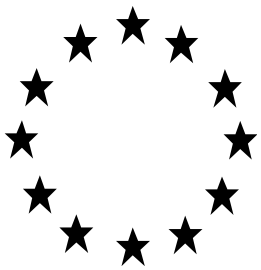
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Document IIIA



Chlorocresol (CMK)

Product-type 6
(Preservatives for products during storage)

FINAL CAR

April 2016

FRANCE

Section A4.3	**Analytical Methods for Detection and Identification**
BPD Annex Point IIIA, IV.1	ANALYTICAL METHOD FOR THE DETERMINATION OF ACTIVE SUBSTANCE RESIDUES IN/ON FOOD OR FEEDSTUFFS

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	**Official use only**
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	[redacted]	
Undertaking of intended data submission [ ]	–	

Section A4.3	**Analytical Methods for Detection and Identification**
BPD Annex Point IIIA, IV.1	ANALYTICAL METHOD FOR THE DETERMINATION OF ACTIVE SUBSTANCE RESIDUES IN/ON FOOD OR FEEDSTUFFS

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*22/11/12*
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	[redacted]
	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 A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test - Limit test)

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1 REFERENCE

1.1	**Reference**	[redacted](1988), Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten [redacted] 1988-08-18 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	84/449/EC, EEC Method B.1
2.2	**GLP**	Yes.
2.3	**Deviations**	Yes. – acclimatisation period was only 4 days – only one dose was tested in spite of mortality

3 MATERIALS AND METHODS

3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	colourless powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stability of the test substance in vehicle was analysed and assured.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar (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	Age: approx. 8 weeks Mean weight: 179 g(males); 171 g (females)
3.2.6	Number of animals per group	5 per sex
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days

Section A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test - Limit test)

3.3.2	Type	Gavage
3.3.3	Concentration	2000 mg/kg bw
3.3.4	Vehicle	Polyethyleneglycol 400
3.3.5	Concentration in vehicle	No data
3.3.6	Total volume applied	10 mL/kg bw
3.3.7	Control	No.
3.4	**Examinations**	Clinical observations, necropsy, body weights.
3.5	**Method of determination of LD_{50}**	Not applicable.
3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	Four males and 3 females died within 24 hours after application (see Table A6_1_1-1). The clinical signs observed were increased salivation, tremor, sedation, poor general condition. These signs were of slight to moderate intensity, and occurred 15 minutes after application and lasted up to five days.
4.2	**Pathology**	Animals that died within 1 day after treatment showed a strong redness of the stomach mucosa. The stomachs of these animals were inflated and filled with an aqueous fluid. No findings were noted in animals sacrificed at study termination.
4.3	**Other**	Body weight gain was normal in the surviving rats.
4.4	**LD_{50}**	LD_{50} < 2000 mg/kg bw (males and females)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A study for acute oral toxicity in the rat was conducted with the test substance *p*-chloro-*m*-cresol (CMK). 5 Wistar rats per sex received 2000 mg CMK/kg bw as a solution in polyethyleneglycol 400 by single-dose oral gavage. In-life observations were made frequently on the day of treatment and twice each working day and once daily on weekends throughout the two-week observation period. Surviving animals were weighed before treatment, after one week and at study termination. Pathological-anatomical examinations were performed on all animals.

Section A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test - Limit test)

5.2	**Results and discussion**	All animals showed slight to moderate signs of toxicity beginning 15 minutes after application and lasting up to 5 days. The clinical signs observed were increased salivation, tremor, sedation, poor general condition. The poor general conditions were of slight intensity whereas the other symptoms were of moderate intensity. Mortalities in males occurred from 1 hour after application until 24 hours after application. Females died 4 hours after application. According to the results of this study the LD_{50} was considered to be below 2000 mg/kg bw for males and females.
5.3	**Conclusion**	
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	An LD_{50} could not be determined.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	13/03/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test - Limit test)

Table A6_1_1-1. Table for acute oral toxicity

Dose [mg/kg bw]	Toxicological results*	Time of death	Mortality (%)
Males			
2000	4/5/5	1h - 24h	80
LD_{50} < 2000 mg/kg bw			
Females			
2000	3/5/5	4h	60
LD_{50} < 2000 mg/kg bw			

* first number = number of dead animals
second number = number of animals with signs of toxicity
third number = number of animals used

Section A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test)

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1 REFERENCE

1.1	**Reference**	[redacted] (1978 and 1992 (revised report)), Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten [redacted] 1992-11-24 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No, but in accordance with OECD 401 with deviations.
2.2	**GLP**	No GLP was not compulsory during conduct of study.
2.3	**Deviations**	Yes. – only male rats were used – acclimatisation period was only 3 days – results of gross pathological examination was not reported

3 MATERIALS AND METHODS

3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	colourless powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	No data.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar (Strain Bor: WISW (SPF Cpb))
3.2.3	Source	[redacted]
3.2.4	Sex	Males
3.2.5	Age/weight at study initiation	Age: No exact data; young adult. Weight: 160 - 180 g
3.2.6	Number of animals per group	10 per group
3.2.7	Control animals	No

Section A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test)

3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days
3.3.2	Type	Gavage
3.3.3	Doses	1000, 1500, 2000, 3100 and 5000 mg/kg bw
3.3.4	Vehicle	Polyethyleneglycol 400
3.3.5	Control	–
3.4	**Examinations**	Clinical observations, necropsy, body weights.
3.5	**Method of determination of LD_{50}**	LD_{50} value was calculated according to Fink and Hund (1965).
3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	The clinical signs observed were increased diuresis, sedation, respiratory disturbance, side position, tremor and tonical cramps.
4.2	**Pathology**	Not reported.
4.3	**Other**	-
4.4	**LD_{50}**	LD_{50} = 1830 mg/kg bw (males)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A study for acute oral toxicity in the rat was conducted with the test substance *p*-chloro-*m*-cresol (CMK). 10 male Wistar rats per group received 1000, 1500, 2000, 3100 and 5000 mg CMK/kg bw as a solution in Polyethyleneglycol 400 by single-dose oral gavage. In-life observations were made frequently on the day of treatment and twice each working day and once daily on weekends throughout the two-week observation period. Surviving animals were weighed before treatment, after one week and at study termination. Pathological-anatomical examinations were performed on all animals.
5.2	**Results and discussion**	The clinical signs observed were increased diuresis, sedation, respiratory disturbance, side position, tremor and tonical cramps. Mortalities occurred from 1 hour after application until day 7 (see Table A6_1_1-1).
5.3	**Conclusion**	
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	Yes Reporting deficiencies: Results of pathological examinations were not reported.

Section A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test)

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/03/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.1 Acute Toxicity

Annex Point IIA VI.6.1.1 6.1.1 Acute oral toxicity in rats (LD_{50} test)

Table A6_1_1-1. Table for acute oral toxicity

Dose [mg/kg bw]	Toxicological results*	Time of death	Mortality (%)
1000	0/10/10	-	0
1500	4/10/10	2 d - 7 d	40
2000	7/10/10	3 h - 2 d	70
3100	8/10/10	3 h - 2 d	80
5000	10/10/10	1 h	100
LD_{50} = 1830 mg/kg bw			

* first number = number of dead animals
second number = number of animals with signs of toxicity
third number = number of animals used

Section A6.1.2 Acute Toxicity

Annex Point IIA VI.6.1.2 6.1.2 Acute dermal toxicity in rats (LD_{50} test)

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted](1999), Acute Dermal Toxicity Study with Preventol CMK Pastillen in Rats [redacted]1999-10-29 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA.
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes US-EPA OPPTS 870.1200, OECD 402, JMAFF no. 4200
2.2	**GLP**	Yes
2.3	**Deviations**	Deviations from OECD 402: The test was not performed as an LD50 test but similar to the oral ATC method (OECD 423).
		3 MATERIALS AND METHODS
3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	White pellets
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	September 29, 2000
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar Hannover (Crl:WI(Glx/BRL/Han)IGS BR)
3.2.3	Source	[redacted]
3.2.4	Sex	Males and females
3.2.5	Age/weight at study initiation	Age: approx. 9 weeks (males), approx. 12 weeks (females) Weight: 230 - 269 g (males); 202 - 227 g (females)
3.2.6	Number of animals per group	6 per sex per group
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Dermal
3.3.1	Postexposure period	14 days

Section A6.1.2 Acute Toxicity

Annex Point IIA VI.6.1.2 6.1.2 Acute dermal toxicity in rats (LD_{50} test)

3.3.2	Area covered	10 % of total body surface	
3.3.3	Occlusion	Occlusive gauze patch	
3.3.4	Vehicle	None; substance was applied undiluted as a paste prepared with 0.2 mL de-ionised water	X
3.3.5	Concentration in vehicle	–	
3.3.6	Total volume applied	–	
3.3.7	Applied doses	0, 2000, 5000 mg/kg bw	
3.3.8	Duration of exposure	24 hours	
3.3.9	Removal of test substance	By wiping of test site with paper towels, which were dampened with tap water.	
3.3.10	Control	De-ionised water	
3.4	**Examinations**	Clinical observations, necropsy, body weights.	
3.5	**Method of determination of LD_{50}**	According to ATC flow chart (Figure A6_1_2-1) adjusted for the doubled number of animals in each group.	
3.6	**Further remarks**	-	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Compound-related clinical signs in males and females of the 5000 mg/kg bw dose group and females of the 2000 mg/kg bw dose group were: ataxia, decreased activity, eye twitching, clear lacrimation, red lacrimation (females), myoclonus (females) and urine staining (Table A6_1_2.1). In the most test-substance treated animals survived until study termination the following additional compound-related clinical signs at the dose sites were found: oedema, erythema, exfoliation, induration and sloughing.	
4.2	**Pathology**	Compound-related gross observations in animals that died prior to study termination were: lacrimation, urine-stained ventrum, discoloured urine and discoloured treated skin. In animals sacrificed at study termination compound-related gross observations included crusty zones and thickened skin. No gross observations were found in control animals.	
4.3	**Other**	The rate of body weight gain, relative to controls, was significantly decreased on post-treatment day 7 for males exposed to 5000 mg/kg bw and was considered to be compound-related. At study termination body weights of the 5000 mg/kg bw males were comparable to control animals. In females, body weight gain was not affected.	
4.4	**LD_{50}**	LD_{50} > 5000 mg/kg bw (males) LD_{50} > 2000 mg/kg bw (females)	

Section A6.1.2 Acute Toxicity

Annex Point IIA VI.6.1.2 6.1.2 Acute dermal toxicity in rats (LD_{50} test)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

p-Chloro-m-cresol (CMK) was applied dermally to young-adult male and female Wistar Hanover rats. Six rats per sex and dose group received a single dermal dose of 0 and 5000 mg/kg bw test substance. 6 additional females received also a dose of 2000 mg/kg bw. The test substance was prepared as a paste using 0.5 mL (for the 2000 mg dose group) and 1 mL (for the 5000 mg dose group) of de-ionised water and applied occlusively to the shaved skin of the animals (~10% of body surface). The dressing was removed after 24 h and residual test substance was removed with paper towels moistened with tap water. The animals were inspected at least twice daily during the 14-day observation period (once on weekends and holidays) for mortality, moribundity and clinical signs of toxicity. The animals were weighed individually directly before administration (day 0) and for all surviving animals on day 7 and 14. Terminal body weights were recorded for all animals found dead. A complete gross necropsy was performed on all animals of the study.

Group mean body weight changes were evaluated with an Analysis of variance test and, where significant differences were detected, the Dunnett´s t-test was used to determine whether specific dose groups were significantly different from controls.

5.2 Results and discussion

As a result of dermal application of p-chloro-m-cresol, two females died in females treated with 2000 mg/kg bw and 3 females died in the 5000 mg/kg bw group. No mortalities occurred in male animals. Compound-related clinical signs were observed in all males and females of the treatment groups and included signs indicative of systemic toxicity as well as tissue damage and irritation at the application sites. A significant decrease in body weight gain was observed for the males of the 5000 mg/kg bw group on day 7 and was considered to be compound-related. Compound-related gross pathological observations were found at necropsy in all treated males and females.

5.3 Conclusion

5.3.1 Reliability [redacted]

5.3.2 Deficiencies No. Although the method used is not compliant to common guidelines, it can be concluded that the percutaneous LD50 of CMK is estimated correctly.

Section A6.1.2 Acute Toxicity

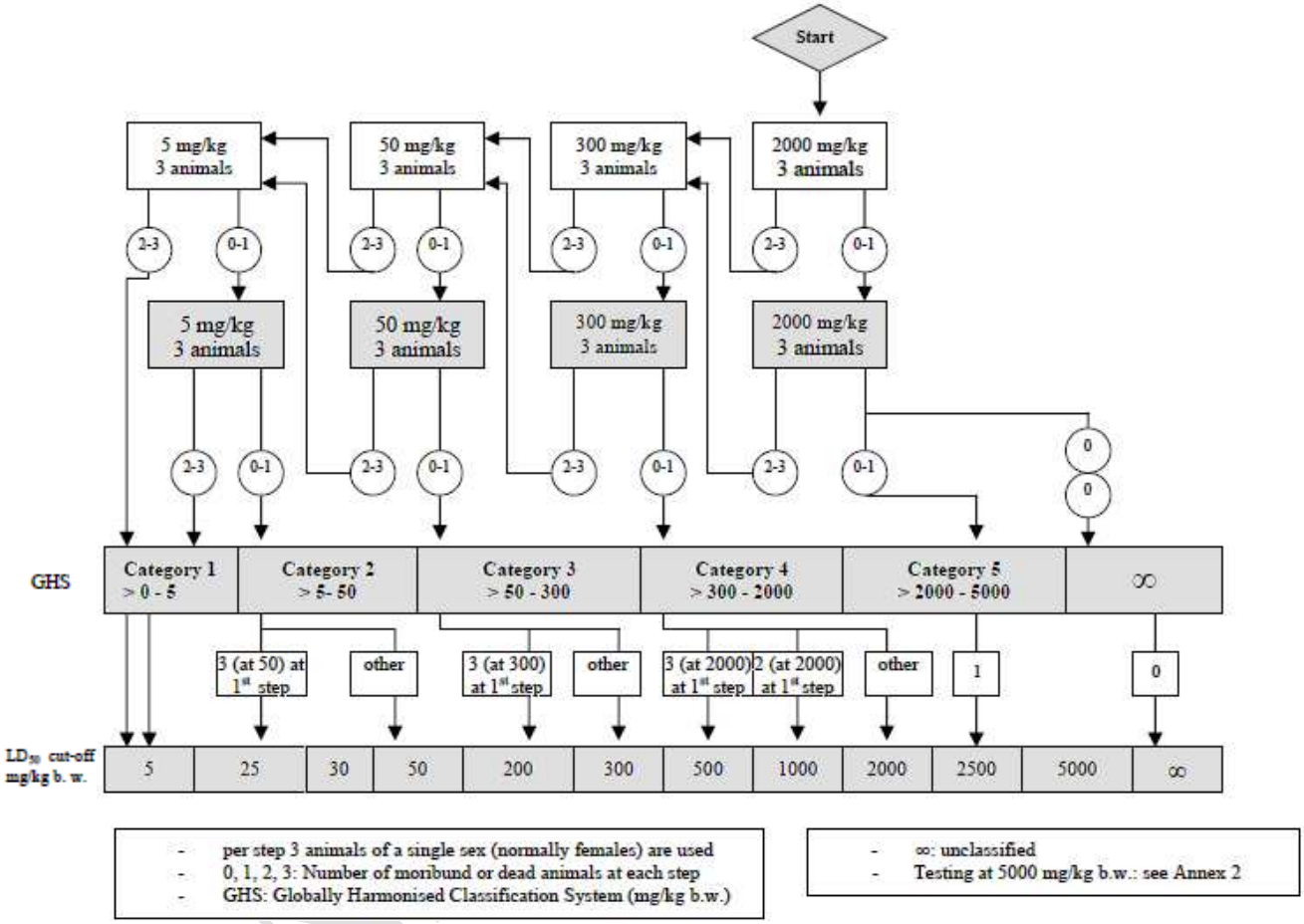
Annex Point IIA VI.6.1.2 6.1.2 Acute dermal toxicity in rats (LD_{50} test)

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/03/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.2 Acute Toxicity

Annex Point IIA VI.6.1.2 6.1.2 Acute dermal toxicity in rats (LD_{50} test)

Figure A6_1_2.1: Test procedure and classification according to OECD 423 (ATC method)



Section A6.1.2 Acute Toxicity

Annex Point IIA VI.6.1.2 6.1.2 Acute dermal toxicity in rats (LD_{50} test)

Table A6_1_2-1. Table for acute dermal toxicity

Dose [mg/kg bw]	Toxicological results*	Duration of clinical signs	Time of death	Mortality (%)
Females				
0	0/5/6	day 0 - day 2	---	0
2000	2/6/6	day 0 - end	day 1, day 3	33.33
5000	3/6/6	day 0 - end	day 1	50
LD_{50} > 2000 mg/kg bw				
Males				
0	0/6/6	day 0 - day 1	---	0
5000	0/6/6	day 0 - end	---	0
LD_{50} > 5000 mg/kg bw				

* first number = number of dead animals
second number = number of animals with signs of toxicity
third number = number of animals used

Section A6.1.3 Acute Toxicity

Annex Point IIA VI.6.1.3 6.1.3 Acute inhalation toxicity to the rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2003): PREVENTOL CMK Study on Acute Inhalation Toxicity Study in Rats according to OECD No. 403 [redacted] 2003-01-28 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after May 2000 on existing a.s. for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OECD-Guideline No. 403 US-EPA OPPTS 870.1300 92/69/EEC Method B.2	
2.2	**GLP**	Yes	
2.3	**Deviations**	None	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	White pellets	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Certified for the duration of the study.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar SPF (Hsd Cpb:WU (SPF)	
3.2.3	Source	[redacted]	
3.2.4	Sex	Males & females	
3.2.5	Age/weight at study initiation	Age: approx. 2 month Weight: 192 - 218 g (males); 163 - 185 g (females)	
3.2.6	Number of animals per group	5 per sex	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Inhalation	
3.3.1	Postexposure period	14 days	
3.3.2	Concentrations	2000 and 3000 mg/m^3	

Section A6.1.3 Acute Toxicity

Annex Point IIA VI.6.1.3 6.1.3 Acute inhalation toxicity to the rat

		Analytical concentrations (mean values): 1337 and 2871 mg/m³ (= maximum practically attainable aerosol concentration)	
3.3.3	Particle size	More than 50% of the particles were less than 1 µm aerodynamic diameter MMAD (mass median aerodynamic diameter): 3.09 µm (1337 mg/m^3 group) 4.20 µm (2871 mg/m^3 group) GSD (geometric standard deviation): 1.99 (1337 mg/m^3 group) 2.43 (2871 mg/m^3 group)	
3.3.4	Type or preparation of particles	Aerosols were generated using a Wright-Dust-Feeder (BGI Inc., Waltham, MA 02154, USA)	
3.3.5	Type of exposure	Nose-only	
3.3.6	Vehicle	Not applicable	
3.3.7	Concentration in vehicle	Not applicable	
3.3.8	Duration of exposure	4 h	
3.3.9	Controls	Yes	
3.4	**Examinations**	Detailed clinical examinations were made several times on the day of exposure and at least once daily thereafter. Body weights were recorded before exposure, on days 3, 7 and at study termination. Necropsy with gross pathological examination was performed on all animals. Rectal temperatures were recorded on all animals within 30 minutes after cessation of exposure. Several reflex measurements were made on the first post-exposure day.	
3.5	**Method of determination of LC_{50}**	The LC_{50} was determined according to the method of Rosiello *et al.* (1977) as modified by Pauluhn (1983). This method is based on the maximum-likelihood method of Bliss (1938).	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	No signs of toxicity were found in control animals. Males and females of the 2000 and 3000 mg/m^3 groups: Bradypnoea, laboured breathing pattern, dyspnoea, rales, stridor, nasal discharge (serous), nostrils reddened, nostrils: red encrustrations, piloerection, hair-coat ungroomed, motility reduced, limp, high-legged gait 2000 mg/m^3 males: abdomen bloated, muzzle: red encrustration, salivation 2000 mg/m^3 females: giddiness, nose: oedema/necrosis, nares: red encrustration, salivation 2000 and 3000 mg/m^3 males and females: cyanosis and tremor 3000 mg/m^3 males: nares: red encrustration 3000 mg/m^3 females: emaciation, abdomen bloated, tremor 3000 mg/m^3 males and females: corneal opacity, nose: oedema/necrosis	X
4.2	**Pathology**	Gross pathological examinations of the rats sacrificed at the end of the observation period revealed an increase incidence of macroscopic	

Section A6.1.3 Acute Toxicity

Annex Point IIA VI.6.1.3 6.1.3 Acute inhalation toxicity to the rat

		findings (less collapsed lung, trachea with abundant secretions) in animals that were exposed to the test substance.	
4.3	**Other**	Body temperatures of the treated animals were significant decreased compared to the control animals. Reflex measurements revealed a reduced tonus, righting response, and grip strength of the 3000 mg/m^3 group compared to the control animals. Animals of the 2000 mg/m^3 group showed no differences compared to control animals	
4.4	**LC_{50}**	LC_{50} > 2871 mg/m³ air for males and females.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Five male and five female Wistar rats per dose group were nose-only exposed for four hours to a solid aerosol of CMK at target concentrations of 2000 and 3000 mg/m^3 air. The average dust concentrations reached were 1337 mg/m^3 and 2871 mg/m^3, which was the highest attainable aerosol concentration. 49% and 36.4% of the particles of the 2000 and 3000 mg/m^3 group were smaller than 3 µm in aerodynamic diameter, respectively. Analysis of the aerosol particle-size distribution from the breathing zone samples demonstrates that the aerosol generated was within the respirable range. Detailed clinical observations were made and body weights were taken during a two week post-exposure period. Rectal temperatures were determined within 30 minutes after exposure and reflex-measurements were performed on the first post-exposure day. A complete gross pathological examination was conducted on each rat at the end of the 2-week post-exposure period.	
5.2	**Results and discussion**	Exposure to the maximum technically attainable concentration of 2871 mg/m³ did not result in mortality. The clinical signs observed were indicative of respiratory distress, associated with subdued demeanour, decreased body weights, emaciation, and hypothermia. In some rats the clinical signs lasted until the end of the 2-week post-exposure period. However, most rats showed evidence of recovery during the study period. Necropsy findings consisted of a less collapsed lung and secretions in the trachea. The hypothermia is considered to be related to upper respiratory irritation caused by the high concentrations of aerosol tested. According to the results, the test substance has an irritant potential to the respiratory tract, although it is of low acute inhalation toxicity to rats.	X
5.3	**Conclusion**		
5.3.1	Reliability	[redacted]	
5.3.2	Deficiencies	No	

Section A6.1.3 Acute Toxicity

Annex Point IIA VI.6.1.3 6.1.3 Acute inhalation toxicity to the rat

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	20/03/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.3 Acute Toxicity

Annex Point IIA VI.6.1.3 6.1.3 Acute inhalation toxicity to the rat

Table A6_1-1.3 Table for acute inhalation toxicity

Target Concentration [mg/m^3 air]	Toxicological results*	Duration of clinical signs	Time of death	Mortality [%]	Rectal Temperature [°C]
Males					
0	0/0/5	---	---	0	38.0
2000	0/5/5	0d - 9d	---	0	26.5**
3000	0/5/5	0d - 12d	---	0	25.9**
LC_{50} > 2871 mg/m^3 air					
Females					
0	0/0/5	---	---	0	38.5
2000	0/5/5	0d - 8d	---	0	26.6**
3000	0/5/5	0d - 14d	---	0	26.7**
LC_{50} > 2871 mg/m^3 air					

*first number = number of dead animals
second number = number of animals with signs
third number = number of animals used
** $p < 0.01$

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA VI.6.1.4 6.1.4(1) Acute dermal irritation

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted] Preventol CMK – The eye and dermal irritancy of sample p-Chloro-m-cresol. [redacted] 1976-11-30, (unpublished).
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes Federal Hazardous Substances Act, 21 CFR 191.11 (≅ OECD 404)
2.2	**GLP**	No, study was conducted before the enactment of GLP regulations
2.3	**Deviations**	Deviations from OECD 404: – Test material was not characterised – Sex and age of the test animals are not reported – Test included application on abraded skin – First scoring at 4 hours instead of at 60 minutes. – No reading was performed at 72 h post exposure
		3 MATERIALS AND METHODS
3.1	**Test material**	p-Chloro-m-cresol, no further characterisation
3.2	**Test Animals**	
3.2.1	Species	Rabbit
3.2.2	Strain	New Zealand White
3.2.3	Source	[redacted]
3.2.4	Sex	Not specified
3.2.5	Age/weight at study initiation	Not specified
3.2.6	Number of animals per group	6
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Dermal
3.3.1	Application	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA VI.6.1.4 6.1.4(1) Acute dermal irritation

3.3.1.1	Preparation of test substance	0.5 g of the test substance was applied as delivered.	
3.3.1.2	Test site and preparation of test site	The test substance was tested on intact as well as abraded skin. The test sites were shaved. The application sites were loosely covered with 5 × 5 cm² gauze patches.	
3.3.2	Occlusion	Semi-occlusive	
3.3.3	Vehicle	None	
3.3.4	Concentration in vehicle	Not applicable	
3.3.5	Total volume applied	Not applicable	
3.3.6	Removal of test substance	Yes	
3.3.7	Duration of exposure	4 h	
3.3.8	Postexposure period	96 h	X
3.3.9	Controls	none	
3.4	**Examinations**		
3.4.1	Clinical signs	No	
3.4.2	Dermal examination	Yes	
3.4.2.1	Scoring system	According to Draize scoring system. Erythema 0-4: 0: No erythema, 1: very slight erythema (barely perceptible), 2: well-defined erythema, 3 moderate to severe erythema, 4: severe erythema (beet redness) to slight eschar formation (injuries in depth) Oedema 0-4: 0: No oedema, 1: very slight oedema (barely perceptible), 2: well-defined oedema (edges of area well-defined by definite raising), 3: moderate to severe oedema (raised approximately 1mm), 4: severe oedema (raised more than 1 mm extending beyond the area of exposure)	
3.4.2.2	Examination time points	4 h, 24 h, 48 h	
3.4.3	Other examinations	–	
3.5	**Further remarks**	None	
		4 RESULTS AND DISCUSSION	
4.1	**Average score**	Intact skin only	
4.1.1	Erythema	1.9 at 24 and 48 h	
4.1.2	Oedema	0.5 at 24 and 48 h	
4.2	**Reversibility**	Not determined	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA VI.6.1.4 6.1.4(1) Acute dermal irritation

4.3	**Other examinations**	–	
4.4	**Overall result**	CMK is weakly irritating to the skin of rabbits. The average (24+48 h) erythema and oedema scores of are below 2.0.	X
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The dermal irritancy of CMK was tested in six New Zealand White rabbits. The procedure followed the current OECD Guideline 404 with minor deviations. The test was conducted by applying 500 mg CMK to the shaved skin of rabbits for 4 h. The Draize scale was used for scoring the skin reactions at 4, 24, 48, and 96 h post exposure.	
5.2	**Results and discussion**	Scores for dermal irritation are given in Table A6_1_4S-1. The average erythema and oedema scores over all 6 animals (24 + 48 h) are 1.9 and 0.5, respectively.	
5.3	**Conclusion**	CMK is not irritating to skin according to the criteria of Directive 2001/59/EC.	X
5.3.1	Reliability	[redacted]	
5.3.2	Deficiencies	No. The exact purity of the test material or the age/sex of the animals is unlikely to have an influence on the outcome of the test.	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA VI.6.1.4 6.1.4(1) Acute dermal irritation

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	31/03/2008
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*

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA VI.6.1.4 6.1.4(1) Acute dermal irritation

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

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA VI.6.1.4 6.1.4(1) Acute dermal irritation

Table A6_1-4S-1. Table for skin irritation study

Observation time	Rabbit no.											
	53		54		57		58		63		64	
	E*	O*	E	O	E	O	E	O	E	O	E	O
4 h	0	4	0	3	0	1	0	1	0	1	0	2
24 h	2	2	2	1	2	1	2	0	2	0	2	1
48 h	2	1	2	0	2	0	2	0	2	0	1	0
Mean value 24 +48 h	**2.0**	**1.5**	**2.0**	**0.5**	**2.0**	**0.5**	**2.0**	**0.0**	**2.0**	**0.0**	**1.5**	**0.5**
Mean value 24 +48 h, all animals	**1.9**	**0.5**										

* E: erythema, O: oedema (according to Draize Score)

Section A6.1.4 Acute Eye Irritation

Annex Point IIA VI.6.1.4 6.1.4(2) Acute eye irritation

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted] (1976) Preventol CMK – The eye and dermal irritancy of [redacted] sample p-Chloro-m-cresol. [redacted] 1976-11-30, (unpublished).
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes Federal Hazardous Substances Act, 21 CFR 191.11 (≅ OECD 405)
2.2	**GLP**	No, study was conducted before the enactment of GLP regulations
2.3	**Deviations**	Deviations from OECD 405: – Test material was not characterised – Sex and age of the test animals are not reported – First scoring at 4 hours instead of at 60 minutes. – No reading was performed at 72 h post exposure
		3 MATERIALS AND METHODS
3.1	**Test material**	p-Chloro-m-cresol, no further characterisation
3.2	**Test Animals**	
3.2.1	Species	Rabbit
3.2.2	Strain	New Zealand White
3.2.3	Source	[redacted]
3.2.4	Sex	Not specified
3.2.5	Age/weight at study initiation	Not specified
3.2.6	Number of animals per group	5 (5 min exposure) 3 (24 h exposure)
3.2.7	Control animals	No

Section A6.1.4 Acute Eye Irritation

Annex Point IIA VI.6.1.4 6.1.4(2) Acute eye irritation

3.3	**Administration/ Exposure**	Ocular instillation
3.3.1	Preparation of test substance	Test substance was used as delivered.
3.3.2	Amount of active substance instilled	100 µL
3.3.3	Exposure period	5 min or 24 h, eyes were rinsed thereafter
3.3.4	Postexposure period	21 days
3.4	**Examinations**	
3.4.1	Ophthalmoscopic examination	Yes
3.4.1.1	Scoring system	Grades of ocular lesions: Cornea 0 – 4 (0 = no finding, 1 = slight, disperse, diffuse opacity, 2 = extensive, diffuse opacity, iris blurred, 3 = mother-of-pearl-like opacity, iris and pupil hardly recognisable, 4 = complete opacity, ulceration) Iris 0 – 2 (0 = no finding, 1 = swelling, reddening, positive light reaction, 2 = severe reddening and swelling, no light reaction) Conjunctivae Redness 0 – 3 (0 = blood vessels normal, 1 = vessels abnormally filled, 2 = diffuse reddening, 3 = diffuse deep reddening) Swelling 0 – 4 (0 = no swelling, 1 = slight swelling, 2 =severe swelling, lids everted, 3 = lids cover one half of eye, 4 = lids cover more than half eye, necroses and ulcers on the conjunctivas)
3.4.1.2	Examination time points	1 h, 24 h, 48 h, 72 h, 7 d, 14 d, 21 d
3.4.2	Other examinations	None
3.5	**Further remarks**	The scoring of ocular reactions was aided by fluorescein instillation.

4 RESULTS AND DISCUSSION

4.1 Average score *(see Tables A6_1_4E-1 and A6_1_4E-2)*

		5-min exposure	**24- h exposure**
4.1.1	Cornea	1.9	2.0
4.1.2	Iris	0.7	0.9
4.1.3	Conjunctiva		
4.1.3.1	Redness	2.5	2.9
4.1.3.2	Chemosis	2.5	3.1

4.2 Reversibility No. The lesions were not reversible within 21 days except for iritis which reversed within 9-14 days in most animals.

Section A6.1.4 Acute Eye Irritation

Annex Point IIA VI.6.1.4 6.1.4(2) Acute eye irritation

4.3	**Other**	Within 3 min after compound instillation, the cornea and conjunctivae of all treated eyed were coated white. A purulent discharge was observed from all eyes through the Day 3 examination.	X
4.4	**Overall result**	The test substance is strongly irritating to the eyes of rabbits.	X
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The eye irritation potential of CMK was tested in NZW rabbits. The test substance (100 µL bulk volume) was instilled into the conjunctival sac of the lower eyelid of five (5-min exposure) or three (24-h exposure) rabbits. Exposure was terminated by rinsing of the eye. Ocular reactions were scored at 1, 24, 48 and 72 h, and 7, 14, and 21 days after test substance administration. The Draize system was used for scoring eventual lesions. The methods used in this study are in general accordance with OECD Guideline 405.	
5.2	**Results and discussion**	CMK produced strong ocular irritation characterised by corneal and iridial involvement and conjunctival irritation (see Tables A6_1_4E-1 and A6_1_4E-2). Ocular irritation was already triggered by 5-min exposure. Positive irritation reactions were observed in all animals beginning one hour post instillation and were mostly not resolved at the end of study on day 21.	
5.3	**Conclusion**	CMK is strongly irritating to eyes. It meets the criteria of Directive 2001/59/EC for classification as Xi, R41 - Risk of serious damage to eyes.	X
5.3.1	Reliability	[redacted]	
5.3.2	Deficiencies	No. The reporting deficits do not impair the validity of the study for the classification of CMK.	

Section A6.1.4 Acute Eye Irritation

Annex Point IIA VI.6.1.4 6.1.4(2) Acute eye irritation

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	04/04/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.4 Acute Eye Irritation

Annex Point IIA VI.6.1.4 6.1.4(2) Acute eye irritation

Table A6_1_4E-1. Results of eye irritation study (5-min exposure)

	Cornea	Iris	Conjunctiva	
			Redness	Chemosis
Score (average of animals investigated)	0 to 4	0 to 2	0 to 3	0 to 4
1 h	1.80	0.00	1.00	1.60
24 h	2.00	0.40	2.20	3.00
48 h	2.00	0.80	2.40	2.00
72 h	1.80	0.80	2.80	2.40
Average 24 h, 48 h, 72 h	**1.93**	**0.67**	**2.47**	**2.47**
Reversibility*	n	n.c.	n	n
Average time for reversion	> 21 d	14 d	> 21 d	> 21 d
* *c :* *completely reversible* *n c :* *not completely reversible* *n :* *not reversible*				

Table A6_1_4E-2. Results of eye irritation study (24-h exposure)

	Cornea	Iris	Conjunctiva	
			Redness	Chemosis
Score (average of animals investigated)	0 to 4	0 to 2	0 to 3	0 to 4
1 h	2.00	0.67	1.00	1.67
24 h	2.00	0.67	2.67	3.33
48 h	2.00	1.00	3.00	3.00
72 h	2.00	1.00	3.00	3.00
Average 24 h, 48 h, 72 h	**2.00**	**0.89**	**2.89**	**3.11**
Reversibility*	n	c	n	n
Average time for reversion	> 21 d	9 d	> 21 d	> 21 d
* *c :* *completely reversible* *n c :* *not completely reversible* *n :* *not reversible*				

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5 Skin sensitisation test in mice (modified LLNA/IMDS)

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted](2000): Preventol CMK, Pastillen LOCAL LYMPH NODE ASSAY IN MICE(LLNA/IMDS) [redacted] 2000-11-13 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA Guidelines and Quality Assurance[Tapez une citation prise dans le document ou la synthèse d'un passage intéressant. Vous pouvez placer la zone de texte n'importe où dans le document. Utilisez l'onglet Outils de zone de texte pour modifier la mise en forme de la zone de texte de la citation.]	
		2	
2.1	**Guideline study**	Yes OECD Guideline No. 406 US-EPA OPPTS 870.2600 EEC Method B.6 No statement claimed, but also in accordance with EEC Method B.42 (= OECD 429) with modifications.	X
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes – Measuring of cell counts instead of radioactive labelling – Additional ear swelling measurement – Sacrifice 1 day after last treatment	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	white pastilles	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	September 29, 2000	
3.1.2.4	Preparation of test substance for application	Test item was formulated in DEA 433 (mixture of dimethylacetamide (40%), acetone (30%) and ethanol (30%) = vehicle	
3.1.2.5	Pretest performed on irritant effects	No	
3.2	**Test Animals**		
3.2.1	Species	Mouse	
3.2.2	Strain	SPF NMRI mice (Hsd Win:NMRI)	

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5 Skin sensitisation test in mice (modified LLNA/IMDS)

3.2.3	Source	[redacted]
3.2.4	Sex	Females
3.2.5	Age/weight at study initiation	No data
3.2.6	Number of animals per group	6
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	
3.3.1	Treatment schedule	Day 0, 1 and 2
3.3.2	Application	Epicutaneous application onto the dorsal part of both ears.
3.3.3	Concentrations used	0 (vehicle), 1, 10, 50% test substance in vehicle
3.3.4	Application volumes	25 µL
3.3.5	Challenge schedule	NA
3.4	**Examinations**	
3.4.1	Pilot study	No
3.5	**Further remarks**	–

4 RESULTS AND DISCUSSION

4.1	**Results of test**	
4.1.1	LLNA	In the highest dose group the "positive level", which is 1.25 for the cell count index, was exceeded. Therefore, the LLNA/IMDS test show a weak but specific immunostimulating (sensitising) potential of the test item.
4.1.2	MEST	The "positive level" of ear swelling which is $2x10^{-2}$ mm increase has not been reached in all dose groups. In addition, there was no significant increase of the ear weights. Thus, under the described conditions an irritating potential of the test item can be excluded.
4.1.3	Other findings	None
4.2	**Overall result**	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A modified local lymph node assay (LLNA) was performed in NMRI mice to determine the sensitising potential and the irritating potential of CMK. The test was done according EEC method B.42 with the following modifications. Instead of radioactive labelling cell counts were measured. Therefore animals were sacrificed one day after the last application instead of three days after the last application. In addition, a measurement of the ear swelling after treatment was included in the test. Groups of 6 female NMRI mice received 25 µL of test item formulations applied epicutaneous onto the dorsal part of both ears on three consecutive days. The formulations contained 0, 1, 10 and 50% test item in DEA 133. After the third application animals were sacrificed and the auricular lymph nodes were transferred into sterile physiological saline. After preparation the

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5 Skin sensitisation test in mice (modified LLNA/IMDS)

		weight and cell counts were determined and the stimulation index was calculated by dividing the absolute number of weight or cell counts of the substance treated lymph nodes by the vehicle treated ones. In addition, on day 0 and 3 the ear swelling was measured using a spring-loaded micrometer and the mean ear swelling was determined. After sacrifice the ear weights were determined and the ratio ear swelling / ear weight was calculated. For the determination an 8 mm in diameter ear punch was weighed.
5.2	**Results and discussion**	The NMRI mice showed a slight increase in the stimulation indices for cell counts and for weights of the draining lymph nodes after application of the test item. The results show that the test item (Preventol CMK, Pastillen) has a weak sensitising potential in mice after dermal application. There was an increase compared to vehicle treated animals regarding the cell counts and the weight of the draining lymph nodes in the highest dose group. An irritating potential at the same doses measured by ear swelling or ear weights could not be determined.
5.3	**Conclusion**	
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	Yes - Age and weight of test animals were not reported. - Data of validation studies (e.g. for positive controls) are not reported.

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5 Skin sensitisation test in mice (modified LLNA/IMDS)

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	15/05/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5 Skin sensitisation test in mice (modified LLNA/IMDS)

Table A6_1_5-1. Detailed information including induction/challenge/scoring schedule for skin sensitisation test

Treatment	LLNA/IMDS	Observations/Remarks
	Day of treatment or time point	
Application 1	Day 0	25 µL / ear
Application 2	Day 1	25 µL / ear
Application 3	Day 2	25 µL / ear
Draining lymph node preparation	Day 5	Modification of LLNA test; no radioactive labelling
Measuring of cell counts	Day 5	Measuring of cell counts instead of scintillation counting

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5 Skin sensitisation test in mice (modified LLNA/IMDS)

Table A6_1_5-2. Result of skin sensitisation test (LLNA/IMDS)

Direct LLNA / number of animals in group		
Dose (%)	**Weight index**	**Cell count index**
	mean ± SD in %	
0	1.00 ± 17.78	1.00 ± 30.72
1	1.07 ± 18.06	0.99 ± 35.59
10	0.97 ± 19.06	0.71 ± 33.61
50	1.34 ± 20.43	1.28 ± 27.04

Table A6_1_5-3. Result of skin sensitisation test (ear swelling)

Ear swelling (NMRI mice, female, 6 animals/group, in 0.01 mm)			
Dose (%)	**day 0**	**day3**	**Index day 3**
	mean ± SD in %		
0	19.75 ± 5.34	19.92 ± 8.14	1.00
1	19.83 ± 4.73	19.50 ± 6.74	0.98
10	19.58 ± 7.04	19.50 ± 6.38	0.98
50	19.17 ± 6.61	19.33 ± 6.74	0.97

Table A6_1_5-4. Result of skin sensitisation test (ear weight)

Ear weight (NMRI mice, female, 6 animals/group, in mg per 8 mm diameter punch)		
Dose (%)	**day 3 (mean ± SD in%)**	**Index day 3**
0	14.49 ± 7.27	1.00
1	13.60 ± 6.39	0.94
10	13.84 ± 8.11	0.96
50	13.48 ± 5.17	0.93

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5(2) Guinea pig maximisation test

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		1 REFERENCE
1.1	**Reference**	[redacted](1980): Preventol CMK–Investigation of sensitizing effect (Maximisation test after Magnusson and Kligman) [redacted] 1980-01-23 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	LANXESS Deutschland GmbH
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No Study was conducted prior to establishing of accepted guidelines, but general accordance with EC Method B.6 (= OECD 406) can be stated.
2.2	**GLP**	No, study was conducted prior to the enactment of GLP principles.
2.3	**Deviations**	Deviations from OECD 406: – No reliability check was included. – The concentration used for induction was not irritating.
		3 MATERIALS AND METHODS
3.1	**Test material**	As given in Section 2
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2
3.1.2.1	Description	not reported
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	September 29, 2000
3.1.2.4	Preparation of test substance for application	Test item was formulated in Lutrol 300/ethanol (3:1) = vehicle
3.1.2.5	Pre-test performed on irritant effects	Yes
3.2	**Test Animals**	
3.2.1	Species	Guinea pig
3.2.2	Strain	Pirbright White
3.2.3	Source	[redacted]
3.2.4	Sex	♂ (1st study), ♀ (2nd study)
3.2.5	Age/weight at study initiation	400 g (1st study); 300 g (2nd study)
3.2.6	Number of animals per group	15
3.2.7	Control animals	Yes, vehicle-induced controls

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5(2) Guinea pig maximisation test

3.3	**Administration/ Exposure**	Guinea pig maximisation test (GPMT)	
3.3.1	Induction schedule	Day 0 + day 7	X
3.3.2	Duration of topical induction exposure	48 h	
3.3.3	Way of induction	Intradermal application, topical application to the shaved dorsal skin	
3.3.4	Vehicle	Lutrol 300/ethanol (3:1)	
3.3.5	Concentrations used for induction	Induction (Day 0): 25% (1st study) and 1% CMK (2nd study) in vehicle in Freund's adjuvant Induction (Day 7) 25% (1st study) and 1% CMK (2nd study) in vehicle	X
3.3.6	Challenge schedule	Day 21	
3.3.7	Duration of challenge exposure	6 h	X
3.3.8	Concentrations used for challenge	1st study: 25% (right flank), 12.5% CMK (left flank) in vehicle 2nd study: 50% (right flank), 25% CMK (left flank) in vehicle	
3.3.9	Rechallenge	No	
3.3.10	Scoring schedule	24 h and 48 h after end of challenge exposure	
3.3.11	Removal of the test substance	Not reported	
3.3.12	Positive control substance	No	
3.4	**Examinations**	Skin reactions of treated skin areas at the following time points: Induction: 24 h Challenge: 48 h, 72 h	
3.4.1	Pilot study	Skin irritation (4 animals, 12.5%, 25%, 50%, 100% test substance in vehicle, 24 h, occlusive exposure)	
3.5	**Further remarks**	–	
		4 RESULTS AND DISCUSSION	
4.1	**Results of pilot studies**	A suspension of 50% CMK in vehicle was confirmed as the highest non-irritating dose, after topical dermal application to the skin of guinea pigs for 24 hours.	
4.2	**Results of test**		
4.2.1	24 h after challenge	1st study: CMK 1/7/15, vehicle 0/0/15; 2nd study: CMK 0/4/15, vehicle 0/0/15 (left flank reactions/right flank reactions/number of animals)	
4.2.2	48 h after challenge	1st study: CMK 3/13/15, vehicle 0/1/15; 2nd study: CMK 0/2/15, vehicle 0/0/15 (left flank reactions/right flank reactions/number of animals)	
4.2.3	Other findings	None	
4.3	**Overall result**	CMK was sensitizing to the skin of guinea pigs in the maximisation test when a 25% CMK solution was used for induction. .	

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5(2) Guinea pig maximisation test

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The test was basically compliant to the OECD Guideline 406 (GPMT) although this guideline was not yet in existence at the time of the study.

A study for skin sensitisation in guinea pigs was conducted with the test substance p-chloro-m-cresol (CMK) using the Magnusson-Kligman method.

Groups of 15 Pirbright White guinea pigs each were used in two legs of the study. In the 1st study, male animals received intradermal and topical induction treatments with 25% CMK in vehicle. In the 2nd study, female animals were induced with a 1% solution of CMK. Both studies included respective vehicle control groups (Lutrol 300/ethanol (3:1)) with 15 animals each. Each induction exposure was 48 h in duration.

In the 1st study, guinea pigs were challenged with a 25% (right flank) or 12.5% (left flank) CMK suspension in vehicle.

In the 2nd study, guinea pigs were challenged with a 50% (right flank) or 25% (left flank) CMK suspension in vehicle

The challenge was performed two weeks after the last induction application. Fifteen naïve animals each also received an identical challenge application with CMK. Each challenge exposure was 6 h in duration. The Magnusson-Kligman scoring system was used to rate the skin reactions.

5.2 Overall result

In the 1st study, skin reactions were noted in 13 out of 15 animals. According to the criteria of Directive 2001/59/EC, CMK should be classified as a skin sensitizer (R43).

5.3 Conclusion

5.3.1 Reliability [redacted]

5.3.2 Deficiencies No. Since the study yielded positive results with CMK, a reliability check with a moderately sensitising compound is not required.

