Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		Low dose 100 mg/kg	medium dose 300 mg/kg	high dose 1000 mg/kg	dose-response + / -
	historical	study				
Corpora lutea *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	
Implantations *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	
Resorptions *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	
total number of fetuses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
pre-implantation loss *state %*						
post-implantation loss *state %*						
total number of litters		[redacted]	[redacted]	[redacted]	[redacted]	
fetuses / litter		[redacted]	[redacted]	[redacted]	[redacted]	
live fetuses / litter *state ratio*		[redacted]	[redacted]	[redacted]	[redacted]	
dead fetuses / litter *state ratio*		[redacted]	[redacted]	[redacted]	[redacted]	
fetus weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
placenta weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
crown-rump length (mean) *[mm]*		[redacted]	[redacted]	[redacted]	[redacted]	
Fetal sex ratio *[state ratio m/f]*		[redacted]	[redacted]	[redacted]	[redacted]	

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	Control data		Low dose 100 mg/kg	medium dose 300 mg/kg	high dose 1000 mg/kg	dose-response + / -
	Historical	study				
External malformations[*1] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
External anomalies[*] *[%]*						
Skeletal malformations[*2] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Skeletal anomalies[*] *[%]*						
Skeletal variants[*] *[%] minor deviations*		[redacted]	[redacted]	[redacted]	[redacted]	
Visceral malformations[*3] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Visceral anomalies[*] *[%]*						
Variants visceral[*] *[%]*						

*1: Control group: [redacted]

*2: Control group: [redacted]

*3: Control group: [redacted]

Section A6.8.1(04) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1995**, Limit test for embryotoxicity (including teratogenicity) with HWG 1608 technical (Tebuconazole) in the **rat** (dermal application)

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1 REFERENCE

1.1	**Reference**	[redacted], 1995, Limit test for embryotoxicity (including teratogenicity) with HWG 1608 technical (c.n. Tebuconazole) in the rat (dermal application), [redacted], Report No: [redacted], 1995-04-07 (unpublished).
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. OECD guidelines 414 "Teratogenicity" and EPA 83-3 "Teratogenicity Study".
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608 Technical (Tebuconazole)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	
3.1.2.1	Description	Colourless-beige powder
3.1.2.2	Purity	[redacted] active substance (TOX 3175-00) or [redacted] active substance (TOX 3175-01). The dose level was **not** adjusted to the content of active ingredient – **Only one batch number. Sic!!**
3.1.2.3	Stability	Approved until 10.08.1992 (room temperature in the dark). Stability in the vehicle – at least 6 hours.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	WIST HanIbm (SPF)
3.2.3	Source	[redacted]
3.2.4	Sex	Mated females
3.2.5	Age/weight at study initiation	Minimum 11 weeks/ 178-218 g
3.2.6	Number of animals per group	25

Section A6.8.1(04)	Teratogenicity Study
Annex Point IIA6.8.1	[redacted], **1995**, Limit test for embryotoxicity (including teratogenicity) with HWG 1608 technical (Tebuconazole) in the **rat** (dermal application)

3.2.7	Control animals	Yes
3.2.8	Mating period	Until spermatozoa in vaginal smear or a vaginal plug had been observed
3.3	**Administration/ Exposure**	Dermal application
3.3.1	Duration of exposure	Rat: day 6-15 post mating
3.3.2	Postexposure period	Day 16 to day 21 post mating
		Dermal
3.3.3	Type	Applied to shaved skin with occlusive dressing for six hours once daily
3.3.4	Concentration	0 or 1000 mg/kg bw
3.3.5	Vehicle	Suspended in a 1% aqueous Cremophor EL emulsion
3.3.6	Concentration in vehicle	Tried to use a concentration of 80 % w/v but this turned out to be too viscous within very short time, so instead a concentration of 40 % w/v was used after 1 (5 rats) or 2 days (7 rats). For the rest of the group the concentration had been 40 % w/v from the start of dosing.
3.3.7	Total volume applied	After a short period (see above and just below) 2.5 ml/kg bw/day (nine vehicle control animals received 1.25 ml/kg bw on days 1, 2 and 3, another nine on days 1 and 2, and 5 vehicle control animals received the 1.25 ml/kg bw on the very first day of dosing).
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes – daily
3.4.2	Food consumption	Yes, day 0-6, day 6-11, day 11-16 and day 16-21
3.4.3	Clinical signs	Yes – at least twice daily – including local skin reaction on the application site.
3.4.4	Examination of uterine content	Gravid uterine weight – yes Number of corpora lutea – yes Number of implantations – yes
3.4.4.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight, and Sex Ratio
3.4.4.2	Skeleton	Yes
3.4.4.3	Soft tissue	Yes
3.5	**Further remarks**	

Section A6.8.1(04)

Annex Point IIA6.8.1

Teratogenicity Study

[redacted], **1995**, Limit test for embryotoxicity (including teratogenicity) with HWG 1608 technical (Tebuconazole) in the **rat** (dermal application)

4 RESULTS AND DISCUSSION

4.1	**Maternal toxic Effects**	Persistent skin irritation was noted in 9 dosed females (very slight to moderate/severe erythema) and only in 4 females from the control group (slight scaling and very slight erythema). No other differences were noted between dosed females and controls.
4.2	**Teratogenic / embryotoxic effects**	No effects
4.3	**Other effects**	No other effects have been seen

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In accordance with OECD guideline 414 "Teratogenicity" and EPA Guideline 83-3, "Teratology Study" and OECD Principles of Good Laboratory Practice were 2 groups of 25 mated female Wistar rats applied daily doses of 0, or 1000 mg/kg [redacted] pure HWG 1608 on days 6 to 15 of gestation. The substance (dose level not adjusted to the content of active ingredient) was suspended in 1 % aqueous Cremophor EL emulsion which was applied evenly to the shorn skin of the backs and were held in position using occlusive bandage. Six hours after the application the bandage was removed and the skin was rinsed with lukewarm tap water. The animals were inspected at least twice daily for mortality, systemic clinical signs, changed appearance and behaviour. The animals were weighed daily and food consumption was recorded at regular intervals. On day 21of gestation the animals were sacrificed and caesarean sections were performed. The following examinations were performed: Gross macroscopic findings on dams, determination of implantation sites, number of corpora lutea and of uterus weight. Determination of number of live and dead foetuses or embryos, determination of the sex and weight of each live foetus, and recording of number of runts, determination of individual placenta weights. Examination of all foetuses for external malformations, a number of the foetuses for visceral malformations (modified Wilson's method) and the rest of the foetuses for bone alterations (alizarin red S stained).
5.2	**Results and discussion**	Only the local skin irritation on the treated area was more common and more severe in females treated with the active substance than in control animals treated with vehicle only (statistically significant). No other effects were seen in this study on any of the parameters studied.
5.3	**Conclusion**	HWG 1608 showed no embryotoxicity or teratogenicity toxicity in this "limit test" in rats using only 2 dose groups – controls and (high) dose (1000 mg/kg bw) treated animals. The daily administration of the test substance to the skin of rats on days 6-15 of gestation resulted in severe skin irritation in 9 treated animals while only 4 control animals had skin irritation at all and not as severe.
5.3.1	LO(A)EL maternal toxic effects	1000 mg/kg bw due to severe skin irritation at the application site.
5.3.2	NO(A)EL maternal toxic effects	Not found

Section A6.8.1(04) **Annex Point IIA6.8.1**		**Teratogenicity Study** [redacted], **1995**, Limit test for embryotoxicity (including teratogenicity) with HWG 1608 technical (Tebuconazole) in the **rat** (dermal application)
5.3.3	LO(A)EL embryotoxic / teratogenic effects	No effects were seen
5.3.4	NO(A)EL embryotoxic / teratogenic effects	1000 mg/kg bw.
5.3.5	Reliability	[redacted]
5.3.6	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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose 1000 mg/kg	dose-response + / -
	historical 1987-91 dermal	study				
Number of dams examined	**125**	**24**			**25**	
Clinical findings during application of test substance skin reactions		[redacted]			[redacted]	
Mortality of dams *state %*		[redacted]			[redacted]	
Abortions		[redacted]			[redacted]	
Body weight gain *day 0-end of test,*		[redacted]			[redacted]	
Food consumption *Day0-6, day 6-11, day11-16, day16-21*		[redacted]			[redacted]	
Water consumption *if test substance is applied with drinking water*						
Pregnancies *pregnancy rate or %*		[redacted]			[redacted]	
Necropsy findings in dams dead before end of test						

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	High dose 1000 mg/kg	dose-response + / -
	historical 1987-91 dermal	Study				
Corpora lutea *state total/number of dams*	[redacted]	[redacted]			[redacted]	
Implantations *state total/number of dams*	[redacted]	[redacted]			[redacted]	
Resorptions *state total/number of dams*	[redacted]	[redacted]			[redacted]	
total number of fetuses	[redacted]	[redacted]			[redacted]	
pre-implantation loss *state %*		[redacted]			[redacted]	
post-implantation loss *state %*	[redacted]	[redacted]			[redacted]	
total number of litters		[redacted]			[redacted]	
fetuses / litter		[redacted]			[redacted]	
live fetuses / litter *state ratio*	[redacted]	[redacted]			[redacted]	
dead fetuses / litter *state ratio*	[redacted]	[redacted]			[redacted]	
fetus weight (mean) *[g]*	[redacted]	[redacted]			[redacted]	
placenta weight (mean) *[g]*		[redacted]			[redacted]	
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*	[redacted]	[redacted]			[redacted]	

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose 1000 mg/kg	dose-response + / -
	historical	study				
External malformations[*1] *[%]*	[redacted]	[redacted]			[redacted]	
External anomalies[*] *[%]*						
Skeletal malformations[*2] *[%]*	[redacted]	[redacted]			[redacted]	
Skeletal anomalies[*] *[%]*						
Skeletal variants[*] *[%] retarded ossification of the forelimbs*		[redacted]			[redacted]	
Visceral malformations[*3] *[%]*	[redacted]	[redacted]			[redacted]	
Visceral anomalies[*] *[%]*						
Variants visceral[*] *[%]*						

[redacted]

[redacted]

[redacted]

[redacted]

Section A6.8.1(05) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1985**, HWG 1608 – Study for embryotoxic effects on **rabbits** after oral administration.

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1 REFERENCE

1.1	**Reference**	[redacted], 1985, HWG 1608 – Study for embryotoxic effects on rabbits after oral administration. [redacted]. Report No: [redacted], 1985-02-15 (unpublished).
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**	No but very close to OECD guideline 414 (Teratogenicity)
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	Not given in the report (checked and approved for identity, stability and homogeneity by PF analyses, is the postulate)
3.1.2.1	Description	Not given
3.1.2.2	Purity	[redacted] active substance
3.1.2.3	Stability	Not described, though – checked and approved for identity, stability and homogeneity by PF analyses, is the postulate.
3.2	**Test Animals**	
3.2.1	Species	Rabbit
3.2.2	Strain	Himalayan, CHBB:HM
3.2.3	Source	[redacted]
3.2.4	Sex	Sexually mature males and females
3.2.5	Age/weight at study initiation	Males – 2500 g Females 2049-2563 g
3.2.6	Number of animals per group	15 inseminated females
3.2.7	Control animals	Yes
3.2.8	Mating period	Until mating had been observed (day zero of gestation)

Section A6.8.1(05) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1985**, HWG 1608 – Study for embryotoxic effects on **rabbits** after oral administration.

3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	rabbit: day 6-18 post mating
3.3.2	Postexposure period	Until day 29 of gestation
		Oral
3.3.3	Type	Gavage
3.3.4	Concentration	Gavage 0, 3, 10 or 30 mg/kg bw
3.3.5	Vehicle	0.5 % aqueous Cremophor emulsion
3.3.6	Concentration in vehicle	0, 0.06, 0.20 or 0.60 %
3.3.7	Total volume applied	5 ml/kg bw (actual body weight)
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes
3.4.2	Food consumption	Yes – but not reported
3.4.3	Clinical signs	Yes
3.4.4	Examination of uterine content	Gravid uterine weight – No – but placental weight recorded. Number of corpora lutea – No Number of implantations – Yes
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight (individual) and Sex Ratio
3.4.5.2	Skeleton	Yes
3.4.5.3	Soft tissue	Yes
3.5	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Maternal toxic Effects**	No effects
4.2	**Teratogenic / embryotoxic effects**	No effects
4.3	**Other effects**	No other effects

Section A6.8.1(05) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1985**, HWG 1608 – Study for embryotoxic effects on **rabbits** after oral administration.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Groups of 15 mated female Himalayan CHBB:HM were given by gavage daily doses of 0, 3, 10, or 30 mg/kg [redacted] pure HWG 1608 on days 6 to 18 of gestation. The rabbits were inspected daily for deaths and clinical signs and were weighed daily (dosing was related to the recent body weight). On day 29 of gestation the animals were killed and the uteri were removed by Caesarean section. The following determinations were made: Number of implantation, number of live or dead foetuses or embryos, sex of all live foetuses, litter weight and mean foetus weight per litter and total and mean placenta weight. The foetuses were inspected in detail for external malformation, and the skull were examined for visceral malformations (stained by a modified Wilson's technique) and finale the foetuses were exenterated for appraisal of abdominal and thoracic organs and subsequently cleared with diluted potassium hydroxide solution and stained for appraisal of the bone system (with Alizarin Red S).
5.2	**Results and discussion**	There was significantly increased number of losses at a dose of 30 mg/kg, maybe indicating a dose marginally toxic to the dams.
5.3	**Conclusion**	HWG 1608 was not embryotoxic in any of the tested concentrations
5.3.1	LO(A)EL maternal toxic effects	30 mg/kg HWG 1608/kg bw (?)
5.3.2	NO(A)EL maternal toxic effects	10 mg HWG 1608/kg bw (?)
5.3.3	LO(A)EL embryotoxic / teratogenic effects	Not embryotoxic/teratogenic at tested doses
5.3.4	NO(A)EL embryotoxic / teratogenic effects	30 mg HWG 1608/kg bw
5.3.5	Reliability	[redacted] *
5.3.6	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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	control data		low dose 3 mg/kg	medium dose 10 mg/kg	high dose 30 mg/kg	dose-response + / -
	historical	study				
Number of dams examined		**13**	**14**	**14**	**15**	
Clinical findings during application of test substance						
Mortality of dams *state %*		[redacted]	[redacted]	[redacted]	[redacted]	
Abortions		[redacted]	[redacted]	[redacted]	[redacted]	
Body weight gain *day 6-18, day 0-29,*		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Food consumption						
Water consumption *if test substance is applied with drinking water*						
Pregnancies *pregnancy rate or %*		[redacted]	[redacted]	[redacted]	[redacted]	
Necropsy findings in dams dead before end of test		[redacted]				

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		low dose 3 mg/kg	medium dose 10 mg/kg	high dose 30 mg/kg	dose-response + / -
	historical	study				
Corpora lutea *state total/number of dams*						
Implantations *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	
Resorptions *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
total number of fetuses		[redacted]	[redacted]	[redacted]	[redacted]	
pre-implantation loss *state %*						
post-implantation loss *state %*		[redacted]	[redacted]	[redacted]	[redacted]	
total number of litters		[redacted]	[redacted]	[redacted]	[redacted]	
fetuses / litter		[redacted]	[redacted]	[redacted]	[redacted]	
live fetuses / litter *state ratio*		[redacted]	[redacted]	[redacted]	[redacted]	
dead fetuses / litter *state ratio*		[redacted]	[redacted]	[redacted]	[redacted]	
fetus weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
placenta weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Parameter	control data		low dose 3 mg/kg	medium dose 10 mg/kg	high dose 30 mg/kg	dose-response + / -
	historical	study				
External malformations[*1] *[%]*		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
External anomalies[*] *[%]*						
Skeletal malformations[*] *[%]*						
Skeletal anomalies[*] *[%]*						
Skeletal variants[*] *[%]*		[redacted]	[redacted]	[redacted]	[redacted]	
Visceral malformations[*] *[%]*						
Visceral anomalies[*] *[%]*						
Variants visceral[*] *[%]*						

[redacted]

Section A6.8.1(06) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1988**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **rabbit.**

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1 REFERENCE

1.1	**Reference**	[redacted] 1988, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the rabbit. [redacted], Report No: [redacted]; 1988-02-26 (unpublished).
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, OECD Guidelines for the Testing of Chemicals, 414 "Teratogenicity".
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608 technical
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	
3.1.2.1	Description	Colourless crystals
3.1.2.2	Purity	[redacted] active substance
3.1.2.3	Stability	Stored at room temperature and in the dark at least stable until July 1987.
3.2	**Test Animals**	
3.2.1	Species	rabbit
3.2.2	Strain	Chinchilla, CHIN, hybrids, SPF quality
3.2.3	Source	[redacted]
3.2.4	Sex	Mated females
3.2.5	Age/weight at study initiation	13-18 weeks at mating/2426-4231 g
3.2.6	Number of animals per group	16
3.2.7	Control animals	Yes
3.2.8	Mating period	Until mating observed
3.3	**Administration/ Exposure**	Oral

Section A6.8.1(06) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1988**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **rabbit.**

3.3.1	Duration of exposure	Rabbit: day 6-18 post mating
3.3.2	Postexposure period	day 19 to day 28
		Oral
3.3.3	Type	Gavage
3.3.4	Concentration	Gavage 0, 10, 30, or 100 mg/kg bw
3.3.5	Vehicle	0.5 % aqueous Cremophor EL solution
3.3.6	Concentration in vehicle	0, 0.25, 0.75, or 2.5 %
3.3.7	Total volume applied	4 ml/kg bw, corrected according to actual bw
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes
3.4.2	Food consumption	Yes
3.4.3	Clinical signs	Yes
3.4.4	Examination of uterine content	Gravid uterine weight – yes Number of corpora lutea – yes Number of implantations – yes
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight, Sex Ratio
3.4.5.2	Skeleton	Yes
3.4.5.3	Soft tissue	Yes
3.5	**Further remarks**	—

4 RESULTS AND DISCUSSION

4.1	**Maternal toxic Effects**	Only 100 mg HWG 1608 technical/kg bw resulted in maternal toxic effects (related to dosing): Mean body weight gain relative to weight on day 0 post coitum was reduced (statistically significant) most days between day 7 and day 25. Post-implantation loss significantly increased.
4.2	**Teratogenic / embryotoxic effects**	Only 100 mg HWG 1608 technical/kg bw resulted in teratogenic/ embryotoxic effects: Mean body weight of foetuses in the high dose group was slightly (not statistically significant) reduced. Malformations and anomalies were found in 8.9 % of the foetuses of the high dose group (in 35.7 % of the 14 litters), whereas no malformations or anomalies were found in any other group.

