	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	31st August 2006
Materials and methods	As described by the applicant
Conclusion	As described by the applicant
Reliability	2
Acceptability	Acceptable
Remarks	Appendix II to the study report notes the following points of non-compliance with FIFRA Testing Procedure Guidelines and FFDCA GLP Requirements: The standard operating procedure on data handling, storage and retrieval was available in draft form only; the same laboratory person did not perform all necropsies; animals were not fasted before dosing; animals were not observed both morning and afternoon at weekends. In accordance with the provisions laid down in Council Directive 67/548/EEC, bendiocarb should be regarded as 'Toxic if swallowed' and labelled with R25 (LD50 > 25 ≤ 200mg/kg).
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1977) The Acute Oral Toxicity to the Hamster of Technical Bendiocarb [redacted] Document A90384 6.1.1/06 April 1977 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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, but the study was conducted in line with good scientific practice.	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR 4799/1	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Not specified but bendiocarb is known as a white/beige powder	
3.1.2.2	Purity	Not specified	
3.1.2.3	Stability	The active substance was found to be stable in the test suspension	
3.2	**Test Animals**		
3.2.1	Species	Hamster	
3.2.2	Strain	Syrian	
3.2.3	Source	Coomberhurst Breeding Establishment, West Heath, Baughurst, U.K.	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	80-108 g	
3.2.6	Number of animals per group	4	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Postexposure period	7 days	
3.3.2	Type	Gavage	

3.3.3	Concentration	25, 100, 200, 400 or 1600 mg/kg bw	
3.3.4	Vehicle	Water	
3.3.5	Concentration in vehicle	Aqueous cream containing 20% w/v a.s.	
3.3.6	Total volume applied	-	
3.3.7	Controls	No	
3.4	**Examinations**	Clinical observations, necropsy and gross post-mortem examination	
3.5	**Method of determination of LD_{50}**	Weil	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Toxic effects and their timing were typical of a quick acting rapidly reversible direct inhibitor of cholinesterase, survivors showing no macroscopic pathology.	
4.2	**Pathology**	No macroscopic pathology was found in the survivors	
4.3	**Other**	-	
4.4	**LD_{50}**	141 mg/kg bw	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Syrian female hamsters (4 animals/dose) were dosed by oral gavage with bendiocarb at doses of 25, 100, 200, 400 or 1600 mg/kg with an aqueous cream containing 20% w/v a.s..	
5.2	**Results and discussion**	Toxic effects and their timing were typical of a quick acting rapidly reversible direct inhibitor of cholinesterase, survivors showing no macroscopic pathology. The acute oral LD_{50} for female hamster was established at 141 mg/kg bw.	
5.3	**Conclusion**		
5.3.1	Reliability	2	
5.3.2	Deficiencies	No	

Table A6.1.1-6 Table for Acute Toxicity

Dose [mg/kg]	Number of dead/ number of investigated	Time of death (range)	Observations
Female hamster			
25	0/4	-	
100	0/4	-	
200	4/4	35 – 57 min	
400	4/4	11 – 54 min	
1600	4/4	5 – 17 min	
LD_{50} value:	141 (100 - 200) mg/kg bw		

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	31st August 2006
Materials and methods	As described by the applicant
Conclusion	As described by the applicant
Reliability	2
Acceptability	Acceptable
Remarks	The UK CA notes that the purity of bendiocarb is not specified but is technical grade, which is considered by the applicant to be equivalent to the technical grade chemical produced currently. In accordance with the provisions laid down in Council Directive 67/548/EEC, bendiocarb should be regarded as 'Toxic if swallowed' and labelled with R25 (LD50 > 25 ≤ 200mg/kg).
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.1.2 Acute dermal

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1972a) The Toxicology of NC 6897: Acute Dermal Toxicity of Technical Bendiocarb [redacted] Document A90347 6.1.2/01 February 1972 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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, but the study was conducted in line with good scientific practice.	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	Batch CR 4500/24	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Not specified but bendiocarb is known as a white/beige powder	
3.1.2.2	Purity	Not specified in the report but historically would be 96%	X
3.1.2.3	Stability	Not specified, but bendiocarb is not known to decompose at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar	
3.2.3	Source	Carworth – Europe	
3.2.4	Sex	Male/Female	
3.2.5	Age/weight at study initiation	200 – 416 g	
3.2.6	Number of animals per group	4M/4F	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal	

3.3.1	Postexposure period	7 days	
3.3.2	Area covered	Not specified	
3.3.3	Occlusion	Occlusive	
3.3.4	Vehicle	Glycerol	
3.3.5	Concentration in vehicle	32%	
3.3.6	Total volume applied	Dose rates: 400 and 800 mg a.s./kg bodyweight	
3.3.7	Duration of exposure	24h	
3.3.8	Removal of test substance	Water	
3.3.9	Controls	No	
3.4	**Examinations**	Toxic effects and mortality	
3.5	**Method of determination of LD_{50}**	Weil – moving average method (1952)	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Toxic effects, observed at both dose levels, were reported to be 'typically cholinergic' and started 45 – 55, and 12 – 16 min after exposure, in males and females respectively. No further details on the nature of the observed toxic effects were given, although their duration was reported as 1 – 2 d. Whilst the onset of toxic effects was more rapid in females, there was no observed sex difference in mortality. No evidence of primary skin irritation was seen.	
4.2	**Pathology**	No data	
4.3	**Other**	-	
4.4	**LD_{50}**	566 mg as/kg bw (male and female)	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Technical bendiocarb was applied to the skin of Wistar rats (4/sex/dose), as a 32 % solution in glycerol and held in contact by an occlusive patch for 24 h at 2 dose levels, 400 and 800 mg kg^{-1}. Animals were observed for toxic effects and mortality for 7 d post-application, and a dermal LD_{50} value determined.	
5.2	**Results and discussion**	Deaths (8/8 animals treated) occurred at 800 mg kg^{-1}, 26 – 36 h after treatment. Toxic effects, observed at both dose levels, were reported to be 'typically cholinergic' and started 45 – 55, and 12 – 16 min after exposure, in males and females respectively. No further details on the nature of the observed toxic effects were given, although their duration was reported as 1 – 2 d. Whilst the onset of toxic effects was more rapid in females, there was no observed sex difference in mortality. No evidence of primary skin irritation was seen. A dermal LD_{50} value of 566 mg kg^{-1} was established for both males and females. No acute dermal toxicity NOAEL was identified since there were adverse effects seen at the lowest dose tested of 400 mg kg^{-1}.	

5.3	**Conclusion**		
5.3.1	Reliability	2	
5.3.2	Deficiencies	None	

Table A6.1.2-1 Table for Acute Dermal Toxicity

Dose [mg as/kg]		Number of dead/number of investigated	Time of death (range)
Male	400	0/4	n.a.
	800	4/4	26 – 36 h
Female	400	0/4	n.a.
	800	4/4	26 – 36 h
LD_{50} value	566 mg as/kg bodyweight		

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	31st August 2006
Materials and methods	As described by the applicant
Results and discussion	As described by the applicant
Conclusion	As described by the applicant
Reliability	2
Acceptability	Acceptable
Remarks	3.1.2.2 The purity of the tested substance was not specified in the report, but the Applicant expects that it would be 96%. In accordance with the provisions laid down in Council Directive 67/548/EEC, bendiocarb should be regarded as 'Harmful in contact with skin' and labelled with R21 (400 < LD50 ≤ 2000 mg/kg).
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1971a) The Toxicology of NC 6897: Acute Toxicity of Pure NC 6897 [redacted] Document A90940 6.1.2/02 January 1971 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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, but the study was conducted in line with good scientific practice.	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	Batch 15	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Not specified but bendiocarb is known as a white/beige powder	
3.1.2.2	Purity	Specified as 'pure' without any additional information.	
3.1.2.3	Stability	Not specified, but bendiocarb is not known to decompose at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar	
3.2.3	Source	No data	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	146 – 188 g	
3.2.6	Number of animals per group	2	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Postexposure period	7 days	
3.3.2	Area covered	Not specified	

3.3.3	Occlusion	Occlusive	
3.3.4	Vehicle	Glycerol formal	
3.3.5	Concentration in vehicle	32%	
3.3.6	Total volume applied	Dose rates: 400 and 800 mg a.s./kg bodyweight	
3.3.7	Duration of exposure	24h	
3.3.8	Removal of test substance	Water	
3.3.9	Controls	No	
3.4	**Examinations**	Toxic effects and mortality	
3.5	**Method of determination of LD_{50}**	Weil – moving average method (1952)	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Clinical signs, stated to be 'typical of a direct inhibitor of cholinesterase', commenced between 2 – 21 h post-application at both doses, with one mortality occurring at 800 mg kg^{-1} after 2.5 d.	
4.2	**Pathology**	No data	
4.3	**Other**	-	
4.4	**LD_{50}**	800 mg/kg (female)	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	2 pairs of rats (female) received 400 and 800 mg kg^{-1} 'pure' bendiocarb on the skin as a 32 % solution in glycerol for 24 h.	
5.2	**Results and discussion**	Clinical signs, stated to be 'typical of a direct inhibitor of cholinesterase', commenced between 2 – 21 h post-application at both doses, with one mortality occurring at 800 mg kg^{-1} after 2.5 d. A dermal LD_{50} value of 800 mg kg^{-1} was established. Recovery of survivors from the observed cholinesterase inhibitory effects was slow.	
5.3	**Conclusion**		
5.3.1	Reliability	2	
5.3.2	Deficiencies	None	

Table A6.1.2-2 Table for Acute Dermal Toxicity

Dose [mg/kg]	Number of dead/number of investigated	Time of death (range)
400	0/2	n.a.
800	1/2	2.5 days
LD_{50} value	800 mg a.s./kg bodyweight	

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	5th September 2006
Materials and methods	As described by the applicant
Results and discussion	As described by the applicant
Conclusion	As described by the applicant
Reliability	2
Acceptability	Acceptable
Remarks	The purity of the tested substance was not specified in the report, but the applicant expects that it would be 96%. In accordance with the provisions laid down in Council Directive 67/548/EEC, bendiocarb should be regarded as 'Harmful in contact with skin' and labelled with R21 ($400 < LD50 \leq 2000$ mg/kg).
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.1.3 Acute Inhalation

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1988) Technical Bendiocarb: Acute (4-Hour Exposure) Inhalation Toxicity Study in Rats [redacted] Document A90617 6.1.3/01 25 August 1988 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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 403, USEPA 81-3	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR 19048/1	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	97.9%	
3.1.2.3	Stability	Stability data was not provided (as indicated in the report), but bendiocarb is not known to decompose at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley	
3.2.3	Source	Charles River UK Ltd, Margate	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	ca 200g	
3.2.6	Number of animals per group	5M/5F	
3.2.7	Control animals	Yes; 5M/5F	
3.3	**Administration/ Exposure**	Inhalation	

3.3.1	Postexposure period	14 days	
3.3.2	Vehicle	None	
3.3.3	Concentration in vehicle	n.a.	
3.3.4	Total volume applied	0, 248, 377, 512 or 701 mg m^{-3} applied by dust generator at a rate of 25 litres per minute	
3.3.5	Controls	Clean air	
3.4	**Examinations**	Clinical observations, bodyweight, food and water consumption, necropsy and macroscopic examination.	
3.5	**Method of determination of LD_{50}**	Miller and Tainter	
3.6	**Further remarks**		
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Clinical signs of toxicity, indicative of cholinesterase inhibition, were observed at all exposure levels. Salivation, wet fur around the eyes and snout, exaggerated respiratory movements; irregular respiratory rate, restless behaviour and tremors were noted during exposure. Exophthalamus, lethargy, wet fur, discharge from the eyes, brown staining around the snout and jaws and abnormal breathing (increased rate and exaggerated movements) were seen post-exposure up to day 12.	
4.2	**Pathology**	At the macroscopic examination, congestion of the lungs was the principal finding in those animals that died before the end of the observation period. Additionally, lung to body weight ratios of treated decedents were higher than controls.	
4.3	**Other**	-	
4.4	**LD_{50}**	4-hour LC_{50} value was 550 mg bendiocarb m^{-3} of air (equivalent to 0.55 mg bendiocarb l^{-1} of air).	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of Sprague-Dawley rats (5 per sex), were exposed whole body for 4 h to 0, 248, 377, 512 or 701 mg m^{-3} of technical bendiocarb (purity 97.9 %). Test animals were observed during the exposure period and for 14 d post-exposure.	
		The particle size distribution showed that between 51 and 65.5 % of particles produced were <5.5 mm in diameter and therefore respirable by rats. Five air samples were taken from the chamber during each exposure.	X

5.2	**Results and discussion**	At 701 mg m^{-3}, 3 males and 5 females died, with 5 of those deaths occurring during exposure. In the 512 mg m^{-3} exposure group, 2 males and 2 females died, with 3 of those deaths occurring during exposure. At 377 mg m^{-3}, 1 female died during exposure. No deaths were observed at 248 mg m^{-3} or in controls. Clinical signs of toxicity, indicative of cholinesterase inhibition, were observed at all exposure levels. Salivation, wet fur around the eyes and snout, exaggerated respiratory movements; irregular respiratory rate, restless behaviour and tremors were noted during exposure. Exophthalamus, lethargy, wet fur, discharge from the eyes, brown staining around the snout and jaws and abnormal breathing (increased rate and exaggerated movements) were seen post-exposure up to day 12. At the macroscopic examination, congestion of the lungs was the principal finding in those animals that died before the end of the observation period. Additionally, lung to body weight ratios of treated decedents were higher than controls. Apart from dark areas on the lungs of one animal, no other abnormalities were observed in surviving animals. The calculated 4-hour LC_{50} value was 550 mg bendiocarb m^{-3} of air (equivalent to 0.55 mg bendiocarb l^{-1} of air) (0.61 mg bendiocarb l^{-1} of air in males and 0.47 mg bendiocarb l^{-1} of air in females).	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	None	

Table A6.1.3-1 Table for Acute Inhalation Toxicity

Dose [mg/l]	Number of dead/number of investigated	Time of death (range)	Observations
0	0/10	n.a.	
0.248	0/10	n.a.	
0.377	1/10		Female
0.512	4/10	Day 0 – 2	2 male, 2 female
0.701	8/10	Day 0 – 3	3 male, 5 female
LC_{50} value	550 mg bendiocarb m^{-3} of air (equivalent to 0.55 mg bendiocarb l^{-1} of air)		

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	5th September 2006
Materials and methods	Section 5.1. The particle size distribution showed that between 51 and 65.5% of particles produced were < 5.5 micrometres in diameter, not millimetres as stated by the applicant.
Results and discussion	As described by the applicant
Conclusion	As described by the applicant
Reliability	1
Acceptability	Acceptable
Remarks	In accordance with the provisions laid down in Council Directive 67/548/EEC, bendiocarb should be regarded as 'Toxic by inhalation' and labelled with R23 (LC50 > 0.25 ≤ 1 mg/l/4 hr).
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.1.4 Acute skin and eye irritation

		1. REFERENCE	Official use only
1.1	**Reference**	[redacted] (1980) Technical Bendiocarb Ex-Muskegon Primary Eye Irritancy in Rabbits [redacted] Document A90435 6.1.4/01 December 1979 and February 1980/1981 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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. US EPA 40 CFR 162	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but was conducted to in-house QA standards.	
2.3	**Deviations**	No.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR4971/1, A01919	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	99.2%	
3.1.2.3	Stability	Bendiocarb is not known to decompose at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	New Zealand White	
3.2.3	Source	Cheshire Rabbit Farms, UK	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	2.5 – 3.0 kg	
3.2.6	Number of animals per group	Group 1: 3 (2M/1F) (irrigation after 20–30 sec) Group 2: 6 (3M/3F) (no irrigation)	
3.2.7	Control animals	The left conjunctival sac of each animal acted as control	
3.3	**Administration/ Exposure**		

3.3.1	Preparation of test substance	Technical bendiocarb was prepared in 100 mg capsules which were opened for dispensing into the eyes.	
3.3.2	Amount of active substance instilled	100 mg	
3.3.3	Exposure period	7 days	
3.3.4	Postexposure period	7 days	
3.4	**Examinations**		
3.4.1	Opthalmoscopic examination	Yes	
3.4.1.1	Scoring system	Draize	
3.4.1.2	Examination time points	24h, 48h, 72h , 4 days and 7 days	
3.4.2	Other investigations	-	
3.5	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	None	
4.2	**Average score**	The following are the averages of readings at 24, 48 and 72 h	
4.2.1	Cornea	0.0	
4.2.2	Iris	0.0	
4.2.3	Conjunctiva		
4.2.3.1	Redness	0.67	
4.2.3.2	Chemosis	0.22	
4.3	**Reversibility**	Yes	
4.4	**Other**	-	
4.5	**Overall result**	The results of this study demonstrated that bendiocarb is not an eye irritant and does not merit classification under the EU system	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In an eye irritation study carried out to EPA guidelines and in-house QA standards, 100 mg bendiocarb powder (purity 99.2 %; dosed without any vehicle) was instilled into the right conjunctival sac of New Zealand white rabbits, (3 males and 3 females), with the other eye acting as a control. Another group of 3 animals (2 males and 1 female) were treated identically but treated eyes were irrigated 20–30 seconds after treatment. The eyes of all the rabbits were assessed for irritation of the cornea, iris and conjunctivae at 24, 48 and 72 h and also 4 and 7 d post-instillation.	
5.2	**Results and discussion**	Mean scores for the 24, 48 and 72 h reading times calculated over all animals tested were 0.67 and 0.22 for conjunctival redness and chemosis respectively. No corneal or iris response was observed after instillation. Bendiocarb would not be considered as an eye irritant.	
5.3	**Conclusion**		
5.3.1	Reliability	1	

5.3.2 Deficiencies	No	

Table A6.1.4-1 Results of Eye Irritation Study

	Cornea	Iris	Conjunctiva	
			Redness	Chemosis
Score (average animals investigated)	0 to 4	0 to 2	0 to 3	0 to 4
24 h	0.0	0.0	1.0	0.7
48 h	0.0	0.0	0.7	0.0
72 h	0.0	0.0	0.3	0.0
4 days	0.0	0.0	0.1	0.0
7 days	0.0	0.0	0.0	0.0
Average 24 h, 48 h, 72 h, 4 days, 7 days	0.0	0.0	0.4	0.1
Average 24 h, 48 h, 72 h	0.0	0.0	0.67	0.22
Maximum average score (including area affected, max 110)	80	10	20	
Reversibility *	n.a.	n.a.	c	c
Average time for reversion	n.a.	n.a.	7 days	48h