Section A6.1.5 Skin sensitisation

Annex Point IIA VI.6.1.5 6.1.5(2) Guinea pig maximisation test

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16/05/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted](1980): Excretion kinetics of Preventol CMK after single oral administration to rats [redacted] 1980-12-02 (unpublished).
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No
2.2	**GLP**	No
2.3	**Deviations**	N.A.
		3 MATERIALS AND METHODS
3.1	**Test material**	Preventol CMK, unlabelled
3.2	**Non-labelled parent compound**	Preventol CMK
3.2.1	Lot/Batch number	[redacted]
3.2.2	Specification	Not reported
3.2.2.1	Description	Not reported
3.2.2.2	Purity	[redacted]
3.2.2.3	Stability	Not reported
3.2.3	**Labelled parent compound**	Not applicable
3.2.4	Lot/Batch number	[redacted]
3.2.5	Specification	-
3.2.5.1	Description	-
3.2.5.2	Purity	[redacted]
3.2.5.3	Stability	–
3.2.5.4	Radiolabelling	-
3.3	**Test animals**	
3.3.1	Species	Rat
3.3.2	Strain	Wistar II rats
3.3.3	Source	[redacted]
3.3.4	Sex	Males
3.3.5	Age/weight at study initiation	Age: no data Body weight: 159 - 174 g
3.3.6	Number of animals	5

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

3.3.7	Control animals	No
3.4	**Administration/ Exposure**	Oral
3.4.1	Application	Gavage
3.4.1.1	Concentration of test substance	300 mg/kg bw
3.4.1.2	Duration of treatment	Rats: single oral dose
3.4.1.3	Post-exposure period	Rats: 72 hours
3.4.1.4	Specific activity of test substance	Not applicable.
3.4.1.5	Vehicle	Lutrol
3.4.1.6	Concentration in vehicle	Rats: 300 mg/kg bw
3.4.1.7	Amount applied	No data.
3.5	**Examinations**	
3.5.1	Biokinetic parameters	Excretion
3.5.2	Samples	Urine, faeces
3.5.3	Sampling time (0 h = start of application)	Urine: 4, 8, 24, 32,48, 56 and 72 h post-dosing Faeces: 24, 48 h and 72 h post-dosing
		4 RESULTS AND DISCUSSION
4.1	**Toxic effects, clinical signs**	Not reported.
4.2	**Recovery of labelled compound**	Not applicable.
4.3	**Percutaneous absorption**	Not applicable.
4.4	**Excretion**	See Table A6_2-1 in appendix. The excretion of Preventol was rapid and extensive. The majority of the test substance was excreted unchanged via the kidneys within 24 hours. Small amounts of Preventol CMK were also found in two samples from the time period 56-72 hours. The mean excretion over 72 hours was 60.5%, which after correction by the recovery rates gives a value of 67.2%. Only a small amount of the test substance was excreted in faeces. Measurable amounts were found only in the period 0 - 24 hours. Then, a mean of 0.24% of the applied amount was excreted.
4.5	**Distribution**	Not done.
4.6	**Metabolism**	Thin layer chromatography of the urine extracts showed two highly polar metabolites in addition to the unchanged test substance. The

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

		structure of these metabolites was not clarified.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The excretion of Preventol CMK was investigated in young adult male Wistar II rats. Five male rats received a single oral dose of 300 mg Preventol CMK/kg bw and housed individually in metabolism cages. Urine samples were taken at 4, 8, 24, 32, 48, 56 and 72 hours after application and analysed by HPLC. Faeces were samples at 24, 48 and 72 hours after application and measured by gas chromatography. In addition, the urine samples were analysed by thin layer chromatography (TLC).	
5.2	**Results and discussion**	- The major excretory route was via the urine with 67.2% recovery of the applied dose. The excretion was rapid within the first 24 hours after application. Low concentrations were also detected up to 72 hours. - The faeces represent a minor excretory route, with only 0.40% recovery of the applied dose within 24 hours post-dosing. - Two highly polar metabolites were found in the urine samples after TLC analysis. These metabolites are not included in the quantification and could be the explanation for the remaining 30%. Due to the rapid elimination of the substance, accumulation in fatty or liver tissue might be unlikely.	
5.3	**Conclusion**		
5.3.1	Reliability	[redacted]	X
5.3.2	Deficiencies	The methodology of the study is not today's state of the art. However, the study was able to demonstrate rapid and quantitative excretion of CMK. Furthermore, it is known that phenolic compounds are subject to rapid conjugation with sulphate and glucuronate followed by predominantly urinary excretion. This is underscored by the two very polar metabolites detected in urine.	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	26/02/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Table A6_2-1 Excretion of Preventol CMK in urine and faeces (µmol)

	applied amount mg/kg bw	**µmol**	**% of dose**	
		mean 0 - 72 h (urine) **0 - 24 h** (faeces)	**mean 0 - 72 h**	**mean 0 - 72 h after correction by the recovery rate***
Compound applied	300			
Compound detected				
Urine		213.4	60.5	67.2
Faeces		0.85	0.24	0.40

* urine: 90%; faeces: 60%

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Distribution of CMK in rats

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted] (1981): Investigation into the detection of Preventol CMK in fatty tissue and liver tissue in rats [redacted] 1981-02-17 (unpublished).
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No
2.2	**GLP**	No
2.3	**Deviations**	N.A.
		3 MATERIALS AND METHODS
3.1	**Test material**	Preventol CMK, unlabelled
3.2	**Non-labelled parent compound**	Preventol CMK
3.2.1	Lot/Batch number	[redacted]
3.2.2	Specification	Not reported
3.2.2.1	Description	Not reported
3.2.2.2	Purity	[redacted]
3.2.2.3	Stability	Not reported
3.2.3	**Labelled parent compound**	Not applicable
3.2.4	Lot/Batch number	[redacted]
3.2.5	Specification	-
3.2.5.1	Description	-
3.2.5.2	Purity	[redacted]
3.2.5.3	Stability	–
3.2.5.4	Radiolabelling	-
3.3	**Test animals**	
3.3.1	Species	Rat
3.3.2	Strain	Wistar TNO/W 74 rats
3.3.3	Source	[redacted]
3.3.4	Sex	Males
3.3.5	Age/weight at study initiation	Age: 4-5 weeks Body weight: 45 - 55 g
3.3.6	Number of animals	36 (12/dose group)

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Distribution of CMK in rats

3.3.7	Control animals	No.	
3.4	**Administration/ Exposure**	Oral	
3.4.1	Application	in food	
3.4.1.1	Concentration of test substance	150, 500, 1500 ppm	
3.4.1.2	Duration of treatment	13 weeks	
3.4.1.3	Post-exposure period	None.	
3.4.1.4	Specific activity of test substance	Not applicable.	
3.4.1.5	Vehicle	No	
3.4.1.6	Amount applied	No data.	
3.5	**Examinations**		
3.5.1	Samples	Liver and fatty tissues from the abdominal cavity	
3.5.2	Sampling time (0 h = start of application)	Week 1, 4, 8 and 13 after start of treatment.	
		4 RESULTS AND DISCUSSION	
4.1	**Toxic effects, clinical signs**	Not reported.	
4.2	**Recovery of labelled compound**	Not applicable.	
4.3	**Percutaneous absorption**	Not applicable.	
4.4	**Concentration in samples**	Liver tissues: No Preventol CMK concentrations above the detection limit (10 nmol/g) were detected in any of the liver tissue samples (see Table A6_2-1). Fatty tissues: Isolated values above the detection limit (4 nmol/g) were found in fatty tissue sample extracts (see Table A6_2-1). No cumulative effect could be detected.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Three groups of male Wistar TNO/W74 rats received oral doses of 150, 500 or 1500 ppm Preventol CMK in diet over 13 weeks. The liver and samples of fatty tissue from the abdominal cavity were removed from 3 animals per dose group 1, 4, 8 and 13 weeks after start of treatment. The samples were extracted and analysed by gas chromatography.	
5.2	**Results and discussion**	Detectable concentrations of Preventol CMK were not found in any of the liver samples. In the fatty tissue samples, concentrations of the test substance were occasionally above the detection limit of 4 nmol/g. No correlation was found between the applied dose and the amount of test substance in the	X

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Distribution of CMK in rats

		samples. No cumulative effect was observed. Preventol CMK does not accumulate in liver and fatty tissues.	
5.3	**Conclusion**		
5.3.1	Reliability	[redacted]	X
5.3.2	Deficiencies	No The test relies on non-labelled test material which might impair the sensitivity of the method. However, the detection limit using the employed method is in the range of 0.6-1.4 ppm and can be regarded sufficiently sensitive. Experience with other phenolic compounds shows that the molecules are readily conjugated to glucuronic acid and sulphate. The conjugates are then rapidly excreted via urine. Thus, accumulation in tissues is unlikely because of the intrinsic properties of the parent compound.	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Distribution of CMK in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	28/02/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Distribution of CMK in rats

Table A6_2-1 CMK concentrations in adipose and liver tissue

Dose group [ppm]	time of study [weeks]	Tissue concentration [nmol/g]*	
		Fatty tissue	Liver tissue
150	1	< LOD	< LOD
	4	11	
	8	< LOD	< LOD
	13	< LOD	< LOD
500	1	15	< LOD
	4	13	< LOD
	8	< LOD	< LOD
	13	< LOD	< LOD
1,500	1	10	< LOD
	4	10	< LOD
	8	< LOD	< LOD
	13	< LOD	< LOD

*Average of non-zero values

Section A6.2 Percutaneous absorption (*in-vivo* test)

Annex Point IIA VI.6.2 6.2 Dermal Absorption *in vivo*

Official use only

		1 REFERENCE
1.1	**Reference**	Roberts, M.S. *et al.* (1977): Permeability of human epidermis to phenolic compounds. Pharmacy Dept., Univ. of Sydney, Australia, published report: *J. Pharm. Pharmac.* **29**, 677-683
1.2	**Data protection**	No
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No guideline
2.2	**GLP**	No
2.3	**Deviations**	No
		3 MATERIALS AND METHODS
3.1	**Test material**	Freshly redistilled CMK
3.1.1	**Non-labelled parent compound**	CMK
3.1.2	Lot/Batch number	[redacted]
3.1.3	Specification	Not given
3.2	**Test Subjects**	
3.2.1	Species	Human
3.2.2	Source	Abdominal skin from autopsies
3.2.3	Sex	Not reported
3.2.4	Age/weight at study initiation	Not reported
3.2.5	Number of subjects per group	Not reported
3.2.6	Control subjects	No
3.3	**Administration/ Exposure**	**Dermal**
3.3.1	Preparation of test site	None
3.3.2	Concentration of test substance	0.4% w/v in water
3.3.3	Volume applied	9 mL
3.3.4	Size of test site	2.5 cm²
3.3.5	Exposure period	4 hours
3.3.6	Sampling time	Not reported, about once every 30 minutes, judging from the figures.
3.3.7	Samples	Receptor fluid
		4 RESULTS AND DISCUSSION
4.1	**Dermal irritation**	The skin remained intact throughout the exposure time.

Section A6.2 Percutaneous absorption (*in-vivo* test)

Annex Point IIA VI.6.2 6.2 Dermal Absorption *in vivo*

4.2	**Percutaneous absorption**	$K_P = 9.16 \times 10^{-4}$ cm/min = 0.055 cm/h	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Human epidermal membranes were obtained from abdominal skin samples by exposure to ammonia fumes for 30 min.	
		To ensure reproducibility, skin samples from one area of' one subject were used for each series of experiments. If necessary each membrane was used for several experiments. Its integrity was examined at the end of each series by repeating the initial experiment and comparing the fluxes obtained.	
		Penetration fluxes and permeability coefficients were estimated from the steady state slopes of the relations between the cumulative amount of solute penetrating through unit area of membrane with time.	
		The skin sample (2.5 cm² exposed surface) was exposed to 9 mL of CMK in distilled water (4% w/v) for up to 4 h in a Pyrex glass cell.	X
		The cell was sealed to prevent loss by evaporation. Distilled water was used as receptor fluid.	
		CMK concentrations in receptor fluid were determined by UV spectrometry. Samples drawn from the receptor side were replaced by either the original sample or an equivalent amount of distilled water.	
5.2	**Results and discussion**	The solubility of CMK in water at 25°C was determined to be 0.5% (w/v). This demonstrates that the solubility in receptor fluid did not limit percutaneous absorption.	
		A lag time of 17 min was determined by the absorption/time curve. Membrane integrity was maintained throughout the exposure period.	
		The permeability coefficient was determined to be 9.16×10^{-4} cm/min (= 0.055 cm/h).	
5.3	**Conclusion**	The K_P value of 0.055 cm/h is used to assess systemic uptake resulting from rinse-off products.	
5.3.1	Reliability	[redacted]	X
5.3.2	Deficiencies	Yes	
		Reporting deficits (substance identity). This is not influential for the determination of percutaneous absorption.	X

Section A6.2 Percutaneous absorption (*in-vivo* test)

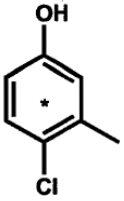
Annex Point IIA VI.6.2 6.2 Dermal Absorption *in vivo*

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	April 2009
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted](2009): Mass Balance and Metabolism of [^{14}C]-4-Chloro-3-methylphenol in Male and Female Rats After Single Oral Administration. [redacted] 2009-02-19 (unpublished).
1.2	**Data protection**	Yes
1.2.1	Data owner	LANXESS Deutschland GmbH
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes, OECD 417 (April 1984)
2.2	**GLP**	Yes
2.3	**Deviations**	– Only a single high-dose regimen was tested. – Metabolites were not identified
		3 MATERIALS AND METHODS
3.1	**Test material**	
3.2	**Non-labelled parent compound**	4-Chloro-3-methylphenol
3.2.1	Lot/Batch number	[redacted]
3.2.2	Specification	
3.2.2.1	Description	–
3.2.2.2	Purity	[redacted]
3.2.2.3	Stability	Expiry date: October, 2009
3.2.3	**Labelled parent compound**	4-Chloro-3-methyl[U-^{14}C]phenol
3.2.4	Lot/Batch number	[redacted]
3.2.5	Specification	
3.2.5.1	Description	–
3.2.5.2	Purity	Radiochemical purity: [redacted]
3.2.5.3	Stability	The radiochemical purity was checked at the time point of administration. Therefore no expiration date was needed.
3.2.5.4	Radiolabelling	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

3.3	**Test animals**	
3.3.1	Species	Rat
3.3.2	Strain	HanRcc:WIST
3.3.3	Source	[redacted]
3.3.4	Sex	♂ + ♀
3.3.5	Age/weight at study initiation	♂: 172 ± 5 g ♀: 174 ± 5 g
3.3.6	Number of animals	4 per sex
3.3.7	Control animals	No
3.4	**Administration/ Exposure**	Oral
3.4.1	Application	Gavage
3.4.1.1	Concentration of test substance	300 mg/kg bw
3.4.1.2	Duration of treatment	Rats: single oral dose
3.4.1.3	Post-exposure period	168 hours
3.4.1.4	Specific activity of test substance	Stock solution: 16 mCi/mmol (0.112 mCi/mg; 4.14 MBq/mg) Dosing solution: 62.01 kBq/mg
3.4.1.5	Vehicle	PEG 400
3.4.1.6	Concentration in vehicle	60 mg/mL
3.4.1.7	Amount applied	5 mL/kg bw
3.5	**Examinations**	
3.5.1	Biokinetic parameters	Absorption, excretion, metabolism, distribution
3.5.2	Samples	Urine, faeces, expired air, adrenals, bone, brain, carcass, epididymis (males), fat, femur, heart, intestine (small/large), intestinal contents, kidneys, liver lung, muscle, ovaries (females), pancreas, prostate (males), spleen, stomach, testis (males), thymus, thyroids, uterus (females)
3.5.3	Sampling time (0 h = start of application)	Urine and faeces: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours Expired air: In all animals: 0-24, 24-48, 48-72, and 72-96 hours In selected animals: 96-120, and 120-144 hours Tissues: 168 h

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

		4 RESULTS AND DISCUSSION	
4.1	**Toxic effects, clinical signs**	No unusual appearance or behaviour was observed.	
4.2	**Recovery of labelled compound**	A mean total recovery of 121.48% and 119.46% was reached in male and female rats, respectively. The high recovery values were probably due to the fact that the major part of radioactivity was detected in the first urine fraction. As a consequence only small volumes were used for LSC measurement. In combination with a certain degree of inaccuracy in the volume determination this resulted in overestimation of the measured values. All mean values reported were therefore normalized to a recovery of 100%.	
4.3	**Absorption**	Complete and rapid absorption judging from the high recovery and rapid urinary excretion.	
4.4	**Excretion**	(see Table A6_2-1) The majority of the administered test item was rapidly excreted with urine, i.e. 91.54% and 92.96% of the administered dose within 24 hours after administration in male and female rats, respectively. Only minor amounts of the test item were excreted with faeces, i.e. 3.70% and 1.44% of the administered dose within 24 hours after administration in males and females, respectively. The only exception was animal 1 of group 1. In this animal approximately 50% of the administered test item was found in urine, whereas approximately 50% of the administered test item was found in faeces within 24 hours after administration suggesting a soaking of the faeces sample with urine. Animal 1 of group 1 was therefore excluded from mean calculations. The amount of radioactivity found in the absorption traps of the expired air was fairly low, not exceeding 1% of the administered dose. Within 7 days after oral administration 99.03% and 98.94% of the dose was totally excreted in males and females, respectively. In consequence, the remaining amount of radioactivity, which was still present in the animals after 7 days was very low, not exceeding 1% of the dose.	X
4.5	**Distribution**	Due to the very low extent of absorption and the fast excretion, the tissue residues determined 168 hours after oral administration, resulted in generally very low residues measurable in the tissues. Residues above LOQ were only found in selected tissues and organs (see Table A6_2-2).	X
4.6	**Metabolism**	<u>Urine:</u> The 0 – 24 hours and 24 – 48 hours urines were pooled according to time and gender. The urine pools U1 (0 – 24 hours) and U2 (24 - 48 hours) were quantitatively analyzed by HPLC. The quantitative distribution of the metabolite fractions based on HPLC analysis is given in Table A6_2-3 (in % administered of dose). The HPLC analysis revealed a metabolite pattern which consists of 5 metabolite fractions in males and 6 metabolite fractions in females. Unchanged parent (U3) was found in urinary metabolite pattern as checked by co-chromatography with unlabeled test item accounting for 4.97% and 11.35% of the administered dose in males and in females, respectively. In both groups two major metabolites (U4 and U5) and two respectively three minor metabolites (U1, U2 and U6) were detected.	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

		Faeces: About 90% of the faeces radioactivity was extractable at room temperature. The extracted radioactivity was quantitatively analyzed by HPLC. The quantitative distribution of the metabolite fractions based on HPLC analysis is given in Table A6_2-4 (in % administered of dose). The HPLC analysis revealed a metabolite pattern which consists of 5 metabolite fractions in both groups. Unchanged parent (F3) was found in faeces metabolite pattern as checked by co-chromatography with unlabeled test item accounting for 4.93% and 2.67% of the administered dose in males and in females, respectively. All other metabolites identified (F1, F2, F4 and F5) were minor metabolites accounting for less than 1% of the administered dose.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The fate of [^{14}C]-4-chloro-3-methylphenol was investigated in male and female rats after single oral administration. [^{14}C]-4-Chloro-3-methylphenol was orally administered to male and female rats at a nominal dose level of 300 mg/kg body weight. The excretion of radioactivity in urine, faeces and expired air was measured in daily intervals up to 7 days after administration. Tissues were collected 7 days after administration.	
5.2	**Results and discussion**	A mean total recovery of 121.47% and 119.46% was reached in male and female rats, respectively. All mean values reported were normalized to a recovery of 100%. The orally administered test item was rapidly excreted in urine and faeces. Within 24 hours after administration 91.54% and 92.96% of the administered dose was excreted in urine of male and female rats, respectively. During the same period of time 6.69% and 4.35% was excreted in faeces in male and female rats, respectively. The radioactivity excreted in the expired air was low, i.e. less than 1% of the administered dose. After 7 days almost the entire administered dose was excreted (males: 99.03%, females: 98.94%) and only a very low amount of radioactivity was found in the remaining carcass and GI-tract, i.e. less than 1% of the dose. The investigation of the metabolite pattern in urine and faeces revealed that the test item was extensively metabolized. In total, about 10-14% of the radioactivity was found as unchanged parent in urine and faeces. The majority of radiolabelled metabolites were excreted with the urine. The urinary metabolite pattern consisted of at least 5 metabolite fractions. It was dominated by two major fractions, i.e. U4 (37-39% of the dose) and U5 (41-47% of the dose). In the faecal metabolite pattern the major fraction was found as unchanged parent, i.e. 3-5% of the dose. The metabolite pattern was very similar for both sexes with some quantitative differences. In summary, after oral administration of [^{14}C]-4-chloro-3-methylphenol to male and female rats, the recovery of radioactivity in urine, faeces, expired air and cage wash was almost complete. The radioactivity was mainly recovered in urine and to a lower extent in faeces but not in the	X

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

		expired air.
5.3	**Conclusion**	CMK is quantitatively and rapidly absorbed following oral administration. It is extensively metabolised and rapidly excreted; predominantly via urine.
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	The metabolism of phenolic compounds in the rat is highly predictable. The hydroxyl group is subject to hydroxylation and glucuronidation. In addition, ring hydroxylation will occur and give rise to mixed hydroxylation/conjugation products which are predominantly excreted via urine. Thus, identification of metabolites is expendable for CMK. Furthermore, the effect of dose on the ratio of glucuronidation vs. sulfatation is also well described in rodents. Sulfatation is a high-affinity, low-capacity pathway that is preferred at low doses. At increasing doses, glucuronidation becomes more important. Thus, the use of only one high-dose group does not affect the quality of this study.

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16/03/09
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Table A6_2-1 Excretion of CMK (% of dose administered)

		Group 1*		Group 2	
		Males measured	**Males normalized**	**Females measured**	**Females normalized**
Urine	0 – 24 h	103.51	85.21	100.70	84.30
	24 – 48 h	6.1	5.02	8.36	7.00
	48 – 72 h	1.16	0.95	1.10	0.92
	72 – 96 h	0.43	0.35	0.89	0.75
	96 – 120 h	0.28	0.23	0.47	0.39
	120 – 144 h	0.11	0.09	0.24	0.20
	144 – 168 h	0.06	0.05	0.18	0.15
Subtotal		111.19	91.54	111.05	92.96
Faeces	0 – 24 h	4.5	3.70	1.72	1.44
	24 – 48 h	2.42	1.99	1.98	1.66
	48 – 72 h	0.86	0.71	0.76	0.64
	72 – 96 h	0.35	0.29	0.74	0.62
	96 – 120 h	0.12	0.10	0.17	0.14
	120 – 144 h	0.08	0.07	0.22	0.18
	144 – 168 h	0.06	0.05	0.25	0.21
Subtotal		8.13	6.69	5.20	4.35
Expired Air	0 – 24 h	0.1	0.08	0.27	0.23
	24 – 48 h	0.26	0.21	0.30	0.25
	48 – 72 h	0.16	0.13	0.15	0.13
	72 – 96 h	0.09	0.07	0.10	0.08
	96 – 168 h	0.18	0.15	0.18	0.15
Subtotal		0.62	0.51	0.82	0.69
Cage Wash		0.98	0.81	1.94	1.62
Total Excretion		120.29	99.03	118.19	98.94
Tissues		<0.01	<0.01	<0.01	<0.01
Carcass		0.55	0.45	0.46	0.39
Total Recovery		121.47	100.00	119.46	100.00

* Animal 1 of group 1 was excluded from mean calculations.

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Table A6_2-2 Tissue distribution of CMK

Tissues	Males*: Mean µg equivalents/g	Females: Mean µg equivalents/g	LOQ µg equivalents/g
Adrenals	<LOQ	0.073	0.058
Blood	0.071	0.144	0.028
Brain	<LOQ	0.057	0.051
Epididymis	<LOQ	n.d.	0.056
Fat (renal, white)	<LOQ	0.107	0.090
Femur	0.041	0.067	0.018
Heart	<LOQ	<LOQ	0.056
Kidneys	0.226	0.359	0.056
Large intestine	0.044	0.059	0.019
Liver	0.207	0.321	0.064
Lung	0.039	0.091	0.029
Muscle	<LOQ	<LOQ	0.059
Ovaries	n.d.	0.150	0.110
Pancreas	<LOQ	0.151	0.057
Plasma	<LOQ	<LOQ	0.058
Prostate	<LOQ	n.d.	0.072
Small intestine	0.089	0.085	0.051
Spleen	<LOQ	0.098	0.057
Stomach	<LOQ	0.098	0.055
Thymus	<LOQ	<LOQ	0.051
Thyroid	<LOQ	<LOQ	0.052
Uterus	n.d.	0.069	0.052

* Animal 1 of group 1 was excluded from mean calculations

Section A6.2 Absorption, distribution, metabolism and excretion

Annex Point IIA VI.6.2 6.2 Excretion of CMK in rats

Table A6_2-3 Urinary metabolite pattern

Metabolite Pattern Urine (% of Administered Dose)						
	Group 1*			Group 2		
Pool	U1	U2	Sum	U1	U2	Sum
Sampling Time	0 - 24 h	24 - 48 h	0 - 48 h	0 - 24 h	24 - 48 h	0 - 48 h
Metabolite Fraction						
U1	-	-	-	-	0.12	0.12
U2	0.90	0.08	0.98	1.79	0.18	1.97
U3	3.61	1.35	4.97	9.38	1.96	11.35
U4	36.13	2.38	38.51	33.59	3.32	36.91
U5	44.56	1.12	45.68	39.54	1.32	40.86
U6	-	0.10	0.10	0.00	0.10	0.10
Total	85.21	5.02	90.23	84.30	7.00	91.30

* Animal 1 of group 1 was excluded from mean calculations

Table A6_2-4 Faecal metabolite pattern

Metabolite Pattern Faeces (% of Administered Dose)						
	Group 1*			Group 2		
Pool	F1	F2	Sum	F1	F2	Sum
Sampling Time	0 - 24 h	24 - 48 h	0 – 48 h	0 - 24 h	24 - 48 h	0 – 48 h
Metabolite Fraction						
F1	-	0.11	0.11	-	0.10	0.10
F2	0.06	0.10	0.16	-	-	-
F3	3.45	1.48	4.93	1.25	1.41	2.67
F4	0.09	-	0.09	-	-	-
F5	0.10	0.29	0.39	0.19	0.15	0.34
Total	3.70	1.99	5.69	1.44	1.66	3.10

* Animal 1 of group 1 was excluded from mean calculations

Section 6.3.1 Repeated dose toxicity

Annex Point IIA VI.6.3.1 6.3.1 Four-week oral toxicity study in rats

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1989), Preventol CMK – Range-finding subacute toxicological investigations in Wistar rats for the determination of a maximum tolerable dosage (Administration with food over 4 weeks) [redacted] 1989-02-20 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OECD Guideline 407 (1981)	
2.2	**GLP**	Yes	X
2.3	**Deviations**	Study performed according to GLP, but without quality check by the quality assurance unit.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	Solid colourless powder	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	No data	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	SPF bred Wistar rats strain Bor:WISW (SPF Cpb)	
3.2.3	Source	[redacted]	
3.2.4	Sex	Males & females	
3.2.5	Age/weight at study initiation	Approx. 6 weeks; ♂: 162 - 176 g, ♀: 124 - 137 g	
3.2.6	Number of animals per group	6 per sex and group	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	4 weeks	
3.3.2	Frequency of exposure	*ad libitum*	

Section 6.3.1 Repeated dose toxicity

Annex Point IIA VI.6.3.1 6.3.1 Four-week oral toxicity study in rats

3.3.3	Post-exposure period	–	
3.3.4	**Oral**		
3.3.4.1	Type	In food	
3.3.4.2	Concentration	500, 5000, 10,000 ppm ≅ ♂: 189.4, 384.5, 790.0 mg/kg bw/day ♀: 216.1, 443.1, 920.2 mg/kg bw/day	X
3.3.4.3	Vehicle	Diet, 1% peanut oil was added as formulation agent	
3.3.4.4	Controls	Plain diet	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes, twice daily (once on weekends and holidays)	
3.4.1.2	Mortality	Yes, twice daily (once on weekends and holidays).	
3.4.2	Body weight	Yes, twice weekly.	
3.4.3	Food consumption	Yes, once weekly.	
3.4.4	Water consumption	Yes, once weekly.	
3.4.5	Ophthalmoscopic examination		
3.4.6	Haematology	Yes, all surviving animals after 4 weeks on study Parameters: differential blood count, erythrocyte morphology, erythrocyte count, haemoglobin concentration, haematocrit, leukocyte count, platelet count, thromboplastin time	
3.4.7	Clinical chemistry	Yes, all surviving animals after 4 weeks on study Parameters: sodium, potassium, chloride, calcium, inorganic phosphate, glucose, cholesterol, triglyceride, urea, total bilirubin, creatinine, total protein, albumin, creatine kinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase	
3.4.8	Urinalysis	Yes, all animals; Parameters (semi-quantitative): ketone body, pH value, sediment, urobilinogen Parameters (quantitative): density, creatinine, protein, volume	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes Organs: brain, heart, testis (paired), liver, lung, spleen, kidneys (paired), adrenals (paired), ovaries (paired), thymus	
3.5.2	Gross and histopathology	Yes. Gross pathology: all dose groups; Organs: adrenals, aorta, bone marrow (in femur and breast bone), brain, breast bone, breast region, caecum, colon, duodenum, epididymides, oesophagus, eyes with eyelids and nervi optici, extra orbital glands, femur, gross lesions, Harderian glands, head residue, heart, hypophysis, ileum, jejunum, kidneys, larynx, liver, lungs, lymph nodes (mesenteric and mandibular), muscular system (thigh), nervus ischiadicus, ovaries,	

Section 6.3.1 Repeated dose toxicity

Annex Point IIA VI.6.3.1 6.3.1 Four-week oral toxicity study in rats

		oviducts, pancreas, parathyroid, prostate, rectum, residual intestine, salivary glands, skin, spinal marrow (cervical, thoracic, lumbar), spermatocysts, spleen, stomach, testes, thymus, thyroid gland, tongue, trachea, ureter, urethra, urinary bladder, uterus, vagina, Histopathology: No	
3.5.3	Other examinations	–	
3.5.4	Statistics	Only means and standard deviations were conducted.	
		4 RESULTS AND DISCUSSION *see Table A6_3_1-2*	
4.1	**Observations**		
4.1.1	Clinical signs	No clinical signs were observed.	
4.1.2	Mortality	No mortalities occurred at any dose level.	
4.2	**Body weight gain**	Body weight gain of the 10,000 ppm males were approx. 8% lower than those of the control animals (at all 4 weighing times). No effects were recorded in any other dose group and in the female animals.	
4.3	**Food consumption and compound intake**	No effects.	
4.4	**Ophthalmoscopic examination**	Not performed.	
4.5	**Blood analysis**		
4.5.1	Haematology	No treatment-related changes in any measured parameter were found. All differences between mean values for treated and control group rats were attributed to normal variability between animals. There was no dose-response pattern, and all the data were within the normal historical control range of the laboratory. These observations were not interpreted to be toxicologically significant.	
4.5.2	Clinical chemistry	No treatment related changes were found.	
4.6	**Urinalysis**	No treatment-related effects were observed.	X
4.7	**Sacrifice and pathology**		
4.7.1	Organ weights	No treatment-related effects.	
4.7.2	Gross and histopathology	2,500 ppm: One female had dark red colour changes at the margins of the liver 5,000 ppm: Two ovaries of one female were smaller 10,000 ppm: Two males had a relatively small liver These findings were assumed to be not treatment related.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In the four-week study, six rats per sex and dose level were given 0, 2500, 5000 or 10,000 ppm Preventol CMK 7 days/week in food with 1% peanut oil as a formulant. All rats were observed at least twice daily during the workweek and	

Section 6.3.1 Repeated dose toxicity

Annex Point IIA VI.6.3.1 6.3.1 Four-week oral toxicity study in rats

		once on weekends and holidays for evidence of treatment-related effects. Body weights and feed consumption were measured once weekly. Fasted blood samples for haematological determinations were obtained from all rats prior to necropsy. Haematological determinations included: differential blood count, erythrocyte morphology, erythrocyte count, haemoglobin concentration, haematocrit, leucocyte count, platelet count, thromboplastin time. Clinical chemistry determinations included: the activities of AP, ALT, AST, creatinine kinase, blood urea, creatinine, total protein, albumin, glucose, total bilirubin, cholesterol, triglycerides, electrolytes (Na, Ca, K, Cl, P). Urine specimens were collected in 16-hour intervals. Urinalyses included a semi-quantitative determination of pH, sediment, ketones and urobilinogen. In addition, the density, creatinine, protein and volume were determined quantitatively. A complete necropsy examination was conducted on all rats surviving to scheduled termination. Weights of the brain, heart, testis (paired), liver, lung, spleen, kidneys (paired), adrenals (paired), ovaries (paired), and thymus were recorded and organ/body weight ratios were calculated.	
5.2	**Results and discussion**	The daily observations of the animals provided no indications of dose-related findings on the physical condition or general behaviour. No mortalities occurred. The average food and water consumption was not affected in all animals. The body weight gain of the 10,000 ppm male dose group was approx. 8% lower compared to control animals. No effect on the body weight gain was observed in the 10,000 ppm female dose group and in any animal of the other dose groups. Blood analysis showed no indications of blood dyscrasias or an effect on the coagulation ability of blood in any animal of any dose group. No test-substance related organic lesions or pathological influence on metabolic functions were found. Urinalysis revealed no indication of a deterioration of the renal functions or damage of the kidneys.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	LOAEL = 10,000 / > 10,000 ppm = 790/>920 mg/kg bw/day (♂/♀)	X
5.3.2	NO(A)EL	NOAEL = 5000 / 10,000 ppm = 385/920 mg/kg bw/day (♂/♀)	X
5.3.3	Other	–	
5.3.4	Reliability	[redacted]	
5.3.5	Deficiencies	Yes. No quality check of report by Quality Assurance Unit.	

Section 6.3.1 Repeated dose toxicity

Annex Point IIA VI.6.3.1 6.3.1 Four-week oral toxicity study in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	22/05/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.3.1 Repeated dose toxicity

Annex Point IIA VI.6.3.1 6.3.1 Four-week oral toxicity study in rats

Table A6_3_1-1. Results of clinical chemistry, haematology and urinalysis

No treatment related changes were found.

Table A6_3_1-2. Results of repeated dose toxicity study

Parameter	Control		2500 ppm		5000 ppm		10,000 ppm		Dose-response +/–	
	m[a]	f[a]	m[a]	f[a]	m[a]	f[a]	m[a]	f[a]	m	f
Number of animals examined	6	6	6	6	6	6	6	6		
Body weight gain	–	–	–	–	–	–	↓	–	+	–
Necropsy										
dark red colour changes of the liver	0/6	0/6	0/6	1/6	0/6	0/6	0/6	0/6	–	–
smaller ovaries	0/6	0/6	0/6	0/6	0/6	1/6	0/6	0/6	–	–
relatively small liver	0/6	0/6	0/6	0/6	0/6	0/6	2/6	0/6	+	–

* $p < 0.05$

[a] number of animals affected/total number of animals

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

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		1 REFERENCE
1.1	**Reference**	[redacted] (1993): PREVENTOL CMK - Pre-test for dose-finding for a sub-chronic study, on male Wistar rats (dermal application for 4 weeks) [redacted] 1993-10-19 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No No guideline statement, but study conducted in general accordance with OECD Guideline 410.
2.2	**GLP**	No Study performed according to GLP, but without GLP check and statement of quality assurance.
2.3	**Deviations**	Deviations from OECD 410: - Only rats of one sex were tested - Clinical chemistry, haematology and histopathology examinations were not conducted - No satellite group for post-treatment period
		3 MATERIALS AND METHODS
3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	Colourless powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Approved for the study period.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar (BOR:WISW(SPF-Cpb)
3.2.3	Source	[redacted]
3.2.4	Sex	Males
3.2.5	Age/weight at study initiation	8 - 9 weeks; ♂: 186-202 g
3.2.6	Number of animals per group	6 per group
3.2.7	Control animals	Yes

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

3.3	**Administration/ Exposure**	Dermal	
3.3.1	Duration of treatment	4 weeks	
3.3.2	Frequency of exposure	Daily; 5 days /week	
3.3.3	Post-exposure period	–	
3.3.4	**Dermal**		
3.3.4.1	Area covered	Approx. 5 x 5 cm² of the back	
3.3.4.2	Occlusion	Occlusive	
3.3.4.3	Vehicle	Polyethyleneglycol 400 (PEG 400)	
3.3.4.4	Concentration in vehicle	Nominal doses: 0, 40, 200, 1000 mg/kg bw	
3.3.4.5	Total volume applied	1 mL/kg bw	
3.3.4.6	Duration of exposure	6 hours/day, 5 days/week	
3.3.4.7	Removal of test substance	PEG 400	
3.3.4.8	Controls	PEG 400	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes, twice daily (once daily on weekends and holidays)	
3.4.1.2	Mortality	Yes, twice daily (once daily on weekends and holidays)	
3.4.2	Body weight	Yes, before first application, then once weekly.	
3.4.3	Food consumption	Yes, before first application, then once weekly	
3.4.4	Water consumption	Yes, before first application, then once weekly	
3.4.5	Ophthalmoscopic examination	No	
3.4.6	Haematology	No	
3.4.7	Clinical chemistry	No	
3.4.8	Urinalysis	No	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes Organs: adrenals (in pairs), brain, heart, testicles (in pairs), liver, kidneys (in pairs), spleen,	X
3.5.2	Gross and histopathology	Yes. Gross pathology: all dose groups; Organs: adrenals, aorta, femoral bone, femoral bone marrow, brain, caecum, colon, duodenum, epididymides, oesophagus, extraorbital glands, eyes with eyelids and nervi optici, femoral muscle, gross lesions, Harderian glands, head, heart, ileum, jejunum, kidneys, liver,	

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

		lymph nodes (mesenterial and mandibular), mammary gland, nervus ischiadicus, pancreas, parathyroid, pituitary, prostate, rectum, salivary glands, seminal vesicles, skin (treated and untreated), spinal cord (cervical, thoracal, lumbar), spleen, stomach, sternum with bone marrow, testes, thymus, thyroid gland, tongue, trachea, ureters, urethra, urinary bladder, Zymbal glands Histopathology: No	
3.5.3	Other examinations	From the 4th application until termination: After removal of test substance, skin thickness was measured of all animals of the control and high dose group.	
3.5.4	Statistics	Only means and standard deviations were calculated. Comparisons of results of treated animals with controls were performed using significance test (U-Test by Mann and Whitney, Ann. Math. Stat. 18, 50 (1947) or Wilcoxon, Biometrics 1, 80 (1945)) with the significance level $\alpha = 5\%$ and $\alpha = 1\%$. Statistically significant differences ($p \leq 0.05$ and $p \leq 0.01$) are identified.	
		4 RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	0 - 200 mg/kg bw: No effects. 1000 mg/kg bw: The application sites of all animals showed slight erythema and oedema. The intensity of these findings increased until the end of the first treatment week. In addition, the application sites became sore and crustrated. After the treatment-free weekends, the symptoms recurred in a reduced manner after the first applications in week 2 and 3. In week 4 the intensity of theses symptoms decreased. Skin thickness in this group was increased up to 50% compared to controls. One animal excreted bloody urine and was in a distinct bad general condition on day 16.	
4.1.2	Mortality	No mortality occurred. One animal of the 1000 mg/kg bw dose group was killed in moribund condition on day 16.	
4.2	**Body weight gain**	0 - 200 mg/kg bw: No effects. 1000 mg/kg bw: Mean body weight gain was about 50% reduced.	X
4.3	**Food consumption and compound intake**	0 - 200 mg/kg bw: No effects. 1000 mg/kg bw: Compared to controls, the daily food consumption was reduced by about 14%.	
4.4	**Ophthalmoscopic examination**	Not applicable.	
4.5	**Blood analysis**		
4.5.1	Haematology	Not applicable.	
4.5.2	Clinical chemistry	Not applicable.	
4.5.3	Urinalysis	Not applicable.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	No treatment-related effects.	

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

4.6.2	Gross and histopathology	0 - 200 mg/kg bw: No effects 1000 mg/kg bw: The following findings were noted for the one animal that was killed moribund. Skin crustification at treatment site (left side of back), pale left kidney, both ureters were expanded, septum of urinary bladder was thickened with blood clot, pale liver with distinct delineation of liver lobes, light red and brown - black areas of the glands and gastro-oesophageal vestibule, jejunum with red-brown, creamy content. The following findings were found on other animals of this dose group at sacrifice. 4 animals with crustifications at the application site, one animal with expanded ureters and urinary bladder with blood clot.	
4.7	**Other**	Water consumption: 1000 mg/kg bw: Mean daily water-intake (g/animal) was about 14% increased, compared to controls.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The subacute four-week dermal study was used as a dose finding study for a dermal subchronic toxicity study. In the four-week study, six male Wistar rats per dose group received daily doses of 0, 40, 200 or 1000 mg Preventol CMK/kg bw for five days/week. The test substance was applied as solution in polyethyleneglycol 400 for 6 hours/day under occlusive conditions. All animals were inspected for mortality and signs of toxicity twice daily (once on weekends and holidays). Detailed clinical observations as well as determinations of body weights, food and water consumption were performed pre-exposure and weekly thereafter. Gross pathological examinations were performed on all animals killed moribund or were sacrificed at termination. Organ weights of adrenals, brain, heart, liver, lung, spleen and testicles were recorded and relative organ weights were determined. All gross lesions were recorded.	
5.2	**Results and discussion**	No effects were noted in any animal of the 0, 40 and 200 mg/kg bw dose group. After a few applications the application sites of all animals of the 1000 mg/kg bw dose group showed erythema, oedema, wounds and crustifications, as well as hard and leathery skin sites. The skin thickness of these animals was considerably increased compared to control animals. The intensity of these findings decreased during the 4th treatment week. One animal of the 1000 mg/kg bw dose group was killed on day 16 in moribund condition. Gross pathological examination of this animal and another animal of this dose group revealed expanded ureters and blood clots of the urinary bladder. Body weight gain in this group was about 50% reduced compared to controls. Feed consumption was about 14% reduced, water-intake about 12% increased in the highest dose group compared to controls.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	LOAEL = 1000 mg/kg bw/day, based on reduced bw gain	X
5.3.2	NO(A)EL	NOAEL = 200 mg/kg bw/day	

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

5.3.3	Other	–
5.3.4	Reliability	[redacted]
5.3.5	Deficiencies	None

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	23/05/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

Table A6_3-1. Results of clinical chemistry, haematology and urinalysis

No treatment-related changes

Table A6_3-2. Results of repeated dose toxicity study

Parameter	**Control**	**40 mg/kg**	**200 mg/kg**	**1000 mg/kg**	**Dose-response +/–**
	m[a]	**m[a]**	**m[a]**	**m[a]**	**m**
Number of animals examined	6	6	6	6	
Mortality	0/6	0/6	0/6	1[#]/6	+
At application site					
Erythema	0/6	0/6	0/6	6/6	+
Oedema	0/6	0/6	0/6	6/6	+
Crustifications	0/6	0/6	0/6	6/6	+
Hard, leathery skin	0/6	0/6	0/6	6/6	+
Skin thickness increased	0/6	n.e.	n.e.	6/6	+
Gross pathology					
Pale kidney	0/6	0/6	0/6	1/6	+
Ureters expanded	0/6	0/6	0/6	2/6	+
Pale liver	0/6	0/6	0/6	1/6	+
Liver: distinctive lobe delineation	0/6	0/6	0/6	1/6	+
Gastro ioesophageal vestibue: light red areals	0/6	0/6	0/6	1/6	+
Stomach: brown-black areals	0/6	0/6	0/6	1/6	+
Intestine: red-brown, creamy content	0/6	0/6	0/6	1/6	+
Urinary bladder: expanded wall, blood clots	0/6	0/6	0/6	2/6	+
Mean body weight				↓**	+
Reduced body weight gain	0/6	0/6	0/6	6/6	+
Food intake (g/animal)				↓**	+
Water-intake (g/kg body weight)				↑**	+

* $p \leq 0.05$; ** $p \leq 0.01$

[a] number of animals affected/total number of animals
n.e.: not examined

[#] Animal killed in moribund condition

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1980): Subchronic Dermal Study in Rabbits. Preventol CMK. [redacted] 1980-07-31 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Lanxess Deutschland GmbH	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No Study was conducted prior to the enactment of relevant guidelines, but study design in general accordance with OECD Guideline 410 (1981).	
2.2	**GLP**	Yes	
2.3	**Deviations**	Deviations from OECD 410: None	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	White solid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	New Zealand White	
3.2.3	Source	[redacted]	
3.2.4	Sex	♂ + ♀	
3.2.5	Age/weight at study initiation	Age: not reported BW: ♂: 2505 to 3135 g, ♀: 2480 to 3045 g	
3.2.6	Number of animals per group	10 per sex (6 intact skin, 4 abraded skin)	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Dose groups	10, 40, and 160 mg/kg bw/day.	
3.3.2	Duration of treatment	3 weeks	

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

3.3.3	Frequency of exposure	Daily; 5 days/week
3.3.4	Post-exposure period	–
3.3.5	**Dermal**	
3.3.5.1	Area covered	10% of body surface
3.3.5.2	Occlusion	Occlusive
3.3.5.3	Vehicle	None
3.3.5.4	Duration of exposure	6 hours/day, 5 days/week
3.3.5.5	Removal of test substance	With cotton pads
3.3.5.6	Controls	Sham exposure
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes, once daily
3.4.1.2	Mortality	Yes, once daily
3.4.2	Body weight	Body weights were recorded during Days 1, 4 , 8, 11, 15, 18, 21, and prior to terminal sacrifice of each animal.
3.4.3	Food consumption	Food consumption was recorded during Days 3, 5, 8 (Week 11, 10, 12, 15 (Week 21, 17, 19, and 22 (Week 3)
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	No
3.4.6	Haematology	Yes, 5 animals/sex/group prior to initiation of treatment (Day 0) and prior to terminal sacrifice (Day 22). Parameters: haematocrit, haemoglobin, erythrocyte count, total leukocyte count, platelet count, reticulocyte count (Day 0 only), and differential leukocyte count
3.4.7	Clinical chemistry	Yes, 5 animals/sex/group prior to initiation of treatment (Day 0) and prior to terminal sacrifice (Day 22). Parameters: calcium, potassium, lactic dehydrogenase, fasting glucose, blood urea nitrogen, direct and total bilirubin , total cholesterol , alkaline phosphatase, albumin, globulin, total protein, and glutamic pyruvic transaminase.
3.4.8	Urinalysis	No
3.5	**Sacrifice and pathology**	
3.5.1	Organ weights	Yes Organs: pituitary, thyroid (with parathyroid), adrenals, heart, liver, kidneys, and gonads.
3.5.2	Gross and histopathology	Yes. Gross pathology: all animals. Histopathology: skin (treated and untreated), liver, kidneys, brain, pituitary, heart, thyroid, parathyroid, adrenals, testes or ovaries, and unusual lesions.
3.5.3	Other examinations	Dermal irritation was graded and scored each morning (before

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

		application of CMK according to the Draize Scoring System.
3.5.4	Statistics	Individual body weights and weight changes, individual weekly food consumption values and three weeks total food consumption values of the control groups were compared statistically to data of the treated groups of the same sex by Bartlett's test for homogeneity of variance and one-way ANOVA. If significant results were obtained from both Bartlett's test and ANOVA, a multiple pairwise comparison procedure was used to compare the group mean values. If a significant result was not obtained from Bartlett's test, but was obtained from ANOVA, Scheffe's multiple pairwise comparison procedure was used to compare the group mean values. Clinical laboratory and organ weight data of the analysed by Bartlett's test. This analysis was followed by a one-way ANOVA if the variances proved to be homogeneous. If the variances proved to be heterogeneous, a $\log_{10}$ transformation was performed, which was followed by Bartlett's test. If the $\log_{10}$ transformation was ineffective in removing variance heterogeneity, a $\log_e$ transformation of the original data was performed which was followed by Bartlett's test. If homogeneity could not be achieved by transformation, ANOVA of the non-transformed data was completed. If ANOVA of homogeneous data was significant, Scheffe's multiple pairwise comparison procedure was used to compare the group mean values. If ANOVA of heterogeneous data was significant, Games and Howell's multiple pairwise comparison procedure was used to compare the group mean values. All analyses were evaluated at the 5.0% probability level.
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	All animals were normal in appearance and behaviour throughout the study except one high-dose female (E23118). Haemorrhage and shock were noted during a physical examination performed on Day 5. Examination of a tissue mass in the uterus presented the impression of haemangioma, a pedunculated, blood-filled tissue mass. Moribund sacrifice was performed since the poor condition of the animal precluded surgical correction.
4.1.2	Mortality	No mortality occurred. One animal was subjected to moribund sacrifice (see above).
4.1.3	Dermal irritation	Control animals generally showed no dermal effects. Low-dose animals generally showed very slight erythema (and very slight oedema, Week 1) throughout the study. Mid-dose animals generally showed very slight to well-defined erythema (and very slight oedema, Week 1) throughout the study, with a few instances of moderate to severe erythema (Week 1). High-dose animals generally showed very slight to well-defined erythema (and very slight to slight oedema, Week 1) throughout the study, with numerous instances of moderate to severe erythema (Week 1). The incidence of skin thickening and epidermal scaling was generally

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

		comparable among all treated groups. While the occurrences of blanching, raw areas, necrosis, and brown scab-like areas were noted for all treated groups, the frequency was more pronounced in the mid- and high-dose groups. Fissuring occurred in three animals - without bleeding in one mid-dose female (Day 9), with and without bleeding in one high-dose male (Days 14-20), and with bleeding in one high-dose male (Day 18).	
4.2	**Body weight gain**	No treatment-related effects.	
4.3	**Food consumption**	No treatment-related effects.	
4.4	**Blood analysis**		
4.4.1	Haematology	(see Table A6_3_2-1) at 40 mg/kg/day: platelet counts ↑ (♀, not statistically significant) at 160 mg/kg/day: platelet counts ↑ (♂, not statistically significant) platelet counts ↑ (♀, statistically significant) The marginally increased platelet counts are in all likelihood a secondary effect caused by the inflammation at the application site.	X
4.4.2	Clinical chemistry	No treatment-related effects.	
4.5	**Sacrifice and pathology**		
4.5.1	Organ weights	No treatment-related effects.	
4.5.2	Gross and histopathology	Gross pathology (see Table A6_3_2-2): Treated skin, all treatment groups: light, dark brown, or dark red scab(s); dark brown and/or crusty area(s); necrotic or raw areas; hair loss ; and epidermal thickening, scaling, or sloughing. Histopathology (see Table A6_3_2-2): Microscopic evaluation revealed compound-related histomorphologic alterations in the treated skin sections from rabbits at all dose levels. Marked epidermal and dermal necroses were present along with destruction of adnexal structures in 18 of 20 rabbits in the high-dose group and in occasional rabbits of the mid-dose group. Diffuse pleocellular inflammatory infiltrate, acanthosis, hyperkeratosis, and subepidermal congestion were relatively consistent findings in treated skin sections from rabbits of all groups. The severe epidermal and dermal necroses with destruction of adnexal structures were not observed in rabbits of the low-dose (10 mg/kg) group.	
4.6	**Other**	–	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	A subchronic dermal study with Preventol CMK was conducted in close accordance to OECD Guideline 410 (1981). Eighty (10 animals/sex/group) New Zealand White rabbits received a total of 15 skin applications (on the back) of Preventol CMK a t levels of 10, 40, and 160 mg/kg/day. Evaluated for treatment-related effects were mortality and moribundity, clinical observations, dermal irritation (Draize Scoring System), body weight and food consumption values, clinical laboratory studies, terminal body weights, organ weights, and organ/body weight ratios,	

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

		and gross and microscopic findings.
5.2	**Results and discussion**	Treatment-related dermal irritation findings were: In the low-dose group, slight to well-defined erythema and very slight oedema; in the mid-dose group, slight to well-defined erythema, with a few instances of moderate to severe erythema, and very slight oedema; in the high-dose group, very slight to well-defined erythema, with numerous instances of moderate to severe erythema, and very slight to slight oedema; a comparable frequency of skin thickening and epidermal scaling in all treated, groups; and a pronounced frequency of blanching, raw areas, necrosis, and brown scab-like areas in the mid- and high-dose groups. The findings were confirmed by dermal observations during terminal necropsies, which revealed compound-related abnormalities: light, dark brown or dark red scab(s); dark brown and/or crusty area(s); necrotic or raw areas hair loss; epidermal thickening, scaling or sloughing. Microscopic evaluation revealed compound-related findings: epidermal and dermal necrosis with destruction of adnexal structures in the mid- and high-dose rabbits with somewhat less severe dermal irritation in the low-dose rabbits; diffuse pleocellular inflammation infiltrate; acanthosis; hyperkeratosis; necrotic cell debris on the epidermis; and subepidermal congestion. Although there were dermal or local effects, there was no consistent evidence of treatment-related systemic effects of Preventol CMK when applied repeatedly to the skin of albino rabbits. Increased platelet counts are probably secondary to the local skin inflammation and are not regarded as a specific systemic effect.
5.3	**Conclusion**	
5.3.1	LO(A)EL	systemic LOAEL > 160 mg/kg bw/day local LOAEL ≤ 10 mg/kg bw/day
5.3.2	NO(A)EL	systemic NOAEL ≥ 160 mg/kg bw/day local NOAEL < 10 mg/kg bw/day
5.3.3	Other	–
5.3.4	Reliability	[redacted]
5.3.5	Deficiencies	None

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	20/03/2009
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.3.2 Repeated dose toxicity

Annex Point IIA VI.6.3.2 6.3.2 Four-week dermal toxicity study in rats

Table A6_3-1. Results of clinical chemistry, haematology and urinalysis

Parameter	Control		10 mg/kg/day		40 mg/kg/day		160 mg/kg/day		Dose-response +/–	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Number of animals examined	5	5	5	5	5	5	5	5		
Platelets [10^3/µL] Day 0	328	398	343	494	414	391	536	363	–	–
Day 22 [10^3/µL]	331	409	366	469	378	516	566*	537	+	+

*Statistically significant difference to controls, $p < 0.05$

Table A6_3-2. Results of repeated dose toxicity study

Parameter	Control		10 mg/kg/day		40 mg/kg/day		160 mg/kg/day		Dose-response +/–	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Number of animals examined	10	10	10	10	10	10	10	10		
Mortality	0	0	0	0	0	0	0	1	–	–
Gross pathology										
Treated skin, epidermal thickening	0	0	1	0	4	2	8	3	+	+
Treated skin,' necrotic areas	0	0	1	0	7	5	10	7	+	+
Histopathology										
Treated skin, acanthosis	0	0	10	10	10	10	10	10	+	+

Section 6.3.3 **Annex Point IIA VI.6.3.3**	**Short-term repeated-dose toxicity test** **Subacute inhalation toxicity test in rats**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	[redacted]	

Section 6.3.3 **Annex Point IIA VI.6.3.3**	**Short-term repeated-dose toxicity test** **Subacute inhalation toxicity test in rats**
	[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	June 2009

Section 6.3.3 **Annex Point IIA VI.6.3.3**	**Short-term repeated-dose toxicity test** **Subacute inhalation toxicity test in rats**
Evaluation of applicant's justification	[redacted]

Section 6.3.3 **Annex Point IIA VI.6.3.3**	**Short-term repeated-dose toxicity test** **Subacute inhalation toxicity test in rats**
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 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted] (2011), 14-Day Repeated Dose Inhalation Toxicity Study with Preventol CMK [redacted]
1.2	**Data protection**	Yes
1.2.1	Data owner	LANXESS Deutschland GmbH
1.2.2	Company with letter of access	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes OECD-Guideline No. 412 (adopted 7 September, 2009)
2.2	**GLP**	Yes
2.3	**Deviations**	None
		3 MATERIALS AND METHODS
3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	White coloured pellets
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Certified for the duration of the study. (Expiry date: 29 October, 2011)
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar (Crl: WI)
3.2.3	Source	[redacted]
3.2.4	Sex	males and females
3.2.5	Age/weight at study initiation	Age: 7 - 9 weeks; Weight: 210 - 235 g (males); 180 - 213 g (females)
3.2.6	Number of animals per group	10/group (5 males, 5 females)
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Inhalation
3.3.1	Duration of treatment	14 days
3.3.2	Frequency of exposure	7 days/week

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

3.3.3	Post-exposure period	Main groups: no Recovery groups (control and high concentration satellite group): yes, 14 days
3.3.4	**Inhalation**	
3.3.4.1	Concentrations	Nominal concentration [mg/m³]: 340, 1730, and 2910 Actual concentration [mg/m³]: 50, 250, and 510
3.3.4.2	Particle size	Mean MMAD [µm] (± GSD [µm]) Low dose: 2.30 (2.66) Mid dose: 2.57 (2.39) High dose: 2.35 (1.97)
3.3.4.3	Type or preparation of particles	The test substance (pellets) was finely grounded using a ball mill PM 100 to generate particles of inhalable size.
3.3.4.4	Type of exposure	Nose only.
3.3.4.5	Vehicle	-
3.3.4.6	Duration of exposure	6 hours
3.3.4.7	Controls	Yes, air alone
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes, during and after exposure
3.4.1.2	Mortality	Yes, once daily.
3.4.2	Body weight	Yes, before treatment and twice weekly thereafter
3.4.3	Food consumption	Yes, cage-wise, recorded daily, reported weekly
3.4.4	Water consumption	Yes, cage-wise, recorded daily, reported weekly
3.4.5	Ophthalmoscopic examination	No.
3.4.6	Haematology	Yes, all groups: at the end of treatment period (Day 15), recovery groups: additionally at termination (Day 29) Parameters: RBC count, WBC count, haematocrit (HCT), platelet count, haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC), differential count (5 parts), reticulocyte count, clotting time, prothrombin time
3.4.7	Clinical chemistry	Yes, all groups: at the end of treatment period (Day 15), recovery groups: additionally at termination (Day 29) Parameters: glucose, total cholesterol, triglycerides, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatise (ALP), blood urea nitrogen (BUN), urea, creatinine, total protein, albumin, globulin, phosphorus, calcium, sodium, chloride, potassium
3.4.8	Urinalysis	Yes, all groups: at the end of treatment period (Day 15), recovery groups: additionally at termination (Day 29) Parameters: colour, pH, specific gravity, sediment, albumin, glucose, ,

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

		bilirubin, ketones, blood, WBC, RBC, epithelial cells, casts, crystals, organisms, abnormal constituents
3.5	**Sacrifice and pathology**	
3.5.1	Organ weights	Yes, all animals Organs: brain, heart, lungs, liver, kidneys, spleen, thymus, adrenals, testis, ovaries
3.5.2	Gross and histopathology	Gross pathology Yes, at the end of observation period (treatment group: Day 15; recovery group: Day 29) *All animals*: Assessment for external and internal pathological lesions, particular attention to changes in the respiratory tract Histopathology Yes, at the end of observation period (treatment group: Day 15; recovery group: Day 29) *All animals*: Nasopharyngeal tissues, tongue, larynx, trachea, lungs, lymph nodes (mandibular, cervical, mediastinal, tracheobronchial); additional selected organs (weight changes determined): heart, aorta, liver, kidneys, pituitary, thyroid with parathyroid, adrenals, esophagus, stomach, small intestine, large intestine, pancreas, spleen, thymus brain, spinal cord, eyes, urinary bladder, seminal vesicles, testis, ovaries, uterus, bone marrow (sternum)
3.5.3	Other examinations	Two recovery groups (control, high concentration) were subject to a two-week post-exposure period after which they were sacrificed and examined for reversibility of eventual effects.
3.5.4	Statistics	MODIFIED-LEVENE EQUAL VARIANCE test for homogeneity. Homogenous data was submitted to Analysis of Variance (ANOVA) followed by STUDENT-NEWMAN-KEUL´s test.