Section A6.8.1(06) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1988**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **rabbit.**

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

In accordance with OECD Guideline for the Testing of Chemicals No. 414 (Teratogenicity) (and GLP) four groups of each 16 mated female Chinchilla rabbits (CHIN hybrids, SPF quality) were given by gavage daily doses of [redacted] pure HWG 1608 technical, 0, 10, 30, or 100 mg/kg bw suspended in 0.5 % aqueous Cremophor EL solution on days 6 – 18 of gestation. The animals were observed daily for mortality, clinical signs and behaviour. The animals were weighed daily and the test substance was dosed according to the actual body weight. Food consumption was recorded on days 6, 11, 15, 19, 24 and 28 post coitum.

The dams were killed (by cervical dislocation) on day 28 of gestation and foetuses removed by Caesarean section and the livers of all dams were weighed and fixed in formaldehyde solution. Necropsy included: gross macroscopic examination of all internal organs, with emphasis on the uterus, uterine contents, position of foetuses in the uteri and number of corpora lutea. The foetuses were removed from the uterus, weighed, examined for gross external abnormalities and prepared for internal examinations. Foetuses were dissected and body cavities (thorax, abdomen, pelvis) and all organs were examined and abnormalities recorded. Skin was removed and the crania of all foetuses were examined for ossification. The heads were serially sectioned and examined. The skeletons were examined (after clearing in potassium hydroxide solution and staining with Alizarin Red S). All abnormalities and variations were recorded. Abnormal foetuses were photographed.

The uteri and uterine contents of all pregnant females were weighed (non pregnant uteri were placed in an ammonium sulphide solution to accentuate possible haemorrhagic areas of implantation sites).

5.2 Results and discussion

No mortalities or clinical signs related to dosing were observed in any dose or control group. Food consumption was reduced in the high dose group during dosing and mean body weight gain in dams when compared with control group were significantly reduced most of the day from day 7 to day 25. Non of the necropsy findings in the dams were considered to be related to dosing with HWG 1608 technical. In the high dose group – 100 mg/kg bw – there was statistically increased post-implantation loss and in this group only were recorded malformations and/or anomalies after external examination of foetuses. Only foetuses from the same high dose group exhibited skeletal anomalies to a larger extent. The percentage of foetuses with non-ossifies phalangeal nuclei was slightly increased in the 100 mg/kg bw group.

5.3 Conclusion

5.3.1 LO(A)EL maternal toxic effects

100 mg HWG 1608 technical/kg bw

due to impaired mean body weight gain of the dams during dosing and the statistically increased post-implantation loss.

5.3.2 NO(A)EL maternal toxic effects

30 mg HWG 1608 technical/kg bw

Section A6.8.1(06) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1988**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **rabbit.**

5.3.3	LO(A)EL embryotoxic / teratogenic effects	100 mg HWG 1608 technical/kg bw due to the increase in malformations and anomalies in this group after external examinations and skeletal examinations of the foetuses of this group.
5.3.4	NO(A)EL embryotoxic / teratogenic effects	30 mg HWG 1608 technical/kg bw
5.3.5	Reliability	[redacted]
5.3.6	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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
Number of dams examined	**224**	**15**	**14**	**15**	**14**	
Clinical findings during application of test substance						
Mortality of dams *state %*		[redacted]	[redacted]	[redacted]	[redacted]	
Abortions		[redacted]	[redacted]	[redacted]	[redacted]	
Body weight gain *day 6-18, day 0-end of test,*		[redacted]	[redacted]	[redacted]	[redacted]	
Food consumption *day 6-19*		[redacted]	[redacted]	[redacted]	[redacted]	
Water consumption *if test substance is applied with drinking water*						
Pregnancies *%*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Necropsy findings in dams dead before end of test					[redacted]	

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
Corpora lutea *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Implantations *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Resorptions *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
total number of fetuses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pre-implantation loss *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
post-implantation loss *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of litters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fetuses / litter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Live fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dead fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fetus weight (mean) *[g]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Placenta weight (mean) *[g]*						
Crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

1: [redacted]

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
External malformations* *[%]*						
External anomalies*1 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Skeletal malformations* *[%]*						
Skeletal anomalies*2 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skeletal variants* *[%]*						
Visceral malformations* *[%]*						
Visceral anomalies*3 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Variants visceral* *[%]*						

[redacted]

Section A6.8.1(07) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1995**, Combined report of embryotoxicity study (including teratogenicity) and supplementary investigations on the maternal toxicity of HWG 1608 technical (Tebuconazole) in pregnant **rabbits**.

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1 REFERENCE

1.1	**Reference**	[redacted], 1995, Combined report of embryotoxicity study (including teratogenicity) and supplementary investigations on the maternal toxicity of HWG 1608 technical (c.n. Tebuconazole) in pregnant rabbits. [redacted], Report No: [redacted], 1995-05-31 (unpublished).
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 – OECD Guideline for the Testing of Chemicals No. 414 ("Teratogenicity"), May 1981, and EPA, Pesticide Assessment Guidelines 83-3 ("Teratogenicity Study) revised edition, November 1984.
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608 Technical (common name: Tebuconazole)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	

Section A6.8.1(07) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1995**, Combined report of embryotoxicity study (including teratogenicity) and supplementary investigations on the maternal toxicity of HWG 1608 technical (Tebuconazole) in pregnant **rabbits**.

3.1.2.1	Description	Colourless-beige powder
3.1.2.2	Purity	[redacted] for the main study and [redacted] in the supplementary study
3.1.2.3	Stability	Main study: The pure test article was approved until August 1992 (4 months after termination of dosing) and in the vehicle the stability was at least 2 hours. Supplementary study: The pure test article was approved until December1993 (approx. 6 months after termination of dosing) and in the vehicle the stability was at least 2 hours.
3.2	**Test Animals**	
3.2.1	Species	Rabbit
3.2.2	Strain	Chinchilla (CHbb: CH, Hybrids, SPF quality)
3.2.3	Source	[redacted]
3.2.4	Sex	Mated females
3.2.5	Age/weight at study initiation	16-18 weeks (suppl: 29-32 weeks)/3199-4620 g (suppl: 3290-4745 g)
3.2.6	Number of animals per group	16 in the main study and 5 in the supplementary
3.2.7	Control animals	Yes
3.2.8	Mating period	Until copulation had been observed
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	rabbit: day 6-18 post mating
3.3.2	Postexposure period	Main study: day 19-28 Supplementary study: None
3.3.3	Type	Gavage
3.3.4	Concentration	Gavage 0, 10, 30, or 100 mg/kg bw
3.3.5	Vehicle	0.5 % Cremophor EL in bidistilled water
3.3.6	Concentration in vehicle	0, 0.25 %, 0.75 %, or 2.5 %
3.3.7	Total volume applied	4 ml/kg bw
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes
3.4.2	Food consumption	Yes
3.4.3	Clinical signs	Yes

Section A6.8.1(07)		**Teratogenicity Study**
Annex Point IIA6.8.1		[redacted], **1995**, Combined report of embryotoxicity study (including teratogenicity) and supplementary investigations on the maternal toxicity of HWG 1608 technical (Tebuconazole) in pregnant **rabbits**.
3.4.4	Examination of uterine content	Gravid uterine weight – yes Number of corpora lutea – yes Number of implantations – yes
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight, and Sex Ratio
3.4.5.2	Skeleton	Yes – main study
3.4.5.3	Soft tissue	Yes – main study
3.5	**Further remarks**	The supplementary study examined the following parameters: Blood specimens taken on day 6, day 12 and day 19 were subjected to full haematology and clinical chemistry. Organs that were weighed were: Adrenals, kidneys, liver, spleen, and the same organs plus all gross lesions were examined histopathologically.
		4 RESULTS AND DISCUSSION
4.1	**Maternal toxic Effects**	Reduced food consumption and weight gains in the 100 mg/kg bw group. Changes in the liver in the 10 mg, 30 mg and 100 mg/kg bw groups in the supplementary study.
4.2	**Teratogenic / embryotoxic effects**	Increased foetal lethality, abnormal findings and retardations in litters from dams treated with 100 mg/kg bw.
4.3	**Other effects**	
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	In accordance with the OECD Guideline for the Testing of Chemicals No. 414 ("Teratogenicity"), May 1981, and the EPA, Pesticide Assessment Guidelines 83-3 ("Teratogenicity Study) revised edition, November 1984, groups of 16 (main study) or 5 (supplementary study) mated Chinchilla rabbits (CHbb: CH, Hybrids, SPF quality) were given by gavage once daily on day 6 through to day 18 of gestation doses of HWG 1608. The test substance ([redacted] pure) was given suspended in 0.5 % Cremophor EL solution in doses of 0, 10, 30, or 100 mg/kg bw. The animals were inspected for mortality, clinical signs and changes in appearance or behaviour at least twice daily. Body weight was recorded daily and food consumption at regular intervals. Main study: The dams were necropsied on day 28 of gestation, and the gravid uteri were removed by caesarean section and weighed before opening. The following data were recorded in pregnant dams: Number of corpora lutea, number of implantation sites, litter size, position, weight and sex of each live foetus, and number of dead foetuses. The foetuses were examined for external abnormalities, and visceral and skeletal abnormalities and skeletal retardations. Supplementary study: Blood specimens were taken from the marginal ear vein on days 6, 12 and 19 post coitum and subjected to full

Section A6.8.1(07)		**Teratogenicity Study**	
Annex Point IIA6.8.1		[redacted], **1995**, Combined report of embryotoxicity study (including teratogenicity) and supplementary investigations on the maternal toxicity of HWG 1608 technical (Tebuconazole) in pregnant **rabbits**.	
		haematological and clinical chemistry analysis. The dams were sacrificed just after the last blood specimens had been taken, and the gravid uteri were removed by caesarean operation and were weighed. All reproduction parameters were recorded (as above). The adrenals, the kidneys, the liver and the spleen from all gravid dams were weighed separately and prepared for histological examinations. Two portions of each 10 grams were before the preparation taken from each liver for determination of the cytochrome P-450, the N-demethylase and the O-demethylase activities and the triglyceride content.	
5.2	**Results and discussion**	The 100 mg/kg bw dams consumed significantly less food than control animals from day 6 to day 11 post coitum. Body weight gain was slightly decreased in the high dose group from day 6 to day 11 (notably on day 6-8) of gestation. The only reproduction parameter affected in the 100 mg/kg bw groups was a slightly increased mean post-implantation loss. The 100 mg/kg bw groups had statistically significant increase in abnormal foetuses. The supplementary study revealed affected livers – single cell necrosis – in females of all three dosed groups of animals (10, 30, and 100 mg/kg bw) but none in the control animals.	*
5.3	**Conclusion**	In this combination of studies HWG 1608 Technical showed maternal toxicity down to 10 mg/kg bw and embryotoxicity/teratogenicity in the 100 mg/kg bw dose group.	
5.3.1	LO(A)EL maternal toxic effects	10 mg/kg bw due to single cell necrosis in the examined livers of this dose group.	*
5.3.2	NO(A)EL maternal toxic effects	Not identified	*
5.3.3	LO(A)EL embryotoxic / teratogenic effects	100 mg/kg bw – increase in post-implantation loss and increased number of foetuses with abnormalities.	*
5.3.4	NO(A)EL embryotoxic / teratogenic effects	30 mg/kg bw	*
5.3.5	Reliability	[redacted]	
5.3.6	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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects – main study

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
Number of dams examined	**272**	**16**	**15**	**14**	**14**	
Clinical findings during application of test substance						
Mortality of dams *state %*						
Abortions						
Body weight gain *day 6-19*						
Food consumption *day 6-19*						
Water consumption *if test substance is applied with drinking water*						
Pregnancies *%*						
Necropsy findings in dams dead before end of test						

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
Corpora lutea *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Implantations *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Resorptions *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
total number of fetuses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
pre-implantation loss *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
post-implantation loss *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
total number of litters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
fetuses / litter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
live fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
dead fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
fetus weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
placenta weight (mean) *[g]*						
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
External malformations[*1] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
External anomalies[*] *[%]*						
Skeletal malformations[*2] *[%]of the heads*					[redacted]	
Skeletal anomalies[*3] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skeletal variants[*] *[%]*						
Visceral malformations[*4] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visceral anomalies[*] *[%]*						
Variants visceral[*] *[%]*						

[redacted]

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects – supplementary study

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response
	historical	study	10 mg/kg	30 mg/kg	100 mg/kg	+ / -
Number of dams examined	**272**	**4**	**4**	**5**	**3**	
Clinical findings during application of test substance		[redacted]	[redacted]	[redacted]	[redacted]	
Mortality of dams *state %*		[redacted]	[redacted]	[redacted]	[redacted]	
Abortions		[redacted]	[redacted]	[redacted]	[redacted]	
Body weight gain *day 6-19*		[redacted]	[redacted]	[redacted]	[redacted]	
Food consumption *day 6-19*		[redacted]	[redacted]	[redacted]	[redacted]	
Water consumption *if test substance is applied with drinking water*						
Pregnancies *%*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Necropsy findings in dams dead before end of test						

Table A6_8-2. **Table for Teratogenic effects (separate data for all dosage groups)**

Litter response (Caesarean section data) Supplementary study

Modify if necessary and give historical data if available

Parameter	control data study	low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
Corpora lutea *state total/number of dams*					
Implantations *state total/number of dams*					
Resorptions *state total/number of dams*					
total number of fetuses					
pre-implantation loss *state %*					
post-implantation loss *state %*					
total number of litters					
fetuses / litter					
live fetuses / litter *state ratio*					
dead fetuses / litter *state ratio*					
fetus weight (mean) *[g]*					
placenta weight (mean) *[g]*					
crown-rump length (mean) *[mm]*					
Fetal sex ratio *[state ratio m/f]*					

No abnormal foetuses were discovered

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Section A6.8.1(08) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1999**, HWG 1608. Mechanistic study on embryotoxic effects in **rabbits** after oral administration.

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1 REFERENCE

1.1	**Reference**	[redacted] 1999, HWG 1608 (c.n. Tebuconazole). Mechanistic study on embryotoxic effects in rabbits after oral administration. [redacted]. Report No: [redacted], 1999-09-20 (unpublished).
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**	No Only one dosed group and one vehicle control group. Dosing of the animals and most examinations were performed by methods comparable to the OECD guideline 414 "Teratogenicity".
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608, Tebuconazole
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	
3.1.2.1	Description	Colourless to cream-coloured powder
3.1.2.2	Purity	[redacted] active substance
3.1.2.3	Stability	Approved for use until May 4, 1999
3.2	**Test Animals**	
3.2.1	Species	Rabbit, Chinchilla
3.2.2	Strain	CHB-W
3.2.3	Source	[redacted]
3.2.4	Sex	Only females were dosed
3.2.5	Age/weight at study initiation	156-165 days old/ 3283-4067 g
3.2.6	Number of animals	14 controls – 15 dosed animals

	per group	
3.2.7	Control animals	Yes
3.2.8	Mating period	Two times copulation – observed.
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	rabbit: day 6-19 post mating
3.3.2	Postexposure period	None
3.3.3	Type	Gavage
3.3.4	Concentration	Gavage 0 or 100 mg/kg bw
3.3.5	Vehicle	0.5 % Cremophor EL in demineralised water
3.3.6	Concentration in vehicle	0 or 25 mg/ml
3.3.7	Total volume applied	4 ml/kg
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes
3.4.2	Food consumption	Yes
3.4.3	Clinical signs	Yes
3.4.4	Examination of uterine content	Gravid uterine weight – No Number of corpora lutea – Yes Number of implantations – Yes
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight
3.4.5.2	Skeleton	No
3.4.5.3	Soft tissue	No
3.5	**Further remarks**	Maternal plasma and foetal tissue concentrations of HWG 1608 were measured, 2.66 µg/ml and 2.30 µg/g respectively
		4 RESULTS AND DISCUSSION
4.1	**Maternal toxic Effects**	Feed intake was reduced in dosed animals on days 6-9 and 9-12 of gestation. Body weight gain was statistically significant reduced on days 6-10 in dosed animals. Animals dosed with 100 mg/kg bw exhibited also: absolute and relative adrenals weights were marginally increased, and histopathology revealed distinct hypertrophy of the cells of zona fasciculata in 2 out of 3 examined specimens; increased activity of the 7-ethoxycoumarin deethylase was statistically significant; glutathione-S-transferase was statistically significantly decreased; many other liver enzymes were marginally increased.
4.2	**Teratogenic /**	In dosed animals the foetal weight was statistically significantly lower than

Section A6.8.1(08) **Teratogenicity Study**

Annex Point IIA6.8.1 [redacted] **1999**, HWG 1608. Mechanistic study on embryotoxic effects in **rabbits** after oral administration.

	embryotoxic effects	in controls. No external findings were observed in either of the groups.
4.3	**Other effects**	–

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	No test guideline was referred to but administration of HWG 1608 took place much like OECD guideline 414 "Teratogenicity". Chincilla rabbits (CHB-W) were used for this study. Fourteen mated females were used as controls and 15 mated females were given daily doses of 100 mg/kg bw HWG 1608 ([redacted] pure) suspended in 0.5 % Cremophor EL in demineralised water by gavage on days 6 to 19 of gestation. Control animals were given 0.5 % Cremophor EL in demineralised water. The animals were inspected at least once daily for mortality, clinical signs and behaviour. The feed intake was recorded as were body weights at regular intervals. On day 19 of gestation the dams were killed 2 hours after the last dosing. Blood was drawn from an extremity vein just prior to this. Caesarean section was performed on all females and normal reproductive parameters were recorded. The liver, the ovaries (pairwise), the adrenals (pairwise) and the placentas of all pregnant females (surviving) were weighed. The right liver lobes and two placentas with foetuses from each of the pregnant females were fixed in buffered 4 % formaldehyde. The same happened to the adrenals and ovaries of 3 females from each group. Enzyme activities of the livers were determined. The blood samples were analysed for content of HWG 1608, as were foetal tissues.
5.2	**Results and discussion**	Two animals died during the study due to intubation errors. Dosing did not affect appearance or behaviour of the animals. Feed consumption was decreased (days 6-12), weight loss was recorded (day 6-10), enzyme activity of the liver was increased (but only for one enzyme significantly), glutathione-S-tranferase was significantly decreased, though, reproduction data were not affected, gestation rate was unaltered, foetal weights were significantly depressed and finally the external appearance of the foetuses was not affected by dosing. HWG 1608 shows maternal toxicity. The report discusses the possibility of formerly (in two studies) recorded increased number of external, skeletal and visceral anomalies and variations could have been due to elevated levels of corticosteroids produced by the dams themselves as a respond to stress (see table below) – because of the maternal toxicity. This study and its results can not support this theory since the increase in plasma levels is marginal in this test with distinct hypertrophy of steroid forming areas of the adrenals in 2 out of 3 histologically examined adrenals but where on the other hand no malformed foetuses are seen.
5.3	**Conclusion**	HWG 1608 – Tebuconazole – 100 mg/kg bw is toxic to inseminated female rabbits in daily oral doses from day 6 to day 19 of gestation. The maternal toxicity affects the foetal weights and can be responsible for late development of foetuses. However, the maternal toxicity has not been shown to be responsible for the teratogenic activity of HWG 1608 via stress induction of elevated levels of corticosteroidal compounds.
5.3.1	LO(A)EL maternal toxic effects	100 mg/kg bw
5.3.2	NO(A)EL maternal toxic effects	

Section A6.8.1(08) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1999**, HWG 1608. Mechanistic study on embryotoxic effects in **rabbits** after oral administration.

