U-9 and U-11 in male rats, accounting for 9.0-18.1% and 1.0-9.9% of the dose, respectively, and U-11 and U-14 in female rats, accounting for 4.7-19.1% and 0.4-5.5% of the dose, respectively. U-9, U-11 and U-14 were sulphate conjugates of U-10b, CGA 294851 and CGA 294850, respectively. No unidentified metabolite exceeded 4.4% of the administered dose.

Unchanged fenoxycarb was present at very low levels, accounting for <0.1% of the dose.

Faecal metabolites (see Table A6_2-5): The major faecal metabolite identified was F-8, accounting for approximately 24% of the dose at the low dose level and approximately 42% at the high dose level. Unchanged fenoxycarb was present at low levels in faeces, accounting for up to 4.6% of the dose. No marked sex difference was observed in the faecal metabolite profiles.

Based on the structures identified, the metabolism of fenoxycarb involves hydroxylation at the para position of the (A)-phenyl ring to form CGA 294850 followed by stepwise oxidations of the ethyl ester terminal carbon to an alcohol (CGA 294851) and then an acid (F-8, U-10b).

A second major pathway involves phase II conjugation with sulphate to form aryl-O-sulphate conjugates. Minor pathways involve N-dealkylation at the carbamate moiety to give an acid (CGA 294848) and conjugation of the primary alcohol in CGA 294851 to form an alkyl-O-sulphate conjugate (F-9, U-13). A minor pathway observed only in faeces involved cleavage of the diphenylether moiety to form metabolite F-4.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The metabolic fate of fenoxycarb was investigated in rats dosed with [^{14}C]-fenoxycarb. The absorption, excretion and tissue distribution of fenoxycarb in rats administered a single intravenous dose of 1 mg/kg bw (group A), a single oral dose of 1 mg/kg bw (group B), 14 consecutive oral doses of non-radiolabelled fenoxycarb followed by a single oral dose of 1 mg/kg bodyweight (group C), or a single oral dose of 300 mg/kg bodyweight (groups P-H and D) was investigated in a previous study [redacted] (1993), samples from which were used during this study (see Table A6_2-2). In [redacted] (1993), at the low dose level of 1 mg/kg, approximately 75% of the administered dose was excreted in faeces and a further 20% was excreted in urine. At the high dose level of 300 mg/kg, approximately 58% of the administered dose was excreted in faeces and 36% was excreted in urine. The current study was concerned with the identification of individual metabolites of fenoxycarb and the determination of the metabolic pathway for fenoxycarb in the rat.

The pooled urine samples were profiled directly by HPLC.

The faeces samples had previously been homogenised in water. The pooled faeces homogenates were centrifuged and the aqueous supernatant reserved. For each sample, the faeces residue was sequentially extracted with methanol, and the methanol extracts separated by centrifugation. Aliquots of the combined aqueous and methanol extracts were concentrated and filtered prior to profiling by HPLC. The remaining faeces residue was extracted similarly with aqueous 5% sodium hydroxide. For groups A, B and C, the combined aqueous sodium hydroxide extracts were neutralised and aliquots

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concentrated and filtered prior to profiling by HPLC. For the group D male combined sodium hydroxide extract, the sample was concentrated to near dryness and reconstituted in methanol for analysis by HPLC. For the group D female combined sodium hydroxide extract, the sample was brought to dryness and reconstituted in methanol/water (20:80) for HPLC analysis. The post-extraction solids were analysed by sample oxidation.

To confirm the presence of aryl-O-sulphate conjugated metabolites, isolated conjugated metabolites and composite urine samples were treated with aryl sulphatase in Tris-HCl buffer, pH 7.5 at 37°C for 24-48 hours. Following enzymatic hydrolysis, samples were centrifuged and the supernatants profiled by HPLC.

Urinary and faecal metabolites were isolated by partitioning and appropriate chromatographic techniques including HPLC, and identified by NMR, mass spectrometry, TLC and HPLC techniques and by co-chromatography with authentic reference standards. Radioactivity in all samples was measured by liquid scintillation counting.

5.2 Results and discussion

Fenoxycarb was extensively metabolised in the rat following administration of single oral or intravenous doses or multiple oral doses at the low dose level of 1 mg/kg, or following a single oral dose at the high dose level of 300 mg/kg.

Little or no unchanged fenoxycarb was found in urine or faeces. The major metabolite identified in faeces was F-8 (U-10b), accounting for approximately 24% of the dose at the low dose level and approximately 42% at the high dose level. The major metabolites identified in urine were U-9 and U-11 in male rats and U-11 and U-14 in female rats.

The metabolism of fenoxycarb in the rat proceeds by hydroxylation of the (A)-phenyl ring to form CGA 294850, followed by stepwise oxidations and conjugation with sulphate. Minor pathways include N-dealkylation at the carbamate moiety to give an acid (CGA 294848) and alkyl oxidation to form CGA 294851 followed by conjugation with sulphate.

A summary of all excreted metabolites is given in Table A6_2-6. A proposed metabolic pathway based on the present study is depicted in Figure A6_2-1.

5.3 Conclusion

5.3.1 Reliability 1

5.3.2 Deficiencies None

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	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/07/26
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

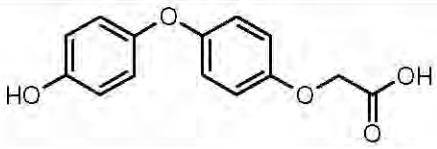
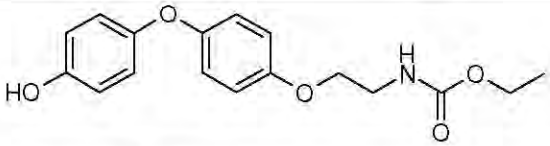
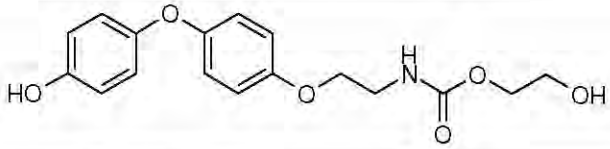
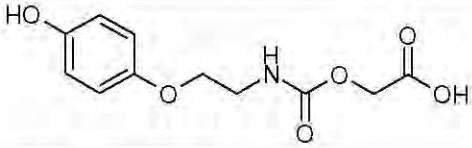
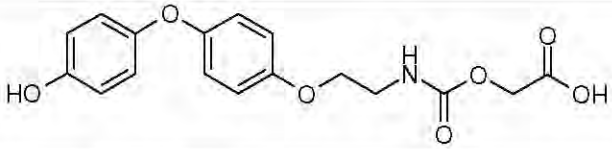
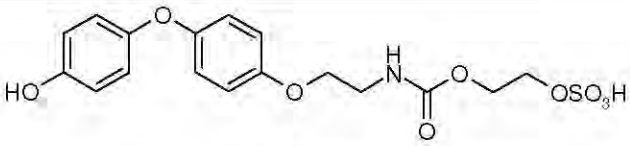
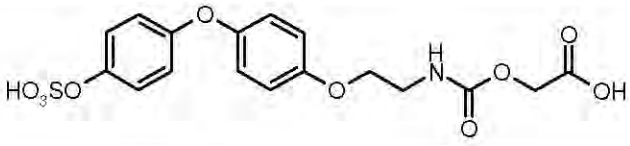
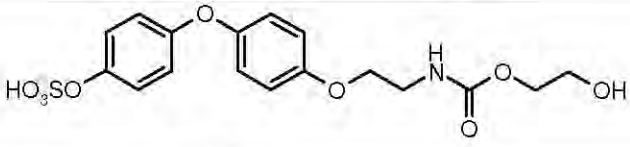
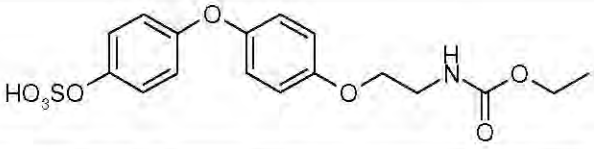
Table A6_2-1 Toxicokinetic studies in the rat - experimental scheme