4 RESULTS AND DISCUSSION

4.1	**Observations**		
4.1.1	Clinical signs	Control group:	No treatment related effects.
		Low concentration group:	No treatment related effects.
		Mid concentration group:	Dullness, nasal irritation
		High concentration group:	Lacrimation, nasal irritation, dullness, nostril discharge, gasping, change of body coat, facial swelling, reddened nostrils, edematous forelimbs, forelimbs with red encrustations
		Control recovery group:	No treatment related effects
		High concentration recovery group:	Lacrimation, nasal irritation, dullness, nostril discharge, facial swelling, reddened nostrils, edematous forelimbs
4.1.2	Mortality	None of the animals died pre-terminally.	

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

4.2	**Body weight gain**	A significant decrease of body weight gain was observed in males and females of the high concentration groups and the mid concentration group. The effects in the high concentration groups were accompanied by severe clinical signs and less consumption of food and water. Recovery was complete in females at Day 22 but incomplete in males at Day 29. The significant increase in body weight observed in the low concentration group (Day 7) was not considered to be of toxicological relevance. No effects were noted in the other animals.
4.3	**Food consumption and compound intake**	The males and females of both high concentration groups (main, recovery) showed significantly decreased food consumption up to exposure week 2. In the recovery group, food consumption was normal during recovery period. Females of the mid concentration showed significantly decreased food consumption at exposure week 1. The effects were accompanied by severe clinical signs due to the test substance exposure. No effects were noted in the other animals.
4.4	**Water consumption**	The males and females of both high concentration groups (main, recovery) showed significantly decreased water consumption up to exposure week 2 (females of recovery group: up to week 1, all others: up to week 2). The findings were reversible in both sexes. Both sexes of the mid concentration group as well as females of the low concentration group showed significantly decreased water consumption at the end of exposure week 2. No effects were noted in the other animals.
4.5	**Ophthalmoscopic examination**	Not applicable.
4.6	**Blood analysis**	
4.6.1	Haematology	A significant decrease in basophils was observed in both sexes in the low and mid concentration group. Males of the high concentration recovery group showed an increase in MCH and prothrombin time. Due to the lack of a dose relation, the changes were regarded to be incidental and not to be treatment-related.
4.6.2	Clinical chemistry	High concentration animals (females in main group, males in recovery group) showed a significant decrease in glucose levels on Day 15. (A (not statistically significant) trend towards decrease in glucose levels was observed in both sexes in all groups, which is presumed to be related to the reduction in food consumption.) The significant decrease in protein concentration and in globulin levels observed in males of the low and mid concentration group were considered to be incidental as they were not dose-related and well within the historical control data. Chlorides were significantly decreased in the high concentration groups (main group: both sexes, recovery group: females). These changes were not considered treatment-related as no other electrolyte parameter did show concomitant significant changes.

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

		A significant increase in phosphorus levels and a decrease in the sodium levels were observed in females of the high concentration main or recovery group, respectively. Males of the latter showed increased total bilirubuin levels. At examination on Day 29, females of the high concentration recovery group showed again an increase in potassium and a significant decrease in sodium levels. These changes were considered to be incidental as they were well within the historical control data.
4.6.3	Urinalysis	No significant changes were observed in any of the groups on Day 15 or 29, respectively.
4.7	**Sacrifice and pathology**	
4.7.1	Organ weights	<u>Absolute organ weights:</u> Changes were observed in males only. A test-article-related and statistically significant decrease in the thymus (all main groups), spleen (mid and high concentration (main) group) and liver (high concentration main group) was observed. The mean absolute liver weight of high concentration recovery males showed a statistically significant increase. The effect on thymus weights is correlated with the reduced relative thymus weights as well as with histopathological findings (atrophy) and is considered to be test substance-related for the mid and high concentration group. Changes observed in spleen and liver were not correlated with relative organ weight changes and were thus not considered to be toxicologically relevant. A significant decrease in absolute brain weights in the low and mid concentration group was considered incidental as the changes were not dose-related. <u>Relative organ weights:</u> The mean relative thymus weights were significantly decreased in males in all main groups. Significant increases in relative brain weights (both sexes, high concentration), heart (males, mid concentration, both sexes, high concentration), gonads (males, mid and high concentration), kidney (both sexes, high concentration main group, males, high concentration recovery group) and lungs (females, high concentration main group, males, high concentration recovery group) were observed, but considered to be the effect of reduced body weight or considered to be incidental. In males of the high concentration groups (main and recovery) a significant increase in relative adrenal weights was considered to be stress-related. The significant decrease in lung weight of high concentration males was considered incidental as no correlation to macroscopical or microscopical changes was determined. The significant increase in relative liver weights (females, mid and high concentration) was considered incidental, since there was no

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3	6.3.3 Repeated dose toxicity (inhalation) in rats
	biochemical or histopathological correlate determined.

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

4.7.2	Gross and histopathology	Gross pathology The following substance-related findings were observed in the mid and high concentration group: • High concentration main group: emaciation (1 male and 4 females), reddened nostrils (3 males and 2 females), swollen forelimbs with red encrustations on the digits (2 males), forelimbs with red encrustations on the digits (3 males and 1 female), reduction in thymus size (2 males and 2 females), bloated intestinal tract (1 male), reduction in size of accessory sex organs (1 male). The latter two effects were insignificant and inconsistent. • High concentration recovery group: diaphragmatic nodule in the liver (1 male). This is a congenital lesion and of the type routinely observed in Wistar rats. • Mid concentration group: reduction in thymus size (1 female). The thymus effect was correlated with the reduced organ weight and microscopic findings. Histopathology Test item-related findings were noted in the in thymus and nasopharyngeal tissues (mid and high concentration) and in trachea (high concentration). These findings consisted of: • Atrophy of thymus in 1 female (mid concentration); 2 males and 2 females (high concentration). • minimal to moderate mucus cell hyperplasia of the respiratory epithelium of the nasopharyngeal tissues in 1 male and 2 females (mid concentration) and 4 males and 4 females (high concentration) suggesting a slight irritation at the upper respiratory system. (Minimal mucus cell hyperplasia in 1 low concentration female is well within the range of historical data and therefore not considered as adverse effect) • Minimal inflammatory cell foci in the trachea of 1 male and 1 female. Since all these microscopic findings are reversible after discontinuation of the exposure, they were considered to be an acute adaptive response to the test-item. All other microscopic findings observed in this study were either related to incidental, congenital or agonal changes and of the type routinely observed microscopically in Wistar rats of this age.
4.8	**Other**	-
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	10 Wistar rats per group (5 males, 5 females) were exposed to Preventol CMK via inhalation (nose only exposure) in a subacute toxicity study (14 days) according to OECD Guideline 412. Six groups were used in the study: low concentration animals were exposed to 50 mg/m³, mid concentration animals to 250 mg/m³ and high concentration animals to 510 mg/m³ of air (mean actual concentration)

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

		of Preventol CMK continuously for 6 h/day over fourteen days. The control group was exposed to air alone. In addition, two satellite (recovery) groups were included, an additional control group and a high concentration group. After the treatment period, the recovery groups were subjected to a 14-days recovery period. All animals were observed daily for mortality and clinical signs. Body weights were determined twice weekly. Food and water consumption were recorded daily. At the end of the treatment period (Day 15) the main group animals were sacrificed, the recovery animals were sacrificed after the recovery period (Day 29). All animals were subjected to a gross pathological examination, including determination of organ weights (absolute and relative) as well as to histopathology. Special attention was attributed to irritating effects in the respiratory tract and the associated lymphnodes. In addition, haematological, clinical chemistry and urinalysis were determined.
5.2	**Results and discussion**	None of the animals died during the study. In the low concentration group (50 mg/m^3), no signs of toxicity were observed. Dullness and nasal irritation were seen in mid concentration animals (250 mg/m^3). In the high concentration groups (510 mg/m^3, main and recovery) clinical signs included signs for irritation and swelling/edema of/in different body parts. All findings were reversible after 1 - 2 days of discontinuation of exposure. A significant decrease in body weights was observed in mid and high concentration animals. The effects were reversible in females, but not in males. Food and water consumption was decreased in mid and high concentration animals (both sexes) and water consumption also in low concentration females. Both effects were reversible. The test substance-related decrease in body weights was associated with decreased food and water consumption. Haematology and urinalysis did not reveal treatment-related changes. A tendency towards decreased glucose levels was observed in all animals presumably being related to the reduction in food consumption. The effect was significant in high concentration animals. All other significant changes in biochemistry were considered to be not treatment-related, as they were not concentration-related and/or within the range of historical control data. A significant decrease in mean absolute and relative organ weight was observed in the thymus at all concentrations in males. In females, the concentration-related tendency was without statistical significance. These findings were accompanied macroscopically by reduced thymus size and histopathologically by atrophy at a 250 and 510 mg/m3. The effects were fully reversible. Minimal to moderate mucus cell hyperplasia of the nasopharyngeal respiratory epithelium was observed in mid and high concentration and minimal inflammatory cell foci in the trachea in high concentration

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

		animals being indicative for slight irritation in the upper respiratory system. Since all histopathological findings were reversible, they were considered to be an acute adaptive response to the test-item.
5.3	**Conclusion**	
5.3.1	LO(A)EL	LOAEC = 250 mg/m³ (based on thymus effects)
5.3.2	NO(A)EL	NOAEC = 50 mg/m³
5.3.3	Other	–
5.3.4	Reliability	[redacted]
5.3.5	Deficiencies	No

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*January 2011*
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3 6.3.3 Repeated dose toxicity (inhalation) in rats

Table A6_3-1. Results of clinical chemistry, haematology and urinalysis

Parameter changed	**Unit**	**Controls**			**50 mg/m³**	**250 mg/m³**	**510 mg/m³**		
Time point		Day 15		Day 29	Day 15	Day 15	Day 15		Day 29
		main	recov.	recov.	main	main	main	recov.	recov.
Males									
glucose	mg/dL	113.2	111.6	119.2	106.8	109.6	99.4	90.8*	114.4
protein	g/dL	6.3	6.5	5.9	5.7*	5.9*	6.3	6.6	5.7
globulin	g/dL	4.9	5.1	4.5	4.4*	4.6*	5.0	5.2	4.4
total bilirubin	mg/dL	0.14	0.12	0.20	0.16	0.15	0.18	0.20*	0.21
chloride	mmol/L	104.2	100.6	105.6	107.0	106.2	101.0*	99.4	107.4
phosphorus	mg/dL	7.6	6.9	6.2	6.9	7.4	7.0	6.9	6.4
sodium	mmol/L	144.6	141.4	144.2	145.8	144.8	142.8	141.6	146.8
potassium	mmol/L	3.1	3.2	3.2	3.2	3.1	3.0	3.2	3.2
basophils	%	0.4	0.2	0.2	0.02*	0.04*	0.2	0.3	0.2
MCH	pg	18.7	18.4	19.1	18.6	19.1	18.1	19.3*	19.8
prothrombin time	sec	10	9.3	10.2	10.5	9.3	9.1	9.9*	10.1
Females									
glucose	mg/dL	119.2	105.6	119.2	105.4	104.0	95.8*	108.6	117.6
protein	g/dL	6.1	6.8	6.3	6.1	6.0	6.1	6.4	6.2
globulin	g/dL	4.8	5.3	4.8	4.7	4.6	4.8	5.0	4.7
total bilirubin	mg/dL	0.12	0.12	0.17	0.16	0.15	0.14	0.16	0.15
chloride	mmol/L	104.2	103.0	107.0	104.4	105.2	99.8*	99.8*	106.2
phosphorus	mg/dL	5.5	5.9	5.1	6.1	6.3	6.6*	5.3	5.7
sodium	mmol/L	143.0	142.0	144.6	142.2	145.4	142.2	139.0*	142.2*
potassium	mmol/L	2.9	2.8	3.0	3.2	3.1	3.0	2.8	3.4*
basophils	%	0.2	0.3	0.3	0.04*	0.1*	0.1	0.2	0.4
MCH	pg	18.4	18.4	19.4	18.9	18.9	18.2	18.8	19.8
prothrombin time	sec	8.9	9.4	10.0	10.1	10.0	9.2	9.4	9.8

* $p \leq 0.05$

recov. = recovery group

The recovery high concentration group values were compared to the recovery control group values.

Table A6_3-2. Results of repeated dose toxicity study - main groups

	Control		**50 mg/m³**		**250 mg/m³**		**510 mg/m³**		**dose response +/-**	
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
Number of animals examined	5	5	5	5	5	5	5	5	–	–
Mortality	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	–	–
Clinical signs										
Dullness	–	–	–	–	↑	↑	↑	↑	+	+
Nasal irritation	–	–	–	–	↑	↑	↑	↑	+	+
Lacrimation	–	–	–	–	–	–	↑	↑	+	+
Nostril discharge	–	–	–	–	–	–	↑	↑	+	+
Facial swelling	–	–	–	–	–	–	↑	↑	+	+
Reddened nostrils	–	–	–	–	–	–	↑	↑	+	+
edematous forelimbs	–	–	–	–	–	–	↑	↑	+	+
forelimbs with red encrustations	–	–	–	–	–	–	↑	↑	+	+
gasping	–	–	–	–	–	–	↑	↑	+	+
Body weight	–	–	–	–	↓	↓	↓	↓	+	+
Food consumption	–	–	–	–	↓	↓	↓	↓	+	+
Water consumption	–	–	–	↓	↓	↓	↓	↓	+	+
Clinical chemistry										
glucose	–	–	–	–	–	–	–	↓	–	+
protein	–	–	↓	–	↓	–	–	–	–	–
globulin	–	–	↓	–	↓	–	–	–	–	–
chloride	–	–	–	–	–	–	↓	↓	+	+
phosphorus	–	–	–	–	–	–	–	↓	–	+
Haematology										
basophils	–	–	↓	↓	↓	↓	–	–	–	–
<u>Thymus</u>										
Rel. organ weight	–	–	↑	–	↑	–	↑	–	+	–
Gross pathology: reduced size	0/5	0/5	0/5	0/5	0/5	1/5	2/5	2/5	+	+
Histopathology: atrophy	0/5	0/5	0/5	0/5	0/5	1/5	2/5	2/5	+	+
<u>Liver</u>										
Rel. organ weight	–	–	–	–	–	↑	–	↑	–	+
<u>Adrenals</u>										
Rel. organ weight	–	–	–	–	–	–	↑	–	+	–
<u>Brain</u>										
Rel. organ weight	–	–	–	–	–	–	↑	↑	+	+

Heart										
Rel. organ weight	–	–	–	–	↑	–	↑	↑	+	+
Kidney										
Rel. organ weight	–	–	–	–	–	–	↑	↑	+	+
Gonads										
Rel. organ weight	–	–	–	–	↑	–	↑	–	+	–
Lungs										
Rel. organ weight	–	–	–	–	–	–	↑	↑	+	+
Nasopharyngeal tissue										
Histopathology: mucus cell hyperplasia	0/5	0/5	0/5	1/5	1/5	2/5	4/5	4/5	+	+
Trachea										
Histopathology: inflammatory cell foci	0/5	0/5	0/5	0/5	0/5	0/5	1/5	1/5	+	+

Section 6.4.1 **Annex Point IIA VI.6.4.1**	**Subchronic oral toxicity test** **Subchronic toxicity study in non-rodents**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	[redacted]	

Section 6.4.1 **Annex Point IIA VI.6.4.1**	**Subchronic oral toxicity test** **Subchronic toxicity study in non-rodents**
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	16/12/08
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	

Table A6_4-1: Comparison of repeated-dose oral toxicity data in rats and dogs for different phenolic antimicrobials

Section 6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 90 days dietary toxicity study in rats

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1988), Preventol CMK: Subchronic toxicological study in rats (feeding study lasting 3 [redacted] 1988-11-24 (unpublished) [redacted]	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes US-EPA Guideline 82-1 ≅ OECD 408	
2.2	**GLP**	Yes	X
2.3	**Deviations**	No check of study conduct by quality assurance unit was performed.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	Solid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stability of pure substance and substance in diet was confirmed for the study period.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	SPF-bred Wistar rats, strain TNO W. 74 (Bor:WISW (SPF Cpb))	
3.2.3	Source	[redacted]	
3.2.4	Sex	♂ and ♀	
3.2.5	Age/weight at study initiation	Age ♂ and ♀: about 5 weeks Weight: ♂ 65 - 87 g, ♀ 63 - 82 g	
3.2.6	Number of animals per group	20/sex/dose level	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	3 months	

Section 6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 90 days dietary toxicity study in rats

3.3.2	Frequency of exposure	*ad libitum*	
3.3.3	Post-exposure period	None	
3.3.4	**Oral**		
3.3.4.1	Type	In food	
3.3.4.2	Concentration	150, 500, 1500 ppm ♂: 10, 40, 120 mg/kg bw/day ♀: 20, 50, 170 mg/kg bw/day	X
3.3.4.3	Controls	Plain diet	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes, twice daily (on weekends and holidays: once daily).	
3.4.1.2	Mortality	Yes, twice daily (on weekends and holidays: once daily).	
3.4.2	Body weight	Yes, before treatment, then once weekly and prior to necropsy.	
3.4.3	Food consumption	Yes, once weekly.	
3.4.4	Water consumption	No	
3.4.5	Ophthalmoscopic examination	No	
3.4.6	Haematology	Yes, all surviving animals after 4 weeks and at study termination Parameters: differential blood count, erythrocyte count, haemoglobin concentration, haematocrit, leukocyte count, MCH, MCHC, MCV, thromboplastin time, thrombocyte count	
3.4.7	Clinical chemistry	Yes, all surviving animals after 4 weeks and at termination Parameters: glucose, cholesterol, urea, total bilirubin, creatinine, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)	
3.4.8	Urinalysis	Yes, all animals Urines were collected over approx. 16-hour intervals at various time points during this study, in each case a few days before blood sampling. Parameters (semi-quantitative): ketone body, pH value, blood, glucose, bilirubin, urobilinogen, sediment (leucocytes, erythrocytes, epithelia, cylinders and other) Parameters (quantitative): total protein	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes, from all animals sacrificed at termination. Organs: heart, testis (paired), liver, lung, spleen, kidneys (paired), adrenals (paired), thymus	
3.5.2	Gross and histopathology	Yes, all animals which died or were moribund and sacrificed during the study period were dissected at the earliest possible time and organs/tissues were subjected through gross pathological examination. All surviving animals were sacrificed at study termination and a gross pathological examination was performed. Histopathology: from ten males and ten females of the control and	

Section 6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 90 days dietary toxicity study in rats

		highest dose group Organs: adrenals, aorta, femur with bone marrow, brain, colon, duodenum, epididymis, eyes, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes, mamma, oesophagus, ovaries, pancreas, pituitary, prostate, salivary glands, seminal vesicles, skeletal musculature with nervus ischiadicus, spleen, sternum with bone marrow, testicles, thymus, thyroid gland, trachea, urinary bladder, uterus, and all tissues with grossly apparent lesions.	
3.5.3	Other examinations	None.	
3.5.4	Statistics	Arithmetic group means, standard deviations and in the case of organ weights the upper and lower confidence limits on the confidence level of 1-α = 95% and 1-α = 99%. The values for the test collective were compared with the control collective by significance test (U-test) using H.B. Mann and D.R. Whitney´s method, or by Wilcoxon´s method on the significance level α = 5% and α = 1% (two-tailed). Differences with p-values ≤ 0.01 and ≤ 0.05 were considered statistically significant.	
3.6	**Further remarks**	–	
		4 RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	No abnormalities were noted.	
4.1.2	Mortality	One female rat of the 150 and 500 ppm dose group died in connection with blood sampling in the fourth study week. The autopsy of this animal provided no indication of treatment-related effects.	
4.2	**Body weight gain**	500 and 1500 ppm males: reduced body weight gain. Body weight gain of males of the 0 and 150 ppm dose groups and of all females was unaffected.	X
4.3	**Food consumption and compound intake**	No effects.	
4.4	**Ophthalmoscopic examination**	Not applicable.	
4.5	**Blood analysis**		
4.5.1	Haematology	No effects.	
4.5.2	Clinical chemistry	Males 500 ppm dose group: After 1 month, the ALP activity and creatinine content were significant lower compared to control animals (see Table A6_4-2). In any of the males of the other dose groups as well as in the females no relevant dose-dependent effect was found. At termination no dose-related effect was found in any animal of any dose group.	
4.5.3	Urinalysis	No dose-related effects.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	Organ weights: 1500 ppm males: significantly lower liver weight, which is attributed to the lower body weights of these animals.	

Section 6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4	6.4.1	90 days dietary toxicity study in rats
		Relative organ weights: 1500 ppm males: heart and lung were significantly heavier. 500 ppm females: livers were lighter. 1500 ppm females: kidneys were lighter.
4.6.2	Gross and histopathology	Gross pathology: No indication of organ damage was found in any animal sacrificed at study termination. Histology: No substance-related effects were found. Only isolated non-specific cellular or inflammatory cellular infiltrations in various organs and vacuole formation in the males in the cortical area of the adrenals were noted both in animals of the control and 1500 ppm group.
4.7	**Other**	
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	20 male and female Wistar rats per sex and dose group received CMK-concentrations of 0, 150, 500 and 1500 ppm in diet for 3 continuous months. Observations for clinical signs and mortality were made twice daily (once daily on weekends and holidays). Individual body weights, food consumption as well as detailed physical examinations for clinical signs of toxicity were determined/performed once each week on all animals. Urine specimens were collected in 16-hour intervals at several timepoints during the study period. Urinalyses included a semi-quantitative determination of ketone body, pH value, blood, glucose, bilirubin, urobilinogen, sediment (leucocytes, erythrocytes, epithelia, cylinders and other). In addition, total protein was determined quantitative. All animals found death or were moribund and sacrificed during the study period were dissected and the organs/tissues were subjected to through gross pathological examination. All surviving animals were sacrificed at termination and a gross pathological examination was performed. Organ weights of the heart, testicles, liver, lung, spleen, kidneys, adrenals and thymus were determined. Histopathological examinations were performed with the tissues from 10 males and females of the control and high dose group.
5.2	**Results and discussion**	Appearance, general behaviour, mortality and food intake were unaffected in any dose group. Body weight gain was retarded in 500- and 1500-ppm males, but was unaffected in females. Urinalysis, haematological and clinical chemistry examinations provided no effects. No treatment-related effects or abnormalities were found during gross pathological and histopathological examinations. The autopsies and blood examination of the two females (one at 150 ppm, one at 500 ppm) which died during the study period revealed no indications of a relation between treatment and the death.
5.3	**Conclusion**	
5.3.1	LO(A)EL	LOEL = 500 ppm (40 mg/kg bw/day), based on reduced bw gain in males; no effects in females

Section 6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 90 days dietary toxicity study in rats

		LOAEL > 1500 ppm (120/170 mg/kg bw/day, ♂/♀), no adverse effects	
5.3.2	NO(A)EL	NOAEL = 1500 ppm (120/170 mg/kg bw/day, ♂/♀)	X
5.3.3	Reliability	[redacted]	X
5.3.4	Deficiencies	No check of study conduct by quality assurance unit was performed.	

Section 6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 90 days dietary toxicity study in rats

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27/05/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 90 days dietary toxicity study in rats

Table A6_4-1. Results of clinical chemistry, haematology and urinalysis

No treatment-related effects were found.

Table A6_4-2. Results of repeated dose toxicity study

Parameter	Control		150 ppm		500 ppm		1500 ppm		Dose-response +/–	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Number of animals examined	20	20	20	20	20	20	20	20		
Mortality	0/20	0/20	0/20	1/20	0/20	1/20	0/20	0/20	–	–
Clinical signs	0/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20	–	–
Retarded body weight gain	0/20	0/20	0/20	0/20	20/20	0/20	20/20	0/20	+	–
Clinical chemistry										
AP	–	–		–	↓*	–	↓*	–	+	–
Creatinine	–	–	–	–	–	–	↓*	–	+	–
Organ weights										
Liver, absolute	–	–	–	–	–	–	↓	–	+	–
Liver, relative	–	–	–	–	–	↓	–	↓	–	+
Heart, relative	–	–	–	–	–	–	↑	–	+	–
Lung, relative	–	–	↑	–	–	–	↑	–	–	–
Kidney, relative	–	–	–	–	–	–	–	↓	–	+

* After one month. After three months, values were in normal range.

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1991), Preventol CMK: Subchronic Toxicity Study in Wistar Rats (Dermal Treatment for 13 Weeks) [redacted] 1991-08-30 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes, According to EU Directive 87/302/EEC ≅ OECD 411 and US-EPA Guideline 82-3	
2.2	**GLP**	Yes	
2.3	**Deviations**	No.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	Colourless powder	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stability of pure substance and substance in vehicle was confirmed for the study period.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	SPF-bred Wistar rats, (Bor:WISW (SPF Cpb))	
3.2.3	Source	[redacted]	
3.2.4	Sex	♂ and ♀	
3.2.5	Age/weight at study initiation	Age ♂ and ♀: about 8-10 weeks Weight: ♂ 196 - 213 g, ♀ 165 - 186 g	
3.2.6	Number of animals per group	10/sex/dose level	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Duration of treatment	13 weeks	

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

3.3.2	Frequency of exposure	Daily (5 days/week)
3.3.3	Post-exposure period	None.
3.3.4	**Dermal**	
3.3.4.1	Area covered	About 5 x 5 cm² (left flank)
3.3.4.2	Occlusion	Occlusive
3.3.4.3	Vehicle	Polyethyleneglycol 400
3.3.4.4	Concentration in vehicle	0, 20, 100, 500 mg/mL
3.3.4.5	Total volume applied	1 mL/kg bw
3.3.4.6	Dose applied	0, 20, 100, 500 mg/kg bw
3.3.4.7	Duration of exposure	6 h/day
3.3.4.8	Removal of test substance	Yes, wiping with polyethyleneglycol 400
3.3.4.9	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes, twice daily (on weekends and holidays: once daily).
3.4.1.2	Mortality	Yes, twice daily (on weekends and holidays: once daily).
3.4.2	Body weight	Yes, before treatment, then once weekly and prior to necropsy.
3.4.3	Food consumption	Yes, before treatment, then once weekly.
3.4.4	Water consumption	Yes, before treatment, then once weekly.
3.4.5	Ophthalmoscopic examination	Yes, on all rats of the control and high dose group. Examinations were performed 3 days before start of treatment and on day 80 in week 12.
3.4.6	Haematology	Yes, all surviving animals in week 5 or 6 and at study termination. Sampling was done after urine sampling. Parameters: differential blood count, erythrocyte morphology, erythrocyte count, haemoglobin concentration, haematocrit, leukocyte count, MCH, MCHC, MCV, thromboplastin time, thrombocyte count, reticulocyte count
3.4.7	Clinical chemistry	Yes, all surviving animals after in week 5 or 6 and at study termination. Sampling was done after urine sampling. Parameters: albumin, glucose, cholesterol, urea, total bilirubin, creatinine, total protein, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamate dehydrogenase (GLDH), P, Cl, Ca, K, Na
3.4.8	Urinalysis	Yes, all animals Urines were collected in week 5 or 6 and at termination in week 13. Samples were collected over a 16-hour period (over night). No food was provided during this period.

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

		Parameters (semi-quantitative): ketone body, pH value, blood, glucose, bilirubin, protein, urobilinogen, sediment Parameters (quantitative): total protein, volume, density, protein, creatinine
3.5	**Sacrifice and pathology**	
3.5.1	Organ weights	Yes, from all animals sacrificed at termination. Organs: brain, heart, testis (paired), liver, lung, spleen, kidneys (paired), adrenals (paired).
3.5.2	Gross and histopathology	All surviving animals were sacrificed at study termination and a gross pathological examination was performed. Histopathology: from all animals of the control and highest dose group Organs: adrenals, aorta, femur with bone marrow, brain, colon, caecum, duodenum, ileum, jejunum, rectum, duodenum, epididymis, , eyes with nervi optici, femoral muscle heart, kidneys, liver, lungs, lymph nodes, mamma with skin, oesophagus, ovaries, pancreas, pituitary, prostate, salivary glands, seminal vesicles, nervus ischiadicus, skin of back (treated and normal skin), spleen, spinal cord, stomach, sternum with bone marrow, testicles, thymus, thyroid gland, trachea, urinary bladder, uterus, vagina, and all tissues with grossly apparent lesions. In addition, liver, lungs and kidneys of all animals of the 20 and 100 mg/kg bw dose groups.
3.5.3	Other examinations	In a detailed clinical examination, performed once weekly, the total body surface, orifices, posture, behaviour, respiration, excrements and all abnormal findings were examined. Thickness of skin folds were examined in all animals on treatment days 20 and 60.
3.5.4	Statistics	Arithmetic group means and standard deviations for bw, food consumption, water-intake, blood and urine analysis and organ weights were determined. The values for the test collective were compared with the control collective by significance test (U-test) using H.B. Mann and D.R. Whitney´s method, or by Wilcoxon´s method on the significance level $\alpha = 5\%$ and $\alpha = 1\%$ (two-tailed). Differences with p-values ≤ 0.01 and ≤ 0.05 were considered statistically significant.
3.6	**Further remarks**	–
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	During the first 10 treatment days, all females of all dose groups showed an unsettled behaviour (increased motility with bounding, throwing down, jumping off, running around, biting into cage cover and occlusion). These symptoms decreased from day 11 to 13. From day 14 onwards females behaved like the males. No other signs were noted.
4.1.2	Mortality	No mortalities occurred.
4.2	**Body weight gain**	Body weight gain of all males and females treated with the test substance was comparable to the body weight gain of control animals.

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

		The reduced mean body weights of all females of all dose and control groups in week 10 were considered to be not treatment-related.
4.3	**Food consumption and compound intake**	No compound-related effects.
4.4	**Ophthalmoscopic examination**	No effects.
4.5	**Blood analysis**	
4.5.1	Haematology	No effects.
4.5.2	Clinical chemistry	Males, 500 mg/kg dose group: In week 6 the triglyceride values were significant lower compared to control animals. Since the differences were small, only present in one sex and in week 6, this effect was considered to be of no toxicological relevance. Males, 500 mg/kg dose group: In week 13 the protein concentration was significant lower compared to control animals. Since the mean value was within the range of historical controls and only slightly different from control animals, this effect was considered to be of no toxicological relevance. Males and females of the 100 and 500 mg/kg dose group: In week 6, Ca-values of the females, in week 13, Ca-values of males and females were significant lower compared to control animals. This was considered to be not toxicological relevant. No other effects were found.
4.5.3	Urinalysis	No dose-related effects.
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	No abnormal findings.
4.6.2	Gross and histopathology	Gross pathology: Control group: 2 males had smaller testis. This was considered to be of no toxicological relevance. 20 mg/kg dose group: Epididymis of one male showed several yellow areas, which were considered to be of no toxicological relevance. 500 mg/kg dose group: 2 males and one female had a pale kidney. Histopathology: No abnormal findings.
4.7	**Other**	Examination of the skin thickness revealed no significant differences between the control and test substance groups.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	10 male and female Wistar rats per sex and dose group received dermal CMK-doses of 0, 20, 100 and 500 mg/kg bw for 13 continuous weeks. The applications were performed 5 days per week for a duration of 6 hours each. Observations for clinical signs and mortality were made twice daily (once daily on weekends and holidays). Individual body weights were determined before start of treatment, weekly thereafter and prior to necropsy. Food consumption and water-intake were performed once per

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

		week. A detailed physical examination of all animals was performed before treatment and then weekly thereafter. Blood samples for haematology and clinical chemistry examination were taken in week 5 or 6 and week 13. Urine specimens were collected in 16-hour intervals in week 5 or 6 and 13 after blood sampling. On treatment days 20 and 60 the thickness of the skin was determined on all animals. All surviving animals were sacrificed at termination and a gross pathological examination was performed. Organ weights of the brain, heart, testis (paired), liver, lung, spleen, kidneys (paired) and adrenals (paired) were determined. Histopathological examinations were performed with the tissues of all animals of the control and high dose group. In addition, ophthalmoscopic examinations were performed on all animals of the control and high dose group 3 days before the first treatment and on day 80.
5.2	**Results and discussion**	No mortalities occurred and no treatment-related clinical symptoms were noted during the study period. Body weight gain, food-consumption and water-intake of the treated animals were comparable to those of the control group. Haematological and clinical chemistry examinations as well as urine analyses revealed no treatment-related effects. Absolute and relative organ weights, gross pathological and histopathological examinations showed no evidence of organ damage.
5.3	**Conclusion**	
5.3.1	LO(A)EL	LOAEL > 500 mg/kg bw/day, no treatment-related effects
5.3.2	NO(A)EL	NOAEL ≥ 500 mg/kg bw/day
5.3.3	Other	–
5.3.4	Reliability	[redacted]
5.3.5	Deficiencies	–

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	26/06/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

Table A6_4-1. Results of clinical chemistry, haematology and urinalysis

Parameter changed	Unit	Weeks after treatment	Controls	20 mg/kg bw	100 mg/kg bw	500 mg/kg bw	Dose-response +/–
Males							
Triglycerides	mmol/L	6	1.04	0.90	1.09	0.76**	–
		13	1.00	0.96	0.96	0.88	–
Total protein	g/L	6	61.8	61.3	62.5	60.9	–
		13	64.7	63.2	62.1	61.7*	+
Calcium	mM	6	2.65	2.67	2.46**	2.46**	+
		13	2.55	2.56	2.53	2.50	–
Females			–	–	–		–
Calcium	mM	6	2.61	2.62	2.46**	2.42**	+
		13	2.55	2.55	2.46**	2.49*	–

* $p \leq 0.05$; ** $p \leq 0.01$

Section 6.4.2 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.2 90-day dermal toxicity study in rats

Table A6_4-2. Results of repeated dose toxicity study

Parameter	Control		20 mg/kg bw		100 mg/kg bw		500 mg/kg bw		Dose-response +/–	
	♂[a]	♀[a]	♂[a]	♀[a]	♂[a]	♀[a]	♂[a]	♀[a]	♂	♀
Number of animals examined	10	10	10	10	10	10	10	10		
Clinical signs									–	–
restlessness	0/10	10/10	0/10	10/10	0/10	10/10	0/10	10/10		–
Gross pathology										
smaller testis	2/10	–	0/10	–	0/10	–	0/10	–	–	–
yellow areas in epididymis	0/10	–	1/10	–	0/10	–	0/10	–	–	–
pale kidney	0/10	0/10	0/10	0/10	0/10	0/10	2/10	1/10	–	–

[a] number of animals affected/total number of animals

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

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		1 REFERENCE
1.1	**Reference**	[redacted](1993): Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks) [redacted] [redacted]1993-04-02 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes OECD 453 (1981)
2.2	**GLP**	Yes
2.3	**Deviations**	Yes Haematological examinations were only performed on 10 instead of 20 rats/sex/group.
		3 MATERIALS AND METHODS
3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	colourless powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stability of the test substance in feed was confirmed for the study period.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	SPF-bred Wistar rats (strain: Bor:WISW (SPF Cpb))
3.2.3	Source	[redacted]
3.2.4	Sex	♂ + ♀
3.2.5	Age/weight at study initiation	approx. 5-6 weeks; ♂: 102-139 g, ♀: 94-125 g
3.2.6	Number of animals per group	50 per sex and dose level (2-year group) 10 per sex and dose level (interim sacrifice group (53 weeks)
3.2.7	Control animals	Yes
3.2.8	Replacement group	No
3.3	**Administration/ Exposure**	Oral

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

3.3.1	Duration of treatment	24 month and 53 weeks (interim sacrifice group)
3.3.2	Interim sacrifice(s)	After 53 weeks
3.3.3	Final sacrifice	After 104 weeks
3.3.4	Frequency of exposure	*ad libitum*
3.3.5	Postexposure period	None
		Oral
3.3.6	Type	In food
3.3.7	Concentration	0, 400, 2000 and 10,000 ppm ≅ 21.0, 103.1 and 558.9 mg/kg bw/day for males ≅ 27.7, 134.3 and 743.5 mg/kg bw/day for females
3.3.8	Vehicle	peanut oil
3.3.9	Concentration in vehicle	100% of nominal concentrations
3.3.10	Total volume applied	Not applicable
3.3.11	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes, Before start of treatment, then once weekly and prior to necropsy
3.4.2	Food consumption	Yes week 1-13: once weekly week 14-termination: once monthly
3.4.3	Water consumption	Yes, once monthly
3.4.4	Clinical signs	Yes, at least twice daily (once daily on weekends and bank holidays)
3.4.5	Mortality	Yes, at least twice daily (once daily on weekends and bank holidays)
3.4.6	Ophthalmoscopic examination	Yes, 20 animals per sex per group: prior to start additional 20 animals per sex of the control and highest dose group: after 53 and 104 weeks
3.4.7	Haematology	Yes,
	No. of animals:	10 rats/sex/group
	Time points:	At 6 month intervals
	Parameters:	Differential blood count using smears, haematocrit, haemoglobin concentration, erythrocyte count, leukocyte count, reticulocyte count, total platelet count, MCH, MCHC, MCV

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

3.4.8	Clinical Chemistry	Yes
	No. of animals:	10 rats/sex/group
	Time points:	At weeks 26/27, 51/52, 78/79, 103/104
	Parameters:	Sodium, potassium, chloride, calcium, phosphate, glucose, total cholesterol, triglyceride, urea, total bilirubin, creatinine, total protein, albumin, creatine phosphokinase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase
3.4.9	Urinalysis	Yes
	No. of animals:	10 rats/sex/group
	Time points:	At 6 month intervals. Urine was collected during 16 hour intervals (overnight)
	Parameters:	Semi-quantitative: pH, protein, glucose, ketone bodies, blood, bilirubin, sediment, urobilinogen Quantitative: density, creatinine, protein, volume
3.4.10	Pathology	Yes
3.4.10.1	Gross pathology	All surviving animals at terminal sacrifice and on all animals dying spontaneously or sacrificed moribund during the study. At interim sacrifice 10 rats per sex and dose level.
3.4.10.2	Organ Weights	Yes
	from:	All surviving animals at interim and terminal sacrifice.
	Organs:	Brain, heart, kidneys (in pairs), liver, ovaries (in pairs), testicles (in pairs), spleen
3.4.11	Histopathology	Yes
	from:	All surviving animals at terminal sacrifice and from 10 animals per sex and dose level at interim sacrifice.
	Organs:	Adrenals, aorta, bone, bone marrow (in femur and sternum), brain, caecum, cervix, colon, duodenum, tattooed ears, epididymides, Esophagus, eyes, eyelids, extraorbital lachrymal glands, femur with knee-joint, gross lesions, Harderian glands, head, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (mandibular and mesenteric), mammary gland, optic nerve, ovaries, oviducts, pancreas, pituitary, prostate gland, rectum, salivary glands, sciatic nerve, seminal vesicle, muscle (thigh), skin, spinal cord, spleen, sternum, stomach, testicles, thymus, thyroid gland, tongue, trachea, ureters, urethra, urinary bladder, uterus, vagina, Zymbal glands
3.4.12	Other examinations	A detailed clinical investigation of all animals was performed once weekly. Assessed were body surfaces and orifices, posture, general behaviour, respiration and excretory products.
3.5	**Statistics**	Arithmetic group means and standard deviations for bw, food consumption, water-intake, blood and urine analysis and organ weights were determined. The values for the test collective were compared with the control collective by significance test (U-test) using the Mann-Whitney test or by Wilcoxon´s method on the significance level $\alpha = 5\%$ and $\alpha = 1\%$ (two-tailed). Differences with p-values ≤ 0.01 and ≤ 0.05 were considered statistically significant.

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7	6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

3.6 Further remarks –

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

		4 RESULTS AND DISCUSSION	
4.1	**Body weight**	Body weight development was not significantly affected up to 2000 ppm. At 10,000 ppm, both sexes showed delayed body weight development.	X
4.2	**Food consumption**	No treatment-related effects.	
4.3	**Water consumption**	Water intake of males at 10,000 ppm was higher than that of control animals. In all other groups and in females no effects.	X
4.4	**Clinical signs**	Approx. from week 90 females exhibited more frequently increased abdominal circumference. After 2000 and 10,000 ppm there was a significant decrease in the frequency of this finding compared to control animals. Females showed a dose-related increase in the frequency of poor general condition, which was statistically significant in the highest dose group.	
4.5	**Mortality**	The number of animals of the main groups dying during the study period was slightly lower than that of controls in the case of males, and in the case of treated females slightly higher (after 400 and 10,000 ppm) or comparable to controls. The deaths were considered to be not treatment-related.	
4.6	**Ophthalmoscopic examination**	No treatment-related effects.	
4.7	**Haematology**	No treatment-related effects.	
4.8	**Clinical Chemistry**	Males and females of the highest dose group showed partly statistically significantly reduced cholesterol and triglyceride concentrations at all investigation time points. After 2000 ppm males and females showed a tendency to lower potassium values. Phosphate values of males and females at 10,000 ppm were statistically significant lower. For the other electrolytes isolated statistically significant higher and lower values were recorded at different time points. These findings were considered to be not dose-related.	
4.9	**Urinalysis**	No treatment-related effects.	X
4.10	**Pathology**	Interim sacrifice: No treatment-related effects were noted. Terminal sacrifice: Males at 10,000 ppm: 6 males showed a deformation of kidneys There were no other treatment-related gross pathological findings.	
4.11	**Organ Weights**	Interim sacrifice: No effects Terminal sacrifice: Males at 2000 and 10,000 ppm: slightly increased kidney weights Females at 10,000 ppm: slightly increased kidney weights and increased relative ovary weights.	
4.12	**Histopathology**	Males at 10,000 ppm: increased number of papillary necroses and cortical dilatation of the collecting tubules and cortical fibroses in the kidneys.	X

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

4.13	**Other**	–	X

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Fifty rats per sex and dose level were given 0, 400, 2000, or 10,000 ppm daily in a peanut oil solution via food for 104 weeks. Satellite groups, for interim sacrifice, of 10 rats per sex and dose-level received the same doses for 52 weeks. These animals were sacrificed after 52 weeks. The other animals were necropsied after 104 weeks of treatment.

Detailed pre-exposure ophthalmoscopic examinations were performed on 20 animals per sex per dose group. Additional 20 rats per sex of the control and highest dose group were examined ophthalmoscopically after 53 and 104 weeks.

Observations for clinical signs and mortality were made twice daily (once daily on weekends and holidays). Individual body weights were determined before start of treatment, weekly thereafter and prior to necropsy. Food consumption and water-intake were performed once per week during week 1 to 13 and then monthly thereafter. Water-uptake was recorded once per month. A detailed physical examination of all animals was performed before treatment and then weekly thereafter.

Blood samples for haematology and clinical chemistry examination were taken after 6, 12, 18, and 24 months. Urine specimens were collected in 16-hour intervals in week 26, 51, 78 and 103.

Gross pathological examinations were performed on all surviving animals at termination as well as on all animals dying or killed moribund during the study. Gross pathology was also performed on 10 rats per sex and group sacrificed after 52 weeks of treatment.

Organ weights of brain, heart, kidneys (in pairs), liver, ovaries (in pairs), testicles (in pairs) and spleen were determined for all surviving animals at interim and terminal sacrifice.

Histopathological examinations were performed with the tissues of all surviving animals at termination and on 10 rats per sex and group sacrificed after 52 weeks of treatment.

5.2 Results and discussion

Fifty rats per sex and dose group were treated with Preventol CMK doses of 0, 400, 2000 and 10,000 ppm in feed for 24 month. Additionally, 10 animals per sex and dose were treated with the same Preventol CMK concentrations in feed for 53 weeks (interim necropsy group).

The average food consumption over 105 weeks was determined to be 21.0, 103.1 and 558.9 for males and 27.7, 134.3 and 743.5 mg/kg bw/day for females.

