03		Ames test (+/- S9) using *S. typhimurium* and *E. coli*
4.1.2	with metabolic activation	None of the observed results fulfilled the criteria of a positive response [redacted]
4.2	**Cytotoxicity**	Plate incorporation assay (experiment 1): no indication for inhibition of bacterial growth [redacted]
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Evaluation of the *in vitro* gene mutation potential in *S. typhimurium* strains; no relevant deviation from guidelines (2000/32/EC B13/14, OECD 471, EPA FIFRA 84-2, Japan Maff)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 did not induce gene mutations in this test system. The barely positive result in the study by Thompson (2000) in strain TA 1535 could not be reproduced in this study using similar concentrations of TI-435. Therefore no relevant potential for bacterial gene mutation is considered for TI-435.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities
[redacted]
[redacted] **Remarks**

Section A6.6.1 Genotoxicity *In vitro* gene mutation in bacteria

Annex Point IIA VI.6.6.1/03

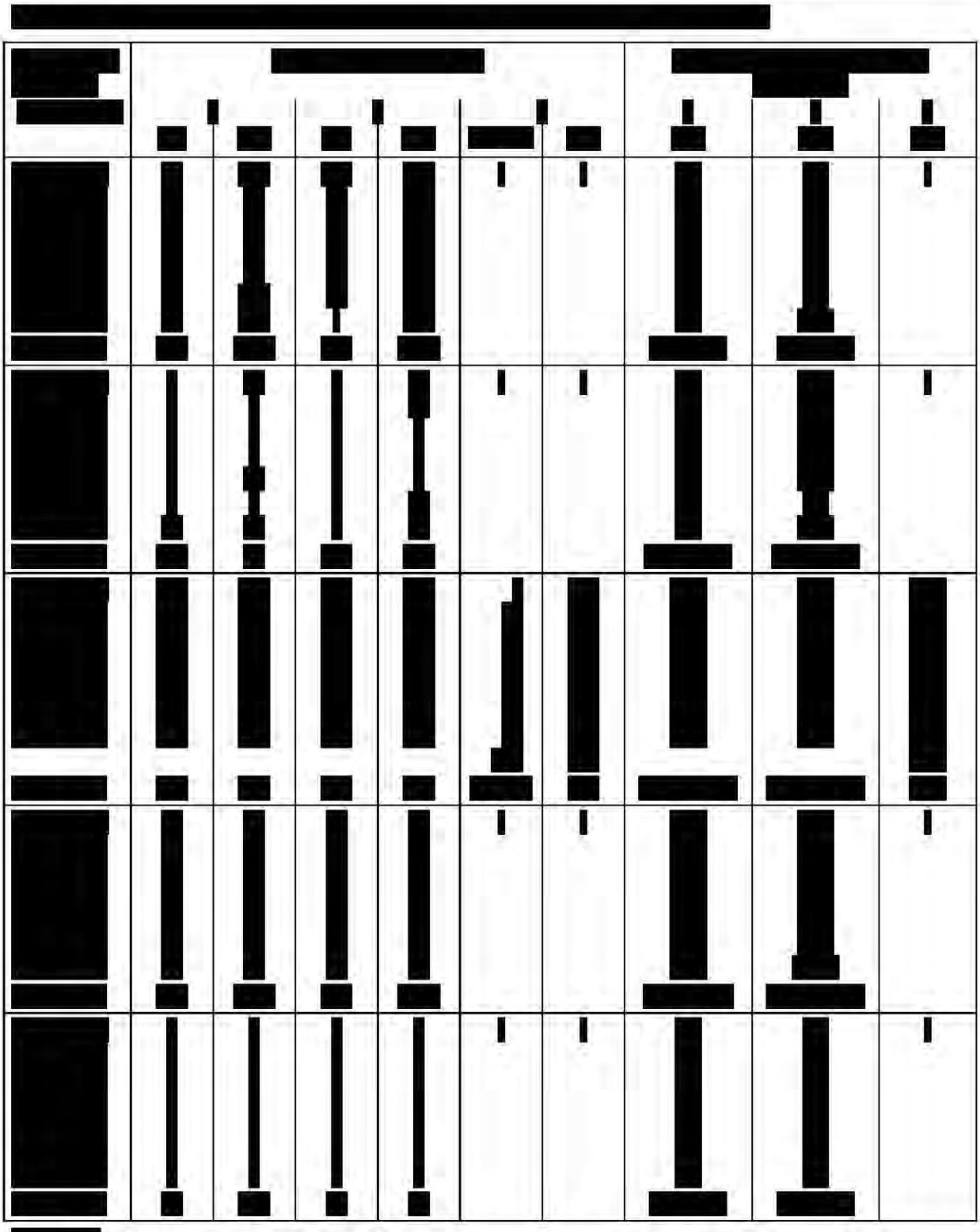
Ames test (+/- S9) using *S. typhimurium* and *E. coli*

	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 A6.6.1 **Genotoxicity *In vitro* gene mutation in bacteria**

Annex Point IIA
VI.6.6.1/03

Ames test (+/- S9) using *S. typhimurium* and *E. coli*



Section A6.6.1 Genotoxicity In vitro gene mutation in bacteria

Annex Point IIA VI.6.6.1/04 Ames test (+/- S9) using *S. typhimurium* TA 1535

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1999b); [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	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes [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	As given in section 2
3.1.2.1	Description	beige powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stable under conditions of this study (stability in solvent was tested)
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	*S. typhimurium* TA 1535

Section A6.6.1 **Genotoxicity In vitro gene mutation in bacteria**

Annex Point IIA VI.6.6.1/04 Ames test (+/- S9) using *S. typhimurium* TA 1535

3.2.2	Deficiencies / Proficiencies	Histidine deficient
3.2.3	Metabolic activation system	S9 mix [redacted]
3.2.4	Positive control	In absence of S9: Sodium azide (SA) at 10 µg/plate In presence of S9: 2-Aminoantracene (2AA) at 3 µg/plate
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	Plate incorporation assay (+/- S9): 0, 1000, 2000, 3000, 4000 and 5000 g/plate (batch NLL 6100-3) and 0, 3000, 5000 and 7000 µg/plate (batch 30034708) Pre-incubation assay (+/- S9): 0, 1000, 2000, 4000, 6000 and 8000 µg/plate (both batches)
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	None for the plate incorporation assay 20 min at 37°C for the pre-incubation assay
3.3.4	Other modifications	-
3.4	**Examinations**	[redacted]