Group	Number and sex	Route and dose level of [^{14}C]-fenoxycarb	Sample collection times
P-H	2♂, 2♀	Single oral dose at high dose level of 300 mg/kg	Urine and faeces: 0-12 and 12-24 hours and then daily up to 7 days. Expired air: 0-12 and 12-24 hours and then daily up to 7 days.
A	5♂, 5♀	Single intravenous dose at low dose level of 1.0 mg/kg	Urine and faeces: 0-6, 6-12 and 12-24 hours and then daily up to 7 days. Tissues: Collected 7 days after dosing.
B	5♂, 5♀	Single oral dose at low dose level of 1.0 mg/kg	
C	5♂, 5♀	14 daily non-radiolabelled oral doses followed by a single radiolabelled oral dose at low dose level of 1.0 mg/kg	
D	5♂, 5♀	Single oral dose at high dose level of 300 mg/kg	
E	1♂, 1♀	Control single intravenous dose (for low dose level)	Urine, faeces, blood and tissues collected at selected time intervals.
F	1♂, 1♀	Control single oral dose (for low dose level)	
G	1♂, 1♀	Control 15 consecutive daily oral doses (for low dose level)	
H	1♂, 1♀	Control single oral dose (for high dose level)	

Table A6_2-2 Representative samples of urine and faeces extracts taken from [redacted],*(1993)* that were used for metabolite identification and quantification

Sample	Dose (Group)	Sex	Total radioactivity present (% of dose)
Urine (0-48 h pool)	Single oral dose of 300 mg/kg (Group P-H)	Male Female	36.9 37.5
Urine (0-48 h pool)	Single intravenous dose of 1 mg/kg (Group A)	Male Female	19.6 22.2
Urine (0-48 h pool)	Single oral dose of 1 mg/kg (Group B)	Male Female	15.5 15.5
Urine (0-48 h pool)	14 daily oral non-radiolabelled doses followed by a single oral dose of 1 mg/kg (Group C)	Male Female	20.1 21.4
Urine (0-48 h pool)	Single oral dose of 300 mg/kg (Group D)	Male Female	33.6 32.5
Faeces (0-72 h pool)	Single oral dose of 300 mg/kg (Group P-H)	Male Female	54.35 57.07
Faeces (0-72 h pool)	Single intravenous dose of 1 mg/kg (Group A)	Male Female	69.08 66.67
Faeces (0-72 h pool)	Single oral dose of 1 mg/kg (Group B)	Male Female	72.80 77.18
Faeces (0-72 h pool)	14 daily oral non-radiolabelled doses followed by a single oral dose of 1 mg/kg (Group C)	Male Female	80.42 79.84
Faeces (0-72 h pool)	Single oral dose of 300 mg/kg (Group D)	Male Female	58.53 54.39

Table A6_2-3 Identity of Fenoxycarb metabolites that were isolated and characterised

Metabolite*	Structure
CGA 294848 (F-6, U-8)	
CGA 294850 (F-15, U-17)	
CGA 294851 (F-12, U-15)	
F-4	
F-8, U-10b	
F-9, U-13	
U-9	
U-11	
U-14	

* In the nomenclature used above, 'F' pre-fixes a faecal metabolite, and 'U' pre-fixes a urinary metabolite. Under this system, therefore, the same metabolite may have two labels.

Table A6_2-4 Relative proportions of metabolites in urine following dosing with [^{14}C]-fenoxycarb
(values are expressed as percentages of dose)

Metabolite Fraction		Group P-H (preliminary oral high dose)		Group A (i.v. low dose)		Group B (oral low dose)		Group C (oral low dose, preconditioned)		Group D (oral high dose)	
		male	female	male	female	male	female	male	female	male	female
Dose (mg/kg)		**281**	**280**	**0.93**	**0.94**	**1.00**	**1.00**	**0.90**	**0.92**	**289**	**292**
U-8	CGA 294848	0.8	1.8	0.8	1.9	0.8	0.9	0.8	1.2	0.7	1.9
U-9 [a]		15.3	2.8	9.0	2.3	9.1	1.8	12.2	2.7	18.1	2.4
U-10b		0.7	1.1	0.2	0.3	0.2	0.3	0.1	0.4	0.7	0.3
U-11 [b]		9.9	19.1	2.6	8.7	1.0	4.7	1.1	6.4	6.5	17.2
U-13 [c]		0.2	0.8	<0.1	1.7	0.1	0.7	0.1	1.1	0.1	1.2
U-14 [d]		0.6	5.5	0.3	0.9	0.1	0.4	0.1	0.6	0.4	3.8
U-15	CGA 294851	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	0.1
U-17	CGA 294850	0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.3	<0.1	0.4
U-18	fenoxycarb	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
% of dose identified		27.6	31.3	12.9	16.0	11.3	9.0	14.4	12.8	26.5	27.3
% of urine identified		73.6	80.7	61.4	64.8	69.3	54.5	68.6	56.4	73.6	76.0

[a] U-9 is the aryl-O-sulphate conjugate of U-10b
[b] U-11 is the aryl-O-sulphate conjugate of U-15 (CGA 294851)
[c] U-13 is the alkyl-O-sulphate conjugate of U-15 (CGA 294851)
[d] U-14 is the aryl-O-sulphate conjugate of U-17 (CGA 294850)

Table A6_2-5 Relative proportions of metabolites in faeces following dosing with [^{14}C]-fenoxycarb
(values are expressed as percentages of dose)

Metabolite Fraction		Group P-H (preliminary oral high dose)		Group A (i.v. low dose)		Group B (oral low dose)		Group C (oral low dose, preconditioned)		Group D (oral high dose)	
		male	female	male	female	male	female	male	female	male	female
Dose (mg/kg)		**281**	**280**	**0.93**	**0.94**	**1.00**	**1.00**	**0.90**	**0.92**	**289**	**292**
F-4		2.0	2.7	4.1	4.5	6.2	6.2	2.2	4.3	1.0	1.9
F-6	CGA 294848	2.2	3.0	3.1	4.2	2.7	4.7	3.2	5.4	2.1	2.8
F-8		21.4	21.1	20.5	23.4	29.3	28.6	41.2	41.8	26.6	19.7
F-9 [a]		3.8	1.7	6.2	3.1	3.4	3.1	3.6	1.5	3.9	2.0
F-12	CGA 294851	7.7	5.7	15.3	9.8	7.4	5.1	9.5	5.1	9.4	6.4
F-15	CGA 294850	3.7	8.2	2.5	4.4	3.6	5.3	4.1	3.3	4.6	10.8
F-17	fenoxycarb	4.6	4.3	0.2	0.2	0.7	0.6	0.7	0.3	1.4	2.5
% of dose identified		45.5	46.7	51.9	49.6	53.3	53.6	64.5	61.7	49.0	46.1
% of faeces identified		81.5	80.7	74.1	72.3	72.6	69.0	79.7	76.7	82.2	81.7