Up to and including 2000 ppm no treatment-related increased incidences of clinical signs were recorded. After 10,000 ppm the number of females with poor general condition was higher than in the control group. Ophthalmological and histopathological investigations showed no toxicological effects on the eyes. No treatment-related deaths occurred. The body weight gain was not affected up to doses of 2000 ppm. After 10,000 ppm body weight development was delayed in both sexes. Feed intake was comparable in all dose groups. Water intake was comparable for all treated females and for males up to and including 2000 ppm. At 10,000 ppm, water intake of males was higher than that of

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

		controls. No treatment-related damages on haematological parameters or haematopoietic organs were found. Urine analyses, organ weights, gross pathological and histopathological investigations revealed no treatment-related effects in females up to and including 10,000 ppm and in males up to and including 2000 ppm. At 10,000 ppm, males exhibited papillary necroses, cortical dilatations and fibroses of the kidneys, which were regarded as test substance induced. Clinical chemistry, gross pathological and histopathological examinations as well as organ weight determinations showed no indication of test substance related damage to any other organs or metabolic functions.	
		Gross pathological and histopathological investigations gave no indication of carcinogenic effects of the test compound at doses up to and including 10,000 ppm.	X
5.3	**Conclusion**		
5.3.1	LO(A)EL	10,000 ppm (559 / 744 mg/kg bw/day (♂/♀)), based on decreased bw gain in both sexes and kidney effects in males	X
5.3.2	NO(A)EL	2000 ppm (103 / 134 mg/kg bw/day (♂/♀))	
5.3.3	Other	–	
5.3.4	Reliability	[redacted]	
5.3.5	Deficiencies	No	

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	01/07/08
Materials and Methods	[redacted]
Results and discussion	[redacted]

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

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

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

Section A6.5 / A6.7 Chronic Toxicity / Carcinogenicity

Annex Point IIA VI.6.5 / 6.7 6.5 / 6.7 Combined chronic toxicity / carcinogenicity study in the rat

Table A6_7-1. Table for clinical chemistry, haematology and urinalysis

parameter changed	Controls		400 ppm		2000 ppm		10,000 ppm		Dose-related	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Cholesterol	–	–	–	↓**	–	–	↓**	↓**	–	–
Triglycerides	–	–	–	↓*	↑**	↑*	↓*	↓**	–	–
Potassium	–	–	–	–	↓*	↓**	↓**	↓**	+	+
Phosphate	–	–	–	–	–	–	↓**	↓**	+	+
* $p < 0.05$; ** $p < 0.01$										

Table A6_7-2. Results of chronic toxicity / carcinogenicity study**, submitted by applicant**

Parameter	Control		400 ppm		2000 ppm		10,000 ppm		Dose-response + / –		
	♂#	♀#	♂#	♀#	♂#	♀#	♂#	♀#	♂	♀	
Mortality	8/50	13/50	5/50	17/50	5/50	11/50	6/50	16/50	–	–	
Body weight gain	–	↓	–	↓*	–	↓*	↓**	↓**	–	–	X
Organ weights (rel.)											
brain	–	–	–	–	–	–	–	↑**	–	–	
kidneys	–	–	–	–	↑*	–	↑**	↑*	+	+	
ovaries	–	–	–	–	–	–	–	↑*	–	+	
spleen	–	–	–	↑**	–	–	–	↑*	–	–	
liver	–	–	–	↓*	–	–	–	–	–	–	
Gross pathology Kidney deformation	0/42	0/37	0/45	0/33	0/45	0/39	6/44	0/34	+	–	
Histopathology incidence non-neoplastic changes											
Kidneys, papillary necrosis											
unilateral	2/50 A	0/49	0/49	1/50	0/50	0/50	8/50	1/48	+		
bilateral	0/50	0/49	0/49	0/50	0/50	0/50	1/50	1/48	+		X
truncated papilla	0/50 B	0/49	0/49	0/50	0/50	0/50	6/50*	0/48			
collecting duct dilatation											
unilateral	0/50 A	0/49	0/49	0/50	0/50	0/50	3/50	1/48	+	+	
bilateral	0/50	0/49	0/49	0/50	0/50	0/50	0/50	1/48	–	+	
Cortical fibrosis	0/50 C	0/49	0/49	0/50	0/50	0/50	7/50*	1/48	+	–	
Epididymides, reduced spermatozoa	3/50	–	3/49	–	9/50	–	11*/50	–	–	–	X
Testicles, degeneration of seminiferous tubules	2/50	–	4/49	–	7/50	–	9/50	–	–	–	X
No. of animals with neoplastic changes	21/42	21/37	23/45	22/33	20/45	24/39	19/44	19/34	–	–	X

[#] number of animals affected / total number of animals
Significant trend: A, $p < 0.05$; B, $p < 0.01$; C, $p < 0.001$
Significantly different from controls: *$p < 0.05$; **$p < 0.01$

Table A6_7-2. Results of chronic toxicity / carcinogenicity study**, with modifications included**

Parameter	Control		400 ppm		2000 ppm		10,000 ppm		Dose-response + / –		
	♂#	♀#	♂#	♀#	♂#	♀#	♂#	♀#	♂	♀	
Mortality	8/50	13/50	5/50	17/50	5/50	11/50	6/50	16/50	–	–	
Body weight gain	–	↓	–	↓*	–	↓*	↓**	↓**	+	+	X
Organ weights (rel.)											
brain	–	–	–	–	–	–	–	↑**	–	–	
kidneys	–	–	–	–	↑*	–	↑**	↑*	+	+	
ovaries	–	–	–	–	–	–	–	↑*	–	+	
spleen	–	–	–	↑**	–	–	–	↑*	–	–	
liver	–	–	–	↓*	–	–	–	–	–	–	
Gross pathology Kidney deformation	0/42	0/37	0/45	0/33	0/45	0/39	6/44	0/34	+	–	
Histopathology incidence non-neoplastic changes											
Kidneys, papillary necrosis											
unilateral	2/50 A	0/49	0/49	1/50	0/50	0/50	8/50	1/48	+	–	
bilateral	0/50	0/49	0/49	0/50	0/50	0/50	1/50	1/48	+	+	X
+truncated papilla	0/50 B	0/49	0/49	0/50	0/50	0/50	6/50*	0/48	+	–	
collecting duct dilatation											
unilateral	0/50 A	0/49	0/49	0/50	0/50	0/50	3/50	1/48	+	+	
bilateral	0/50	0/49	0/49	0/50	0/50	0/50	0/50	1/48	–	+	
Cortical fibrosis	0/50 C	0/49	0/49	0/50	0/50	0/50	7/50*	1/48	+	–	
Epididymides, reduced spermatozoa	3/50	–	3/49	–	9/50	–	11*/50	–	+	–	X
Testicles, degeneration of seminiferous tubules	2/50	–	4/49	–	7/50	–	9/50	–	+	–	X
~~No. of a~~Animals with neoplastic changes	~~21/42~~	~~21/37~~	~~23/45~~	~~22/33~~	~~20/45~~	~~24/39~~	~~19/44~~	~~19/34~~	–	–	
Pituitary adenomas (%)	5/50 (10)	18/50 (37)	13/49* (27)	20/49 (42)	9/50 (18)	28/50* (56)	4/50 (8)	25/49 (51)	–	+	X
Testes, Leydig cell tumors (%)	2/50 (4)	-	1/49 (2)	-	5/49 (10)	-	6/50 (12)	-	+		

number of animals affected / total number of animals
Significant trend: A, $p < 0.05$; B, $p < 0.01$; C, $p < 0.001$
Significantly different from controls: *$p < 0.05$; **$p < 0.01$

Section A6.6.1 Genotoxicity in vitro

Annex Point IIA VI.6.6.1 6.6.1 Mutagenicity testing in bacteria – Salmonella/microsome test

Official use only

1 REFERENCE

1.1	**Reference**	Herbold BA (1991): Preventol CMK - Salmonella/Microsome Plate Test. Bayer AG, Wuppertal, Germany, Report No. 20516, 1991-08-08 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer AG
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Directive 84/449/EEC, Method B.14, OECD Guideline 471 (1983)
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	White powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stability of the test substance was assured by the study sponsor. Stability of the test substance in ethanol was assured by the study sponsor for 4 hours at room temperature.
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	S. typhimurium: TA 98, TA 1537, TA 100, TA 1535
3.2.2	Deficiencies / Proficiencies	Histidine auxotroph (TA 100 and TA 1535) Histidine prototroph (TA 98 and TA 1537) Ampicillin resistance (TA 98 and TA 100)
3.2.3	Metabolic activation system	S9 mix from livers of Aroclor-1254-treated male Sprague-Dawley or Wistar rats. (single i.p. injection, 500 mg/kg bw in corn oil, 5 days prior to sacrifice)
3.2.4	Positive control	TA 98: 4-nitro-1,2-phenylene diamine, 0.5 µg/plate (-S9) TA 1537: 4-nitro-1,2-phenylene diamine, 10 µg/plate (-S9) TA 100: Nitrofurantoin, 0.2 µg/plate (-S9) TA 1535: Sodium azide, 10 µg/plate (-S9) All strains: 2-aminoanthracene, 3 µg/plate (+S9) The solvent for positive controls was DMSO.
3.3	**Application of test substance**	

Section A6.6.1 Genotoxicity in vitro

Annex Point IIA VI.6.6.1 6.6.1 Mutagenicity testing in bacteria – Salmonella/microsome test

3.3.1	Concentrations	First test: 0, 8, 40, 200, 1000 and 5000 µg/plate (-S9 and +S9) Repeat tests: 0, 30, 60, 120, 240, 480, 960 µg/plate (-S9 and +S9)	
3.3.2	Way of application	0.1 mL of test-substance in ethanol or positive control in DMSO were added to 0.1 mL of bacteria solution (grown for 17 hours at 37 °C at 90 rpm), 0.5 mL S9-mix or buffer and 2.0 mL soft-agar. After incubation for a maximum of 30 sec at 45 °C in a water bath and mixing, the solution was poured onto solid agar plates. The plates were incubated for 48 hours at 37 °C before the colonies were counted.	
3.3.3	Pre-incubation time	None	
3.3.4	Other modifications	–	
3.4	**Examinations**	See tables in appendix for examinations and results.	
		4 RESULTS AND DISCUSSION	
4.1	**Genotoxicity**		
4.1.1	without metabolic activation	No	
4.1.2	with metabolic activation	No	
4.2	**Cytotoxicity**	Yes 1000 µg/plate without S9 1000 µg/plate with S9	X
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The mutagenic potential of Preventol CMK was tested in the Salmonella/Microsome test according to Ames *et al.* (*Proc. Nat. Acad. Sci.* (USA) 70, 2281-2285, 1973 and *Mutation Res.* **31**, 374-364, 1975) and Maron & Ames (*Mutation Res.* **113**, 173-215, 1983). Tester strains used were the *Salmonella typhimurium* histidine auxotrophs TA98, TA100, TA 1535and TA 1537. Liver microsomal enzymes were prepared from at least 6 male Sprague-Dawley or male Wistar rats which had received a peritoneal injection of Aroclor 1254 at 500 mg/kg bw. In a dose range-finding test, 6 dose levels from 0-5,000 µg/plate were plated with overnight cultures of TA 98, TA 100, TA 1535 and TA 1537 in the presence or absence of rat S9 mix. As a result, the appropriate maximum dose to be plated in the main study would be 960 µg/plate with and without metabolic activation, respectively. The test article was tested at 5 dose levels along with appropriate vehicle and positive controls in the absence or presence of rat microsomal enzymes. Ethanol was used as vehicle for Preventol CMK and DMSO for positive controls. 0.1 mL of test-substance in ethanol or positive control in DMSO were added to 0.1 mL of bacteria solution (grown for 17 hours at 37 °C at 90 rpm) and 0.5 mL S9 mix or buffer (for non-activating tests) were added to 2.0 mL molten top-agar. After incubation for a maximum of 30 sec at 45 °C in a water bath and mixing, this solution was poured onto solid agar plates. Four replicates were plated for all dose levels and controls. The plates were incubated at 37 °C for 48 hours, before the colonies were counted. Please refer to the respective tables below for concentrations of test substance and the	

Section A6.6.1 Genotoxicity in vitro

Annex Point IIA VI.6.6.1		6.6.1 Mutagenicity testing in bacteria – Salmonella/microsome test	
		strain-specific positive controls used in the various tests. A result was evaluated as positive when it caused a doubling in the mean number of revertants per plate in at least one tester strain. This increase must be accompanied by a positive dose response.	
5.2	**Results and discussion**	There was no indication of bacteriotoxic effects of Preventol CMK at doses of up to and including 200 µg/plate. Total bacteria counts were comparable to or only slightly different from the negative controls. No inhibition of growth was noted (see Table A6_6_1-1 and Table A6_6_1-2). Higher doses at and above 240 µg/plate caused bacteriotoxic effects. Due to this cytotoxicity, the complete assay was repeated with a different dose range (Table A6_6_1-3 and Table A6_6_1-4). None of the four strains tested showed a dose-related and biologically relevant increase in mutant counts over those of the negative controls, with and without metabolic activation. The respective positive controls caused an increase in the number of revertants (Table A6_6_1-3 and Table A6_6_1-4), which proved the sensitivity of the test. Therefore, no indications of mutagenic effects of Preventol CMK could be found at doses up to 960 µg/plate in any of the *S. typhimurium* strains tested.	X
5.3	**Conclusion**		
5.3.1	Reliability	[redacted]	X
5.3.2	Deficiencies	No	

Section A6.6.1 Genotoxicity in vitro

Annex Point IIA VI.6.6.1 6.6.1 Mutagenicity testing in bacteria – Salmonella/microsome test

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18/09/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.1 Genotoxicity in vitro

Annex Point IIA VI.6.6.1 6.6.1 Mutagenicity testing in bacteria – Salmonella/microsome test

Table A6_6_1-1: Table for gene mutation assay - Test 1 (pre-test)
Average revertants per plate in tester strains TA98, TA 100, TA 1535 and TA 1537 without S9-mix (rat)

Concentration [µg/plate]	Revertants/plate [mean]			
	TA 1535	TA 100	TA 1537	TA 98
0	13	89	8	32
8	13	94	9	34
40	15	99	6	37
200	14	89	8	30
1000	5	18	4	7
5000	0	0	0	0
Na-azide[1]	603			
NF[2]		477		
4-NPDA[3]			70	167

Positive controls: [1]: Sodium-azide, 10 µg/plate (only TA 1535)
[2]: Nitrofurantoin, 0.2 µg/plate (only TA 100)
[3]: 4-nitro-1,2-phenylenediamine, 10 µg/plate (only TA 1537), 0.5 µg/plate (only TA 98)

Table A6_6_1-2: Table for gene mutation assay - Test 1 (pre-test)
Average revertants per plate in tester strains TA98, TA 100, TA 1535 and TA 1537 with 30% S9-mix (rat)

Concentration [µg/plate]	Revertants/plate [mean]			
	TA 1535	TA 100	TA 1537	TA 98
0	20	111	9	38
8	21	124	10	46
40	20	120	10	46
200	11	100	6	51
1000	7	35	3	13
5000	0	0	0	0
2-AA[4]	164	1211	74	446

Positive controls: [4]: 2-aminoanthracene, 3 µg/plate

Section A6.6.1 Genotoxicity in vitro

Annex Point IIA VI.6.6.1 6.6.1 Mutagenicity testing in bacteria – Salmonella/microsome test

Table A6_6_1-3: Table for gene mutation assay - Test 2
Average revertants per plate in tester strains TA98, TA 100, TA 1535 and TA 1537 without S9-mix (rat)

Concentration [µg/plate]	Revertants/plate [mean]			
	TA 1535	TA 100	TA 1537	TA 98
0	14	78	9	25
30	13	86	9	28
60	13	89	9	28
120	12	91	12	29
240	12	89	7	29
480	14	66	5	23
960	5	35	2	17
Na-azide[1]	732			
NF[2]		364		
4-NPDA[3]			58	67

Positive controls: [1]: Sodium-azide, 10 µg/plate (only TA 1535)
[2]: Nitrofurantoin, 0.2 µg/plate (only TA 100)
[3]: 4-nitro-1,2-phenylenediamine, 10 µg/plate (only TA 1537), 0.5 µg/plate (only TA 98)

Table A6_6_1-4: Table for gene mutation assay - Test 2
Average revertants per plate in tester strains TA98, TA 100, TA 1535 and TA 1537 with 30% S9-mix (rat)

Concentration [µg/plate]	Revertants/plate [mean]			
	TA 1535	TA 100	TA 1537	TA 98
0	24	143	12	45
30	30	135	12	48
60	29	94	8	43
120	29	117	10	50
240	27	138	7	44
480	19	75	6	24
960	21	47	3	7
2-AA[4]	188	756	77	372

Positive controls: [4]: 2-aminoanthracene, 3 µg/plate

Section 6.6.2 **Annex Point IIA VI.6.6.2**	***In-vitro* cytogenicity study in mammalian cells**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	[redacted]	X X
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	18/09/2008	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	

Section 6.6.2 **Annex Point IIA VI.6.6.2**	***In-vitro* cytogenicity study in mammalian cells**
Remarks	[redacted]
	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 A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 Mutagenicity testing in mammalian cells – CHO-HGPRT test

Official use only

	1 REFERENCE	
1.1	**Reference**	Lehn H (1989): Preventol CMK - Mutagenicity Study For The Detection Of Induced Forward Mutations in the CHO-HGPRT Assay in vitro Bayer AG, Wuppertal, Germany, Report No. 17755, 1989-02-22 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer AG
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No Guideline statement, but study was performed in accordance with EEC Directive 2000/32/EC, Method B.17 and OECD Guideline 476
2.2	**GLP**	Yes
2.3	**Deviations**	Not applicable.
	3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	White odourless powder
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Stability of the test substance was assured by the study sponsor. Stability of the test substance in vehicle was approved for the concentration range from 20 µg/mL to 125 mg/mL.
3.2	**Study Type**	*in vitro* mammalian cell gene mutation test
3.2.1	Organism/cell type	Chinese hamster ovary (CHO) / CHO-K1-BH_4
3.2.2	Deficiencies / Proficiencies	6-thioguanine (6-TG) sensitive, rapid population doubling time, high cloning efficiency
3.2.3	Metabolic activation system	S9 mix from livers of Aroclor-1254-treated male Sprague-Dawley rats. (prior to the HGPRT test the S9-fraction was tested for contamination and cytotoxicity)
3.2.4	Positive control	Without S9-mix: Ethylmethanesulfonate (EMS); 0.9 mg/mL With S9-mix: Dimethylbenzanthracene (DMBA); 20 µg/mL
3.3	**Application of test substance**	
3.3.1	Concentrations	Cytotoxicity test: 0, 1.25, 2.5, 5.0, 10.0, 20.0, 40.0, 80.0, 160.0, 320.0 µg/mL (-S9 and +S9) Mutagenicity test: 0, 50, 100, 150, 200, 250, 300 µg/mL (-S9 and +S9)
3.3.2	Way of application	The test substance was dissolved in DMSO

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 Mutagenicity testing in mammalian cells – CHO-HGPRT test

3.3.3	Pre-incubation time	Not applicable.
3.3.4	Other modifications	–
3.4	**Examinations**	See tables in appendix for examinations and results.
3.4.1	Number of cells evaluated	2×10^5 per dish

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No
4.1.2	with metabolic activation	No
4.2	**Cytotoxicity**	Yes 250 µg/mL with and without S9

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In a dose range-finding test (cytotoxicity test), 9 dose levels from 1.25-320 µg/mL were tested in the presence or absence of rat microsomal enzymes. As a result, the appropriate maximum dose to be plated in the main study would be 300 µg/mL with and without metabolic activation, respectively. Preventol CMK was evaluated for mutagenic effects at the HGPRT locus (forward mutation assay) in CHO-K1-BH_4 cell cultures after in-vitro treatment at concentrations of up to 300 µg/mL with and without S9. The test was conducted according a procedure based on the report of Myhr and DiPaolo (1978) [*Cancer Res*. 38, 2539-2543, 1978]. The S9 mix was obtained from Aroclor 1254-treated rat liver. Dimethylbenzanthracene (DMBA) and ethylmethanesulfonate (EMS) were used as positive controls in activation and non-activation assays, respectively. Negative controls included both untreated controls and vehicle (DMSO) controls. The number of cells seeded for analysis of mutant frequency was 2×10^5 per dish (8 dishes per dose level). The test was performed as two independent trials.
5.2	**Results and discussion**	As a result of the cytotoxicity test 6 (see Table A6_6_3-1 and Table A6_6_3-2) concentrations of Preventol CMK were chosen for the mutation assay. The concentrations ranged from 50.0 to 300.0 µg/mL test substance in vehicle (DMSO). Additional test with positive and negative controls were performed. Two independent test series were performed with and without metabolic activation. Cytotoxic effects were noted at doses of 250 µg/mL and above. Due to this cytotoxicity, only 4 dose levels could be used for mutagenicity evaluation. In the mutagenicity tests, a dose-related decrease was observed in both, the relative survival and relative population growth. There was no statistically significant increase in mutant frequency noted at any of the 4 dose levels, under both activating and non-activating conditions. The positive controls EMS and DMBA showed a clear

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 Mutagenicity testing in mammalian cells – CHO-HGPRT test

		mutagenic effect. The vehicle control mutation frequencies were all in the normal range of background frequencies for the assay (see Table A6_6_3-3 and Table A6_6_3-4). According to the results of these tests and the relating evaluation criteria, Preventol CMK is considered to be non-mutagenic in the CHO-HGPRT Forward Mutation Assay.	
5.3	**Conclusion**		
5.3.1	Reliability	[redacted]	X
5.3.2	Deficiencies	No	X

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 Mutagenicity testing in mammalian cells – CHO-HGPRT test

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	02/10/2009
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 Mutagenicity testing in mammalian cells – CHO-HGPRT test

Table A6_6_3-1: Table for cytotoxicity assay (pre-test) - without S9-mix (rat)

Concentration [µg/mL]	Average colony count (± SD)	Relative survival [%][a]	Cloning efficiency [%]
Vehicle control[b]	140 ± 21	100.0	70.0
1.25	154 ± 18	109.8	
2.50	156 ± 19	111.3	
5.0	134 ± 10	95.9	
10.0[c]	149 ± 24	106.4	
20.0[d]	149 ± 12	106.7	
40.0	142 ± 11	101.6	
80.0[d]	119 ± 14	85.2	
160.0	108 ± 19	77.0	
320.0	0		

[a]: relative to vehicle control
[b]: 1% vehicle in culture medium without S9-mix
[c]: Only 2 dishes of four could be used (2 dishes lost due to contamination)
[d]: Only 3 dishes of four could be used (1 dish lost due to contamination)

Table A6_6_3-2: Table for cytotoxicity assay (pre-test) - with S9-mix (rat)

Concentration [µg/mL]	Average colony count (± SD)	Relative survival [%][a]	Cloning efficiency [%]
Vehicle control[b]	152 ± 5	100	76.0
1.25	156 ± 14	102.5	
2.50	163 ± 17	107.2	
5.0[d]	148 ± 6	97.4	
10.0[d]	174 ± 6	114.5	
20.0	149 ± 11	97.7	
40.0	148 ± 19	97.5	
80.0	136 ± 20	89.3	
160.0	84 ± 18	55.1	
320.0	0		

[a]: relative to vehicle control
[b]: 1% vehicle in culture medium with S9-mix
[d]: Only 3 dishes of four could be used (1 dish lost due to contamination)

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 Mutagenicity testing in mammalian cells – CHO-HGPRT test

Table A6_6_3-3: Table for gene mutation assay - CHO-HGPRT-test - non-activation

Concentration [µg/mL]	1st trial			2nd trial		
	Flask #1+#2	Flask #1	Flask #2	Flask #1+#2	Flask #1	Flask #2
	Survival[a]	MF[b]	MF[b]	Survival[a]	MF[b]	MF[b]
Negative control[1]	154.7	19.0	16.5	98.4	6.5	2.8
Vehicle control[2]	100.0	3.9	12.8	100.0	4.9	6.7
50.0	91.5	1.0	3.8	97.7	1.0	5.8
100.0	77.5	11.1	12.4	82.7	7.2	2.7
150.0	91.5	3.4	11.0	112.6	3.9	3.7
200.0	52.7	7.8	3.0	23.0	6.2	4.6
250.0	0	nd	nd	1.2	nd	nd
300.0	0	nd	nd	0	nd	nd
Positive control[3]	14.0	226.1*	257.7*	7.8	283.8*	467.3*

[1]Culture medium
[2]Culture medium with ≤ 1% vehicle
[3]EMS (ethylmethan esulfonate), 0.9 mg/mL
[a]Survival to treatment [% vehicle control]
[b]Mutation frequency [× 10^{-6}]
nd: not cloned due to cytotoxicity
* Significant increase, ($p < 0.05$, POISSON heterogeneity test)

Table A6_6_3-4: Table for gene mutation assay - CHO-HGPRT-test - activation

Concentration [µg/mL]	1st trial			2nd trial		
	Flask #1+#2	Flask #1	Flask #2	Flask #1+#2	Flask #1	Flask #2
	Survival[a]	MF[b]	MF[b]	Survival[a]	MF[b]	MF[b]
Negative control[1]	103.2	5.5	3.2	97.8	1.7	3.3
Vehicle control[2]	100.0	3.8	2.5	100.0	0.7	2.8
50.0	85.1	8.0	7.1	41.7	1.3	0.8
100.0	60.3	3.8	3.8	26.7	2.4	1.6
150.0	35.9	4.8	1.3	9.6	3.4	1.3
200.0	11.5	1.4	9.7	43.2	1.5	1.5
250.0	1.5	nd	nd	0	nd	nd
300.0	0	nd	nd	0	nd	nd
Positive control[3]	131.8	54.4*	71.3*	56.5	137.9*	178.4*

[1]Culture medium
[2]Culture medium with ≤ 1% vehicle
[3]DMBA (7,12-dimethylbenzanthracene), 20 µg/mL
[a]Survival to treatment [% vehicle control]
[b]Mutation frequency [× 10^{-6}]
nd: not cloned due to cytotoxicity
* Significant increase, ($p < 0.05$, POISSON heterogeneity test)

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2 6.6.2 *In-vitro* unscheduled DNA synthesis in rat primary hepatocytes

			Official use only
		1 REFERENCE	
1.1	**Reference**	Cifone, M.A. (1988), Mutagenicity Test on Preventol CMK in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay. Hazelton Laboratories America, Inc., Kensington, MD, USA Report No. R 4545, 1988-10-04 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer AG	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No guideline statement, but general compliance with OECD Guideline 482 (1986)	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	White crystals	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Not reported	
3.2	**Study Type**	Unscheduled DNA synthesis in mammalian cells in vitro	
3.2.1	Organism/cell type	Rat primary hepatocytes from an adult male F344 rat (150-300 g bw). A single animal was used for each trial.	
3.2.2	Metabolic activation system	Intrinsic	
3.2.3	Positive control	2-Acetylaminofluorene (AAF), 0.1 µg/mL, vehicle: DMSO	
3.3	**Application of test substance**		
3.3.1	Concentrations	0, 0.25, 0.5, 2.5, 7.5, 10, 20 µg/mL	
3.3.2	Way of application	Dissolved in DMSO	X
3.3.3	Exposure times	18-19 h	
3.4	**Examinations**	^{3}H-incorporation (silver grain formation) and cytotoxicity (trypan blue exclusion)	
3.4.1	Number of cells evaluated	50 cells per slide, 3 slides per dose group	

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2 6.6.2 *In-vitro* unscheduled DNA synthesis in rat primary hepatocytes

4 RESULTS AND DISCUSSION

4.1 Genotoxicity No (see Tables A6_6_2-1 and A6_6_2-2).

4.2 Cytotoxicity Yes, at 10 and 20 µg/mL (67% and 43% survival, respectively)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

CMK was evaluated for unscheduled DNA synthesis (UDS) in cultured primary rat hepatocytes. Despite the lacking guideline statement, the study was performed according to OECD Guideline 482.

Freshly prepared rat hepatocytes were exposed to 7 concentrations of Icaridin ranging from 0.25 µg/mL to 20 µg/mL in the presence of 5 µCi/mL ^{3}H-thymidine for 18-19 hours in medium with reduced serum content (1% FCS).

The cells were fixed, washed and air-dried prior to coating in the dark with photographic emulsion. The coated slides were stored at 4°C for 4-10 days and then developed. The slides were then rinsed and stained with haematoxylin/eosin.

Grain counting was done manually using a microscope with 1500x magnification and oil immersion. Each slide was examined by counting 50 cells per slide, normally with 3 slides per dose group.

The assay was deemed acceptable if the following criteria were met:

1. The viability of the hepatocytes must exceed 50%.
2. The viability of the monolayer cell cultures used for the UDS assay must be 70% or greater.
3. The number of viable cells in the vehicle control cultures should remain reasonably stable throughout the experiment; the number of viable cells in the vehicle control cultures must be ≥ 50% at the beginning of the treatment period.
4. For each of the 50 cells on each slide, the number of nuclear grains is scored, as well as numbers of three cytoplasmic grain counts from nuclear-sized areas adjacent to each nucleus.
5. The average net nuclear grain counts (NG) in the negative control cultures should range between -5 to +1. No more than 10% of the cells should contain ≥ 6 grains, or 1% of the cells ≥ 20 grains.
6. For the positive control 2-AAF (0.1 µg/mL), one might expect mean values of 13 NG with 83% and 21% of the nuclei having more than 6 and 20 grains, respectively.
7. For the conditions described, if a chemical yields ≥ 6 NG in the population average or ≥ 6 NG in ≥ 10% of the cells or ≥ 20 NG in ≥ 2% of the cells, the response is considered positive.
8. Grain count data obtained for a given treatment are acceptable as part of the evaluation if obtained from at least two replicate cultures and at least fifty cells per culture.
9. A minimum of 6 dose levels will be analysed for NG. Repeat trials need only augment the number of analysed dose levels in the first trial to achieve a total of 6 different dose levels.
10. The highest analysed dose must give rise to cytotoxicity or result in insolubility of the test material or reach a maximum concentration of 5 mg/mL.

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2	6.6.2 *In-vitro* unscheduled DNA synthesis in rat primary hepatocytes

5.2	**Results and discussion**	The test substance was not soluble in medium and was dissolved in DMSO at a concentration of 502 mg/mL forming a clear, colourless solution. With DMSO as vehicle, CMK was soluble in the medium at concentrations up to 2010 µg/mL. A good range of cytotoxicity was seen in this assay (78-43% relative survival). Three trials of the UDS assay were performed. The first trial was terminated due to high toxicity resulting in too few analysable dose levels. None of the criteria applied to indicate UDS were met or exceeded by the treatment with CMK and no dose-related response was observed. There was also no evidence for a dose-dependent response (see Tables A6_6_2-1 and A6_6_2-2. The positive control, 2-acetylaminofluorene, produced a clearly positive effect. CMK is negative in the *in-vitro* UDS assay in primary rat hepatocytes.	X
5.3	**Conclusion**		
5.3.1	Reliability	[redacted]	
5.3.2	Deficiencies	No	

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2 6.6.2 *In-vitro* unscheduled DNA synthesis in rat primary hepatocytes

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	29/09/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2 6.6.2 *In-vitro* unscheduled DNA synthesis in rat primary hepatocytes

Table A6_6_2-1 Table for UDS assay in primary rat hepatocytes, second assay*

Concentration [µg/mL]	Net grains [a] per nucleus	Avg % nuclei with ≥ 6 grains	Avg % nuclei with ≥ 20 grains	Survival [d] at 21.5 h [%]
Vehicle control	-2.63	0.7	0.0	100.0
0.250	-2.69	3.3	0.0	n.d.
0.500	-2.05	2.7	0.0	100.3
2.50	-1.40	2.0	0.0	95.2
7.50	-1.32	1.4[b]	0.0[b]	77.9
10.0	-1.83	0.7	0.0	67.0
20.0	-1.62[b]	0.7[b]	0.0[b]	42.8
Pos. control	21.77[b]	98.6[b]	57.3[b]	99.8

*1st assay was discarded due to excessive cytotoxicity
[a] Average of net nuclear grain counts on triplicate coverslips (150 total cells)
[b] Average of net nuclear grain counts on duplicate coverslips (150 total cells for UDS)
[c] Means of percentages of cells with 5 or more net nuclear grains on triplicate coverslips
[d] Number of viable cells relative to vehicle controls
n.d.: not determined

Table A6_6_2-2 Table for UDS assay in primary rat hepatocytes, third assay

Concentration [µg/mL]	Net grains [a] per nucleus	Avg % nuclei with ≥ 6 grains	Avg % nuclei with ≥ 20 grains	Survival [d] at 20 h [%]
Vehicle control	-0.03	6.0	0.0	100.0
2.53	-0.43	3.3	0.0	100.6
5.06	-0.31	0.7	0.0	98.8
7.58	-0.62	0.7	0.0	98.2
10.1	-0.21	2.0	0.0	99.1
15.2	-0.62[b]	0.0[b]	0.0[b]	98.7
20.2	0.14	0.7	0.0	87.7
30.3	n.d.	n.d.	n.d.	53.0
Pos. control	21.69	99.3	52.0	99.4

[a] Average of net nuclear grain counts on triplicate coverslips (150 total cells)
[b] Average of net nuclear grain counts on duplicate coverslips (100 total cells for UDS)
[c] Means of percentages of cells with 5 or more net nuclear grains on triplicate coverslips
[d] Number of viable cells relative to vehicle controls
n.d.: not determined

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.4 *In vivo* micronucleus test in mice

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]. (1990): Preventol CMK MICRONUCLEUS TEST ON THE MOUSE [redacted] 1991-08-08 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No guideline statement, but in accordance with OECD Guideline 474 with deviations.	
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes - Only 1 dose level + controls - Vehicle produces signs of toxicity - Only 1000 erythrocytes/animal were scored for micronuclei	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	White to colourless crystalline powder	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Approved for use during the study period.	
3.2	**Test Animals**		
3.2.1	Species	Mouse	
3.2.2	Strain	Bor:NMRI (SPF Han)	
3.2.3	Source	[redacted]	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	8-12weeks of age, 29-44 g bw	
3.2.6	Number of animals per group	5 per sex	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**		
3.3.1	Number of applications	1	

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.4 *In vivo* micronucleus test in mice

3.3.2	Interval between applications	Not applicable	
3.3.3	Postexposure period	Treatment groups: 24, 48 and 72 hours after treatment Control groups: 24 hours after treatment	
		Intraperitoneal	
3.3.4	Type	Injection	
3.3.5	Concentration	125 mg/kg bw positive control 20 mg/kg bw cyclophosphamide	X1
3.3.6	Vehicle	Polyethyleneglycol 400 (PEG 400)	X
3.3.7	Concentration in vehicle	Test substance: 25 mg/mL Pos. control: 2 mg/mL	
3.3.8	Total volume applied	Treatment groups and negative control: 5 mL/kg bw Positive control: 10 mL/kg bw	
3.3.9	Substance used as positive control	Cyclophosphamide 20 mg/kg bw (in deionised water)	
3.3.10	Controls	Vehicle and positive control	
3.4	**Examinations**		
3.4.1	Clinical signs	Yes	
3.4.2	Tissue	Femoral bone marrow	
	Number of animals:	All animals	
	Number of cells:	1000	
	Time points:	24, 48, 72 h after treatment	
	Type of cells	Erythrocytes of bone marrow	
	Parameters:	Polychromatic/normochromatic erythrocytes ratio	
3.5	**Further remarks**	–	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Mice treated with 125 mg/kg Preventol CMK showed the following compound-related symptoms for up to 72 hours: apathy, roughened fur, staggering gait, prone position, spasm, twitching and diarrhoea. 4 of 40 treated animals died during the test period, due to acute toxicity of 125 mg/kg Preventol CMK. The time points of death are listed in the following. 24 hours group: 1 male found death after 24 hours 48 hours group: 1 female found death after 48 hours 72 hours group: 1 male found death after 48 hours Replacement group: 1 male found death after 72 hours In the negative control group, animals showed apathy and spasm, lasting for up to 24 hours. Thereafter, their external appearance and physical activity remained unaffected. Their feeding behaviour was normal. In the positive control group no symptoms of toxicity were noted.	
4.2	**Genotoxicity**	No	
4.3	**Other**	–	

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.4 *In vivo* micronucleus test in mice

		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Preventol CMK was tested in an *in vivo* micronucleus test in male and female NMRI mice. Five mice per sex and group received a single intraperitoneal injection of 125 mg/kg bw. The known clastogen, cyclophosphamide (20 mg/kg bw), served as positive control. Negative control mice were given vehicle (polyethyleneglycol 400). Mice of the control groups were sacrificed 24 hours after treatment. The mice of the test groups were sacrificed at 24, 48 and 72 hours after treatment. All animals were observed for clinical signs of toxicity until sacrifice. Femoral bone marrow cells were prepared 24, 48, and 72 h after administration and smears were produced according to Schmid´s method (Schmid, W. *Mut. Res.* 31, 9-15, 1975 and DFG, Kommission für Mutagenitätsfragen, Mitteilungen III, 53-61, 1975). The ratio of polychromatic to normochromatic erythrocytes was determined.	X1
5.2	**Results and discussion**	Animals treated with 125 mg/kg bw Preventol CMK showed symptoms of toxicity which comprise apathy, roughened fur, staggering gait, prone position, spasm, twitching and diarrhoea. The symptoms lasted until sacrifice. Four mice died during the study period. The ratio of polychromatic to normochromatic erythrocytes was not altered in the groups which received the test substance (see Table A6_6_4-1). No indications of clastogenic effects of Preventol CMK were found after treatment. The positive control cyclophosphamide caused a clear clastogenic effect which is shown by the significant increase of polychromatic erythrocytes with micronuclei. The ratio of polychromatic to normochromatic erythrocytes was not altered.	X
5.3	**Conclusion**		
5.3.1	Reliability	[redacted]	
5.3.2	Deficiencies	No	X

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.4 *In vivo* micronucleus test in mice

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	02/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.4 *In vivo* micronucleus test in mice

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

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.4 *In vivo* micronucleus test in mice

Table A6_6_4-1. Table for In Vivo Micronucleus test

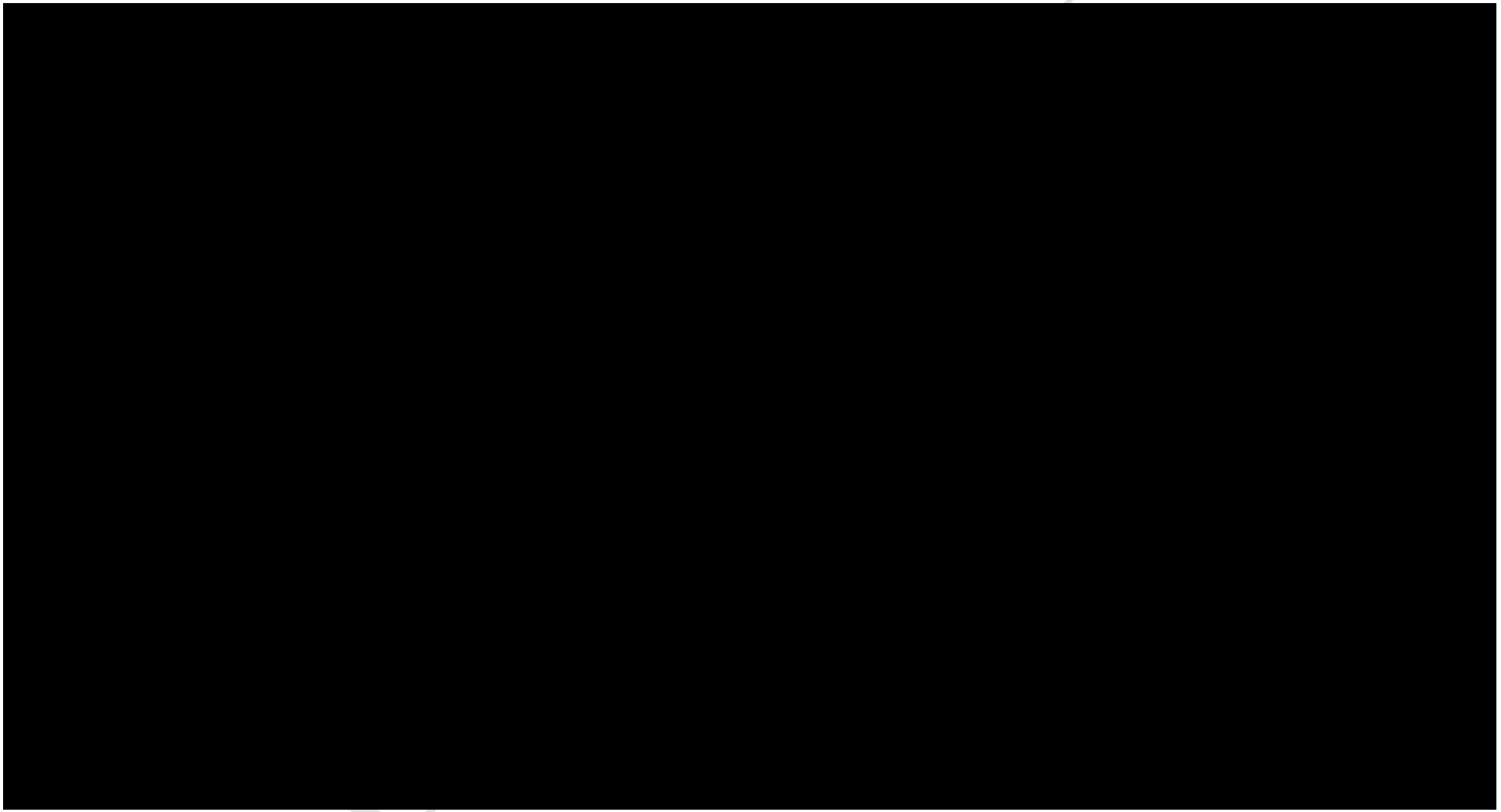
Experimental group	Time of sacrifice [hours after treatment]	Number of evaluated polychromatic erythrocytes per animal	No. of normo-chromatic erythrocytes per 1000 poly-chromatic erythrocytes [mean ± SD]	Micronucleated cells per 1000	
				normochromatic erythrocytes [mean ± SD]	polychromatic erythrocytes [mean ± SD]
Negative control [a]	24	1000	1179 ± 495	1.3 ± 1.1	1.2 ± 0.9
Test substance [b]	24	1000	1319 ± 439	0.7 ± 0.9	1.3 ± 1.4
Test substance [b]	48	1000	1595 ± 633	1.2 ± 0.9	0.7 ± 0.8
Test substance [b]	72	1000	1524 ± 1185	0.7 ± 0.7	1.1 ± 0.7
Positive control[c]	24	1000	881 ± 160	1.3 ± 1.2	16.1* ± 6.4

[a] Polyethyleneglycol 400 (as intraperitoneal injection)
[b] 125 mg/kg bw (as intraperitoneal injection)
[c] 20 mg/kg bw cyclophosphamide (as intraperitoneal injection)
* $p < 0.01$ in non-parametric Wilcoxon ranking test

Section 6.7 **Annex Point IIA VI.6.7**	**Carcinogenicity** **Carcinogenicity study in mice**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	[redacted]	

Section 6.7 **Annex Point IIA VI.6.7**	**Carcinogenicity** **Carcinogenicity study in mice**
	[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	19/12/2008
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	

Table A6_7-1: Comparison of carcinogenicity studies with CMK and BCP

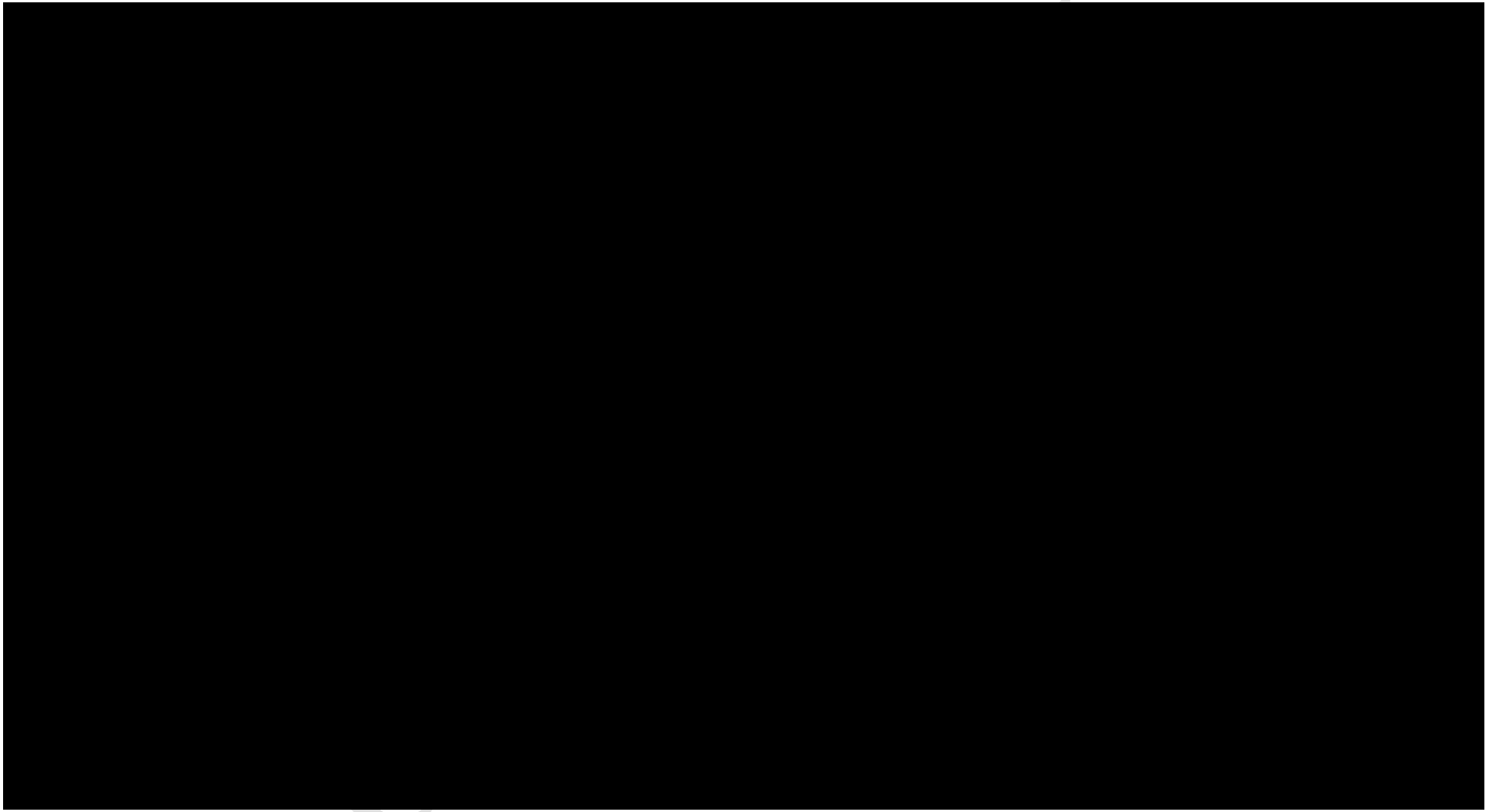


Section 6.8.1	**Developmental toxicity**	
Annex Point IIA VI.6.8.1	**Developmental toxicity study in rabbits**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	[redacted]	
Undertaking of intended data submission [ ]		
Evaluation by Competent Authorities		
	Use separate "evaluation boxes" to provide transparency as to the	

Section 6.8.1	**Developmental toxicity**
Annex Point IIA VI.6.8.1	**Developmental toxicity study in rabbits**
	comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2009
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	[redacted]
	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*

Section 6.8.1	**Developmental toxicity**
Annex Point IIA VI.6.8.1	**Developmental toxicity study in rabbits**
Remarks	

Table A6_8-1: Comparison of developmental toxicity studies in rats and rabbits for different phenolic antimicrobials



Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted](1991): Preventol CMK - Study for embryotoxic effects in rats after oral administration [redacted] 1991-11-29 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OECD Guideline 414 (1981) and US-EPA TSCA-Guideline 798.4900 (revised 1987)	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2 of dossier.	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Description	Solid, colourless powder	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Was approved by the study sponsor.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar (Bor:WISW(SPF Cpb))	
3.2.3	Source	[redacted]	
3.2.4	Sex	♀	
3.2.5	Age/weight at study initiation	Age: no data Body weight: 186 - 248 g	
3.2.6	Number of animals per group	25 females	
3.2.7	Control animals	Yes	
3.2.8	Mating period	One night	
3.3	**Administration/ Exposure**	**Oral**	
3.3.1	Duration of exposure	Day 6-15 post mating	
3.3.2	Postexposure period	Day 15 -20 post mating	

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

3.3.3	Type	Gavage
3.3.4	Concentration	0, 30, 100, 300 mg/kg bw
3.3.5	Vehicle	0.5% aqueous tylose solution
3.3.6	Concentration in vehicle	0, 3.0, 10.0, 30.0 mg/mL
3.3.7	Total volume applied	10 mL/kg bw
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes Day 0 p.c.; Days 6 to 15 p.c.: once daily; day 20 p.c.
3.4.2	Food consumption	Yes Days of gestation: 0-6, 6-11, 11-16 and 16-20
3.4.3	Clinical signs	Yes From day 0 to 20 of gestation: twice daily (once on weekends and bank holidays)
3.4.4	Examination of uterine content	Number of implantations, number of corpora lutea, uterus weight, number of live and death foetuses or embryos
3.4.5	Maternal organ weights	Yes Uterus weight
3.4.6	Examination of foetuses	Sex, weight, occurrence of malformations discernable from the outside and other findings deviating from standard, occurrence of visceral malformations (investigations of half of the foetuses according to the modified WILSON technique, occurrence of changes in the abdominal and thoracic organs and skeletal system (evisceration and evaluation of the other foetuses according to the DAWSON technique)
3.4.6.1	General	Individual weights and outward appearance of placentas
3.4.6.2	Skeleton	Yes
3.4.6.3	Soft tissue	Yes
3.5	**Further remarks**	Water consumption assessment was performed during inspections by visual inspection of the quantities left over.
		4 RESULTS AND DISCUSSION
4.1	**Maternal toxic effects**	Clinical signs: 0 and 30 mg/kg bw: no effects 100 mg/kg bw: on days 8 and 16 two animals showed laboured breathing 300 mg/kg bw: from day 8 p.c. marked clinical signs (rough coat, sunken flanks, bloody muzzle, laboured breathing, reduced mobility, high-stepping gait) were noted. From day 6 p.c. the following signs occurred from about 10 minutes until 1 hour after application: lying on side, somnolence, abdominal position, spastic convulsion. In addition, one animal showed gasped breathing. Mortality:

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

		0 - 100 mg/kg bw: no mortalities occurred 300 mg/kg bw: 6 animals died during the study period, one of them was killed in moribund condition. Food intake: 0 and 30 mg/kg bw: no effects 100 mg/kg bw: statistically significant reduced food intake during the application period. 300 mg/kg bw: statistically significant reduced food intake during the application and gestation period. Water intake: 0 and 30 mg/kg bw: no effects 100 mg/kg bw: reduced in one animal on day 9 p.c. 300 mg/kg bw: reduced for several animals from day 9 p.c., in some cases lasting for 1-6 days. Urine/faeces excretion: 0 and 30 mg/kg bw: no effects 100 mg/kg bw: increased urine excretion in some isolated cases from day 9 p.c.; reduced amount of faeces over a period of 1-5 days in several animals from day 9 p.c. 300 mg/kg bw: increased urine excretion in several animals from day 8 p.c. for a period of 1-5 days; reduced amount of faeces in several animals from day 8 p.c. (lasting for 1-5 days). Body weight development: 0 and 30 mg/kg bw: no effects 100, 300 mg/kg bw: body weight gain was reduced during the treatment period. Body weight development during pregnancy as well as corrected body weight gain was statistically significant reduced. Gross pathology: 0, 30, 100 mg/kg bw: no effects 300 mg/kg bw: Of the 6 animals that died or were killed moribund during the study period, 3 animals each had inflated intestines and bloody vaginas, respectively. Additional significant findings were noted in these animals. No findings were observed in the surviving animals of this dose group. (see Table A6_8_1-1)	
4.2	**Teratogenic / embryo toxic effects**	Embryotoxicity: 0 to 100 mg/kg group: No effects 300 mg/kg group: Reduced foetal weight. Due to an increased rate of resorption, the gestation rate and number of foetuses were also reduced. Teratogenicity: No effects. (see Tables A6_8_1-2)	X X
4.3	**Other effects**	–	