4 RESULTS AND DISCUSSION

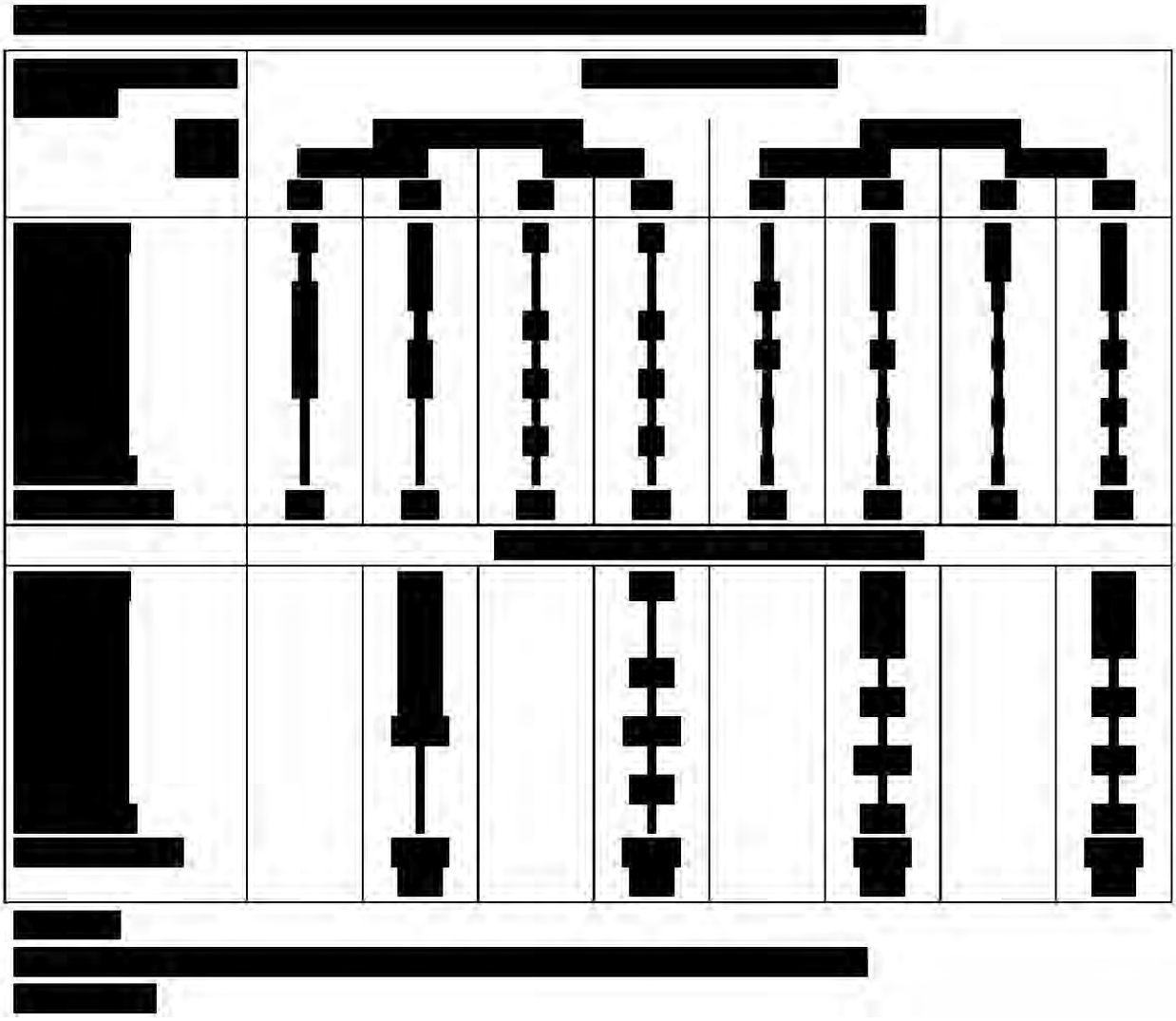
4.1	**Genotoxicity**	
4.1.1	without metabolic activation	[redacted]
4.1.2	with metabolic activation	[redacted]

Section A6.6.1		**Genotoxicity In vitro gene mutation in bacteria**
Annex Point IIA VI.6.6.1/04		Ames test (+/- S9) using *S. typhimurium* TA 1535
4.2	**Cytotoxicity**	Reduction in bacterial titres at ≥5000 µg/plate
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Evaluation of the *in vitro* gene mutation potential in *S. typhimurium* strain TA 1535; no relevant deviation from guidelines (2000/32/EC B13/14, OECD 471, EPA FIFRA 84-2, Japan Maff)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 did not induce gene mutations in this test system. The barely positive result in the study by Thompson (2000) in strain TA 1535 could not be reproduced in this study using the same and another batch of TI-435 and similar or higher concentrations of TI-435. Therefore no relevant potential for bacterial gene mutation is considered for TI-435.
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	2004-10-07
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 A6.6.1 **Genotoxicity In vitro gene mutation in bacteria**

Annex Point IIA VI.6.6.1/04 Ames test (+/- S9) using *S. typhimurium* TA 1535



Section A6.6.2 **Genotoxicity *In vitro* cytogenicity in mammalian cells**

Annex Point IIA VI.6.6.2/01 Chromosome aberration study in Chinese hamster lung cells

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2000) [redacted] 08.03.2000
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	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 2000/32/EC (successor of 92/69/EEC) B10, OECD no. 473 (1983), EPA FIFRA section 84-2 (1984), 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	Considered stable under conditions of this study
3.2	**Study Type**	*In Vitro* mammalian chromosome aberration test:
3.2.1	Organism/cell type	Chinese hamster lung (CHL) cells
3.2.2	Deficiencies / Proficiencies	-
3.2.3	Metabolic activation system	S9 mix [redacted]
3.2.4	Positive control	0.075, 0.05 and 0.025 µg/mL mitomycin C (MMC) was used in absence of metabolic activation for the 12, 24 and 48 hour harvests; 10 µg/mL cyclophosphamide (CP) was used as positive control in the experiments in presence of metabolic activation and for the 6 (18) hour harvest in absence of metabolic activation