5.3.3	LO(A)EL embryotoxic / teratogenic effects	[redacted]
5.3.4	NO(A)EL embryotoxic / teratogenic effects	[redacted]
5.3.5	Reliability	[redacted]
5.3.6	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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose 100 mg/kg	dose-response + / -
	historical	study				
Number of dams examined		[redacted]			[redacted]	
Clinical findings during application of test substance		[redacted]			[redacted]	
Mortality of dams 2 dams died due to intubation error *state %*						
Abortions		[redacted]			[redacted]	
Body weight gain *day 6-10, day 0-end of test,*		[redacted]			[redacted]	
Food consumption day 6-12		[redacted]			[redacted]	
Water consumption *if test substance is applied with drinking water*						
Pregnancies *%*		[redacted]			[redacted]	
Necropsy findings in dams dead before end of test						

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	High dose 100 mg/kg	dose-response + / -
	historical	study				
Corpora lutea *state total/number of dams*		[redacted]			[redacted]	
Implantations *state total/number of dams*		[redacted]			[redacted]	
Resorptions *state total/number of dams*		[redacted]			[redacted]	
total number of fetuses		[redacted]			[redacted]	
pre-implantation loss *state %*		[redacted]			[redacted]	
post-implantation loss *state %*		[redacted]			[redacted]	
total number of litters		[redacted]			[redacted]	
fetuses / litter		[redacted]			[redacted]	
live fetuses / litter *state ratio*		[redacted]			[redacted]	
dead fetuses / litter *state ratio*		[redacted]			[redacted]	
fetus weight (mean) *[g]*		[redacted]			[redacted]	
placenta weight (mean) *[g]*		[redacted]			[redacted]	
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*						

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
External malformations* *[%]*						
External anomalies* *[%]*						
Skeletal malformations* *[%]*						
Skeletal anomalies* *[%]*						
Skeletal variants* *[%]*						
Visceral malformations* *[%]*						
Visceral anomalies* *[%]*						
Variants visceral* *[%]*						

Not examined

Section A6.8.1(09) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1988**, HWG 1608 – Study for embryotoxic effects on **mice** following oral administration.

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1 REFERENCE

1.1	**Reference**	[redacted], 1988, HWG 1608 – Study for embryotoxic effects on mice following oral administration. [redacted] Report No. [redacted], 1988-03-14 (unpublished).
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 – Pesticide Assessment Guidelines Subdivison F, Hazard Evaluation: Human and Domestic Animals, EPA, 83-3, "Teratogenicity Study", Revised Edition, November 1984.
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608
3.1.1	Lot/Batch number	1616002/84
3.1.2	Specification	
3.1.2.1	Description	Colourless crystals
3.1.2.2	Purity	[redacted] - impurities: [redacted]
3.1.2.3	Stability	Had been tested and approved
3.2	**Test Animals**	
3.2.1	Species	Mouse
3.2.2	Strain	NMRI/ORIG Kisslegg
3.2.3	Source	[redacted]
3.2.4	Sex	Mated females
3.2.5	Age/weight at study initiation	/ 28-39 g
3.2.6	Number of animals per group	25
3.2.7	Control animals	Yes
3.2.8	Mating period	Until vaginal plug appeared (day zero of gestation)

Section A6.8.1(09) Teratogenicity Study

Annex Point IIA6.8.1

[redacted] **1988**, HWG 1608 – Study for embryotoxic effects on **mice** following oral administration.

3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	mouse: day 6-15 post mating
3.3.2	Postexposure period	day 16-18
3.3.3	Type	Gavage
3.3.4	Concentration	Gavage 0, 10, 30, or 100 mg/kg bw
3.3.5	Vehicle	0.5 % aqueous Cremophor EL solution
3.3.6	Concentration in vehicle	0, 0.2, 0.6, or 2.0 %
3.3.7	Total volume applied	5 ml/kg bw (according to current body weight)
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes
3.4.2	Food consumption	Yes
3.4.3	Clinical signs	Yes
3.4.4	Examination of uterine content	Gravid uterine weight – No, but placental weight instead Number of corpora lutea – No Number of implantations – Yes
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight and Sex Ratio
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**	No effects
4.2	**Teratogenic / embryotoxic effects**	HWG 1608 exerts embryotoxic effects – increased number of runts – already at 30 mg/kg in mice. At 100 mg/kg bw HWG 1608 is teratogenic – increased number of foetal malformations.
4.3	**Other effects**	The number of runts is included as a parameter indicating embryotoxicity

Section A6.8.1(09) **Teratogenicity Study**

Annex Point IIA6.8.1 [redacted] **1988**, HWG 1608 – Study for embryotoxic effects on **mice** following oral administration.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

In accordance with EPA Pesticide Assessment Guidlines, Subdivision F, 83-3, "Teratogenicity Study", November 1984 and under the principles of Good Laboratory Practice.

Groups of 25 inseminated NMRI mice were given by gavage daily doses of 0, 10, 30, or 100 mg HWG 1608 ([redacted] pure)/kg bw on days 6-15 after mating. The test substance was suspended in 0.5 % Cremophor EL aqueous solution. The dams were inspected daily with respect to mortality, appearance and behaviour and were weighed daily. On day 18 of gestation the foetuses were obtained by caesarean section and examinations were performed on the foetuses and the uteri to determine possible embryotoxic and teratogenic effects of the dosing. Numbers of implantations, live and dead foetuses and resorptions were recorded and the foetuses were weighed individually and sexed The placentas were weighed and the weight recorded. The foetuses were examined morphologically for possible internal and external abnormalities. Around 30 % of the foetuses were stained a.m. Wilson and examined for visceral malformations and the rest of the foetuses were stained with Alizarin Red S after clearing with potassium hydroxide solution (Dawson technique) for evaluation of the bone system.

5.2 Results and discussion

No overt signs of maternal toxicity at any dose. There was an increased number of runts from 30 mg HWG 1608/kg bw and increased number of malformations and increased placental weights in the high dose group, 100 mg HWG 1608/kg bw.

5.3 Conclusion

5.3.1	LO(A)EL maternal toxic effects	No signs of maternal toxicity in mice of dose up to 100 mg/kg bw
5.3.2	NO(A)EL maternal toxic effects	100 mg HWG 1608/kg bw
5.3.3	LO(A)EL embryotoxic / teratogenic effects	30 mg HWG 1608/kg bw due to increased number of runts in this dose group
5.3.4	NO(A)EL embryotoxic / teratogenic effects	10 mg HWG 1608/kg bw
5.3.5	Reliability	[redacted]
5.3.6	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	July 2005
Materials and Methods	[redacted]
	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
Number of dams examined		**24**	**23**	**23**	**20**	
Clinical findings during application of test substance		▮	▮	▮	▮	
Mortality of dams *state %*		▮	▮	▮	▮	
Abortions						
Body weight gain *Day 6-15, day 0-end of test,*		▬	▬	▬	▬	▮
Food consumption						
Water consumption *if test substance is applied with drinking water*						
Pregnancies *pregnancy rate or %*		▬	▬	▬	▬	
Necropsy findings in dams dead before end of test		▮	▮	▮	▮	

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	High dose 100 mg/kg	dose-response + / -
	historical	study				
Corpora lutea *state total/number of dams*						
Implantations *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	
Resorptions *state total/number of dams*		[redacted]	[redacted]	[redacted]	[redacted]	
total number of fetuses		[redacted]	[redacted]	[redacted]	[redacted]	
pre-implantation loss *state %*						
post-implantation loss *state %*		[redacted]	[redacted]	[redacted]	[redacted]	
total number of litters		[redacted]	[redacted]	[redacted]	[redacted]	
fetuses / litter		[redacted]	[redacted]	[redacted]	[redacted]	
live fetuses / litter *state ratio*		[redacted]	[redacted]	[redacted]	[redacted]	
dead fetuses / litter *state ratio*		[redacted]	[redacted]	[redacted]	[redacted]	
fetus weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
placenta weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*		[redacted]	[redacted]	[redacted]	[redacted]	

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	Control data		low dose	medium dose	high dose	dose-response + / -
	Historical	study	10 mg/kg	30 mg/kg	100 mg/kg	
External malformations[*1] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
External anomalies[*] *[%]*						
Skeletal malformations[*] *[%]*						
Skeletal anomalies[*2] *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skeletal variants[*] *[%]*						
Visceral malformations[*] *[%]*						
Visceral anomalies[*] *[%]*						
Variants visceral[*] *[%]*						

[redacted]

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Section A6.8.1(10) Teratogenicity Study

Annex Point IIA6.8.1

[redacted]: **1988**, HWG 1608 – Supplementary study for maternal toxicity on **mice** following oral administration.

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] 1988, HWG 1608 – Supplementary study for maternal toxicity on mice following oral administration. [redacted]. Report No. [redacted], 1988-03-09 (unpublished).	
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**	No – the method used *relates to* "Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation, Human and Domestic Animals", EPA, 83-3, "Teratogenicity Study", Revised Edition; November 1984.	
2.2	**GLP**	[redacted]	
2.3	**Deviations**	[redacted]	
		3 MATERIALS AND METHODS	
3.1	**Test material**	HWG 1608	
3.1.1	Lot/Batch number	[redacted] (Stability tests were performed on HWG 1608 from batch number – [redacted]).	
3.1.2	Specification		
3.1.2.1	Description	Grey-white powdery crystals	
3.1.2.2	Purity	[redacted] active substance	*
3.1.2.3	Stability	The administration formula was stable for at least 7 days	
3.2	**Test Animals**		
3.2.1	Species	Mouse	
3.2.2	Strain	NMRI/ORIG Kisslegg	
3.2.3	Source	[redacted]	
3.2.4	Sex	Mated females	
3.2.5	Age/weight at study initiation	Sexually mature (nulliparous)/ 24-40 g	
3.2.6	Number of animals per group	10	

Section A6.8.1(10) **Teratogenicity Study**

Annex Point IIA6.8.1 [redacted]: **1988**, HWG 1608 – Supplementary study for maternal toxicity on **mice** following oral administration.

3.2.7	Control animals	Yes
3.2.8	Mating period	Until vaginal plug appears (day zero)
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	Mouse: day 6-15 post mating
3.3.2	Postexposure period	None
3.3.3	Type	Gavage
3.3.4	Concentration	Gavage 0. 10. 20, 30 or 100 mg/kg bw
3.3.5	Vehicle	0.5 % aqueous Cremophor EL solution
3.3.6	Concentration in vehicle	0, 0.2, 0.4, 0.6 or 2.0 %
3.3.7	Total volume applied	5 ml/kg bw
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes
3.4.2	Food consumption	No
3.4.3	Clinical signs	Yes, at least once daily
3.4.4	Examination of uterine content	Gravid uterine weight – No Number of corpora lutea – No Number of implantations – No
3.4.5	Examination of foetuses	
3.4.5.1	General	None
3.4.5.2	Skeleton	No
3.4.5.3	Soft tissue	No
3.5	**Further remarks**	The study concentrates on the maternal toxicity, and thus, parameters aimed for discovering this are examined.

4 RESULTS AND DISCUSSION

4.1	**Maternal toxic Effects**	No deaths and no clinical signs were observed, which could be attributed to dosing. **Histopathological changes in livers of 100 mg HWG 1608/kg bw treated animals.** Liver weights in all dosed animals were increased but not statistically significant and not in a dose dependent way. No other organ weights were increased over controls. Statistically significant positive findings – related to dosing – in clinical chemistry were: increased levels of transaminases ALT (10 and 30 mg) and AST (30 mg) and **increased levels of triglycerides in liver homogenate (almost three-fold) in the 100 mg/kg group**. Haematocrit values were significantly lower than controls in the 30 mg and the 100 mg/kg bw dose groups and the mean cell volume (MCV – erythrocytes) was decreased in 20, 30 and 100 mg/kg bw dose groups.

Section A6.8.1(10) **Teratogenicity Study**

Annex Point IIA6.8.1 [redacted]: **1988**, HWG 1608 – Supplementary study for maternal toxicity on **mice** following oral administration.

4.2	**Teratogenic / embryotoxic effects**	Not studied
4.3	**Other effects**	Various statistically significant results appear scattered over doses and are most probably not related to dosing.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Not a guideline study but dosing was performed in accordance with the EPA Human and Domestic Animals Health Effects Testing Guideline 83-3, November 1984. Five groups of each 10 inseminated female NMRI/ORIG Kisslegg mice were given daily doses of 0, 10, 20, 30, or 100 mg/kg bw, respectively, of [redacted] pure HWG 1608 in an 0.5 % aqueous Cremophor solution on days 6-15 of gestation. All animals were inspected at least once daily with respect to mortality and appearance and behaviour. The dams were killed on the 16th day of gestation and blood was taken from half of them for clinical chemical and haematological testing. The livers were removed from the other half for determination of the weight and histopathological examination. A number of organs were removed for having the weight recorded.
5.2	**Results and discussion**	Only the high triglyceride level and the histopathologically changed livers (cytoplasmic vacuoles containing lipids) in the 100 mg HWG 1608/kg bw group seems to be important and dose related. All the other results are unclear (see below in table, results are not suitable for conclusions). It should be noted, though, that the livers (and the blood) were taken from pregnant and non-pregnant animals among each other – so the importance of inseminating the dams is not obvious. The livers used for the homogenates in the high dose group were taken from pregnant mice only whereas 3 of the livers from examined histopathologically were from non-pregnant mice.
5.3	**Conclusion**	Livers containing high triglyceride levels and exhibiting cytoplasmic vacuoles containing elevated amounts of lipids indicate maternal toxicity of dosing with 100 mg HWG 1608/kg bw.
5.3.1	LO(A)EL maternal toxic effects	100 mg HWG 1608/kg bw. Liver homogenates with 3-fold increased level of triglyceride and cytoplasmic vacuoles containing elevated amounts of lipids.
5.3.2	NO(A)EL maternal toxic effects	30 mg HWG 1608/kg bw.
5.3.3	LO(A)EL embryotoxic / teratogenic effects	Not examined
5.3.4	NO(A)EL embryotoxic / teratogenic effects	Not examined
5.3.5	Reliability	[redacted]
5.3.6	Deficiencies	[redacted]

Section A6.8.1(10) **Teratogenicity Study**

Annex Point IIA6.8.1 [redacted]: **1988**, HWG 1608 – Supplementary study for maternal toxicity on **mice** following oral administration.

	Control	10 mg/kg bw	20 mg/kg bw	30 mg/kg bw	100 mg/kg bw
[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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	Control	10 mg	20 mg	30 mg	100 mg	dose-response + / -
Number of dams examined	10	10	10	10	10	
Clinical findings during application of test substance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Mortality of dams *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Abortions						
Body weight gain *Days of administration, day 0-end of test,*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Food consumption						
Water consumption *if test substance is applied with drinking water*						
Pregnancies[*1] *pregnancy rate*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Necropsy findings in dams dead before end of test						

***1: the low number of pregnancies should be noted**

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Corpora lutea* *state total/number of dams*						
Implantations* *state total/number of dams*						
Resorptions* *state total/number of dams*						
total number of fetuses*						
pre-implantation loss* *state %*						
post-implantation loss* *state %*						
total number of litters*						
fetuses / litter*						
live fetuses / litter* *state ratio*						
dead fetuses / litter* *state ratio*						
fetus weight (mean)* *[g]*						
placenta weight (mean)* *[g]*						
crown-rump length (mean)* *[mm]*						
Fetal sex ratio* *[state ratio m/f]*						

*** no examinations performed**

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
External malformations* *[%]*						
External anomalies* *[%]*						
Skeletal malformations* *[%]*						
Skeletal anomalies* *[%]*						
Skeletal variants* *[%]*						
Visceral malformations* *[%]*						
Visceral anomalies* *[%]*						
Variants visceral* *[%]*						

*** no examinations performed**

Section A6.8.1(11) Teratogenicity Study

Annex Point IIA6.8.1

[redacted]**1990**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **mouse** (dermal application).