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Wistar rats were used in this study. Virgin female rats were mated overnight individually with males. Females revealing vaginal plugs or spermatozoa in vaginal smears in the following morning were designated as being in day 0 of gestation. The pregnant females were divided into four groups of 25 rats each and were given Preventol CMK by gavage at daily doses of 0, 30, 100 or 300 mg/kg bw (10 mL/kg bw) on days 6-15 of gestation. The test substance was applied in 0.5 % aqueous tylose solution. On day 20 of gestation animals delivered by caesarean section. Investigations were performed on general tolerance of the test substance by the dams as well as its effect on intra-uterine development.	
5.2	**Results and discussion**	Preventol CMK at doses of 30 mg/kg bw/day was tolerated without any effects. At 100 mg/kg bw/day some animals showed laboured breathing. At 300 mg/kg bw/day all dams exhibited marked clinical signs (rough coat, sunken flanks, bloody muzzle, laboured breathing, reduced mobility, high-stepping gait). Within 1 hour after application, animals of this group showed additional clinical signs of more frequently lying on side, somnolence, abdominal position, spastic convulsions, gasping breathing. After treatment with ≥ 100 mg/kg bw/day, feed and water intake, excretion of faeces and body weight gain was diminished. Urine excretion was increased at 100 and 300 mg/kg bw/day. Mortalities occurred only in the 300 mg/kg bw/day dose group. These animals, which died or were killed moribund showed gross pathological findings during necropsy (see Table A6_8_1-1). Weight and external appearance of placentas, sex ratio of foetuses and development of the skeletal system was not affected up to and including 300 mg/kg bw/day. Gestation and resorption rates, number and weight of foetuses as well as number and kind of malformations were not affected at doses of ≤ 100 mg/kg bw/day. At 300 mg/kg bw/day foetal weight, gestation rate and the number of foetuses were diminished due to an increased resorption rate. The slightly increased number of malformations observed in this group, were considered as spontaneous malformations which were not dose-dependent. The embryotoxic effects observed correlated with the marked maternal toxicity (see Table A6_8_1-2 and Table A6_8_1-3).	
5.3	**Conclusion**		
5.3.1	LO(A)EL maternal toxic effects	LOAEL = 100 mg/kg bw/day, based on decreased bw gain, reduced urine and faeces excretion	X
5.3.2	NO(A)EL maternal toxic effects	NOAEL = 30 mg/kg bw/day	
5.3.3	LO(A)EL embryo toxic / teratogenic effects	LOAEL = 300 mg/kg bw/day, based on decreased foetal weight, gestation rate, increased resorption rate	
5.3.4	NO(A)EL embryo toxic / teratogenic effects	NOAEL = 100 mg/kg bw/day	
5.3.5	Reliability	[redacted]	

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1	6.8.1 Teratogenicity test in the rat
5.3.6 Deficiencies	No

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21/01/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

Table A6_8_1-1. Table for teratogenic effects (separate data for all dosage groups)

Maternal effects

Parameter	**Control data**		**30 mg/kg**	**100 mg/kg**	**300 mg/kg**	**Dose-response + / –**
	historical	study **0 mg/kg**				
Number of dams examined	-	25	25	25	25	
Clinical findings						
audible breathing sounds	-	0	0	1	4	+
gasping breathing	-	0	0	1	1	+
bloody lip	-	0	1	0	0	–
rough coat	3	0	0	0	7	+
bloody muzzle	1 (nose)	0	0	0	4	+
sunken flanks	1	0	0	0	3	+
reduced motility	-	0	0	0	2	+
abdominal knots	-	0	1	0	0	–
bloody forelimbs	-	0	0	0	1	–
high-stepping gait	-	0	0	0	1	+
reduced water intake	7#	0	0	1	12	+
light-brown, hard faeces	4	1	0	0	0	
small amount of faeces	4	0	0	4	14	+
increased urine excretion	5#	0	0	3	9	+
after application						
gasping breathing	-	0	0	0	1	+
lying on side	-	0	0	0	7	+
somnolence	-	0	0	0	13	+
abdominal position	-	0	0	0	9	+
spastic convulsion	-	0	0	0	5	+
Mortality of dams	-	0	0	0	6	+
Body weight gain [g] Mean day 0 – 20	73.0-101.9	98.5	95.8	90.9	66.8*	+
Body weight gain [g] corrected, day 0 – 20	-	37.6	35.3	31.0	13.7***	+
Mean food consumption (Day 0-20) [g/rat/day]	-	18.5	18.4	18.0	15.5***	+
Pregnancies	7-24	22	24	22	24	–

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

Necropsy findings in dams dead before end of test						
reddened oesophagus	-				1	+
suppurative foci in lung tissue	-				1	+
fluid in thorax	-				1	+
thorax filled with serous fluid	-				1	+
stomach appears smaller	-				1	+
stomach + intestines extremely distended	-				1	+
reduced spleen size	-				1	+
gas-inflated intestines	-				2	+
bloody vagina	1				3	+
organs autolytic	-				1	+
Necropsy findings in dams at termination						
Ovariary cysts	1	2	0	0	0	–
intestinal worms	56	3	8	7	6	–

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

Table A6_8_1-2. Table for teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Parameter	**Control data**		**30 mg/kg**	**100 mg/kg**	**300 mg/kg**	**Dose-response + / –**
	Historical (1984-1990)	Study **0 mg/kg**				
Corpora lutea [mean no./dam]	-	13.0	13.2	12.4	12.6	
Implantations [mean no./dam]	8.3-12.5	11.4	11.3	11.2	10.6	–
Resorptions [mean no./dam][a]	0.3-2.3	0.6	0.8	0.6	1.8***	+
Resorptions [mean no./dam][b]		0.6	0.8	0.6	0.7	–
Foetuses [mean no./dam]	7.6-11.7	10.7	10.5	10.6	9.9	–
Foetus weight (mean) [g][b]	3.17-3.68	3.71	3.69	3.65	3.42**	+
Placenta weight [mean/dam] [g][b]	0.55-0.68	0.62	0.65	0.62	0.60	–
Skeletal changes [mean foetus no/dam][b]	1.44-3.18#	2.09	1.46	2.18	1.38	–
Malformations [mean foetus no/dam][b]	0.00-0.39	0.14	0.08	0.05	0.38	–
Sex ratio (m:f)[b]	-	1:0.8	1:0.9	1:1.22	1:1.03	–

[a] with implantations
[b] with live foetuses
Skeletal retardations
Statistically significant difference from controls: *p < 0.05; ** p < 0.005; *** p < 0.001

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Teratogenicity test in the rat

Table A6_8_1-3. Table for teratogenic effects (separate data for all dosage groups)

Examination of the foetuses

Parameter	**Control data**		**30 mg/kg**	**100 mg/kg**	**300 mg/kg**	**Dose-response + / –**
	historical	Study **0 mg/kg**				
External Examinations						
No. of foetuses examined	-	236	253	233	158	
No. of foetuses malformed						
hydronephrosis, hydro-ureter	9	1	0	0	0	–
cryptorchism	13	2	1	1	1	–
microphthalmia or anophthalmia	23	0	1	0	2	–
multiple malformation	1	0	0	0	1	–
dysplasia of humerus	4	0	0	0	1	–
hernia of diaphragm, with lung hypoplasia, heart and lung dystopia	1	0	0	0	1	–
Total malformed foetuses	51	3	2	1	6	–

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

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1 REFERENCE

1.1	**Reference**	[redacted], 4-Chloro-3-methylphenol – Two-Generation [redacted] 2006-12-19 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	LANXESS Deutschland GmbH
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes OECD Guideline 416 (2001) US EPA Guideline 870.3800 (1998) M.A.F.F. in Japan 12 Nousan No 8147 (2000)
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in Section 2 of dossier.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Description	Pastilles
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Compound stability until 2006-10-07 or 2007-12-12 Stability and homogeneity in diet approved for up to 15 days in 15 kg mixtures
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar Crl: (WI) WU BR
3.2.3	Source	[redacted]
3.2.4	Sex	♂+♀
3.2.5	Age/weight at study initiation	Age: F0: 5-6 weeks, F1: 4 weeks Weight: F0 ♂: 113-149 g; F0 ♀: 95-122 g F1 ♂: 61-120 g; F1 ♀: 62-110 g
3.2.6	Number of animals per group	25/sex/group
3.2.7	Mating	The first F0 or F1 male was caged overnight with the first F0 or F1 female from the same test group and so on at a maximum of 12 times.
3.2.8	Duration of mating	Up to 3 weeks or until spermatozoa were observed in vaginal smears taken the next morning.

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

3.2.9	Deviations from standard protocol	Litters were culled to 8 pups/litter on day 4 of lactation A second mating of F1 animals was performed giving rise to F2b litters.
3.2.10	Control animals	Yes
3.3	**Administration/ Exposure**	Oral / diet
3.3.1	Animal assignment to dosage groups	See Table A6_8_2-1 below
3.3.2	Duration of exposure before mating	10 weeks
3.3.3	Duration of exposure in general F0, F1, F2 males, females	F0animals: from beginning of the study until sacrifice F1 animals: from weaning until sacrifice F2 animals: sacrifice after weaning
		Oral
3.3.4	Type	in food
3.3.5	Concentration	750, 3000, 12,000 ppm
3.3.6	Vehicle	Diet
3.3.7	Dose levels	Pre-mating dose levels: F0: 63.8 / 80.1, 247.8 / 298.2, 1043.0 / 1189.7 mg/kg bw/day (♂/♀) F1: 74.5 / 90.4, 288.4 / 364.5, 1204.9 / 1263.4 mg/kg bw/day (♂/♀) See Table A6_8_2-2 for dose levels achieved in dams during gestation and lactation.
3.3.8	Duration of exposure	*ad libitum*
3.3.9	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Clinical signs	Yes, once daily for clinical signs and twice daily for mortality and morbidity.
3.4.2	Body weight	Body weights were recorded directly prior to the first administration and thereafter weekly up to necropsy (males and females not pregnant) and during the pregnancy and lactation periods as follows: - During pregnancy on Day p.c. 0, 7, 14 and 20. - During lactation on Day p.p .0, 4, 7, 14, 21 and 28. - On the day of scheduled necropsy.
3.4.3	Food consumption	The individual food consumption was measured as follows: - Males: Weekly from week 1 up to necropsy (except during mating period). - Females: Weekly from week 1 up to mating. During pregnancy Day p.c. 0-7; 7-14; 14-20. During lactation Day p.p. 0-4; 4-7.
3.4.4	Oestrus cycle	Oestrus cycle length determination was done by evaluation of vaginal smears (see above) received daily over 19 consecutive days prior to the mating period. The smears were examined microscopically for large set-rated cells indicating that oestrus had occurred. This data was used to

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

		determine the oestrus cycle length and whether females were cycling properly.	
3.4.5	Sperm parameters	Spermatological investigations were performed in all surviving F0 and F1 males of the 0 and 12,000 ppm group on the day of necropsy. The following spermatozoa parameters were assessed: motility and viability, morphology, epididymal spermatozoa count, count of homogenisation-resistant spermatid heads in the testis	
3.4.6	Offspring	Number of live and dead pups, pup weight, external alterations, ano-genital distance, sex of each pup, developmental milestones (balano-preputial separation, vaginal opening)	
3.4.7	Organ weights P and F1	Adrenals, brain, epididymides, kidneys, liver, ovaries and oviducts, pituitary, prostate, seminal vesicle and coagulating glands, spleen, testes, thyroid/parathyroids, uterus w/ cervix	
3.4.8	Histopathology P and F1	The following organs and tissues were examined at least in the control and high-dose group. This included also all F0/F1 rats which died intercurrently and those which were killed moribund. Abnormalities, adrenals, brain, epididymides, oesophagus, kidneys, larynx, liver, ovaries and oviducts, pituitary, prostate, seminal vesicle and coagulating glands, skin in mammary region, testes, thyroid/parathyroids, trachea, uterus w/ cervix, vagina, head w/ scull cap	
3.4.9	Histopathology F1 not selected for mating, F2	Apparently abnormal tissues, if any, were fixed in all pups/weanlings. In F1, F2a and F2b weanlings, brain, spleen, thymus, uterus and kidneys of one male and one female out of the first necropsied 5 litters per group were preserved in formalin.	
3.5	**Further remarks**	The brain, spleen, thymus and uterus of one male and one female per F F2a and F2b litter were trimmed and weighed as soon as possible after dissection. The ratio of organ weights to body weights was calculated. Therefore, all these weanlings were weighed at day of necropsy.	
		4 RESULTS AND DISCUSSION	
4.1	**Effects**	see Table A6_8_2-3	
4.1.1	F0 males	At 12,000 ppm: bw: reduced during pre-mating liver: reduced glycogen, altered fat deposition kidney: hyaline casts / tubulus dilation	
4.1.2	F0 females	At 12,000 ppm: bw: reduced during pre-mating, gestation and lactation ovaries: atrophy/changed cycle, smaller vagina: epithelium atrophy liver: increased relative weight, hypertrophy, reduced glycogen, altered fat deposition kidney: increased tubulus epithelium inclusion, tubulus dilation, basophilic tubules	X
4.1.3	F1 pups	At 12,000 ppm: reduced pup weights, reduced litter weights, reduced absolute and/or relative spleen and thymus weights	

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

4.1.4	F1 adult males	At 3000 ppm: liver: reduced abs. + rel. weight	
		At 12,000 ppm: bw: reduced during pre-mating liver: reduced abs. + rel. weight, reduced glycogen, altered fat deposition kidney: necrosis, hyaline casts / simple tubulus dilation	X
4.1.5	F1 adult females	At 3000 ppm: reduced bw during lactation liver: hypertrophy, altered fat deposition, kidney: simple tubulus dilation, tubulus dilation	
		At 12,000 ppm: reduced bw during pre-mating stomach/caecum dilated, emaciation, ovaries: atrophy/changed cycle, smaller, reduced growing follicles, reduced corpora lutea liver: reduced glycogen, altered fat deposition kidney: necrosis, tubulus dilation, increased rel. weight adrenals: increased rel. weight spleen: increased rel. weight	X
4.1.6	F2a pups	At 12,000 ppm: reduced pup weights, clinical signs, reduced absolute and/or relative spleen and thymus weights	
4.1.7	F2b pups	At 3000 ppm: reduced pup weights	
		At 12,000 ppm: reduced pup weights, reduced litter weights, reduced absolute and/or relative spleen and thymus weights	
4.2	**Other**	–	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The purpose of this two-generation reproduction study was to evaluate possible effects of CMK on the entire reproduction process in Wistar rats. CMK was administered to groups of 25 male and 25 female rats at concentrations of 0 (control), 750, 3000, or 12,000 ppm in their diet. During the pre-mating period the test compound intake was: F0: 638, 247.8 or 1043.0 mg/kg in males and 80.1, 298.2,01 1189.7 mg/kg in females. F1: 74.5, 288.4 or 1204.9 mg/kg in males and 904, 364.5 or 1263.4 mg/kg in females. Test compound intake by dams during gestation and lactation is presented in Table A6_8_2-2. Parental F0 animals received the test substance for a period of about 10 weeks and were then allowed to mate over a period of up to three weeks. F1 offspring were nursed up to an age of four weeks. Some of them were selected for further treatment (12 weeks) and for breeding an F2a generation. A second mating was done on F1 rats to clarify relatively low viability indices at 0 and 3000 ppm. Generally, the test substance was administered to the animals up to necropsy. Mortality, clinical signs, body weights and food intake as well as reproduction parameters such as mating performance, fertility, gestation, rearing, oestrus cycling and sperm analyses were examined in F0 and F1

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

		rats. Furthermore, litter parameters such as litter size, percentage of males born and pup weight at birth as well as viability and lactation indices, body weight gain and clinical signs were studied in F1, F2a and F2b offspring. Developmental milestones were evaluated in F1 post weanlings and ano-genital distance was measured in F2a pups. Necropsies were done on all rats. Implantation sites in F0 and F1 females were recorded. Selected organs were weighed in adult rats and weanlings and histopathology including ovarian follicle staging (only F1) was performed in a number of organs of F0 and F1 parental rats.
5.2	**Results and discussion**	No changes in clinical behaviour and appearance of parental rats were evident up to 12,000 ppm. At 12,000 ppm increased water intake was seen in two F1 females during lactation. No adverse effects on body weights were evident in F0 rats up to 3000 ppm and F1 rats at 750 ppm. In 12,000 ppm F0 and F1 rats statistically significantly decreased body weights were noted. At necropsy this led to some emaciated F1 females, which showed partly also a dilated stomach and/or caecum. A statistical significant decrease in body weight gain was noted in lactating 3000 ppm F1 females from Day 0 p.p. to Day 4 p.p. At 12,000 ppm F1 females ingested less diet as controls. Nevertheless the test intake corresponded to roughly theoretical dose factor. There were statistically significantly increased relative weights of the adrenals and spleen in F1 females, which were not adverse as histological correlates are missing. At 12,000 ppm increased weights of the seminal vesicles were noted in F1 males. Examinations on sperms and evaluations of oestrus cycle revealed no treatment-related effect. Histopathology examination revealed treatment-related findings in the ovaries, vagina, liver and kidneys partly from 3000 ppm onwards as follows: At 12,000 ppm ovarian atrophy, increased metoestrus, decreased dioestrus and atrophy of the vaginal epithelium appeared in F0 and F1 females. Histopathological evaluations of ovarian follicles and corpora lutea revealed a statistically significant decrease in the number of growing follicles and corpora lutea in F1 rats treated at 12,000 ppm. These findings are discussed as possible secondary due to weight loss and are correlated with reduced ovary weights and/or smaller ovaries. In the liver, periportal cytoplasmic change, often coincided with reduced hepatocellular glycogen storage, was increasingly found in 12,000 ppm males of both generations. Simultaneously, periportal fat storage was reduced in favour of a more diffuse pattern. In contrast, adaptive periportal hypertrophy/eosinophilia occurred in F0 females at 12,000 ppm and in F1 females increasingly at 3000 ppm and above. At 12,000 ppm, increased relative liver weights occurred in females. Hepatocellular glycogen storage was reduced in both generations at 12,000 ppm. Changes in the fat storage became slightly evident in F1 females at 3000 ppm and above. These liver changes might also reflect secondary catabolic effects in course of a significant body weight loss in high dose animals and are associated with decreased liver weights in 3000 and 12,000 ppm F1 males. In the kidneys, papillary necroses were found in both genders of the F1

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

		generation at 12,000 ppm. Simple dilation of the papillary tubules was increased at 12,000 ppm in both male generations and in the female F1 generation at 3000 ppm and above. These findings are interpreted as adverse. Brownish inclusions in the proximal tubules and dilated cortico-medullary tubules were only found in females and raised at 12,000 ppm in both generations, a small number of F1 females also showed dilated cortico-medullary tubules at 3000 ppm. Secondary changes belonging to chronic progressive nephropathy (CPN) either increased (F0 females: basophilic tubules) or decreased (F0/F1 males: hyaline casts/dilated tubules; F1 males: basophilic tubules) under high dose treatment. In 12,000 ppm F1 females, relative kidney weights were increased. Investigation of animals without progeny did not demonstrate any compound-related aetiology. The parameters of the reproductive performance such as insemination, fertility, gestation and rearing indices as well as gestation length were not influenced by the treatment with the test substance up to 12,000 ppm. There was no test substance-related reduction in viability and lactation indices up to 12,000 ppm. At 12,000 ppm F2a pups exhibited respiration sounds and blue discolorations. At 12,000 ppm depressed pup and litter weights occurred in all generations. At 3000 ppm slightly reduced body weights were observed for female F2b pups. The occurrence of developmental milestones (balano-preputial separation and vaginal opening) was delayed in 12,000 ppm F1 rats. No effect was seen at measurements of the ano-genital distance in F2a pups. At 12,000 ppm more autolytic F2a pups were found than in the other groups. The spleen and thymus weights were decreased in nearly all pup generations at 12,000 ppm.	
5.3	**Conclusion**	The NOAEL for the reproduction is at 750 ppm (47 mg/kg bw/day) based on effects on pup weights (F2b). The parental NOAEL is at 750 ppm (64 mg/kg bw/day) based on body weight depression during lactation (F1).	
5.3.1	LO(A)EL	LOAELs for pup effects are based on the lowest maternal dose during gestation/lactation (Table A6_8_2-2).	
5.3.1.1	F0 males	12,000 ppm ≅ 1043 mg/kg bw/day, reduced bw, liver + kidney effects	
5.3.1.2	F0 females	12,000 ppm ≅ 1190 mg/kg bw/day, reduced bw, liver + kidney + ovarian effects	X
5.3.1.3	F1 males	3000 ppm ≅ 248 mg/kg bw/day, reduced bw, liver + kidney effects	X
5.3.1.4	F1 females	3000 ppm ≅ 298 mg/kg bw/day, reduced bw, liver + kidney effects	
5.3.1.5	F1 pups	12,000 ppm ≅ 862 mg/kg bw/day, reduced pup/litter weight, reduced spleen and thymus weights	
5.3.1.6	F2a pups	12,000 ppm ≅ 982 mg/kg bw/day, reduced bw, liver + kidney effects	X
5.3.1.7	F2b pups	3000 ppm ≅ 195 mg/kg bw/day, reduced bw	
5.3.2	NO(A)EL	NOAELs for pup effects are based on the lowest maternal dose during gestation/lactation (Table A6_8_2-2).	

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

5.3.2.1	F0 males	3000 ppm ≅ 248 mg/kg bw/day
5.3.2.2	F0 females	3000 ppm ≅ 288 mg/kg bw/day
5.3.2.3	F1 males	750 ppm ≅ 75 mg/kg bw/day
5.3.2.4	F1 females	750 ppm ≅ 90 mg/kg bw/day
5.3.2.5	F1 pups	750 ppm ≅ 54 mg/kg bw/day
5.3.2.6	F2a pups	3000 ppm ≅ 235 mg/kg bw/day
5.3.2.7	F2b pups	750 ppm ≅ 47 mg/kg bw/day
5.3.3	Reliability	[redacted]
5.3.4	Deficiencies	No

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/12/2007
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*

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

Remarks

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

Table A6_8_2-1. Table for animal assignment for mating

Test group	Dose in diet [a] (ppm)	Animals/group			
		F0 Males	F0 Females	F1 Males	F1 Females
Control	0	25	25	25	25
Low (LDT)	750	25	25	25	25
Mid (MDT)	3000	25	25	25	25
High (HDT)	12000	25	25	25	25

a Diets were administered from beginning of the study until sacrifice

Table A6_8_2-2. Test substance intake by dams during gestation and lactation

Observation in study days	Dietary concentration (ppm)		
	750	3000	12000
F0 Females [a)]			
Mean test substance consumption day 14 to 20 p.c. (mg/kg body weight/day)	**54.2** ±3.08	**216.8** ±14.60	**861.8** ±85.46
Mean test substance consumption day 0 to 4 p.p. (mg/kg body weight/day)	**89.2** ±32.97	**320.7** ±110.53	**1385.8** ±431.38
F1 Females [b)] →F2a			
Mean test substance consumption day 14 to 20 p.c. (mg/kg body weight/day)	**55.8** ±7.55	**235.3** ±35.55	**982.3** ±199.80
Mean test substance consumption day 0 to 4 p.p. (mg/kg body weight/day)	**83.0** ±31.65	**345.1** ±125.47	**1582.8** ±525.45
F1 Females [c)] →F2b			
Mean test substance consumption day 14 to 20 p.c. (mg/kg body weight/day)	**46.6** ±6.78	**195.1** ±24.36	**773.4** ±100.17
Mean test substance consumption day 0 to 4 p.p. (mg/kg body weight/day)	**86.7** ±27.61	**279.7** ±84.01	**1495.3** ±417.14

5Section A6.8.2 Multi-Generation Reproduction Toxicity Study

Annex Point IIA VI.6.8.2 6.8.2 Oral two-generation study in the rat

Table A6_8_2-3. Summary of remarkable study findings

Dose ppm	F0 rearing F1			F1 rearing F2a			F1 rearing F2b		
	750	3000	12000	750	3000	12000	750	3000	12000
Parental Animals									
Body weights: Premating			↓			↓	-	-	-
Body weights: Gestation			↓			↓			↓
Body weights: Lactation			↓		↓	↓		↓	↓
Food intake: Premating						↓F	-	-	-
Developemtal milestones	-	-	-			→	-	-	-
Necropsy									
Liver weights#								↓M	↓M
Liver weights ###			↑F						↑F
Seminal vesicles weight#									↑
Ovaries weight#			↓	-	-	-			↓
Ovaries diminished in size			yes	-	-	-			
Ovaries growing follicles	-	-	-						↓
Ovaries corpora lutea	-	-	-						↓
Stomach/cecum dilated									yesF
Emaciation									yesF
Ovary atrophy/changed cycle			yesF						YesF
Vagina epithelium athrophy			yesF						yesF
Kidney, adrenals, spleen weight ###									↑F
Liver hypertrophy			yesF					yesF	yesF
Liver reduced glycogen			yes						yes
Liver fat deposition changed			yes					yesF	yes
Kidney necrosis									yes
Kidney simple tubulus dilation								yesF	yes
Kidneys tubulus epithel inclusion			↑F						↑F
Tubulus dilation			yesF					yesF	yesF
Kidney basophilic tubules			yesF						yesM
Hyaline casts/tubulus dilation			yesM						↓M
Litter/Pup Data									
Pup weights			↓			↓		↓	↓
Litter weights			↓						↓
Clinical signs						yes			
Spleen weights##			↓			↓			↓
Thymus weights##			↓			↓			↓

↑ = increased
↓ = decreased
→ = delayed
- = not measured
# = absolute and relative; ## = absolute and/or relative; ### = relative
yes = finding present
M = males only; F = females only

Section 6.9 **Annex Point IIIA VI. 1**	**Neurotoxicity**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
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	20/10/2008	
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 A6.12 Human Case Report

Annex Point IIA VI.6.9.1 6.12.1 Medical surveillance data on manufacturing plant personnel

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted] (2006), Medical statement – chlorocresol (CMK)
1.2	**Data protection**	Yes
1.2.1	Data owner	Lanxess Deutschland GmbH
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA.
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	CMK
3.2	**Persons exposed**	Workers employed in the Alkylation plant [redacted]
3.3	**Examinations**	Regularly (for most workers every second year) a medical examination based on [redacted] rules is performed including e.g. medical history, physical examination, lung function, ECG/Ergometry, vision-testing, audiometry, laboratory examinations of blood and urine as well as a biomonitoring (measuring of working substances in blood and urine). In the biomonitoring investigations phenol has regularly been determined in urine of workers since 1997. Moreover o-, m-, p- cresol as well as o-, m-, p-chlorophenol was determined.
		4 RESULTS
4.1	**Results of examinations**	CMK is handled by workers employed in the Alkylation plant at [redacted] Biomonitoring showed that in case of routine handling of CMK with required protection devices cresols, phenols as well as chlorophenols were in all cases below the limiting value. Occupational medical surveillance did not reveal any health effects which could be derived to be from a possible CMK exposure.
4.2	**Conclusion**	No problems related to handling / production of CMK were reported.

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.1 6.12.1 Medical surveillance data on manufacturing plant personnel

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12.2 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Allergic phlebitis

Official use only

1 REFERENCE

1.1	**Reference**	Ainley, E.J., Mackie, I.G., Macarthur, D. (1977): Adverse reaction to chlorocresol-preserved heparin *Lancet* **1**: 705, 1977 (published)

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Mucous heparin, preserved with 0.15% chlorocresol
3.2	**Persons exposed**	
3.2.1	Sex	1 female
3.2.2	Age/weight	21 years
3.2.3	Known Diseases	No data
3.2.4	Number of persons	1
3.2.5	Other information	Heparin-treatment after deep-vein thrombosis and sub-sequent pulmonary embolus after cholecystectomy
3.3	**Exposure**	Intravenous
3.3.1	Reason of exposure	Treatment of deep-vein thrombosis
3.3.2	Frequency of exposure	Two
3.3.3	Overall time period of exposure	No data
3.3.4	Duration of single exposure	6 hours
3.3.5	Exposure concentration/dose	5000 units
3.3.6	Other information	-
3.4	**Examinations**	Clinical examinations. Intradermal skin testing with chlorocresol-preserved and preservative-free heparin.
3.5	**Treatment**	Chlorocresol-preserved heparin was replaced with chlorocresol-free heparin.
3.6	**Remarks**	-

4 RESULTS

4.1	**Clinical Signs**	During administration of heparin (preserved with chlorocresol): o severe burning pain at the injection site and the veins of the forearm and arm. Shortly afterwards the patient felt nauseated and light-headed and became drowsy with pallor and sweating. o Two days later a bright red papule was present at the injection site.

Section A6.12.2 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Allergic phlebitis

		o - Intradermal skin application preserved heparin produced r reaction at the application site.
4.2	**Results of examinations**	The reaction was considered as hypersensitivity to chlorocresol.
4.3	**Effectivity of medical treatment**	No data
4.4	**Outcome**	Hypersensitivity to chlorocresol.
4.5	**Other**	-
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	A 21-year old female patient received heparin-treatment after deep-vein thrombosis and sub-sequent pulmonary embolus after cholecystectomy. During administration patient experienced severe burning pain at the injection site and the veins of the forearm and arm. Shortly afterwards the patient felt nauseated and light-headed and became drowsy with pallor and sweating. Two days later a bright red papule was present at the injection site. Intradermal tests with preserved and preservative-free heparin were conducted.
5.2	**Results and discussion**	Hypersensitivity reaction after intraveneous application of chlorocresol-preserved heparin. Considered as an irritant or allergic phlebitis. After replacement with chlorocresol-free heparin no clinical signs or effects occurred.
5.3	**Conclusion**	Recommendation of preservative-free heparin.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Hypersensitivity

			Official use only
		1 REFERENCE	
1.1	**Reference**	Hancock, B.W. and Naysmith, A. (1975): Hypersensitivity to Chlorocresol-preserved Heparin *British Medical Journal* : 746 - 747, 1975 (published)	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Mucous heparin, preserved with 0.15% chlorocresol.	
3.2	**Persons exposed**		
3.2.1	Sex	Case 1: female. Case 2: male. Cases 3-9: No data.	
3.2.2	Age/weight	Case 1: 35 years; weight: no data. Case 2: 55 years; weight. no data. Cases 3-9: No data.	
3.2.3	Known Diseases	Case 1: no data. Case 2: no data. Cases 3-9: Suspected myocardial infarction	
3.2.4	Number of persons	9	
3.2.5	Other information	-	
3.3	**Exposure**		
3.3.1	Reason of exposure	Cases 1, 2: Treatment of deep-vein thrombosis (concomitant with pulmonary embolus) Cases 3-9: prophylactic treatment	
3.3.2	Exposure route	Case 1, 2: intraveneous Case 3-9: subcutaneous	
3.3.3	Frequency of exposure	Case 1: 2 Case 2: 1 Case 3-9: 2/day	
3.3.4	Overall time period of exposure	No data	
3.3.5	Duration of single exposure	No data	
3.3.6	Exposure concentration/dose	10,000 units	X
3.3.7	Other information	-	
3.4	**Examinations**	Clinical examinations and intradermal skin testing with chlorocresol-preserved and preservative-free heparin.	
3.4.1	Results of intradermal skin	Case 1: positive reactions to both chlorocresol-preserved and preservative-free heparin	

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Hypersensitivity

	testing	Case 2: No reaction with preservative-free heparin Case 3-9: In four patients no reaction with preservative-free heparin.	
3.5	**Treatment**	Case 1: Anticoagulation with warfarin. Case 2: None. Case 3-9: No data.	
3.6	**Remarks**	Case 2: Further treatment with preservative-free heparin.	
		4 RESULTS	
4.1	**Clinical Signs**	During administration of heparin (preserved with chlorocresol): Case 1: patient collapsed immediately after second dose of chlorocresol-preserved heparin. Additional clinical signs were: Pallor, sweating, hypotension, tachycardia Case 2: During 1 hour after application patient developed nasal congestion, profuse sweating and a generalised urticarial rash, that faded within a few hours. Case 3: Within a few hours of the first and subsequent injections an indurated erythematous reaction developed at the site of injection.	
4.2	**Results of examinations**	The reaction was considered as hypersensitivity to chlorocresol.	
4.3	**Effectivity of medical treatment**	No data	
4.4	**Outcome**	Hypersensitivity to chlorocresol.	
4.5	**Other**	-	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	A 21-year old female patient received heparin-treatment after deep-vein thrombosis and sub-sequent pulmonary embolus. Seven patients received prophylactic treatment with chlorocresol-preserved heparin. Intradermal tests with preserved and preservative-free heparin were conducted.	X
5.2	**Results and discussion**	Hypersensitivity reaction after intraveneous and subcutaneous application of chlorocresol-preserved heparin.	
5.3	**Conclusion**	Treatment may be continued with preservative-free heparin.	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21/10/2008
Materials and Methods	[redacted]

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Hypersensitivity

Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Poisoning

Official use only

		1 REFERENCE
1.1	**Reference**	Joppich G. (1960): Tödliche Vergiftung durch Sagrotan bei Säuglingen *Deut. Med. J.*:11; 20 -21, 1960 (published)
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Sagrotan (disinfectant, contains CMK and chloroxylenol)
3.2	**Persons exposed**	
3.2.1	Sex	Males
3.2.2	Age/weight	Age: approx. 3 month; weight: no data
3.2.3	Known Diseases	No data
3.2.4	Number of persons	2
3.2.5	Other information	Twins; shortly breastfeed, feeding with condensed milk
3.3	**Exposure**	Oral
3.3.1	Reason of exposure	Homicidal intent.
3.3.2	Frequency of exposure	No data.
3.3.3	Overall time period of exposure	No data
3.3.4	Duration of single exposure	No data
3.3.5	Exposure concentration/dose	No data
3.3.6	Other information	Sagrotan was administered with milk.
3.4	**Examinations**	Clinical examinations, autopsy
3.5	**Treatment**	Not possible, since both patients died shortly after arrival in hospital.
3.6	**Remarks**	Signs of intoxication.
		4 RESULTS
4.1	**Clinical Signs**	Direct after exposure: vomiting. 1st case: poor general condition combined with diarrhoea, vomiting, somnolence and circulatory collapse with cyanosis and unconsciousness. 2nd case: moribund condition combined with circulatory collapse with cyanosis and unconsciousness, but no gastro-intestinal effects
4.2	**Results of examinations**	Autopsy 1st case: moderate gastritis and enteritis, liver damage (was considered as a long-term effect) 2nd case: stomach contained fluid with a cresolic odour

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Poisoning

		Chemical analysis of stomach content: cresol
4.3	**Effectivity of medical treatment**	Not applicable.
4.4	**Outcome**	Fatal: Both children died within a few hours after application.
4.5	**Other**	-
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Two male twin brothers (3 months of age) were poisoned with Sagrotan-containing milk, applied by their mother. The amount of Sagrotan is not known. Mother stated that she had added "a shot of Sagrotan" to the milk.
5.2	**Results and discussion**	According to the mother, clinical signs of poisoning occurred 3-4 hours after administration of the poisoned milk. Clinical signs consisted of vomiting, diarrhoea, whining and moaning. Both children arrived at the hospital in a moribund state. Somnolence, vomiting and cyanosis were observed. Death occurred after circulatory collapse. Post mortem examination revealed moderate gastritis and enteritis and cresolic odour of the gastric content.
5.3	**Conclusion**	These fatal cases of poisoning with Sagrotan cannot be clearly ascribed to CMK due to the more complex composition of the disinfectant.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	23/10/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Acute poisoning - survey of cases

Official use only

		1 REFERENCE
1.1	**Reference**	Wiseman, H.M. *et al.* (1980): Acute poisoning to Wright´s Vaporizing Fluid *Postgraduate Medical Journal* : 56, 166 - 168 (1980) (published)
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Wright´s Vaporizing Fluid old formulation: 90% (v/v) cresol new formulation: 10% (v/v) chlorocresol
3.2	**Persons exposed**	
3.2.1	Sex	No data
3.2.2	Age/weight	Adults (14-75 years) and children (2 month - 9 years); weight no data
3.2.3	Known Diseases	No data
3.2.4	Number of persons	311 (286 children)
3.2.5	Other information	-
3.3	**Exposure**	
3.3.1	Reason of exposure	Wright´s vaporization fluid was recommended for the relief of soreness and congestion of the upper respiratory tract. The vapour itself is apparently free of adverse effects. Accidental exposure of un-volatilised fluid due to non-recommended or improper use
3.3.2	Exposure route	oral and dermal
3.3.3	Frequency of exposure	No data
3.3.4	Overall time period of exposure	No data
3.3.5	Duration of single exposure	No data
3.3.6	Exposure concentration/dose	No data
3.3.7	Other information	-
3.4	**Examinations**	Clinical signs
3.5	**Treatment**	Mainly supportive: - after spillage skin should be washed with water for up to 15 minutes, followed by repeated application of castor - after ingestion: application of a milky drink, activated charcoal or castor oil, followed by a mild purge (e.g. sodium sulphate) - after respiration: administration of oxygen, adjustment of intravenous fluids, antibiotics and hydrocortisone may help to prevent stricture

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Acute poisoning - survey of cases

formation. Diazepam treatment for anti-convulsion, in severe cases: dialysis

3.6 Remarks

4 RESULTS

4.1 Clinical Signs

Type A symptoms: superficial skin burns only (on hands, fingers, face and lips) from liquid having been spilt,

Type B symptoms: inflammation, burning sensation in mouth and throat, sometimes vomiting, abdominal pain, dysphagia lasting some days

Type C symptoms: severe poisoning often with blistering and ulceration of oral mucosa, oedema of pharynx and glottis, salivation and coughing, abdominal pain, vomiting, haematemesis, dyspnoea, pneumonia, cough, collapse, sometimes with phenolic staining of urine with liver and kidney damage

4.2 Results of examinations

(results only for cases with follow up information)

4.2.1 Results by incidence of symptoms

	Number (%) cases				
	no symptoms	type A	type B	type C	Total number of cases
Children	64	54	31	11*	160
Adults	3	1	6	2	12
Total	67 (38)	55 (31)	37 (21.5)	13 (7.5)	172

* includes one death

4.2.2 Results by formulation type

	Symptoms				
Formula-tion	None	type A	type B	type C	Total number
90% cresol	8	18	11	6	43
10 % chloro-cresol	28	4	10	3*	45
unknown	14	12	8	1	35
Total	50	34	29	10	123

* includes one death

4.3 Effectivity of medical treatment

-

4.4 Outcome

One child died, all other cases resolved without long-term effects.

4.5 Other

-

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

5.2 Results and discussion

Of 160 children and 12 adults, 12.5% had moderate symptoms, 7.5% had severe symptoms and one child died. With the 90% cresol

Section A6.12 Human Case Report

Annex Point IIA VI.6.9.2 6.12.2 Acute poisoning - survey of cases

	formulation over 50% of the persons exhibit skin burns or moderate systemic symptoms. With the 10% chlorocresol formulation over 50% of the patients had neither symptoms nor exhibited skin burns. However, there was no significance difference in the incidence of severe systemic symptoms between the two formulations. Even the new formulation can cause severe poisoning.
5.3 Conclusion	To prevent further accidental intoxication or misuse measures like child-resistant containers and improved labelling have to be considered.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	23/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12 Health records

Annex Point IIA VI.6.9.3 6.12.3 Health records, both from industry and any other available sources

Official use only

		1 REFERENCE
1.1	**Reference**	Leng, G. (2006), Medical statement – chlorocresol (CMK)
1.2	**Data protection**	Yes
1.2.1	Data owner	Lanxess Deutschland GmbH
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I/IA.
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	CMK
3.2	**Persons exposed**	Workers employed in the Alkylation plant [redacted]
3.3	**Examinations**	Regularly (for most workers every second year) a medical examination based on [redacted] rules is performed including e.g. medical history, physical examination, lung function, ECG/Ergometry, vision-testing, audiometry, laboratory examinations of blood and urine as well as a biomonitoring (measuring of working substances in blood and urine). In the biomonitoring investigations phenol has regularly been determined in urine of workers since 1997. Moreover o-, m-, p- cresol as well as o-, m-, p-chlorophenol was determined.
		4 RESULTS
4.1	**Results of examinations**	CMK is handled by workers employed in the [redacted].
		Biomonitoring showed that in case of routine handling of CMK with required protection devices cresols, phenols as well as chlorophenols were in all cases below the limiting value.
		Occupational medical surveillance did not reveal any health effects which could be derived to be from a possible CMK exposure.
4.2	**Conclusion**	No problems related to handling / production of CMK were reported.
		No adverse reactions to CMK are on record.

Section A6.12 Health records

Annex Point IIA VI.6.9.3 6.12.3 Health records, both from industry and any other available sources

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	[redacted]
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12.4 **Annex Point IIA VI.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:	[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	28/10/2008	
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 A6.12.5 **Annex Point IIA VI.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:	[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	28/10/2008	
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 A6.12 Allergy observation

Annex Point IIA VI.6.9.6 6.12.6 Patch tests in eczema patients

Official use only

		1 REFERENCE
1.1	**Reference**	Angelini, G. *et al.* 1975: Contact dermatitis in patients with leg ulcers *Contact dermatitis* **1**: 81-87, 1975 (published)
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Test material**	2% chlorocresol in petrolatum
3.2	**Type of study**	Patch tests; clinical study
3.3	**Method of data collection**	Clinical study
3.4	**Test Persons /Study Population**	
3.4.1	Selection criteria	Patients with leg ulcers (stasis dermatitis)
3.4.2	Number of test persons per group/ cohort size	127
3.4.3	Sex	No data
3.4.4	Age	No data
3.4.5	Known Diseases	Patients with stasis dermatitis
3.5	**Controls**	No
3.6	**Administration/ Exposure**	
3.6.1	Exposure route	Patch tests; topical application
3.6.2	Exposure situation	-
3.6.3	Exposure concentrations	2% in petrolatum
3.6.4	Methods to determine exposure	Clinical examination
3.6.5	Postexposure period	No data
3.7	**Examinations**	
3.7.1	Parameters	Clinical signs
3.8	**Further Remarks**	-
		4 RESULTS
4.1	**Results of examinations**	
4.1.1	Positive reactions	1 (= 0.8 %)
4.1.2	Clinical signs	Contact dermatitis

Section A6.12 Allergy observation

Annex Point IIA VI.6.9.6 6.12.6 Patch tests in eczema patients

4.1.3	Result / outcome	Sensitivity against test substance
4.2	**Other**	-
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	In a clinical allergological study in patients with leg ulcers, patch tests were performed with a large series of substances (incl. chlorocresol), to examine the sensitising potential of the test substances.
5.2	**Results and discussion**	In one of 127 patch tests performed with chlorocresol, a positive reaction was observed.
5.3	**Conclusion**	CMK has a low sensitisation potential in humans.
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	No
5.4	**Other**	-

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27/10/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Allergic skin reaction

Official use only

		1 REFERENCE
1.1	**Reference**	Oleffe J.A., Blondeel A., de Coninck A.. (1979): Allergy to chlorocresol and propylene glycol in a steroid cream to chlorocresol-preserved heparin *Contact Dermatitis* **5**: 53-54, 1979 (published)
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Steroid cream containing chlorocresol; steroid ointment containing chlorocresol and propylene glycol
3.2	**Persons exposed**	
3.2.1	Sex	Case 1: Male Case 2: female
3.2.2	Age/weight	Case 1: 24 years, weight: no data Case 2: 40 years, weight: no data
3.2.3	Known Diseases	Case 1: Contact dermatitis to chinoform Case 2: eczema
3.2.4	Number of persons	2
3.2.5	Other information	Both patients were treated with the chlorocresol and/or propylenglycol containing steroid cream or ointment.
3.3	**Exposure**	Dermal
3.3.1	Reason of exposure	Case 1: treatment of contact dermatitis Case 2: treatment of eczema
3.3.2	Frequency of exposure	Multiple.
3.3.3	Overall time period of exposure	No data.
3.3.4	Duration of single exposure	No data.
3.3.5	Exposure concentration/dose	No data.
3.3.6	Other information	-
3.4	**Examinations**	Clinical examinations. Case 1: Patch tests with the pharmaceutical test series of the Belgian Contact Dermatitis group. Case 2: Patch tests with steroid cream and ointment, and with various components of both these formulations.
3.5	**Treatment**	No data.
3.6	**Remarks**	-

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Allergic skin reaction

		4 RESULTS	
4.1	**Clinical Signs**	Case 1: exacerbation of dermatitis. Case 2: deterioration of eczema.	
4.2	**Results of examinations**	Case 1: Patch test readings at 48 and 96 hours showed sensitivity to chlorocresol and propylene glycol. Case 2: Patch test readings at 48 hours showed only a slight sensitivity to propylenglycol and sensitivity to chlorocresol from one pharmaceutical company, whilst the 96 hour reading reveal a skin sensitivity to both chlorocresol and propylene glycol substances obtained from different manufacturers. The chlorocresol normally used for pharmacological patch test series produced also a positive reaction at 48 hours.	
4.3	**Effectivity of medical treatment**	No data	
4.4	**Outcome**	Allergy to chlorocresol and propylene glycol.	
4.5	**Other**	-	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	A 24-year old male patient received treatment with a chlorocresol and propylene glycol containing steroid cream after contact dermatitis. During administration a worsening of the dermatitis occurred. Patch tests with the pharmaceutical test series of the Belgian Contact Dermatitis group were performed. A 40-year old female nurse was treated with the chlorocresol containing steroid cream after exhibiting an eczema. The eczema detoriated during treatment. Patch tests with steroid cream and ointment, and with various components of both these formulations were performed.	
5.2	**Results and discussion**	Both patients exhibited allergic reaction to chlorocresol and propylene glycol contained in a steroid cream. In one case, the sensitivity to chlorocresol might be induced by an ECG paste containing chloroxylenol. In the second case it might be possible that the steroid in the cream masked the skin reaction at least for up to 48 hours. There was also a difference in the reactions to chlorocresol and propylene glycol obtained from different manufacturers.	X
5.3	**Conclusion**	-	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Allergic skin reaction

	[redacted]
Conclusion	[redacted]
Remarks	

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Contact allergy from chlorocresol

Official use only

		1 REFERENCE
1.1	**Reference**	Lewis PG & Emmett EA.. (1987): Irritant dermatitis from tri-butyl tin oxide and contact allergy from chlorocresol *Contact Dermatitis* **17**: 129-132, 1987 (published)
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	CMK containing cortico-steroid cream
3.2	**Persons exposed**	
3.2.1	Sex	Male
3.2.2	Age/weight	39 years, weight: no data.
3.2.3	Known Diseases	Hypertension.
3.2.4	Number of persons	1
3.2.5	Other information	-
3.3	**Exposure**	Dermal
3.3.1	Reason of exposure	Treatment of contact dermatitis caused by an anti fouling paint containing tri-butyl tin oxide (TBTO).
3.3.2	Frequency of exposure	No data.
3.3.3	Overall time period of exposure	No data.
3.3.4	Duration of single exposure	No data.
3.3.5	Exposure concentration/dose	No data.
3.3.6	Other information	At least 4 other workers developed dermatitis after using a TBTO containing paint.
3.4	**Examinations**	Clinical examinations, patch tests.
3.5	**Treatment**	No data.
3.6	**Remarks**	No cross sensitisation with 4-chloro-3,5-xylenol was detected.
		4 RESULTS
4.1	**Clinical Signs**	Erythematous reaction on the legs
4.2	**Results of examinations**	Patch tests Allergic contact dermatitis to CMK present in the steroid cream, used for TBTO allergy treatment.
4.3	**Effectivity of medical treatment**	No data
4.4	**Outcome**	Allergy to chlorocresol

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Contact allergy from chlorocresol

4.5	**Other**	-
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	A 39-year old male shipwright received treatment with a CMK containing cream after development of a corrosive contact dermatitis to tri-butyl tin oxide. Patch tests with several creams, serial dilutions of TBTO and the North American Contact Dermatitis Group Standard, vehicle and preservative and fragrance trays were performed. Additional patch tests with CMK and the steroid cream were performed after resolution of the dermatitis.
5.2	**Results and discussion**	Patch tests showed a contact allergy to CMK.
5.3	**Conclusion**	Initial corrosive dermatitis in the patient was induced by TBTO-containing paint. The second dermatitis was caused by CMK contained in the steroid cream for treatment.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	28/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Hypersensitivity to chlorocresol

Official use only

		1 REFERENCE
1.1	**Reference**	Hancock, BW & Naysmith, A. (1975): Hypersensitivity to Chlorocresol-preserved Heparin *British Medical Journal*: 746-747, 1975 (published)
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	CMK preserved heparin
3.2	**Persons exposed**	
3.2.1	Sex	Case 1: female Case 2: male Cases 3-9: no data
3.2.2	Age/weight	Case 1: 35 years; weight: no data Case 2: 55 years; weight: no data Case 3-9: no data
3.2.3	Known Diseases	Case 1: deep vein thrombosis, pulmonary embolus Case 2: deep vein thrombosis, pulmonary embolus Case 3-9: suspected myocardial infarction
3.2.4	Number of persons	9
3.2.5	Other information	-
3.3	**Exposure**	intravenous, subcutaneous (cases 3-9)
3.3.1	Reason of exposure	Cases 1-2: Treatment of deep vein thrombosis Cases 3-9: suspected myocardial infarction
3.3.2	Frequency of exposure	Case 1: 2 Case 2: 1 Case 3-9: several (twice daily)
3.3.3	Exposure concentration/dose	Case 1: 10,000 units Case 2: 10,000 units Case 3-9: 10,000 units
3.3.4	Other information	-
3.4	**Examinations**	Clinical examinations, intradermal skin tests
3.5	**Treatment**	Case 1: further anticoagulation with warfarin Case 2: further anticoagulation with CMK-free heparin Case 3-9: no data.
3.6	**Remarks**	Case 1: spontaneous recovery after 30 minutes, without treatment. Case 2: Recovery within a few hours after application.