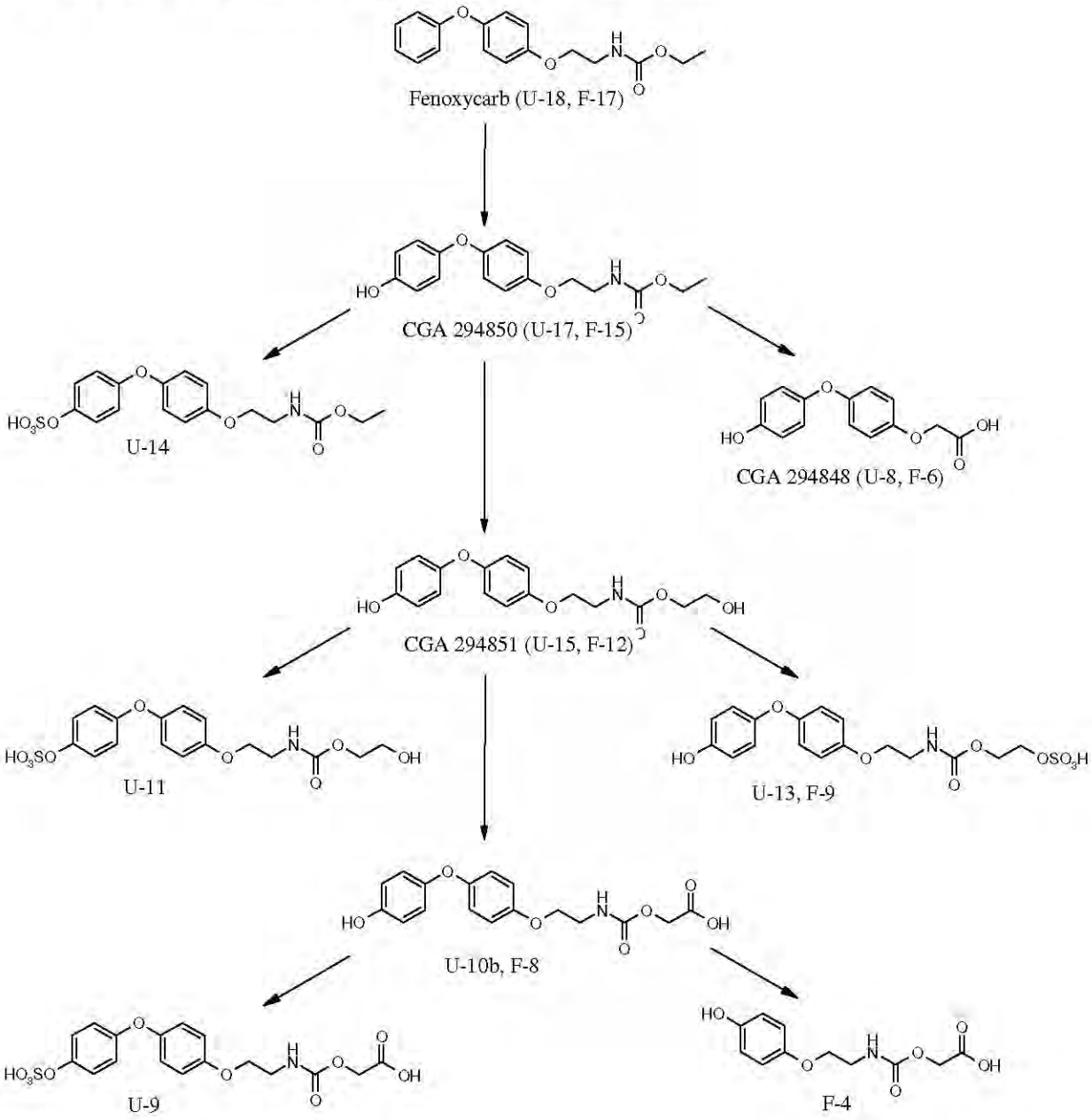
[a] F-9 is the alkyl-O-sulphate conjugate of F-12 (CGA 294851)

Table A6_2-6 Quantitative distribution of metabolites totally excreted by rats following dosing with [^{14}C]-fenoxycarb (values are expressed as percentages of dose)

	Group P-H (preliminary oral high dose)		Group A (i.v. low dose)		Group B (oral low dose)		Group C (oral low dose, preconditioned)		Group D (oral high dose)	
Metabolite Fraction	**male**	**female**	**male**	**female**	**male**	**female**	**male**	**female**	**male**	**female**
Dose (mg/kg)	**281**	**280**	**0.93**	**0.94**	**1.00**	**1.00**	**0.90**	**0.92**	**289**	**292**
fenoxycarb	4.7	4.4	0.4	0.3	0.8	0.7	0.8	0.4	1.5	2.6
F-4	2.0	2.7	4.1	4.5	6.2	6.2	2.2	4.3	1.0	1.9
CGA 294848	3.0	4.8	3.9	6.1	3.5	5.6	4.0	6.6	2.8	4.7
U-10b, F-8 (free)	22.1	22.2	20.7	23.7	29.5	28.9	41.3	42.2	27.3	20.0
U-9 (conjugated)a	15.3	2.8	9.0	2.3	9.1	1.8	12.2	2.7	18.1	2.4
CGA 294851 (free)	7.8	5.8	15.4	9.9	7.5	5.2	9.6	5.2	9.5	6.5
U-11 (conjugated)b	9.9	19.1	2.6	8.7	1.0	4.7	1.1	6.4	6.5	17.2
U-13,F-9 (conjugated)c	4.0	2.5	6.3	4.8	3.5	3.8	3.7	2.6	4.0	3.2
CGA 294850 (free)	3.8	8.4	2.6	4.6	3.7	5.5	4.2	3.6	4.7	11.2
U-14 (conjugated)d	0.6	5.5	0.3	0.9	0.1	0.4	0.1	0.6	0.4	3.8
Total identified	73.1	78.0	64.8	65.6	64.6	62.6	78.9	74.5	75.5	73.4
Non-identified	14.2	13.1	15.3	18.8	15.5	20.8	14.8	20.5	15.7	13.1
Total analysed	87.3	91.1	80.1	84.4	80.1	83.4	93.7	95.0	91.2	86.5
Non-extractable	2.8	2.5	4.6	5.5	9.0	9.4	6.2	7.4	4.9	3.6
Not analysed	2.3	2.0	2.3	4.4	1.4	1.5	1.4	2.4	1.1	2.0
Losses/gains	1.2	1.0	4.0	1.0	0.8	0.1	0.6	1.7	1.6	0.2
Totally excreted	93.6	96.6	91.0	93.3	89.7	94.2	101.9	103.1	95.6	92.3

[a] U-9 is the aryl-O-sulphate conjugate of U-10b
[b] U-11 is the aryl-O-sulphate conjugate of CGA 294851
[c] U-13 (F-9) is the alkyl-O-sulphate conjugate of CGA 294851
[d] U-14 is the aryl-O-sulphate conjugate of CGA 294850

Figure A6_2-1 Proposed metabolic pathway of fenoxycarb in the rat



Section A6.3.1 Short-term repeated dose toxicity – oral

Annex Point IIA VI.6.3 6.3.1 28-day oral toxicity study in rats

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		1 REFERENCE
1.1	**Reference**	[redacted] (1986), 28-Day Cumulative Toxicity (Gavage) Study with CGA 114597 in the Rat. [redacted], Report No. 056283 / 850908, 14 August 1986 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No 96/54/EC B.7 (1996) ≅ OECD 407 (1995) The study was conducted prior to the above guidelines but has been checked for compliance to the above.
2.2	**GLP**	Yes
2.3	**Deviations**	The liver, thyroids and tissues with gross lesions only were examined histopathologically. The deviations are considered not to compromise the scientific validity of the study. This study type is not mandatory since a subchronic study is available.
		3 MATERIALS AND METHODS
3.1	**Test material**	Fenoxycarb (CGA 114597) technical
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	The stability and concentration of the preparations were analysed at the beginning of the study. The stability of fenoxycarb in the dosing preparations for at least 90 minutes was measured.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	KFM-han, SPF, Wistar
3.2.3	Sex	♂ + ♀
3.2.4	Number of animals per group	10 per sex and group
3.2.5	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	28 days
3.3.2	Frequency of exposure	Once daily