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1 REFERENCE

1.1	**Reference**	[redacted] 1990, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the mouse (dermal application). [redacted], Report No: [redacted], 1990-08-02 (unpublished).
1.2	**Data protection**	[redacted]
1.1.1	Data owner	[redacted]
1.1.2	Companies with letter of access	[redacted]
1.1.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes, EPA guidelines 83-3 (November 1984) and OECD Guidelines 414 (Teratogenicity)
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608 Technical
3.1.1	Lot/Batch number	[redacted] (main Study) and [redacted] (supplementary study)
3.1.2	Specification	
3.1.2.1	Description	Colourless crystals
3.1.2.2	Purity	[redacted] active HWG in main study and [redacted] active substance in supplementary study.
3.1.2.3	Stability	In the vehicle – at least 6 hours.
3.2	**Test Animals**	
3.2.1	Species	Mouse
3.2.2	Strain	NMRI KFM- HAN (Outbred SPF Quality)
3.2.3	Source	[redacted]
3.2.4	Sex	128 mated females (main study) and 80 mated females (supplementary study).
3.2.5	Age/weight at study initiation	8 weeks at pairing / 22-38 g

Section A6.8.1(11) Teratogenicity Study

Annex Point IIA6.8.1

[redacted]**1990**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **mouse** (dermal application).

3.2.6	Number of animals per group	Main study	Suppl. Study a (Histol. Exam)	Suppl. Study b (Clin. Lab. Exam.)	Dose group
		34	10	10	Vehicle control
		30	10	10	100 mg/kg bw
		34	10	10	300 mg/kg bw
		30	10	10	1000 mg/kg bw
3.2.7	Control animals	Yes			
3.2.8	Mating period	Till vaginal plug was discovered – day zero post coitum.			
3.3	**Administration/ Exposure**	Dermal application			
3.3.1	Duration of exposure	mouse: day 6-15 post mating			
3.3.2	Postexposure period	Main study: day 16 – day 18 Supplementary study: the animals were killed on day 16.			
3.3.3	Type	Dermally on 10 % of the body surface, under occlusive dressings for six hours prior to rinsing with lukewarm water			
3.3.4	Concentration	Dermally 0, 100, 300, or 1000 mg/kg bw			
3.3.5	Vehicle	4 % CMC (carboxymethylcellulose sodium salt) in distilled water			
3.3.6	Concentration in vehicle	0, 4 %, 12 %, or 40 %			
3.3.7	Total volume applied	2.5 ml/kg bw			
3.3.8	Controls	Vehicle			
3.4	**Examinations**				
3.4.1	Body weight	Yes			
3.4.2	Food consumption	Yes			
3.4.3	Clinical signs	Yes – at least twice daily			
3.4.4	Examination of uterine content	Gravid uterine weight Number of corpora lutea – yes Number of implantations – yes			

Section A6.8.1(11) **Teratogenicity Study**

Annex Point IIA6.8.1 [redacted]**1990**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **mouse** (dermal application).

3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight, and Sex Ratio
3.4.5.2	Skelet	Yes – main study
3.4.5.3	Soft tissue	Yes – main study
3.5	**Further remarks**	The main study concerned the normal study parameter for a teratogenicity study whereas the supplementary study concentrated on reproduction data and histology of liver and adrenals (A) and clinical chemistry (B), respectively.

4 RESULTS AND DISCUSSION

4.1	**Maternal toxic Effects**	Toxic effects were confirmed in the supplementary study in dams of all dosed groups with respect to decreased weight of the adrenals and dose related decreased in weight of the adrenals relative to body weight (only significant in the 1000 mg/kg bw group). Livers of all dams of the 1000 mg/kg bw and of most of dams of the 300 hepatic fatty change of the periportal liver area. Slight (statistically significant) increase in the alanine aminotranferase (ALAT) activity was found only in the 1000 mg/kg group. Moderate and significant increases in cytochrome p-450 content and N-demethylase activity as well as a smaller but still statistically significant increase in O-demethylase activity were found in both 300 mg/kg and 1000 mg/kg groups.
4.2	**Teratogenic / embryotoxic effects**	There was no influence of dermal dosing with up to 1000 mg/kg bw HWG 1608 Technical on any teratogenic parameters. Slightly increased number of palatoschisis and supernumerary ribs were found in foetuses of the 1000 mg/kg bw day group, and these findings were interpreted as resulting from maternal toxic effects.
4.3	**Other effects**	The number of resorptions in the 100 and 300 mg/kg groups was significantly increased, and the mean post-implantation loss was significantly increased. This is most probably due to the unusually high number of implantations in these two groups.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	**The main study** was performed in accordance with OECD guidelines 414 and EPA guideline 83-3. Groups of 34 (control and mid dose groups) or 30 (low and high dose groups) mated females NMRI KFM-HAN mice were given daily dermal applications of 0, 100, 300, or 1000 mg/kg bw HWG 1608 Technical ([redacted] pure) on days 6 to 15 post coitum. The substance was dissolved in a 4 % carboxymethylcellulose sodium salt solution and was applied to shaved skin of the back (about 10 % of the body surface) in a volume of 2.5 ml/kg bw. The application was covered with an occlusive bandage and left for 6 hours and was then rinsed off with lukewarm water. The dams were inspected at least twice daily for mortality, clinical signs and changes in appearance and behaviour. Weights of the animals and food consumption were recorded at regular intervals. The dams were killed on day 18 post coitum (CO_2 asphyxiation) and the foetuses were removed by caesarean section. Post mortem examination, including gross macroscopic examination of all internal and all external organs, with emphasis on the uterus, uterine contents, position of foetuses in the uterus and number of corpora lutea, was performed and the data recorded. The foetuses were removed from

Section A6.8.1(11) **Teratogenicity Study**

Annex Point IIA6.8.1 [redacted]**1990**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **mouse** (dermal application).

		the uterus, sexed weighed individually, examined for gross external abnormalities and allocated to either Wilson's slicing techniques for examination of the viscera and brain – half of the live foetuses. The other half placed in potassium hydroxide solution and stained with alizarin red S and examined for skeleton abnormalities and all abnormalities were recorded. The uteri and contents of all uteri with live foetuses were weighed at necropsy on day 18 post coitum to enable calculation of the corrected body weight gain. If no implantation sites were evident, the uterus was placed in an ammonium sulphide solution. In **the supplementary study** groups of 2 x 10 mated females (part A and B) of the above strain were dosed in exactly the same manner as described above. The HWG 1608 technical used was [redacted] pure. Also observations and weighing of animals and food at regular intervals were performed as in the main study. All dams were sacrificed on day 16 post coitum and necropsied and the liver and adrenals of group A animals were weighed, the pregnancy status of the animals was recorded, and sections of liver and adrenals were examined histopathologically (group A). Before sacrifice of the study B dams blood samples were collected from non-fasted animals. Following this the females were sacrificed and necropsied. The pregnancy status was recorded and the entire liver was taken for analysis of the cytochrome P-450 content, and the N-demethylase and O-demethylase activities. The blood samples were analysed for aspartate aminotransferase, alanine aminotransferase, glutamate dehydrogenase and alkaline phosphatase.	
5.2	**Results and discussion**	Main study result: The external findings in the foetuses were similar in all groups (control and dosed animals) but the number was increased in the 1000 mg/kg group. Supplementary study results: The weight of the adrenals were decreased in all dosed animals, but the mean adrenal weight relative to the body weight was statistically significantly decreased in the 1000 mg/kg group when compared to controls. Histological examination revealed that all females of the 1000 mg/kg group and most of the females of the 300 mg/kg group had fatty changes of the periportal liver areas. The plasma alanine aminotransferase activity of the high dose dams was statistically significantly increased over controls. Mice of both the 300 and the 1000 mg/kg groups had significantly increased increased cytochrome P-450 contents and N-demethylase activities in the liver, but only the highest dose group had statistically significant increase in O-demethylase activity.	*
5.3	**Conclusion**	Only maternal toxicity was considered to be related to dermal application of doses up to 1000 mg/kg bw and only the high dose produced this maternal toxicity. The critical effect was fatty changes in the periportal liver area, accompanied by increases the activity of in mixed liver oxidase functions.	
5.3.1	LO(A)EL maternal toxic effects	300 mg/kg bw applied to shaved dorsal skin for 6 hours/day on day 6-15 post coitum. The critical effects are fatty changes of the periportal liver area, and stimulation of mixed-function oxidase activities.	
5.3.2	NO(A)EL maternal toxic effects	100 mg/kg bw applied to shaved dorsal skin for 6 hours/day on day 6-15 post coitum.	
5.3.3	LO(A)EL embryotoxic / teratogenic effects	None of the affections recorded are considered to be related to dosing with HWG 1608 Technical.	

Section A6.8.1(11) Teratogenicity Study

Annex Point IIA6.8.1

[redacted]**1990**, Embryotoxicity study (including teratogenicity) with HWG 1608 technical in the **mouse** (dermal application).

5.3.4	NO(A)EL embryotoxic / teratogenic effects	1000 mg/kg bw applied to shaved dorsal skin for 6 hours/day on day 6-15 post coitum.	
5.3.5	Reliability	[redacted]	*
5.3.6	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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	Control data		low dose 100 mg/kg	Medium dose 300 mg/kg	high dose 1000 mg/kg	dose-response + / -
	Historical	Study				
Number of dams examined	**25**	**26**	**25**	**26**	**27**	
Clinical findings during application of test substance						
Mortality of dams *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Abortions						
Body weight gain *day 0-end of test,*		[redacted]	[redacted]	[redacted]	[redacted]	
Food consumption *Day 6-16*		[redacted]	[redacted]	[redacted]	[redacted]	
Water consumption *if test substance is applied with drinking water*						
Pregnancies *%*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Necropsy findings in dams dead before end of test						

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	Control data		low dose 100 mg/kg	Medium dose 300 mg/kg	high dose 1000 mg/kg	dose-response + / -
	Historical	study				
Corpora lutea *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Implantations *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Resorptions *[*1] *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
total number of fetuses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
pre-implantation loss *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
post-implantation loss *[*1] *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
total number of litters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
fetuses / litter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
live fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
dead fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
fetus weight (mean) *[g]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
placenta weight (mean) *[g]*						
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

***1: A high number of dams were affected – but only in the low dose group**

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose 100 mg/kg	Medium dose 300 mg/kg	high dose 1000 mg/kg	dose-response + / -
	historical	study				
External malformations* *[%]*						
External anomalies*1 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Skeletal malformations* *[%]*						
Skeletal anomalies*2 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Skeletal variants*3						
Visceral malformations* *[%]*						
Visceral anomalies*4 *[%]*		[redacted]	[redacted]	[redacted]	[redacted]	
Variants visceral* *[%]*						

[redacted]

Section A6.8.1(12) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1995**, Combined report of embryotoxicity study and supplementary embryotoxicity study with HWG 1608 Technical (Tebuconazole) in the **mouse**.

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1 REFERENCE

1.1	**Reference**	[redacted], 1995, Combined report of embryotoxicity study (including teratogenicity) and supplementary embryotoxicity study (including teratogenicity) HWG 1608 (Tebuconazole) in the mouse. [redacted], Report No: [redacted], 1995-05-31 (unpublished).
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 – OECD Guideline for the Testing of Chemicals No. 414 ("Teratogenicity"), May 1981, and EPA, Pesticide Assessment Guidelines 83-3 ("Teratogenicity Study) revised edition, November 1984.
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608 Technical – common name Tebuconazole
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	
3.1.2.1	Description	Colourless-beige powder
3.1.2.2	Purity	[redacted] active substance in [redacted] and [redacted] active substance in [redacted]
3.1.2.3	Stability	The pure test article was in both studies stable for at least 4-5 month after termination of the dosing.
3.2	**Test Animals**	
3.2.1	Species	Mouse
3.2.2	Strain	NMRI KFM-HAN (outbred, SPF quality)
3.2.3	Source	[redacted]
3.2.4	Sex	Mated Females

Section A6.8.1(12) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1995**, Combined report of embryotoxicity study and supplementary embryotoxicity study with HWG 1608 Technical (Tebuconazole) in the **mouse**.

3.2.5	Age/weight at study initiation	Minimum 8 weeks/ 21-32 g ([redacted]) Minimum 8 weeks/ 22-33 g ([redacted])
3.2.6	Number of animals per group	RCC 319432: MAIN 35, SUBGROUP 10; RCC 360270: MAIN 30, SUBGROUP 7
3.2.7	Control animals	Yes
3.2.8	Mating period	Until spermatozoa in vaginal smear or vaginal plug observed
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure	mouse: day 6-15 post mating
3.3.2	Postexposure period	Day 16-18 post coitum for main groups – no postexposure period for subgroups
3.3.3	Type	Gavage
3.3.4	Concentration	Gavage 0, 10, 30, or 100 mg/kg bw ([redacted]) Gavage 0, 1, 3 mg/kg bw ([redacted])
3.3.5	Vehicle	0.5 % Cremophor EL in bidistilled water
3.3.6	Concentration in vehicle	0, 0.1, 0.3, or 1 % ([redacted]) 0, 0.01, or 0.03 % ([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
3.4.2	Food consumption	Yes
3.4.3	Clinical signs	Yes
3.4.4	Examination of uterine content	Gravid uterine weight Number of corpora lutea – yes Number of implantations – yes
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter Size, Nr. of dead Foetuses, Foetal Weight, Sex Ratio
3.4.5.2	Skeleton	Yes – main groups only
3.4.5.3	Soft tissue	Yes – main groups only

Section A6.8.1(12) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1995**, Combined report of embryotoxicity study and supplementary embryotoxicity study with HWG 1608 Technical (Tebuconazole) in the **mouse**.

3.5	**Further remarks**	The subgroup studies examined the following parameters: Blood was drawn from the pentobarbitone sacrificed mice (retro-orbital plexus) and subjected to full haematology and clinical chemistry. Organs that were weighed were: Adrenals, kidneys, liver, spleen, and the same organs plus all gross lesions were examined histopathologically. Furthermore liver tissue was examined for cytochrom P-450, N- and O-demethylase activities and for the content of triglycerides.	
		4 RESULTS AND DISCUSSION	
4.1	**Maternal toxic Effects**	10 mg/kg bw/day caused enzyme induction and vacuolisation of the livers of the maternal organism. 30 mg/kg bw/day caused marginally reduced food consumption and increase in the relative liver weight. Other signs of liver damage were pathological findings including lipid storage, increased levels of alkaline phosphatase in blood and increased activities of the cytochrom P-450 and N-demethylase in the liver tissue. 100 mg/kg bw/day resulted in reduced mean food consumption, marginally reduced weight gain, significantly increased liver weight and slight effects on the reticulocytes. Cytochrom P-450, N-demethylase and O-demethylase activities were all significantly increased in the livers of the high dose subgroup.	*
4.2	**Teratogenic / embryotoxic effects**	30 mg/kg bw/day caused marginally increases in post-implantation loss and in the frequency of external developmental findings and slight retardation of skeletal development. 100 mg/kg bw/day resulted in increases in the post-implantation loss and in the frequency of abnormal external findings in foetuses, reduced mean body weight of male foetuses, and retarded development of various ossification centres in both sexes.	
4.3	**Other effects**		
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In accordance with the OECD Guideline for the Testing of Chemicals No. 414 ("Teratogenicity"), May 1981, and the EPA, Pesticide Assessment Guidelines 83-3 ("Teratogenicity Study) revised edition, November 1984, groups of 35 or 30 (main studies) or 10 or 7 (subgroup studies) mated female NMRI (KFM-HAN) mice were given by gavage once daily on day 6 through to day 15 of gestation doses of HWG 1608. The test substance ([redacted] pure) was given suspended in 0.5 % Cremophor EL solution in doses of 0, 1, 3, 10, 30, or 100 mg/kg bw. The animals were inspected for mortality, clinical signs and changes in appearance or behaviour at least twice daily. Body weights were recorded daily and food consumption at regular intervals. Main group studies: The dams were necropsied on day 18 of gestation. Post mortem examination, including gross macroscopic examination of all internal organs was performed. The adrenals, the kidneys, the liver and the spleen from all gravid dams were weighed separately and prepared for histological examinations, and the gravid uteri were removed by caesarean section and weighed before opening. The following data were recorded in pregnant dams: Number of corpora lutea, number of implantation sites, litter size, position, weight and sex of each live foetus, and number of dead foetuses. The foetuses were	

Section A6.8.1(12) Teratogenicity Study

Annex Point IIA6.8.1

[redacted], **1995**, Combined report of embryotoxicity study and supplementary embryotoxicity study with HWG 1608 Technical (Tebuconazole) in the **mouse**.

		examined for external abnormalities, and visceral (half of the animals) and skeletal abnormalities and skeletal retardations (the other half of the animals). Subgroup studies: Blood specimens were taken from the retro-orbital plexus just prior to sacrifice of the dams on day 16 post coitum and were subjected to full haematological and clinical chemistry analysis. The gravid uteri were removed by caesarean operation and were weighed. All reproduction parameters were recorded (as above). The adrenals, the kidneys, the liver and the spleen from all gravid dams were weighed separately and prepared for histological examinations. Portions were taken from some livers for determination of the cytochrome P-450, the N-demethylase and the O-demethylase activities and the triglyceride content.	
5.2	**Results and discussion**	HWG 1608 Technical – Tebuconazole – exhibits maternal toxicity in pregnant NMRI mice in doses from 10 mg/kg bw/day administered orally on day 6 through to day 15 of gestation. The target organ is the liver. Doses of 30 and 100 mg/kg bw/day result in dose dependent increase in the post-implantation loss, and increased frequency of external developmental findings besides retarded development of various ossification centres. The mean weight of male foetuses was decreased in the high dose group. As the findings through examination of the foetuses are the normal findings in this mouse strain the increase in frequency is most probably caused by the maternal toxicity of the substance not an indication of primary developmental toxicity.	
5.3	**Conclusion**	HWG 1608 Technical is toxic to pregnant female NMRI mice in daily doses of 10 mg/kg bw administered by gavage on day 6 to day 15 of gestation. Daily doses of 30 mg/kg bw are toxic to reproduction – giving increased post-implantation loss, increased number of foetal anomalities and retarded ossification of the foetuses.	
5.3.1	LO(A)EL maternal toxic effects	10 mg/kg bw/day – enzyme induction and vacuolisation of the livers of the maternal organism.	*
5.3.2	NO(A)EL maternal toxic effects	3 mg/kg bw/day	*
5.3.3	LO(A)EL embryotoxic / teratogenic effects	30 mg/kg bw/day – marginal increase in abnormal external findings and in retardation of skeletal development.	
5.3.4	NO(A)EL embryotoxic / teratogenic effects	10 mg/kg bw/day	
5.3.5	Reliability	[redacted]	
5.3.6	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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects ([redacted])