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Hypersensitivity to chlorocresol

		4 RESULTS
4.1	**Clinical Signs**	Case 1: patient collapsed with pallor, sweating, hypotension, and tachycardia. Case 2: nasal congestion, profuse sweating, generalised urticarial rash that faded within a few hours. Cases 3-9: indurated erythematous reaction at the injection site.
4.2	**Results of examinations**	Intradermal skin testing: Case 1: positive reactions to CMK-containing and CMK-free heparin. Case 2: no reaction with preservative-free heparin Cases 3-9: 4 patients showed no response to preservative-free heparin.
4.3	**Effectivity of medical treatment**	No data
4.4	**Outcome**	Hypersensitivity to CMK.
4.5	**Other**	-
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Intradermal skin tests with preserved- and preservative-free heparin were performed.
5.2	**Results and discussion**	6 of the patients showed no response to preservative-free heparin. One patient showed also a positive response to preservative free heparin.
5.3	**Conclusion**	Sensitivity reactions were considered to be caused by CMK. In one case patient was also sensitive to preservative-free heparin.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	28/10/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	[redacted]
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

Section A6.12.6 Allergy Report

Annex Point IIA VI.6.9.6 6.12.6 Hypersensitivity to chlorocresol

Remarks

Section A6.12.7 Specific treatment in case of an accident or poisoning

Annex Point IIA VI.6.9.7 6.12.7 Treatment of Poisoning

Official use only

		1 REFERENCE
1.1	**Reference**	Joppich G. (1962): Klinik und Behandlung der Sagrotanvergiftung *Deut. Med. J.*:22; 691 - 693, 1962 (published)
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Sagrotan (disinfectant, contains CMK)
3.2	**Persons exposed**	
3.2.1	Sex	1 male
3.2.2	Age/weight	Age: 2 years 4 month; weight: no data
3.2.3	Known Diseases	No data
3.2.4	Number of persons	1
3.2.5	Other information	Accidental exposure.
3.3	**Exposure**	Oral
3.3.1	Reason of exposure	Accident.
3.3.2	Frequency of exposure	1
3.3.3	Overall time period of exposure	No data
3.3.4	Duration of single exposure	No data
3.3.5	Exposure concentration/dose	Approx. 50 g
3.3.6	Other information	Shortly after exposure, vomiting and application of milk.
3.4	**Examinations**	Clinical examinations. Endoscopic examination of oesophagus (after recovery).
3.5	**Treatment**	Initial treatment: gastric lavage, followed by application of animal carbon and sodium sulphate. Permanent i.v. infusion of 10 % laevulose and Reducdyn. Treatment of coma hepatiticum: cation exchange. Potassium deficiency (caused by the cation exchange) was treated with a permanent infusion of Darrow's solution (i.v.). Treatment of second coma hepaticum: cation exchange and blood transfusion.
3.6	**Remarks**	-
		4 RESULTS
4.1	**Clinical Signs**	Directly after exposure: vomiting. 24 hours after exposure of Sagrotan, patient collapsed and became unconscious combined with muscle convulsions, cyanosis. Body

Section A6.12.7 Specific treatment in case of an accident or poisoning

Annex Point IIA VI.6.9.7 6.12.7 Treatment of Poisoning

		temperature rose up to 42 °C. The coma was considered as a coma hepatiticum due to liver damage. Since laevulose and Reducdyn infusion was not effective, cation exchange was performed. After a short period patient awaked. The potassium deficiency caused by the cation exchange was treated with a permanent infusion of Darrowsche solution (i.v.). After a few hours the collapse and unconsciousness recurred and was treated again with a cation exchange and additional blood transfusion. Body temperature decreases and diarrhoea occurred. Additional liver enlargement was observed.
4.2	**Results of examinations**	Clinical signs: poisoning due to oral exposure to Sagrotan. Endoscopic examination of oesophagus: only minor sparsely mucosa damages.
4.3	**Effectivity of medical treatment**	See 5.1.
4.4	**Outcome**	Survival
4.5	**Other**	Since the clinical signs differ from those of a phenol-based poisoning, it was considered that the effects were caused by the chlorine of CMK.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	A two years old male child drank accidentally Sagrotan. In hospital the child was treated by gastric lavage, followed by application of animal carbon and sodium sulphate. Also, a permanent i.v. infusion of 10 % laevulose and Reducdyn was given. 24 hours after exposure of Sagrotan, patient collapsed and became unconscious combined with muscle convulsions, cyanosis. Body temperature rose up to 42 °C. Coma was considered as a coma hepatiticum due to liver damage. Since laevulose and Reducdyn infusion was not effective, cation exchange was performed. After a short period patient awaked. The potassium deficiency caused by the cation exchange was treated with a permanent infusion of Darrow's solution (i.v.). After a few hours the collapse and unconsciousness recurred and must be treated again with a cation exchange and additional blood transfusion. Body temperature decreases and diarrhoea occurred. Additional liver enlargement was observed.
5.2	**Results and discussion**	Poisoning due to accidentally oral exposure of CMK containing disinfectant. The patient survived.
5.3	**Conclusion**	Sagrotan contains other ingredients (solvents, other phenolics) besides CMK. The observed toxicity cannot be clearly ascribed to CMK.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	15/12/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	

Section A6.12.7 Specific treatment in case of an accident or poisoning

Annex Point IIA VI.6.9.7 6.12.7 Treatment of Poisoning

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12.7 Specific treatment in case of an accident or poisoning

Annex Point IIA VI.6.9.7 6.12.7(02) First Aid Measures

Official use only

1 REFERENCE

1.1	**Reference**	Lanxess (2005):Safety Data Sheet 690981/13, revised version, date 2005-10-06

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 FIRST AID MEASURES

3.1	**General information**	Remove all contaminated clothing immediately. Also heed the risks to your own person.
3.2	**Following skin contact**	Wash the skin immediately with plenty of soap and water; cleaning immediately with polyethylene glycol 300 / ethanol (2:1(v/v)) or polyethylene glycol 400 and washing subsequently with plenty of soap and water would be more effective. If skin reactions occur, contact a physician.
3.3	**Following eye contact**	Open the eyelids and rinse for an adequate length of time with water. Consult an eye specialist immediately.
3.4	**Upon inhalation**	Bring accident victims out into the fresh air. If there is difficulty in breathing, medical attention should be obtained
3.5	**Upon swallowing**	Make the patient drink a large quantity of water, if possible with an addition of activated carbon, immediately and then at frequent intervals. The mouth should be rinsed out several times. Do not induce vomiting. Seek medical advice immediately.

4 INFORMATION FOR THE PHYSICIAN

4.1	**Therapeutic measures**	Basic aid, decontamination, symptomatic treatment.

Section A6.12.7 Specific treatment in case of an accident or poisoning

Annex Point IIA VI.6.9.7 6.12.7(02) First Aid Measures

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	15/12/2008
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*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*
Remarks	

Section A6.12.8 **Annex Point IIA VI.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:	[redacted]	X
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	28/10/2008	
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 6.13 **Annex Point IIIA VI. 2**	**Toxic effects on livestock and pets**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [X]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
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	16/12/08	
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 A6.15 **Annex Point IIB VI.6.7.1**	**Food and feedingstuffs studies**	
	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]	X
Undertaking of intended data submission [ ]		

Section A6.15 **Annex Point IIB VI.6.7.1**	**Food and feedingstuffs studies**
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*01/03/2013*
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 A8 **Subsection A8.6** **Annex Point IIA, VIII 8.6**	**Measures necessary to protect man, animals and the environment** OBSERVATIONS ON UNDESIRABLE OR UNINTENDED SIDE-EFFECTS, E.G. ON BENEFICIAL AND OTHER NON-TARGET ORGANISMS	
	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	*June 2013*	
Evaluation of applicant's justification		
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 A8 MEASURES NECESSARY TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

Subsection (Annex point)			Official use only
8.1 (IIA, VIII 8.1)		**Recommended methods and precautions concerning handling, use, storage, transport or fire**	
8.1.0	**Methods and precautions concerning placing on the market**	Please refer to the information given below.	
8.1.1	**Methods and precautions concerning handling and use of the active substance**	Personal protection equipment: Suitable protective clothing, including protective gloves (e.g. Polychloroprene-CR, Polyvinyl chloride-PVC) and closely fitting goggles must be worn. In case of dust formation respiratory protection (combination filter against organic vapours and particles, e.g. DIN 3181 ABEK/P2) must be worn. Take measures to prevent dust formation; remove any dust with air extractors where it is formed. Vent waste air only via suitable separators or scrubbers. Take precautionary measures against electrostatic charges according to the equipment used and the way the product is handled and packaged. Avoid inhaling aerosols and vapours. Avoid contact with eyes and skin. Keep away from food and drink stuffs. Do not eat, drink or smoke at work. Wash hands before breaks and at end of work and use skin-protecting ointment. After contamination with product change the gloves immediately and remove them according to relevant national and local regulations. (Reference: Anonymous, 2005)	
8.1.2	**Methods and precautions concerning storage of the active substance**	Store in original container. Protect from moisture and do not expose to temperatures above 40 °C. VCI Storage class: 11 (Reference: Anonymous, 2005) Suitable container materials for the direct contact with the active substance: paper, glass, PE, steel (zinc coated) and high-grade steel. (Reference: Kraus. 2006d)	
8.1.3	**Methods and precautions concerning transport of the active substance**	Transport information: Environmentally hazardous substance (GGVSE, RID/ADR). Risk of serious damage to eyes. Avoid heat above 40 °C. Keep dry. Keep separated from foodstuffs. Transport code number: UN-No.: 3077 (Reference: Anonymous, 2005)	
8.1.4	**Methods and precautions concerning fire of the active substance**	Extinguishing media: All extinguishing materials are suitable. Firemen have to wear self-contained breathing apparatus. Fight fire in early stages if safe to do so. Containers at risk from fire should be cooled with water and, if possible, removed from the danger area. When extinguishing with water pay attention to caustic burns. Do not let enter contaminated extinguishing water into the soil, groundwater or surface waters. (Reference: Anonymous, 2005)	

Section A8 MEASURES NECESSARY TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

8.2 (IIA, VIII 8.2) **In case of fire, nature of reaction products, combustion gases, etc.**

No thermal decomposition, no hazardous decomposition products and no hazardous reactions when stored and handled as directed.

Formation of carbon monoxide, carbon dioxide, hydrogen chloride and other toxic gases in the event of fire.

(Reference: Anonymous, 2005)

8.3 (IIA, VIII 8.3) **Emergency measures in case of an accident**

8.3.1 Specific treatment in case of an accident, e.g. first-aid measures, antidotes, medical treatment, if available

Personal precautions:

Wear personal protective equipment.

First aid measures:

GENERAL INFORMATION: Remove all contaminated clothing immediately. Also heed the risks to your own person.

FOLLOWING SKIN CONTACT: Wash the skin immediately with plenty of soap and water; cleaning immediately with polyethyleneglycol 300 / ethanol (2:1, v/v) or polyethyleneglycol 400 and washing subsequently with plenty of soap and water would be more effective. If skin reaction occurs, contact a physician.

FOLLOWING EYE CONTACT: Open the eyelids and rinse for an adequate length of time with water. Consult an eye specialist immediately.

UPON SWALLOWING: Make the patient drink a large quantity of water, if possible with an addition of activated carbon, immediately, and then at frequent intervals. The mouth should be rinsed out several times. Do not induce vomiting. Seek medical advice immediately.

UPON INHALATION: Bring accident victims out into the fresh air. If there is difficulty in breathing, medical attention should be obtained.

INFORMATION TO THE PHYSICIAN: Therapeutic measures: Basic aid, decontamination, symptomatic treatment.

(Reference: Anonymous, 2005)

8.3.2 Emergency measures to protect the environment

Personal precautions:

Wear personal protective equipment.

Environmental precautions:

Do not let enter into the soil, groundwater or surface waters.

Accidental release measures:

Take up mechanically, fill into labelled, closable containers. Ensure adequate ventilation/exhaust ventilation. Keep unauthorised persons away.

(Reference: Anonymous, 2005)

8.4 (IIA, VIII 8.4) **Possibility of destruction or decontamination following release in or on the following: (a) air, (b) water, including drinking water, and (c) soil**

Section A8 MEASURES NECESSARY TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

8.4.1	**Possibility of destruction or decontamination following release in the air**	The active substance CMK is a solid with a low vapour pressure. A contamination of the environmental compartment air is therefore unlikely after the release of CMK into the environment due to an accidental misuse.
8.4.2	**Possibility of destruction or decontamination following release in water, including drinking water**	No possibility of destruction or decontamination of CMK following its release in water can be mentioned. A chemical decontamination is not possible.
8.4.3	**Possibility of destruction or decontamination following release in or on soil**	Take up mechanically, fill into labelled, closable containers. Ensure adequate ventilation/exhaust ventilation. Keep unauthorised persons away. (Reference: Anonymous, 2005)
8.5 (IIA, VIII 8.5)		**Procedures for waste management of the active substance for industry or professional users**
8.5.1	**Possibility of re-use or recycling (IIA, VIII 8.5.1)**	Disposal considerations: If utilisation or recycling of the product is not possible, it should be disposed of according to the local regulations and laws, e.g. by incineration in a suitable plant. Contaminated, empty containers are to be treated in the same way as the contents. For disposal in the EU, the appropriate code according to the European Waste Catalogue (EWC) should be used. It is among the tasks of the polluter to assign the waste to waste codes specific to industrial sectors and processes according to the European Waste Catalogue. (Reference: Anonymous, 2005)
8.5.2	**Possibility of neutralisation of effects (IIA, VIII 8.5.2)**	Please refer to the disposal considerations given above.
8.5.3	**Conditions for controlled discharge including leachate qualities on disposal (IIA, VIII 8.5.3)**	Please refer to the disposal considerations given above.
8.5.4	**Conditions for controlled incineration (IIA, VIII 8.5.4)**	Please refer to the disposal considerations given above.
8.6 (IIA, VIII 8.6)		**Observations on undesirable or unintended side-effects, e.g. on beneficial and other non-target organisms** No undesirable or unintended side-effects on beneficial or other non-target organisms were observed.

Section A8 MEASURES NECESSARY TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

8.7 (IIIA, VIII 1)

Identification of any substances falling within the scope of List I or List II of the Annex to Directive 80/68/EEC on the protection of ground water against pollution caused by certain dangerous substances

Organohalogen compounds are covered by List I of the Annex to Directive 80/68/EEC.

Biocides and their derivatives are covered by List II of the Annex to Directive 80/68/EEC.

Section A8 MEASURES NECESSARY TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*June 2013*
Materials and Methods	
Results and discussion	
Conclusion	[redacted]
Reliability	
Acceptability	
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 A9 Classification and Labelling

Annex Point IIA, IX

Current classification / labelling according to Directive 1967/548/EEC:		
Hazard symbol:	Xn; N	
Indication of danger:	Harmful Dangerous for the environment	
Risk phrases:	R21/22:	Harmful in contact with skin and if swallowed.
	R41:	Risk of serious damage to eyes.
	R43:	May cause sensitisation by skin contact.
	R 50:	Very toxic to aquatic organisms.
Safety phrases:	S26:	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
	S36/37/39:	Wear suitable protective clothing, gloves and eye/face protection.
	S61:	Avoid release to the environment. Refer to special instructions/safety data sheets.
Proposed classification / labelling according to Directive 1967/548/EEC:	It is proposed that the classification of CMK with R21 -Harmful in contact with skin- be deleted. The acute percutaneous LD50 is greater than 2000 mg/kg bw. Thus, the criteria for assigning R21 as laid down in Annex VI to Directive 2001/59/EC are not met.	
Hazard symbol:	Xn; N	
Indication of danger:	Harmful Dangerous for the environment	
Risk phrases:	R22:	Harmful if swallowed.
	R41:	Risk of serious damage to eyes.
	R43:	May cause sensitisation by skin contact.
	R 50:	Very toxic to aquatic organisms.
Safety phrases:	S26:	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
	S36/37/39:	Wear suitable protective clothing, gloves and eye/face protection.
	S61:	Avoid release to the environment. Refer to special instructions/safety data sheets.
Justification:	Concerning the physico-chemical properties, the active substance CMK does not fulfil the criteria for a classification according to Council Directive 67/548/EEC. Therefore no labelling is required for physico-chemical hazards. CMK is harmful if swallowed. It presents risk of serious damage to eyes and may cause sensitisation by skin contact. CMK is very toxic to aquatic organisms. With regard to its toxicological and ecotoxicological properties, the active substance is classified as harmful and dangerous for the environment and has to be labelled with the hazard symbols Xn and N and the R-phrases R22-41-43-50.	

Section A9 Classification and Labelling

Annex Point IIA, IX

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*June 2013*
Materials and Methods	
Results and discussion	
Conclusion	[redacted]
Reliability	
Acceptability	
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	

Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

List of Submitted Studies

Part A

Chlorocresol (CMK)

Product-type 6

(Preservatives for products during storage)

FINAL CAR

April 2016

FRANCE

This document is a list of all the studies submitted by the Applicant to support the PT06 dossier.

1. **List by section**
2. **List by author**

1. List by section

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.10(01) A3.1(01)	Erstling, K.	2001a	Physicochemical properties: Preventol CMK (pellets). Date: 2001-11-15 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.10(02)	Ambroz, J.	2000	Determination of the stability of Preventol CMK to normal and elevated temperature. Date: 2000-09-12	ABC Laboratories, Inc., Columbia, Missouri, USA	Study No.: 46189	Yes	No	Yes	LANXESS Deutschland GmbH
A3.10(03)	Königer, A.	2010	Amendment to Physicochemical properties: Preventol CMK (pellets). Date: 2010-02-24	CURRENTA GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.11(01)	Heitkamp, D.	2006	Determination of safety-relevant data of Preventol CMK Pastillen. Date: 2006-03-29	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/00416	Yes	No	Yes	LANXESS Deutschland GmbH
A3.13(01)	Olf, G.	2006b	Surface tension, Physical-chemical properties. Date: 2006-03-17 Amended: 2006-05-10	Bayer AG, BTS-PT-RPT-KPM, Leverkusen, Germany	06/002/03	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.15(01)	Kraus, H.	2006b	4-Chloro-3-methylphenol / Explosive properties. Date: 2006-03-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.16(01)	Kraus, H.	2006c	4-Chloro-3-methylphenol / Oxidising properties. Date: 2006-03-03	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.17(01)	Kraus, H.	2006d	4-Chloro-3-methylphenol (CMK) / Reactivity towards container material. Date: 2006-06-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.2(01)	Olf, G.	2006a	Vapour pressure, Physical-chemical properties. Date: 2006-04-25 Amended: 2006-05-10	Bayer AG, BTS-PT-RPT-KPM, Leverkusen, Germany	06/002/01	Yes	No	Yes	LANXESS Deutschland GmbH
A3.2(02)	Beiell, U.	2006	Calculation of Henry's Law Constant of p-chloro-m-cresol (CMK). Date: 2006-05-17	Dr. Knoell Consult GmbH, Leverkusen, Germany	2006/05/17/UB	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.2(03)	Wielpütz, T.	2008	4-Chloro-3-methylphenol (Preventol CMK), Batch No.: [redacted], Vapour pressure A.4 (OECD 104). Date: 2008-08-19	Siemens AG, Prozess-Sicherheit, Industriepark Hoechst, Frankfurt am Main, Germany	20080599.01	Yes	No	Yes	LANXESS Deutschland GmbH
A3.3(01)	Kraus, H.	2006a	4-Chloro-3-methylphenol / Appearance. Date: 2006-05-23	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.3(02)	Güldner, W.	2009	Determination of dustiness (optical dust factor) of Preventol CMK pastilles. Date: 2009-09-30	Bayer CropScience AG, Development, Formulation Technology, Monheim, Germany	FM0045(RP00)G01	Yes	No	Yes	Bayer CropScience AG
A3.4(01)	Wesener, J.	2006	Spectra. Date: 2006-03-14 Amended: 2006-04-03	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/03	No	No	Yes	LANXESS Deutschland GmbH
A3.5(01)	Erstling, K.	2001b	Water solubility. Date: 2001-09-11	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/02 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.6(01) A3.9(01)	Reusche, W.	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.6(02) A3.9(02)	Erstling, K.	2001c	Partition coefficient (n-octanol/water) / dissociation constant, Preventol CMK (pellets). Date: 2001-10-23 Amended: 2001-11-14 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.6(03)	Feldhues, E.	2006a	Statement, Dissociation constant of 4-chloro-3-methylphenol Preventol CMK. Date: 2006-08-31	Bayer Industry Services, BIS-SUA-PUA I, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.7(01)	Jungheim, R.	2006a	Solubility of Preventol CMK (pellets) in different organic solvents at 10 °C, 20 °C and 30 °C. Date: 2006-11-30	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/09	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.9(01) A3.6(01)	Reusche, W.	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.9(02) A3.6(02)	Erstling, K.	2001c	Partition coefficient (n-octanol/water) / dissociation constant, Preventol CMK (pellets). Date: 2001-10-23 Amended: 2001-11-14 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.9(03)	Jungheim, R.	2006b	Calculation of the partition coefficient (1-octanol/water) at 10 °C, 20 °C and 30 °C based on water solubility and 1-octanol solubility of Preventol CMK (pellets) determined under study number A 01/0108/02 LEV and 2006/0025/09. Date: 2006-12-01	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/08	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.9(04)	Feldhues, E.	2007	Appraisal of the results obtained in Bayer Report A 90/0107/03 LEV, Bayer Report A 01/0108/03 LEV and in Bayer Industry Services Report 2006/0025/08 for the partition coefficient of Preventol CMK. Date: 2007-01-29	Bayer Industry Services, BIS-SUA-PUA I, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A4.1(01)	Jungheim, R.	2006c	Validation of a GC-Method for Preventol CMK (Pellets). Date: 2006-04-21 **CONFIDENTIAL**	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	Study No.: 2006/0014/01	Yes	No	Yes	LANXESS Deutschland GmbH
A4.2(01)	Brumhard, B.	2006	Analytical method 00998 for the determination of residues of Preventol CMK (4-chloro-3-methylphenol) in soil by HPLC-MS/MS. Date: 2006-08-24	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/102	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A4.2(02)	Feldhues, E.	2006b	Validation of an analytical method for the determination of Preventol CMK in air samples. Date: 2006-08-30	Bayer Industry Services, BIS-SUA-Analytics, Leverkusen, Germany	2006/0014/03	Yes	No	Yes	LANXESS Deutschland GmbH
A4.2(03)	Krebber, R.	2006	Analytical method 01004 for the determination of Preventol CMK (4-chloro-3-methylphenol) in drinking and surface water by HPLC-MS/MS. Date: 2006-09-05	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/112	Yes	No	Yes	LANXESS Deutschland GmbH
A5.3.1	Gerharz, T.	2011a	Determination of disinfectant properties of Preventol® CMK in accordance to EN 1040. Date: 2011-05-26	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
A5.3.1	Gerharz, T.	2011b	Determination of disinfectant properties of Preventol® CMK in accordance to EN 1656 and EN 1657. Date: 2011-05-25	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A5.3.1(01)	Kugler, M.	2003	Determination of the antimicrobial effects of Preventol CMK against bacteria and fungi. Date: 2003-05-22	Bayer Chemicals AG, Leverkusen, Germany	Report No. 2003-05-21	No	No	Yes	LANXESS Deutschland GmbH
A6.1.1(01)	[redacted]	1988a	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1988-08-18	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.1.1(02)	[redacted]	1978 and 1992	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1992-11-24 (revised report)	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.1 Non-key study	[redacted]	1981	Acute Oral Toxicity of PCMC (p-Chloro-m-cresol) to rats. Date: 1981-01-06	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.1.2(01)	[redacted]	1999	Acute Dermal Toxicity Study with Preventol CMK Pastillen in Rats. Date: 1999-10-29	[redacted]	[redacted]	Yes	No	Yes	Bayer Corporation
A6.1.2 Non key study	[redacted]	1988b	Preventol CMK – Investigation of acute cutaneous toxicity in male and female Wistar rats. Date: 1988-08-18	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.1.2 Non-key study	[redacted]	1979	Acute Dermal Administration Study in Male and Female Rabbits. Preventol CMK. Date: 1979-10-12	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.3(01)	[redacted].	2003	PREVENTOL CMK Study on Acute Inhalation Toxicity Study in Rats according to OECD No. 403. Date: 2003-01-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.1.3 Non-key study	[redacted]	1981	Preventol CMK, Study for Acute Toxicity of Fumes and Dusts after Inhalation. Date: 1981-10-21	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.1.4(01)	[redacted]	1976	Preventol CMK – The eye and dermal irritancy of [redacted] sample p-Chloro-m-cresol. Date: 1976-11-30	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.4 Non-key study	[redacted]	1991	Preventol CMK. Date: 1991-02-14	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.4 Non-key study	[redacted]	2006a	Preventol CMK – Acute Skin Irritation/ Corrosion on Rabbits. Date: 2006-07-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.4 Non-key study	[redacted]	2006b	Preventol CMK – T 7053199 – Acute Eye Irritation on Rabbits. Date: 2006-07-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.4 Non-key study	[redacted]	1978	Preventol CMK, Investigation of Skin and Mucous Membrane Tolerance. Date: 1978-09-20 Addendum: 1983-01-11	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.1.5(01)	[redacted]	2000	Preventol CMK, Pastillen LOCAL LYMPH NODE ASSAY IN MICE (LLNA/IMDS). Date: 2000-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.1.5(02)	[redacted]	1980	Preventol CMK– Investigation of sensitizing effect (Maximisation test after Magnusson and Kligman). Date: 1980-01-23	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.5 Non-key study	[redacted]	1981	Preventol CMK, Evaluation to determine the sensitisation effect by means of the open epicutaneous test. Date: 1981-09-25	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.2(01) Non-key study	[redacted]	1980	Excretion kinetics of Preventol CMK after a single oral administration to rats. Date: 1980-12-02	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.2(02) Non-key study	[redacted]	1981	Investigation into the detection of Preventol CMK in fatty tissue and liver tissue in rats. Date: 1981-02-17	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.2(03) Published	Roberts, M.S. *et al.*	1977	Permeability of human epidermis to phenolic compounds.	Pharmacy Dept., Univ. of Sydney, Australia	*J. Pharm. Pharmac.* **29**, 677-683	No	Yes	No	–
A6.2(04)	[redacted]	2009	Mass Balance and Metabolism of [14C]-4-Chloro-3-methylphenol in Male and Female Rats After Single Oral Administration. Date: 2009-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.2 Non-key Published	Bartels, M.J. *et al.*	1998	Comparative metabolism of *ortho*-phenylphenol in mouse, rat and man.	Dow Chemical Company, Midland, MI, USA	*Xenobiotica* **28**(6), 579-594	No	Yes	No	–
A6.2 Non-key study Published	Huq, A.S. *et al.*	1986	Permeation of Water Contaminative Phenols Through Hairless Mouse Skin.	College of Pharmacy, University of Michigan, Ann Arbor, MI, USA	*Arch. Environ. Contam. Toxicol*. **15**, 557-566	No	Yes	No	--

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.2 Non-key study Published	Kao, L.R. and Birnbaum, L.S.	1986	Disposition of *o*-Benzyl-*p*-Chlorophenol in Male Rats	Systemic Toxicology Branch, NIEHS, Research Triangle Park, NC, USA	*Journal of Toxicology and Environmental Health*, 18, 441 - 458, 1986	No	Yes	No	–
A6.3.1(01)	[redacted]	1989	Preventol CMK – Range-finding subacute toxicological investigations in Wistar rats for the determination of a maximum tolerable dosage (Administration with food over 4 weeks). Date: 1989-02-20	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.3.2(01)	[redacted]	1993a	PREVENTOL CMK – Preliminary trial for determining the dose for a sub-chronic study on male Wistar rats (dermal treatment for 4 weeks). Date: 1993-10-19	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.3.2(02)	[redacted]	1980	Subchronic Dermal Study in Rabbits. Preventol CMK. Date: 1980-07-31	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.3.3	[redacted]	2011	14-Day Repeated Dose Inhalation Toxicity Study with Preventol CMK	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.4.1(01)	[redacted]	1988	Preventol CMK: Subchronic toxicological study in rats (feeding study lasting 3 month). Date: 1988-11-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.4.2(01)	[redacted]	1991	Preventol CMK: Subchronic Toxicity Study in Wistar Rats (Dermal Treatment for 13 Weeks). Date: 1991-08-30	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.4.1 Non-key study	[redacted]	1981	Preventol CMK: Subchronic toxicological test in rats. 3-Month feeding test. Date: 1981-10-21	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.5(01) A6.7(01)	[redacted]	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.6.1(01)	Herbold, B.A.	1991	Preventol CMK – Salmonella/Microsome Plate Test. Date: 1991-08-08	Bayer AG, Wuppertal, Germany	20516	Yes	No	Yes	LANXESS Deutschland GmbH
A6.6.2(01)	Cifone, M.A.	1988	Mutagenicity Test on Preventol CMK in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay. Date: 1988-10-04	Hazelton Laboratories America, Inc., Kensington, MD, USA	R 4545	Yes	No	Yes	LANXESS Deutschland GmbH
A6.6.3(01)	Lehn, H.	1989	Preventol CMK – Mutagenicity Study For The Detection Of Induced Forward Mutations in the CHO-HGPRT Assay in vitro. Date: 1989-02-22	Bayer AG, Wuppertal, Germany	17755	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.6.4(01)	[redacted]	1990	Preventol CMK MICRONUCLEUS TEST ON THE MOUSE. Date: 1990-01-17 Amended: 1991-08-08	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.6.4 Non-key study	[redacted]	1981	Preventol CMK. Micronucleus Test on the Mouse to test for a Mutagenic Effect. Date: 1981-10-16	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.7(01) A6.5(01)	[redacted]	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.8.1(01)	[redacted].	1991	Preventol CMK - Study for embryotoxic effects in rats after oral administration. Date: 1991-11-29	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.8.2(01)	[redacted]	2006b	4-Chloro-3-methylphenol – Two-Generation Reproduction Study in Rats by Administration in the Diet. Date: 2006-12-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.8.2 Non-key	[redacted]	2006a	4-Chloro-3-methylphenol (Preventol CMK), One-Generation Reproduction Study in Wistar Rats (Pilot Study for a Two-Generation Reproduction Study with Administration in the Diet). Date: 2006-02-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.9 Non-key study	[redacted]	1992	Preventol CMK (PCMC) / Adverse neurological effects. Date: 1992-09-07	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.10 Non-key study Published	Meiss, R. *et al.*	1981	New aspects of the origin of hepatocellular vacuoles.	Univ. of Münster, Germany	*Exp. Path.* **19**, 239-246	No	Yes	No	–

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.10 Non-key study Published	Robenek, H. *et al.*	1980	Alterations in the Rat Liver Induced by p-Chlor-m-Cresol with Emphasis on the Intercellular Junctions.	Univ. of Münster, Germany	*J. Submicrosc. Cytol.* **12**(4), 635-646	No	Yes	No	–
A6.11 Non-key study Published	Wien, R.	1939	The Toxicity of *Para*chloro*meta*cresol and of Phenylmercuric Nitrate.	–	*Q.J. Pharm. Pharmacol.* **12**, 212-229	No	Yes	No	–
A6.12.2(01)	Ainley, E.J., Mackie, I.G. and Macarthur, D.	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
A6.12.2(02) A6.12.6	Hancock, B.W. and Naysmith, A.	1975	Hypersensitivity to Chlorocresol-preserved Heparin. *British Medical Journal:* 746-747, 1975	Royal Hospital, Sheffield, UK	*British Medical Journal*, 746 – 747,	No	Yes	No	--
A6.12.2(03)	Joppich, G.	1960	Tödliche Vergiftung durch Sagrotan bei Säuglingen.	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **11**; 20 -21	No	Yes	No	--
A6.12.2(04) Published	Wiseman, H.M. *et al.*	1980	Acute poisoning to Wright´s Vaporizing Fluid.	National Poisons Information Service, London, UK	*Postgraduate Medical Journal:* 56, 166 - 168 (1980)	No	Yes	No	--

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.12.2 Non-key Published	Jonsson, J. and Voigt, G.E.	1984	Homicidal intoxications by lye- and parachlorcresol-containing disinfectants.	State Dept. of Forensic Chemistry, Linköping, Sweden	*Am. J. Forensic Med. Pathol.* **5**(1), 57-63	No	Yes	No	--
A6.12.6(01)	Angelini, G. *et al.*	1975	Contact dermatitis in patients with leg ulcers.	Dept. of Dermatology, Univ. of Bari, Italy	*Contact Dermatitis* **1**, 81-87	No	Yes	No	–
A6.12.6(02) published	Oleffe J.A. *et al.*	1979	Allergy to chlorocresol and propylene glycol in a steroid cream to chlorocresol-preserved heparin	–	*Contact Dermatitis* **5**: 53-54	No	Yes	No	--
A6.12.6(03) published	Lewis, P.G. and Emmett, E.A.	1987	Irritant dermatitis from tri-butyl tin oxide and contact allergy from chlorocresol.	Johns Hopkins Medical Institutions, Baltimore, MD, USA	*Contact Dermatitis* **7**: 129-132, 1987	No	Yes	No	--
A6.12.6 Non-key study Published	Andersen, K.E. and Veien, N.K.	1985	Biocide patch tests	Gentofte Hospital, Hellerup, Denmark	*Contact Dermatitis* **12**, 99-103	No	Yes	No	–
A6.12.6 Non-key Published	Archer, C.B. and MacDonald, D.M.	1984	Chlorocresol sensitivity induced by treatment of allergic contact dermatitis with steroid creams.	Dept. of Dermatology, Guy's Hospital, London, UK	*Contact Dermatitis* **11**, 144-145	No	Yes	No	–
A6.12.6 Non-key study Published	Brasch, J. *et al.*	1993	Patch Test Reactions to a Preliminary Preservative Series.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **41**,2; 71-76	No	Yes	No	--

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.12.6 Non-key study Published	Burry, J.N. *et al.*	1975	Chlorocresol sensitivity	St. Peters, South Australia	*Contact Dermatitis* **1**, 41-42	No	Yes	No	--
A6.12.6 Non-key study Published	de Boer, E.M. *et al.*	1989	Dermatoses in metal workers (II). Allergic contact dermatitis.	Free University Academic Hospital, Amsterdam, The Netherlands	*Contact Dermatitis* **20**, 280-286	No	Yes	No	–
A6.12.6 Non-key study Published	Dooms-Goossen, A. *Et al.*	1981	Chlorocresol and chloracetamide: Allergens in medications, glues, and cosmetics	Dept. Of Dermatology, Academisch Ziekenhuis St.Peter, Leuven, Belgium	*Contact Dermatitis* **7**, 51-52	No	Yes	No	–
A6.12.6 Non-key study Published	Freitas, J.P. and Brandao, F.M.	1986	Contact urticaria to chlorocresol.	Dept. Of Dermatology, Santa Maria Hospital, Lisbon, Portugal	*Contact Dermatitis* **15**, 252	No	Yes	No	–
A6.12.6 Non-key study Published	Geier, J. *et al.*	1996	Contact Allergy due to Industrial Biocides.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **44** (4), 154-159	No	Yes	No	--
A6.12.6 Non-key study Published	Goncalo, M. *et al.*	1987	Immediate and delayed sensitivity to chlorocresol.	Clinica de Dermatologica e Venereologica, Coimbra, Portugal	*Contact Dermatitis* **17**, 46-47	No	Yes	No	--
A6.12.6 A6.12.2(02)	Hancock, B.W. and Naysmith, A.	1975	Hypersensitivity to Chlorocresol-preserved Heparin. *British Medical Journal:* 746-747, 1975	Royal Hospital, Sheffield, UK	*British Medical Journal*, 746 – 747,	No	Yes	No	--

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.12.6 Non-key study published	Rudner, E.J.	1977	North American Group Results	–	*Contact Dermatitis* **3**: 208-209	No	Yes	No	–
A6.12.6 Non-key study Published	Uter, W. *et al.*	1993	Contact Allergy in Metal Workers.	Information Network of Dermatological Clinics (IVDK) in Germany	*Dermatosen* **41**(6), 220-227	No	Yes	No	–
A6.12.6 Non-key study Published	Wilkinson, J.D. *et al.*	1980	Comparison of Patch Test Results in Two Adjacent Areas of England. II. Medicaments.	Slade Hospital, Oxford & Wycombe General Hospital, England	*Acta Dermatovener (Stockholm)* **60**, 245-249	No	Yes	No	
A6.12.7 A6.12.8	Joppich, G.	1962	Klinik und Behandlung der Sagrotanvergiftung. *Deut. Med. J.*:11; 20 - 21, 1960	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **13**; 691-693	No	Yes	No	--
A7.1.1.1.1(01)	Erstling, K. and Feldhues, E.	2001a	Abiotic degradation. Date: 2001-08-31 Amended: 2007-02-22	Bayer AG, Zentrale Analytik, Leverkusen, Germany	A 01/0108/04 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.1.1.2(01)	Wilmes, R.	1988	Tests to determine the photodegradation of 4-chloro-3-methylphenol (Preventol CMK) in water. Determination of the quantum yield of direct photodegradation in water in polychromatic light (ECETOC method). Date: 1988-05-30	Bayer AG, Sector 5. Agrochemicals Business Group, PF-F/CE-ME, Monheim, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(01)	Müller, G.	1992	Investigations of the ecological behaviour of Preventol CMK Date: 1992-02-25	Bayer AG, Institut für Umweltananlyse und Bewertungen, Leverkusen, Gemany	A 330 A/91	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(02)	Weyers, A.	2007	Preventol CMK – Biodegradation. Re-Evaluation based on Study Report 330 A/91, corresponding raw data and additional information provided by the sponsor. Date: 2007-03-09 Amended: 2007-03-16	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.1.2.1(01, 02, 04)	Neuhahn, A.	2012	2. Amendment to GLP-Final Report Study Title: Biodegradation. Re-evaluation based on study report 330 A/91. Date: 2012-05-14	Currenta GmbH & Co. OHG, Leverkusen, Germany	-	No	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(03)	Hanstveit, A.O. and Pullens, M.A.H.L.	1993	The biodegradability of the product Preventol CMK in a closed bottle test according to a draft OECD guideline: ready biodegradability; the influence of inoculum activity. Date: 1993-01-15 Amended: 2007-03-30	TNO Institute of Environmental Sciences, Delft, The Netherlands	R 92/198	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(04) A7.1.1.2.2(02) Non-key study	Neuhahn	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(05) Non-key study	N.N.	1985	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 C. Date: July 1985	Bayer AG, WV-UWS/LE, Microbiology, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.1.2.1(06) A7.1.2.1.1(01) Non-key study	Cernick, S.L.	1999	A study of the biodegradability of 4-chloro-3-methylphenol by aerobic biological treatment. Date: 1999-05-13	Duquesne University	--	No	Yes	No	--
A7.1.1.2.2(01)	Thompson, R.S.	1993	Parachlorometacresol: Further study of inherent biodegradability. Date: 1993-06-29	Brixham Environmental Laboratory, Zeneca limited, Brixham Devon, UK	BL4783/B	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.2(02) A7.1.1.2.1(04) Non-key study	Neuhahn	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(01) A7.1.1.2.1(06) Non-key study	Cernick, S.L.	1999	A study of the biodegradability of 4-chloro-3-methylphenol by aerobic biological treatment. Date: 1999-05-13	Duquesne University	--	No	Yes	No	--
A7.1.2.1.1(02) Non-key study	Dohm	1981	Biodegradability of Preventol CMK. Date: 1981-08-20	Bayer Uerdingen Site, Organic Chemicals Division, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.1(03) Non-key study	Dohm	1984	CMK content in ppb in wastewater, Uerdingen wastewater treatment plant. Date: 1984-07-03	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(04) Non-key study	Dohm	1985	CMK in the wastewater treatment plant outlet. Date: 1985-03-01	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(05) Non-key study	N.N.	1981	Degradability of p-chloro-m-cresol in the central biological wastewater treatment plant Uerdingen. Date: 1981-08-25	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(06) Non-key study	N.N.	1983	Elimination of p-chloro-m-cresol (CMK) in the biological wastewater treatment plant Uerdingen. Date: 1983-01-07	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(07) Non-key study	N.N.	1986	Elimination of chlorometacresol (CMK) in the 2-stage biological wastewater treatment plant UE. Date: 1986-05-16	Bayer Uerdingen Works, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.1(08) Non-key study	N.N.	1988	CMK concentration in the discharge of the Uerdingen biological wastewater treatment plant. Date: 1988-12-02	Bayer Uerdingen Site, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(09) Non-key study	Rother	1996	Preventol CMK, CMK-Na: Analysis of Wastewater from the Leather Industry Date: 1996-01-25	Bayer, Material Protection Unit, Organic Chemicals Business Group, Uerdingen	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(10) Non-key study	Morris, R.	2002	Bench Scale Biological Treatment of Preventol CMK for General Motor's Lansing Plant #5 Date: 2002-08-30	Bayer's Corporate Environmental Testing Services Laboratory, New Martinsville, West Virginia	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1 (11) Non-key Published	Bolz, U. et al.	1999	Determination of phenolic xenoestrogens in sediments and sewage sludges by HRGC/LRMS. *Organohalogen Compounds, Vol. 40, 65-68.*	-	-	No	Yes	No	-

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.1 (11) Non-key Published	Bolz, U. et al.	2001	Phenolic xenoestrogens in surface water, sediments, and sewage sludge from Baden-Württemberg, south-west Germany. *Environmental Pollution, 115, 291-301*	-	-	No	Yes	No	-
A7.1.2.1.1 Non-key Published	Körner, W. et al.	1998	Input/output balance of estrogenic active compounds in a major municipal sewage plant in Germany. *Organohalogen Compounds, Vol. 37, 269-272.*	-	-	No	Yes	No	-
A7.1.2.1.1(11) Non-key Published	Körner, W. et al.	2000	Input/output balance of estrogenic active compounds in a major municipal sewage plant in Germany. *Chemosphere, Vol. 40, 1131-1142*	-	-	No	Yes	No	-

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.1(11) Non-key published	Schnaak, W. et al.	1997	Organic contaminants in sewage sludge and their ecotoxicological significance in the agricultural utilization of sewage sludge. *Chemosphere, Vol. 35, 5-11.*	-	-	No	Yes	No	-
A7.1.2.1.1(11) Non-key published	Ternes, Th. A.	1998	Simultaneous determination of antiseptics and acidic drugs in sewage and river water. *Vom Wasser, 90, 295-309.*	-	-	No	Yes	No	-
A7.1.2.1.2(01)	Reis, K.-H.	2007	Anaerobic biodegradability of 4-chloro-3-methylphenol (Preventol CMK) in digested sludge: Measurement of gas production	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32321168	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.2(02)	Voets, J.P., Pipyn, P., van Lancker, P. and Verstrate, W.	1976	Degradation of Microbiocides under Different Environmental Conditions. *J. appl. Bact., 40, 67 - 72, 1976*	Laboratory of General and Industrial Microbiology, State University of Gent, Gent, Belgium.	--	No	Yes	No	--

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.2(03)	O'Conner, O.A. & Young, L.Y.	1989	Toxicity and anaerobic biodegradability of substituted phenols under methanogenic conditions. *Environ. Toxicol. Chem.* 8, 853 – 862, 1989	Institute of Environmental Medicine and Department of Microbiology, New York University Medical Center, New York, USA	--	No	Yes	No	--
A7.1.2.1.2(04)	Kirk, P.W.W. & Lester, J.N.	1989	Degradation of phenol, selected chlorophenols and chlorophenoxy herbicides during anaerobic sludge digestion. *Environm. Technol. Lett. 10, 405 – 414, 1989*	Public Health Engineering Laboratory, Department of Civil Engineering, Imperial College of Science, Technology and Medicine, London, UK	--	No	Yes	No	--
A7.1.2.1.2(05)	Feil, N.	2009	Anaerobic biodegradability of 4-Chloro-3-methylphenol (Preventol CMK) in digested sludge: Measurement of gas production.	Institut für biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45822168	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.2(06)	Möndel, M.	2010a	Anaerobic biodegradability of Preventol CMK in digested sludge Date: 2010-05-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 142	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.2(07) A7.2.1/A7.2.2	Gerharz, T.	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.2.1(01)	Rast, H.-G. and Kölbl, H.	1987	Microbial degradation of Preventol CMK in Rhine water. Date: 1987-10-20 Amended:	Bayer AG, FBT Leverkusen, Germany	LEV 14/76 and LEV 11/76	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.2.1(02) A7.2.1/A7.2.2	Gerharz, T.	2011b	Degradation of 4-chloro-3-cresol in a liquid environment (washing water after stable cleaning – stable with laying hens). Date: 2011-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.2.2(01)	Möndel, M.	2009	^{14}C-Preventol CMK: Aerobic degradation of ^{14}C-Preventol CMK in two different aquatic sediment systems. Date: 2009-03-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 85	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.2.2(02)	Möndel, M.	2010b	^{14}C-Preventol CMK: Characterisation of non-identified radioactivity of ^{14}C-Preventol CMK in aquatic sediment systems. Date: 2010-05-21	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 139	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.2.2.2(03)/ B7.5(05)	Dixon, E.M.	1997	Proposed environmental quality standards for 4-chloro-3-methyl-phenol in water. Draft final report to the Department of the Environment, UK. 72p	-	No	Yes	No	-	-
A7.1.2.2.2(03)	Bolz, U. *et al.*	1999	Determination of phenolic xenoestrogens in sediments and sewage sludges by HRGC/LRMS. *Organohalogen Compounds, Vol. 40, 65-68.*	-	-	No	Yes	No	-

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.2.2(03)/ B7.5(04)	Bolz, U. *et al.*	2001	Phenolic xenoestrogens in surface water, sediments, and sewage sludge from Baden-Württemberg, south-west Germany. *Environmental Pollution, 115, 291-301*	-	-	No	Yes	No	-
A7.1.2.2.2(03)	Körner, W. *et al.*	2001	Steroid analysis and xenosteroid potentials in two small streams in southwest Germany. *Journal of Aquatic Ecosystem Stress and Recovery, 8, 215-229.*	-	-	No	Yes	No	-
A7.1.2.2.2(03)/ B7.5(06)	Lacorte, S. *et al.*	2001	Main findings and conclusions of the implementation of Directive 76/464/CEE concerning the monitoring of organic pollutants in surface waters (Portugal, April 1999 – May 2000). Journal of Environmental Monitoring, 3, 475-482	-	-	No	Yes	No	-

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.2.2(03)/ B7.5(03)	Schmidt-Bäumler, K., *et al.*	1999	Occurrence and distribution of organic contaminants in the aquatic system in Berlin. Part II: substituted phenols in Berlin surface water.	-	-	No	Yes	No	-
B7.5(01) Non-key study	Grote	1987	No title. Date: 1987-07-14	LE Environmental Protection/ AWALU, Analytics, Air Laboratory, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
B7.5(02) Non-key study	Oblak	1989	Determination of 4-chloro-3-methylphenol (CMK) in Rhine water (Ultra Trace range). Date: 1989-12-06	Bayer AG, Uerdingen, Central Analytics, Uerdingen, Germany	LM Ue 50/89	No	No	Yes	LANXESS Deutschland GmbH
A7.1.3(01)	Erstling, K. and Feldhues, E.	2001b	Adsorption/Desorption. Date: 2001-09-13 Amended: 2001-11-13 and 2007-02-22	Bayer AG, ZF – Zentrale Analytik, Leverkusen, Germany	A 01/0108/05/ LEV	Yes	No	Yes	LANXESS Deutschland GmbH

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A7.1.3(01) Non-key study/ published	Ohlenbusch, G., Kumke, M.U. and Frimmel, F.H.	2000	Sorption of phenols to dissolved organic matter investigated by solid phase microextraction. *The Science of the Total Environment 253, 63 – 74, 2000*	Bereich Wasserchemie, Universität Karlsruhe, Germany	--	No	Yes	No	--
A7.1.3(02) and A7.2.3.1(01)	Meinerling, M.	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.3(02) and A7.2.3.1(01)	Meinerling, M.	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH
A7.2.1/ A7.2.2 Non-key study/ published	Federle, T.W.	1988	Mineralization of monosubstituted aromatic compounds in unsaturated and saturated subsurface soils. Can. J. Microbiol. 34: 1037-1042	-	-	No	Yes	No	--

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A7.2.1/A7.2.2/ A7.1.2.1.2(07)	Gerharz, T.	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH
A7.2.1/A7.2.2 A7.1.2.2.1(02)	Gerharz, T.	2011b	Degradation of 4-chloro-3-cresol in a liquid environment (washing water after stable cleaning – stable with laying hens). Date: 2011-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
A7.2.1/ A7.2.2 Non-key study/ published	Gerharz, T.	2011c	Vaporisation behaviour of 4-chloro-3-methylphenol from an inert surface (glass petri dish)	LANXESS Deutschland GmbH, Leverkusen, Germany	Lab Report ID: D 2011-22.1.5	No	No	Yes	LANXESS Deutschland GmbH
A7.2.1/ A7.2.2 Non-key study/ published	Loehr, R.C. and Matthews, J.E.	1992	Loss of organic chemicals in soil. Pure compound treatability studies. *Journal of Soil Contamination **1(4)**, 339-360, 1992*	Environmental and Water Resources Engineering Laboratories, Texas, Austin, USA	--	No	Yes	No	--