* c: completely reversible
nc: not completely reversible
n: not reversible

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	5th September 2006
Materials and methods	As described by the applicant
Conclusion	As described by the applicant
Reliability	1
Acceptability	Accepable
Remarks	
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1978) Technical Bendiocarb Primary Skin Irritancy Study on Rabbits [redacted] Document A90987 6.1.4/02 September 1978 and December 1978 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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. US EPA 40 CFR 162	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	No.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	Bx 625	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Pure white powder	
3.1.2.2	Purity	Not specified in the report but historically would be 96%	
3.1.2.3	Stability	Not specified, but bendiocarb is not known to decompose at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	New Zealand White	
3.2.3	Source	Bantin and Kingman, Hull, UK	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	2.5 – 3.0 kg	
3.2.6	Number of animals per group	3M/3F	
3.2.7	Control animals	10% (w/v) aqueous sodium lauryl sulphate was applied as a control material to the test animals as well as bendiocarb (2 patches of each material per animal).	
3.3	**Administration/ Exposure**	Dermal	

3.3.1	Postexposure period	5 days	
3.3.1.1	Preparation of test substance	Powdered bendiocarb (0.5 g) was moistened with physiological saline before application to skin.	
3.3.1.2	Test site and preparation of test site	The hair was clipped from the back and flanks of each animal 6 days after receipt. One day later, 2 of the 4 test areas were abraded, prior to application of the test and control materials.	
3.3.2	Occlusion	Occlusive	
3.3.3	Vehicle	Physiological saline	
3.3.4	Concentration in vehicle	Moistened technical material.	
3.3.5	Total volume applied	0.5 g test material; 0.5 ml control material.	
3.3.6	Removal of test substance	Water	
3.3.7	Duration of exposure	24h	
3.3.8	Postexposure period	5 days	
3.3.9	Controls	10% sodium lauryl sulphate	
3.4	**Examinations**	Clinical observations and dermal examination	
3.4.1	Clinical signs	Yes	
3.4.2	Dermal examination	Yes	
3.4.2.1	Scoring system	FDA	
3.4.2.2	Examination time points	24h, 72h, 4d and 5d	
3.4.3	Other examinations	-	
3.5	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Average score**	Averages of intact and abraded skin combined.	
4.1.1	Erythema	0.71 (24 and 72h combined)	
4.1.2	Oedema	0.60 (24 and 72h combined)	
4.2	**Reversibility**	Yes – most by Day 4 and all by Day 5	
4.3	**Other examinations**	-	
4.4	**Overall result**	Primary irritation score 1.35	X
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Powdered bendiocarb (0.5 g) moistened with physiological saline was applied to 2 areas of intact skin on 6 New Zealand white rabbits under an occlusive gauze patch for 24 h (which is longer than required under current OECD guidelines). Scoring of skin irritation was made when the patches were removed, 48 h later (= 72 h total) and at 4 d. This study was performed to EPA guidelines.	

5.2	**Results and discussion**	Post-patch removal, mild erythema and oedema (mean scores of 1.17 for both) were evident. At the 48-hour time point (= 72 h total), 2 out of the 6 animals showed a persisting, but mild response to bendiocarb (mean scores of 0.08 for erythema and oedema respectively); there were no reactions in the other 4 animals. At the 4-day observation time point all treated skin sites appeared normal apart from in one animal where slight persistent erythema and oedema were seen (score of 0.5 for both erythema and oedema). At 5 d all the test sites were normal. The results of this study indicated that bendiocarb is not a skin irritant and does not require classification under the EU scheme.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.1.4-2 Table for Skin Irritation Study

Score (average animals investigated)	Time	Erythema	Oedema
Average score (intact skin) Draize scores (0 to maximum 4)	24h	1.17	1.17
	72h	0.08	0.08
	4 days	0.10	0.08
	5 days	0.0	0.0
Average score (intact and abraded skin combined)	24h, 72h	0.71	0.60
Reversibility: *		c	c
Average time for reversibility		72h	72h

* c: completely reversible
nc: not completely reversible
n: not reversible

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	6th September 2006
Materials and methods	As described by the applicant
Results and discussion	4.4: The UK CA agrees with the results presented, but notes the primary irritation score of 10% sodium lauryl sulphate is 4.50.
Conclusion	As described by the applicant.
Reliability	1
Acceptability	Acceptable
Remarks	The scoring system used in the US EPA 40 CFR 162 guideline differs from that used in OECD guideline 404, in which responses are scored at 24, 48 and 72 hours. In the presented study, the responses were scored at 24 and 72 hours. Under the FDA scoring system used, bendiocarb does not meet the definition of an irritant. It is noted that the primary irritation score of the positive control is slightly below the cut-off value to be classed under this scoring system as an irritant, but the UK CA does not consider that this affects the validity of the result.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.1.5 Acute skin sensitisation

		1. REFERENCE	Official use only
1.1	Reference	[redacted] (1992) Technical Bendiocarb Guinea Pig Skin Sensitisation Study (Buehler Test) [redacted] Document A90639 6.1.5/01 6 July 1992 Unpublished	
1.2	Data protection	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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 406	
2.2	GLP	Yes	
2.3	Deviations	No	X
		3. MATERIALS AND METHODS	
3.1	Test material	Bendiocarb	
3.1.1	Lot/Batch number	CR 19306/01/890501	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Beige powder	
3.1.2.2	Purity	97.5%	
3.1.2.3	Stability	Stable as stored at room temperature in the dark and bendiocarb is not known to decompose at room temperature	
3.1.2.4	Preparation of test substance for application	Technical bendiocarb was dissolved/suspended (60%) in Alembicol D (a product of coconut oil)	
3.1.2.5	Pretest performed on irritant effects	Yes	
3.2	Test Animals		
3.2.1	Species	Guinea pigs	
3.2.2	Strain	Dunkin/Hartley albino	
3.2.3	Source	D Hall, Newchurch, Staffordshire, UK	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	388 – 492 g	

3.2.6	Number of animals per group	10	
3.2.7	Control animals	Yes (10)	
3.3	**Administration/ Exposure**	Buehler test	
3.3.1	Induction schedule	Day 1 – day 8 – day 15	
3.3.2	Way of induction	Topical Occlusive	
3.3.3	Concentrations used for induction	0.5 ml technical bendiocarb 60% (w/w) in Alembicol D. This was the maximum achievable concentration.	
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	n.a.	
3.3.5	Challenge schedule	Day 29	
3.3.6	Concentrations used for challenge	0.5 ml technical bendiocarb 60% (w/w) in Alembicol D. This was the maximum achievable concentration.	
3.3.7	Rechallenge	No	
3.3.8	Scoring schedule	24 h, 48 h and 72 h after challenge	
3.3.9	Removal of test substance	Water	
3.3.10	Positive control substance	Formalin	
3.4	**Examinations**		
3.4.1	Pilot study	Yes	
3.5	**Further remarks**		X
		4. RESULTS AND DISCUSSION	
4.1	**Results of pilot studies**	No irritation observed	
4.2	**Results of test**		
4.2.1	24h after challenge	No irritation observed	
4.2.2	48h after challenge	No irritation observed	
4.2.3	Other findings	-	
4.3	**Overall result**	Overall, the results of this study indicated that bendiocarb was not a skin sensitiser.	

		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In a Buehler test, largely performed to OECD guidelines and GLP compliant, female Dunkin-Hartley guinea pigs (10 animals) received a total of three topical 6-hour induction applications of 60 % technical grade bendiocarb (purity 97.5 %) in fractionated coconut oil, at weekly intervals over 3 w. Ten negative control animals received a dry gauze patch at the same time intervals. Two weeks after the last induction application, all test and control guinea pigs received a topical 6-hour challenge application of 60 % technical grade bendiocarb in fractionated coconut oil. The concentrations of bendiocarb used in the main study were based on the results of a preliminary investigation, which showed that 60 % bendiocarb in fractionated coconut oil was the maximum practical concentration that could be prepared and applied topically. Skin reactions were scored 24 h after each of the 3 induction treatments and 24, 48 and 72 h after the challenge application. Historical positive control data obtained with formalin showed the test system to be working.	
5.2	**Results and discussion**	No irritation was seen with bendiocarb treatment at induction. At challenge, no dermal reactions were seen in any of the test or control animals. Overall, the results of this study indicated that bendiocarb was not a skin sensitizer.	
5.3	**Conclusion**		
5.3.1	Reliability	1	X
5.3.2	Deficiencies	No	

Table A6.1.5-1 Detailed information including induction/challenge/scoring schedule for skin sensitisation test

Inductions	**Buehler test** **Day of treatment**	**Observations/Remarks give information on irritation effects**
Induction 1	Day 1	No irritation observed
Induction 2	8	No irritation observed
Induction 3	15	No irritation observed
Challenge	29	No irritation observed
Scoring 1	30	No irritation observed
Scoring 2	31	No irritation observed
Scoring 3	32	No irritation observed

Table A6.1.5-2 Result of skin sensitisation test

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	Test group	Positive control
Scored after 24 h	0/10	0/10	10/10
Scored after 48 h	0/10	0/10	10/10

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	6th September 2006
Materials and methods	2.3. The UK CA notes the following deviations from OECD guideline 406: • ten animals were used in the treatment group instead of the required twenty; • the third induction lasted for five hours instead of six. 3.5. The UK CA notes that the maximum concentration of bendiocarb that could be obtained in the chosen vehicle was not irritant; OECD guideline 406 requires mild irritation during the induction phase.
Results and discussion	As described by the applicant
Conclusion	5.3.1. In view of the major deviation from OECD guideline 406, namely that half the recommended number of animals was used in the treatment group, the UK CA considers that a reliability score of 2 should be assigned to this study.
Reliability	2
Acceptability	Acceptable
Remarks	There were some deviations from OECD guideline 406, the main one being that ten animals were used in the treatment group instead of twenty. In addition, the third induction exposure lasted for five hours rather than six. The induction concentration did not produce irritation. However, the UK CA considers that the concentration of active substance used (60%) was high and notes that it was the maximum obtainable in the chosen vehicle, so that this does not affect the validity of the result.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

		1. REFERENCE	Official use only
1.1	Reference	[redacted] (1980) Sensitisation Potential of Ficam 80W [redacted] Document A90451 6.1.5/02 August 1980 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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 406	
2.2	**GLP**	No	
2.3	**Deviations**	No	X
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb as an 80%WP	
3.1.1	Lot/Batch number	CR 4944/9	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity		
3.1.2.3	Stability	Nothing specified on the stability, but bendiocarb is not known to decompose at room temperature	
3.1.2.4	Preparation of test substance for application	See 3.3.1	
3.1.2.5	Pretest performed on irritant effects	See 3.4.1	
3.2	**Test Animals**		
3.2.1	Species	Guinea pigs	
3.2.2	Strain	Dunkin/Hartley albino	
3.2.3	Source	Porcellus Animals Limited, UK	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	300 – 400 g; age not reported	
3.2.6	Number of animals per group	20	

3.2.7	Control animals	Yes; 10
3.3	**Administration/ Exposure**	Intradermal injections followed by topical induction and challenge
3.3.1	Induction schedule	6 intradermal injections, 3 in a line each side of and parallel to the mid-line in the shaved region (4 x 6 cm) as follow: 0.1 ml Freund's Complete Adjuvant (anterior injection) 0.1 ml Test material formulation (middle injection) 0.05 ml Test material formulation emulsified with 0.05 ml of Freund's Complete Adjuvant (posterior injection).
3.3.2	Way of induction	Intradermal induction Six days after the injection phase the injection site was shaved again. Twenty four hours later, a 2 x 4 cm patch of filter paper, charged with test material (5% w/w in distilled water) was applied to the pre-treated area and the patch covered by an overlapping patch of impermeable plastic adhesive tape. The whole area was then firmly bound by occlusive tape, and the dressing was left in place for 48 h before removal.
3.3.3	Concentrations used for induction	The test material in each test was injected at a concentration of 5% w/w in distilled water.
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	See Point 3.3.1 above.
3.3.5	Challenge schedule	Two weeks after the topical induction, both the test group and control group guinea pigs were challenged with the test material at a concentration of 10% (w/w in distilled water). A 5 x 5 cm area on the right flank of each animal was shaved and the selected concentration of test material was applied to the prepared test site on a 2 x 2 cm piece of filter paper. The patch was held in place for 24 h by the same method employed for the topical induction.
3.3.6	Concentrations used for challenge	See Point 3.3.5 above.
3.3.7	Rechallenge	None
3.3.8	Scoring schedule	24 h after challenge patch removed
3.3.9	Removal of test substance	Not specified
3.3.10	Positive control substance	Dinitrochlorobenzene tested routinely by the laboratory
3.4	**Examinations**	24 h after challenge patch was removed.
3.4.1	Pilot study	Yes. Before the challenge phase a maximum non-irritant concentration of test material was determined in preliminary experiments on 2 dose finding guinea pigs pre-treated at the induction phase with Freund's Adjuvant only. The test material was applied 13 days after injection with Freund's adjuvant to the shaved flanks of the guinea pigs at concentrations of 10%, 5%, 2% and 1% (w/w in distilled water) under the same occlusive patch system used for the topical induction. No irritant responses were observed, therefore Ficam 80W at a concentration of 10% w/w in distilled water was selected for the challenge phase.

3.5	**Further remarks**		
		4. RESULTS AND DISCUSSION	
4.1	**Results of pilot studies**	The test material Ficam 80W should be non-irritant at a concentration of 10% w/w in distilled water on adjuvant pre-treated guinea pigs when applied to the shaved flank under occlusion.	
4.2	**Results of test**		
4.2.1	24h after challenge	Not sensitising	
4.2.2	48h after challenge	Not measured	
4.2.3	Other findings	-	
4.3	**Overall result**	Not sensitising	X
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The sensitisation potential of Ficam 80W was investigated by means of a Magnusson-Kligman Maximisation test in guinea pigs.	
5.2	**Results and discussion**	Overall, the results of this study indicated that Ficam 80W (a wettable powder containing 80% bendiocarb) was not a skin sensitizer.	
5.3	**Conclusion**		
5.3.1	Reliability	1	X
5.3.2	Deficiencies	No	X

Table A6.1.5-3 Detailed information including induction/challenge/scoring schedule for skin sensitisation test

Inductions	GPMT Day of treatment	Application	Observations/Remarks give information on irritation effects
Induction 1	Day 1	Intradermal	-
Induction 2	8	Topical	-
Challenge	22	Topical	-
Scoring 1	24		No effects were observed

Table A6.1.5-4 Result of skin sensitisation test

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	**Test group**	**Positive control***
Scored after 24 h	*0/10*	*0/19***	Positive

*Based on laboratory historical data
***One animal died before this stage of the study*

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	
Materials and methods	2.3. The UK CA notes the following deviations from OECD guideline 406: • the concentration of the test substance applied at topical induction should have been sufficiently high to cause mild-to-moderate skin irritation. If it was not possible to achieve high enough concentrations to cause irritation, a pre-treatment of sodium lauryl sulphate should have been applied. No irritation was observed in the main study, and the induction concentration was known not to be irritant. A pilot study to determine suitable concentrations to be used was only conducted for the challenge phase (section 3.4.1); • the concentration of substance used during the topical induction phase was lower than that used during challenge; • skin reactions were scored only at 24 hours and not at 48 and 72 hours after challenge (section 3.3.8); • the positive control substance was a strong sensitiser, so that the sensitivity of the study to detect weak to moderate sensitisers was not demonstrated.
Results and discussion	4.3 The UK CA does not consider that this study provides adequate data to determine that bendiocarb is not a skin sensitiser. Table A6.1.5-4. The UK CA has added information on the number of animals positive/number of animals in group.
Conclusion	
Reliability	3
Acceptability	Not acceptable
Remarks	5.3.1 The UK CA considers the lack of irritation during the induction phase, the low topical induction concentration and the absence of scoring data at 48 and 72 hours after challenge to be major methodological flaws, such that the study is not acceptable for assessing the skin sensitisation potential of bendiocarb.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.2 Metabolism studies in mammals

6.2.1 Metabolism

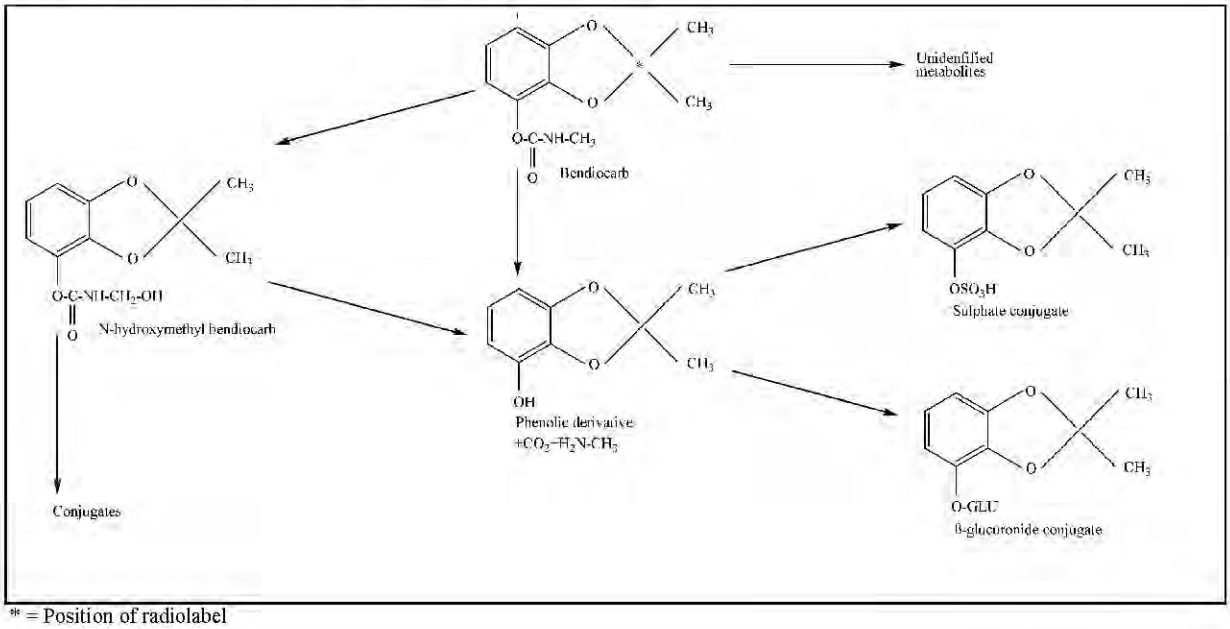
			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1976) The Metabolism of ^{14}C-Bendiocarb in the Rat [redacted] Document A90170 6.2.1/01 April 1976 Unpublished	
1.2	Data protection	Yes	
1.2.1	Data owner	Bayer CropScience	
1.2.2	Companies with letter of access	n.a.	
1.2.3	Criteria for 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, but the study was conducted in line with good scientific practice.	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	^{14}C Bendiocarb	
3.1.1	Lot/Batch number	Laboratory synthesis	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	> 99%	
3.1.2.3	Stability	Not specified but the material is not known to decompose at room temperature.	
3.1.2.4	Radiolabelling	The specific activity was 4.04 µCi/mg and the radiolabel was incorporated into the heterocyclic ring. The radiochemical purity of the sample was >99% as determined by thin layer chromatography.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Not specified	
3.2.3	Source	No data	
3.2.4	Sex	M/F	
3.2.5	Age/weight at study initiation	150 – 200g	
3.2.6	Number of animals per group	4 male and 3 female (10 mg/kg dose) 12 male and 12 female (1 mg/kg dose)	