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	Historical	Study				
Number of dams examined	**93**	**35 (10)**	**35 (10)**	**35 (10)**	**35 (10)**	
Clinical findings during application of test substance			[redacted]			
Mortality of dams *state %*		[redacted]		[redacted]	[redacted]	
Abortions		[redacted]				
Body weight gain *day 6-16*		[redacted]	[redacted]	[redacted]	[redacted]	
Food consumption *day 6-16*		[redacted]	[redacted]	[redacted]	[redacted]	
Water consumption *if test substance is applied with drinking water*						
Pregnancies *%*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Necropsy findings in dams dead before end of test		[redacted]				

Figures (and other information) in bracket relate to the subgroups-study

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data) ([redacted])

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
Corpora lutea *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Implantations *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Resorptions *state total/number of dams*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
total number of fetuses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
pre-implantation loss *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
post-implantation loss *state %*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
total number of litters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
fetuses / litter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
live fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
dead fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
fetus weight (mean) *[g]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
placenta weight (mean) *[g]*		[redacted]	[redacted]	[redacted]	[redacted]	
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Figures (and other information) in bracket relate to the subgroups-study

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses ([redacted])

Modify if necessary and give historical data if available

Parameter	control data		low dose 10 mg/kg	medium dose 30 mg/kg	high dose 100 mg/kg	dose-response + / -
	historical	study				
External malformations*[%]						
External anomalies*1 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Skeletal malformations*[%]						
Skeletal anomalies*2 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Visceral malformations* *[%]*						
Visceral anomalies*3 *[%]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[redacted]

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects ([redacted])

Modify if necessary and give historical data if available

Parameter	control data		low dose 1 mg/kg	medium dose	high dose 3 mg/kg	dose-response + / -
	historical	Study				
Number of dams examined	**98**	**30 (10)**	**30 (10)**		**30 (10)**	
Clinical findings during application of test substance						
Mortality of dams *state %*			[redacted]			
Abortions						
Body weight gain *day 6-16*		[redacted]	[redacted]		[redacted]	
Food consumption		[redacted]	[redacted]		[redacted]	
Water consumption *if test substance is applied with drinking water*						
Pregnancies *%*	[redacted]	[redacted]	[redacted]		[redacted]	
Necropsy findings in dams dead before end of test						

Figures (and other information) in bracket relate to the subgroups-study

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data) ([redacted])

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study	1 mg/kg		3 mg/kg	
Corpora lutea *state total/number of dams*	[redacted]	[redacted]	[redacted]		[redacted]	
Implantations *state total/number of dams*	[redacted]	[redacted]	[redacted]		[redacted]	
Resorptions *state total/number of dams*	[redacted]	[redacted]	[redacted]		[redacted]	
total number of fetuses	[redacted]	[redacted]	[redacted]		[redacted]	
pre-implantation loss *state %*	[redacted]	[redacted]	[redacted]		[redacted]	
post-implantation loss *state %*	[redacted]	[redacted]	[redacted]		[redacted]	
total number of litters	[redacted]	[redacted]	[redacted]		[redacted]	
fetuses / litter	[redacted]	[redacted]	[redacted]		[redacted]	
live fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]		[redacted]	
dead fetuses / litter *state ratio*	[redacted]	[redacted]	[redacted]		[redacted]	
fetus weight (mean) *[g]*	[redacted]	[redacted]	[redacted]		[redacted]	
placenta weight (mean) *[g]*						
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*	[redacted]	[redacted]	[redacted]		[redacted]	

Figures (and other information) in bracket relate to the subgroups-study

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses ([redacted])

Modify if necessary and give historical data if available

Parameter	control data		low dose 1 mg/kg	medium dose	high dose 3 mg/kg	dose-response + / -
	historical	study				
External malformations* *[%]*						
External anomalies* *[%]*	[redacted]	[redacted]	[redacted]		[redacted]	
Skeletal malformations* *[%]*						
Skeletal anomalies*2 *[%]*	[redacted]	[redacted]	[redacted]		[redacted]	
Skeletal variants* *[%]*						
Visceral malformations* *[%]*						
Visceral anomalies*3 *[%]*	[redacted]	[redacted]	[redacted]		[redacted]	
Variants visceral* *[%]*						

[redacted]

[redacted]

[redacted]

Section A6.8.2 Multigeneration Reproduction Toxicity Study

Annex Point IIA6.8.2 [redacted], **1987**, HWG 1608 – Two Generation Study in **Rats** (with Diet)

Official use only

1 REFERENCE

1.1	**Reference**	[redacted], 1987, HWG 1608 – Two-Generation Study in Rats. [redacted], Report No. [redacted], 1987-11-12 (unpuplished).
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 – OECD Guideline 416 and recommendations published by EPA: Modern Trends in Toxicology, Vol. 1, 1968, 75-85 Toxicol. Appl. Pharmacol. , Vol. 16, 1970, 264-369 Pesticide Assessment Guidelines, Subdivision F, 1983.
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	HWG 1608
3.1.1	Lot/Batch number	Mixed batch Fl. No. [redacted]
3.1.2	Specification	
3.1.2.1	Description	Whitish-beige powder
3.1.2.2	Purity	[redacted] active substance
3.1.2.3	Stability	Analysed approximately every 3 months
3.2	**Test Animals**	
3.2.1	Species	Wistar rat
3.2.2	Strain	Bor: WISW (SPF Cpb)
3.2.3	Source	[redacted]
3.2.4	Sex	Males and females
3.2.5	Age/weight at study initiation	Five-6 weeks, 76-107 g.
3.2.6	Number of animals per group	25 males and 25 females
3.2.7	Mating	Premating period in F0 generation until first mating: 120 days First mating period in F0 generation: 20 days Gestation – lactation (F1A pups) – waiting period: 64 days Second mating period F0 generation: 20 days Gestation – lactation (F1B pups) until approx. 100 days old: 91 days First mating period of F1B generation 20 days Gestation – lactation (F2A pups) – waiting period 64 days Second mating period of F1B generation 20 days Gestation period – lactation (F2B pups) 43 days

Section A6.8.2 Multigeneration Reproduction Toxicity Study

Annex Point IIA6.8.2 [redacted], **1987**, HWG 1608 – Two Generation Study in **Rats** (with Diet)

3.2.8	Duration of mating	To sperm positive vaginal smear – day 0 of gestation.
3.2.9	Deviations from standard protocol	Remating of the F0 generation to test insemination took place (instead of analysing sperm parameters).
3.2.10	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Animal assignment to dosage groups	See table below
3.3.2	Duration of exposure before mating	See above
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 or other
3.3.4	Type	in food
3.3.5	Concentration	Food 0, 100, 300, or 1000 ppm (0, 7.12, 21.60, or 72.27 mg/kg bw (F_0); 0, 9.24, 27.06, 97.20 mg/kg bw (F_{1B}) – males) (0, 9.07, 27.77, or 94.81 mg/kg bw (F_0); 0, 11.10, 33.87, 111.40 mg/kg bw (F_{1B}) – females) food consumption per day 19-21g (F_0); 24-22 g (F_{1B}) (males) and 15-16 g (F_0); 17-19 g (F_{1B}) (females) when fed *ad libitum*;
3.3.6	Controls	plain diet
3.4	**Examinations**	
3.4.1	Clinical signs	Yes – twice daily on work days – once daily on weekends
3.4.2	Body weight	Yes – weekly
3.4.3	Food/water consumption	Food consumption but not water consumption was recorded
3.4.4	Oestrus cycle	No measurements
3.4.5	Sperm parameters	testis weight – no epididymis weight – no enumeration of homogenisation-resistant spermatids in testes and epididymis – no enumeration of cauda epididymal sperm reserve – no sperm motility – no sperm morphology – no or other – no

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

Annex Point IIA6.8.2 [redacted], **1987**, HWG 1608 – Two Generation Study in **Rats** (with Diet)

3.4.6	Offspring	number and sex of pups – yes stillbirths – yes live births – yes presence of gross anomalies – yes weight gain – yes physical or behavioural abnormalities – yes
3.4.7	Organ weights P and F1	Uterus – no Ovaries – yes Testes – yes epididymes (total and cauda) – no prostate – no seminal vesicles – no brain – no liver – yes kidneys – yes spleen – yes pituitary – no thyroid – no adrenal glands – yes known target organs – no target organ identified in this study
3.4.8	Histopathology P and F1	Vagina – no Uterus – yes Ovaries – yes Testis – yes Epididymis – yes seminal vesicle – no prostate – yes coagulating gland – no known target organs – no target organ identified in this study
3.4.9	Histopathology F1 not selected for mating, F2	Vagina – no Uterus – yes Ovaries – yes Testis – no Epididymis – no seminal vesicle – no prostate – no coagulating gland – no known target organs – no target organ identified
3.5	**Further remarks**	–

4 RESULTS AND DISCUSSION

4.1	**Effects**	
4.1.1	Parent males	Reduced weight gain in the 1000 ppm group
4.1.2	Parent females	Reduced litter size in 1000 ppm group
4.1.3	F1 males	Reduced body and kidney weights in 1000 ppm group
4.1.4	F1 females	Reduced pup weight in 1000 ppm group
4.1.5	F2 males	Reduced weight a birth in 1000 ppm group
4.1.6	F2 females	Reduced weight a birth in 1000 ppm group
4.2	**Other**	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

In accordance with OECD Guideline 416 and recommendations puplished by EPA: Modern Trends in Toxicology, Vol. 1, 1968, 75-85, Toxicol. Appl. Pharmacol. , Vol. 16, 1970, 264-369, Pesticide Assessment Guidelines, Subdivision F, 1983. HWG 1608 was tested in a two generation study in Wistar rats. Groups of 25 males and females were fed diets containing 0, 100, 300 or 1000 ppm [redacted] pure HWG 1608 for 120 days before mating. No other ration was fed to the test animals throughout the study. The animals were observed for clinical or behavioural symptoms at least once daily. Food and tap water were supplied *ad libitum*. Food consumption and body weights were recorded during the whole study. The F0 generation mated twice to yield first the F1A generation and then the F1B generation (and those dams that had not been inseminated were mated an extra time with surely fertile males to test their fertility – they all produced pups). The F1B generation was mated (siblings mating was avoided) twice to yield F2A and F2B generations. All fertility data were recorded at all matings. Litters were reduced to – as far as possible – 4 male and 4 female pups each after 4 days. Viability data, lactation indices etc. were calculated. Pups of the F1A generation and the F2A generation were killed after weaning and were examined for external malformations. After weaning of the F2B generation all animals were sacrificed and subjected to full necropsy, incl. measuring femur bones, and recording of organ weights. Parent animals were sacrificed as soon as possible after second mating, respectively nursing the pups (read above with respect to "infertile" females and surely fertile males of the F0 generation, though).

5.2 Results and discussion

All doses below 1000 ppm caused no changes in behaviour and appearance of any animals. It did not affect food intake, weight gain, insemination, or gestation parameters, nor did it affect pup weight, viability index or lactation index. Litter size was reduced after 1000 ppm. No malformations were seen up to 1000 ppm. Parents and pups gained weight more slowly after 1000 ppm. All organ weights were reduced after 1000 ppm. No impairing of bone growth was measured. The No-effect level for HWG 1608 is 300 ppm with the food in this 2-generation study in Wistar rats. Negative effects of feeding 1000 ppm HWG 1608 include decreased food consumption, retarded weight gain in parents and pups, and temporarily impaired reproduction.

5.3 Conclusion

All doses up to and including 300 ppm in the diet showed no effects on any parameter measured in this two-generation study in Wistar rats.

5.3.1 LO(A)EL

1000 ppm: Critical effects are – decreased litter size, decreased food consumption, retarded weight gains for parents and pups, and organ weight decrease corresponding to the decreased body weights.

5.3.1.1 Parent males

Reduced weight gain at 1000 ppm.

5.3.1.2 Parent females

Reduced foetal weight at 1000 ppm

5.3.1.3 F1 males

Reduced weight gain at 1000 ppm

5.3.1.4 F1 females

Reduced foetal weight at 1000 ppm

5.3.1.5 F2 males

Retarded weight gain at 1000 ppm

5.3.1.6 F2 females

Reduced foetal weight after 1000 ppm

5.3.2 NO(A)EL

Section A6.8.2	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2	[redacted], **1987**, HWG 1608 – Two Generation Study in **Rats** (with Diet)
5.3.2.1 Parent males	300 ppm
5.3.2.2 Parent females	300 ppm
5.3.2.3 F1 males	300 ppm
5.3.2.4 F1 females	300 ppm
5.3.2.5 F2 males	300 ppm
5.3.2.6 F2 females	300 ppm
5.3.3 Reliability	[redacted]
5.3.4 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	July 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Table A6_8_2-1. Table for animal assignment for mating (modify as appropriate)

F_0 – first mating		Number of animals			
		Controls	Low Dose	Medium Dose	High Dose
Parents	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]
F_{1A}	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]

Table A6_8_2-1. Table for animal assignment for mating (modify as appropriate)

F_0 – second mating		Number of animals			
		Controls	Low Dose	Medium Dose	High Dose
Parents	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]
F_{1B}	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]

Table A6_8_2-1. Table for animal assignment for mating (modify as appropriate)

F_{1B}- first mating		Number of animals			
		Controls	Low Dose	Medium Dose	High Dose
Parents	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]
F_{2A}	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]

Table A6_8_2-1. Table for animal assignment for mating (modify as appropriate)

F_{1B}- second mating		Number of animals			
		Controls	Low Dose	Medium Dose	High Dose
Parents	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]
F_{2B}	m	[redacted]	[redacted]	[redacted]	[redacted]
	f	[redacted]	[redacted]	[redacted]	[redacted]

Table A6_8_2-2. Table for reproductive toxicity study (modify if appropriate)

If effects are found in one generation, the figures for the other generation(s) should be given as well (as shown as an example for mortality). Give only information on endpoints with effects, delete other endpoints.

Parameter			control		low dose 100 ppm		medium dose 300 ppm		High dose 1000 ppm			
		Genera-tion	m	f	m	f	m	f	m	f	m	f
Mortality	incidence	**P**										
		F_{1B}										
		F_2										
F_0-generation												
Food consumption	% of control											
Body weight gain	% of control											
Pathology												
Histopathologic examination *Specify effects*	Incidence											
Reproductive Performance												
First mating												
Mating index												
Fertility index												
Duration of pregnancy	Mean											
Gestation index												
Litter size	Mean											
Pup weight	Mean											
Sex ratio	Male/female											
Viability index												
Lactation index												
Number	% of control											
Deformations – pups reduced in size	No. of litters affected											

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8_2-2. Table for reproductive toxicity study (modify if appropriate)

If effects are found in one generation, the figures for the other generation(s) should be given as well (as shown as an example for mortality). Give only information on endpoints with effects, delete other endpoints.

Parameter			control		Low dose 100 ppm		medium dose 300 ppm		High dose 1000 ppm			
		Genera-tion	m	f	m	f	m	f	m	f	m	f
F_0												
Second mating												
Mating index												
Fertility index												
Duration of pregnancy	Mean											
Gestation index												
Litter size	Mean											
Pup weight	Mean											
Sex ratio	Male/female											
Viability index												
Lactation index												
Number	% of control											
Deformations – pups reduced in size	No of litters affected											

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8_2-2. Table for reproductive toxicity study (modify if appropriate)

If effects are found in one generation, the figures for the other generation(s) should be given as well (as shown as an example for mortality). Give only information on endpoints with effects, delete other endpoints.

Parameter			Control		Low dose 100 ppm		medium dose 300 ppm		High dose 1000 ppm			
			m	f	m	f	m	f	m	f	m	f
F_{1B}-generation												
Food consumption	% of control											
Body weight gain	% of control											
Organ weights	% of control	**Body**										
Organ weights	% of control	**Liver**										
Organ weights	% of control	**Kidneys**										
Organ weights	% of control	**Adrenals**										
Rel. Organ weights	% of control	**Liver/ body**										
Rel. Organ weights	% of control	**Kidney/ body**										
Rel. Organ weights	% of control	**Adrenal/ body**										
Rel. Organ weights	% of control	**Testes/ body**										
Pathology												
Histopathologic examination *specify effects*	Incidence											
Reproductive Performance												
First mating												
Mating index												
Fertility index												
Duration of pregnancy	Mean											
Gestation index												
Litter size	Mean											
Pup weight	Mean											
Sex ratio	Male/female											
Viability index												
Lactation index												
Number	% of control											
Deformations – pups reduced in size	% of control											

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Table A6_8_2-2. Table for reproductive toxicity study (modify if appropriate)

If effects are found in one generation, the figures for the other generation(s) should be given as well (as shown as an example for mortality). Give only information on endpoints with effects, delete other endpoints.