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A7.2.1/ A7.2.2 Non-key study/ published	Sattar, M.A.	1989	Fate of chlorinated cresols from environmental samples. *Chemosphere **19** (8/9), 1421 – 1426, 1989*	Department of Soil Science, Agricultural University, Mymensingh, Bangladesh	--	No	Yes	No	--
A7.2.2.1	Nitsche, M.	2011	Biodegradation of Preventol® CMK (4-Chloro-3-methylphenol) in soil under aerobic conditions.	LANXESS Deutschland GmbH	2011-07-25	No	No	Yes	LANXESS Deutschland GmbH
A7.2.3.1(01) and A7.1.3(02)	Meinerling, M.	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH
A7.2.3.1(02) and A7.1.3(02)	Meinerling, M.	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.2.3.2 Non-key study	Brown, K.W., Barbee, G.C. and Thomas, J.C.	1990	Detecting organic contaminants in the unsaturated zone using soil and soil-pore water samples.	--	*Hazardous Waste and Hazardous Materials **7 (2)**, 151 – 168*	No	Yes	No	--
A7.3.1(01)	Anthe, M.	2006	p-Chloro-m-cresol. Calculation of indirect photodegradation. Date: 2006-07-05	Dr. Knoell Consult GmbH, Leverkusen, Germany	KC-PD-04/06	No	No	Yes	LANXESS Deutschland GmbH
A7.4.1.1(01)	[redacted]	1993a	Acute Toxicity of Preventol CMK Technical to the Rainbow Trout (*Oncorhynchus mykiss*) Under Static Renewal Conditions. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.1.2(01)	Gagliano, G.G. and Bowers, L.M.	1993b	Acute Toxicity of Preventol CMK technical to the Waterflea (*Daphnia magna*) under static conditions. Date: 1993-02-19	Miles Incorporated, Agriculture Division, South Metcalf, Stilwell, Kansas, US	105021	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.1.3(01)	Caspers, N.	1983/1991	Preventol CMK (4-chloro-3-methyl-phenol) – Growth Inhibition Test Algae. Date: 1991-01-28	Bayer AG, WV-Umweltschutz, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.1.3(02)	Weyers, A.	2006a	Preventol CMK – Algae, Growth Inhibition Test. Re-Evaluation based on Study Report Growth Inhibition Test Algae (1983) and the corresponding raw data. Date: 2006-07-07	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.4.1.3(03)	Vinken, R. and Wydra, V.	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to *Desmodesmus subspicatus* in an Algal Growth Inhibition Test. Date: 2007-01-04	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32324210	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.1.4(01)	Kanne, R.	1988	Preventol CMK – Toxicity towards Bacteria. Date: 1988-02-10	Bayer AG, WV-LE Umweltschutz, Leverkusen, Germany	88105507	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.1.4(02)	Weyers, A.	2006b	Preventol CMK – Toxicity towards Bacteria. Re-Evaluation based on Study Report No. 88105507, corresponding raw data and additional information provided by the sponsor. Date: 2006-06-29	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.4.1.4(03)	Neuhahn, A.	2008	Activated Sludge, Respiration Inhibition Test with Preventol CMK Pastillen. Date: 2008-08-19	Currenta GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	2006/0025/16	Yes	No	Yes	Lanxess Deutschland GmbH
A7.4.2(01)	Paul, A.	2007	p-Chloro-m-cresol (CMK) – Calculation of the bioconcentration factor (BCF) Date: 2007-05-31	DR. KNOELL CONSULT GmbH, Mannheim, Germany	KC-BCF-07/07	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.2(02) Non-key study/ published	MITI (Ministry of International Trade & Industry)	1992	Biodegradation and bioaccumulation: Data of existing chemicals based on the CSCL Japan. Published by Japan Chemical Industry Ecology-Toxicology & Information Center, 1992	--	--	No	Yes	No	--
A7.4.2(03) Non-key study/ published	Jennings, J.G., de Nys, R., Charlton, T.S., Duncan, M.W. and Steinberg, P.D.	1996	Phenolic compounds in the nearshore waters of Sidney, Australia. *Mar. Freshwater Res.* ***47****, 951 – 959, 1996*	--	--	No	Yes	No	--
A7.4.3.1(01)	[redacted]	1991	Preventol CMK: Prolonged Toxicity Test with Zebrafish (Brachydanio rerio). Date: 1991-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.3.1(02)	[redacted]	2006c	Preventol CMK – Fish, prolonged toxicity test. Re-Evaluation based on Study Report 212 A/90FL, corresponding raw data and additional information provided by the sponsor. Date: 2006-07-05	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.3.2(01)	[redacted]	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to Rainbow Trout (*Oncorhynchus mykiss*) in a Prolonged Semi Static Test over 28 Days. Date: 2007-03-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.3.4(01) Non-key study/ published	Kühn, R., Pattard, M., Pernak, K.-D. Winter, A.	1988	Research Report 10603052: Harmful effects of chemicals in the *Daphnia* reproduction test as a basis for assessing their environmental hazard in aquatic systems. Date: 1988-03-31	Instiute for Water, Land and Air Hygiene of the Federal German Health Office	--	No	Yes	No	--
A7.4.3.4(01) Non-key study/ published	Jungheim R	2006	Addendum to Research Report 10603052: Harmful effects of chemicals in the *Daphnia* reproduction test as a basis for assessing their environmental hazard in aquatic systems.	Bayer Industry Services, Leverkusen, Germany	--	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.3.4(02)	Weyers, A.	2007	Preventol CMK Pastillen - Daphnia magna Reproduction Test. Date: 2007-03-08	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/0025/10	Yes	No	Yes	Lanxess Deutschland GmbH
A7.5.1.1(01)	Reis, K.-H.	2007	Effects of 4-Chloro-3-methylphenol (Preventol CMK) on the activity of the soil microflora in the laboratory.	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32322080	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.1.1(02)	Schulz, L.	2012	Preventol CMK – Effects on the activity of soil microflora (Nitrogen transformation test). Date: 2012-04-13.	BioChem agrar, Labor für biologische und chemische Analytik GmbH 04827 Gerichshain, Germany	Project-No. 12 10 48 011 N,	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.1.2	Lührs, U.	2007	Acute Toxicity (14 Days) of 4-Chloro-3-methylphenol (Preventol CMK) to the Earthworm *Eisenia fetida* in Artificial Soil with 5% Peat. Date: 2007-01-17	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32326021	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.5.1.3(01)	Buetzler, R. and Meinerling, M.	2007	Effects of Preventol CMK on terrestrial (non-target) plants: Seedling emergence and seedling growth test	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32327086	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.3.1.1(01)	[redacted]	1993a	Preventol CMK: An acute oral LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.3.1.2(01)	[redacted]	1993b	Preventol CMK: A subacute dietary LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.5(01)	Fàbregas, E.	2007	p-Chloro-m-cresol (CMK) – Calculation of the bioconcentration factor in earthworms (BCFearthworm). Date: 2007-05-30	DR. KNOELL CONSULT GmbH, Mannheim, Germany	KC-BCF-06/07	No	No	Yes	LANXESS Deutschland GmbH
Published	European Commission	2000	IUCLID Dataset – CAS No. 108-95-2 - Phenol	-	-	No	Yes	No	-
Published	United States Environmental Protection Agency (EPA) (Ed.)	2009	Reregistration Eligibility Decision for Phenol & Salts	-	EPA 739-R-08-010	No	Yes	No	-

2. List by author

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Ambroz, J.	A3.10(02)	2000	Determination of the stability of Preventol CMK to normal and elevated temperature. Date: 2000-09-12	ABC Laboratories, Inc., Columbia, Missouri, USA	Study No.: 46189	Yes	No	Yes	LANXESS Deutschland GmbH
Andersen, K.E. and Veien, N.K.	A6.12.6 Non-key study Published	1985	Biocide patch tests	Gentofte Hospital, Hellerup, Denmark	*Contact Dermatitis* **12**, 99-103	No	Yes	No	–
Angelini, G. *et al.*	A6.12.6(01)	1975	Contact dermatitis in patients with leg ulcers.	Dept. of Dermatology, Univ. of Bari, Italy	*Contact Dermatitis* **1**, 81-87	No	Yes	No	–
Anthe, M.	A7.3.1(01)	2006	p-Chloro-m-cresol. Calculation of indirect photodegradation. Date: 2006-07-05	Dr. Knoell Consult GmbH, Leverkusen, Germany	KC-PD-04/06	No	No	Yes	LANXESS Deutschland GmbH
Archer, C.B. and MacDonald, D.M.	A6.12.6 Non-key Published	1984	Chlorocresol sensitivity induced by treatment of allergic contact dermatitis with steroid creams.	Dept. of Dermatology, Guy's Hospital, London, UK	*Contact Dermatitis* **11**, 144-145	No	Yes	No	–

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Bartels, M.J. *et al.*	A6.2 Non-key Published	1998	Comparative metabolism of *ortho*-phenylphenol in mouse, rat and man.	Dow Chemical Company, Midland, MI, USA	*Xenobiotica* **28**(6), 579-594	No	Yes	No	–
[redacted]	A6.8.1(01)	1991	Preventol CMK - Study for embryotoxic effects in rats after oral administration. Date: 1991-11-29	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Beiell, U.	A3.2(02)	2006	Calculation of Henry's Law Constant of p-chloro-m-cresol (CMK). Date: 2006-05-17	Dr. Knoell Consult GmbH, Leverkusen, Germany	2006/05/17/UB	No	No	Yes	LANXESS Deutschland GmbH
Bolz, U. et al.	A7.1.2.1.1 (11) Non-key Published	1999	Determination of phenolic xenoestrogens in sediments and sewage sludges by HRGC/LRMS. *Organohalogen Compounds, Vol. 40, 65-68.*	-	-	No	Yes	No	-
Bolz, U. et al.	A7.1.2.1.1 (11) Non-key Published	2001	Phenolic xenoestrogens in surface water, sediments, and sewage sludge from Baden-Württemberg, south-west Germany. *Environmental Pollution, 115, 291-301*	-	-	No	Yes	No	-

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Bolz, U. *et al.*	A7.1.2.2.2(03)	1999	Determination of phenolic xenoestrogens in sediments and sewage sludges by HRGC/LRMS. *Organohalogen Compounds, Vol. 40, 65-68.*	-	-	No	Yes	No	-
Bolz, U. *et al.*	A7.1.2.2.2(03)/ B7.5(04)	2001	Phenolic xenoestrogens in surface water, sediments, and sewage sludge from Baden-Württemberg, south-west Germany. *Environmental Pollution, 115, 291-301*	-	-	No	Yes	No	-
[redacted]	A6.1.1(01)	1988a	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1988-08-18	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.2 Non key study	1988b	Preventol CMK – Investigation of acute cutaneous toxicity in male and female Wistar rats. Date: 1988-08-18	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A6.1.1(02)	1978 and 1992	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1992-11-24 (revised report)	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.5 Non-key study	1981	Preventol CMK, Evaluation to determine the sensitisation effect by means of the open epicutaneous test. Date: 1981-09-25	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.5(02)	1980	Preventol CMK–Investigation of sensitizing effect (Maximisation test after Magnusson and Kligman). Date: 1980-01-23	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Brasch, J. *et al.*	A6.12.6 Non-key study Published	1993	Patch Test Reactions to a Preliminary Preservative Series.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **41**,2; 71-76	No	Yes	No	--
Brown, K.W., Barbee, G.C. and Thomas, J.C.	A7.2.3.2 Non-key study	1990	Detecting organic contaminants in the unsaturated zone using soil and soil-pore water samples.	--	*Hazardous Waste and Hazardous Materials **7 (2)**, 151 – 168*	No	Yes	No	--

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Brumhard, B.	A4.2(01)	2006	Analytical method 00998 for the determination of residues of Preventol CMK (4-chloro-3-methylphenol) in soil by HPLC-MS/MS. Date: 2006-08-24	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/102	Yes	No	Yes	LANXESS Deutschland GmbH
Buetzler, R. and Meinerling, M.	A7.5.1.3(01)	2007	Effects of Preventol CMK on terrestrial (non-target) plants: Seedling emergence and seedling growth test	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32327086	Yes	No	Yes	LANXESS Deutschland GmbH
Burry, J.N. *et al.*	A6.12.6 Non-key study Published	1975	Chlorocresol sensitivity	St. Peters, South Australia	*Contact Dermatitis* **1**, 41-42	No	Yes	No	--
Caspers, N.	A7.4.1.3(01)	1983/1991	Preventol CMK (4-chloro-3-methyl-phenol) – Growth Inhibition Test Algae. Date: 1991-01-28	Bayer AG, WV-Umweltschutz, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A7.4.3.1(01)	1991	Preventol CMK: Prolonged Toxicity Test with Zebrafish (Brachydanio rerio). Date: 1991-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Cernick, S.L.	A7.1.1.2.1(06) A7.1.2.1.1(01) Non-key study	1999	A study of the biodegradability of 4-chloro-3-methylphenol by aerobic biological treatment. Date: 1999-05-13	Duquesne University	--	No	Yes	No	--
Cernick, S.L.	A7.1.2.1.1(01) A7.1.1.2.1(06) Non-key study	1999	A study of the biodegradability of 4-chloro-3-methylphenol by aerobic biological treatment. Date: 1999-05-13	Duquesne University	--	No	Yes	No	--
Cifone, M.A.	A6.6.2(01)	1988	Mutagenicity Test on Preventol CMK in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay. Date: 1988-10-04	Hazelton Laboratories America, Inc., Kensington, MD, USA	R 4545	Yes	No	Yes	LANXESS Deutschland GmbH
de Boer, E.M. *et al.*	A6.12.6 Non-key study Published	1989	Dermatoses in metal workers (II). Allergic contact dermatitis.	Free University Academic Hospital, Amsterdam, The Netherlands	*Contact Dermatitis* **20**, 280-286	No	Yes	No	–
Dixon, E.M.	A7.1.2.2.2(03)/ B7.5(05)	1997	Proposed environmental quality standards for 4-chloro-3-methyl-phenol in water. Draft final report to the Department of the Environment, UK. 72p	-	No	Yes	No	-	-

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Dohm	A7.1.2.1.1(02) Non-key study	1981	Biodegradability of Preventol CMK. Date: 1981-08-20	Bayer Uerdingen Site, Organic Chemicals Division, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Dohm	A7.1.2.1.1(03) Non-key study	1984	CMK content in ppb in wastewater, Uerdingen wastewater treatment plant. Date: 1984-07-03	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Dohm	A7.1.2.1.1(04) Non-key study	1985	CMK in the wastewater treatment plant outlet. Date: 1985-03-01	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Dooms-Goossen, A. *Et al.*	A6.12.6 Non-key study Published	1981	Chlorocresol and chloracetamide: Allergens in medications, glues, and cosmetics	Dept. Of Dermatology, Academisch Ziekenhuis St.Peter, Leuven, Belgium	*Contact Dermatitis* **7**, 51-52	No	Yes	No	–
[redacted]	A6.8.2 Non-key	2006a	4-Chloro-3-methylphenol (Preventol CMK), One-Generation Reproduction Study in Wistar Rats (Pilot Study for a Two-Generation Reproduction Study with Administration in the Diet). Date: 2006-02-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A6.8.2(01)	2006b	4-Chloro-3-methylphenol – Two-Generation Reproduction Study in Rats by Administration in the Diet. Date: 2006-12-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.4.1 Non-key study	1981	Preventol CMK: Subchronic toxicological test in rats. 3-Month feeding test. Date: 1981-10-21	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.4.1(01)	1988	Preventol CMK: Subchronic toxicological study in rats (feeding study lasting 3 month). Date: 1988-11-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Erstling, K.	A3.10(01) A3.1(01)	2001a	Physicochemical properties: Preventol CMK (pellets). Date: 2001-11-15 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K.	A3.5(01)	2001b	Water solubility. Date: 2001-09-11	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/02 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Erstling, K.	A3.6(02) A3.9(02)	2001c	Partition coefficient (n-octanol/water) / dissociation constant, Preventol CMK (pellets). Date: 2001-10-23 Amended: 2001-11-14 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K.	A3.9(02) A3.6(02)	2001c	Partition coefficient (n-octanol/water) / dissociation constant, Preventol CMK (pellets). Date: 2001-10-23 Amended: 2001-11-14 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K. and Feldhues, E.	A7.1.1.1.1(01)	2001a	Abiotic degradation. Date: 2001-08-31 Amended: 2007-02-22	Bayer AG, Zentrale Analytik, Leverkusen, Germany	A 01/0108/04 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K. and Feldhues, E.	A7.1.3(01)	2001b	Adsorption/Desorption. Date: 2001-09-13 Amended: 2001-11-13 and 2007-02-22	Bayer AG, ZF – Zentrale Analytik, Leverkusen, Germany	A 01/0108/05/ LEV	Yes	No	Yes	LANXESS Deutschland GmbH
European Commission	Published	2000	IUCLID Dataset – CAS No. 108-95-2 - Phenol	-	-	No	Yes	No	-

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Fàbregas, E.	A7.5.5(01)	2007	p-Chloro-m-cresol (CMK) – Calculation of the bioconcentration factor in earthworms (BCFearthworm). Date: 2007-05-30	DR. KNOELL CONSULT GmbH, Mannheim, Germany	KC-BCF-06/07	No	No	Yes	LANXESS Deutschland GmbH
Federle, T.W.	A7.2.1/ A7.2.2 Non-key study/ published	1988	Mineralization of monosubstituted aromatic compounds in unsaturated and saturated subsurface soils. Can. J. Microbiol. 34: 1037-1042	-	-	No	Yes	No	--
Feil, N.	A7.1.2.1.2(05)	2009	Anaerobic biodegradability of 4-Chloro-3-methylphenol (Preventol CMK) in digested sludge: Measurement of gas production.	Institut für biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45822168	Yes	No	Yes	LANXESS Deutschland GmbH
Feldhues, E.	A3.6(03)	2006a	Statement, Dissociation constant of 4-chloro-3-methylphenol Preventol CMK. Date: 2006-08-31	Bayer Industry Services, BIS-SUA-PUA I, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Feldhues, E.	A3.9(04)	2007	Appraisal of the results obtained in Bayer Report A 90/0107/03 LEV, Bayer Report A 01/0108/03 LEV and in Bayer Industry Services Report 2006/0025/08 for the partition coefficient of Preventol CMK. Date: 2007-01-29	Bayer Industry Services, BIS-SUA-PUA I, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Feldhues, E.	A4.2(02)	2006b	Validation of an analytical method for the determination of Preventol CMK in air samples. Date: 2006-08-30	Bayer Industry Services, BIS-SUA-Analytics, Leverkusen, Germany	2006/0014/03	Yes	No	Yes	LANXESS Deutschland GmbH
Freitas, J.P. and Brandao, F.M.	A6.12.6 Non-key study Published	1986	Contact urticaria to chlorocresol.	Dept. Of Dermatology, Santa Maria Hospital, Lisbon, Portugal	*Contact Dermatitis* **15**, 252	No	Yes	No	–
[redacted].	A7.4.1.1(01)	1993a	Acute Toxicity of Preventol CMK Technical to the Rainbow Trout (*Oncorhynchus mykiss*) Under Static Renewal Conditions. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Gagliano, G.G. and Bowers, L.M.	A7.4.1.2(01)	1993b	Acute Toxicity of Preventol CMK technical to the Waterflea (*Daphnia magna*) under static conditions. Date: 1993-02-19	Miles Incorporated, Agriculture Division, South Metcalf, Stilwell, Kansas, US	105021	Yes	No	Yes	LANXESS Deutschland GmbH
Geier, J. *et al.*	A6.12.6 Non-key study Published	1996	Contact Allergy due to Industrial Biocides.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **44** (4), 154-159	No	Yes	No	--
Gerharz, T.	A5.3.1	2011a	Determination of disinfectant properties o**f** Preventol® CMK in accordance to EN 1040. Date: 2011-05-26	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
Gerharz, T.	A5.3.1	2011b	Determination of disinfectant properties of Preventol® CMK in accordance to EN 1656 and EN 1657. Date: 2011-05-25	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
Gerharz, T.	A7.1.2.1.2(07) A7.2.1/A7.2.2	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Gerharz, T.	A7.1.2.2.1(02) A7.2.1/A7.2.2	2011b	Degradation of 4-chloro-3-cresol in a liquid environment (washing water after stable cleaning – stable with laying hens). Date: 2011-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
Gerharz, T.	A7.2.1/ A7.2.2 Non-key study/ published	2011c	Vaporisation behaviour of 4-chloro-3-methylphenol from an inert surface (glass petri dish)	LANXESS Deutschland GmbH, Leverkusen, Germany	Lab Report ID: D 2011-22.1.5	No	No	Yes	LANXESS Deutschland GmbH
Gerharz, T.	A7.2.1/A7.2.2 A7.1.2.2.1(02)	2011b	Degradation of 4-chloro-3-cresol in a liquid environment (washing water after stable cleaning – stable with laying hens). Date: 2011-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
Gerharz, T.	A7.2.1/A7.2.2/ A7.1.2.1.2(07)	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH
Goncalo, M. *et al.*	A6.12.6 Non-key study Published	1987	Immediate and delayed sensitivity to chlorocresol.	Clinica de Dermatologica e Venereologica, Coimbra, Portugal	*Contact Dermatitis* **17**, 46-47	No	Yes	No	--

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Grote	B7.5(01) Non-key study	1987	No title. Date: 1987-07-14	LE Environmental Protection/ AWALU, Analytics, Air Laboratory, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Güldner, W.	A3.3(02)	2009	Determination of dustiness (optical dust factor) of Preventol CMK pastilles. Date: 2009-09-30	Bayer CropScience AG, Development, Formulation Technology, Monheim, Germany	FM0045(RP00)G 01	Yes	No	Yes	Bayer CropScience AG
Hancock, B.W. and Naysmith, A.	A6.12.2(02) A6.12.6	1975	Hypersensitivity to Chlorocresol-preserved Heparin. *British Medical Journal:* 746-747, 1975	Royal Hospital, Sheffield, UK	*British Medical Journal*, 746 – 747,	No	Yes	No	--
Hancock, B.W. and Naysmith, A.	A6.12.6 A6.12.2(02)	1975	Hypersensitivity to Chlorocresol-preserved Heparin. *British Medical Journal:* 746-747, 1975	Royal Hospital, Sheffield, UK	*British Medical Journal*, 746 – 747,	No	Yes	No	--
[redacted]	A7.5.3.1.1(01)	1993a	Preventol CMK: An acute oral LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A7.5.3.1.2(01)	1993b	Preventol CMK: A subacute dietary LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Hanstveit, A.O. and Pullens, M.A.H.L.	A7.1.1.2.1(03)	1993	The biodegradability of the product Preventol CMK in a closed bottle test according to a draft OECD guideline: ready biodegradability; the influence of inoculum activity. Date: 1993-01-15 Amended: 2007-03-30	TNO Institute of Environmental Sciences, Delft, The Netherlands	R 92/198	Yes	No	Yes	LANXESS Deutschland GmbH
Heitkamp, D.	A3.11(01)	2006	Determination of safety-relevant data of Preventol CMK Pastillen. Date: 2006-03-29	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/00416	Yes	No	Yes	LANXESS Deutschland GmbH
Herbold, B.A.	A6.6.1(01)	1991	Preventol CMK – Salmonella/Microsome Plate Test. Date: 1991-08-08	Bayer AG, Wuppertal, Germany	20516	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.6.4 Non-key study	1981	Preventol CMK. Micronucleus Test on the Mouse to test for a Mutagenic Effect. Date: 1981-10-16	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A6.6.4(01)	1990	Preventol CMK MICRONUCLEUS TEST ON THE MOUSE. Date: 1990-01-17 Amended: 1991-08-08	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted].	A6.1.1 Non-key study	1981	Acute Oral Toxicity of PCMC (p-Chloro-m-cresol) to rats. Date: 1981-01-06	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Huq, A.S. *et al.*	A6.2 Non-key study Published	1986	Permeation of Water Contaminative Phenols Through Hairless Mouse Skin.	College of Pharmacy, University of Michigan, Ann Arbor, MI, USA	*Arch. Environ. Contam. Toxicol.* **15**, 557-566	No	Yes	No	--
Jennings, J.G., de Nys, R., Charlton, T.S., Duncan, M.W. and Steinberg, P.D.	A7.4.2(03) Non-key study/ published	1996	Phenolic compounds in the nearshore waters of Sidney, Australia. *Mar. Freshwater Res.* ***47****, 951 – 959, 1996*	--	--	No	Yes	No	--
Jonsson, J. and Voigt, G.E.	A6.12.2 Non-key Published	1984	Homicidal intoxications by lye- and parachlorcresol-containing disinfectants.	State Dept. of Forensic Chemistry, Linköping, Sweden	*Am. J. Forensic Med. Pathol.* **5**(1), 57-63	No	Yes	No	--

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Joppich, G.	A6.12.2(03)	1960	Tödliche Vergiftung durch Sagrotan bei Säuglingen.	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **11**; 20 -21	No	Yes	No	--
Joppich, G.	A6.12.7 A6.12.8	1962	Klinik und Behandlung der Sagrotanvergiftung. *Deut. Med. J.*:11; 20 -21, 1960	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **13**; 691-693	No	Yes	No	--
Jungheim R	A7.4.3.4(01) Non-key study/ published	2006	Addendum to Research Report 10603052: Harmful effects of chemicals in the *Daphnia* reproduction test as a basis for assessing their environmental hazard in aquatic systems.	Bayer Industry Services, Leverkusen, Germany	--	Yes	No	Yes	LANXESS Deutschland GmbH
Jungheim, R.	A3.7(01)	2006a	Solubility of Preventol CMK (pellets) in different organic solvents at 10 °C, 20 °C and 30 °C. Date: 2006-11-30	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/09	Yes	No	Yes	LANXESS Deutschland GmbH
Jungheim, R.	A3.9(03)	2006b	Calculation of the partition coefficient (1-octanol/water) at 10 °C, 20 °C and 30 °C based on water solubility and 1-octanol solubility of Preventol CMK (pellets) determined under study number A 01/0108/02 LEV and 2006/0025/09. Date: 2006-12-01	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/08	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Jungheim, R.	A4.1(01)	2006c	Validation of a GC-Method for Preventol CMK (Pellets). Date: 2006-04-21 **CONFIDENTIAL**	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	Study No.: 2006/0014/01	Yes	No	Yes	LANXESS Deutschland GmbH
Kanne, R.	A7.4.1.4(01)	1988	Preventol CMK – Toxicity towards Bacteria. Date: 1988-02-10	Bayer AG, WV-LE Umweltschutz, Leverkusen, Germany	88105507	No	No	Yes	LANXESS Deutschland GmbH
Kao, L.R. and Birnbaum, L.S.	A6.2 Non-key study Published	1986	Disposition of *o*-Benzyl-*p*-Chlorophenol in Male Rats	Systemic Toxicology Branch, NIEHS, Research Triangle Park, NC, USA	*Journal of Toxicology and Environmental Health*, 18, 441 - 458, 1986	No	Yes	No	–
Kirk, P.W.W. & Lester, J.N.	A7.1.2.1.2(04)	1989	Degradation of phenol, selected chlorophenols and chlorophenoxy herbicides during anaerobic sludge digestion. *Environm. Technol. Lett. 10, 405 – 414, 1989*	Public Health Engineering Laboratory, Department of Civil Engineering, Imperial College of Science, Technology and Medicine, London, UK	--	No	Yes	No	--
Königer, A.	A3.10(03)	2010	Amendment to Physicochemical properties: Preventol CMK (pellets). Date: 2010-02-24	CURRENTA GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Körner, W. et al.	A7.1.2.1.1 Non-key Published	1998	Input/output balance of estrogenic active compounds in a major municipal sewage plant in Germany. *Organohalogen Compounds, Vol. 37, 269-272.*	-	-	No	Yes	No	-
Körner, W. et al.	A7.1.2.1.1(11) Non-key Published	2000	Input/output balance of estrogenic active compounds in a major municipal sewage plant in Germany. *Chemosphere, Vol. 40, 1131-1142*	-	-	No	Yes	No	-
Körner, W. *et al.*	A7.1.2.2.2(03)	2001	Steroid analysis and xenosteroid potentials in two small streams in southwest Germany. *Journal of Aquatic Ecosystem Stress and Recovery, 8, 215-229.*	-	-	No	Yes	No	-
Kraus, H.	A3.15(01)	2006b	4-Chloro-3-methylphenol / Explosive properties. Date: 2006-03-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Kraus, H.	A3.16(01)	2006c	4-Chloro-3-methylphenol / Oxidising properties. Date: 2006-03-03	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Kraus, H.	A3.17(01)	2006d	4-Chloro-3-methylphenol (CMK) / Reactivity towards container material. Date: 2006-06-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Kraus, H.	A3.3(01)	2006a	4-Chloro-3-methylphenol / Appearance. Date: 2006-05-23	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Krebber, R.	A4.2(03)	2006	Analytical method 01004 for the determination of Preventol CMK (4-chloro-3-methylphenol) in drinking and surface water by HPLC-MS/MS. Date: 2006-09-05	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/112	Yes	No	Yes	LANXESS Deutschland GmbH
Krötlinger, F.	A6.1.4 Non-key study	1991	Preventol CMK. Date: 1991-02-14	Bayer AG, Fachbereich Toxikologie, Wuppertal, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Kugler, M.	A5.3.1(01)	2003	Determination of the antimicrobial effects of Preventol CMK against bacteria and fungi. Date: 2003-05-22	Bayer Chemicals AG, Leverkusen, Germany	Report No. 2003-05-21	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Kühn, R., Pattard, M., Pernak, K.-D. Winter, A.	A7.4.3.4(01) Non-key study/ published	1988	Research Report 10603052: Harmful effects of chemicals in the *Daphnia* reproduction test as a basis for assessing their environmental hazard in aquatic systems. Date: 1988-03-31	Instiute for Water, Land and Air Hygiene of the Federal German Health Office	--	No	Yes	No	--
Lacorte, S. *et al.*	A7.1.2.2.2(03)/ B7.5(06)	2001	Main findings and conclusions of the implementation of Directive 76/464/CEE concerning the monitoring of organic pollutants in surface waters (Portugal, April 1999 – May 2000). Journal of Environmental Monitoring, 3, 475-482	-	-	No	Yes	No	-
[redacted]	A6.1.4(01)	1976	Preventol CMK – The eye and dermal irritancy of [redacted] sample p-Chloro-m-cresol. Date: 1976-11-30	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Lehn, H.	A6.6.3(01)	1989	Preventol CMK – Mutagenicity Study For The Detection Of Induced Forward Mutations in the CHO-HGPRT Assay in vitro. Date: 1989-02-22	Bayer AG, Wuppertal, Germany	17755	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A6.3.1(01)	1989	Preventol CMK – Range-finding subacute toxicological investigations in Wistar rats for the determination of a maximum tolerable dosage (Administration with food over 4 weeks). Date: 1989-02-20	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.3.2(01)	1993a	PREVENTOL CMK – Preliminary trial for determining the dose for a sub-chronic study on male Wistar rats (dermal treatment for 4 weeks). Date: 1993-10-19	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted].	A6.4.2(01)	1991	Preventol CMK: Subchronic Toxicity Study in Wistar Rats (Dermal Treatment for 13 Weeks). Date: 1991-08-30	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.5(01) A6.7(01)	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A6.7(01) A6.5(01)	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.9 Non-key study	1992	Preventol CMK (PCMC) / Adverse neurological effects. Date: 1992-09-07	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Lewis, P.G. and Emmett, E.A.	A6.12.6(03) published	1987	Irritant dermatitis from tri-butyl tin oxide and contact allergy from chlorocresol.	Johns Hopkins Medical Institutions, Baltimore, MD, USA	*Contact Dermatitis* **7**: 129-132, 1987	No	Yes	No	--
Loehr, R.C. and Matthews, J.E.	A7.2.1/ A7.2.2 Non-key study/ published	1992	Loss of organic chemicals in soil. Pure compound treatability studies. *Journal of Soil Contamination* ***1(4)****, 339-360, 1992*	Environmental and Water Resources Engineering Laboratories, Texas, Austin, USA	--	No	Yes	No	--
Lührs, U.	A7.5.1.2	2007	Acute Toxicity (14 Days) of 4-Chloro-3-methylphenol (Preventol CMK) to the Earthworm *Eisenia fetida* in Artificial Soil with 5% Peat. Date: 2007-01-17	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32326021	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Meinerling, M.	A7.1.3(02) and A7.2.3.1(01)	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH
Meinerling, M.	A7.1.3(02) and A7.2.3.1(01)	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH
Meinerling, M.	A7.2.3.1(01) and A7.1.3(02)	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH
Meinerling, M.	A7.2.3.1(02) and A7.1.3(02)	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH
Meiss, R. *et al.*	A6.10 Non-key study Published	1981	New aspects of the origin of hepatocellular vacuoles.	Univ. of Münster, Germany	*Exp. Path.* **19**, 239-246	No	Yes	No	–

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
MITI (Ministry of International Trade & Industry)	A7.4.2(02) Non-key study/ published	1992	Biodegradation and bioaccumulation: Data of existing chemicals based on the CSCL Japan. Published by Japan Chemical Industry Ecology-Toxicology & Information Center, 1992	--	--	No	Yes	No	--
Möndel, M.	A7.1.2.1.2(06)	2010a	Anaerobic biodegradability of Preventol CMK in digested sludge Date: 2010-05-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 142	Yes	No	Yes	LANXESS Deutschland GmbH
Möndel, M.	A7.1.2.2.2(01)	2009	^{14}C-Preventol CMK: Aerobic degradation of ^{14}C-Preventol CMK in two different aquatic sediment systems. Date: 2009-03-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 85	Yes	No	Yes	LANXESS Deutschland GmbH
Möndel, M.	A7.1.2.2.2(02)	2010b	^{14}C-Preventol CMK: Characterisation of non-identified radioactivity of ^{14}C-Preventol CMK in aquatic sediment systems. Date: 2010-05-21	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 139	Yes	No	Yes	LANXESS Deutschland GmbH
Morris, R.	A7.1.2.1.1(10) Non-key study	2002	Bench Scale Biological Treatment of Preventol CMK for General Motor's Lansing Plant #5 Date: 2002-08-30	Bayer's Corporate Environmental Testing Services Laboratory, New Martinsville, West Virginia	--	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Müller, G.	A7.1.1.2.1(01)	1992	Investigations of the ecological behaviour of Preventol CMK Date: 1992-02-25	Bayer AG, Institut für Umweltananlyse und Bewertungen, Leverkusen, Gemany	A 330 A/91	Yes	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.1.2.1(05) Non-key study	1985	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 C. Date: July 1985	Bayer AG, WV-UWS/LE, Microbiology, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.2.1.1(05) Non-key study	1981	Degradability of p-chloro-m-cresol in the central biological wastewater treatment plant Uerdingen. Date: 1981-08-25	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.2.1.1(06) Non-key study	1983	Elimination of p-chloro-m-cresol (CMK) in the biological wastewater treatment plant Uerdingen. Date: 1983-01-07	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.2.1.1(07) Non-key study	1986	Elimination of chlorometacresol (CMK) in the 2-stage biological wastewater treatment plant UE. Date: 1986-05-16	Bayer Uerdingen Works, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
N.N.	A7.1.2.1.1(08) Non-key study	1988	CMK concentration in the discharge of the Uerdingen biological wastewater treatment plant. Date: 1988-12-02	Bayer Uerdingen Site, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Neuhahn	A7.1.1.2.1(04) A7.1.1.2.2(02) Non-key study	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
Neuhahn	A7.1.1.2.2(02) A7.1.1.2.1(04) Non-key study	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
Neuhahn, A.	A7.1.1.2.1(01, 02, 04)	2012	2. Amendment to GLP-Final Report Study Title: Biodegradation. Re-evaluation based on study report 330 A/91. Date: 2012-05-14	Currenta GmbH & Co. OHG, Leverkusen, Germany	-	No	No	Yes	LANXESS Deutschland GmbH
Neuhahn, A.	A7.4.1.4(03)	2008	Activated Sludge, Respiration Inhibition Test with Preventol CMK Pastillen. Date: 2008-08-19	Currenta GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	2006/0025/16	Yes	No	Yes	Lanxess Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Nitsche, M.	A7.2.2.1	2011	Biodegradation of Preventol® CMK (4-Chloro-3-methylphenol) in soil under aerobic conditions.	LANXESS Deutschland GmbH	2011-07-25	No	No	Yes	LANXESS Deutschland GmbH
O'Conner, O.A. & Young, L.Y.	A7.1.2.1.2(03)	1989	Toxicity and anaerobic biodegradability of substituted phenols under methanogenic conditions. *Environ. Toxicol. Chem.* 8, 853 – 862, 1989	Institute of Environmental Medicine and Department of Microbiology, New York University Medical Center, New York, USA	--	No	Yes	No	--
Oblak	B7.5(02) Non-key study	1989	Determination of 4-chloro-3-methylphenol (CMK) in Rhine water (Ultra Trace range). Date: 1989-12-06	Bayer AG, Uerdingen, Central Analytics, Uerdingen, Germany	LM Ue 50/89	No	No	Yes	LANXESS Deutschland GmbH
Ohlenbusch, G., Kumke, M.U. and Frimmel, F.H.	A7.1.3(01) Non-key study/ published	2000	Sorption of phenols to dissolved organic matter investigated by solid phase microextraction. *The Science of the Total Environment 253, 63 – 74, 2000*	Bereich Wasserchemie, Universität Karlsruhe, Germany	--	No	Yes	No	--
Oleffe J.A. *et al.*	A6.12.6(02) published	1979	Allergy to chlorocresol and propylene glycol in a steroid cream to chlorocresol-preserved heparin	–	*Contact Dermatitis* **5**: 53-54	No	Yes	No	--

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Olf, G.	A3.13(01)	2006b	Surface tension, Physical-chemical properties. Date: 2006-03-17 Amended: 2006-05-10	Bayer AG, BTS-PT-RPT-KPM, Leverkusen, Germany	06/002/03	Yes	No	Yes	LANXESS Deutschland GmbH
Olf, G.	A3.2(01)	2006a	Vapour pressure, Physical-chemical properties. Date: 2006-04-25 Amended: 2006-05-10	Bayer AG, BTS-PT-RPT-KPM, Leverkusen, Germany	06/002/01	Yes	No	Yes	LANXESS Deutschland GmbH
Paul, A.	A7.4.2(01)	2007	p-Chloro-m-cresol (CMK) – Calculation of the bioconcentration factor (BCF) Date: 2007-05-31	DR. KNOELL CONSULT GmbH, Mannheim, Germany	KC-BCF-07/07	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.3(01)	2003	PREVENTOL CMK Study on Acute Inhalation Toxicity Study in Rats according to OECD No. 403. Date: 2003-01-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.3.3	2011	14-Day Repeated Dose Inhalation Toxicity Study with Preventol CMK	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Rast, H.-G. and Kölbl, H.	A7.1.2.2.1(01)	1987	Microbial degradation of Preventol CMK in Rhine water. Date: 1987-10-20 Amended:	Bayer AG, FBT Leverkusen, Germany	LEV 14/76 and LEV 11/76	No	No	Yes	LANXESS Deutschland GmbH
Reis, K.-H.	A7.1.2.1.2(01)	2007	Anaerobic biodegradability of 4-chloro-3-methylphenol (Preventol CMK) in digested sludge: Measurement of gas production	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32321168	Yes	No	Yes	LANXESS Deutschland GmbH
Reis, K.-H.	A7.5.1.1(01)	2007	Effects of 4-Chloro-3-methylphenol (Preventol CMK) on the activity of the soil microflora in the laboratory.	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32322080	Yes	No	Yes	LANXESS Deutschland GmbH
Reusche, W.	A3.6(01) A3.9(01)	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Reusche, W.	A3.9(01) A3.6(01)	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Robenek, H. *et al.*	A6.10 Non-key study Published	1980	Alterations in the Rat Liver Induced by p-Chlor-m-Cresol with Emphasis on the Intercellular Junctions.	Univ. of Münster, Germany	*J. Submicrosc. Cytol.* **12**(4), 635-646	No	Yes	No	–
Roberts, M.S. *et al.*	A6.2(03) Published	1977	Permeability of human epidermis to phenolic compounds.	Pharmacy Dept., Univ. of Sydney, Australia	*J. Pharm. Pharmac.* **29**, 677-683	No	Yes	No	–
Rother	A7.1.2.1.1(09) Non-key study	1996	Preventol CMK, CMK-Na: Analysis of Wastewater from the Leather Industry Date: 1996-01-25	Bayer, Material Protection Unit, Organic Chemicals Business Group, Uerdingen	--	No	No	Yes	LANXESS Deutschland GmbH
Rudner, E.J.	A6.12.6 Non-key study published	1977	North American Group Results	–	*Contact Dermatitis* **3**: 208-209	No	Yes	No	–
[redacted]	A6.2(04)	2009	Mass Balance and Metabolism of [14C]-4-Chloro-3-methylphenol in Male and Female Rats After Single Oral Administration. Date: 2009-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.2 Non-key study	1979	Acute Dermal Administration Study in Male and Female Rabbits. Preventol CMK. Date: 1979-10-12	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A6.3.2(02)	1980	Subchronic Dermal Study in Rabbits. Preventol CMK. Date: 1980-07-31	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Sattar, M.A.	A7.2.1/ A7.2.2 Non-key study/ published	1989	Fate of chlorinated cresols from environmental samples. *Chemosphere **19** (8/9), 1421 – 1426, 1989*	Department of Soil Science, Agricultural University, Mymensingh, Bangladesh	--	No	Yes	No	--
[redacted].	A6.2(01) Non-key study	1980	Excretion kinetics of Preventol CMK after a single oral administration to rats. Date: 1980-12-02	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.2(02) Non-key study	1981	Investigation into the detection of Preventol CMK in fatty tissue and liver tissue in rats. Date: 1981-02-17	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Schmidt-Bäumler, K., *et al.*	A7.1.2.2.2(03)/ B7.5(03)	1999	Occurrence and distribution of organic contaminants in the aquatic system in Berlin. Part II: substituted phenols in Berlin surface water.	-	-	No	Yes	No	-

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Schnaak, W. et al.	A7.1.2.1.1(11) Non-key published	1997	Organic contaminants in sewage sludge and their ecotoxicological significance in the agricultural utilization of sewage sludge. *Chemosphere, Vol. 35, 5-11.*	-	-	No	Yes	No	-
[redacted]	A7.4.3.2(01)	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to Rainbow Trout (*Oncorhynchus mykiss*) in a Prolonged Semi Static Test over 28 Days. Date: 2007-03-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Schulz, L.	A7.5.1.1(02)	2012	Preventol CMK – Effects on the activity of soil microflora (Nitrogen transformation test). Date: 2012-04-13.	BioChem agrar, Labor für biologische und chemische Analytik GmbH 04827 Gerichshain, Germany	Project-No. 12 10 48 011 N,	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.4 Non-key study	2006a	Preventol CMK – Acute Skin Irritation/ Corrosion on Rabbits. Date: 2006-07-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted].	A6.1.4 Non-key study	2006b	Preventol CMK – T 7053199 – Acute Eye Irritation on Rabbits. Date: 2006-07-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A6.1.2(01)	1999	Acute Dermal Toxicity Study with Preventol CMK Pastillen in Rats. Date: 1999-10-29	[redacted]	[redacted]	Yes	No	Yes	[redacted]
Ternes, Th. A.	A7.1.2.1.1(11) Non-key published	1998	Simultaneous determination of antiseptics and acidic drugs in sewage and river water. *Vom Wasser, 90, 295-309.*	-	-	No	Yes	No	-
Thompson, R.S.	A7.1.1.2.2(01)	1993	Parachlorometacresol: Further study of inherent biodegradability. Date: 1993-06-29	Brixham Environmental Laboratory, Zeneca limited, Brixham Devon, UK	BL4783/B	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.3 Non-key study	1981	Preventol CMK, Study for Acute Toxicity of Fumes and Dusts after Inhalation. Date: 1981-10-21	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.4 Non-key study	1978	Preventol CMK, Investigation of Skin and Mucous Membrane Tolerance. Date: 1978-09-20 Addendum: 1983-01-11	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
United States Environmental Protection Agency (EPA) (Ed.)	Published	2009	Reregistration Eligibility Decision for Phenol & Salts	-	EPA 739-R-08-010	No	Yes	No	-

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Uter, W. *et al.*	A6.12.6 Non-key study Published	1993	Contact Allergy in Metal Workers.	Information Network of Dermatological Clinics (IVDK) in Germany	*Dermatosen* **41**(6), 220-227	No	Yes	No	–
Vinken, R. and Wydra, V.	A7.4.1.3(03)	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to *Desmodesmus subspicatus* in an Algal Growth Inhibition Test. Date: 2007-01-04	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32324210	Yes	No	Yes	LANXESS Deutschland GmbH
Voets, J.P., Pipyn, P., van Lancker, P. and Verstrate, W.	A7.1.2.1.2(02)	1976	Degradation of Microbiocides under Different Environmental Conditions. *J. appl. Bact., 40, 67 - 72, 1976*	Laboratory of General and Industrial Microbiology, State University of Gent, Gent, Belgium.	--	No	Yes	No	--
[redacted]	A6.1.5(01)	2000	Preventol CMK, Pastillen LOCAL LYMPH NODE ASSAY IN MICE (LLNA/IMDS). Date: 2000-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Wesener, J.	A3.4(01)	2006	Spectra. Date: 2006-03-14 Amended: 2006-04-03	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/03	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Weyers, A.	A7.1.1.2.1(02)	2007	Preventol CMK – Biodegradation. Re-Evaluation based on Study Report 330 A/91, corresponding raw data and additional information provided by the sponsor. Date: 2007-03-09 Amended: 2007-03-16	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Weyers, A.	A7.4.1.3(02)	2006a	Preventol CMK – Algae, Growth Inhibition Test. Re-Evaluation based on Study Report Growth Inhibition Test Algae (1983) and the corresponding raw data. Date: 2006-07-07	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Weyers, A.	A7.4.1.4(02)	2006b	Preventol CMK – Toxicity towards Bacteria. Re-Evaluation based on Study Report No. 88105507, corresponding raw data and additional information provided by the sponsor. Date: 2006-06-29	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
[redacted]	A7.4.3.1(02)	2006c	Preventol CMK – Fish, prolonged toxicity test. Re-Evaluation based on Study Report 212 A/90FL, corresponding raw data and additional information provided by the sponsor. Date: 2006-07-05	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Weyers, A.	A7.4.3.4(02)	2007	Preventol CMK Pastillen - Daphnia magna Reproduction Test. Date: 2007-03-08	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/0025/10	Yes	No	Yes	Lanxess Deutschland GmbH
Wielpütz, T.	A3.2(03)	2008	4-Chloro-3-methylphenol (Preventol CMK), Batch No.: [redacted] Vapour pressure A.4 (OECD 104). Date: 2008-08-19	Siemens AG, Prozess-Sicherheit, Industriepark Hoechst, Frankfurt am Main, Germany	20080599.01	Yes	No	Yes	LANXESS Deutschland GmbH
Wien, R.	A6.11 Non-key study Published	1939	The Toxicity of *Para*chloro*meta*cresol and of Phenylmercuric Nitrate.	–	*Q.J. Pharm. Pharmacol.* **12**, 212-229	No	Yes	No	–
Wilkinson, J.D. *et al.*	A6.12.6 Non-key study Published	1980	Comparison of Patch Test Results in Two Adjacent Areas of England. II. Medicaments.	Slade Hospital, Oxford & Wycombe General Hospital, England	*Acta Dermatovener (Stockholm)* **60**, 245-249	No	Yes	No	

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Wilmes, R.	A7.1.1.1.2(01)	1988	Tests to determine the photodegradation of 4-chloro-3-methylphenol (Preventol CMK) in water. Determination of the quantum yield of direct photodegradation in water in polychromatic light (ECETOC method). Date: 1988-05-30	Bayer AG, Sector 5. Agrochemicals Business Group, PF-F/CE-ME, Monheim, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Wiseman, H.M. *et al.*	A6.12.2(04) Published	1980	Acute poisoning to Wright´s Vaporizing Fluid.	National Poisons Information Service, London, UK	*Postgraduate Medical Journal:* 56, 166 - 168 (1980)	No	Yes	No	--

Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

List of Studies from which endpoints were established
Part A

Chlorocresol (CMK)

Product-type 6
(Preservatives for products during storage)

FINAL CAR

April 2016

FRANCE

This document is a list of all the validated studies in the PT06 dossier ***from which endpoints were established****.*

1. **List by section**
2. **List by author**

1. List by section

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A2.7(01)	Anonymous	2002	Product specification Preventol CMK pellets. Date: 2002-08-16	LANXESS Deutschland GmbH, Leverkusen, Germany	Art.-No.: 04189671	No	No	Yes	LANXESS Deutschland GmbH
A3.1(01) A3.10(01)	Erstling, K.	2001a	Physicochemical properties: Preventol CMK (pellets). Date: 2001-11-15 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.1(02)	Haßmann, V.	1992	Preventol CMK – Bulk density. Date: 1992-03-06	Bayer AG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.1(03)	Erstling, K.	2007	Melting point of Preventol CMK. Date: 2007-10-17	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0014/04	Yes	No	Yes	LANXESS Deutschland GmbH
A3.1(04)	Erstling, K.	2008	Boiling point of Preventol CMK. Date: 2008-05-15	CURRENTA GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	2006/0025/13	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.10(02)	Ambroz, J.	2000	Determination of the stability of Preventol CMK to normal and elevated temperature. Date: 2000-09-12	ABC Laboratories, Inc., Columbia, Missouri, USA	Study No.: 46189	Yes	No	Yes	LANXESS Deutschland GmbH
A3.10(03)	Königer, A.	2010	Amendment to Physicochemical properties: Preventol CMK (pellets). Date: 2010-02-24	CURRENTA GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.11(01)	Heitkamp, D.	2006	Determination of safety-relevant data of Preventol CMK Pastillen. Date: 2006-03-29	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/00416	Yes	No	Yes	LANXESS Deutschland GmbH
A3.13(01)	Olf, G.	2006b	Surface tension, Physical-chemical properties. Date: 2006-03-17 Amended: 2006-05-10	Bayer AG, BTS-PT-RPT-KPM, Leverkusen, Germany	06/002/03	Yes	No	Yes	LANXESS Deutschland GmbH
A3.15(01)	Kraus, H.	2006b	4-Chloro-3-methylphenol / Explosive properties. Date: 2006-03-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.16(01)	Kraus, H.	2006c	4-Chloro-3-methylphenol / Oxidising properties. Date: 2006-03-03	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.17(01)	Kraus, H.	2006d	4-Chloro-3-methylphenol (CMK) / Reactivity towards container material. Date: 2006-06-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.2(03)	Wielpütz, T.	2008	4-Chloro-3-methylphenol (Preventol CMK), Batch No.: [redacted], Vapour pressure A.4 (OECD 104). Date: 2008-08-19	Siemens AG, Prozess-Sicherheit, Industriepark Hoechst, Frankfurt am Main, Germany	20080599.01	Yes	No	Yes	LANXESS Deutschland GmbH
A3.3(01)	Kraus, H.	2006a	4-Chloro-3-methylphenol / Appearance. Date: 2006-05-23	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A3.4(01)	Wesener, J.	2006	Spectra. Date: 2006-03-14 Amended: 2006-04-03	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/03	No	No	Yes	LANXESS Deutschland GmbH
A3.5(01)	Erstling, K.	2001b	Water solubility. Date: 2001-09-11	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/02 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.6(01) A3.9(01)	Reusche, W.	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.7(01)	Jungheim, R.	2006a	Solubility of Preventol CMK (pellets) in different organic solvents at 10 °C, 20 °C and 30 °C. Date: 2006-11-30	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/09	Yes	No	Yes	LANXESS Deutschland GmbH
A3.9(01) A3.6(01)	Reusche, W.	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A3.9(02) A3.6(02)	Erstling, K.	2001c	Partition coefficient (n-octanol/water) / dissociation constant, Preventol CMK (pellets). Date: 2001-10-23 Amended: 2001-11-14 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A4.1(01)	Jungheim, R.	2006c	Validation of a GC-Method for Preventol CMK (Pellets). Date: 2006-04-21 **CONFIDENTIAL**	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	Study No.: 2006/0014/01	Yes	No	Yes	LANXESS Deutschland GmbH
A4.2(01)	Brumhard, B.	2006	Analytical method 00998 for the determination of residues of Preventol CMK (4-chloro-3-methylphenol) in soil by HPLC-MS/MS. Date: 2006-08-24	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/102	Yes	No	Yes	LANXESS Deutschland GmbH
A4.2(02)	Feldhues, E.	2006b	Validation of an analytical method for the determination of Preventol CMK in air samples. Date: 2006-08-30	Bayer Industry Services, BIS-SUA-Analytics, Leverkusen, Germany	2006/0014/03	Yes	No	Yes	LANXESS Deutschland GmbH
A4.2(03)	Krebber, R.	2006	Analytical method 01004 for the determination of Preventol CMK (4-chloro-3-methylphenol) in drinking and surface water by HPLC-MS/MS. Date: 2006-09-05	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/112	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A5.3.1	Gerharz, T.	2011a	Determination of disinfectant properties of Preventol® CMK in accordance to EN 1040. Date: 2011-05-26	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
A5.3.1	Gerharz, T.	2011b	Determination of disinfectant properties of Preventol® CMK in accordance to EN 1656 and EN 1657. Date: 2011-05-25	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
A5.3.1(01)	Kugler, M.	2003	Determination of the antimicrobial effects of Preventol CMK against bacteria and fungi. Date: 2003-05-22	Bayer Chemicals AG, Leverkusen, Germany	Report No. 2003-05-21	No	No	Yes	LANXESS Deutschland GmbH
A6.1.1(01)	[redacted]	1988a	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1988-08-18	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