3.2.7	Control animals	No
		4. APPLICANT'S SUMMARY AND CONCLUSION
4.1	**Materials and methods**	Groups of 4 male and 3 female rats (strain not specified) were given single oral gavage doses of 10 mg kg^{-1} bendiocarb (> 99 % radiochemical purity) in glycerol, radiolabelled with ^{14}C in position 2 of the heterocyclic ring. The animals were then placed individually in metabolism cages, with urine and faeces collected over a 46 h period post-dosing. Exhaled air was also collected from these animals for radioactivity measurements. Additional groups of rats (12/sex) were given single oral gavage doses of 1 mg kg^{-1} ^{14}C-bendiocarb in glycerol, and blood samples collected 10, 20 and 30 min, 1, 2, 3, 4, 5, 6, 7 and 8 h after dosing.
4.2	**Results and discussion**	After a single dose of 10 mg kg^{-1}, in both sexes approximately 76 % of the radioactivity was recovered in the urine by 24 h. By 48 h, the total recovery from all sources was nearly 100 % of the dose, with 89 % in the urine, 2 % in the faeces and 6 % as carbon ^{14} radiolabelled carbon dioxide ($^{14}CO_2$) in the exhaled air. This indicated that bendiocarb was rapidly and almost completely absorbed from the GI tract, and that elimination, mainly in the urine, was completed within 48 h of dosing. Elimination of $^{14}CO_2$ in the expired air was minor, indicating that no extensive breakdown of the heterocyclic ring occurred. Measurements of radioactivity in plasma indicated attainment of peak levels within 10 min of dosing (1 mg kg^{-1}) in both sexes. By 8 h post-dosing, the plasma radioactivity levels had dropped to 8 – 10 % of the peak levels. A plasma half-life of around 4.4 h was determined for both sexes. Urine analysis carried out using thin layer chromatography (TLC), high performance liquid chromatography (HPLC) and/or gas liquid chromatography (GLC)/mass spectrometry revealed that no unchanged ^{14}C-bendiocarb was present, and that the radioactivity fractions consisted entirely of polar, conjugated metabolites. The pattern of metabolites obtained indicated that the major route of metabolism involves the cleavage of the carbamate ester group to yield the phenolic derivative (NC 7312). This compound, excreted as sulphate (62 – 70 %) and ß-glucuronide (18 – 23 %) conjugates, accounted for approximately 85 % of the total amount of ^{14}C eliminated in the urine within 24 h. The remainder of the ^{14}C eliminated over this time period consisted of a complex mixture of sulphate and ß-glucuronide conjugates of at least seven minor metabolites, one of which appeared to be N-hydroxymethyl bendiocarb, (see Figure A6.2.1-1). Faecal metabolites were also investigated with the major component identified being the free phenolic derivative (NC 7312). No investigation of distribution aspects was conducted in this study.
4.3	**Conclusion**	
4.3.1	Reliability	2
4.3.2	Deficiencies	No

Table A6.2.1-1 Excretion of ^{14}C by Rats in the 2 Days Following Oral Administration of ^{14}C-Bendiocarb (10 mg/kg)

	% recovery of administered radioactivity (range)	
	Male rats (4 animals)	Female rats (3 animals)
Urine 3 hours 1 day 2 days	 24.4 (16.9 – 36.9) 75.6 (67.8 – 82.7) 90.2 (88.5 – 92.6)	 14.4 (13.1 – 15.3) 76.5 (70.0 – 83.3) 87.7 (83.9 – 90.7)
Faeces 2 days	2.4 (1.3 – 3.8)	2.0 (0.6 – 3.2)
CO_2 2 days	6.2 (5.2 – 7.1)	5.8 (1.5 – 8.2)
Total recovery	99.1 (97.2 -101.6)	95.5 (92.7 - 98.5)

Figure A6.2.1-1 Proposed Metabolic Pathway for Bendiocarb



* = Position of radiolabel

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	20th September 2006
Materials and methods	As described by the applicant
Conclusion	As described by the applicant
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1979) The metabolism and Disposition of Bendiocarb in the Rat [redacted] Document A90201 6.2.1/02 June 1979 Unpublished	
1.2	Data protection	Yes	
1.2.1	Data owner	Bayer CropScience	
1.2.2	Companies with letter of access	n.a.	
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**	Study conducted in accordance with the US-EPA, Pesticide Assessment Guidelines, 85-1	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	^{14}C-bendiocarb and unlabelled bendiocarb	
3.1.1	Lot/Batch number	^{14}C-bendiocarb: CFQ 1598 Unlabelled bendiocarb: laboratory synthesis	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Not specified but bendiocarb is known as a beige-white powder	
3.1.2.2	Purity	^{14}C-bendiocarb: 97% Unlabelled bendiocarb: 98%	
3.1.2.3	Stability	Stable at room temperature	
3.1.2.4	Radiolabelling	^{14}C-bendiocarb (specific activity 45.9 µCi/mg) was obtained from the Radiochemical Centre, Amersham, and was shown to be 97% radiochemically pure by thin layer chromatography. The radiolabel was incorporated into the heterocyclic ring.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley CFY [for all the metabolism (balance) studies (except i.v. dosed females)] and Sprague Dawley CD (for plasma level studies and i.v. dosed females).	
3.2.3	Source	Anglia Laboratory Animals, Huntingdon, U.K. (for Sprague Dawley CFY rats) and Charles River (UK) Ltd., Margate, Kent (for Sprague Dawley CD rats). The change of supply was due to an outbreak of Tyzzers' disease at the breeding centre (Anglia Lab.) during the course of the study.	

3.2.4	Sex	M/F	
3.2.5	Age/weight at study initiation	135-169 g	
3.2.6	Number of animals per group	5-6M/6F for metabolism (balance) studies 17-18M/17-18F for plasma level studies	
3.2.7	Control animals	No	
		4. APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	The metabolism and disposition of bendiocarb has been investigated in male and female rats using two dose levels: 0.125 mg/kg and 2.5 mg/kg. Four groups of animals were treated with ^{14}C-bendiocarb (97% radiochemical purity) as follows: - Group A was dosed intravenously at 0.125 mg/kg - Group B was dosed orally at 0.125 mg/kg - Groups C was dosed orally with unlabelled bendiocarb (98% purity) for 14 days and on the 15th day was dosed orally with ^{14}C-bendiocarb. All doses were at 0.125 mg/kg - Group D was dosed orally at 2.5 mg/kg. All groups consisted of at least 5 male and 5 female animals on which metabolism (balance) studies were carried out, and up to 18 male and 18 female animals on which plasma level studies were carried out.	
		During plasma level studies and prior to dosing with ^{14}C-bendiocarb, each group of 8 animals were subdivided into three cages containing 5 animals and one cage containing three (or two) animals. After dosing each cage of five animals was bled at different time intervals to give samples at 30 min., 1, 2, 3, 4, 6, 8, 10 and 12 hours after dosing. Each cage of three (or two animals) was bled at time intervals from 5 min. to 47 min. after dosing. Thus each rat was bled up to three times and never on consecutive time intervals (blood was taken from the retro-orbital sinus). Animals were sacrificed after the final blood sample was taken.	X
		During the metabolism studies and after dosing with ^{14}C-bendiocarb, all rats were individually housed in glass metabolism cages which were equipped with urine and faeces separators. Complete collection of urine and faeces was made over a 72 hour period following dosing with ^{14}C-bendiocarb. Urine was collected 8, 24, 48 and 72 hours after dosing. Faeces were collected 24, 48 and 72 hours after dosing. Animals were sacrificed 72 hours after dosing with ^{14}C-bendiocarb. Samples of heart, lung, liver, spleen, eye, gonads, fat, muscle, bone and brain were obtained from all animals used in the balance studies. After these samples were obtained the residual carcases were minced. Residue levels of radioactivity (ppm equivalent to bendiocarb) were calculated from the scintillation counting data produced from the combustion of the samples.	X
4.2	**Results and discussion**	^{14}C-Bendiocarb was rapidly and extensively absorbed (83-96 %, 24 hours after dosing) following single and repeat oral administration.	

		For all groups of animals excretion took place very rapidly with 50-90% of the administered dose being recovered within 8 hours. The major route of excretion was in the urine, 77-99% of the dose being recovered in the urine over the 72 hours of the study. The route and rate of excretion appeared to be very similar for all animals, no significant differences being observed between male and female animals or between groups of animals. The metabolic and kinetic profile of bendiocarb in the rat appears to be virtually independent of sex, mode of dosing (single oral/repeat oral/intravenous) or dose level over the range studied. The plasma half-life of radioactivity was between 4 and 9 hours for all groups of animals. The major route of metabolism involved detoxification by cleavage of the carbamate ester group to yield the phenol NC 7312. This compound, excreted in conjugated form, accounted for > 70% of the radioactivity present in the urine after 8 hours. The remainder of the radioactivity excreted over this time period consisted of a mixture of minor metabolites and polar (presumably unhydrolysed) materials. Tissue residues 72 hours after dosing were very low in all groups (< 0.001 to 0.080 ppm = ^{14}C-bendiocarb) and there was no evidence of selective storage in any of the tissues examined.	X
4.3	**Conclusion**		
4.3.1	Reliability	1	
4.3.2	Deficiencies	No	

Table A6.2.1-2 Excretion of Radioactivity by Rats Following Administration of ^{14}C-bendiocarb (expressed as percentage of administered dose ± standard deviation)

Treatment group	A (i.v.) (0.125 mg/kg)	A (i.v.) (0.125 mg/kg)	B (oral) (0.125 mg/kg)	B (oral) (0.125 mg/kg)	C (oral) (0.125 mg/kg)	C (oral) (0.125 mg/kg)	D (oral) (2.5 mg/kg)	D (oral) (2.5 mg/kg)
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
% recovery of administered radioactivity								
Urine 0-8 h 8-24 h 24-48 h 48-72 h	86.8 ± 2.1 5.1 ± 2.5 0.3 ± 0.1 < 0.1	89.8 ± 4.0 7.9 ± 1.2 0.7 ± 0.3 0.3 ± 0.2	81.3 ± 9.4 6.8 ± 2.7 0.4 ± 0.2 < 0.1	74.0 ± 4.4 15.8 ± 5.1 1.2 ± 0.7 0.2 ± 0.0	54.8 ± 5.6 21.4 ± 9.2 0.8 ± 0.3 0.2 ± 0.1	76.3 ± 3.3 13.6 ± 3.8 0.8 ± 0.5 0.4 ± 0.2	70.8 ± 6.8 17.9 ± 8.5 0.6 ± 0.4 0.1 ± 0.0	49.7 ± 25.3 37.1 ± 28.9 1.5 ± 0.3 0.5 ± 0.3
Total	92.2 ± 2.7	98.6 ± 2.7	88.5 ± 7.3	91.2 ± 2.7	77.1 ± 5.6	91.1 ± 5.7	89.4 ± 2.6	88.8 ± 4.1
Faeces 0-24 h 24-48 h 48-72 h	3.3 ± 2.5 0.8 ± 0.5 0.4 ± 0.2	4.3 ± 1.3 0.5 ± 0.3 0.3 ± 0.2	6.5 ±5.0 1.4 ± 0.8 0.1 ± 0.1	2.4 ± 2.8 1.4 ± 0.8 < 0.1	9.1 ± 4.6 2.0 ± 1.4 0.6 ± 0.6	1.9 ± 1.5 2.1 ± 1.0 0.2 ± 0.0	3.3 ± 0.8 1.8 ± 0.9 0.1 ± 0.1	1.7 ± 1.9 1.6 ± 1.0 0.3 ± 0.2
Total	4.5 ± 2.6	5.1 ± 0.9	8.1 ± 5.3	3.9 ± 2.7	11.7 ± 4.1	4.2 ± 1.8	5.1 ± 1.3	3.6 ± 1.4
$^{14}CO_2$ 0-24 h 24-48 h 48-72 h	1.6 ± 0.5 0.3 ± 0.0 0.1 ± 0.0	2.8 ± 0.1 0.7 ± 0.1 0.5 ± 0.1	0.9 ± 0.3 0.3 ± 0.1 0.1 ± 0.1	2.1 ± 1.4 0.7 ± 0.7 < 0.1	2.2 ± 0.9 0.4 ± 0.1 0.2 ± 0.0	2.2 ± 0.3 0.3 ± 0.1 0.1 ± 0.0	3.1 ± 1.5 0.3 ± 0.0 < 0.1	2.8 ± 0.5 0.5 ± 0.2 < 0.1
Total	2.1 ± 0.6	4.0 ± 0.3	1.3 ± 0.2	2.8 ± 2.1	2.8 ± 1.0	2.7 ± 0.4	3.4 ± 1.5	3.3 ± 1.5
Total recovery	98.8 ± 1.9	107.9 ± 2.4	97.9 ± 3.0	97.9 ± 3.3	91.7 ± 3.4	98.0 ± 3.9	98.1 ± 0.4	96.0 ±3.5

Table A6.2.1-3 Extent of Absorption of bendiocarb following oral dosing

Treatment group	B (0.125 mg/kg)	B (0.125 mg/kg)	C (0.125 mg/kg)	C (0.125 mg/kg)	D (2.5 mg/kg)	D (2.5 mg/kg)
Sex	**M**	**F**	**M**	**F**	**M**	**F**
Time (h)	% absorbed					
8 24 48 72	93.7 ± 10.8 95.8 ± 7.9 96.0 ± 7.9 96.0 ± 7.9	82.4 ± 4.9 91.2 ± 2.5 92.5 ± 2.8 92.4 ± 2.8	63.1 ± 6.4 82.9 ± 5.9 83.5 ± 6.1 83.6 ± 6.1	85.0 ± 3.8 92.0 ± 5.5 91.9 ± 5.8 92.3 ± 5.8	81.6 ± 7.8 96.5 ± 2.4 96.8 ± 2.8 97.0 ± 2.8	64.6 ± 9.9 88.9 ± 4.3 89.8 ± 4.2 90.0 ± 4.0

Table A6.2.1-4 Metabolite levels in hydrolysed rat urine (% of total ^{14}C in urine sample)

Treatment group	A (i.v.) (0.125 mg/kg)	A (i.v.) (0.125 mg/kg)	B (oral) (0.125 mg/kg)	B (oral) (0.125 mg/kg)	C (oral) (0.125 mg/kg)	C (oral) (0.125 mg/kg)	D (oral) (2.5 mg/kg)	D (oral) (2.5 mg/kg)
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
8 hour urine								
Major metabolite	78 ± 12	79 ± 6	82 ± 5	75 ± 10	84 ± 6	73 ± 6	71 ± 5	78 ± 5
Minor metabolites	5 ± 3	9 ± 5	11 ± 4	4 ± 5	5 ± 3	10 ± 7	15 ± 4	9 ± 4
Polar materials (presumably unhydrolysed)	17 ± 3	14 ± 6	6 ± 2	22 ± 11	12 ± 7	17 ± 8	14 ± 2	12 ± 3
24 hour urine								
Major metabolite	NA	NA	NA	NA	NA	NA	54 ± 13	59 ± 10
Minor metabolite	NA	NA	NA	NA	NA	NA	4 ± 5	3 ± 3
Polar materials (presumably unhydrolysed)	NA	NA	NA	NA	NA	NA	42 ± 15	37 ± 13

NA: not analysed

Table A6.2.1-5 Tissue residue levels following dosing with ^{14}C-bendiocarb

Treatment group	A (i.v.) (0.125 mg/kg)	A (i.v.) (0.125 mg/kg)	B (oral) (0.125 mg/kg)	B (oral) (0.125 mg/kg)	C (oral) (0.125 mg/kg)	C (oral) (0.125 mg/kg)	D (oral) (2.5 mg/kg)	D (oral) (2.5 mg/kg)
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Residue level (ppm = = ^{14}C-bendiocarb)								
Heart	0.001	0.002	0.001	0.007	0.002	0.001	0.023	0.023
Lung	0.001	0.001	0.001	0.009	0.003	0.002	0.026	0.030
Liver	0.002	0.002	0.001	0.009	0.002	0.002	0.035	0.039
Kidney	0.002	0.002	0.001	0.009	0.002	0.002	0.034	0.041
Spleen	0.002	0.002	0.001	0.010	0.002	0.002	0.032	0.040
Eye	< 0.001	0.001	0.001	0.062	0.003	0.010	0.015	0.028
Testes	0.001		0.001		0.003		0.023	
Ovary		0.002		0.080		0.003		0.061
Fat	0.002	0.003	0.001	0.058	0.003	0.002	0.031	0.032
Muscle	0.001	0.001	0.001	0.011	0.001	0.001	0.022	0.025
Bone	0.001	0.001	0.001	0.012	0.001	0.001	0.029	0.028
Brain	< 0.001	< 0.001	0.001	0.011	0.001	0.001	0.021	0.026
Carcase	0.002	0.001	0.001	0.005	0.001	0.004	0.034	0.040

Limit of sensitivity = 0.001 ppm = ^{14}C-bendiocarb

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	20th September 2006
Materials and methods	4.1. For plasma level studies, each group comprised 18 animals. Collections of exhaled air were also made. Otherwise, as described by the applicant.
Conclusion	4.2. The peak plasma levels occurred within 15 minutes of single and repeat dosing in males and females. The plasma time profiles following single and repeat dosing with 0.125 mg/kg were very similar, with a calculated plasma half-life of 5.0 to 8.6 hours. The plasma half-life with the higher, single dose of 2.5 mg/kg was slightly lower, being 4.7 hours in males and 5.0 hours in females. Otherwise, as described by the applicant.
Reliability	1
Acceptability	Acceptable
Remarks	
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.2.2 Percutaneous absorption

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2004a) Ficam W Formulation: *In Vitro* Dermal Absorption Study using Human Skin [redacted] Document C040850 6.2.2/01 23 March 2004 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience	
1.2.2	Companies with letter of access	n.a.	
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 428 EC Guidance Document Sanco/222/rev.6	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Ficam 80W (80% bendiocarb water dispersible powder)	
3.1.1	Lot/Batch number	Non isotopically-labelled bendiocarb (Reference Substance AE B052020, Batch number: 860402; purity of 98.5%)	
3.1.2	Specification	80% bendiocarb (min purity 97%)	
3.1.2.1	Description	Light beige powder	
3.1.2.2	Purity	Non isotopically-labelled bendiocarb: purity 98.5% Radiolabelled-bendiocarb : purity > 99%	
3.1.2.3	Stability	Stable (for 7 days at room temperature)	
3.1.2.4	Radiolabelling	[Phenyl-UL-^{14}C]-bendiocarb was identified by the reference synthesis number SEL/1281 and indicated to have a radiopurity > 99% (by HPLC). The initial specific activity was 9.3 MBq/mg (251.35 µCi/mg).	
3.2	**Test Animals**		
3.2.1	Species	Human skin	
3.2.2	Strain	n.a.	
3.2.3	Source	n.a.	
3.2.4	Sex	n.a.	
3.2.5	Age/weight at study initiation	n.a.	