Parameter			Control		low dose 100 ppm		medium dose 300 ppm		High dose 1000 ppm			
			m	f	m	f	m	f	m	f	m	f
F_{1B}												
Second mating												
Mating index			[redacted]									
Fertility index			[redacted]									
Duration of pregnancy	Mean		[redacted]									
Gestation index			[redacted]									
Litter size	Mean		[redacted]									
Pup weight	Mean		[redacted]									
Sex ratio	Male/female		[redacted]									
Viability index			[redacted]									
Lactation index			[redacted]									
Number	% of control		[redacted]									
Deformations – pups reduced in size	% of control											

* Significantly different from study controls ($p \leq 0.05$)

** Significantly different from study controls ($p \leq 0.01$)

Section 6.11 Annex Point IIIA 11.2	Studies on other routes of administration (parenteral routes)	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	Studies on parenteral routes are not a data requirement with respect to actives used in wood preservatives.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.12.2 Annex Point IIA 6.9.2	Direct observations, e.g. clinical cases, poisoning incidents, if available	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	No direct observations of poisoning incidents etc. are available.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.12.4 Annex Point IIA 6.9.4	Epidemiological studies on the general population, if available	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	No epidemiological studies on tebuconazole on the general population are available.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.12.5 Annex Point IIA 6.9.5	Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	No information on specific signs of poisoning and clinical tests is available.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.12.6 Annex Point IIA 6.9.6	Sensitisation/allergenicity observations, if available	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	No information on sensitisation/allergenicity is available.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.12.8 Annex Point IIA 6.9.8	Prognosis following poisoning	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	Because no information on poisoning is available also no information is available on the prognosis after poisoning.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.14 / 6.16 Annex Point IIIA 11.2	Other tests related to humans / any other tests relating to human exposure of the active in the proposed biocidal products	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	[redacted]	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.15.1 - 6.15.6 Annex Point IIIA 11.1.1 - 11.1.9	Residues in Food and Feedstuffs	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...] **Limited exposure [X]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	[redacted] [redacted] Due to the non-intended exposure to food and feedstuffs it is justified not to submit data on residues in food and feedstuffs in the scope of the BPD submission as active in wood preservatives.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section 6.17 Annex Point IIIA	Toxic effects of metabolites in plants	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [...]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [X]	**Other justification [X]**	
Detailed justification:	[redacted] Therefore Point 6.17 does not apply and it is justified not to submit data on this point.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	July 2005	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Competent Authority Report

According to Directive 98/8/EC on Biocidal Products

Tebuconazole

CAS No.: 107534-96-3

ELINCS No.: 403-640-2

Document III-A.7

Documentation summaries

from Lanxess Deutschland GmbH

for use in wood preservatives (Product type 8)

Reporting Member State: Denmark

May 2007

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

Official use only

		1 REFERENCE
1.1	**Reference**	Coffmann, M.W. and Sietsema, W.K. (1984), Hydrolysis Study of BAY HWG 1608 in Sterile Aqueous Buffered Solutions. Mobay Corporation Agricultural Chemicals Division Research and Development Department, USA, Report MR 88726
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**	EPA Pesticide Guidelines, Ref. 161-1 Hydrolysis studies
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]
		3 MATERIALS AND METHODS
3.1	**Test material**	Phenyl-UL-14- radiolabelled test substance
3.1.1	Lot/Batch number	Vial number C-316 prepared by [redacted] (1984)
3.1.2	Specification	
3.1.4	Purity	Radiochemical purity [redacted]
3.1.5	Further relevant properties	
3.2	**Reference substance**	No
3.2.1	Initial concentration of reference substance	A solution of 1800 mg/l[phenyl.UL-14C) BAY HWG 1608 (tebuconazole) in acetonitrile was used to fortify 0.1 M phosphate buffer solutions to an initial concentration of 18 mg tebuconazole/l
3.3	**Test solution**	For details see also table A7_1_1_1_1-1and A7_1_1_1_1-2
3.4	**Testing procedure**	
3.4.1	Test system	60 ml Teflon bottles were sterilised, filled with sterilised buffer solutions and incubated for 28 days in the dark.
3.4.2	Temperature	All experiments run at 25 ± 1 °C
3.4.3	pH	5.05 -> 5.1 / 7.05 -> 6. 90 / 8.95 -> 9.1 (initial -> final)

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

3.4.4	Duration of the test	28 days
3.4.5	Number of replicates	Two replicates per sampling (except day 0)
3.4.6	Sampling	Sampling after 0, 1, 4, 7, 14, 21and 28 days, aliquots from each sample (40 ml fortified buffer) were taken at the beginning and at the end of each sampling period during the experiment.
3.4.7	Analytical methods	HPLC (reversed phase chromatography), identification of representative samples by mass spectroscopy
3.5	**Preliminary test**	No

4 RESULTS

4.1	**Concentration and hydrolysis values**	Tebuconazole (BAY HWG 1608) was stable during the experiment at all pH values tested (for details see table A7_1_1_1_1-4)
4.2	**Hydrolysis rate constant (kh)**	no hydrolysis rate was observed at all pH values
4.3	**Dissipation time**	no DT 50 or DT 90 can be given due to the stability of the a.i. (tabular form; see table A7_1_1_1_1-5)
4.4	**Concentration – time data**	Nominal concentration of a.i. was 18 mg/. For variations see table 1 in the report. No graph available.
4.5	**Specification of the transformation products**	not applicable (no transformation products).

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The hydrolysis test was performed according the EPA Guideline at pH 5, 7, and 9 at 25 °C in sterile phosphate buffer solutions. The buffer solutions were fortified with a stock solution of radiolabelled tebuconazole (> 99%). The resulting 0.1 M test solutions contained about 18 mg/l tebuconazole/l and were incubated 28 days in the dark.
5.2	**Results and discussion**	No degradation of tebuconazole was observed during the experiment. The material balance was between 97.3 and 106.9%, indicating that no volatilisation took place.
5.2.1	k_H	-
5.2.2	DT_{50}	-
5.2.3	r^2	-
5.3	**Conclusion**	The results of the hydrolysis study are in accordance with a previous study at higher temperatures which resulted in extrapolated half-lives of > 100 days for 22 °C and pH 4, 7 and 9 (Krohn, May 1984) . Taking in account also the chemical structure of tebuconazole, it can be concluded that abiotic hydrolysis does not contribute to the degradation of the active under environmental conditions.
5.3.1	Reliability	Reliability indicator [redacted]

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

5.3.2 Deficiencies [redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*01 04 04*
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 A7_1_1_1_1-1: Type and composition of buffer solutions (specify kind of water if necessary)

pH	Type of buffer (final molarity)	Composition
5	0.1 M phosphate buffer	0.1 M KH_2PO_4 in distilled water adjusted to pH 5 with 0.1 M Na_2HPO_4 in distilled water
7	0.1 M phosphate buffer	0.1 M KH_2PO_4 in distilled water adjusted to pH 7 with 0.1 M Na_2HPO_4 in distilled water
9	0.1 M phosphate buffer	0.1 M KH_2PO_4 in distilled water adjusted to pH 9 with 0.1 M Na_3PO_4 in distilled water

Table A7_1_1_1_1-2: Description of test solution

Criteria	Details
Purity of water	Distilled, sterile water
Preparation of test medium	The buffer solutions were sterilised and fortified with a stock solution (1800 mg/l) of tebuconazole.
Test concentrations (mg a.i./L)	About 18 mg/l
Temperature (°C)	25 °C
Controls	No
Identity and concentration of co-solvent	Acetonitrile (1%) from the 1800 mg/l stock solution
Replicates	Day zero no replicate, one replicate on each following sampling point (1, 4, 7, 14, 21, 28 days)

Table A7_1_1_1_1-3: Description of test system

Glassware	60 ml teflon flasks, glass pipettes etc.
Other equipment	HPLC (Varian) , autoclave, pH-meter, water bath, thermostat
Method of sterilisation	1 hour at 121°C in an autoclave (buffer solutions), all transfers under a flame canopy

Table A7_1_1_1_1-4: Hydrolysis of test compound expressed as measured difference between initial and final concentration (mg/l, mean from replicate samplings, nominal initial concentration = 18 mg/l) at pH 5, pH 7 and pH 9. For source data, see table I in the report.

Parent compound	Sampling times (*days*)							
	0	1	4	7	14	21	28	
pH 5	[redacted]							
pH 7	[redacted]							
pH 9	[redacted]							
Total % recovery								

Table A7_1_1_1_1-5: Dissipation times of parent compound, transformation products and reference compound at pH 5, pH 7 and pH 9

	pH 5		pH 7		pH 9	
	DT_{50}	DT_{90}	DT_{50}	DT_{90}	DT_{50}	DT_{90}
Parent compound	[redacted]					
Transformation product 1						
Transformation product 2						
Transformation product n						
Reference compound						

* > 100 days at pH 4, 7 and 9 based on extrapolation from higher temperatures (Krohn, Bayer/Mobay Report October 28, 1983, enlarged OECD preliminary test)

Table A7_1_1_1_1-6: Specification and amount of transformation products

CAS-Number	*CAS and/or IUPAC* Chemical Name*(s)*	Amount [%] of parent compound measured at		
		pH 5	pH 7	pH 9
[redacted]				

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	Spare, W.C. (1983), Determination of the hydrolysis rate constants of 1,2,4-triazole. Ciba-Geigy Corporation (U.S.A.), meanwhile owned by the TDMG; unpublished report No. 83-E-074	1.1
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**	Not available at time of study	
2.2	**GLP**	[redacted]	
2.3	**Deviations**	[redacted]	
		3 MATERIALS AND METHODS	
3.1	**Test material**	[3,5-^{14}C]-1,2,4-triazole	
3.1.1	Lot/Batch number		
3.1.2	Specification	0.7 MBq/mg (= 18.8mCi/mg)	
3.1.4	Purity	Radiochemical purity [redacted]	
3.1.5	Further relevant properties		
3.2	**Reference substance**	No	
3.2.1	Initial concentration of reference substance		
3.3	**Test solution**	Test solutions were prepared under sterile conditions. Aliquots of a stock solution with a concentration of 1 mg/mL were added to buffer solutions to achieve a final concentration of 10 mg/L.	
3.4	**Testing procedure**		
3.4.1	Test system	The sterile, buffered test solutions (pH 5, 7 and 9, concentration of test compound 10 mg/L) were left to stand at 25 °C and under exclusion of light.	
3.4.2	Temperature	25 ± 1°C	
3.4.3	pH	See Table A7_1_1_1_1-1 pH 5: sodium acetate adjusted with acetic acid	

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

		pH 7: $NaH_2PO_4 + K_2PO_4$ pH 9: $Na_2B_4O_7$ adjusted with acetic acid
3.4.4	Duration of the test	30 days
3.4.5	Number of replicates	Two replicates per sampling (samples were taken 6 times at day)
3.4.6	Sampling	Sampling after 0, 1, 3 6, 13 and 30 days.
3.4.7	Analytical methods	TLC (silica gel), autoradiography and the radioactive spots were scrapped off and radioactivity was quantified by liquid scintillation counting (LSC)
3.5	**Preliminary test**	No
		4 RESULTS
4.1	**Concentration and hydrolysis values**	No degradation of 1,2,4-triazole was observed.
4.2	**Hydrolysis rate constant (kh)**	No hydrolysis rate was observed at all pH values
4.3	**Dissipation time**	No DT50 or DT90 can be given due to the stability of the test compound.
4.4	**Concentration – time data**	Nominal concentration of 1,2,4-triazole was 10 mg/L.
4.5	**Specification of the transformation products**	not applicable (no transformation products).
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	The hydrolysis test was performed at pH 5, 7, and 9 at 25 °C in sterile buffer solutions. The buffer solutions were fortified with a stock solution of radiolabelled 1,2,4-triazole (radiochemical purity [redacted] The resulting test solutions contained about 10 mg/1,2,4-triazole and were incubated 30 days in the dark.
5.2	**Results and discussion**	No degradation of 1,2,4-triazole was observed during the experiment.
5.2.1	k_H	-
5.2.2	DT_{50}	-
5.2.3	r^2	-
5.3	**Conclusion**	At all three tested pH values 5, 7 and 9 1,2,4-triazolewas found to be stable for 30 days at 25°C.
5.3.1	Reliability	Reliability indicator: [redacted]
5.3.2	Deficiencies	[redacted]

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*April 07*
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 A7_1_1_1_1-1: Type and composition of buffer solutions (specify kind of water if necessary)

pH	Type of buffer (final molarity)	Composition
5	0.01 mol/L acetate buffer	0.01 mol/L sodium acetate solution adjusted to pH5 with acetic acid, sterile
7	0.067 mol/L phosphate buffer	30 mL of sodiumdihydrogenphosphate solution, c(NaH2PO4)=0.067 mol/L added with 61 mL of dipotassiumhydrogenphosphate solution, c(K2HPO4)=0.067 mol/L diluted at a ratio 1:10 with water, sterile
9	0.025 mol/L borate buffer	sodiumtetraborate--solution, c($Na_2B_4O_7$)=0.025 mol/L adjusted to pH 9 with acetic acid, sterile

Section A7.1.1.1.2 Phototransformation in water including identity of transformation products

Annex Point IIA7.6.2.2

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		1 REFERENCE
1.1	**Reference**	E. Hellpointner, 1990, Determination of the Quantum yield and Assessment of the Environmental Half-Life of the Direct Phtotodegradation in Water, Bayer AG, Crop Protection Research, Environmental Research, Institute for Metabolism Research, Study No. M 112 0342–3
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**	No, but Draft Test Guideline "Phototransformation of Chemicals in Water", UBA (German "Umweltbundesamt"); November 1998
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]
		3 MATERIALS AND METHODS
3.1	**Test material**	Tebuconazole = alpha[2-(4-chlorophenyl)ethyl].alpha-(1,1-dimethylethyl)-1H-1,2,4-traizole-1-ethanol
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	Reference substance
3.1.4	Purity	[redacted]
3.1.5	Radiolabelling	no
3.1.6	UV/VIS absorption spectra and absorbance value	UV/VIS absorption spectra and extinction data are given in the report: -> **no measurable absorbance at wavelengths above 289 nm**
3.1.7	Further relevant properties	-
3.2	**Reference substance**	not available from the report

Section A7.1.1.1.2 Phototransformation in water including identity of transformation products

Annex Point IIA7.6.2.2

3.3	**Test solution**	For the recording of the UV absorption spectrum a solution of tebuconazole in highly pure water was prepared by stirring about 20 mg over night in pure water. This resulted in a solution of 16.4 mg/l (analysed by HPLC). To prepare a higher concentrated solution for verification of the UV spectral data 45.2 mg tebuconazole were dissolved in 10 ml acetonitrile and diluted 1: 100 with highly pure water.
3.4	**Testing procedure**	
3.4.1	Test system	According to the UBA guideline the photodegradation experiment was not carried out, because the UV spectrum showed no UV absorption above 290 nm.
3.4.2	Properties of light source	n.a.
3.4.3	Determination of irradiance	n.a.
3.4.4	Temperature	n.a.
3.4.5	pH	n.a.
3.4.6	Duration of the test	n.a.
3.4.7	Number of replicates	n.a.
3.4.8	Sampling	
3.4.9	Analytical methods	HPLC with UV detection (for the analysis of the aqueous solutions of tebuconazole for UV-spectral measurements)
3.5	**Transformation products**	No
3.5.1	Method of analysis for transformation products	n.a.
		4 RESULTS
4.1	**Screening test**	-> UV absorption spectrum
4.2	**Actinometer data**	n.a.
4.3	**Controls**	n.a.
4.4	**Photolysis data**	
4.4.1	Concentration values	n.a.
4.4.2	Mass balance	n.a.
4.4.3	k^c_p	n.a.
4.4.4	Kinetic order	n.a.

Section A7.1.1.1.2 Phototransformation in water including identity of transformation products

Annex Point IIA7.6.2.2

4.4.5	k^c_p / k^a_p	n.a.
4.4.6	Reaction quantum yield (ϕ^c_E)	not determined
4.4.7	k_{pE}	see 4.4.8
4.4.8	Half-life ($t_{1/2E}$)	Assuming the maximum quantum yield of 1 a half-live of > 1 year in environmental water bodies results due to the missing sunlight absorption of the tebuconazole molecule.
4.5	**Specification of the transformation products**	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The UV spectra were recorded using a UV-Vis spectrometer DMS 90 (Varian Co.) with Apple IIe as evaluation unit
5.2	**Results and discussion**	No light absorbance above 289 nm was found in the UV spectrum of tebuconazole in water. Therefore tebuconazole is assumed to be stable against direct photolysis in water.
5.2.1	½k^c_p	
5.2.2	K_{pE}	
5.2.3	ϕ^c_E	
5.2.4	$t_{1/2E}$	
5.3	**Conclusion**	Due to its lack of UV absorbance in the sunlight region tebuconazole is not degradable by <u>direct</u> phototransformation. Nevertheless some simulation experiments show that due to indirect photolysis (e.g. via oxygen related radicals) an enhancement of the degradation of tebuconazole in surface waters occur **(see annex)**
5.3.1	Reliability	Reliability indicator = [redacted]
5.3.2	Deficiencies	[redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	*01 04 04*
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]

Section A7.1.1.1.2 Phototransformation in water including identity of transformation products

Annex Point IIA7.6.2.2

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	

Annex (Photolysis)

Research projects were initiated to investigate the degradation and metabolism of [phenyl-UL-^{14}C]- and [triazole-3,5-^{14}C] tebuconazole in natural water, considering realistic environmental conditions (Fritz and Brauner, 1990; Fritz, 1990 a+b).

In the first study (Fritz and Brauner, 1990) surface water containing environmentally relevant amounts of nitrate (50 mg/L) and humic acids (10-50 mg/L) was treated with tebuconazole (phenyl- and triazolyl-labelled) at a concentration of 0.375 mg/L. The glass aquaria were installed outdoors on a temperature controlled table (adjusted to 20 °C) under natural insolation and they were aerated continuously. After 58 days incubation (257 hours of sunshine) 26.5% of unchanged parent compound could still be determined in the water.

In case of natural water treated at a 5-fold higher rate but without addition of nitrate and humic acids, 30.2% of tebuconazole were found after 243 days (1160 hours of sunshine).

In a parallel running test, natural water (without "sensitizers") treated at a 20-fold higher rate with triazolyl-labelled tebuconazole was exposed to artificial light. At the end of the experiment, after 119 days only 12 % of unchanged tebuconazole were recovered from the surface water.

Main metabolites found in the water were the KFE 1224 and JA-231-2, which amounted 2.7 to 40.2% depending on the experimental conditions. Also triazole was found at higher concentrations from < 3% (field conditions) up to 18.3% (under artificial light), while the other identified metabolites occurred in smaller quantities only of < 2.6%. The low recovery rate (47.4%) in the experiment with the [phenyl-UL-^{14}C]-tebuconazole can be explained basically by the fact of mineralisation to CO_2.