Section A6.3.1 Short-term repeated dose toxicity – oral

Annex Point IIA VI.6.3 6.3.1 28-day oral toxicity study in rats

3.3.3	Post-exposure period	–
3.3.4	**Oral**	
3.3.4.1	Type	Gavage
3.3.4.2	Concentration	0 (control), 10, 50, 200 or 1000 mg fenoxycarb/kg bw
3.3.4.3	Controls	Vehicle (4% solution of carboxymethylcellulose sodium salt)
3.4	**Examinations**	Clinical observations (including ophthalmoscopic examination), bodyweights and food consumption were measured throughout the study. At the end of the scheduled period, the animals were killed and subjected to an examination *post mortem*. Blood and urine samples were taken prior to termination for clinical pathology, selected organs were weighed and specified tissues (liver, thyroids and gross lesions) were taken for subsequent histopathology.
3.4.1	Statistics	Dunnett-Test
		4 RESULTS AND DISCUSSION
4.1	**Observations**	None of the animals died and there were no treatment-related clinical observations.
4.2	**Body weight gain**	There was no evidence of any effect of treatment on bodyweight.
4.3	**Food consumption and compound intake**	No effects
4.4	**Ophtalmoscopic examination**	There were no treatment-related ophthalmoscopic observations.
4.5	**Blood analysis**	
4.5.1	Haematology	Minor changes (compared with the control group) were seen in animals dosed with 1000 mg fenoxycarb/kg bw/day in the following haematological parameters: decreased erythrocyte count (RBC) and haemoglobin concentration (Hb) (in both sexes), haematocrit (HCT) in females only and slightly prolonged partial thromboplastin time (PT) in males only (see A6_3-1.1). These were considered to be adaptive changes and not indicative of a toxic effect.
4.5.2	Clinical chemistry	Slight increases (compared with the control group) were seen in both sexes dosed with 1000 mg fenoxycarb/kg bw day in the following blood biochemistry parameters: alkaline phosphatase activity (ALP), calcium, albumin and albumin to globulin ratio (A/G); and total protein levels (in females only, see Table A6_3-1.2). These were considered to be adaptive changes and not indicative of a toxic effect.
4.5.3	Urinalysis	There were no treatment-related effects on urinary parameters.
4.6	**Sacrifice and pathology**	There were no treatment-related macroscopic findings. There was a dose-related increase in absolute and relative liver weights in both sexes (see Table A6_3-1.2). Other minor statistically significant changes in organ weights were considered to be incidental. Treatment-related findings were detected in the liver and thyroid gland of both sexes dosed with 1000 mg fenoxycarb/kg bw/day. The liver of all animals in this dose group showed slight to moderate diffuse hypertrophy of the hepatocytes whose cytoplasm exhibited a more or less homogenous structure and slight to severe eosinophilia. In the thyroids of six of seven and five of seven investigated males and

		females, respectively, slight to moderate follicular hyperplasia was noted. It was characterised by irregularly shaped acini whose epithelia were high prismatic to elongated. In a few cases they formed small protrusions into the follicular lumen or built double-layered follicle walls. In the other dose groups no findings were noted in the liver, thyroids or any organ examined that might be related to treatment with fenoxycarb.	
4.7	**Other**	–	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of ten male and ten female KFM-han, SPF, Wistar rats were gavage dosed daily with 0 (control), 10, 50, 200 or 1000 mg fenoxycarb/kg bw in a 4% solution of carboxymethylcellulose sodium salt (CMC) for 28 consecutive days. Dosing preparations were prepared daily. The stability and concentration of the preparations were analysed at the beginning of the study. The stability of fenoxycarb in the dosing preparations for at least 90 minutes was measured. Clinical observations (including ophthalmoscopic examination), bodyweights and food consumption were measured throughout the study. At the end of the scheduled period, the animals were killed and subjected to an examination *post mortem*. Blood and urine samples were taken prior to termination for clinical pathology, selected organs were weighed and specified tissues (liver, thyroids and gross lesions) were taken for subsequent histopathology.	
5.2	**Results and discussion**	Rats tolerated the daily oral administration of fenoxycarb at dose levels up to 1000 mg/kg bw/day for four weeks without treatment-related mortality or toxic effects. Minor changes in haematology and clinical biochemistry parameters in animals at the highest dose and dose-related hepatomegaly and follicular hyperplasia of the thyroid are considered to be adaptive and not indicative of any toxic effect. Based on the results of liver weights and liver histology, the liver is considered to be a target organ.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	LOAEL = 50 mg/kg bw/day (increased relative liver weights)	X
5.3.2	NO(A)EL	NOAEL = 10 mg/kg bw/day	
5.3.3	Other	–	
5.3.4	Reliability	2	
5.3.5	Deficiencies	None	

Section A6.3.1 Short-term repeated dose toxicity – oral

Annex Point IIA VI.6.3 6.3.1 28-day oral toxicity study in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/07
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.3.1 Short-term repeated dose toxicity – oral

Annex Point IIA VI.6.3 6.3.1 28-day oral toxicity study in rats

Table A6_3-1.1: Intergroup comparison of selected haematology parameters

	Dose level of fenoxycarb (mg/kg bw/d)									
	Males					Females				
	0	10	50	200	1000	0	10	50	200	1000
RBC	9.1	8.9	9.0	9.0	8.6*	8.9	8.6	8.7	8.6	8.1*
Hb	10.0	9.7	9.8	9.9	9.6*	9.7	9.4	9.7	9.5	9.1*
HCT	0.43	0.42	0.42	0.42	0.41	0.42	0.41	0.42	0.41	0.40*
PT	12.7	12.7	12.7	13.1	13.7*	12.8	12.1*	12.3*	12.4*	11.8*

* Statistically significant difference from control group mean, p<0.05 (Dunnett-Test)

Table A6_3-1.2: Intergroup comparison of liver weights

	Dose level of fenoxycarb (mg/kg bw/d									
	Males					Females				
	0	10	50	200	1000	0	10	50	200	1000
Abs	9.59	10.83	12.10**	13.74**	17.51**	5.81	7.10**	7.15**	8.76**	11.79**
Rel	3.30	3.58	4.02**	4.51**	6.16**	3.24	3.56	3.77**	4.50**	6.42**

Abs absolute weight (g)
Rel relative to final bodyweight (%)
* Statistically significant difference from control group mean, p<0.05 (Dunnett-Test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Dunnett-Test, 2-sided)

Table A6_3-1.3: Intergroup comparison of liver weights

	Dose level of fenoxycarb (mg/kg bw/d									
	Males					Females				
	0	10	50	200	1000	0	10	50	200	1000
Abs	9.59	10.83	12.10**	13.74**	17.51**	5.81	7.10**	7.15**	8.76**	11.79**
Rel	3.30	3.58	4.02**	4.51**	6.16**	3.24	3.56	3.77**	4.50**	6.42**

Abs absolute weight (g)
Rel relative to final bodyweight (%)
* Statistically significant difference from control group mean, p<0.05 (Dunnett-Test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Dunnett-Test, 2-sided)

HEMATOLOGY SUMMARY
MALES

	RBC T/l	HB mmol/l	HCT l/l	MCV fl	MCH fmol	MCHC mmol/l	PLATELETS G/l	RETIC. 1
AFTER 28 DAYS								
GROUP 1	9.1	10.0	0.43	47.1	1.10	23.5	935	0.023
GROUP 2	8.9	9.7	0.42	47.3	1.10	23.2	968	0.023
GROUP 3	9.0	9.8	0.42	46.6	1.08	23.2	926	0.019
GROUP 4	9.0	9.9	0.42	47.1	1.10	23.3	929	0.022
GROUP 5	8.6 *	9.6 *	0.41	47.8	1.12	23.4	1070 *	0.023

DIFF. WBC COUNT (REL)

	NEN /100 WBC	WBC G/l	BAND 1	SEG. 1	EO. 1	BASO. 1	LYMPH. 1	MONO. 1
AFTER 28 DAYS								
GROUP 1	0.3	7.6	0.00	0.20	0.01	0.00	0.76	0.02
GROUP 2	0.3	8.3	0.00	0.19	0.01	0.00	0.78	0.02
GROUP 3	0.4	7.9	0.00	0.17	0.01	0.00	0.80	0.02
GROUP 4	0.2	8.1	0.00	0.14	0.01	0.00	0.82	0.02
GROUP 5	0.1	8.8	0.00	0.18	0.01	0.00	0.80	0.01

	DIFF. WBC COUNT (REL) PLAS. 1	OTHER 1	RED CELL MORPHOLOGY POLY. SCORE 0/3	MICRO. SCORE 0/3	COAGULATION PT SEC	PTT SEC
AFTER 28 DAYS						
GROUP 1	0.00	0.00	0	0	12.7	22.3
GROUP 2	0.00	0.00	0	0	12.7	21.4
GROUP 3	0.00	0.00	0	0	12.7	21.9
GROUP 4	0.00	0.00	0	0	13.1	21.3
GROUP 5	0.00	0.00	0	0	13.7 *	27.0 *