3.3 Administration / Exposure; Application of test substance

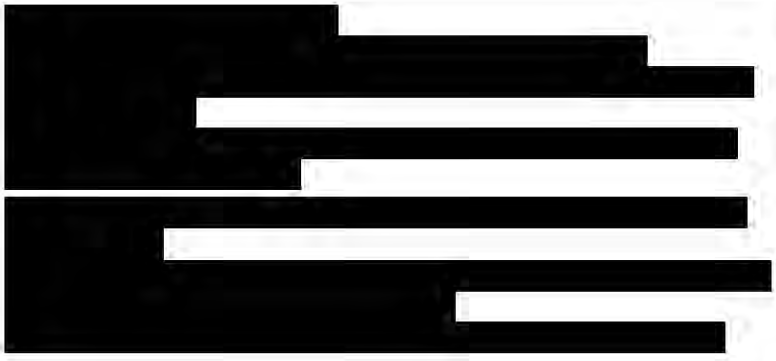
3.3.1 Concentrations

3.3.2 Way of application

3.3.3 Pre-incubation time -

3.3.4 Other modifications -

3.4 Examinations



Section A6.6.2 **Genotoxicity *In vitro* cytogenicity in mammalian cells**

Annex Point IIA VI.6.6.2/01 Chromosome aberration study in Chinese hamster lung cells

3.4.1	Number of cells evaluated	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	See also tables A6_6_2/01-1 and -2
4.1.1	without metabolic activation	[redacted]
4.1.2	with metabolic activation	[redacted]
4.2	**Cytotoxicity**	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Evaluation of the *in vitro* cytogenetic potential in mammalian cells; no relevant deviation from guidelines (2000/32/EC B10, OECD 473, EPA FIFRA 84-2, Japan MAFF)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 induced chromosome aberrations at cytotoxic concentrations *in vitro* in Chinese hamster lung cells. No relevant effect was detected at lower concentrations inducing less or no cytotoxicity.
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	[redacted]

Section A6.6.2 Genotoxicity *In vitro* cytogenicity in mammalian cells

Annex Point IIA VI.6.6.2/01

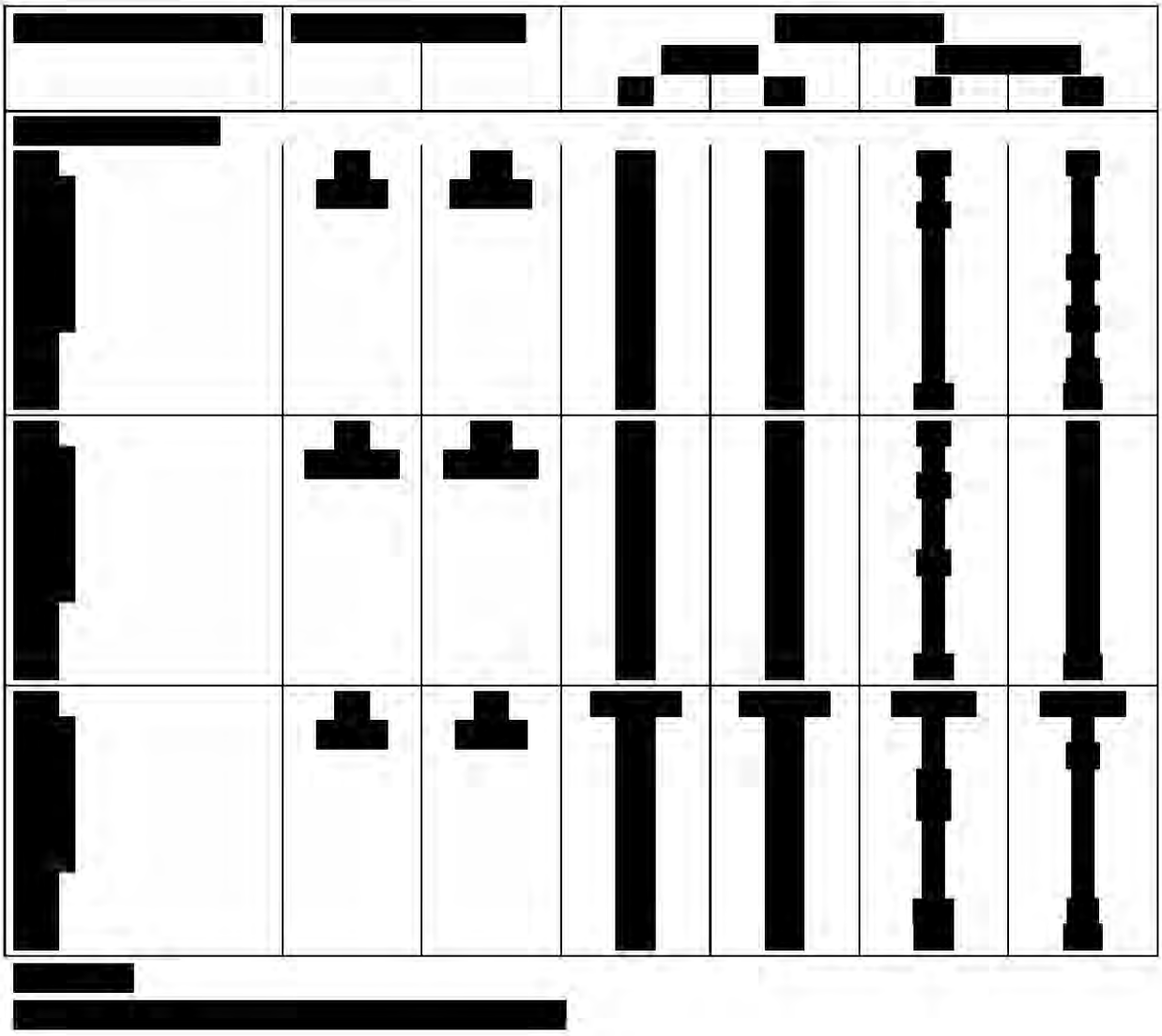
Chromosome aberration study in Chinese hamster lung cells