In the second experiment (Fritz, 1990a) surface water with and without addition of environmentally relevant amounts of nitrate was treated with [phenyl-UL-^{14}C]-tebuconazole at a concentration of 0.375 mg/L and exposed to natural sun light in the field and during winter time incubated in the greenhouse.

The influence of the additional nitrate (50 mg/L) is demonstrated by the fact that only 7% tebuconazole were found after 53 days incubation compared to about 30% from the water without additional nitrate. The corresponding values from the 503 day samples were 0% and about 8%, respectively. It was shown that the degradation rate increased with higher concentrations of the active substance, i.e. after 75 days were found 37% parent compound in case of a 5-fold application rate and 76% in case of a 20-fold higher application rate.

The active ingredient was intensively metabolised, being 22 to 39% of the applied radioactivity transformed into CO_2 already after 54 days and 32 to 54% after 503 days.

In the last study (Fritz, 1990b) sterilized and natural water were treated each at the same rate of 0.375 mg/L tebuconazole (phenyl- and triazolyl-labelled) and incubated under artificial light for 53 days. In the test with sterilized water, 52 to 64% of unchanged parent compound were recovered after 15 to 18 days.

In the natural water experiment 56 to 60% tebuconazole were degraded after 28 days and 92 to 97% at the end of the experiment, after 53 days. After this period only 1% CO_2 had been formed in the natural water with the triazole-labelled tebuconazole compared to about 54% CO_2 liberated from the water treated with the phenyl-labelled compound.

As already found in the study of Fritz and Brauner (1990), KFE 1224 and JA-231-2 were the main metabolites besides triazole. The quantities found of KFE 1224 and JA-231-2 were up to 21 and 26.4%, respectively, while triazole reached the amount of 14% after 53 days.

References:

Fritz, R. and Brauner, A.; (1990)

Experiments on the environmentally relevant degradation of tebuconazole in water.

Report No.: PF3594, Bayer AG, Germany; unpublished, January 15, 1990

Fritz, R.; (1990a)

Experiments on the degradation of tebuconazole in natural water at different rates of application and with the addition of "sensitises" with exposure to sunlight
Report No.: PF3595, Bayer AG, Germany; unpublished, January 15, 1990

Fritz, R.; (1990b)

Balance experiments on the degradation of tebuconazole in natural water with the exposure to artificial light.
Report No.: PF3596, Bayer AG, Germany; unpublished, January 15, 1990

Section A7.1.1.1.2 Phototransformation in water including identity of the products of transformation

Annex Point IIA7.6.2.2

Official use only

1 REFERENCE

1.1	**Reference**	Miller, G.C. (1983), Sunlight photolysis of 1,2,4 triazole in distilled water and humic acid solutions. University of Nevada Reno, USA, ordered by Ciba Geigy, now Syngenta AG, unpublished report, No. M9224
1.2	**Data protection**	[redacted]
1.1.1	Data owner	[redacted]
1.1.2	Companies with letter of access	[redacted]
1.1.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

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

3 MATERIALS AND METHODS

3.1	**Test material**	[3,5-^{14}C]-1,2,4-triazole
3.1.1	Lot/Batch number	Not specified in the report
3.1.2	Specification	
3.1.4	Purity	Not specified in the report
3.1.5	Further relevant properties	0.709 MBq/mg (= 18.9 µCi/mg)
3.2	**Reference substance**	1,2,4-triazole
3.2.1	Initial concentration of reference substance	Not specified as it was only used for comparative chromatography
3.3	**Test solution**	Radioactively labelled 1,2,4-triazole diluted at a concentration of 80 mg/L in distilled water and humic acid solution. In a third experiment 2% acetone was added
3.4	**Testing procedure**	
3.4.1	Test system	Radioactively labelled 1,2,4-triazole diluted at a concentration of 80 mg/L in distilled water and humic acid solution (mixture similar to natural water) was exposed to natural sunlight for 30 days. Additionally, a test with 2% acetone as sensitizer in distilled water was performed.
3.4.2	Temperature	Not specified

Section A7.1.1.1.2 Phototransformation in water including identity of the products of transformation

Annex Point IIA7.6.2.2

3.4.3	pH	initial / final: 6.4 / 7.6 (test in distilled water) 7.8 / 7.6 (test with addition of humic acid)
3.4.4	Duration of the test	30 days
3.4.5	Number of replicates	1
3.4.6	Sampling	Sampling after 3, 10, 20 and 30 days.
3.4.7	Analytical methods	The total radioactivity of the irradiated samples was determined by liquid scintillation counting. TLC methods including co-chromatography with the unlabelled reference substance were applied for the identification of [^{14}C]triazole. The radioactive zones were scraped from the plates and the radioactivity measured by LSC.
3.5	**Preliminary test**	No

4 RESULTS

4.1	**Concentration and hydrolysis values**	No degradation of 1,2,4-triazole was observed.
4.2	**Photolysis rate constant (kh)**	No photolysis was observed.
4.3	**Dissipation time**	No DT50 or DT90 can be given due to the stability of the test compound.
4.4	**Concentration – time data**	Nominal concentration of 1,2,4-triazole was 80 mg/L.
4.5	**Specification of the transformation products**	not applicable (no transformation products).

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Radioactively labelled 1,2,4-triazole diluted at a concentration of 80 mg/L in distilled water and humic acid solution (mixture similar to natural water) was exposed to natural sunlight for 30 days. Samples of the irradiated solution were taken after 3, 10, 20 and 30 days. Additionally, a test with 2% acetone as sensitizer in distilled water was performed. The total radioactivity of the irradiated samples was determined by liquid scintillation counting. TLC methods including co-chromatography with the unlabelled reference substance were applied for the identification of [^{14}C]triazole. The radioactive zones were scraped from the plates and the radioactivity measured by LSC.
5.2	**Results and discussion**	No significant degradation of 1,2,4-triazole by sunlight was observed neither in distilled water nor in humic acid solution or distilled water with acetone as sensitizer.
5.2.1	k_H	-
5.2.2	DT_{50}	-
5.2.3	r^2	-

Section A7.1.1.1.2 Phototransformation in water including identity of the products of transformation

Annex Point IIA7.6.2.2

5.3	**Conclusion**	1,2,4-H-Triazole does not appreciably absorb sunlight. 1,2,4-triazole does not undergo appreciable direct photolysis in sunlight nor does humic acid and acetone have a major effect on increasing the rate of loss by indirect photochemical reactions.
5.3.1	Reliability	Reliability indicator: [redacted]
5.3.2	Deficiencies	[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*April 07*
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 A7.1.1.2.1 Biodegradability (ready, OECD 301C)
Section A7.1.1.2.2

Annex Point IIA7.6.1.1

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		1 REFERENCE
1.1	**Reference**	Kikuo Yoshida (study director), 1991. Ready biodegradability test of Preventol A8. Mitsubishi-kasei Institute of Toxicological and Environmental Sciences. Mites Report No. 1B232G, September 3 ,1991
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, Modified MITI-Test I = OECD 301C (=EC Test C.4-F)
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]
		3 MATERIALS AND METHODS
3.1	**Test material**	Preventol A8 (tebuconazole)
3.1.1	Lot/Batch number	Lot-No. [redacted]
3.1.2	Specification	[redacted]
3.1.3	Purity	[redacted]
3.1.4	Further relevant properties	Water solubility: 32 mg/l, very low vapour pressure (1.7 10^{-6} Pa at 20°C)
3.1.5	Composition of Product	n.a.
3.1.6	TS inhibitory to micro-organisms	> 1000 mg/l (nominal concentration)
3.1.7	Specific chemical analysis	For determining the concentration of the test compound in the test bottles also HPLC was applied as test compound specific analytical technique in addition to the BOD and DOC measurements. For analysis test solution were brought to 1000 ml with methanol. An aliquot from this solution was analysed by HPLC.
3.2	**Reference substance**	Yes, Aniline
3.2.1	Initial concentration of reference substance	100 mg/l

Section A7.1.1.2.1 Biodegradability (ready, OECD 301C)
Section A7.1.1.2.2

Annex Point IIA7.6.1.1

3.3	**Testing procedure**	
3.3.1	Inoculum / test species	Activated sludge (30 mg/l) from the "Chemical Biotesting Center , Chemical Inspection and Testing Institute, Japan"
3.3.2	Test system	Closed system oxygen consumption measuring apparatus with measuring the BOD. After 28 days also the DOC (Dissolved Organic Carbon) and the residual test substance were measured.
3.3.3	Test conditions	Bottle 1: Aniline + activated sludge + basal medium* Bottle 2: Activated sludge + basal medium* Bottle 3-5: Tebuconazole + activated sludge + basal medium* Bottle 6 Tebuconazole + deionised water pH: 6.9-7.1 in bottle 3-6 after 28 days Temperature 25 ± 1 °C *according to the guideline
3.3.4	Method of preparation of test solution	Nominal concentrations by putting each 30 mg tebuconazole into the 300 ml test bottles. HPLC analysis after 28 days (see 3.1.7)
3.3.5	Initial TS concentration	100 mg tebuconazole
3.3.6	Duration of test	28 days
3.3.7	Analytical parameter	Biological oxygen demand (BOD), in addition DOC and compound specific analyses were performed
3.3.8	Sampling	Day 7, 14, 21 and 28
3.3.9	Intermediates/ degradation products	Not identified
3.3.10	Nitrate/nitrite measurement	Not performed, not relevant due to the lack of degradability
3.3.11	Controls	Control without test substance; abiotic controls
3.3.12	Statistics	n.a.
	4 RESULTS	
4.1	**Degradation of test substance**	
4.1.1	Graph	Provided in the report (no degradation of the test compound)
4.1.2	Degradation	0 % degradability after 28 days
4.1.3	Other observations	No
4.1.4	Degradation of TS in abiotic control	No degradation of tebuconazole was observed in a test without activated sludge (bottle 6)

Section A7.1.1.2.1 Section A7.1.1.2.2 Biodegradability (ready, OECD 301C)

Annex Point IIA7.6.1.1

4.1.5	Degradation of reference substance	62% degradability after day 7, 73% degradability after day 14, 76% degradability after day 21, 77% degradability after day 28
4.1.6	Intermediates/ degradation products	n.a.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The test was performed according to the OECD test guideline No. 301C (modified MITI-Test I).
5.2	**Results and discussion**	No biotic degradation of tebuconazole was observed under the conditions of the modified MITI-Test I. Also according to a substance specific analysis (HPLC) no significant degradability was observed. The test with the reference substance Aniline proved the activity of the activated sludge used. Although tebuconazole contains nitrogen molecules a correction for oxygen uptake through nitrification was not necessary (no degradation).
5.3	**Conclusion**	[redacted]
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*01 04 04*
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*

Section A7.1.1.2.1 Biodegradability (ready, OECD 301C)
Section A7.1.1.2.2

Annex Point IIA7.6.1.1

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

Section 7.1.1.2.2 Annex Point IIA 7.6.1.2	Inherent biodegradability, where appropriate	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [...]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ].**	
Detailed justification:	OECD tests on inherent biodegradability on tebuconazole were not performed because higher tiered studies on water and water sediment are available.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*9 September 2004*	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section 7.1.1.2.3 Annex Point IIIA 12.2	Biodegradation in seawater	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [X]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X].**	
Detailed justification:	For tebuconazole used as an active in wood preservatives HC5/UC 5 is not claimed. Therefore a test on biodegradation in seawater was not performed.	
Undertaking of intended data submission [ ]	–	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*10. September 2004*	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A7.1.2. Rate and route of degradation in aquatic systems:
Annex Point IIIA-XII2.1 Dissipation in outdoor microcosm

Official use only

1 REFERENCE

1.1	**Reference**	Heimbach, F. (2003): Fate of tebuconazole EW 250 in outdoor microcosms. Bayer CropScience AG, Report No. HBF / Mt 15, unpublished. Chapple, A; Hammel, K and Schad, T. (2003): Kinetic evaluation of the dissipation of tebuconazole in a mesocosm water-sediment system by inverse modelling using the PEST program and TOXSWA model. Bayer CropScience AG, Report No. MEF-284/03, unpublished.
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, OECD Guidance Document "Freshwater Lentic Field Tests (Outdoor microcosms and mesocosms), June 2000 (Draft) and Guidance Document on Testing Procedures for Pesticides in Freshwater Microcosms (SETAC-Europe Workshop, Monks Wood (UK), July 1991
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	Tebuconazole EW 250
3.1.1	Lot/Batch number	Batch No. [redacted]
3.1.2	Specification	Formulated product EW 250
3.1.3	Purity	[redacted] g tebuconazole/kg
3.1.4	Further relevant properties	-
3.1.5	Composition of Product	-
3.1.6	TS inhibitory to micro-organisms	

Section A7.1.2. Rate and route of degradation in aquatic systems:
Annex Point IIIA-XII2.1 Dissipation in outdoor microcosm

3.1.7	Specific chemical analysis	Samples from the water body were analysed by HPLC-MS/MS, samples from the sediment analysed by HPLC-MS/MS method. With both methods the HPLC-MS/MS product ions (m/z ratio 308 – 70) were used for identification and quantification. Due to the high selectivity of the method separate confirmatory methods were not necessary.
3.2	**Reference substance**	
3.2.1	Initial concentration of reference substance	
3.3	**Testing procedure**	
3.3.1	Inoculum / test species	**Characterization of the water in the course of the study:** pH fluctuated around 8.0 in the course of the study. Oxygen concentrations varied between 10 and 12 mg/L which indicated a normal productivity of phytoplankton and macrophytes which results in concentrations above, or in the range of, saturation at the corresponding water temperatures. The development of macrophytes and filamentous algae from seeds, spores and winter buds in the natural sediment was assessed visually in the course of the study. The fluctuation of water levels due to evaporation and rainfall varied to a negligible degree during the first months of the study. In the last period of the study the levels rose slightly due to rainfall by an average of 8 cm. Water was not refilled throughout the study period.
3.3.2	Test system	**Design of the microcosms:** Three inter connected test microcosms (diameter 2 m, water depth 1 m, surface area 3.14 m^2) located at Monheim am Rhein, Germany were chosen for the study of the dissipation of tebuconazole in outdoor stagnant water bodies. The microcosms had been filled with natural ground water and sediment half a year before the application of the test substance. Filled to the nominal operating depth of 1 m water, each microcosm contained 3.14 m^3 of water. A plastic tray (diameter 2 m) with a rim height of 0.2 m lies on the bottom of each microcosm. The trays are filled with natural sediment up to a height of 15 cm. The water bodies are connected by three gates in order to ensure similar test conditions in the ponds. The microsoms were separated from each by closing the gates one day before the application of the test substance. A characterisation of the sediment in the microcosms is given in Table 7_1_2.1.
3.3.3	Test conditions	The water temperature at the beginning of the study fluctuated around 17 °C, increased to 25 °C in August and decreased towards the end of the study to 11 °C. The treatment regime was intended to simulate aquatic exposure from drift and to evaluate the fate and distribution of the test substance.

Section A7.1.2. Rate and route of degradation in aquatic systems: Dissipation in outdoor microcosm

Annex Point IIIA-XII2.1

3.3.4	Method of preparation of test solution	**Application of test substance:** Two treatment levels with a nominal concentration of 3.2 µg/L and 32 µg/L were tested. The test substance was applied once by spraying 49.4 or 439.9 mg, respectively of the product EW 250 dissolved in 1300 mL water onto the water surface.
3.3.5	Initial TS concentration	Two treatment levels with a nominal concentration of 3.2 µg/L and 32 µg/L were tested.
3.3.6	Duration of test	Day of application of test substance: May 8, 2002. Last sampling day: November 29, 2002.
3.3.7	Analytical parameter	Samples from the water body were analysed by HPLC-MS/MS (report MR-249/02, method No. 00768), samples from the sediment analysed by HPLC-MS/MS (report MR-316/01, method No. 00708). With both methods the HPLC-MS/MS product ions (m/z ratio 308 – 70) were used for identification and quantification. Due to the high selectivity of the method separate confirmatory methods were not necessary.
3.3.8	Sampling	Water samples were taken with a flask attached to a rod from predetermined sampling positions. For analysis of the a. s. duplicate samples of 20 mL were transferred into 50 mL glass bottles, frozen and stored at < – 20°C. Sediment samples were taken as a core with a surface of 23.8 cm^2 and a height of 12 cm. As it was assumed that adsorbed portions of the a. s. will be found only near the surface, only the upper 3 cm layer were used for analysis. The upper layers from four samples were mixed, frozen and stored until analysis at < -20 °C. Sampling dates are given in Table 7_1_2.2.
3.3.9	Intermediates/ degradation products	Not identified
3.3.10	Nitrate/nitrite measurement	Not applicable
3.3.11	Controls	One of the three mesocosms served as a control.
3.3.12	Statistics	Kinetic evaluation of the dissipation of tebucoanzole in a mesocosm water-sediment system by inverse modelling using the PEST program and TOXSWA model (Chapple et al., 2003).
		4 RESULTS
4.1	**Degradation of test substance**	
4.1.1	Graph	Provided in the report

Section A7.1.2. Rate and route of degradation in aquatic systems: Dissipation in outdoor microcosm