3.2.6	Number of animals per group	n.a.	
3.2.7	Control animals	n.a.	
3.3	Administration/ Exposure	Dermal	
3.3.1	Preparation of test site	Dermatomed human skin from 3 different donors was obtained from a recognised Tissue Bank (supplier: Biopredic, Rennes, France) and stored at approximately -20°C prior to use. Details about the specification of each human skin sample are available in the raw data files of the study. The integrity of the selected skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. Membranes considered to be abnormal (defined in-house policy: visual observation of skin sample and/or TEWL values < 40 g/m²/h) were excluded.	
3.3.2	Concentration of test substance	The solubility of [^{14}C]-bendiocarb in the receptor fluid was demonstrated to be approximately 99.86% of the applied dose, after incubation during 24 hours.	X
3.3.3	Specific activity of test substance	See Point 3.1.2 above.	
3.3.4	Volume applied	The dose preparation was applied to the skin membrane with a pipette at the rate of approximately 10 µl/cm2 exposed skin area. The amount of [^{14}C]-bendiocarb in the Ficam W formulation (SYP12426) was determined using dose checks taken before, during and after dosing application.	
3.3.5	Size of test site	Exposure area of 1cm² skin.	
3.3.6	Exposure period	The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffered saline) using natural sponge swabs. Receptor fluid samples were collected at hourly intervals for the duration of the study (24 hours).	
3.3.7	Sampling time	Hourly after 8 hours exposure until 24 h	
3.3.8	Samples	Receptor fluid samples	
		4. RESULTS AND DISCUSSION	
4.1	**Toxic effects, clinical signs**	n.a.	
4.2	**Dermal irritation**	n.a.	
4.3	**Recovery of labelled compound**	Following the application of Ficam W formulation of [^{14}C]-bendiocarb to human skin, the overall mean recovery of the dose was 91.13%. The total amount of radioactivity considered to be non-absorbed through human skin accounted for 86.53% of the applied dose, corresponding to the sum of the dose recovered in skin swabs at 8 and 24 hours (85.70%), in the two first tape-strips of the stratum corneum corresponding to the surface dose (0.340%) and in the dose retrieved from the donor chamber (0.493%).	

4.4	**Percutaneous absorption**	The total amount of radioactivity directly absorbed through human skin accounted for 3.309% of the applied dose, corresponding to the sum of the dose recovered from the receptor fluid between 0 and 24 hours (2.894%) and at termination (0.040%) and the dose retrieved in the receptor chamber (0.375%). The dose remaining in the skin after tape-stripping and in the stratum corneum was 1.135% and 0.187%, respectively.	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	This report describes the *in vitro* dermal penetration of radioactivity following a single topical application of [^{14}C]-bendiocarb in a liquid formulation (Ficam W formulation) to human dermatomed skin. The liquid formulation was prepared by diluting the WP 80 wettable powder in water. The liquid formulation was tested at one dose level corresponding to the in-use rate of the product. Six flow-through diffusion cells were prepared for human skin. Dermatomed membranes were maintained in the cells at approximately 32°C. The integrity of the membranes was first tested by the TEWL method (Trans-Epidermal Water Loss method). The [^{14}C]-bendiocarb in the formulation was applied to the unoccluded skin samples at a rate of 10 µl/cm^2. The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffered saline) using natural sponge swabs. Receptor fluid samples were collected at hourly intervals for the duration of the study (24 hours). The solubility of bendiocarb in the receptor fluid was demonstrated to be sufficient for the study. At the end of the study (24 hours) the skin samples were tape-stripped to remove residual surface dose and the stratum corneum.	
5.2	**Results and discussion**	The overall amount of [^{14}C]-bendiocarb considered to be directly absorbed was represented by the radioactivity present in the receptor fluid (including receptor fluid at termination and receptor chamber) and accounted for 3.309% for human skin cells. Taking into account that radioactivity recovered in the stratum corneum was considered to be available for absorption, the total amount of [^{14}C]-bendiocarb considered to be absorbable was the sum of the radioactivity present in the receptor fluid (including receptor at termination and receptor chamber) and the radioactivity remaining in the skin following tape-stripping and in the stratum corneum. Therefore, following the application of [^{14}C]-bendiocarb at a dose level which corresponds to the in-use rate of the product Ficam 80W, the dermal absorption in human skin accounted for 4.631% of the applied dose.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.2.2-1. Summary of the group mean distribution of radioactivity (results expressed as the mean % of applied radioactivity)

Ficam W Formulation	
Species	**Human Skin**
	Mean
SURFACE COMPARTMENT	
Surface dose*	0.340
Skin swabs	85.699
Donor chamber	0.493
Total % non-absorbed	***86.532***
SKIN COMPARTMENT	
Skin	1.135
Stratum corneum**	0.187
Total % at dose site	***1.322***
SYSTEMIC COMPARTMENT	
Total % directly absorbed: receptor fluid (including receptor fluid at termination & receptor chamber)	***3.309***
Total % absorbable* **	***4.444***
Total % recovery	***91.132***

* Surface dose = tape strips 1 & 2
** Excluding tape strips 1 & 2, which are considered to be non-absorbed dose
*** Total % absorbable = total % directly absorbed + % in the skin

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21st September 2006
Materials and methods	3.3.2. The concentration of the test substance was 2.23 mg bendiocarb/ml. Otherwise as described by the applicant.
Conclusion	The UK CA has added a table that summarises the distribution of the radioactivity. The entire stratum corneum was removed using only 5 tape strips, the mean residue levels being 0.223, 0.117, 0.100, 0.077 and 0.043 % of the administered dose in strips 1, 2, 3, 4 and 5, respectively. If residues in the first 2 strips of the stratum corneum are not considered to be systemically available, then a dermal absorption value of 4.631 % is obtained. Overall, the UK proposes to round up this figure and use a dermal absorption value of 5 %.
Reliability	1
Acceptability	Acceptable
Remarks	The dermal absorption value from this study (aqueous formulation) to be taken forward for risk characterisation is 5%.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2004b) Ficam D Formulation: *In Vitro* Dermal Absorption Study using Human Skin [redacted] Document C040839 6.2.2/02 23 March 2004 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience	
1.2.2	Companies with letter of access	n.a.	
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 428 EC Guidance Document Sanco/222/rev.6	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Ficam D (1.25% bendiocarb dustable powder)	
3.1.1	**Lot/Batch number**	Non isotopically-labelled bendiocarb (Reference Substance AE B052020, Batch number: 860402; purity of 98.5%)	
3.1.2	**Specification**	1.25% bendiocarb (min purity 97%)	
3.1.2.1	**Description**	Beige powder	
3.1.2.2	**Purity**	Non isotopically-labelled bendiocarb : purity 98.5% Radiolabelled-bendiocarb : purity > 99%	
3.1.2.3	**Stability**	Stable (7 days at room temperature)	
3.1.2.4	**Radiolabelling**	[Phenyl-UL-^{14}C]-bendiocarb was identified by the reference synthesis number SEL/1281 and indicated to have a radiopurity > 99% (by HPLC). The initial specific activity was 9.3 MBq/mg (251.35 µCi/mg).	
3.2	**Test Animals**		
3.2.1	**Species**	Human skin	
3.2.2	**Strain**	n.a.	
3.2.3	**Source**	n.a.	
3.2.4	**Sex**	n.a.	
3.2.5	**Age/weight at study initiation**	n.a.	
3.2.6	**Number of animals per group**	n.a.	

3.2.7	**Control animals**	n.a.
3.3	**Administration/ Exposure**	Dermal
3.3.1	Preparation of test site	Dermatomed human skin from 6 different donors was obtained from a recognised Tissue Bank (supplier: Biopredic, Rennes, France) and stored at approximately -20°C prior to use. Details about the specification of each human skin sample are available in the raw data files of the study. The integrity of the selected skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. Membranes considered to be abnormal (defined in-house policy: visual observation of skin sample and/or TEWL values < 40 g/m²/h) were excluded.
3.3.2	Concentration of test substance	The solubility of [^{14}C]-bendiocarb in the receptor fluid was demonstrated to be approximately 87.25% of the applied dose, after incubation during 24 hours.
3.3.3	Specific activity of test substance	See Point 3.1.2 above.
3.3.4	Volume applied	The dose preparation was applied to the skin membrane with a pipette at the rate of approximately 5 mg/cm² exposed skin area. The amount of [^{14}C]-bendiocarb in the Ficam D formulation was determined using dose checks taken before, during and after dosing application. The dust formulation was not moistened before or during the application.
3.3.5	Size of test site	Area of application = 1 cm² skin.
3.3.6	Exposure period	The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffered saline) using natural sponge swabs. Receptor fluid samples were collected at hourly intervals for the duration of the study (24 hours).
3.3.7	Sampling time	Hourly after 8 hours exposure until 24 h
3.3.8	Samples	Receptor fluid samples
		4. RESULTS AND DISCUSSION
4.1	**Toxic effects, clinical signs**	n.a.
4.2	**Dermal irritation**	n.a.
4.3	**Recovery of labelled compound**	Following application of the Ficam D formulation of [^{14}C]-bendiocarb to human skin, the overall mean recovery of the dose was 95.25%. The total amount of radioactivity considered to be non-absorbed through human skin accounted for 94.99% of the applied dose, corresponding to the sum of the dose recovered in skin swabs at 8 and 24 hours (94.39%), in the two first tape-strips of the stratum corneum corresponding to the surface dose (0.020%) and in the dose retrieved from the donor chamber (0.581%).
4.4	**Percutaneous absorption**	The total amount of radioactivity directly absorbed through human skin accounted for 0.197% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.133%) and at termination (0.019%) and the dose retrieved from the receptor chamber (0.044%).

		The dose remaining in the skin after tape-stripping and in the stratum corneum was 0.058% and 0.008% respectively.	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	This report describes the *in vitro* dermal penetration of radioactivity following a single topical application of [^{14}C]-bendiocarb in a dust formulation (Ficam D formulation) to human dermatomed skin. The dust formulation was tested at one dose level corresponding to the in-use rate of the product. Twelve flow-through diffusion cells were prepared for human skin. Dermatomed membranes were maintained in the cells at approximately 32°C. The integrity of the membranes was first tested by the TEWL method (Trans-Epidermal Water Loss method). The [^{14}C]-bendiocarb in the formulation was applied to the unoccluded skin samples at a rate of 5 mg/cm^2. The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffered saline) using natural sponge swabs. Receptor fluid samples were collected at hourly intervals for the duration of the study (24 hours). The solubility of bendiocarb in the receptor fluid was demonstrated to be sufficient for the study. At the end of the study (24 hours) the skin samples were tape-stripped to remove residual surface dose and the stratum corneum.	
5.2	**Results and discussion**	According to the physical nature of the test chemical, radioactivity residing in the stratum corneum and in the skin after tape-stripping, was considered unavailable for absorption (possible airborne fraction). Therefore, following the application of [^{14}C]-bendiocarb at a dose level which corresponds to the in-use rate of Ficam D, the dermal absorption in human skin accounted for 0.197% of the applied dose.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.2.2-2. Summary of the group mean distribution of radioactivity (results expressed as the mean % of applied radioactivity)

Ficam D Formulation	
Species	**Human Skin**
	Mean
SURFACE COMPARTMENT	
Surface dose*	0.020
Skin swabs	94.388
Donor chamber	0.581
Total % non-absorbed	***94.989***
SKIN COMPARTMENT	
Skin	0.058
Stratum corneum**	0.008
Total % at dose site	***0.065***
SYSTEMIC COMPARTMENT	
Total % directly absorbed: receptor fluid (including receptor fluid at termination & receptor chamber)	***0.197***
Total % absorbable* **	***0.255%***
Total % recovery	***95.252***

* Surface dose = tape strips 1 & 2
** Excluding tape strips 1 & 2, which are considered to be non-absorbed dose
*** Total % absorbable = total % directly absorbed + % in the skin

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21st September 2006
Materials and methods	As described by the applicant.
Conclusion	The UK CA has added a table that summarises the distribution of the radioactivity. Otherwise as described by the applicant.
Reliability	1
Acceptability	Acceptable
Remarks	The dermal absorption value from this study (dust formulation) to be taken forward for risk characterisation is 0.4%.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.3 Short-term repeated dose toxicity

6.3.1 Repeated dose toxicity (oral)

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [✓]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	These studies are not required as a sub-chronic toxicity study is available in a rodent (see Point 6.4.1)	
Undertaking of intended data submission [ ]		

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	7th September 2006
Evaluation of applicant's justification	The availability of a sub-chronic toxicity study in a rodent is justification for not providing a short-term repeated dose toxicity study.
Conclusion	The UK CA considers the justification for non-submission of data acceptable.
Remarks	
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.3.2 Repeated dose toxicity (dermal)

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1972) Toxicology of NC 6897: 15-Dose Cumulative Dermal Study with Ficam 80 in Male Rats [redacted] Document A90343 6.3.2/01 January 1972 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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, but the study was conducted in line with good scientific practice.	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Ficam 80W (80% bendiocarb water dispersible powder)	
3.1.1	Lot/Batch number	CR 13374/4 and CR 13374/6	
3.1.2	Specification	80% bendiocarb	
3.1.2.1	Description	Not specified	
3.1.2.2	Purity	Not specified	
3.1.2.3	Stability	Not specified, but bendiocarb is not known to decompose at room temperature.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar	
3.2.3	Source	No data	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	Young adult; 230 – 300 g	
3.2.6	Number of animals per group	6	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal	

3.3.1	Duration of treatment	3 weeks
3.3.2	Frequency of exposure	5 days per week
3.3.3	Postexposure period	All animals were sacrificed after 21 days (2 days after final dermal application)
3.3.4	**Dermal**	
3.3.4.1	Area covered	Not specified
3.3.4.2	Occlusion	Occlusive
3.3.4.3	Vehicle	Water
3.3.4.4	Concentration in vehicle	The 80% formulation was diluted to a 40 % a.i. w/v suspension in water
3.3.4.5	Total volume applied	Calculated according to dose rate: 50, 100, 200, 400 and 800 mg a.s./kg/day
3.3.4.6	Duration of exposure	6 h per day
3.3.4.7	Removal of test substance	Water
3.3.4.8	Controls	Control skin samples were obtained from rats receiving the lowest dose level, from an untreated area, which had also been shaved and covered with foil and plaster throughout the 3 weeks duration of the study.
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes, daily
3.4.1.2	Mortality	Yes, daily
3.4.2	Body weight	Yes, weekly
3.4.3	Food consumption	No
3.4.4	Water consumption	No
3.4.5	Opthalmoscopic examination	No
3.4.6	Haematology	No
3.4.7	Clinical chemistry	Yes Blood samples were obtained before treatment commenced, and at the end of the 6-hour exposure period on days 1 and 15 of treatment from all treated groups, and on day 5 from the 200 mg kg^{-1} group only, for determination of whole blood cholinesterase activity by the Ellman method.
3.4.8	Urinalysis	No
3.5	**Sacrifice and pathology**	
3.5.1	Organ weights	No
3.5.2	Gross and histopathology	Yes, all dose groups Gross pathology and skin histopathology

3.5.3	Other examinations	-	
3.5.4	Statistics	-	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	Animals receiving the highest dose level tested (800 mg/kg) showed marked toxic effects commencing 30 – 45 min after dosing and lasting for more than 6 h. There was a dose related gradation of response and the maximum dose causing no toxic effects was 100 mg/kg.	
4.1.2	Mortality	No deaths attributed to the administration of Ficam occurred at any dose level during the study. There was however, one death of a rat receiving 200 mg/kg/day on day 5 due to over-exposure to the ether anaesthetic.	
4.2	**Body weight gain**	Group mean bodyweights during the test show no significant dose-related effects except for some reduction in weight gain at 800mg/kg/day where toxic effects were severe.	
4.3	**Food consumption and compound intake**	n.a.	
4.4	**Ophthalmoscopic examination**	n.a.	
4.5	**Blood analysis**		
4.5.1	Haematology	n.a.	
4.5.2	Clinical chemistry	The group mean cholinesterase inhibitions after the first dose were not statistically significantly different from pre-exposure values at 50 or 100 mg/kg. Whole blood cholinesterase activity was significantly lower at 200, 400 and 800 mg/kg after the first dose with 39, 62 and 86% inhibition, respectively. Whole blood cholinesterase inhibition (37%) after the fifth dose at 200 mg/kg/day were similar to those after the first dose. The inhibition of whole blood cholinesterase activity was greater after the fifteenth dose than after the first dose. The terminal group mean inhibitions are all statistically significantly different from the pre-exposure values except at 50 mg/kg/day (24%, 48% and 72% inhibition at 50, 100 and ≥ 200 mg/kg/d, respectively); at this dose however, there was considerable individual variation and some individual rats showed cholinesterase inhibition.	
4.5.3	Urinalysis	n.a.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	n.a.	
4.6.2	Gross and histopathology	No macroscopic pathology or evidence of skin irritancy was found at post-mortem.	
		The application of chemical did not appear to have caused any significant changes in the epidermis, dermis or *panniculus carnosus*. In particular, no hypertrophic or inflammatory changes indicative of dermal irritation were seen.	