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

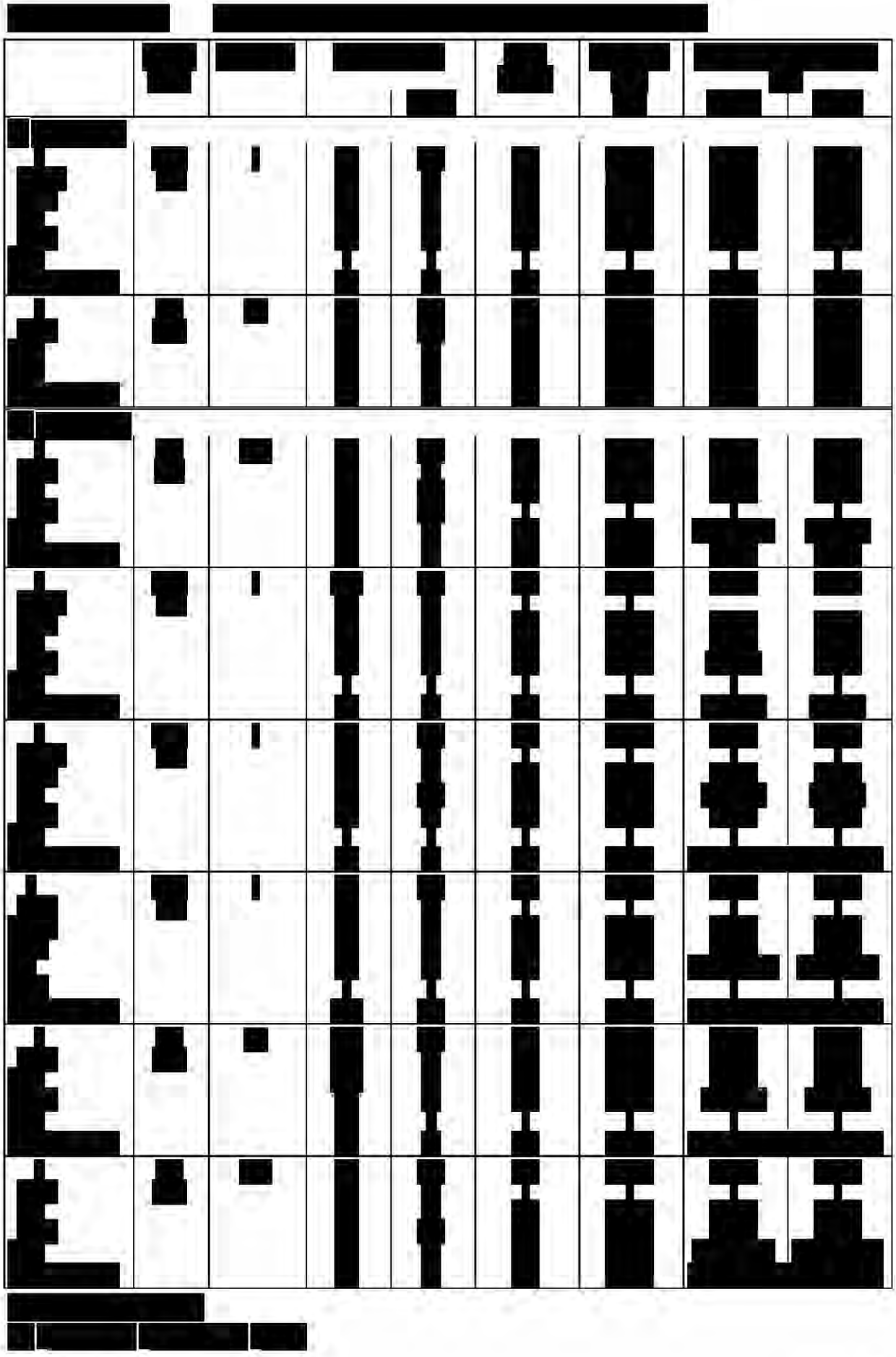
Section A6.6.2 **Genotoxicity *In vitro* cytogenicity in mammalian cells**

Annex Point IIA Chromosome aberration study in Chinese hamster lung cells
VI.6.6.2/01

[redacted]



[redacted]



Section A6.6.3 Genotoxicity *In vitro* gene mutation in mammalian cells

Annex Point IIA
VI.6.6.3/01

In vitro gene mutation in L5178Y mouse lymphoma cells

Official use only

1 REFERENCE

1.1	**Reference**	[redacted]. (2000a); [redacted] 08.03.2000
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 2000/32/EC B17 (successor of 87/303/EEC B14), OECD no. 476 (1984), EPA FIFRA section 84-2 (1984), Japan MAFF (59 NohSan no. 4200, 1985)
2.2	**GLP**	Yes
2.3	**Deviations**	No (study was performed previous to current EU-guideline but was checked for compliance with the above)

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	**Study Type**	*In vitro* mammalian cell gene mutation test
3.2.1	Organism/cell type	Mouse lymphoma L5178Y $TK^{+/-}$ cells
3.2.2	Deficiencies / Proficiencies	Thymidine kinase proficient (heterozygous)
3.2.3	Metabolic activation system	S9 mix [redacted]
3.2.4	Positive control	[redacted]

Section A6.6.3 Genotoxicity *In vitro* gene mutation in mammalian cells

Annex Point IIA VI.6.6.3/01 *In vitro* gene mutation in L5178Y mouse lymphoma cells

3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	[redacted]
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	Treatment time: 3 hours for all experiments Expression period: over night Selective growth: 10-14 days
3.3.4	Other modifications	-
3.4	**Examinations**	[redacted]

Section A6.6.3 **Genotoxicity *In vitro* gene mutation in mammalian cells**

Annex Point IIA VI.6.6.3/01 *In vitro* gene mutation in L5178Y mouse lymphoma cells