HEMATOLOGY SUMMARY
FEMALES

	RBC T/l	HB mmol/l	HCT l/l	MCV fl	MCH fmol	MCHC mmol/l	PLATELETS G/l	RETIC. 1
AFTER 28 DAYS								
GROUP 1	8.9	9.7	0.42	47.4	1.08	22.9	1010	0.020
GROUP 2	8.6	9.4	0.41	47.6	1.10	23.1	985	0.020
GROUP 3	8.7	9.7	0.42	47.9	1.11	23.1	1020	0.022
GROUP 4	8.6	9.5	0.41	47.8	1.11	23.2	1027	0.019
GROUP 5	8.1 *	9.1 *	0.40 *	49.2	1.13	22.9	1081	0.018

DIFF. WBC COUNT (REL)

	NEN /100 WBC	WBC G/l	BAND 1	SEG. 1	EO. 1	BASO. 1	LYMPH. 1	MONO. 1
AFTER 28 DAYS								
GROUP 1	0.4	5.7	0.00	0.23	0.01	0.00	0.75	0.01
GROUP 2	0.1	6.0	0.00	0.19	0.01	0.00	0.78	0.02
GROUP 3	0.1	5.9	0.00	0.17	0.01	0.00	0.81	0.01
GROUP 4	0.2	6.1	0.00	0.16	0.01	0.00	0.81	0.02
GROUP 5	0.2	6.0	0.00	0.21	0.01	0.00	0.77	0.01

	DIFF. WBC COUNT (REL) PLAS. 1	OTHER 1	RED CELL MORPHOLOGY POLY. SCORE 0/3	MICRO. SCORE 0/3	COAGULATION PT SEC	PTT SEC
AFTER 28 DAYS						
GROUP 1	0.00	0.00	0	0	12.8	20.3
GROUP 2	0.00	0.00	0	0	12.1 *	20.7
GROUP 3	0.00	0.00	0	0	12.3 *	20.5
GROUP 4	0.00	0.00	0	0	12.4 *	21.3
GROUP 5	0.00	0.00	0	0	11.8 *	22.0

CA-Figure A6.3_1.1: Summary of haematology parameters (taken from original study report)

CLINICAL BIOCHEMISTRY SUMMARY
MALES

	GLUCOSE mmol/l	UREA mmol/l	CREATININE umol/l	BILI. T. umol/l	BILI. DIR. umol/l	CHOLEST.T. mmol/l	ASAT(GOT) ukat/l	ALAT(GPT) ukat/l
AFTER 28 DAYS								
GROUP 1	5.63	6.03	39	3.0	1.0	2.03	1.39	0.83
GROUP 2	6.06	6.37	39	3.2	1.0	2.06	1.35	0.74
GROUP 3	5.87	5.84	32	2.7	1.0	1.89	1.38	0.73
GROUP 4	5.93	6.32	32	3.0	0.8	1.82	1.31	0.71 *
GROUP 5	6.22	7.26 *	32	2.6	1.0	2.03	1.30	0.77

	LDH ukat/l	ALP ukat/l	G-GT nkat/l	CALCIUM mmol/l	PHOSPHORUS mmol/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
AFTER 28 DAYS								
GROUP 1	2.53	4.07	84.81	2.55	2.22	140.8	3.95	115.4
GROUP 2	2.57	4.12	59.80	2.53	2.23	141.2	4.12	116.8
GROUP 3	2.71	4.38	70.01	2.54	2.22	141.9	4.10	116.2
GROUP 4	2.59	4.53	66.05	2.53	2.13	141.6	3.98	115.6
GROUP 5	3.00 *	6.02 *	65.75	2.62 *	2.27	142.3 *	4.09	116.1

	ALBUMIN g/l	PROTEIN T. g/l	GLOBULIN g/l	A/G RATIO
AFTER 28 DAYS				
GROUP 1	31.2	65.7	34.5	0.91
GROUP 2	31.0	65.4	34.4	0.90
GROUP 3	31.4	63.1	31.8	0.99
GROUP 4	32.0	63.1	31.0 *	1.04 *
GROUP 5	36.0 *	69.0	33.0	1.10 *

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

	GLUCOSE mmol/l	UREA mmol/l	CREATININE umol/l	BILI. T. umol/l	BILI. DIR. umol/l	CHOLEST.T. mmol/l	ASAT(GOT) ukat/l	ALAT(GPT) ukat/l
AFTER 28 DAYS								
GROUP 1	5.49	8.38	34	2.9	1.2	2.16	1.26	0.71
GROUP 2	5.45	7.89	34	3.0	1.1	2.17	1.27	0.67
GROUP 3	5.74	7.95	34	2.3	1.0	2.01	1.23	0.67
GROUP 4	5.87	7.72	33	2.5	1.2	2.01	1.22	0.68
GROUP 5	6.31 *	7.21	42	3.1	1.1	2.44	1.12 *	0.71

	LDH ukat/l	ALP ukat/l	G-GT nkat/l	CALCIUM mmol/l	PHOSPHORUS mmol/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
AFTER 28 DAYS								
GROUP 1	2.55	1.96	65.68	2.51	1.78	141.6	3.77	117.6
GROUP 2	2.47	2.24	70.68	2.50	1.78	142.5	3.96	118.0
GROUP 3	2.41	2.42	66.49	2.51	1.88	141.6	3.84	115.7
GROUP 4	2.52	2.79 *	61.35	2.53	1.92	142.7	3.76	115.4 *
GROUP 5	3.24	3.04 *	68.35	2.71 *	1.93	142.0	3.88	113.9 *

	ALBUMIN g/l	PROTEIN T. g/l	GLOBULIN g/l	A/G RATIO
AFTER 28 DAYS				
GROUP 1	33.1	70.0	37.0	0.90
GROUP 2	32.3	66.8 *	34.6	0.94
GROUP 3	33.4	67.2	33.8 *	1.00 *
GROUP 4	34.2	66.7 *	32.5 *	1.06 *
GROUP 5	40.5 *	78.3 *	37.8	1.08 *

CA-Figure A6.3_1.2: Summary of clinical biochemistry parameters (taken from original study report)

Section A6.3.2 Short-term repeated dose toxicity – dermal

Annex Point IIA VI.6.3.2 6.3.2 21-day dermal toxicity study in rats

Official use only

		1 REFERENCE
1.1	**Reference**	[redacted] (1985), Ro 13-5223/000: 21 Day Dermal Toxicity Study In The Rat. [redacted], Report No. 4552-161/157 (CGA 114597/0043), 03 July 1985 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No 92/69/EEC B.9 (1992) ≅ OECD 410 (1992) ≅ FIFRA § 82-2 The study was performed prior to the above guidelines but has been checked for compliance with the above.
2.2	**GLP**	Yes
2.3	**Deviations**	Chloride, gamma glutamyl transpeptidase and ornithine decarboxylase were not measured. Spleen, testes, adrenals and heart were not examined histopathologically unless abnormal. The deviations are considered not to compromise the scientific validity of the study.
		3 MATERIALS AND METHODS
3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	Dosing preparations were analysed for achieved concentration on days 1 and 15 of the study. Analysis of the dosing suspensions showed that the achieved concentrations were satisfactory.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Crl:CD(SD)BR
3.2.3	Sex	♂ + ♀
3.2.4	Number of animals per group	5 per sex and group
3.2.5	Control animals	Yes
3.3	**Administration/ Exposure**	Dermal
3.3.1	Duration of treatment	21 days
3.3.2	Frequency of exposure	Once daily