4.7	**Other**	-	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Doses of 50, 100, 200, 400 or 800 mg a.s. $kg^{-1}d^{-1}$ using Ficam 80 (a 80 % wettable powder bendiocarb formulation) were applied in aqueous suspension to the skin of 5 groups of 6 male Wistar rats under occlusive dressing for 6 hours per day, 5 days per week for 3 weeks. At the end of the exposure period on each day, the dressing was removed and the skin was washed to remove all traces of the test material applied. Animals were observed daily for mortality and clinical signs of toxicity, and body weights were recorded weekly. Since a preliminary experiment with a single 6-hour dermal application of 800 mg kg^{-1} Ficam 80 had showed that whole blood cholinesterase inhibition was at its highest after about 6 hours exposure, i.e. at the same time that the rats were decontaminated, this time point was therefore selected for the blood sampling conducted during the main test. In the main test, blood samples were obtained before treatment commenced, and at the end of the 6-hour exposure period on days 1 and 15 of treatment from all treated groups, and on day 5 from the 200 mg kg^{-1} group only, for determination of whole blood cholinesterase activity by the Ellman method. In the absence of a control group, the cholinesterase results obtained were expressed as a percentage of the pre-exposure values. At study termination, the animals were autopsied for gross pathological examination, and samples of skin were taken from the treated area for histopathological investigation. 'Control' skin samples were obtained from rats receiving the lowest dose level, from an untreated area, which had also been shaved and covered with foil and plaster throughout the 3 weeks duration of the study.	
5.2	**Results and discussion**	No treatment-related deaths were observed. Clinical signs of toxicity of increased severity were seen at 200 mg $kg^{-1}d^{-1}$ and above. These toxic effects, which were typical of cholinesterase inhibition, tended to appear 30 – 45 minutes after dosing, were still marked when the rats were decontaminated after 6 hours exposure, but had ceased within 24 hours of treatment initiation. The post-mortem examinations revealed no macroscopic abnormalities, and no evidence of skin irritation or of any other significant histopathological change at the examination of the treated skin samples. In this experiment the time course of cholinesterase inhibition during and after a 6-hour period of covered contact showed maximal inhibition after 6 hours followed by recovery to 71% of the pre-exposure value in the following 18 hours. This rapid reversibility is confirmed by the symptoms which were rapid in onset, severe after 6 hours but absent 18 hours after decontamination. The data in this report confirm that by both the oral and dermal routes of administration the effects of bendiocarb are rapidly reversible.	

		The symptom intensity and duration in the current experiment by the dermal route were similar after 1 dose and 15 doses. The 15 dose cumulative dermal LD_{50} is >800mg/kg/day, confirming the low degree of cumulative toxicity previously found in oral studies. The data on whole blood cholinesterase inhibition do, however, show an increased degree of inhibition after 15 doses when compared to those measured after a single exposure. The practical implications of this slow lowering of the whole blood cholinesterase activity are small as evidenced by the similarity of the severity of the toxic effects at the end of the experiment. A dose-related (statistically significant at ≥ 200 mg kg^{-1}) increase in whole blood cholinesterase inhibition was seen on day 1 (7, 11, 39, 62 and 86 % at 50, 100, 200, 400 and 800 mg kg^{-1} respectively). The degree of cholinesterase inhibition observed in the 200 mg kg^{-1} group on day 5 (37 %) was similar to that measured at the same dose level on day 1. On day 15 of treatment, the degree of cholinesterase inhibition was greater at all dose levels than that seen on day 1. On this last day of treatment (after 15 doses), there was indeed a dose-related (statistically significant at ≥ 100 mg $kg^{-1}d^{-1}$) increase in whole blood cholinesterase inhibition, which plateaued at 200 mg $kg^{-1}d^{-1}$ and above (24, 48, 72, 72 and 72 % at 50, 100, 200, 400 and 800 mg $kg^{1}d^{-1}$ respectively). From the data obtained in this study it has been confirmed that the small margin between the maximum dose levels causing (A) no whole blood cholinesterase inhibition and (B) no symptoms found in a cumulative oral study applies equally to the dermal route, 100 mg/kg/day causing no symptoms and 50 mg/kg/day producing inhibition in 3/6 rats and slight or no inhibition in 3/6 rats. During the study no deaths occurred due to the chemical and cholinergic symptoms were only seen at dose levels of 800, 400 and 200 mg/kg/day. Cholinesterase inhibition was not present after the first dose in animals receiving 100 mg/kg/day and below. After 15 doses 6/6 animals showed cholinesterase inhibition at 100 mg/kg/d (48% in average) and 3/6 showed inhibition at 50 mg/kg/d (24% in average). However, in this group (50 mg/kg/d) there was a high variability between individuals illustrated by 1 animal showing a high inhibition, 3 animals showing no inhibition and the range of cholinesterase activity observed in this group (27 – 118% expressed as % of pre-test value). For those reasons the effect at this dose level was considered to be border-line and not to be significant. Histopathological examination of the skin did not show any evidence of skin irritations. In summary, a dose-related decrease in whole blood cholinesterase activity was seen in this study following the topical application of Ficam 80 to male rats for 15 days at dose levels ranging from 100 up to 800 mg /kg/d.	
		Clinical signs of toxicity typical of cholinesterase inhibition were also observed at 200 mg/kg/d and above. Based upon a toxicologically significant inhibition in whole blood cholinesterase at 100 mg/kg/d and above; 50 mg/kg/d was considered to be a NOAEL for this study.	X
5.3	**Conclusion**		
5.3.1	LO(A)EL	100 mg/kg/d	X

5.3.2	NO(A)EL	50 mg/kg/d	X
5.3.3	Other	-	
5.3.4	Reliability	2	
5.3.5	Deficiencies	No	

Table A6.3.2-1 Results of Cholinesterase Monitoring as % of Pre-Exposure

Parameter changed	Dose mg/kg/day									
	1 dose					5 doses	15 doses			
	50	100	200	400	800	200	50	100	200	400
Males Mean of group (% inhibition) Range	93 (7%) 71–119	89 (11%) 70–105	61 (39%) 45–71	38 (62%) 24–58	14 (86%) 2–23	63 (37%) 19–88	76 (24%) 27–118	52 (48%) 37–62	28 (72%) 21–44	28 (72%) 20–37

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	7th September 2006
Materials and methods	As described by the applicant.
Results and discussion	As described by the applicant.
Conclusion	5.2. Based upon overt signs of toxicity, the UK CA considers that the NO(A)EL in this study was 100 mg/kg/d.
Reliability	2
Acceptability	Acceptable
Remarks	Since brain and erythrocyte cholinesterase levels were not measured during this study, the UK CA considers that the NO(A)EL was 100 mg/kg/d and the LO(A)EL was 200mg/kg/day, based on overt signs of toxicity. However, these values will not be taken forward for the risk characterisation.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1986) Ficam Plus WP Formulation: Twenty-one Day Dermal Toxicity Study in Rabbits [redacted] Document A90605 6.3.2/02 15 July 1986 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	US EPA 82-2. Japan Ministry of Agriculture, Forestry and Fisheries, Pesticide Testing Guidelines, 59 NohSan No. 4200, 28 January 1985, 'Repeated dose dermal toxicity: 21 day study'.	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Ficam Plus (water dispersible powder containing 31% bendiocarb, 3.0% natural pyrethrins and 7% piperonyl butoxide)	
3.1.1	Lot/Batch number	CR 20676/1 Batch 4PF15	
3.1.2	Specification	31% bendiocarb + 3.0% natural pyrethrins + 7% piperonyl butoxide	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	Not specified	
3.1.2.3	Stability	Stable (no change after one year at 40 °C)	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	New Zealand White	
3.2.3	Source	Interfauna UK Ltd, Huntingdon	
3.2.4	Sex	M/F	
3.2.5	Age/weight at study initiation	10 – 12 weeks 2.4 – 2.6 kg (M); 2.3 – 2.5 kg (F)	
3.2.6	Number of animals per group	5M/5F	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Dermal	

3.3.1	Duration of treatment	3 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	All animals were sacrificed after 21 days
3.3.4	Dermal	
3.3.4.1	Area covered	10% of body surface
3.3.4.2	Occlusion	Occlusive
3.3.4.3	Vehicle	0.5% w/v aqueous sodium carboxymethylcellulose (SCMC)
3.3.4.4	Concentration in vehicle	As required to produce a spreadable paste
3.3.4.5	Total volume applied	Calculated according to dose rate: 1.67; 5 and 15 mg a.i./kg bw/day
3.3.4.6	Duration of exposure	6 h per day
3.3.4.7	Removal of test substance	Warm water
3.3.4.8	Controls	0.5% w/v aqueous sodium carboxymethylcellulose (SCMC) (2.0 ml/kg/d)
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes, twice daily
3.4.1.2	Mortality	Yes, twice daily
3.4.2	Body weight	Yes, weekly
3.4.3	Food consumption	Yes, weekly
3.4.4	Water consumption	No
3.4.5	Opthalmoscopic examination	No
3.4.6	Haematology	Yes Number of animals: All animals Time points: prior to treatment (week 1) and prior to termination (week 3) Parameters: Haematocrit (Packed Cell Volume), haemoglobin concentration (Hb), erythrocyte count (RBC), total (WBC) and differential leukocyte count (N, L, E, B, M), platelet count (Plts), thrombotest.
3.4.7	Clinical chemistry	Yes Number of animals: All animals Time points: prior to treatment (week 1) and prior to termination (week 3) Parameters: Sodium, potassium, glucose, total cholesterol, urea, blood urea, total bilirubin, creatinine, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, globulin, chloride, calcium, inorganic phosphorus, and plasma, blood (erythrocyte) and brain cholinesterase activity

3.4.8	Urinalysis	No
3.5	**Sacrifice and pathology**	
3.5.1	Organ weights	Yes Adrenals liver brain, ovaries, testes (with epididymides), heart, kidneys
3.5.2	Gross and histopathology	Yes, all dose groups Gross pathology and histopathology [kidneys, liver, skin (treated and untreated), any other macroscopically abnormal tissues]
3.5.3	Other examinations	-
3.5.4	Statistics	Students 't' test; Williams' test, Kruskal-Wallis
3.6	**Further remarks**	-
		4. RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	There were no signs of toxicity considered to be related to administration of FICAM Plus in any of the rabbits during the study. Slight erythema was observed for short periods in one male rabbit receiving Ficam Plus, 1.67 mg ai./kg bw/day and also for one male and two female rabbits receiving Ficam Plus, 15 mg ai./kg bw/day. No dermal reactions were observed for any other rabbit during the study.
4.1.2	Mortality	No mortalities were recorded
4.2	**Body weight gain**	Statistically significantly lower bodyweight gains ($P<0.05$) were observed during Week 2 for female rabbits receiving Ficam Plus, 15 mg ai./kg bw/day in comparison with controls. Bodyweight gains for all other rabbits receiving Ficam Plus were similar to those of the controls.
4.3	**Food consumption and compound intake**	Cumulative food consumption of rabbits receiving Ficam Plus was comparable to that of control rabbits. However, when absolute food values were analysed, food consumption of female rabbits receiving Ficam Plus, 15 mg ai./kg bw/day was significantly lower ($P<0.05$) than that of controls during Week 2. This change correlates with the statistically significantly lower bodyweight gain during Week 2 of female rabbits of this treatment group.
4.4	**Ophthalmoscopic examination**	n.a.
4.5	**Blood analysis**	
4.5.1	Haematology	No haematological changes were apparent at Week 3 that were conclusively attributable to treatment with Ficam Plus. Lower ($P<0.05$) thrombotest times were recorded in male rabbits receiving Ficam Plus, 15 mg ai./kg bw/day in comparison with controls.
4.5.2	Clinical chemistry	Reduced erythrocyte cholinesterase levels ($P<0.05$) in males (-29%) and plasma cholinesterase levels in females ($P<0.01$) (-32.8%)were recorded in rabbits of the high dosage group when compared with the control values at Week 3 and were considered to be related to treatment with Ficam Plus.

		Depression of brain cholinesterase levels was also apparent in both male (-10.5%) and female (-7.7%) rabbits of the high dosage group; these changes were, however, less marked than those seen with plasma and erythrocyte iso-enzymes. An apparent treatment-related reduction in alkaline phosphatase levels was observed in rabbits receiving Ficam Plus, 15 mg ai./kg bw/day with statistical significance being achieved for female rabbits ($P<0.01$). No statistically significant changes in this parameter were seen for rabbits in the low or intermediate groups. Higher GPT and GOT levels were noted for some rabbits receiving Ficam Plus, 15 mg ai./kg bw/day. Statistical significance was not, however, achieved in comparison with control values.	
4.5.3	Urinalysis	n.a.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	No changes in organ weights were seen that were considered to be related to treatment with Ficam Plus.	
4.6.2	Gross and histopathology	No changes in macroscopic pathology were seen that were considered to be related to treatment with Ficam Plus. Diffuse minimal epidermal thickening was seen in the treated skin of all male and three female rabbits in the high dosage group. This change, not observed in control rabbits, was considered to be related to treatment with Ficam Plus. No treatment-related changes were apparent in the treated skin of rabbits receiving Ficam Plus, 1.67 or 5 mg ai./kg bw/day.	
4.7	**Other**	-	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Ficam Plus wettable powder insecticide formulation, nominally containing 31% bendiocarb as active ingredient, was administered daily to the intact skin of rabbits at dosage levels of 1.67, 5 and 15 mg ai./kg bw/day for twenty-one consecutive days. Aqueous sodium carboxymethylcellulose (0.5%) was similarly administered as a control. All animals were observed daily for signs of ill-health, behavioural changes or toxicosis. Any observed changes were recorded. Local irritation was recorded immediately prior to the first daily application of the test substance and subsequently daily. Local dermal reactions (erythema and oedema) resulting from treatment were assessed on a numerical basis according to a modified Draize scoring system. All rabbits were weighed prior to dosing and subsequently at weekly intervals throughout the study. The quantity of food consumed by each rabbit was measured at weekly intervals throughout the study. Blood was withdrawn from the median artery of the ear of all rabbits prior to treatment (Week -1) and prior to termination (Week 3).	

		After 21 days of treatment (Days 22 or 23) all animals were randomly killed by means of an intravenous overdose of pentobarbitone sodium and a complete autopsy undertaken. The macroscopic appearance of the tissues was recorded. Microscopic examinations were carried out for tissues listed in 'Terminal studies' from-all rabbits. All statistical analyses were carried out separately for males and females.	
5.2	**Results and discussion**	Slight erythema was observed for short periods in one male rabbit receiving Ficam Plus, 1.67 mg ai./kg bw/day and also for one male and two female rabbits receiving Ficam Plus, 15 mg ai./kg bw/day. No dermal reactions were observed for any other rabbit during the study. Cumulative food consumption of rabbits receiving Ficam Plus was comparable to that of control rabbits. However, when absolute food values were analysed, food consumption of female rabbits receiving Ficam Plus 15 mg ai./kg bw /day was significantly lower ($P<0.05$) than that of controls during Week 2. This change correlates with the significantly lower bodyweight gain during Week 2 of female rabbits of this treatment group. No haematological changes were apparent at Week 3 that were conclusively attributable to treatment with Ficam Plus. Lower ($P<0.05$) thrombotest times were recorded in male rabbits receiving Ficam Plus, 15 mg ai./kg bw /day in comparison with controls. Reduced erythrocyte cholinesterase levels ($P<0.05$) in males (-29%) and plasma cholinesterase levels in females ($P<0.01$) (-32.8%) were recorded in rabbits of the high dosage group when compared with the control values at Week 3 and were considered to be related to treatment with Ficam Plus. Depression of brain cholinesterase levels was also apparent in both male (-10.5%) and female (-7.7%) rabbits of the high dosage group; these changes were, however, less marked than those seen with plasma and erythrocyte iso-enzymes. An apparent treatment-related reduction in alkaline phosphatase levels was observed in rabbits receiving Ficam Plus, 15 mg ai./kg bw/day with statistical significance being achieved for female rabbits ($P<0.01$). No statistically significant changes in this parameter were seen for rabbits in the low or intermediate groups. Higher GPT and GOT levels were noted for some rabbits receiving Ficam Plus, 15 mg ai./kg bw/day. Statistical significance was not, however, achieved in comparison with control values. No changes in organ weights were seen that were considered to be related to treatment with Ficam Plus. No changes in macroscopic pathology were seen that were considered to be related to treatment with Ficam Plus. Diffuse minimal epidermal thickening was seen in the treated skin of all male and three female rabbits in the high dosage group. This change, not observed in control rabbits, was considered to be related to treatment with Ficam Plus. No treatment-related changes were apparent in the treated skin of rabbits receiving Ficam Plus, 1.67 or 5 mg ai./kg bw/day.	