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	[redacted]
4.1.1	without metabolic activation	No There was no statistically significant nor dose-related increase in mutant frequencies in treated cells as compared to controls.
4.1.2	with metabolic activation	Yes [redacted]
4.2	**Cytotoxicity**	Yes [redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	*In vitro* evaluation of gene mutation in mammalian cells; no relevant deviation from test guidelines (2000/32/EC B17, OECD 476, EPA FIFRA 84-2, Japan MAFF)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 and/or metabolites increased the frequency of mutation at the TK +/- locus of the L5178Y cells indicating a mutagenic effect at cytotoxic dose levels in presence of S9. No positive response was detected in absence of S9.
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]

Section A6.6.3 Genotoxicity *In vitro* gene mutation in mammalian cells

Annex Point IIA VI.6.6.3/01

In vitro gene mutation in L5178Y mouse lymphoma cells

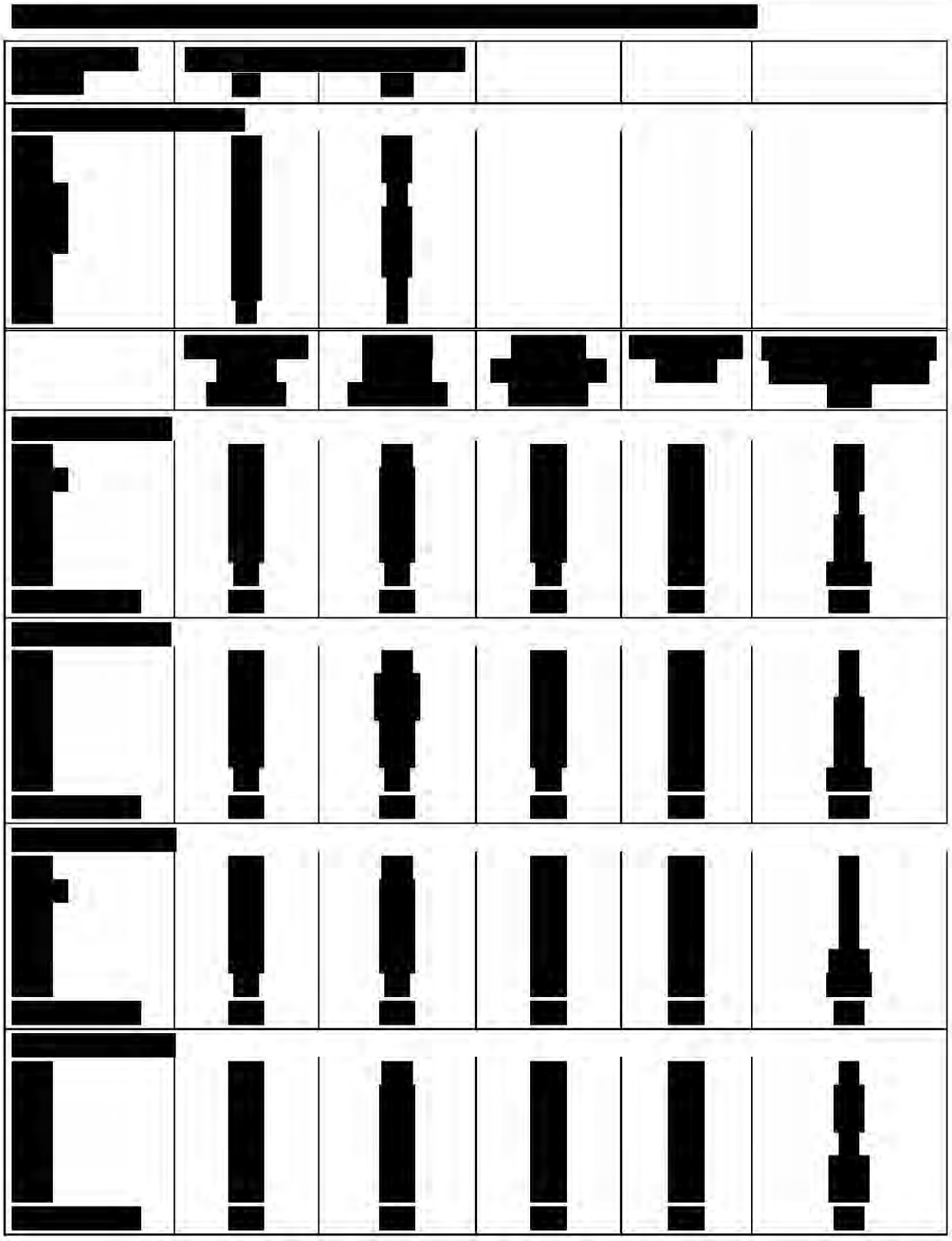
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

	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 A6.6.3 **Genotoxicity *In vitro* gene mutation in mammalian cells**

Annex Point IIA
VI.6.6.3/01

In vitro gene mutation in L5178Y mouse lymphoma cells



* $p < 0.05$

Section A6.6.3 Genotoxicity *In vitro* gene mutation in mammalian cells

Annex Point IIA VI.6.6.3/02

In vitro gene mutation in Chinese hamster lung V79 cells

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1999a); [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]
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	Beige powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study (stability in vehicle tested)
3.2	**Study Type**	*In vitro* mammalian cell gene mutation test
3.2.1	Organism/cell type	Chinese hamster lung V79 cells
3.2.2	Deficiencies / Proficiencies	Hypoxanthine-guanine phosphoribosyl transferase (HRPT) proficient
3.2.3	Metabolic activation system	S9 mix [redacted]
3.2.4	Positive control	[redacted]

Section A6.6.3 **Genotoxicity *In vitro* gene mutation in mammalian cells**

Annex Point IIA VI.6.6.3/02 *In vitro* gene mutation in Chinese hamster lung V79 cells

3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	Dose selection experiment: 0, 62.5, 125, 250, 500, 1000, 1250, 2000 and 2500 µg/mL Mutagenicity tests (two experiments): 0, 156, 313, 625, 1250, 2500 and 5000 µg/mL (+/- S9) 2500 µg/mL corresponds to about 10 mM of TI-435 (limit concentration).
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	-
3.3.4	Other modifications	-
3.4	**Examinations**	[redacted]

Section A6.6.3 **Genotoxicity *In vitro* gene mutation in mammalian cells**

Annex Point IIA VI.6.6.3/02 *In vitro* gene mutation in Chinese hamster lung V79 cells