Section A6.3.2		Short-term repeated dose toxicity – dermal	
Annex Point IIA VI.6.3.2		6.3.2 21-day dermal toxicity study in rats	
3.3.3	Post-exposure period	No	
3.3.4	**Dermal**		
3.3.4.1	Vehicle	Corn oil	
3.3.4.2	Dose volume	4 mL/kg bw	
3.3.4.3	Dose levels	0, 20, 200, 2000 mg/kg bw/day	
3.3.4.4	Duration of exposure	6 hours	X
3.3.4.5	Controls	Vehicle	
3.4	**Examinations**	The animals were assessed daily for any signs of systemic toxicity; bodyweights and food consumption were recorded at weekly intervals throughout the study. Blood samples were collected during the final week of the study for haematological and clinical chemistry analyses.	
3.5	**Sacrifice and pathology**	At the end of the study the animals were killed and subjected to a macroscopic examination *post mortem*. Selected organs were weighed and specified tissues examined histopathologically.	
		4 RESULTS AND DISCUSSION	
4.1	**Observations**	There were no mortalities or treatment-related clinical changes. There was no evidence of skin irritation at the application site in any treated animals.	
4.2	**Body weight gain**	No effects	
4.3	**Food consumption**	No effects	
4.4	**Blood analysis**		
4.4.1	Haematology	No treatment-related effects.	
4.4.2	Clinical chemistry	No treatment-related effects.	
4.5	**Sacrifice and pathology**		
4.5.1	Organ weights	There was a slight increase in absolute and relative liver weights of about 19% in animals dosed with 2000 mg/kg bw compared with controls (see Table A6_3-2.1). There were no other treatment-related effects on organ weights.	
4.5.2	Gross and histopathology	All animals had fur loss on the abdominal skin, accompanied in some cases by sores. The severity was similar in all groups and was considered to be associated with the occlusion technique. There were occasional, non-treatment-related cases of hydronephrosis in the right kidney. Low grade hypergranulosis and acanthosis were present in the skin of vehicle control rats; there was no evidence of increased irritation associated with application of fenoxycarb in corn oil. In the livers of animals from all groups, there were minor foci of leucocyte accumulation. There was no evidence of any degenerative changes in either the liver or kidney to suggest any systemic toxicity due to fenoxycarb application.	

Section A6.3.2 Short-term repeated dose toxicity – dermal

Annex Point IIA VI.6.3.2 6.3.2 21-day dermal toxicity study in rats

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Groups of five male and five female Crl:CD(SD)BR rats received 6-hour dermal applications of 0, 20, 200 or 2000 mg/kg bw in corn oil at a dose volume of 4 mL/kg, once daily for 21 days to shaved, non-abraded areas of skin. Fresh dosing suspensions were prepared daily therefore measurement of stability was not required. Dosing preparations were analysed for achieved concentration on days 1 and 15 of the study.

The animals were assessed daily for any signs of systemic toxicity; bodyweights and food consumption were recorded at weekly intervals throughout the study. Blood samples were collected during the final week of the study for haematological and clinical chemistry analyses. At the end of the study the animals were killed and subjected to a macroscopic examination *post mortem*. Selected organs were weighed and specified tissues examined histopathologically.

5.2 Results and discussion

Dermal application of fenoxycarb at dose levels of up to 2000 mg/kg bw/day for 21 days failed to elicit any adverse skin reactions. The only change associated with treatment was a slight increase in liver weight in animals treated at 2000 mg/kg bw/day, which may have represented an adaptive response to administration of the test compound.

Therefore, despite the absence of any skin irritation and systemic toxicity at a dose level of 2000 mg/kg bw/day, the NOEL (no-effect level) was considered to be 200 mg/kg bw/day as slight liver weight increases representing an adaptive response to the test article were observed at 2000 mg/kg bw/day.

5.3 Conclusion

5.3.1	LO(A)EL	LOAEL = 2000 mg/kg bw/day (liver weight increase)	
5.3.2	NO(A)EL	NOAEL = 200 mg/kg bw/day	
5.3.3	Other	–	
5.3.4	Reliability	1	X
5.3.5	Deficiencies	No	

Section A6.3.2 Short-term repeated dose toxicity – dermal

Annex Point IIA VI.6.3.2 6.3.2 21-day dermal toxicity study in rats

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.3.2 Short-term repeated dose toxicity – dermal

Annex Point IIA VI.6.3.2 6.3.2 21-day dermal toxicity study in rats

Table A6_3-2.1: Intergroup comparison of liver weight

	Dose level of fenoxycarb (mg/kg bw/day)							
	Males				Females			
	0	20	200	2000	0	20	200	2000
Abs	9.31	8.75	9.24	11.39	6.38	6.64	6.74	7.76
Rel	2.681	2.558	2.640	3.194	2.692	2.805	2.805	3.195

Abs – absolute (g) Rel – Relative to final bodyweight (%)

Section A6.3.3 Short-term repeated dose toxicity – inhalation

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

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1987), Ro 13-5223/000: Subacute (28-Day) Repeated Dose Inhalation Toxicity Study In Rats. [redacted] Report No. RCC-085500, 21 September 1987 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Syngenta	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes 92/69/EEC B.8 (1992) ≅ OECD 412 (1981)	
2.2	**GLP**	Yes	
2.3	**Deviations**	Chamber relative humidity was measured during the 1st 2 days of exposure. However, it was found that the alcohol used as a solvent affected the sensor, producing biased readings. As a result, this measurement was discontinued. At the end of the study, blood samples for haematology and clinical biochemistry examinations were made on top dose animals only. It is not stated in the report whether the lungs were perfused with fixative prior to sectioning. Airflow rate through the inhalation equipment given as 1.25 L/min /animal.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification		
3.1.2.1	Purity	[redacted]	
3.1.2.2	Stability	Not reported	X
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar, KFM-Han., outbred, SPF	
3.2.3	Sex	♂ + ♀	
3.2.4	Number of animals per group	5 per sex per group	
3.2.5	Control animals	Yes	
3.3	**Administration/ Exposure**	Inhalation	
3.3.1	Duration of treatment	21 exposures	

Section A6.3.3		**Short-term repeated dose toxicity – inhalation**	
Annex Point IIA VI.6.3		6.3.3 Repeated dose toxicity (inhalation) in the rat	
3.3.2	Frequency of exposure	5 days/week	
3.3.3	Postexposure period	4-week recovery period for 5 animals/sex in the top-dose group	
3.3.4	**Inhalation**		
3.3.4.1	Concentrations	0.01, 0.1 or 1.0 mg/L	
3.3.4.2	Particle size	see Table A6_3-3.1	
3.3.4.3	Type or preparation of particles	The test atmospheres were generated by a constant volume reservoir feeding a nebuliser following dissolution with ethanol.	
3.3.4.4	Type of exposure	Nose only	
3.3.4.5	Vehicle	Ethanol	
3.3.4.6	Duration of exposure	6 h per day	
3.3.4.7	Controls	Vehicle	
3.4	**Examinations**		
3.4.1	Observations	Clinical observations, bodyweights and food consumption were measured throughout the study.	
3.4.2	Ophthalmoscopic examination	All animals were given an ophthalmoscopic examination at week 4.	
3.4.3	Haematology	Blood samples were taken under light ether anaesthesia for haematology and clinical biochemistry investigations from all animals prior to treatment and from top dose animals prior to termination.	X
3.4.4	Clinical Chemisty		X
3.4.5	Urinalysis	No	
3.5	**Sacrifice and pathology**	At the end of the scheduled period, the animals were killed and subjected to an examination *post mortem*. Selected organs were weighed and specified tissues were taken for subsequent histopathology.	
3.5.1	Statistics	Dunnett's *t*-test	
		4 RESULTS AND DISCUSSION	
4.1	**Observations**	There were no mortalities in this study and no clinical signs of toxicity were seen.	
4.2	**Body weight gain**	Bodyweight gain was slightly reduced in the 1.0 mg/L males at the end of the treatment period reflected in reduced terminal bodyweights in this group. The bodyweights and food consumption for all other groups were similar to controls (see Table A6_3-3.2).	
4.3	**Food consumption and compound intake**	Food consumption was slightly reduced in the 1.0 mg/L males at the end of the treatment period (see Table A6_3-3.3).	
4.4	**Ophtalmoscopic examination**	No treatment-related effects were seen at ophthalmoscopic examination.	
4.5	**Blood analysis**		
4.5.1	Haematology	The assessment of haematological data indicated no changes of toxicological significance at the end of the exposure period for all treated groups, or at the end of the treatment-free recovery period for the top dose animals. All differences in the haematology parameters were considered to be incidental and of normal biological variation when compared with that of the controls.	