		In conclusion, Ficam Plus, 15 mg ai./kg bw/day, administered to rabbit skin for 21 days produced minimal epidermal thickening of the treated skin and a reduction in erythrocyte and plasma cholinesterase levels. There were no toxicologically important treatment-related changes at 5 or 1.67 mg a.s./kg bw/day. The no-effect level in this study was 5 mg a.s./kg bw/day.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	15 mg a.s./kg bw/day	X
5.3.2	**NO(A)EL**	5 mg a.s./kg bw/day	X
5.3.3	Other	-	
5.3.4	Reliability	1	
5.3.5	Deficiencies	No	

Table A6.3.2-2 Results of Brain, Plasma and Erythrocyte Cholinesterase Monitoring (change compared to controls in %)

Parameter changed	Unit	Controls 0.5% SCMC	Ficam P 1.67 mg/kg	Ficam P. 5.0 mg/kg	Ficam P 15.0 mg/kg
Males					
Plasma cholinesterase	µmol/ ml/min	0.60	0.57 (-5%)	0.59 (-1.7%)	0.45 (-25%)
Erythrocyte cholinesterase	µmol/ ml/min	2.02	1.85 (-8.4%)	1.56* (-22.8%)	1.43 ** (-29.2%)
Brain cholinesterase	µmol/ g/min	8.38	8.29 (-1.1%)	8.28 (-1.2%)	7.54 (-10.5%)
Females					
Plasma cholinesterase	µmol/ ml/min	0.67	0.54 (-19.4%)	0.57 (-14.9%)	0.45 *** (-32.8%)
Erythrocyte cholinesterase	µmol/ ml/min	1.86	1.65 (-11.3%)	1.70 (-8.6%)	1.67 (-10.2%)
Brain cholinesterase	µmol/ g/min	8.52	9.82 (+15.3%)	7.26 (-14.8%)	7.86 (-7.7%)

* Toxicologically significant
** $p < 0.05$ in comparison with controls using Williams' test
*** $p < 0.01$ in comparison with controls using Williams' test

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	7th September 2006
Materials and methods	As described by the applicant.
Results and discussion	As described by the applicant.
Conclusion	5.3.1 Based on a toxicologically significant decrease in erythrocyte cholinesterase activity, the UK CA has set a LO(A)EL value of 5 mg/kg/d 5.3.2 The UK CA considers that the NO(A)EL is 1.67 mg/kg/d.
Reliability	1
Acceptability	Acceptable
Remarks	The values for the LO(A)EL and NO(A)EL have been set at 5 mg/kg/d and 1.67 mg/kg/d, respectively.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.3.3 Repeated dose toxicity (inhalation)

			Official use only
		1. REFERENCE	
1.1	**Reference**	14-day range-finding study (HRC Report No. SMS 504/942690 in Volume 3 (pp315 – 462) of: [redacted] Bendiocarb: Rat 13-Week Inhalation Toxicity Study (Snout-Only Exposure) and Range Finding Studies [redacted] Document A89120 6.3.3/01 28 February 1995 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	US EPA 82-4	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR21272/01/931201	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	97.1 – 97.2%	
3.1.2.3	Stability	Not specified, but bendiocarb is not known to decompose at room temperature.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley	
3.2.3	Source	Charles River, UK	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	6 – 7 weeks; 188 – 189 g (M), 167 – 168 g (F)	
3.2.6	Number of animals per group	5M/5F	
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	6 hours per day, 5 days per week
3.3.3	Postexposure period	None – all surviving animals were sacrificed at the end of the 2-week exposure period.
3.3.4	**Inhalation**	
3.3.4.1	Concentrations	Nominal concentration 1, 10, 50, 100 mg/m^3 Analytical concentration 1.3, 10.9, 47.8, 90.5 mg/m^3
3.3.4.2	Particle size	Mean MMAD values were 1.3, 1.5, 1.4 and 1.7 µm at 1, 10, 50, and 100 mg/m^3 respectively. 99 – 100% of particles were <7 µm, i.e. within the respirable range
3.3.4.3	Type or preparation of particles	Particulate aerosol produced using a Wright dust feed mechanism
3.3.4.4	Type of exposure	Snout only
3.3.4.5	Vehicle	None – neat technical material
3.3.4.6	Concentration in vehicle	Particulate aerosol produced using a Wright dust feed mechanism
3.3.4.7	Duration of exposure	6 hours per day, 5 days per week for 2 weeks
3.3.4.8	Controls	Air only
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes; half-hourly during exposure
3.4.1.2	Mortality	Yes; half-hourly during exposure
3.4.2	Body weight	Yes; daily
3.4.3	Food consumption	Yes; daily
3.4.4	Water consumption	Yes; daily
3.4.5	Ophthalmoscopic examination	No
3.4.6	Haematology	No
3.4.7	Clinical chemistry	Yes Number of animals: All animals Time points: immediately after the last exposure in week 2 (day 13) Parameters: whole blood and brain cholinesterase activity (Ellman method)
3.4.8	Urinalysis	No
3.5	**Sacrifice and pathology**	
3.5.1	Organ weights	Brain

3.5.2	Gross and histopathology	Yes, all dose groups The macroscopic appearance of all tissues was noted.
		At necropsy (day 15) the brain was weighed and immediately frozen in a cardice/hexane mixture, prior to storage in a deep freeze at -20°C for later brain acetyl cholinesterase analysis. The remaining head and respiratory tract (larynx, trachea and lungs) were preserved in 10% neutral buffered formalin. The preserved tissues were retained for possible microscopic examination at a later date.
3.5.3	Other examinations	-
3.5.4	Statistics	Fisher's Exact Test, Bartlett's Test, Kruskal-Wallis analysis, Students' 't' test, Williams' Test
3.6	**Further remarks**	-
		4. RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	Observation of clinical signs during exposure was severely limited and masked by the soiling of the animals with excreta considered due to the snout-only method of restraint/exposure. No treatment-related clinical signs were recorded during exposure. Treatment-related clinical signs were seen immediately after exposure and were confined to female rats of Group 4 (50 mg/m^3) and both sexes in Group 5 (100 mg/m^3). The signs included rigid tails, unsteady gait and slight tremors. Approximately 1 hour after dosing, signs considered to be treatment-related (e.g. hunched posture, slight body tremors, unsteady gait and closed/half closed eyes) were seen in some individuals, either male or female of Groups 4 (50 mg/m^3) or 5 (100 mg/m^3). The sign of rigid tail was no longer observed in any animal, 1 hour after dosing. Other signs observed (brown staining, matted or wet fur, soiled anal or urogenital region) were considered to be associated with the snout-only method of restraint/exposure. All animals were normal in appearance and behaviour at the weekends when they were not exposed.
4.1.2	Mortality	There were no unscheduled deaths.
4.2	**Body weight gain**	Reduced bodyweight gain was observed in all male exposed groups (slight for rats exposed at 1 mg/m^3) and in females exposed at 100 mg/m^3, statistically significantly so ($P < 0.01$) for males of Groups 4 (50 mg/m^3) and 5 (100 mg/m^3). Female bodyweight gain was less affected than males. A degree of recovery from the effects of exposure to bendiocarb was observed at the weekend. At 50 and 100 mg/m^3, during the first week of exposure of males, there was an initial loss (3 and 4% respectively) followed by a period of reduced gain. Bodyweights were 11 and 13% lower than controls at the end of the treatment period at these respective dose levels. In females, there was an initial loss of weight at both 50 and 100 mg/m^3 but subsequent weight gain resulted in only a +2% difference from controls at 50 mg/m^3 and -1% at 100 mg/m^3.

		At 10 mg/m³, male bodyweight was virtually static following the first two exposures and thereafter gradually increased. By termination, bodyweight was still lower (8%) than controls. There was no effect on bodyweight of females. At 1 mg/m³, male bodyweight gain was initially slightly reduced compared with controls and terminal weight was only 1 % lower. Female bodyweight was unaffected.	
4.3	**Food consumption and compound intake**	Food consumption was slightly reduced when compared with control in male rats exposed at 50 and 100 mg/m³. A degree of recovery was seen at the weekends when dosing did not occur. Female food consumption was unaffected following exposure to bendiocarb. Increased water consumption was recorded for male and female rats exposed at 50 and 100 mg/m³ and in female rats exposed at 10 mg/m³ when compared with control rats.	
4.4	**Ophthalmoscopic examination**	n.a.	
4.5	**Blood analysis**		
4.5.1	Haematology	n.a.	
4.5.2	Clinical chemistry	Whole-blood acetylcholinesterase activity, measured immediately after the last exposure in Week 2, were statistically significantly lower than control for both sexes of all test groups. At 100 mg/m³ activity was 23% and 24% of control values in males and females respectively (77% and 76% inhibition, respectively). Corresponding values at 50 mg/m³ were 25% and 30% of controls (75% and 70% inhibition, respectively) and at 10 mg/m³, 32% and 49% of controls (68% and 51% inhibition, respectively). The slight responses at 1 mg/m³ were 71% and 82% of controls for males and females respectively (29% and 18% inhibition, respectively). Differences were dose-related and were considered to be of toxicological importance in all male treated groups and in females exposed to 10 mg/m³ and above. The slight reduction in activity in both sexes at 1 mg/m³ is considered to be indicative of exposure rather than toxicity.	
4.5.3	Urinalysis	n.a.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	n.a.	
4.6.2	Gross and histopathology	Brain acetylcholinesterase activity measured after necropsy on Day 15 was unaffected in test groups when compared to control. This may reflect the reversal of any inhibition over the weekend, since the last exposure occurred 2 days prior to necropsy. A slight reduction in the brain weight of male rats exposed in 100 mg/m³ achieved a degree of statistical significance when compared with control rats ($P < 0.05$). However, the difference was slight and was considered not to be of toxicological significance. The macroscopic examination performed at termination revealed no changes attributable to treatment with bendiocarb.	
4.7	**Other**		

		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of 5 male and 5 female Sprague-Dawley CD rats were treated by snout-only inhalation at target concentrations of 1, 10, 50 and 100 mg/m^3 for 6 hours a day, 5 days per week over 2 weeks. Parameters measured included mortality, clinical signs, bodyweight, food consumption, water intake and clinical pathology (whole blood and brain cholinesterase analysis).	
5.2	**Results and discussion**	Snout-only inhalation exposure of rats to 50 and 100 mg/m^3 bendiocarb over 2 weeks caused clinical signs (rigid tails, unsteady gait and slight tremors), reduced bodyweight gain in males and marked whole-blood acetylcholinesterase inhibition. Food consumption was also slightly reduced in males. A slight initial loss of bodyweight occurred in females at 100 mg/m^3. Similar exposure to 10 mg/m^3 markedly reduced whole-blood acetylcholinesterase activity (-68 and –51% in males and females respectively). At 1 mg/m^3 there was a slight reduction in whole-blood acetylcholinesterase activity (-29 and -18% in males and females respectively). These variations were considered to reflect more exposure than toxicity. No effect was observed in brain cholinesterase activity at any dose level. However, as necropsy took place two days after the last exposure, it was not clear if this was due to absence of an effect or reversibility. Based on these findings it was recommended that a short term snout-only inhalation study was initiated to determine brain acetylcholinesterase activity immediately after exposure. It was also recommended that the highest exposure concentration in the subsequent rat 13-week inhalation toxicity study should be between 10 and 50 mg/m^3.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	10 mg/m^3	
5.3.2	NO(A)EL	1 mg/m^3	
5.3.3	Other	-	
5.3.4	Reliability	1	
5.3.5	Deficiencies	No	

Table A6.3.3-1 Results of Whole Blood and Brain Cholinesterase Monitoring as % of control (and change compared to controls in %)

Parameter Changed		1 mg/m³	10 mg/m³	50 mg/m³	100 mg/m³
Males	Whole blood (week 2)	71* (-29%)	32* (-68%)	25* (-75%)	23* (-77%)
	Brain (week 3)	100 (na)	92 (-8%)	102 (+8%)	97 (-3%)
Females	Whole blood (week 2)	82* (-18%)	49* (-51%)	30* (-70%)	24* (-76%)
	Brain (week 3)	116 (+16%)	99 (-1%)	108 (+8%)	95 (-5%)

**P < 0.01 compared with controls*

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	12th September 2006
Materials and methods	As described by the applicant.
Results and discussion	As described by the applicant. The UK CA has added an asterisk to those values in Table A6.3.3-1 that were statistically significant.
Conclusion	
Reliability	1
Acceptability	Acceptable.
Remarks	The NO(A)EL and LO(A)EL values established in this study will not be taken forward for the risk characterisation, because of the unreliability of the brain cholinesterase measurements.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.4 Subchronic toxicity

6.4.1 Subchronic oral toxicity test

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1974) 16 Week Sub-Acute Toxicity Study in Dogs (NC 6897 Technical) [redacted] Document A90358 6.4.1/01 August 1974 Unpublished [redacted] (1979) 16 Week Sub-Acute Toxicity Study in Dogs: NC 6897 Technical (Histopathology for Low and Medium Dose Level Groups) [redacted] Document A90359 6.4.1/02 November 1979 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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, but the study was conducted in line with good scientific practice	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but was conducted to in-house QA standards.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR 1413 1/1 1 P640 Batch 14 CR 4710 (week 16 only)	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	CR 1413 1/1 1 P640 Batch 14: 97% CR 4710 (week 16 only): 96%	
3.1.2.3	Stability	Not specified, but bendiocarb is not known to decompose at room temperature.	
3.2	**Test Animals**		
3.2.1	Species	Dog	
3.2.2	Strain	Beagle	
3.2.3	Source	Hazleton Research Laboratories	

3.2.4	Sex	M/F
3.2.5	Age/weight at study initiation	M: 7.9 – 12.4 kg F: 7.5 – 11.4 kg
3.2.6	Number of animals per group	4M/4F
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	16 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	2 animals of each sex from each group were fed control diet for a further 2 days after the 16 week feeding trial (to study recovery from any observed adverse effects) before being terminated.
3.3.4	**Oral**	
3.3.4.1	Type	In food
3.3.4.2	Concentration	0, 20, 100 and 500 ppm (the highest dose rising to 1000 ppm for the last 4 w of the study) These dietary intakes were calculated to be approximately equivalent to dose levels of 0.2, 1.0 and 6.25 mg kg^{-1} d^{-1} for 20, 100 and 500 – 1000 ppm respectively (where 6.25 is the mean cumulative value for 500 – 1000 ppm).
3.3.4.3	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes, daily
3.4.1.2	Mortality	Yes, daily
3.4.2	Body weight	Yes, weekly
3.4.3	Food consumption	Yes, weekly
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	Yes Before treatment commenced and at termination
3.4.6	Haematology	Yes Before treatment commenced, after week 4 and at termination. Parameters: Erythrocyte count, haematocrit (packed cell volume), haemoglobin, total and differential leucocyte count.
3.4.7	Clinical chemistry	Yes Before treatment commenced, after week 4 and at termination. Glucose, BUN, SGFT, alkaline phosphatase, total protein, total bilirubin, cholesterol, prothrombin time.

		Whole blood and plasma cholinesterase activity was also measured initially and during the 5th, 9th, 14th, 15th and 16th weeks (Ellman method), with brain cholinesterase activity being determined after week 16. At weeks 5, 9, 14 and 15, whole blood cholinesterase determinations were not conducted at the same intervals following feeding time and blood collection, and therefore, the measured values for cholinesterase activity are considered to be limited in their reliability.	
3.4.8	Urinalysis	Yes Before treatment commenced after week 4 and at termination. Appearance, pH, specific gravity, glucose, ketones, protein, microscopic examination of sediment.	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes, all surviving animals Organs: liver, kidneys, adrenals, testes with epididymis, ovaries, thyroid, spleen, heart	
3.5.2	Gross and histopathology	Yes, all surviving animals (macroscopic) Control and high level dose group.(microscopic) – later study incorporated low and middle dose groups Organs: brain, liver, testes with epididymis, pituitary, spleen, seminal vesicles, spinal cord, kidneys, ovary, optic nerve, adrenals, uterus, eye, stomach, thymus, thyroids, pancreas, skin, oesophagus, small intestine, bone marrow, trachea, large intestine, skeletal muscle with nerve, lung, mesenteric lymph node, heart, urinary bladder, parathyroids, cervical lymph node, aorta, gallbladder, bone, mammary tissue, visible lesions.	
3.5.3	Other examinations	-	
3.5.4	Statistics	Students 't' test; Williams' test	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	One dog in the high level group showed rough and coarse hair coat starting during week 8. During the 11th week and continuing until the 13th week, red sores developed around the head and neck. No definitive diagnosis was made. One male high level dog had soft faeces for one day during week 8, and soft, bloody stools in week 16. One female high level dog was grossly thin during weeks 10 to 13. None of these findings appear to be compound related. One dog showed no change in appearance or behaviour accompanying the weight loss.	

4.1.2	Mortality	One male dog in the low level group (20 ppm) died during week 15 shortly after collecting; blood for clinical biochemistry examinations. This animal struggled violently during the collection of the blood sample from the jugular vein. The struggle included severe hyperextension of the neck and head. The animal collapsed very shortly after the sample was collected and remained semi-comatose for about three hours. During this period the dog was examined by several staff veterinarians, but no satisfactory diagnosis could be made. The prognosis was that the animal would not survive until the following day, and, therefore, euthanasia was performed and the animal carefully necropsied. Necropsy revealed a rupture of the basilar artery within the skull and haemorrhage in the left jugular furrow. It seems clear that the observed collapse was secondary to the intra-cerebral haemorrhage. All other animals survived the planned study.	
4.2	**Body weight gain**	All dogs generally ate well, maintained or gained weight, and showed good elimination during the course of the study.	
4.3	**Food consumption and compound intake**	Food consumption was unaffected by incorporation of bendiocarb in the diet.	
4.4	**Ophthalmoscopic examination**	No effects were produced at any dosage level	
4.5	**Blood analysis**		
4.5.1	Haematology	No consistent changes were produced at any dosage level in the parameters measured.	
4.5.2	Clinical chemistry	No consistent changes were produced at any dosage level in these parameters. Whole blood, plasma, and brain cholinesterase activity was not altered at any time at the 20 ppm level. At the 100 ppm dosage the whole blood activity was depressed in one female dog, but plasma and brain activity were unaffected. All other dogs were within normal limits. In the high level dosage group, plasma, whole blood, and brain activity were clearly depressed.	
4.5.3	Urinalysis	No changes were produced by incorporation of bendiocarb in the diet at any test level.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	Organ weight analysis performed on dogs killed at the terminal sacrifice revealed no indication of any reaction to treatment.	
4.6.2	Gross and histopathology	No histologic abnormality or lesion was found attributable to the experimental procedure.	
4.7	**Other**		

		5. APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Beagle dogs (4 animals/sex) were fed bendiocarb (technical grade; 96 % to 97 % purity) in the diet for 16 weeks at 0, 20, 100 or 500 ppm (the highest dose rising to 1000 ppm for the last 4 weeks of the study). These dietary intakes were calculated to be approximately equivalent to dose levels of 0.2, 1.0 and 6.25 mg kg^{-1} d^{-1} for 20, 100 and 500 – 1000 ppm respectively (where 6.25 is the mean cumulative value for 500 – 1000 ppm). Of the 4 animals/sex/dose, 2 were terminated at 16 weeks, whilst the remaining 2 were fed control diet for an additional 2-day period (to study recovery from any observed adverse effects) before being terminated. Investigations carried out during the study included behavioural observations for clinical signs of toxicity, food consumption measurements, urine analysis, haematology and blood chemistry determinations and gross and microscopic examinations (carried out on tissues from the control and high dose level groups only). Whole blood and plasma cholinesterase activity was measured in all animals at weeks 0, 5, 9, 14, 15 and 16, with brain cholinesterase activity being determined after week 16. At weeks 5, 9, 14 and 15, whole blood cholinesterase determinations were not conducted at the same intervals following feeding time and blood collection, and therefore, the measured values for cholinesterase inhibition are considered to be limited in their reliability.
5.2	**Results and discussion**	No treatment-related deaths occurred during the study. Whole blood and brain cholinesterase activity were reduced in the highest dose group; during week 9 at 500 ppm (before the top dose level was increased) average whole blood cholinesterase activity had decreased by 30 % (mean from 4 males and 4 females). However, due to the lack of experimental standardisation mentioned above, the accuracy of this value was uncertain. By week 16, the interval between feeding, blood collection and cholinesterase measurements had been optimised. At 16 weeks, mean reductions of 43-46% and 39% in whole blood and plasma cholinesterase activity were measured (4 animals, 2 from each sex) at the top dose. At the same dose, brain cholinesterase activity was also decreased on average by 28-42% compared to the control group. There were no significant/notable effects on any measured cholinesterase activities at 100 and 20 ppm. Additionally, no overt clinical signs of cholinesterase inhibition were detected at any time in any treatment group during the behavioural observations. No other treatment-related clinical chemistry changes were noted at any dose level. Also, no treatment-related haematological, ophthalmological, urinalysis or histopathological findings were observed. In summary, no effects were seen at 20 and 100 ppm (0.2 and 1 mg kg^{-1} d^{-1}). At 500/1000 ppm (6.25 mg kg^{-1} d^{-1}), there were 43-46% and 28-42% inhibition in whole blood and brain cholinesterase activity respectively. A NOAEL of 100 ppm (1.0 mg^{-1} kg^{-1} d^{-1}) was established from this study based upon a toxicologically significant inhibition in brain cholinesterase.