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No [redacted]
4.1.2	with metabolic activation	No [redacted]
4.2	**Cytotoxicity**	Yes [redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	*In vitro* evaluation of gene mutation in mammalian cells; no relevant deviation from test guidelines (2000/32/EC B17, OECD 476, EPA FIFRA 84-2, Japan MAFF)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 and/or metabolites did not indicate any potential for mutagenic effects in this test. TI-435 was considered to be non-mutagenic.
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

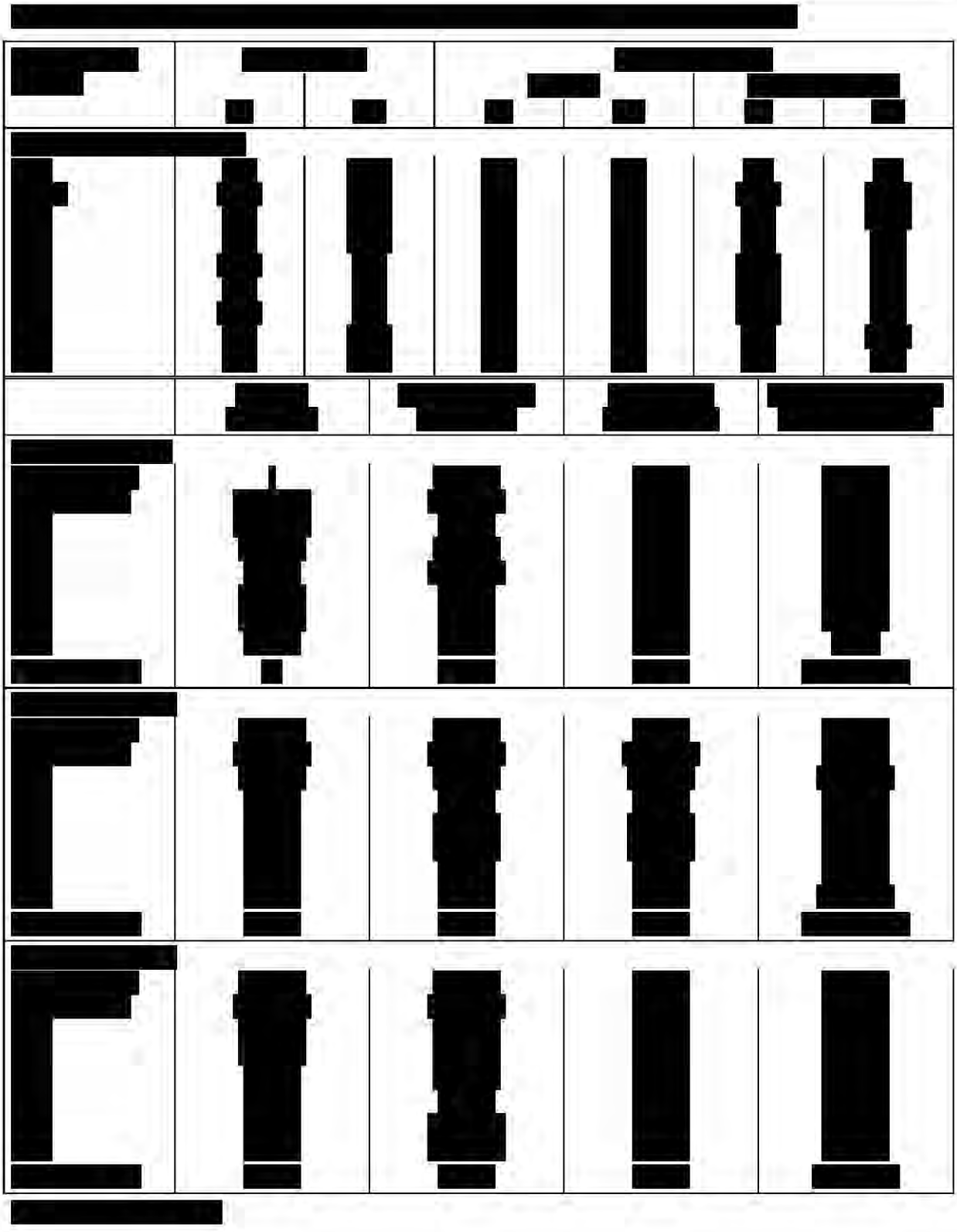
Section A6.6.3	**Genotoxicity *In vitro* gene mutation in mammalian cells**
Annex Point IIA VI.6.6.3/02	*In vitro* gene mutation in Chinese hamster lung V79 cells

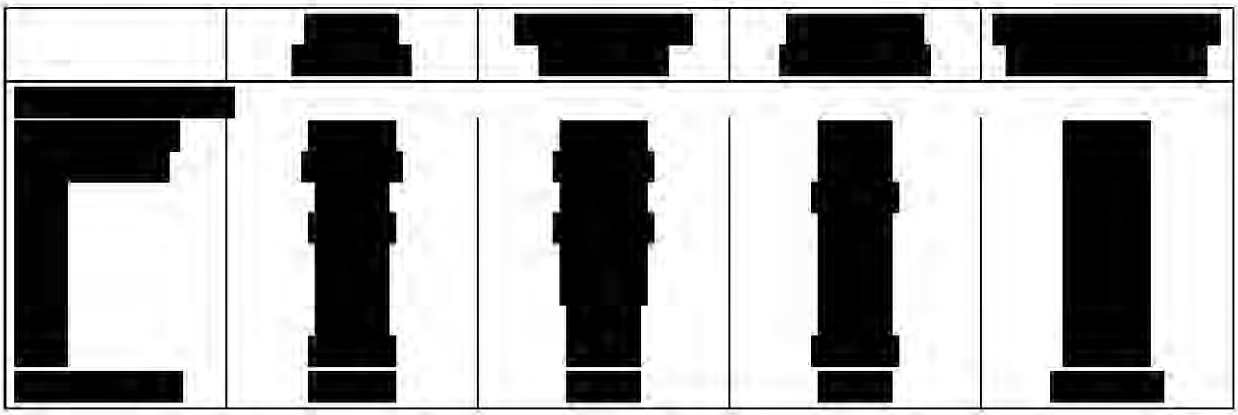
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating 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 A6.6.3 **Genotoxicity *In vitro* gene mutation in mammalian cells**