Section A6.3.3 Short-term repeated dose toxicity – inhalation

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

4.5.2	Clinical chemistry	No changes of toxicological significance were noted in the biochemical data collected at the end of the exposure period from all treated groups. There was a slightly increased potassium level (22%), chloride level (5%) for males, albumin level (11%) and total protein level (9%) for females in the 1.0 mg/L group when compared with controls. These findings were considered to be of an adaptive nature due to the treatment and found to be reversible at the end of the treatment-free (recovery) period (see Table A6_3-3.4). All other differences in the clinical biochemistry parameters were considered to be incidental and of normal biological variation when compared with that of the controls.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	There were statistically significant increases in relative lung weight and relative liver weight in the 1.0 mg/L group males. Liver weights, both absolute and relative, and relative kidney weights of the 1.0 mg/L group females were statistically significantly increased compared with controls (see Table A6_3-3.5). These changes were considered not to be of toxicological significance as they did not correlate with any histological or biochemical findings.	
4.6.2	Gross and histopathology	No treatment-related macroscopic findings were recorded. No treatment-related microscopic findings were recorded. The various spontaneous microscopic findings recorded are within the normal range observed at these ages and in this strain of rat.	
4.7	**Other**		
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Four groups of 5 male and 5 female Wistar, KFM-Han., outbred, SPF rats were exposed nose-only by continuous daily inhalation exposure (6 hours/day, 5 days/week) for a total of 21 exposures to an aerosol concentration of 0.01, 0.1 or 1.0 mg/L. The test atmospheres were generated by a constant volume reservoir feeding a nebuliser following dissolution with ethanol. A similar group of control animals was exposed to the solvent (ethanol) and air only. The reversibility of any treatment related changes was studied with 5 additional animals per sex in the top dose group only over a four-week recovery period. The exposure system used is of the flow-past nose-only type, designed to ensure a rapid equilibration, a uniform exposure of all animals and to avoid rebreathing of the exhaled air. The internal active volume of the chamber for exposing 40 animals by nose-only is one litre. The resulting time for the concentration at an animal port to reach 99% of its ultimate value is 34 seconds for the 40-animal chamber. The rats were placed in individual animal holders, so that only the snouts and nostrils of the animals were exposed to the aerosol. The flow in any individual aerosol delivery tube was standardized to 1.25 L/min/animal. Airflow, aerosol concentration, particle size, temperature, humidity and oxygen content were monitored throughout the whole exposure period. Clinical observations, bodyweights and food consumption were measured throughout the study. All animals were given an ophthalmoscopic examination at week 4. Blood samples were taken under light ether anaesthesia for haematology and clinical biochemistry investigations from all animals prior to treatment and from top dose	X

Section A6.3.3 Short-term repeated dose toxicity – inhalation

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

		animals prior to termination. At the end of the scheduled period, the animals were killed and subjected to an examination *post mortem.* Selected organs were weighed and specified tissues were taken for subsequent histopathology.	
5.2	**Results and discussion**	There were no mortalities in this study and no clinical signs of toxicity were seen. Bodyweight gains and food consumption were slightly reduced in the 1.0 mg/L males at the end of the treatment period reflected in reduced terminal bodyweights in this group. The bodyweights and food consumption for all other groups were similar to controls. No treatment-related effects were seen at ophthalmoscopic examination. The assessment of haematological data indicated no changes of toxicological significance at the end of the exposure period for all treated groups, or at the end of the treatment-free recovery period for the top dose animals. All differences in the haematology parameters were considered to be incidental and of normal biological variation when compared with that of the controls. No changes of toxicological significance were noted in the biochemical data collected at the end of the exposure period from all treated groups. There was a slightly increased potassium level (22%), chloride level (5%) for males, albumin level (11%) and total protein level (9%) for females in the 1.0 mg/L group when compared with controls. These findings were considered to be of an adaptive nature due to the treatment and found to be reversible at the end of the treatment-free (recovery) period. All other differences in the clinical biochemistry parameters were considered to be incidental and of normal biological variation when compared with that of the controls. No treatment-related macroscopic findings were recorded. There were statistically significant increases in relative lung weight and relative liver weight in the 1.0 mg/L group males. Liver weights, both absolute and relative, and relative kidney weights of the 1.0 mg/L group females were statistically significantly increased compared with controls. These changes were considered not to be of toxicological significance as they did not correlate with any histological or biochemical findings. No treatment-related microscopic findings were recorded. The various spontaneous microscopic findings recorded are within the normal range observed at these ages and in this strain of rat.	X
5.3	**Conclusion**		
5.3.1	LO(A)EC	LOAEC = 1.0 mg/L (increased lung and liver weights)	
5.3.2	NO(A)EC	NOAEC = 0.1 mg/L	
5.3.3	Reliability	2	
5.3.4	Deficiencies	The deviations (Section 2.3) are considered not to compromise the scientific validity of the study.	

Section A6.3.3 Short-term repeated dose toxicity – inhalation

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

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_3-3.1: Inhalation atmospheres as measured in the breathing zone of the animals

	Nominal dose level of fenoxycarb (mg/L air)			
Parameter	**0 (Ethanol only)**	**0.01**	**0.1**	**1.0**
Analytical concentration (mg/L/air)	0	0.010	0.103	1.131
Gravimetric concentration (mg/L/air)	0.0015 ± 0.001	0.011 ± 0.002	0.099 ± 0.009	1.05 ± 0.10
MMAD; GSD	Mean % of aerosol sampled collected on the 3 µm stage or less = 97.4 ± 1.91			
Particles > 3 µm (% w/w)	2.6 ± 1.9			
Particles 1.6-3 µm (% w/w)	13.9 ± 8.1			
Particles 0.3-1.6 µm (% w/w)	70.9 ± 8.3			
Particles < 0.3 µm (% w/w)	12.6 ± 9.6			
Flow rate (individual tube)	1.25 L/min/animal			
Temperature [°C]	20-22.8			
Humidity	Measurement discontinued as solvent was affecting sensor			
Oxygen content [%]	20.8			

Table A6_3-3.2: Intergroup comparison of bodyweights (g) (selected timepoints)

	Nominal dose level of fenoxycarb (mg/L air)							
	Males				Females			
Week	**0**	**0.01**	**0.1**	**1**	**0**	**0.01**	**0.1**	**1**
4	285	284	278	269	213	214	215	211
5	297	294	291	277	218	215	216	213

Table A6_3-3.3: Intergroup comparison of food consumption (g/animal/day) (selected timepoints)

	Nominal dose level of fenoxycarb (mg/L air)							
	Males				Females			
Week	**0**	**0.01**	**0.1**	**1**	**0**	**0.01**	**0.1**	**1**
3/4	20.9	22.1	21.7	19.3	15.7	16.2	16.0	17.1
4/5	21.8	22.6	22.8	19.9	16.1	16.8	15.6	16.9

Table A6_3-3.4: Intergroup comparison of clinical biochemistry – selected parameters

	Nominal dose level of fenoxycarb (mg/L air)									
	Males					Females				
Parameter	**0**	**0.01**	**0.1**	**1**	**1.0R**	**0**	**0.01**	**0.1**	**1**	**1.0R**
Potassium [mmol/L]	3.38	3.56	3.73	4.11*	3.72	3.22	3.22	3.11	3.37	3.28
Chloride [mmol/L]	104.0	105.5	105.9	109.5*	94.4	106.7	105.6	107.0	106.1	96.6
Albumin [g/L]	39.9	37.8	39.6	42.3	35.0	41.2	42.4	41.8	45.7*	36.7
Total protein [g/L]	64.6	61.9	64.5	66.1	62.9	62.4	64.0	63.6	68.0*	61.7

* Statistically significant difference from control group mean p<0.05
R Recovery group after a subsequent 4 week treatment-free period

Table A6_3-3.5: Intergroup comparison of selected organ weights and organ weight ratios