5.3	**Conclusion**		
5.3.1	LO(A)EL	500-1000 ppm (6.25 mg^{-1} kg^{-1} d^{-1})	
5.3.2	NO(A)EL	100 ppm (1.0 mg^{-1} kg^{-1} d^{-1})	
5.3.3	Other	-	
5.3.4	Reliability	2	
5.3.5	Deficiencies	No	

Table A6.4.1-1 Results of Whole Blood, Plasma and Brain Cholinesterase Monitoring as % of mean recovery value (and change compared to controls in %)

Parameter changed	Weeks after start of treatment	% of mean recovery value (range) *Change compared to controls in %*					
		Males			Females		
		Whole blood (Range)	Plasma (Range)	Brain (Range)	Whole blood (Range)	Plasma (Range)	Brain (Range)
Controls	16	112.5 (103–122) -	95.5 (87–104) -	89 (89) -	95.5 (91–100) -	101.5 (100–103) -	88 (88) -
Low dose (20 ppm)	16	105.5 (100–111) -6%	93.5 (85–102) -2%	83 (83) -7%	100 92–108) +5%	90 (76–104) -11%	90 (87–93) +2%
Medium dose (100 ppm)	16	112.5 (100–125) 0%	101 (100–102) +6%	80.5 (73–88) -10%	90.5 (62–119) -5%	94.5 (89–100) -7%	92 (90–94) +5%
High dose (500-1000 ppm)	16	64 (54–74) -43%	58 (54–62) -39%	52 (49–55) -42%*	51.5 (40–63) -46%	61.5 (54–69) -39%	63 (59–67) -28%*

* Toxicologically significant

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	13th September 2006
Materials and methods	As described by the applicant
Results and discussion	As described by the applicant The UK CA has added an asterisk to those values that are considered to be toxicologically important in Table 6.4.1-1.
Conclusion	As described by the applicant
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1979) NC 6897 Technical (CR 4799/3) Toxicity to Rats when Administered in the Diet for 13 Weeks (Final Report) [redacted] Document A90957 6.4.1/03 February 1979 Unpublished [redacted] (1978) Determination of Bendiocarb (NC 6897) Dietary Concentrations in a 90-Day Rat Toxicity Study [redacted] Document A90958 6.4.1/04 October 1978 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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, but the study was conducted in line with good scientific practice	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but was conducted to in-house QA standards.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR 4799/3	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	Not specified (however, when considering A90445 (2-y mouse) and A90975 (2-y dog) conducted with same batch but different certificate numbers, purity should be between 92.7 and 98%)	
3.1.2.3	Stability	Stable in diet at ambient temperature for at least 28d	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley CFY	
3.2.3	Source	Anglia Laboratory Animals. Alconbury	
3.2.4	Sex	M/F	

3.2.5	Age/weight at study initiation	ca 28 days old; 70 – 80 g
3.2.6	Number of animals per group	10M/10F
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	90 days
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	At the end of the study, all surviving animals were sacrificed and a gross pathological examination performed
3.3.4	**Oral**	
3.3.4.1	Type	In food
3.3.4.2	Concentration	0, 2, 10, 50 and 250 ppm (equivalent to approximately 0, 0.13, 0.65, 3.45 or 17.3 mg kg^{-1} d^{-1})
3.3.4.3	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes, twice daily
3.4.1.2	Mortality	Yes, twice daily
3.4.2	Body weight	Yes, weekly
3.4.3	Food consumption	Yes, weekly
3.4.4	Water consumption	Yes, daily during weeks 5 and 13
3.4.5	Ophthalmoscopic examination	Yes Before treatment commenced and during week 13, the eyes of all surviving rats of each sex in each group were examined using a Keeler indirect ophthalmoscope.
3.4.6	Haematology	Yes Before treatment commenced and during weeks 4, 8 and 12, a sample of blood was withdrawn from the orbital sinus of 10 males and 10 females from each group under light ether anaesthesia. Blood was sampled at least 48 hours after removing the animals from the urine collection cages. Parameters: Packed cell volume (haematocrit), haemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count, clotting time, prothrombin time, thromboplastin time.
3.4.7	Clinical chemistry	Yes During week 12, a sample of blood was withdrawn from the orbital sinus of five males and five females from each group under light ether anaesthesia.

		Parameters: Sodium, potassium, chloride, inorganic phosphorus, calcium, glucose, total cholesterol, serum urea, creatinine, total protein, albumin, alkaline, phosphatase, glutamic-pyruvic transaminase. During week 4, 9 and 13 samples of blood were obtained from 10 males and 10 females of each group for determination of whole blood cholinesterase activity.	
3.4.8	Urinalysis	Yes During weeks 4, 8 and 12, individual overnight urine samples were collected from ten males and ten females from each group. After measurement of volume of urine collected, the following estimations were performed: pH, specific gravity, reducing substances, glucose, protein, ketones, bile pigments, urobilinogen, haemoglobin	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes, all animals Organs: liver, kidneys, adrenals, testes, uterus, ovaries, thyroid, spleen, brain, heart and pituitary.	
3.5.2	Gross and histopathology	Yes, gross pathology examination was performed on all animals. Complete histopathology examination was performed on all control and high dose animals. Organs: brain, pituitary, thyroid, thymus, oesophagus, salivary glands, stomach, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aeorta, gonads, uterus, female mammary gland, prostate, urinary bladder, lymph nodes, peripheral nerve, bone marrow, skin, eyes, skeletal muscle, mid-colon, caecum, duodenum, ovaries, ileum, tongue, sciatic nerve, seminal vesicles, sternum, jejunum.	
3.5.3	Other examinations	-	
3.5.4	Statistics	Students 't' test; Williams' test	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	None of the clinical signs observed was considered to be indicative of a reaction to treatment with bendiocarb.	
4.1.2	Mortality	There was only one mortality during the study, rat 22 (M), receiving 10 ppm bendiocarb, was killed on humane grounds, during week 8, after trapping its teeth in the wire mesh of the cage. Autopsy findings did not reveal any indication of a reaction to treatment.	
4.2	**Body weight gain**	Overall bodyweight gain of female rats receiving 2 or 250 ppm bendiocarb was statistically significantly greater than weight gain recorded for control females. No intergroup differences in weight gain among male rats attained a level of statistical significance, and as the finding in females was not dosage-related in degree, it was considered to be of no biological significance.	

4.3	**Food consumption and compound intake**	Overall food consumption of female rats receiving 250 ppm bendiocarb was apparently greater than that of control females. However, there was no indication of increased food intake among male rats receiving 250 ppm, and in view of the small number of animals in each group, the finding was considered to be of no biological significance. Compound intake in mg/kg/day in males and males/females is 0.13/0.15 at 3 ppm, 0.65/0.78 at 10 ppm, 3.45/3.94 at 50 ppm and 17.3/20.0 at 250 ppm.
4.4	**Ophthalmoscopic examination**	At the ophthalmic examination carried out before treatment commenced, one male rat with a total cataract was replaced with a spare male showing no ocular abnormality, so that all rats starting on the study showed no abnormal ophthalmic lesions. Further ophthalmic examination carried out during week 13 revealed no ocular abnormalities which were considered to be related to treatment.
4.5	**Blood analysis**	
4.5.1	Haematology	Haematological investigations performed before treatment commenced revealed values which were all considered to be within the accepted normal range for rats of the age and strain employed. Further investigations during weeks 4 and 8 revealed no changes which were considered to be related to treatment. At the haematological investigations carried out during week 12, the thrombotest times recorded for some treated male rats were above the normally accepted upper limit (30 seconds). No abnormal values were recorded among the male rats from the control group, and among the treated males the numbers above 30 seconds were as follows: 7 out of 10 receiving 2 ppm, 5 out of 9 receiving 10 ppm, 2 out of 10 receiving 50 ppm and 6 out of 10 receiving 250 ppm. Thrombotest times recorded for all female rats were well within our accepted normal limits, and no intergroup differences were detected. The other haematological parameters investigated revealed no indication of any reaction to treatment. During week 13, further blood clotting tests were carried out on all male rats. The thrombotest times were repeated, along with activated partial thromboplastin time and prothrombin time. These investigations revealed only 3 abnormally long thrombotest times, in one rat receiving 2 ppm and in 2 rats receiving 250 ppm. However, statistical analysis revealed significantly prolonged thrombotest times in the high dietary level group. Although there was no statistically significant increase in either of the other clotting tests for rats from this group, the group mean activated partial thromboplastin time was higher than the control value. However, these increases in clotting times in the high dietary level group were mainly due to the results recorded for a single animal (Rat No. 50), and it was concluded that the apparent changes in blood clotting times were not associated with treatment with bendiocarb.
4.5.2	Clinical chemistry	Blood chemistry investigations carried out during week 12 of the study revealed no intergroup differences which were considered to be indicative of a reaction to treatment. Minor intergroup differences did attain a level of statistical significance, but none was very large or dosage-related in degree.

		Estimations of cholinesterase activity in whole blood were carried out during weeks 4, 9 and 13. These investigations revealed statistically significantly lower levels of cholinesterase activity at weeks 4 , 9 and 13 (-22 to -60 % compared to control) in rats receiving 250 ppm. At week 13, marginal reduction of cholinesterase activity in rats receiving 50 ppm (-25 and –15% in males and females respectively).	
4.5.3	Urinalysis	Urinalysis performed during weeks 4, 8 and 12 revealed no changes in urine quantity or composition which were considered to be associated with the administration of bendiocarb. The statistically significant decrease in specific gravity of urine recorded for all groups of treated male rats at weeks 4 and 8, and at week 4 for female rats receiving 250 ppm, was not considered large enough to be of any biological significance, nor was it associated with any other change in urine volume or composition.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	Organ weight analysis performed on rats killed at the terminal sacrifice revealed no indication of any reaction to treatment. Minor intergroup differences which attained a level of statistical significance were not considered large enough to be of any biological significance.	
4.6.2	Gross and histopathology	Post mortem examination of rats killed after 13 weeks of treatment revealed no evidence of reaction to treatment. None of the histopathological lesions seen in the tissues examined was considered to be related to treatment with bendiocarb over a period of 13 weeks.	
4.7	**Other**		
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Bendiocarb (technical grade) was administered to groups of Sprague-Dawley rats (10/sex) in the diet at 0, 2, 10, 50 or 250 ppm (equivalent to approximately 0, 0.13, 0.65, 3.45, or 17.3 mg kg^{-1} d^{-1}) for 90 d. Urinalysis, haematological, blood chemistry and whole blood cholinesterase activity determinations, together with ophthalmoscopy, were conducted on all animals. No differentiated measurements for plasma and erythrocyte cholinesterase activities were made. Urinalysis and haematology were performed at weeks 4, 8 and 12, blood chemistry at week 12, whole blood cholinesterase at weeks 4, 9 and 13 and ophthalmoscopy at weeks 0 and 13. At the end of the study, all surviving animals were sacrificed and a gross pathological examination performed. A full spectrum of tissue samples was preserved from each animal and a complete histopathological examination performed on all control and high dose animals. In addition a detailed macroscopic examination was carried out on any decedents and any abnormal tissues subjected to a histological examination. The doses employed in this study were specifically selected to establish a no-effect level for inhibition of whole blood cholinesterase activity.	

5.2	**Results and discussion**	There were no treatment-related deaths or clinical signs of toxicity. A single, 10 ppm-treated female was killed on humane grounds following an accident unrelated to bendiocarb exposure. There was a statistically significant decrease in whole blood cholinesterase activity measured at week 13 at 50 ppm (mean reduction of approximately 20 %) and at weeks 4, 9 and 13 at 250 ppm (24, 53 and 38% mean reductions respectively). However no overt clinical signs of cholinesterase inhibition were seen. No other treatment-related clinical chemistry changes were noted at any dose level. Additionally, no treatment-related haematological, ophthalmological, urinalysis or histopathological findings were observed. In summary, no treatment-related effects were seen at 2 and 10 ppm (0.13 and 0.65 mg kg^{-1} d^{-1}). Up to a 20% inhibition in whole blood cholinesterase was observed at 50 ppm (3.45 mg kg^{-1} d^{-1}), and up to a 53% reduction in whole blood cholinesterase was seen at 250 ppm (17.3 mg kg^{-1} d^{-1}).	
5.3	**Conclusion**		
5.3.1	LO(A)EL	3.45 mg^{-1} kg^{-1} d^{-1}	
5.3.2	NO(A)EL	0.65 mg^{-1} kg^{-1} d^{-1}	
5.3.3	Other	-	
5.3.4	Reliability	2	
5.3.5	Deficiencies	No	

Table A6.4.1-2 Results of Whole Blood Cholinesterase Monitoring as % of control (and change compared to controls in %)

Parameter changed	Group 2 (2 ppm/ 0.13 mg/kg)			Group 3 (10 ppm/ 0.65 mg/kg)			Group 4 (50 ppm/ 3.45 mg/kg)			Group 5 (250 ppm/ 17.3 mg/kg)		
Weeks after start of treatment	4	9	13	4	9	13	4	9	13	4	9	13
Males												
<30 mins after sampling	79 (-21%)	121 (+21%)	109 (+9%)	125 (+25%)	94 (-6%)	100 (na)	105 (+5%)	92 (-8%)	75 (-25%)	78 (-22%)	55 (-45%)	58 (-42%)
24 hours after sampling	93 (-7%)	120 (+20%)	98 (-2%)	102 (+2%)	109 (+9%)	107 (+7%)	93 (-7%)	111 (+11%)	96 (-4%)	93 (-7%)	113 (+13%)	98 (-2%)
Females												
<30 mins after sampling	93 (-7%)	128 (+28%)	99 (-1%)	88 (-12%)	99 (-1%)	103 (+3%)	92 (-8%)	88 (-12%)	85 (-15%)	75 (-25%)	40 (-60%)	66 (-34%)
24 hours after sampling	81 (-19%)	87 (-13%)	89 (-11%)	96 (-4%)	96 (-4%)	94 (-6%)	97 (-3%)	99 (-1%)	92 (-8%)	87 (-13%)	88 (-12%)	96 (-4%)
Combined												
<30 mins after sampling	86 (-14%)	124.5 (+24.5%)	104 (+4%)	106.5 (+6.5%)	96.5 (-3.5%)	101.5 (+1.5%)	98.5 (-1.5%)	90 (-10%)	80 (-20%)	76.5 (-23.5%)	47.5 (-52.5%)	62 (-38%)
24 hours after sampling	87 (-13%)	103.5 (+3.5%)	93.5 (-6.5%)	99 (-1%)	102.5 (+2.5%)	100.5 (+0.5%)	95 (-5%)	105 (+5%)	94 (-6%)	90 (-10%)	100.5 (+0.5%)	97 (-3%)

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	13th September 2006
Materials and methods	As described by the applicant.
Results and discussion	As described by the applicant.
Conclusion	As described by the applicant.
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.4.2 Subchronic dermal toxicity test

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ] Scientifically unjustified [✓]**	
Limited exposure [ ]	**Other justification [..]**	
Detailed justification:	The two dermal repeat dose toxicity studies presented under Point 6.3.2 show that the effects seen in these studies are similar to the ones observed with other routes (effect on acetylcholinesterase activity). The potential dermal exposure for bendiocarb is significant but a systemic approach is possible for dermal exposure since relevant data are available on dermal absorption. Therefore, a subchronic dermal toxicity study is not considered to be required.	
Undertaking of intended data submission [ ]		

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	14th September 2006
Evaluation of applicant's justification	The data from the two repeated-dose dermal toxicity studies of bendiocarb in rats and rabbits indicate that the effects of cholinesterase inhibition are the same as those seen with other routes of exposure. The submitted studies on percutaneous absorption will enable a systemic approach for dermal exposure.
Conclusion	The UK CA considers the justification for non-submission of data acceptable.
Remarks	
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.4.3 Subchronic inhalation toxicity test

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1995b) Bendiocarb: Rat 13-Week Inhalation Toxicity Study (Snout-Only Exposure) and Range Finding Studies [redacted] Document A89120 6.4.3/01 28 February 1995 Unpublished [redacted] (2006) Regulatory Toxicology – Position Paper Benchmark Dose Analysis of Whole Blood Acetylcholinesterase Activity of the Rat 90-day Inhalation Toxicity Study of Bendiocarb [redacted] Document M-266196-01-1 6.4.3/02 06 February 2006 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	US EPA 82-4	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR21272/01/931201	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	97.6% (prior study) – 97.2% (at study termination)	
3.1.2.3	Stability	Stable	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley	
3.2.3	Source	Charles River, UK	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	6 – 7 weeks; 247 – 284 g (M), 176 – 202 g (F)	