Annex Point IIIA-XII2.1

4.1.2	Degradation	Analytical results show a consistent dissipation behaviour of tebuconazole for both treatments. The analytical findings in pond water 4 hours after application were 87.8 and 116.6 % of nominal initial concentration, confirming nominal concentrations. Thereafter the concentrations of tebuconazole in water declined continuously. Concentrations in the sediment increased until day 56. Thereafter the analyzed amounts of tebuconazole fluctuated due to inhomogeneous sampling caused by increasing abundance of macrophytes and decreased step-wise until the end of the study at day 196 (see attached table 7_1_2.2). A balance of the applied test substance shows that less than 10 % of the applied substance was found in the sediment throughout the study (see table7_1_2.2).
4.1.3	Other observations	The dissappearance of tebuconazole from the system can be described by first-order kinetics. The average half-life for the disappearance from the water body was calculated to be 30.9 days, and for the disappearance from the total system (water plus sediment) 38.7 days. These calculations were later refined using inverse modelling. (Chapple, Hammel and Schad, 2003, see below).
4.1.4	Degradation of TS in abiotic control	No abiotic control
4.1.5	Degradation of reference substance	-
4.1.6	Intermediates/ degradation products	n.a.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	OECD Guidance Document "Freshwater Lentic Field Tests (Outdoor microcosms and mesocosms), June 2000 (Draft) and Guidance Document on Testing Procedures for Pesticides in Freshwater Microcosms (SETAC-Europe Workshop, Monks Wood (UK), July 1991
5.2	**Results and discussion**	Analytical results show a consistent dissipation behaviour of tebuconazole for both treatments. The analytical findings in pond water 4 hours after application were 87.8 and 116.6 % of nominal initial concentration, confirming nominal concentrations. Thereafter the concentrations of tebuconazole in water declined continuously. Concentrations in the sediment decreased until day 56. Thereafter the analyzed amounts of tebuconazole fluctuated due to inhomogeneous sampling caused by increasing abundance of macrophytes and decreased step-wise until the end of the study at day 196. A balance of the applied test substance shows that less than 10 % of the applied substance was found in the sediment throughout the study. The disappearance of tebuconazole from the system can be described by first-order kinetics. The average half-life for the disappearance from the water body was calculated to be 30.9 days, and for the disappearance from the total system (water plus sediment) 38.7 days.
5.3	**Conclusion**	[redacted]

Section A7.1.2. Rate and route of degradation in aquatic systems: Dissipation in outdoor microcosm

Annex Point IIIA-XII2.1

5.3.1 Reliability [redacted]

5.3.2 Deficiencies [redacted]

Evaluation by Competent Authorities

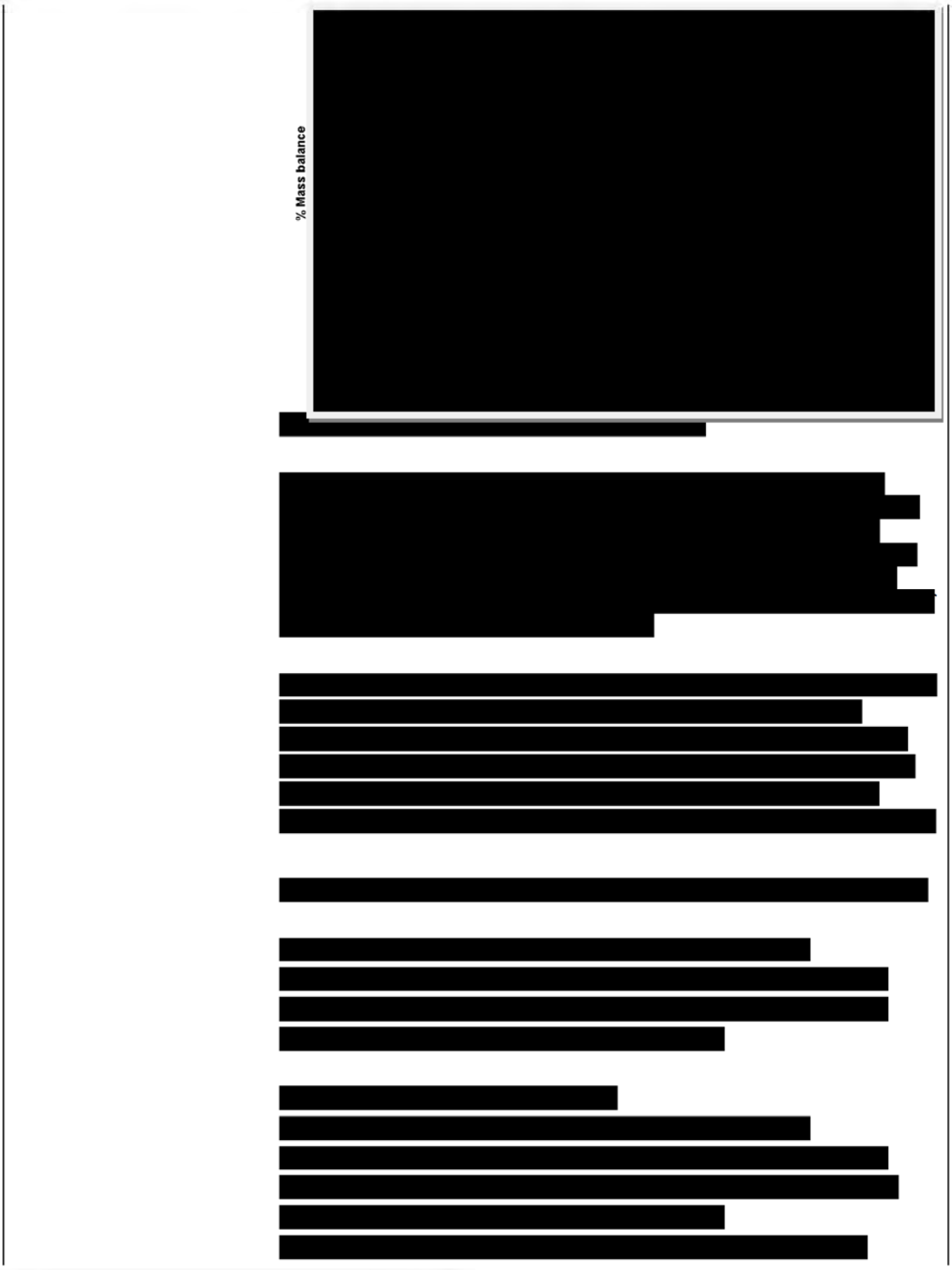
EVALUATION BY RAPPORTEUR MEMBER STATE

Date *October 2005*

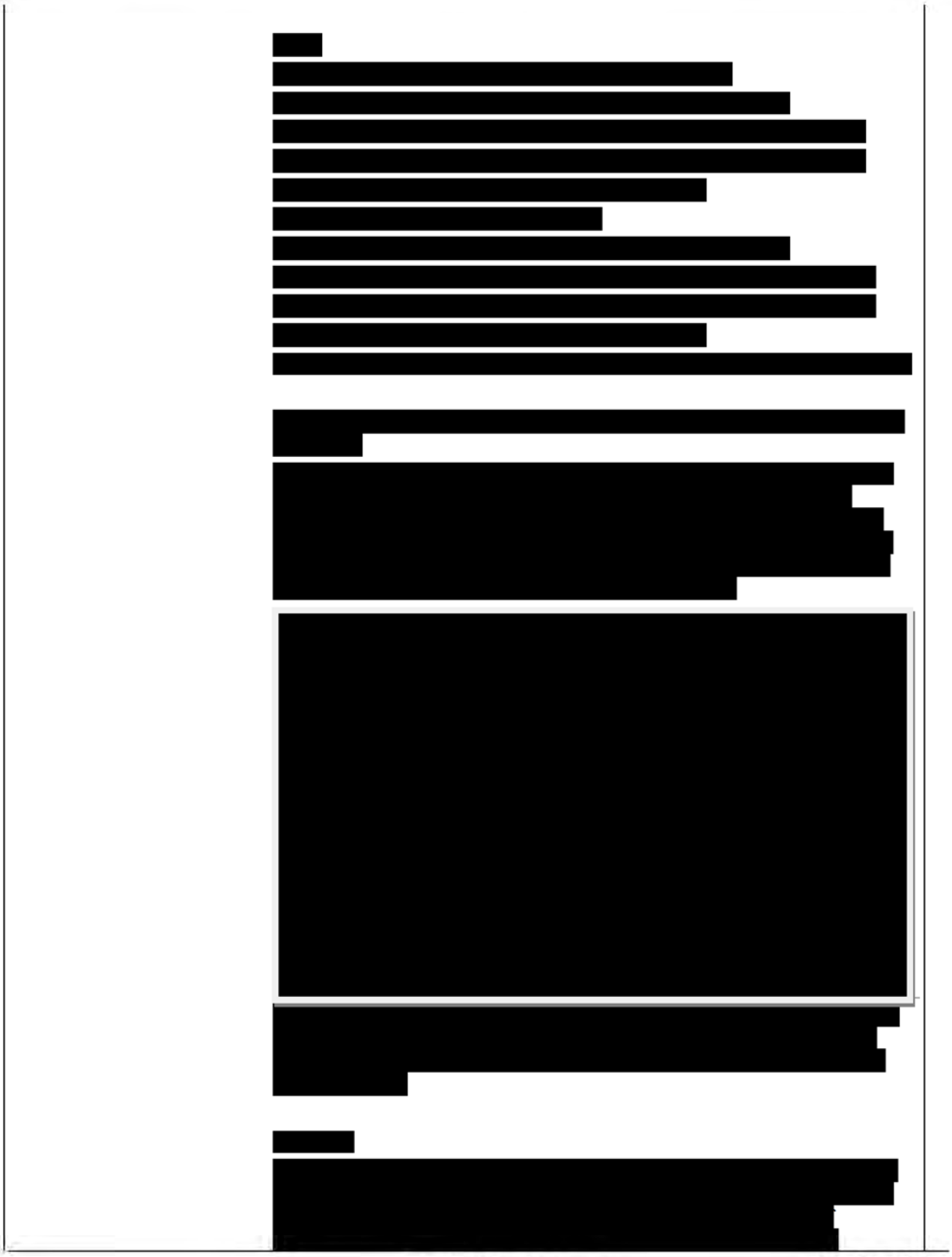
Materials and Methods [redacted]

Results and discussion [redacted]

Section A7.1.2. **Rate and route of degradation in aquatic systems:**
Annex Point IIIA-XII2.1 **Dissipation in outdoor microcosm**



Section A7.1.2. **Rate and route of degradation in aquatic systems:**
Annex Point IIIA-XII2.1 **Dissipation in outdoor microcosm**



Section A7.1.2. **Rate and route of degradation in aquatic systems:**
Annex Point IIIA-XII2.1 **Dissipation in outdoor microcosm**

[redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

Section A7.1.2. Rate and route of degradation in aquatic systems:
Annex Point IIIA-XII2.1 Dissipation in outdoor microcosm

	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 7_1_2.1: Characterization of the sediment (Composition given for dry sediment)

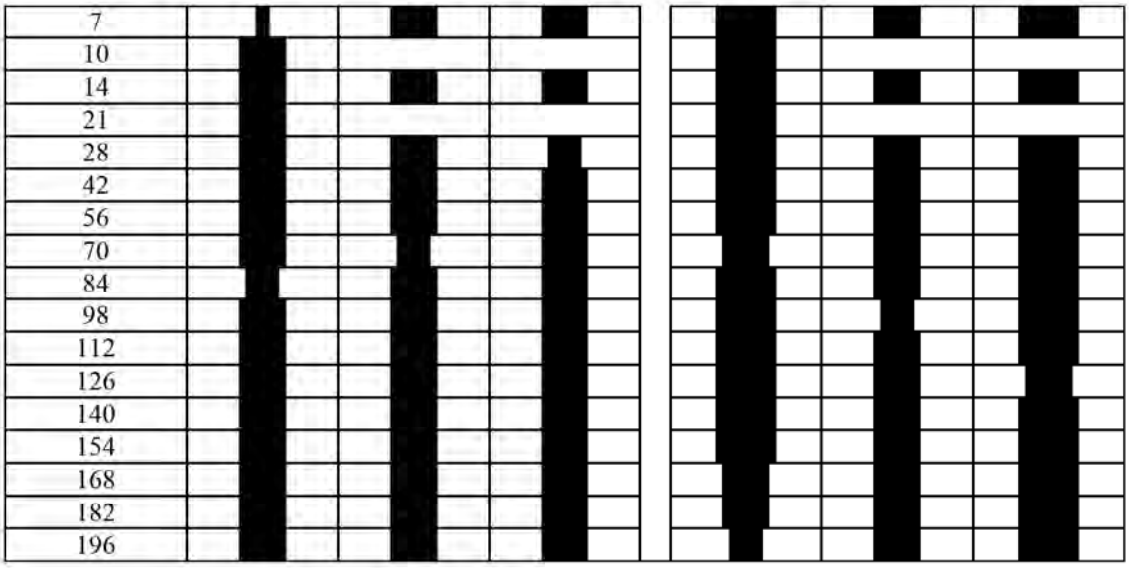
Texture	Sand	Silt	Clay	Cation exchange capacity [meq/100g]	C	N	P
Silt loam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7_1_2.2: Degradation of tebuconazole in two ponds at two concentrations–concentrations in pond water and pond sediment as a function of time

Experimental time [d]	Nominal concentration 3.2 ppb water [µg / L]	Nominal concentration 3.2 ppb sediment [µg / kg]	Nominal concentration 32 ppb water [µg / L]	Nominal concentration 32 ppb sediment [µg / kg]
0.17	[redacted]		[redacted]	
1	[redacted]		[redacted]	
2	[redacted]		[redacted]	
4	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]		[redacted]	
14	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]		[redacted]	
28	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]
98	[redacted]	[redacted]	[redacted]	[redacted]
112	[redacted]	[redacted]	[redacted]	[redacted]
126	[redacted]	[redacted]	[redacted]	[redacted]
140	[redacted]	[redacted]	[redacted]	[redacted]
154	[redacted]	[redacted]	[redacted]	[redacted]
168	[redacted]	[redacted]	[redacted]	[redacted]
182	[redacted]	[redacted]	[redacted]	[redacted]
196	[redacted]	[redacted]	[redacted]	[redacted]

Table 7_1_2.3: Degradation of tebuconazole in two ponds at two concentrations – Mass balance – Recovered amounts of tebuconazole in water, sediment and total system as a function of time

Experimental Time [d]	Nominal concentration 3.2 ppb (≡ 10.05 mg /pond) water [mg/pond]	sediment [mg/pond]	total [mg/pond]	Nominal concentration 32 ppb (≡ 100.5 mg /pond) water [mg/pond]	sediment [mg/pond]	total [mg/pond]
0.17	[redacted]		[redacted]	[redacted]		[redacted]
1	[redacted]		[redacted]	[redacted]		[redacted]
2	[redacted]		[redacted]	[redacted]		[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]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168
182
196

Section A7.1.2. Rate and route of degradation in aquatic systems:
Annex Point IIIA-XII2.1 Dissipation in outdoor microcosm, study 1

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		1 REFERENCE
1.1	**Reference**	Anonymous: Biological Effects as well as Distribution and Fate of WG 1608 EC 250 (®Folicur) in a Pond Ecosystem, Source: Ökolimna, Burgwedel; Bayer AG, unpublished report No: F-89431, Date: 05.07.1989, unpublished. Leicht, W., Grau, R.:Concentrations of Tebuconazole in surface water (PECw) after the use of Folicur Combi in Italian Vineyards, Bayer AG, Report No: MO-00-001159, Date: June 25, 1999; unpublished
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**	Internal test design
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]
		3 MATERIALS AND METHODS
3.1	**Test material**	HWG 1608 EC 250
3.1.1	Lot/Batch number	FL-No. 064A [redacted]
3.1.2	Specification	Emulsifiable concentrate EC 250 with an active ingredient content of [redacted] g/l;
3.1.3	Purity	Formulation with technical HWG 1608 (later common name: tebuconazole)
3.1.4	Further relevant properties	-
3.1.5	Composition of Product	-
3.1.6	TS inhibitory to micro-organisms	

Section A7.1.2. Rate and route of degradation in aquatic systems:
Annex Point IIIA-XII2.1 Dissipation in outdoor microcosm, study 1

3.1.7	Specific chemical analysis	Samples from the water body were analysed by HPLC (RP 18 column) using a UV detector. Limit of Determination was 2µg/L in water and 1 µg/L in surface film. The respective limits of detection were 0.5 and 0.3 µg/L. Sediment samples were analysed by GC with a nitrogen-phosphorus detector. Limit of determination and detection was 0.05 mg/kg (dry weight sediment). Also the analytical determinations in fish and aquatic plants were done by GC.	
3.2	**Reference substance**	No reference substance was applied	
3.2.1	Initial concentration of reference substance	n.a.	
3.3	**Testing procedure**		
3.3.1	Inoculum / test species	The influence of a single application of the product HWG 1608 EC 250 upon an aquatic ecosystem was investigated. **This evaluation focuses on the environmental fate of the active HWG 1608 (tebuconazole)**	
3.3.2	Test system	Ponds on a commercial trout and carp farm situated in northern Germany at Wedemark with natural earth bottom and earth walls. The dimensions of the test ponds and the quality of the pond sediment are compiled in tables 7_1_2.1 and 7_1_2.1a. The ponds were fished out completely, drained and immediately afterwards filled with fresh water from the brook feeding the fish farm ponds.	
3.3.3	Test conditions	The investigations over a period of 15 months cover the biological impact (macroinvertebrates, benthic organisms, zooplankton, phytoplankton and fish) and the residue situation in the water body, at the water surface, in the aquatic plants, in the sediment and in the applied fish.	
3.3.4	Method of preparation of test solution	HWG 1608 (tebuconazole) was applied once by means of spraying onto the water surface, per pond corresponded to 0.375 and 1.5 kg per hectare.	
3.3.5	Initial TS concentration	Two treatment levels with a nominal concentration of 3.2 µg/L and 32 µg/L were tested. Spraying was done with the normal rate of 1.5 l/ha (= 375 g a.i./ha) on pond W1. Pond W4 was sprayed with an amount of 6 l/ha (= 1,500 g a.i./ha). Rate of a. s. per surface area actually applied: 2.99g (W1) and 9.62 (W4).	X
3.3.6	Duration of test	Day of application of test substance: July 6, 1987. Last sampling day with respect to water analysis: December 14, 1987 (day 161). Further sampling was done with respect to sediment up to day 448.	
3.3.7	Analytical parameter	Samples from the water phase were drawn and worked up by extraction with dichloromethane, evaporation and clean-up by means of chromatography on reversed phase cartridges. Solutions resulting from the work-up were analysed by RP-chromatography using UV-detection. See also point 3.1.7	