A6.1.1(02)	[redacted]	1978 and 1992	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1992-11-24 (revised report)	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.2(01)	[redacted]	1999	Acute Dermal Toxicity Study with Preventol CMK Pastillen in Rats. Date: 1999-10-29	[redacted]	[redacted]	Yes	No	Yes	Bayer Corporation
A6.1.3(01)	[redacted]	2003	PREVENTOL CMK Study on Acute Inhalation Toxicity Study in Rats according to OECD No. 403. Date: 2003-01-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.1.4(01/02)	[redacted].	1976	Preventol CMK – The eye and dermal irritancy of [redacted] sample p-Chloro-m-cresol. Date: 1976-11-30	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.1.5(01)	[redacted]	2000	Preventol CMK, Pastillen LOCAL LYMPH NODE ASSAY IN MICE (LLNA/IMDS). Date: 2000-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

A6.1.5(02)	[redacted]	1980	Preventol CMK– Investigation of sensitizing effect (Maximisation test after Magnusson and Kligman). Date: 1980-01-23	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.2(01) Non-key study	[redacted]	1980	Excretion kinetics of Preventol CMK after a single oral administration to rats. Date: 1980-12-02	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.2(02) Non-key study	[redacted]	1981	Investigation into the detection of Preventol CMK in fatty tissue and liver tissue in rats. Date: 1981-02-17	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.2(03) Published	Roberts, M.S. *et al.*	1977	Permeability of human epidermis to phenolic compounds.	Pharmacy Dept., Univ. of Sydney, Australia	*J. Pharm. Pharmac.* **29**, 677-683	No	Yes	No	–
A6.2(04)	[redacted].	2009	Mass Balance and Metabolism of [14C]-4-Chloro-3-methylphenol in Male and Female Rats After Single Oral Administration. Date: 2009-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.2 Non-key study Published	Huq, A.S. *et al.*	1986	Permeation of Water Contaminative Phenols Through Hairless Mouse Skin.	College of Pharmacy, University of Michigan, Ann Arbor, MI, USA	*Arch. Environ. Contam. Toxicol.* **15**, 557-566	No	Yes	No	--

A6.3.1(01)	[redacted]	1989	Preventol CMK – Range-finding subacute toxicological investigations in Wistar rats for the determination of a maximum tolerable dosage (Administration with food over 4 weeks). Date: 1989-02-20	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.3.2(01)	[redacted]	1993a	PREVENTOL CMK – Preliminary trial for determining the dose for a sub-chronic study on male Wistar rats (dermal treatment for 4 weeks). Date: 1993-10-19	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.3.2(02)	Rutter *et al.*	1980	Subchronic Dermal Study in Rabbits. Preventol CMK. Date: 1980-07-31	Hazleton Laboratories America, Inc., Virginia, USA	Project No. 339-109	Yes	No	Yes	LANXESS Deutschland GmbH
A6.3.3	[redacted]	2011	14-Day Repeated Dose Inhalation Toxicity Study with Preventol CMK	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.4.1(01)	[redacted]	1988	Preventol CMK: Subchronic toxicological study in rats (feeding study lasting 3 month). Date: 1988-11-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

A6.4.2(01)	[redacted]	1991	Preventol CMK: Subchronic Toxicity Study in Wistar Rats (Dermal Treatment for 13 Weeks). Date: 1991-08-30	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.4.1 Non-key study	[redacted]	1981	Preventol CMK: Subchronic toxicological test in rats. 3-Month feeding test. Date: 1981-10-21	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
A6.5(01) A6.7(01)	[redacted].	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.6.1(01)	Herbold, B.A.	1991	Preventol CMK – Salmonella/Microsome Plate Test. Date: 1991-08-08	Bayer AG, Wuppertal, Germany	20516	Yes	No	Yes	LANXESS Deutschland GmbH
A6.6.3(02)	Cifone, M.A.	1988	Mutagenicity Test on Preventol CMK in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay. Date: 1988-10-04	Hazelton Laboratories America, Inc., Kensington, MD, USA	R 4545	Yes	No	Yes	LANXESS Deutschland GmbH

A6.6.3(01)	Lehn, H.	1989	Preventol CMK – Mutagenicity Study For The Detection Of Induced Forward Mutations in the CHO-HGPRT Assay in vitro. Date: 1989-02-22	Bayer AG, Wuppertal, Germany	17755	Yes	No	Yes	LANXESS Deutschland GmbH
A6.6.4(01)	[redacted]	1990	Preventol CMK MICRONUCLEUS TEST ON THE MOUSE. Date: 1990-01-17 Amended: 1991-08-08	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.7(01) A6.5(01)	[redacted]	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.8.1(01)	[redacted]	1991	Preventol CMK - Study for embryotoxic effects in rats after oral administration. Date: 1991-11-29	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.8.2(01)	[redacted]	2006b	4-Chloro-3-methylphenol – Two-Generation Reproduction Study in Rats by Administration in the Diet. Date: 2006-12-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

A6.8.2 Non-key	[redacted]	2006a	4-Chloro-3-methylphenol (Preventol CMK), One-Generation Reproduction Study in Wistar Rats (Pilot Study for a Two-Generation Reproduction Study with Administration in the Diet). Date: 2006-02-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A6.10 Non-key study Published	Meiss, R. *et al.*	1981	New aspects of the origin of hepatocellular vacuoles.	Univ. of Münster, Germany	*Exp. Path.* **19**, 239-246	No	Yes	No	–
A6.10 Non-key study Published	Robenek, H. *et al.*	1980	Alterations in the Rat Liver Induced by p-Chlor-m-Cresol with Emphasis on the Intercellular Junctions.	Univ. of Münster, Germany	*J. Submicrosc. Cytol.* **12**(4), 635-646	No	Yes	No	–
A6.11 Non-key study Published	Wien, R.	1939	The Toxicity of *Para*chloro*meta*cresol and of Phenylmercuric Nitrate.	–	*Q.J. Pharm. Pharmacol.* **12**, 212-229	No	Yes	No	–
A6.12.2(01)	Ainley, E.J., Mackie, I.G. and Macarthur, D.	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
A6.12.2(02) A6.12.6	Hancock, B.W. and Naysmith, A.	1975	Hypersensitivity to Chlorocresol-preserved Heparin. *British Medical Journal:* 746-747, 1975	Royal Hospital, Sheffield, UK	*British Medical Journal*, 746 – 747,	No	Yes	No	--

A6.12.2(03)	Joppich, G.	1960	Tödliche Vergiftung durch Sagrotan bei Säuglingen.	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **11**; 20 -21	No	Yes	No	--
A6.12.2(04) Published	Wiseman, H.M. *et al.*	1980	Acute poisoning to Wright´s Vaporizing Fluid.	National Poisons Information Service, London, UK	*Postgraduate Medical Journal:* 56, 166 - 168 (1980)	No	Yes	No	--
A6.12.2 Non-key Published	Jonsson, J. and Voigt, G.E.	1984	Homicidal intoxications by lye- and parachlor-cresol-containing disinfectants.	State Dept. of Forensic Chemistry, Linköping, Sweden	*Am. J. Forensic Med. Pathol.* **5**(1), 57-63	No	Yes	No	--
A6.12.6(01)	Angelini, G. *et al.*	1975	Contact dermatitis in patients with leg ulcers.	Dept. of Dermatology, Univ. of Bari, Italy	*Contact Dermatitis* **1**, 81-87	No	Yes	No	–
A6.12.6(02) published	Oleffe J.A. *et al.*	1979	Allergy to chlorocresol and propylene glycol in a steroid cream to chlorocresol-preserved heparin	–	*Contact Dermatitis* **5**: 53-54	No	Yes	No	--
A6.12.6(03) published	Lewis, P.G. and Emmett, E.A.	1987	Irritant dermatitis from tri-butyl tin oxide and contact allergy from chlorocresol.	Johns Hopkins Medical Institutions, Baltimore, MD, USA	*Contact Dermatitis* **7**: 129-132, 1987	No	Yes	No	--
A6.12.6 Non-key study Published	Andersen, K.E. and Veien, N.K.	1985	Biocide patch tests	Gentofte Hospital, Hellerup, Denmark	*Contact Dermatitis* **12**, 99-103	No	Yes	No	–
A6.12.6 Non-key Published	Archer, C.B. and MacDonald, D.M.	1984	Chlorocresol sensitivity induced by treatment of allergic contact dermatitis with steroid creams.	Dept. of Dermatology, Guy's Hospital, London, UK	*Contact Dermatitis* **11**, 144-145	No	Yes	No	–

A6.12.6 Non-key study Published	Brasch, J. *et al.*	1993	Patch Test Reactions to a Preliminary Preservative Series.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **41**,2; 71-76	No	Yes	No	--
A6.12.6 Non-key study Published	Burry, J.N. *et al.*	1975	Chlorocresol sensitivity	St. Peters, South Australia	*Contact Dermatitis* **1**, 41-42	No	Yes	No	--
A6.12.6 Non-key study Published	de Boer, E.M. *et al.*	1989	Dermatoses in metal workers (II). Allergic contact dermatitis.	Free University Academic Hospital, Amsterdam, The Netherlands	*Contact Dermatitis* **20**, 280-286	No	Yes	No	–
A6.12.6 Non-key study Published	Dooms-Goossen, A. *Et al.*	1981	Chlorocresol and chloracetamide: Allergens in medications, glues, and cosmetics	Dept. Of Dermatology, Academisch Ziekenhuis St.Peter, Leuven, Belgium	*Contact Dermatitis* **7**, 51-52	No	Yes	No	–
A6.12.6 Non-key study Published	Freitas, J.P. and Brandao, F.M.	1986	Contact urticaria to chlorocresol.	Dept. Of Dermatology, Santa Maria Hospital, Lisbon, Portugal	*Contact Dermatitis* **15**, 252	No	Yes	No	–
A6.12.6 Non-key study Published	Geier, J. *et al.*	1996	Contact Allergy due to Industrial Biocides.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **44** (4), 154-159	No	Yes	No	--
A6.12.6 Non-key study Published	Goncalo, M. *et al.*	1987	Immediate and delayed sensitivity to chlorocresol.	Clinica de Dermatologica e Venereologica, Coimbra, Portugal	*Contact Dermatitis* **17**, 46-47	No	Yes	No	--
A6.12.6 Non-key study published	Rudner, E.J.	1977	North American Group Results	–	*Contact Dermatitis* **3**: 208-209	No	Yes	No	–
A6.12.6 Non-key study Published	Uter, W. *et al.*	1993	Contact Allergy in Metal Workers.	Information Network of Dermatological Clinics (IVDK) in Germany	*Dermatosen* **41**(6), 220-227	No	Yes	No	–

A6.12.6 Non-key study Published	Wilkinson, J.D. *et al.*	1980	Comparison of Patch Test Results in Two Adjacent Areas of England. II. Medicaments.	Slade Hospital, Oxford & Wycombe General Hospital, England	*Acta Dermatovener (Stockholm)* **60**, 245-249	No	Yes	No	
A6.12.7 A6.12.8	Joppich, G.	1962	Klinik und Behandlung der Sagrotanvergiftung. *Deut. Med. J.*:11; 20 - 21, 1960	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **13**; 691-693	No	Yes	No	--
A7.1.1.1.1(01)	Erstling, K. and Feldhues, E.	2001a	Abiotic degradation. Date: 2001-08-31 Amended: 2007-02-22	Bayer AG, Zentrale Analytik, Leverkusen, Germany	A 01/0108/04 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(01)	Müller, G.	1992	Investigations of the ecological behaviour of Preventol CMK Date: 1992-02-25	Bayer AG, Institut für Umweltananlyse und Bewertungen, Leverkusen, Gemany	A 330 A/91	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(02)	Weyers, A.	2007	Preventol CMK – Biodegradation. Re-Evaluation based on Study Report 330 A/91, corresponding raw data and additional information provided by the sponsor. Date: 2007-03-09 Amended: 2007-03-16	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(01, 02, 04)	Neuhahn, A.	2012	2. Amendment to GLP-Final Report Study Title: Biodegradation. Re-evaluation based on study report 330 A/91. Date: 2012-05-14	Currenta GmbH & Co. OHG, Leverkusen, Germany	-	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.1.2.1(03)	Hanstveit, A.O. and Pullens, M.A.H.L.	1993	The biodegradability of the product Preventol CMK in a closed bottle test according to a draft OECD guideline: ready biodegradability; the influence of inoculum activity. Date: 1993-01-15 Amended: 2007-03-30	TNO Institute of Environmental Sciences, Delft, The Netherlands	R 92/198	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(04) A7.1.1.2.2(02) Non-key study	Neuhahn	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.1(05) Non-key study	N.N.	1985	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 C. Date: July 1985	Bayer AG, WV-UWS/LE, Microbiology, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.1.2.2(01)	Thompson, R.S.	1993	Parachlorometacresol: Further study of inherent biodegradability. Date: 1993-06-29	Brixham Environmental Laboratory, Zeneca limited, Brixham Devon, UK	BL4783/B	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.1.2.2(02) A7.1.1.2.1(04) Non-key study	Neuhahn	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(02) Non-key study	Dohm	1981	Biodegradability of Preventol CMK. Date: 1981-08-20	Bayer Uerdingen Site, Organic Chemicals Division, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(03) Non-key study	Dohm	1984	CMK content in ppb in wastewater, Uerdingen wastewater treatment plant. Date: 1984-07-03	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(04) Non-key study	Dohm	1985	CMK in the wastewater treatment plant outlet. Date: 1985-03-01	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(05) Non-key study	N.N.	1981	Degradability of p-chloro-m-cresol in the central biological wastewater treatment plant Uerdingen. Date: 1981-08-25	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.1(06) Non-key study	N.N.	1983	Elimination of p-chloro-m-cresol (CMK) in the biological wastewater treatment plant Uerdingen. Date: 1983-01-07	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(07) Non-key study	N.N.	1986	Elimination of chlorometacresol (CMK) in the 2-stage biological wastewater treatment plant UE. Date: 1986-05-16	Bayer Uerdingen Works, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(08) Non-key study	N.N.	1988	CMK concentration in the discharge of the Uerdingen biological wastewater treatment plant. Date: 1988-12-02	Bayer Uerdingen Site, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(09) Non-key study	Rother	1996	Preventol CMK, CMK-Na: Analysis of Wastewater from the Leather Industry Date: 1996-01-25	Bayer, Material Protection Unit, Organic Chemicals Business Group, Uerdingen	--	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.1(10) Non-key study	Morris, R.	2002	Bench Scale Biological Treatment of Preventol CMK for General Motor's Lansing Plant #5 Date: 2002-08-30	Bayer's Corporate Environmental Testing Services Laboratory, New Martinsville, West Virginia	--	No	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.1.2(01)	Reis, K.-H.	2007	Anaerobic biodegradability of 4-chloro-3-methylphenol (Preventol CMK) in digested sludge: Measurement of gas production	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32321168	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.2(06)	Möndel, M.	2010a	Anaerobic biodegradability of Preventol CMK in digested sludge Date: 2010-05-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 142	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.2.1.2(07) A7.2.1/A7.2.2	Gerharz, T.	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.2.1(01)	Rast, H.-G. and Kölbl, H.	1987	Microbial degradation of Preventol CMK in Rhine water. Date: 1987-10-20 Amended:	Bayer AG, FBT Leverkusen, Germany	LEV 14/76 and LEV 11/76	No	No	Yes	LANXESS Deutschland GmbH
A7.1.2.2.2(01)	Möndel, M.	2009	^{14}C-Preventol CMK: Aerobic degradation of ^{14}C-Preventol CMK in two different aquatic sediment systems. Date: 2009-03-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 85	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.2.2(02)	Möndel, M.	2010b	^{14}C-Preventol CMK: Characterisation of non-identified radioactivity of ^{14}C-Preventol CMK in aquatic sediment systems. Date: 2010-05-21	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 139	Yes	No	Yes	LANXESS Deutschland GmbH
B7.5(01) Non-key study	Grote	1987	No title. Date: 1987-07-14	LE Environmental Protection/ AWALU, Analytics, Air Laboratory, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
B7.5(02) Non-key study	Oblak	1989	Determination of 4-chloro-3-methylphenol (CMK) in Rhine water (Ultra Trace range). Date: 1989-12-06	Bayer AG, Uerdingen, Central Analytics, Uerdingen, Germany	LM Ue 50/89	No	No	Yes	LANXESS Deutschland GmbH
A7.1.3(01)	Erstling, K. and Feldhues, E.	2001b	Adsorption/Desorption. Date: 2001-09-13 Amended: 2001-11-13 and 2007-02-22	Bayer AG, ZF – Zentrale Analytik, Leverkusen, Germany	A 01/0108/05/ LEV	Yes	No	Yes	LANXESS Deutschland GmbH
A7.1.3(02) and A7.2.3.1(01)	Meinerling, M.	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.3(02) and A7.2.3.1(01)	Meinerling, M.	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH
A7.2.1/A7.2.2/ A7.1.2.1.2(07)	Gerharz, T.	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH
A7.2.2.1	Nitsche, M.	2011	Biodegradation of Preventol® CMK (4-Chloro-3-methylphenol) in soil under aerobic conditions.	LANXESS Deutschland GmbH	2011-07-25	No	No	Yes	LANXESS Deutschland GmbH
A7.2.3.1(01) and A7.1.3(02)	Meinerling, M.	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH
A7.2.3.1(02) and A7.1.3(02)	Meinerling, M.	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.1.1(01)	[redacted]	1993a	Acute Toxicity of Preventol CMK Technical to the Rainbow Trout (*Oncorhynchus mykiss*) Under Static Renewal Conditions. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.1.2(01)	Gagliano, G.G. and Bowers, L.M.	1993b	Acute Toxicity of Preventol CMK technical to the Waterflea (*Daphnia magna*) under static conditions. Date: 1993-02-19	Miles Incorporated, Agriculture Division, South Metcalf, Stilwell, Kansas, US	105021	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.1.3(03)	Vinken, R. and Wydra, V.	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to *Desmodesmus subspicatus* in an Algal Growth Inhibition Test. Date: 2007-01-04	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32324210	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.1.4(03)	Neuhahn, A.	2008	Activated Sludge, Respiration Inhibition Test with Preventol CMK Pastillen. Date: 2008-08-19	Currenta GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	2006/0025/16	Yes	No	Yes	Lanxess Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.3.1(01)	[redacted]	1991	Preventol CMK: Prolonged Toxicity Test with Zebrafish (Brachydanio rerio). Date: 1991-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.3.1(02)	[redacted]	2006c	Preventol CMK – Fish, prolonged toxicity test. Re-Evaluation based on Study Report 212 A/90FL, corresponding raw data and additional information provided by the sponsor. Date: 2006-07-05	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.3.2(01)	[redacted] and Wydra, V.	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to Rainbow Trout (*Oncorhynchus mykiss*) in a Prolonged Semi Static Test over 28 Days. Date: 2007-03-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.4.3.4(01) Non-key study/	Jungheim R	2006	Addendum to Research Report 10603052: Harmful effects of chemicals in the *Daphnia* reproduction test as a basis for assessing their environmental hazard in aquatic systems.	Bayer Industry Services, Leverkusen, Germany	--	Yes	No	Yes	LANXESS Deutschland GmbH
A7.4.3.4(02)	Weyers, A.	2007	Preventol CMK Pastillen - Daphnia magna Reproduction Test. Date: 2007-03-08	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/0025/10	Yes	No	Yes	Lanxess Deutschland GmbH
A7.5.1.1(01)	Reis, K.-H.	2007	Effects of 4-Chloro-3-methylphenol (Preventol CMK) on the activity of the soil microflora in the laboratory.	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32322080	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.1.1(02)	Schulz, L.	2012	Preventol CMK – Effects on the activity of soil microflora (Nitrogen transformation test). Date: 2012-04-13.	BioChem agrar, Labor für biologische und chemische Analytik GmbH 04827 Gerichshain, Germany	Project-No. 12 10 48 011 N,	Yes	No	Yes	LANXESS Deutschland GmbH

Section No. in Doc III-A	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.5.1.2	Lührs, U.	2007	Acute Toxicity (14 Days) of 4-Chloro-3-methylphenol (Preventol CMK) to the Earthworm *Eisenia fetida* in Artificial Soil with 5% Peat. Date: 2007-01-17	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32326021	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.1.3(01)	Buetzler, R. and Meinerling, M.	2007	Effects of Preventol CMK on terrestrial (non-target) plants: Seedling emergence and seedling growth test	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32327086	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.3.1.1(01)	[redacted]	1993a	Preventol CMK: An acute oral LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
A7.5.3.1.2(01)	[redacted].	1993b	Preventol CMK: A subacute dietary LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

2. List by author

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Ambroz, J.	A3.10(02)	2000	Determination of the stability of Preventol CMK to normal and elevated temperature. Date: 2000-09-12	ABC Laboratories, Inc., Columbia, Missouri, USA	Study No.: 46189	Yes	No	Yes	LANXESS Deutschland GmbH
Andersen, K.E. and Veien, N.K.	A6.12.6 Non-key study Published	1985	Biocide patch tests	Gentofte Hospital, Hellerup, Denmark	*Contact Dermatitis* **12**, 99-103	No	Yes	No	–
Angelini, G. *et al.*	A6.12.6(01)	1975	Contact dermatitis in patients with leg ulcers.	Dept. of Dermatology, Univ. of Bari, Italy	*Contact Dermatitis* **1**, 81-87	No	Yes	No	–
Anonymous	A2.7(01)	2002	Product specification Preventol CMK pellets. Date: 2002-08-16	LANXESS Deutschland GmbH, Leverkusen, Germany	Art.-No.: 04189671	No	No	Yes	LANXESS Deutschland GmbH
Archer, C.B. and MacDonald, D.M.	A6.12.6 Non-key Published	1984	Chlorocresol sensitivity induced by treatment of allergic contact dermatitis with steroid creams.	Dept. of Dermatology, Guy's Hospital, London, UK	*Contact Dermatitis* **11**, 144-145	No	Yes	No	–

[redacted]	A6.8.1(01)	1991	Preventol CMK - Study for embryotoxic effects in rats after oral administration. Date: 1991-11-29	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.1(01)	1988a	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1988-08-18	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.1(02)	1978 and 1992	Preventol CMK Untersuchung zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Date: 1992-11-24 (revised report)	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.5(02)	1980	Preventol CMK–Investigation of sensitizing effect (Maximisation test after Magnusson and Kligman). Date: 1980-01-23	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Brasch, J. *et al.*	A6.12.6 Non-key study Published	1993	Patch Test Reactions to a Preliminary Preservative Series.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **41**,2; 71-76	No	Yes	No	--
Brumhard, B.	A4.2(01)	2006	Analytical method 00998 for the determination of residues of Preventol CMK (4-chloro-3-methylphenol) in soil by HPLC-MS/MS. Date: 2006-08-24	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/102	Yes	No	Yes	LANXESS Deutschland GmbH

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Buetzler, R. and Meinerling, M.	A7.5.1.3(01)	2007	Effects of Preventol CMK on terrestrial (non-target) plants: Seedling emergence and seedling growth test	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32327086	Yes	No	Yes	LANXESS Deutschland GmbH
Burry, J.N. *et al.*	A6.12.6 Non-key study Published	1975	Chlorocresol sensitivity	St. Peters, South Australia	*Contact Dermatitis* **1**, 41-42	No	Yes	No	--
[redacted]	A7.4.3.1(01)	1991	Preventol CMK: Prolonged Toxicity Test with Zebrafish (Brachydanio rerio). Date: 1991-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Cifone, M.A.	A6.6.3(02)	1988	Mutagenicity Test on Preventol CMK in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay. Date: 1988-10-04	Hazelton Laboratories America, Inc., Kensington, MD, USA	R 4545	Yes	No	Yes	LANXESS Deutschland GmbH
de Boer, E.M. *et al.*	A6.12.6 Non-key study Published	1989	Dermatoses in metal workers (II). Allergic contact dermatitis.	Free University Academic Hospital, Amsterdam, The Netherlands	*Contact Dermatitis* **20**, 280-286	No	Yes	No	–

Authors (s)	Section No. in Doc III-A	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Dohm	A7.1.2.1.1(02) Non-key study	1981	Biodegradability of Preventol CMK. Date: 1981-08-20	Bayer Uerdingen Site, Organic Chemicals Division, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Dohm	A7.1.2.1.1(03) Non-key study	1984	CMK content in ppb in wastewater, Uerdingen wastewater treatment plant. Date: 1984-07-03	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Dohm	A7.1.2.1.1(04) Non-key study	1985	CMK in the wastewater treatment plant outlet. Date: 1985-03-01	Bayer Uerdingen Site, Organics BG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Dooms-Goossen, A. *Et al.*	A6.12.6 Non-key study Published	1981	Chlorocresol and chloracetamide: Allergens in medications, glues, and cosmetics	Dept. Of Dermatology, Academisch Ziekenhuis St.Peter, Leuven, Belgium	*Contact Dermatitis* **7**, 51-52	No	Yes	No	–
[redacted]	A6.8.2 Non-key	2006a	4-Chloro-3-methylphenol (Preventol CMK), One-Generation Reproduction Study in Wistar Rats (Pilot Study for a Two-Generation Reproduction Study with Administration in the Diet). Date: 2006-02-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

[redacted]	A6.8.2(01)	2006b	4-Chloro-3-methylphenol – Two-Generation Reproduction Study in Rats by Administration in the Diet. Date: 2006-12-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.4.1 Non-key study	1981	Preventol CMK: Subchronic toxicological test in rats. 3-Month feeding test. Date: 1981-10-21	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.4.1(01)	1988	Preventol CMK: Subchronic toxicological study in rats (feeding study lasting 3 month). Date: 1988-11-24	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
Erstling, K.	A3.1(01) A3.10(01)	2001a	Physicochemical properties: Preventol CMK (pellets). Date: 2001-11-15 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K.	A3.1(03)	2007	Melting point of Preventol CMK. Date: 2007-10-17	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0014/04	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K.	A3.1(04)	2008	Boiling point of Preventol CMK. Date: 2008-05-15	CURRENTA GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	2006/0025/13	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K.	A3.5(01)	2001b	Water solubility. Date: 2001-09-11	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/02 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Erstling, K.	A3.9(02) A3.6(02)	2001c	Partition coefficient (n-octanol/water) / dissociation constant, Preventol CMK (pellets). Date: 2001-10-23 Amended: 2001-11-14 Amended: 2006-03-29	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	A 01/0108/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K. and Feldhues, E.	A7.1.1.1.1(01)	2001a	Abiotic degradation. Date: 2001-08-31 Amended: 2007-02-22	Bayer AG, Zentrale Analytik, Leverkusen, Germany	A 01/0108/04 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Erstling, K. and Feldhues, E.	A7.1.3(01)	2001b	Adsorption/Desorption. Date: 2001-09-13 Amended: 2001-11-13 and 2007-02-22	Bayer AG, ZF – Zentrale Analytik, Leverkusen, Germany	A 01/0108/05/ LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Feldhues, E.	A4.2(02)	2006b	Validation of an analytical method for the determination of Preventol CMK in air samples. Date: 2006-08-30	Bayer Industry Services, BIS-SUA-Analytics, Leverkusen, Germany	2006/0014/03	Yes	No	Yes	LANXESS Deutschland GmbH
Freitas, J.P. and Brandao, F.M.	A6.12.6 Non-key study Published	1986	Contact urticaria to chlorocresol.	Dept. Of Dermatology, Santa Maria Hospital, Lisbon, Portugal	*Contact Dermatitis* **15**, 252	No	Yes	No	–

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
[redacted]	A7.4.1.1(01)	1993a	Acute Toxicity of Preventol CMK Technical to the Rainbow Trout (*Oncorhynchus mykiss*) Under Static Renewal Conditions. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Gagliano, G.G. and Bowers, L.M.	A7.4.1.2(01)	1993b	Acute Toxicity of Preventol CMK technical to the Waterflea (*Daphnia magna*) under static conditions. Date: 1993-02-19	Miles Incorporated, Agriculture Division, South Metcalf, Stilwell, Kansas, US	105021	Yes	No	Yes	LANXESS Deutschland GmbH
Geier, J. *et al.*	A6.12.6 Non-key study Published	1996	Contact Allergy due to Industrial Biocides.	Information Network of Dermatological Clinics (IVDK)	*Dermatosen* **44** (4), 154-159	No	Yes	No	--
Gerharz, T.	A5.3.1	2011a	Determination of disinfectant properties o**f** Preventol® CMK in accordance to EN 1040. Date: 2011-05-26	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH
Gerharz, T.	A5.3.1	2011b	Determination of disinfectant properties of Preventol® CMK in accordance to EN 1656 and EN 1657. Date: 2011-05-25	LANXESS Deutschland GmbH, ACD TM Disinfection & Microbiology, Leverkusen, Germany	None	No	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Gerharz, T.	A7.1.2.1.2(07) A7.2.1/A7.2.2	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH
Gerharz, T.	A7.2.1/A7.2.2/ A7.1.2.1.2(07)	2011a	Degradation of 4-chloro-3-cresol in pork liquid manure under anaerobic conditions. Date: 20111-05-26	LANXESS Deutschland GmbH, Leverkusen, Germany	D 2011-10	No	No	Yes	LANXESS Deutschland GmbH
Goncalo, M. *et al.*	A6.12.6 Non-key study Published	1987	Immediate and delayed sensitivity to chlorocresol.	Clinica de Dermatologica e Venereologica, Coimbra, Portugal	*Contact Dermatitis* **17**, 46-47	No	Yes	No	--
Grote	B7.5(01) Non-key study	1987	No title. Date: 1987-07-14	LE Environmental Protection/ AWALU, Analytics, Air Laboratory, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Hancock, B.W. and Naysmith, A.	A6.12.2(02) A6.12.6	1975	Hypersensitivity to Chlorocresol-preserved Heparin. *British Medical Journal:* 746-747, 1975	Royal Hospital, Sheffield, UK	*British Medical Journal*, 746 – 747,	No	Yes	No	--

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
[redacted]	A7.5.3.1.1(01)	1993a	Preventol CMK: An acute oral LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A7.5.3.1.2(01)	1993b	Preventol CMK: A subacute dietary LD_{50} with Bobwhite Quail. Date: 1993-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Hanstveit, A.O. and Pullens, M.A.H.L.	A7.1.1.2.1(03)	1993	The biodegradability of the product Preventol CMK in a closed bottle test according to a draft OECD guideline: ready biodegradability; the influence of inoculum activity. Date: 1993-01-15 Amended: 2007-03-30	TNO Institute of Environmental Sciences, Delft, The Netherlands	R 92/198	Yes	No	Yes	LANXESS Deutschland GmbH
Haßmann, V.	A3.1(02)	1992	Preventol CMK – Bulk density. Date: 1992-03-06	Bayer AG, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Heitkamp, D.	A3.11(01)	2006	Determination of safety-relevant data of Preventol CMK Pastillen. Date: 2006-03-29	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/00416	Yes	No	Yes	LANXESS Deutschland GmbH

Herbold, B.A.	A6.6.1(01)	1991	Preventol CMK – Salmonella/Microsome Plate Test. Date: 1991-08-08	Bayer AG, Wuppertal, Germany	20516	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.6.4(01)	1990	Preventol CMK MICRONUCLEUS TEST ON THE MOUSE. Date: 1990-01-17 Amended: 1991-08-08	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Huq, A.S. *et al.*	A6.2 Non-key study Published	1986	Permeation of Water Contaminative Phenols Through Hairless Mouse Skin.	College of Pharmacy, University of Michigan, Ann Arbor, MI, USA	*Arch. Environ. Contam. Toxicol*. **15**, 557-566	No	Yes	No	--
Jonsson, J. and Voigt, G.E.	A6.12.2 Non-key Published	1984	Homicidal intoxications by lye- and parachlorcresol-containing disinfectants.	State Dept. of Forensic Chemistry, Linköping, Sweden	*Am. J. Forensic Med. Pathol.* **5**(1), 57-63	No	Yes	No	--
Joppich, G.	A6.12.2(03)	1960	Tödliche Vergiftung durch Sagrotan bei Säuglingen.	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **11**; 20 -21	No	Yes	No	--
Joppich, G.	A6.12.7 A6.12.8	1962	Klinik und Behandlung der Sagrotanvergiftung. *Deut. Med. J.*:11; 20 -21, 1960	University Children's Hospital Göttingen, Germany	*Deut. Med. J.* **13**; 691-693	No	Yes	No	--
Jungheim R	A7.4.3.4(01) Non-key study/	2006	Addendum to Research Report 10603052: Harmful effects of chemicals in the *Daphnia* reproduction test as a basis for assessing their environmental hazard in aquatic systems.	Bayer Industry Services, Leverkusen, Germany	--	Yes	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Jungheim, R.	A3.7(01)	2006a	Solubility of Preventol CMK (pellets) in different organic solvents at 10 °C, 20 °C and 30 °C. Date: 2006-11-30	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/09	Yes	No	Yes	LANXESS Deutschland GmbH
Jungheim, R.	A4.1(01)	2006c	Validation of a GC-Method for Preventol CMK (Pellets). Date: 2006-04-21 **CONFIDENTIAL**	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	Study No.: 2006/0014/01	Yes	No	Yes	LANXESS Deutschland GmbH
Königer, A.	A3.10(03)	2010	Amendment to Physicochemical properties: Preventol CMK (pellets). Date: 2010-02-24	CURRENTA GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	A 01/0108/01 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Kraus, H.	A3.15(01)	2006b	4-Chloro-3-methylphenol / Explosive properties. Date: 2006-03-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Kraus, H.	A3.16(01)	2006c	4-Chloro-3-methylphenol / Oxidising properties. Date: 2006-03-03	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Kraus, H.	A3.17(01)	2006d	4-Chloro-3-methylphenol (CMK) / Reactivity towards container material. Date: 2006-06-01	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Kraus, H.	A3.3(01)	2006a	4-Chloro-3-methylphenol / Appearance. Date: 2006-05-23	LANXESS Deutschland GmbH, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Krebber, R.	A4.2(03)	2006	Analytical method 01004 for the determination of Preventol CMK (4-chloro-3-methylphenol) in drinking and surface water by HPLC-MS/MS. Date: 2006-09-05	Bayer Crop Science AG, Development, Residues, Operator and Consumer Safety, Monheim am Rhein, Germany	MR-06/112	Yes	No	Yes	LANXESS Deutschland GmbH
Kugler, M.	A5.3.1(01)	2003	Determination of the antimicrobial effects of Preventol CMK against bacteria and fungi. Date: 2003-05-22	Bayer Chemicals AG, Leverkusen, Germany	Report No. 2003-05-21	No	No	Yes	LANXESS Deutschland GmbH
[redacted].	A6.1.4(01/02)	1976	Preventol CMK – The eye and dermal irritancy of [redacted] sample p-Chloro-m-cresol. Date: 1976-11-30	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH

Lehn, H.	A6.6.3(01)	1989	Preventol CMK – Mutagenicity Study For The Detection Of Induced Forward Mutations in the CHO-HGPRT Assay in vitro. Date: 1989-02-22	Bayer AG, Wuppertal, Germany	17755	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.3.1(01)	1989	Preventol CMK – Range-finding subacute toxicological investigations in Wistar rats for the determination of a maximum tolerable dosage (Administration with food over 4 weeks). Date: 1989-02-20	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.3.2(01)	1993a	PREVENTOL CMK – Preliminary trial for determining the dose for a sub-chronic study on male Wistar rats (dermal treatment for 4 weeks). Date: 1993-10-19	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.4.2(01)	1991	Preventol CMK: Subchronic Toxicity Study in Wistar Rats (Dermal Treatment for 13 Weeks). Date: 1991-08-30	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted].	A6.5(01) A6.7(01)	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH

[redacted]	A6.7(01) A6.5(01)	1993b	Preventol CMK: Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 105 Weeks). Date: 1993-04-02 Addendum: 1994-12-06	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Lewis, P.G. and Emmett, E.A.	A6.12.6(03) published	1987	Irritant dermatitis from tri-butyl tin oxide and contact allergy from chlorocresol.	Johns Hopkins Medical Institutions, Baltimore, MD, USA	*Contact Dermatitis* **7**: 129-132, 1987	No	Yes	No	--
Lührs, U.	A7.5.1.2	2007	Acute Toxicity (14 Days) of 4-Chloro-3-methylphenol (Preventol CMK) to the Earthworm *Eisenia fetida* in Artificial Soil with 5% Peat. Date: 2007-01-17	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32326021	Yes	No	Yes	LANXESS Deutschland GmbH
Meinerling, M.	A7.1.3(02) and A7.2.3.1(01)	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH
Meinerling, M.	A7.1.3(02) and A7.2.3.1(01)	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH
Meinerling, M.	A7.2.3.1(01) and A7.1.3(02)	2007	Determination of the Adsorption / Desorption behaviour of 4-Chloro-3-methylphenol (Preventol CMK) Date: 2007-06-20	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany,	32323195	Yes	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Meinerling, M.	A7.2.3.1(02) and A7.1.3(02)	2008	Determination of the Stability of 4-Chloro-3-methylphenol (Preventol CMK) in Soils of an Adsorption/Desorption Study	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	45821195	Yes	No	Yes	LANXESS Deutschland GmbH
Meiss, R. *et al.*	A6.10 Non-key study Published	1981	New aspects of the origin of hepatocellular vacuoles.	Univ. of Münster, Germany	*Exp. Path.* **19**, 239-246	No	Yes	No	–
Möndel, M.	A7.1.2.1.2(06)	2010a	Anaerobic biodegradability of Preventol CMK in digested sludge Date: 2010-05-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 142	Yes	No	Yes	LANXESS Deutschland GmbH
Möndel, M.	A7.1.2.2.2(01)	2009	^{14}C-Preventol CMK: Aerobic degradation of ^{14}C-Preventol CMK in two different aquatic sediment systems. Date: 2009-03-26	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 85	Yes	No	Yes	LANXESS Deutschland GmbH
Möndel, M.	A7.1.2.2.2(02)	2010b	^{14}C-Preventol CMK: Characterisation of non-identified radioactivity of ^{14}C-Preventol CMK in aquatic sediment systems. Date: 2010-05-21	RLP AgroScience GmbH, Neustadt a.d. Weinstraße, Gemany	AS 139	Yes	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Morris, R.	A7.1.2.1.1(10) Non-key study	2002	Bench Scale Biological Treatment of Preventol CMK for General Motor's Lansing Plant #5 Date: 2002-08-30	Bayer's Corporate Environmental Testing Services Laboratory, New Martinsville, West Virginia	--	No	No	Yes	LANXESS Deutschland GmbH
Müller, G.	A7.1.1.2.1(01)	1992	Investigations of the ecological behaviour of Preventol CMK Date: 1992-02-25	Bayer AG, Institut für Umweltananlyse und Bewertungen, Leverkusen, Gemany	A 330 A/91	Yes	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.1.2.1(05) Non-key study	1985	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 C. Date: July 1985	Bayer AG, WV-UWS/LE, Microbiology, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.2.1.1(05) Non-key study	1981	Degradability of p-chloro-m-cresol in the central biological wastewater treatment plant Uerdingen. Date: 1981-08-25	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.2.1.1(06) Non-key study	1983	Elimination of p-chloro-m-cresol (CMK) in the biological wastewater treatment plant Uerdingen. Date: 1983-01-07	Bayer Uerdingen Site, UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
N.N.	A7.1.2.1.1(07) Non-key study	1986	Elimination of chlorometacresol (CMK) in the 2-stage biological wastewater treatment plant UE. Date: 1986-05-16	Bayer Uerdingen Works, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
N.N.	A7.1.2.1.1(08) Non-key study	1988	CMK concentration in the discharge of the Uerdingen biological wastewater treatment plant. Date: 1988-12-02	Bayer Uerdingen Site, WV-UE Environmental Protection/AWALU, Krefeld-Uerdingen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
Neuhahn	A7.1.1.2.1(04) A7.1.1.2.2(02) Non-key study	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
Neuhahn	A7.1.1.2.2(02) A7.1.1.2.1(04) Non-key study	1981	Biodegradability of Preventol CMK (4-chloro-3-methyl-phenol), OECD 301 D. Date: 1981-05-26	Bayer AG, OC-P/Ökologie, Leverkusen, Germany	NHH-Go/2694	No	No	Yes	LANXESS Deutschland GmbH
Neuhahn, A.	A7.1.1.2.1(01, 02, 04)	2012	2. Amendment to GLP-Final Report Study Title: Biodegradation. Re-evaluation based on study report 330 A/91. Date: 2012-05-14	Currenta GmbH & Co. OHG, Leverkusen, Germany	-	No	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Neuhahn, A.	A7.4.1.4(03)	2008	Activated Sludge, Respiration Inhibition Test with Preventol CMK Pastillen. Date: 2008-08-19	Currenta GmbH & Co. OHG, Services Analytik, Leverkusen, Germany	2006/0025/16	Yes	No	Yes	Lanxess Deutschland GmbH
Nitsche, M.	A7.2.2.1	2011	Biodegradation of Preventol® CMK (4-Chloro-3-methylphenol) in soil under aerobic conditions.	LANXESS Deutschland GmbH	2011-07-25	No	No	Yes	LANXESS Deutschland GmbH
Oblak	B7.5(02) Non-key study	1989	Determination of 4-chloro-3-methylphenol (CMK) in Rhine water (Ultra Trace range). Date: 1989-12-06	Bayer AG, Uerdingen, Central Analytics, Uerdingen, Germany	LM Ue 50/89	No	No	Yes	LANXESS Deutschland GmbH
Oleffe J.A. *et al.*	A6.12.6(02) published	1979	Allergy to chlorocresol and propylene glycol in a steroid cream to chlorocresol-preserved heparin	–	*Contact Dermatitis* **5**: 53-54	No	Yes	No	--
Olf, G.	A3.13(01)	2006b	Surface tension, Physical-chemical properties. Date: 2006-03-17 Amended: 2006-05-10	Bayer AG, BTS-PT-RPT-KPM, Leverkusen, Germany	06/002/03	Yes	No	Yes	LANXESS Deutschland GmbH

[redacted]	A6.1.3(01)	2003	PREVENTOL CMK Study on Acute Inhalation Toxicity Study in Rats according to OECD No. 403. Date: 2003-01-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.3.3	2011	14-Day Repeated Dose Inhalation Toxicity Study with Preventol CMK	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Rast, H.-G. and Kölbl, H.	A7.1.2.2.1(01)	1987	Microbial degradation of Preventol CMK in Rhine water. Date: 1987-10-20 Amended:	Bayer AG, FBT Leverkusen, Germany	LEV 14/76 and LEV 11/76	No	No	Yes	LANXESS Deutschland GmbH
Reis, K.-H.	A7.1.2.1.2(01)	2007	Anaerobic biodegradability of 4-chloro-3-methylphenol (Preventol CMK) in digested sludge: Measurement of gas production	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32321168	Yes	No	Yes	LANXESS Deutschland GmbH
Reis, K.-H.	A7.5.1.1(01)	2007	Effects of 4-Chloro-3-methylphenol (Preventol CMK) on the activity of the soil microflora in the laboratory.	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	32322080	Yes	No	Yes	LANXESS Deutschland GmbH
Reusche, W.	A3.6(01) A3.9(01)	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Reusche, W.	A3.9(01) A3.6(01)	1991	Partition coefficient, dissociation constant and pH value, Preventol CMK. Date: 1991-01-07 Amended: 2007-03-06	Bayer AG, ZF-D/ Zentrale Analytik, Leverkusen, Germany	A90/0107/03 LEV	Yes	No	Yes	LANXESS Deutschland GmbH
Robenek, H. *et al.*	A6.10 Non-key study Published	1980	Alterations in the Rat Liver Induced by p-Chlor-m-Cresol with Emphasis on the Intercellular Junctions.	Univ. of Münster, Germany	*J. Submicrosc. Cytol.* **12**(4), 635-646	No	Yes	No	–
Roberts, M.S. *et al.*	A6.2(03) Published	1977	Permeability of human epidermis to phenolic compounds.	Pharmacy Dept., Univ. of Sydney, Australia	*J. Pharm. Pharmac.* **29**, 677-683	No	Yes	No	–
Rother	A7.1.2.1.1(09) Non-key study	1996	Preventol CMK, CMK-Na: Analysis of Wastewater from the Leather Industry Date: 1996-01-25	Bayer, Material Protection Unit, Organic Chemicals Business Group, Uerdingen	--	No	No	Yes	LANXESS Deutschland GmbH
Rudner, E.J.	A6.12.6 Non-key study published	1977	North American Group Results	–	*Contact Dermatitis* **3**: 208-209	No	Yes	No	–

[redacted]	A6.2(04)	2009	Mass Balance and Metabolism of [14C]-4-Chloro-3-methylphenol in Male and Female Rats After Single Oral Administration. Date: 2009-02-19	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.3.2(02)	1980	Subchronic Dermal Study in Rabbits. Preventol CMK. Date: 1980-07-31	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.2(01) Non-key study	1980	Excretion kinetics of Preventol CMK after a single oral administration to rats. Date: 1980-12-02	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.2(02) Non-key study	1981	Investigation into the detection of Preventol CMK in fatty tissue and liver tissue in rats. Date: 1981-02-17	[redacted]	[redacted]	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A7.4.3.2(01)	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to Rainbow Trout (*Oncorhynchus mykiss*) in a Prolonged Semi Static Test over 28 Days. Date: 2007-03-28	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Schulz, L.	A7.5.1.1(02)	2012	Preventol CMK – Effects on the activity of soil microflora (Nitrogen transformation test). Date: 2012-04-13.	BioChem agrar, Labor für biologische und chemische Analytik GmbH 04827 Gerichshain, Germany	Project-No. 12 10 48 011 N,	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.2(01)	1999	Acute Dermal Toxicity Study with Preventol CMK Pastillen in Rats. Date: 1999-10-29	[redacted]	[redacted]	Yes	No	Yes	Bayer Corporation

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Thompson, R.S.	A7.1.1.2.2(01)	1993	Parachlorometacresol: Further study of inherent biodegradability. Date: 1993-06-29	Brixham Environmental Laboratory, Zeneca limited, Brixham Devon, UK	BL4783/B	Yes	No	Yes	LANXESS Deutschland GmbH
Uter, W. *et al.*	A6.12.6 Non-key study Published	1993	Contact Allergy in Metal Workers.	Information Network of Dermatological Clinics (IVDK) in Germany	*Dermatosen* **41**(6), 220-227	No	Yes	No	–
Vinken, R. and Wydra, V.	A7.4.1.3(03)	2007	Toxicity of 4-Chloro-3-methylphenol (Preventol CMK) to *Desmodesmus subspicatus* in an Algal Growth Inhibition Test. Date: 2007-01-04	Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany	Project No. 32324210	Yes	No	Yes	LANXESS Deutschland GmbH
[redacted]	A6.1.5(01)	2000	Preventol CMK, Pastillen LOCAL LYMPH NODE ASSAY IN MICE (LLNA/IMDS). Date: 2000-11-13	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Wesener, J.	A3.4(01)	2006	Spectra. Date: 2006-03-14 Amended: 2006-04-03	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	2006/0025/03	No	No	Yes	LANXESS Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Weyers, A.	A7.1.1.2.1(02)	2007	Preventol CMK – Biodegradation. Re-Evaluation based on Study Report 330 A/91, corresponding raw data and additional information provided by the sponsor. Date: 2007-03-09 Amended: 2007-03-16	Bayer Industry Services, Leverkusen, Germany	--	No	No	Yes	LANXESS Deutschland GmbH
[redacted]	A7.4.3.1(02)	2006c	Preventol CMK – Fish, prolonged toxicity test. Re-Evaluation based on Study Report 212 A/90FL, corresponding raw data and additional information provided by the sponsor. Date: 2006-07-05	[redacted]	[redacted]	Yes	No	Yes	LANXESS Deutschland GmbH
Weyers, A.	A7.4.3.4(02)	2007	Preventol CMK Pastillen - Daphnia magna Reproduction Test. Date: 2007-03-08	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/0025/10	Yes	No	Yes	Lanxess Deutschland GmbH

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Ainley, E.J., Mackie, I.G. and Macarthur, D.	A6.12.2(01)	1977	Adverse reaction to chlorocresol-preserved heparin.	University Hospital of Wales, Cardiff, UK	*Lancet* **1**: 705	No	Yes	No	–
Wielpütz, T.	A3.2(03)	2008	4-Chloro-3-methylphenol (Preventol CMK), Batch No.: [redacted], Vapour pressure A.4 (OECD 104). Date: 2008-08-19	Siemens AG, Prozess-Sicherheit, Industriepark Hoechst, Frankfurt am Main, Germany	20080599.01	Yes	No	Yes	LANXESS Deutschland GmbH
Wien, R.	A6.11 Non-key study Published	1939	The Toxicity of *Para*chloro*meta*cresol and of Phenylmercuric Nitrate.	–	*Q.J. Pharm. Pharmacol.* **12**, 212-229	No	Yes	No	–
Wilkinson, J.D. *et al.*	A6.12.6 Non-key study Published	1980	Comparison of Patch Test Results in Two Adjacent Areas of England. II. Medicaments.	Slade Hospital, Oxford & Wycombe General Hospital, England	*Acta Dermatovener (Stockholm)* **60**, 245-249	No	Yes	No	
Wiseman, H.M. *et al.*	A6.12.2(04) Published	1980	Acute poisoning to Wright´s Vaporizing Fluid.	National Poisons Information Service, London, UK	*Postgraduate Medical Journal:* 56, 166 - 168 (1980)	No	Yes	No	--