Annex Point IIA
VI.6.6.3/02

In vitro gene mutation in Chinese hamster lung V79 cells





Section A6.6.4 **Genotoxicity 1st *in vivo* mutagenicity study**

Annex Point IIA
VI.6.6.4/01

Mouse micronucleus test

Official use only

1 REFERENCE

1.1	**Reference**	(2000b); , 08.03.2000
1.2	**Data protection**	Yes
1.2.1	Data owner	
1.2.2	Companies with letter of access	
1.2.3	Criteria for data protection	

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 2000/32/EC (successor of 92/69/EEC) B12, OECD guideline no. 474 (1983), EPA section 84-2 (1984), Japan MAFF, 59 NohSan no. 4200 (1985)
2.2	**GLP**	Yes
2.3	**Deviations**	No (study was performed previous to current EU-guideline but was checked for compliance with the above)

3 MATERIALS AND METHODS

3.1	**Test material**	
3.1.1	Lot/Batch number	
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Pale yellow powder
3.1.2.2	Purity	
3.1.2.3	Stability	
3.1.2.4	Maximum tolerable dose	
3.2	**Test Animals**	male and female albino mice per group (CD-1 strain, including a positive and negative (vehicle) control group
3.3	**Administration/ Exposure**	Oral
3.3.1	Number of applications	1
3.3.2	Interval between applications	-

Section A6.6.4 **Genotoxicity 1st *in vivo* mutagenicity study**

Annex Point IIA VI.6.6.4/01 Mouse micronucleus test

3.3.3	Postexposure period	24, 48, and 72 h after treatment
		Oral
3.3.4	Type	gavage
3.3.5	Concentration	0, 25, 50 and 100 mg/kg bw
3.3.6	Vehicle	[redacted]
3.3.7	Concentration in vehicle	[redacted]
3.3.8	Total volume applied	[redacted]
3.3.9	Controls	Negative control: vehicle Positive control: 50 mg/kg bw cyclophosphamide (CP) in distilled water (sacrifice 24 hours after application)
3.4	**Examinations**	
3.4.1	Clinical signs	Yes
3.4.2	Tissue	bone marrow
	Number of animals:	[redacted]
	Number of cells:	[redacted]
	Time points:	[redacted]
	Type of cells	[redacted]
	Parameters:	[redacted]
3.5	**Further remarks**	-

4 RESULTS AND DISCUSSION

4.1 Clinical signs [redacted]

4.2 Haematology / Tissue examination [redacted]

4.3 Genotoxicity No [redacted]

Section A6.6.4	**Genotoxicity 1st *in vivo* mutagenicity study**
Annex Point IIA VI.6.6.4/01	Mouse micronucleus test

4.4	**Other**	The number of PCE with micronuclei were significantly increased in the positive controls.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Genotoxicity evaluation *in vivo* in the bone marrow of mice after a single oral application o TI-435; no relevant deviations from guidelines (2000/32/EC B12, OECD 474, EPA 84-2, Japan MAFF)
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	TI-435 was not genotoxic in this *in vivo* test system.
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	[redacted]

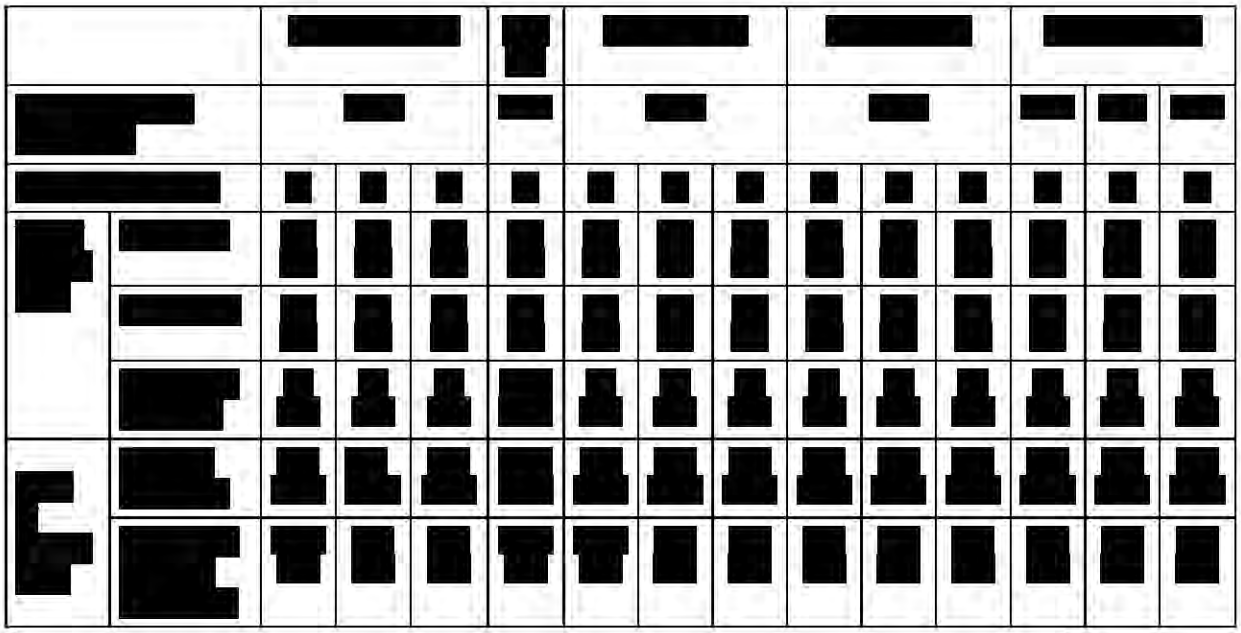
Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[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 A6.6.4 **Genotoxicity** **1st *in vivo* mutagenicity study**

Annex Point IIA
VI.6.6.4/01

Mouse micronucleus test

[redacted]



[redacted]

Section A6.6.5 **Genotoxicity 2nd *in vivo* mutagenicity study**

Annex Point IIA
VI.6.6.5/01

UDS *in vivo* in rats (hepatocytes)