3.2.6	Number of animals per group	10M/10F In addition, satellite groups of 10 animals/sex/dose were used to determine brain and/or whole blood acethylcholinesterase activities after 6 and 13 weeks of treatment.
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Inhalation
3.3.1	Duration of treatment	13 weeks
3.3.2	Frequency of exposure	6 hours per day, 5 days per week
3.3.3	Postexposure period	None – all surviving animals were sacrificed at the end of the 13-week exposure period.
3.3.5	**Inhalation**	
3.3.5.1	Concentrations	Nominal concentration 0, 0.2, 2.0 and 20 mg/m^3 Analytical concentration 0, 0.18, 1.97 and 19.3 mg/m^3
3.3.5.2	Particle size	Mean MMAD values were 1.3, 1.5, and 1.5 µm at 0.2, 2.0 and 20 mg/m^3 respectively. 99 – 100% of particles were < 7 µm, i.e. within the respirable range.
3.3.5.3	Type or preparation of particles	Particulate aerosol produced using a Wright dust feed mechanism
3.3.5.4	Type of exposure	Snout only
3.3.5.5	Vehicle	None – neat technical material
3.3.5.6	Concentration in vehicle	n.a.
3.3.5.7	Duration of exposure	6 hours per day, 5 days per week for 13 weeks
3.3.5.8	Controls	Air only
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes; during and after exposure
3.4.1.2	Mortality	Yes; during and after exposure
3.4.2	Body weight	Yes; weekly starting one week before exposure
3.4.3	Food consumption	Yes; weekly starting one week before exposure
3.4.4	Water consumption	Yes; daily
3.4.5	Ophthalmoscopic examination	Yes; pre-exposure and week 13
3.4.6	Haematology	Yes Number of animals: All animals Time points: during Week 13 Parameters: Packed cell volume, haemoglobin concentration, red cell count, mean corpuscular haemoglobin concentration, mean corpuscular volume, total white cell count, platelet count, differential count (N,L,E,B,M), cell morphology, thrombotest, reticulocyte count

3.4.7	Clinical chemistry	Yes Number of animals: All animals Time points: during Week 13 Parameters: Sodium, potassium, calcium, inorganic phosphorus, chloride, glucose, total cholesterol, urea nitrogen, total bilirubin, creatinine, total protein, albumin, globulin, alanine aminotransferase, aspartate, aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, creatine phosphokinase. Determination of whole blood cholinesterase activity was performed in the satellite animals in all dose groups immediately after exposures 4 and 5 during weeks 6 and 13 of the study. Specifically, samples of whole-blood were removed from each satellite rat, and placed in heparinised tubes, mixed briefly and chilled in ice water prior to analysis to minimise reversibility of any acetyl cholinesterase activity. Samples were then analysed using the method of Ellman, G.L. *et al* (1961) and expressed as µmol/ml/minute and percentage of the control activity. Brain acetylcholinesterase activity: at necropsy, the brain of each satellite rat was weighed and immediately frozen prior to storage in a deep freeze at -20°C. Immediately prior to analysis of brain acetylcholinesterase activity by the Ellman method, batches of up to 10 samples were thawed from being deep frozen to 1 – 4°C, and then homogenised in order to minimise reversal of any inhibition that may have occurred during the time between removal and analysis.
3.4.8	Urinalysis	No
3.5	**Sacrifice and pathology**	
3.5.1	Organ weights	Yes Organs: liver, kidneys, testes, epididymides, lungs, brain
3.5.2	Gross and histopathology	Yes High dose group and controls: Organs: adrenals, alimentary tract, duodenum, jejenum, ileum, caecum, colon, rectum, brain, spinal cord, pituitary, thyroid, parathyroid, thymus, oesophagus, salivary glands, sciatic nerve, seminal vesicle, skeletal muscle, stomach, ovaries, nasal passage, pancreas, spleen, sternum, testes, heart, larynx, trachea, aeorta, uterus, vagina, female mammary gland, prostate, pharynx, urinary bladder, lymph nodes, skin, eyes, femur, tongue. All groups Organs: liver, kidneys, lungs, Gross abnormalities
3.5.3	Other examinations	
3.5.4	Statistics	Fisher's Exact Test, Bartlett's Test, Kruskal-Wallis analysis, Students' 't' test, Williams' Test
3.6	**Further remarks**	-

		4. RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	There were no treatment-related clinical signs
4.1.2	Mortality	Two satellite rats died (one from the low dose and one from the mid dose) as a result of tube restraint on Day 1 of exposure. These animals were replaced by two reserve animals of a similar weight. The loss of a single day exposure for these two animals was not considered to compromise their inclusion as satellite rats for this study as the first acetylcholinesterase determination was scheduled for Week 6.
4.2	**Body weight gain**	Bodyweight gain was unaffected.
4.3	**Food consumption and compound intake**	Food consumption was unaffected and there was no visual effect on water consumption
4.4	**Ophthalmoscopic examination**	There were no ophthalmic changes following 13 weeks of exposure.
4.5	**Blood analysis**	
4.5.1	Haematology	There were no treatment-related effects outside of the concurrent control range.
4.5.2	Clinical chemistry	Whole-blood acetylcholinesterase activity, measured immediately after exposure during Weeks 6 and 13, for both sexes of Groups 3 (2.0 mg/m^3) and 4 (20 mg/m^3) was lower than control. At 2.0 mg/m^3, whole-blood activity was inhibited by 24% and 20% in males and by 20% and 7% in females compared to controls at week 6 and 13 respectively. Corresponding inhibition values at 20 mg/m^3 were 65% and 64% in males, and 51% and 44% in females. There were no other treatment related effects outside the concurrent control range.
4.5.3	Urinalysis	n.a.
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	There were no differences in organ weights of main study rats or brain weights of satellite rats.
4.6.2	Gross and histopathology	There were no treatment-related macroscopic abnormalities. A treatment-related effect was observed on the incidence of aggregations of alveolar macrophages in the lungs of High dose males. There were considered to be no treatment-related microscopic changes in Low and Intermediate dose males and all treated female groups.
4.7	**Other**	Brain acetylcholinesterase activity, measured at necropsy during Week 13, for both sexes of Group 4 (20 mg/m^3) was also lower than control (-26 and -22% in males and females respectively). At 2.0 mg/m^3 no effect was observed (-6 and -3% compared to control in males and females, respectively).

		5. APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Groups of 10 Sprague-Dawley rats of both sexes, were exposed snout-only for 6 hours a day to a particulate aerosol concentration of 0, 0.18, 1.97 or 19.3 mg m^{-3} of bendiocarb (97.2 – 97.6% purity). Exposure was for 5 days per week, for 13 weeks in total. The target exposure concentrations for the study were 0, 0.2, 2.0 or 20 mg m^{-3}. The mean MMAD values for the low, medium and high dose groups were 1.3, 1.5, and 1.5µm respectively, with 99 – 100% of particles less than 7 µm, and therefore respirable. Total chamber airflow was 29 litres/minute and the concentration of bendiocarb present in the exposure chamber was determined on at least 3 occasions during each exposure. Additional "satellite" groups of 10 rats/sex/dose were similarly treated using the same 4 exposure concentrations and these animals were used for whole-blood and/or brain acetylcholinesterase determinations at 6 and 13 weeks of treatment. All animals were observed for mortality, clinical signs of toxicity and water intake. Food consumption and body weights were also recorded. In week 13, blood samples were taken from all the study rats and parameters for clinical biochemistry and haematology investigated. Urinalysis was also performed at week 13. The eyes of all the rats were examined using an ophthalmoscope during the pre-exposure period and all surviving rats from the control, and high dose groups also underwent a further ophthalmic examination during week 13. At the final sacrifice, the macroscopic appearance of all tissues was noted in all the animals and measurement of organ weights was carried out for the brain, liver, lungs, kidneys, testes and epididymides. Histopathology of all tissues from the control and high dose animals was carried out. For the low and intermediate dose animals, organ weight determination and histopathology were only carried out on the lungs, liver and kidneys. Determination of whole blood cholinesterase activity was performed in the satellite animals in all dose groups immediately after exposures 4 and 5 during weeks 6 and 13 of the study. Specifically, samples of whole-blood were removed from each satellite rat, and placed in heparinised tubes, mixed briefly and chilled in ice water prior to analysis to minimise reversibility of any acetyl cholinesterase activity. Samples were then analysed using the method of Ellman, G.L *et al* (1961) and expressed as µmol/ml/minute and percentage of the control activity. At necropsy, the brain of each satellite rat was weighed and immediately frozen prior to storage in a deep freeze at –20°C. Immediately prior to analysis of brain acetylcholinesterase activity by the Ellman method, batches of up to 10 samples were thawed from being deep frozen to 1 – 4°C, and then homogenised in order to minimise reversal of any inhibition that may have occurred during the time between removal and analysis.
5.2	**Results and discussion**	There were no treatment-related clinical signs. Bodyweight gain and food consumption were unaffected and there was no visual effect on water consumption. There were no ophthalmic changes following 13 weeks of exposure. Apart from acetycholinesterase activity (see below), haematology and clinical chemistry did not reveal any treatment related effect.

	Minor differences in reticulocyte counts in Group 4 (20 mg/m^3) females were considered to be incidental because values were within the historical control range. Differences in albumin, urea nitrogen, creatinine, glutamic-oxalacetic transaminase and phosphorus levels during Week 13 of exposure were also considered to be incidental because their incidence was not dose related, within the historical control range and no similar findings occurred in males. At the lowest exposure level of 0.2 mg m^{-3}, whole blood aceylcholinesterase activity was marginally but not adversely reduced in males (-10%) at week 6 and was not affected in females at week 6 and in both sexes at week 13. No reduction in brain acetylcholinesterase activity was measured at this exposure concentration. At an exposure concentration of 2 mg m^{-3}, whole blood acetylcholinesterase activity was not adversely affected at the end of the study (-20 and -7% in males and females respectively at week 13). At week 6, the reduction was 24 and 20% compared to control values in males and females respectively. At this same exposure concentration, brain acetylcholinesterase activity was only marginally reduced by 6% in males and 3% in females by week 13. This was not considered to represent an adverse effect. In the high dose group (20 mg m^{-3}, 0.02 mg/l), whole blood acetylcholinesterase activity was reduced by 65 and 51% in males and females respectively at week 6 compared with control values, and by 64 and 44% respectively at week 13. At this dose level of 20 mg m^{-3}, brain cholinesterase activity was reduced by 26 and 22% in males and females respectively at week 13. There were no treatment-related differences in organ weights or any macroscopic pathology, seen in any study animal. In the majority of high dose males (8/10) and a few mid dose males (3/10), histopathology showed minimal aggregations of alveolar macrophages located either in the subpleura or more generally throughout the lung parenchyma. These lung lesions were statistically significant for the high dose males and were considered to be related to the inhalation of bendiocarb at 20 mg m^{-3}. All other histopathological findings were considered to be incidental and of no toxicological significance or within the normal range for rats of this strain and age. There were considered to be no treatment-related microscopic changes in low and intermediate dose males and all treated female groups. There were no treatment-related effects at 0.2 mg/m^3. Snout only inhalation exposure of rats to 20 mg/m^3 bendiocarb over 13 weeks reduced whole-blood and brain acetylcholinesterase activity and induced aggregations of alveolar macrophages in the subpleura and lung parenchyma.	

		At 2 mg/m³, the only effect was a slight inhibition of whole blood acetylcholinesterase activity at week 6 which, in the absence of any relevant effect on brain acetylcholinesterase activity is considered to reflect exposure rather than to be an adverse effect. The no effect level was 0.2 mg/m³, however, since the effect on whole blood cholinesterase activity observed at 2 mg/m³ was borderline in terms of toxicological significance (closed to the threshold value of 20% inhibition), and because of the dose spacing in the study (10-fold factor between doses), the real NOAEL was probably closer to 2 mg/m³ than to 0.2 mg/m³. Therefore, the benchmark dosing approach was used in order to define more precisely the NOAEL (Document M-266196-01-1). This approach was used for results of whole blood acetylcholinesterase activity for both sexes and for the 2 time-points (week 6 and 13) separately and gave a Bench Mark Dose (BMD) ranging from 1.4 to 2.8 mg/m³ depending on the sex or time-point considered. However, it is usual to consider the lower confidence limit of the BMD which was 0.9 to 1.5 mg/m³. As a conservative approach, the worst case was taken into account and therefore, 0.9 mg/m³ was considered to be the NOAEL in this study.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	2 mg/m³	X
5.3.2	NO(A)EL	0.9 mg/m³	X
5.3.3	Other	-	
5.3.4	Reliability	1	
5.3.5	Deficiencies	No	

Table A6.4.3-1 Results of Whole Blood and Brain Cholinesterase Monitoring as % of control (and change compared to controls in %)

Parameter changed	Low dose (0.2 mg/m³)		Medium dose (2.0 mg/m³)		High dose (20 mg/m³)	
Weeks after start of treatment	6	13	6	13	6	13
Males						
Whole blood	90 (-10%)	101 (+1%)	76 (-24%)	80 (-20%)	35 (-65%)	36 (-64%)
Brain	-	100 (na)	-	94 (-6%)	-	74 (-26%)*
Females						
Whole blood	99 (-1%)	108 (+8%)	80 (-20%)	93 (-7%)	49 (-51%)	56 (-44%)
Brain	-	102 (+2%)	-	97 (-3%)	-	78* (-22%)

* Toxicologically significant

Table A6.4.3-2 Results of Repeated Dose Toxicity Study – Histopathology

Parameter	Control		Low dose (0.2 mg/m³)		Medium dose (2.0 mg/m³)		High dose (20 mg/m³)	
Sex	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
Number of animals examined	10	10	10	10	10	10	10	10
Subpleural aggregations of alveolar macrophages	0	2	0	0	3	0	6 **	3
Aggregations of alveolar macrophages	0	0	1	0	0	1	4 *	1

* $p < 0.05$ with Fisher's Exact Test
** $p < 0.01$ with Fisher's Exact Test

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	14th September 2006
Materials and methods	As described by the applicant
Results and discussion	As described by the applicant
Conclusion	5.3.1. Based on inhibitions of ≥20% in brain cholinesterase activity, the LO(A)EC is 20 mg/m³ 5.3.2. Based on inhibitions of ≥20% in brain cholinesterase activity, the NO(A)EC is 2.0 mg/m³ The UK CA has added an asterisk to those values in Table A6.4.3-1 that it considers to be toxicologically important.
Reliability	1
Acceptability	Acceptable
Remarks	Based on inhibitions of ≥20% in brain cholinesterase activity, the UK CA considers values of 20 mg/m³ for the LO(A)EC and 2.0 mg/m³ for the NO(A)EC to be appropriate.
	COMMENTS FROM …
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

6.5 Chronic toxicity

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1980) NC 6897 Toxicity Study in Beagle Dogs. Final Report: Dietary Intake for 104 Weeks. (Test Compound Technical NC 6897 CR 4799/3) [redacted] Document A90975 6.5/01 April 1980 Unpublished [redacted] (1981) NC 6897 Toxicity Study in Beagle Dogs (Addendum to Final Report containing Retabulated Data) [redacted] Document A90978 6.5/02 January 1981 Unpublished [redacted] (1979a) Determination of Bendiocarb (NC 6897) Dietary Concentrations in a Two Year Feeding Study with Dogs [redacted] Document A90976 6.5/03 November 1979 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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, but the study was conducted in line with good scientific practice	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement.	
2.3	**Deviations**	n.a.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Bendiocarb	
3.1.1	Lot/Batch number	CR 4799/3	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	98.1 – 99%	
3.1.2.3	Stability	Stable	
3.2	**Test Animals**		

3.2.1	Species	Dog
3.2.2	Strain	Beagle
3.2.3	Source	J Stocks, Kirkcaldy, Scotland
3.2.4	Sex	Male/female
3.2.5	Age/weight at study initiation	20 – 24 weeks (1 female 39 weeks) 5.7 – 10.3 kg
3.2.6	Number of animals per group	8M/8F
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	104 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None – all surviving animals sacrificed at the end of 104 weeks dietary intake
3.3.4	**Oral**	
3.3.4.1	Type	In food
3.3.4.2	Concentration	0, 20, 100, 500 ppm in diet
3.3.4.3	Vehicle	Dry powdered diet
3.3.4.4	Concentration in vehicle	0, 20, 100, 500 ppm in diet
3.3.4.5	Total volume applied	400g fresh diet daily
3.3.4.6	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes; daily
3.4.1.2	Mortality	Yes; daily
3.4.2	Body weight	Yes; pre-exposure and then weekly
3.4.3	Food consumption	Yes; daily
3.4.4	Water consumption	Yes; 5 days/weekly
3.4.5	Ophthalmoscopic examination	Yes; pre-exposure and weeks 14, 25, 52, 65, 79, 90, 96 and 103
3.4.6	Haematology	Yes All animals Time points: Weeks 0, 14, 25, 51, 79 and 103 of dietary intake Parameters: erythrocyte sediment rate (ESR), packed cell volume, haemoglobin, red cell count, reticulocyte count, MCHC, MCV, total white cell count, platelet count, thrombotest.

3.4.7	Clinical chemistry	Yes All animals Time points: Weeks 0, 14, 25, 51, 79 and 103 of dietary intake Parameters: plasma urea, plasma glucose, total serum protein, , SGPT, serum alkaline phosphatase, calcium, sodium, potassium, serum cholesterol, serum bilirubin	
3.4.8	Urinalysis	Yes All animals Time points: Weeks 0, 14, 25, 51, 79 and 103 of dietary intake Parameters: volume, pH, specific gravity, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen, haemoglobin, epithelial cells, polymorphonuclear leucocytes, mononuclear leucocytes, erythrocytes, organisms, casts, abnormal constituents	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes At interim sacrifice (52 weeks): 3M/3F from each group At terminal sacrifice (104 weeks): All surviving animals Organs: adrenals, brain, kidneys, liver, pituitary, prostate/uterus, spleen, gonads, thymus, thyroids, heart, lungs, pancreas.	
3.5.2	Gross and histopathology	Yes Dogs dying during the study, those at interim sacrifice and all surviving animals Organs: adrenals, brain, kidneys, liver, pituitary, prostate/uterus, spleen, gonads, thymus, thyroids, heart, lungs, pancreas, aorta, bone marrow, colon, duodenum, eye, gall bladder, ileum, jejunum, lymph nodes, mammary gland, oesophagus, salivary gland, sciatic nerve, seminal vesicle, skeletal muscle, skin, spinal cord, stomach, tongue, trachea, urinary bladder.	
3.5.3	Other examinations	Cholinesterase determination: whole blood – during weeks 7,14, 25, 40, 43, 51, 79 and 103 brain – in weeks 52 and 104 kills	
3.5.4	Statistics	Kruskal Wallis, Bartlett's test, variance analysis and Student's 't' test, Williams' test	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	No treatment-related clinical signs of toxicity were noted.	
4.1.2	Mortality	Two deaths occurred during the study, one in the control and one in the high dose groups, although neither was considered to be treatment-related.	
4.2	**Body weight gain**	There was no adverse effect on bodyweight	
4.3	**Food consumption and compound intake**	The pre-dose trend for lower food consumption by animals from the treatment groups continued throughout the dosing period. No statistically significant intergroup differences were demonstrated and it is considered that food consumption was unaffected by treatment.	