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1 REFERENCE

1.1	**Reference**	[redacted] (1999b); [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 2000/32/EC B.39 (successor of 88/302/EEC), OECD 486
2.2	**GLP**	[redacted]
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	yellow powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Considered stable under conditions of this study
3.1.2.4	Maximum tolerable dose	[redacted]
3.2	**Test Animals**	[redacted] male young adult (10–14 week old) Wistar rats (Crl: (WI) BR strain, [redacted]
3.3	**Administration/ Exposure**	Oral
3.3.1	Number of applications	1
3.3.2	Interval between applications	-

Section A6.6.5 **Genotoxicity 2nd *in vivo* mutagenicity study**

Annex Point IIA VI.6.6.5/01 UDS *in vivo* in rats (hepatocytes)

3.3.3	Postexposure period	4, 16 h after treatment
		Oral
3.3.4	Type	Gavage
3.3.5	Concentration	0, 2500 and 5000 mg/kg bw
3.3.6	Vehicle	0.5% aqueous Cremophor
3.3.7	Concentration in vehicle	-
3.3.8	Total volume applied	[redacted]
3.3.9	Controls	[redacted]
3.4	**Examinations**	
3.4.1	Clinical signs	Yes
3.4.2	Tissue	liver
		Number of animals: [redacted]
		Number of cells: [redacted]
		Time points: [redacted]
		Type of cells [redacted]
		Parameters: [redacted]
3.5	**Further remarks**	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	[redacted]
4.2	**Haematology / Tissue examination**	[redacted]

Section A6.6.5	**Genotoxicity 2nd *in vivo* mutagenicity study**
Annex Point IIA VI.6.6.5/01	UDS *in vivo* in rats (hepatocytes)

4.3	**Genotoxicity**	No [redacted]
4.4	**Other**	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Genotoxicity evaluation (DNA repair activity) after single oral application of TI-435 in rats (hepatoytes); no relevant deviation to guidelines (2000/32/EC B.39, OECD 486)
5.2	**Results and discussion**	[redacted] DNA synthesis in rat hepatocytes following *in vivo* exposure.
5.3	**Conclusion**	TI-435 did not indicate any genotoxic potential *in vivo*.
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	

Section A6.6.5 **Genotoxicity 2nd *in vivo* mutagenicity study**

Annex Point IIA
VI.6.6.5/01 UDS *in vivo* in rats (hepatocytes)

	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 A6.5/6.7 Carcinogenicity study (2-year) Rat

Annex Point IIA VI.6.5 and 6.7/01 2-year dietary chronic toxicity/carcinogenicity study in rats

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1 REFERENCE

1.1	**Reference**	[redacted] (2000a); [redacted] 11.04.2000
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 B.33 (May 1988); Japan MAFF (59 NohSan no. 4200, 1985); EPA-FIFRA section 83-5; OECD no. 453 (1981) and EPA-OPPTS 870.4300 (June 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 of the compound and its homogeneity and stability in food were tested).
3.2	**Test Animals**	[redacted] male and [redacted] female albino rats per group (Crl:CD(SD)BR [redacted]
3.3	**Administration/ Exposure**	Oral (dietary)
3.3.1	Duration of treatment	104 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None

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

3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	0 [redacted] 0, 8.1, 27.4, 82 and 157 mg/kg bw/day for males and 0, 9.7, 32.5, 97.8 and 193 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), [redacted]
3.4.1.2	Mortality	yes (twice daily)
3.4.2	Body weight	yes [redacted]
3.4.3	Food consumption	yes [redacted]
3.4.4	Water consumption	yes [redacted]
3.4.5	Ophthalmoscopic examination	yes [redacted]
3.4.6	Haematology	yes, [redacted]
3.4.7	Clinical Chemisty	yes, [redacted]
3.4.8	Urinalysis	Yes [redacted]
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes [redacted]

[redacted]

3.5.2 Gross and histopathology: Yes [redacted]

3.5.3 Other examinations: -

3.5.4 Statistics: Body weights, bw changes, food consumption, food efficiency, organ weights, organ-body weight ratios and organ-brain weight ratios: one-way analysis of variance (ANOVA).
Levene's test was performed to test for heterogeneity, and, where appropriate, transformations were performed to stabilise the variances. ANOVA was then performed on the transformed data.
If ANOVA was significant, Dunnett's multiple comparison t-test was used for pairwise comparisons between treated and control groups.
Survival data. log-rank test at the 5%, two-tailed probability level for group comparisons.
Dose-response relationship of mortality: logistic regression method at the 5% one-tailed probability level.
Fatal, non-fatal and incidental tumours: Peto's mortality-prevalence test.

3.6 Further remarks [redacted]

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs [redacted]

4.1.2 Mortality [redacted]

4.2 Body weight gain [redacted]

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

[redacted]

4.3 Food/water consumption and compound intake

[redacted]

4.4 Ophtalmoscopic examination

[redacted]

4.5 Blood analysis

4.5.1 Haematology

[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 A6.5/6.7 **Carcinogenicity study (2-year) Rat**

Annex Point IIA VI.6.5 and 6.7/01 2-year dietary chronic toxicity/carcinogenicity study in rats

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Toxicity evaluation after chronic (2-year) dietary exposure of rats to TI-435; no relevant deviation from guidelines (87/302/EEC; Japan MAFF; EPA-FIFRA 83-5; OECD 453 and EPA-OPPTS 870.4300)

5.2 Results and discussion

[redacted]

5.3 Conclusion

Chronic treatment with up to 3000 ppm TI-435 for two years was tolerated well in rats and the high dose represented the MTD. Main effects of treatment were reduced food consumption and bw development leading to a better survival, and some histopathological changes in the stomach (slight irritation), kidney and ovaries (age-related, of dubious toxicological relevance).
Treatment with TI-435 did not result in any indication for a carcinogenic response.

5.3.1 LO(A)EL

LC[redacted]

5.3.2 NO(A)EL

NOAEL = 500 and 150 ppm for males and females, respectively, corresponding to 27.4 and 9.7 mg/kg bw/day for males and females, respectively

5.3.3 Other

-