	Nominal dose level of fenoxycarb (mg/L air)							
	Males				Females			
	0	**0.01**	**0.1**	**1**	**0**	**0.01**	**0.1**	**1**
Body weight (g)	275.2	269.9	266.3	246.0	198.9	195.8	195.8	187.4
Lung								
Absolute wt (g)	1.34	1.29	1.29	1.40	1.16	1.15	1.15	1.13
Lung:body wt ratio (%)	0.49	0.48	0.49	0.57**	0.58	0.59	0.59	0.61
Liver								
Absolute wt (g)	7.84	7.66	7.84	8.00	5.69	5.51	5.71	7.21**
Liver:body wt ratio (%)	2.85	2.84	2.95	3.25**	2.86	2.83	2.92	3.84**
Kidney								
Absolute wt (g)	1.76	1.91	1.91	1.76	1.26	1.33	1.33	1.37
Kidney:body wt ratio (%)	0.64	0.71	0.72	0.72	0.63	0.68	0.68	0.73**

* Statistically significant difference from control group mean, p<0.05 (Dunnett's t-test)
** Statistically significant difference from control group mean, p<0.01 (Dunnett's t-test)

Section A6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 Thirteen-week dietary toxicity study in rats

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1993), 3-Month Oral Toxicity Study In Rats (Administration In Food). CGA 114597 tech. [redacted], Report No. 922116, 09 November 1993 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC B.26 (1988) ≅ OECD 408 (1998) ≅ FIFRA § 82-1
2.2	**GLP**	Yes
2.3	**Deviations**	Ornithine decarboxylase was not measured. Small and large intestine were examined, but specific areas are not identified. Muscle and rectum were not examined histopathologically.

3 MATERIALS AND METHODS

3.1	**Test material**	Fenoxycarb technical (CGA 114597 tech.)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	Analyses showed that the achieved dietary concentrations were within 89-105% of nominal. The stability of fenoxycarb in the experimental diets over a 5 week period when stored at room temperature was confirmed. Homogeneity was demonstrated in the pretest food preparations.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Tif:RAIf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived)
3.2.3	Sex	♂ + ♀
3.2.4	Number of animals per group	10 per sex
3.2.5	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	3 months
3.3.2	Frequency of exposure	*Ad libitum*
3.3.3	Post-exposure period	4-week recovery groups (control and top dose) with 10 rats per sex and group

Section A6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 Thirteen-week dietary toxicity study in rats

3.3.4	**Oral**	
3.3.4.1	Type	In food
3.3.4.2	Concentration	Nominal doses: 30, 150, 750, 3000 ppm Actual intake: ♂: 2.2, 9.7, 45, 199 mg/kg bw/day ♀: 2.3, 10.1, 50, 203 mg/kg bw/day
3.3.4.3	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	Clinical observations, bodyweights, food and water consumption were recorded at intervals during the study.
3.4.1.1	Clinical signs	Yes, once weekly.
3.4.1.2	Mortality	Yes, once daily.
3.4.2	Ophthalmoscopic examination	Yes
3.4.3	Haematology	Haematology and clinical biochemistry were measured at the end of the treatment or recovery periods as appropriate.
3.4.4	Clinical chemistry	
3.4.5	Urinalysis	Yes
3.5	**Sacrifice and pathology**	At the end of the scheduled period, the animals were killed and subjected to a full examination *post mortem*. Selected organs were weighed and specified tissues were taken for subsequent histopathology examination.
3.5.1	Statistics	Lepage test and Jonckheere test

4 RESULTS AND DISCUSSION

4.1	**Observations**	None of the animals died and there were no treatment-related clinical observations.
4.2	**Body weight gain**	Lower bodyweight gains were seen in both sexes fed 3000 ppm fenoxycarb, with mean bodyweights approximately 5% and 10% lower for males and females, respectively, than control values by the end of the treatment period. By the end of the recovery period, mean bodyweight for males at this dose was similar to controls, but was still reduced in females. Bodyweights in other treated groups were unaffected (see Table A6_4-1.1).
4.3	**Food consumption and compound intake**	During the treatment period, lower food consumption (9% below control) was seen in females at 3000 ppm fenoxycarb. No other group showed any adverse effect of treatment (see Table A6_4-1.2).
4.4	**Ophtalmoscopic examination**	There were no treatment-related ophthalmoscopic observations.
4.5	**Blood analysis**	Not applicable
4.5.1	Haematology	There was no evidence of any treatment-related effect on haematological parameters. Minor, but statistically significant, differences between the groups were considered to be incidental.
4.5.2	Clinical chemistry	Blood biochemistry showed that at the end of the treatment period, plasma cholesterol levels were slightly increased in both sexes fed 750 and 3000 ppm fenoxycarb. Males fed 3000 ppm fenoxycarb also had minimally lower triglyceride levels, increased activities of alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and alkaline phosphatase (ALP). Females fed 3000 ppm fenoxycarb had only minimally increased alkaline phosphatase activities. Both sexes fed 3000 ppm fenoxycarb showed higher albumin to globulin ratios that in

		males resulted mainly from lower globulin levels and in females from higher albumin levels (see Table A6_4-1.3). Any other statistically significant differences between the groups were considered to be incidental. All these changes were reversible within the recovery period.
4.5.3	Urinalysis	There were no treatment-related changes in urine biochemistry.
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	Liver weights in both sexes and female thyroid weights were increased in animals fed 3000 ppm fenoxycarb, and liver weights were increased in animals fed 750 ppm fenoxycarb. At the end of the recovery period, mean weights for both liver and thyroid were similar to the control values (see Table A6_4-1.4).
4.6.2	Gross and histopathology	Enlarged liver was seen in some animals fed 750 or 3000 ppm fenoxycarb, which correlated with a hypertrophy of the hepatocytes that was considered to be treatment-related. No other macroscopic findings were considered to be related to treatment. Microscopic examination of the liver showed a hypertrophy of the hepatocytes in some females fed 750 ppm fenoxycarb and all animals in the 3000 ppm fenoxycarb group in the main study. This change, mainly confined to the centrilobular region of the liver, was minimal in females at 750 ppm fenoxycarb and minimal to moderate in both sexes at 3000 ppm fenoxycarb (see Table A6_4-1.5). This cellular hypertrophy was considered to be a treatment-related adaptive response. A hypertrophy of the follicular epithelium of the thyroid gland, associated with numerous resorption vacuoles in the cytoplasm of follicular cells and paler and more vacuolated colloid, was seen in some animals fed 750 and 3000 ppm fenoxycarb; this was minimal in females at 750 ppm fenoxycarb and males at 3000 ppm fenoxycarb and minimal to moderate in females at 3000 ppm fenoxycarb. The thyroid gland changes were considered to be secondary to the increased metabolism of the liver, leading to an accelerated break-down of thyroid hormones. Both the liver and thyroid changes were fully reversible within the four-week recovery period. Other microscopic findings were considered to be common in rats of this age and strain, and incidental to the administration of fenoxycarb.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Groups of 10 male and 10 female Tif:RAIf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats were fed diets containing 0 (control), 30, 150, 750 or 3000 ppm fenoxycarb for 3 months. An additional 10 male and 10 female rats in the control and 3000 ppm fenoxycarb group remained on study and were fed control diet to allow assessment for reversibility evaluation after 4 weeks of recovery. Dietary samples from all groups (including controls) were taken at intervals throughout the study and analysed for achieved concentration. Stability for a period of up to 5 weeks and homogeneity were measured. Clinical observations (including ophthalmoscopy), bodyweights, food and water consumption were recorded at intervals during the study. Haematology and clinical biochemistry (blood and urine) were measured at the end of the treatment or recovery periods as appropriate. At the end of the scheduled period, the animals were killed and subjected to a full examination *post mortem*. Selected organs were weighed and specified tissues were taken for subsequent histopathology

Section A6.4.1		Repeated dose toxicity
Annex Point IIA VI.6.4		6.4.1 Thirteen-week dietary toxicity study in rats
		examination.
5.2	**Results and discussion**	Treatment with CGA 114597 tech. resulted in reduced food intake and depressed bodyweight gain in high dose animals. Changes in the liver at the higher dose levels were substantiated by increased weight, hepatocellular hypertrophy and changes to plasma levels for protein, cholesterol and liver enzymes. Hypertrophy of thyroid follicular epithelium was considered of secondary nature. This slight liver toxicity accompanied by adaptive changes of a functional nature, indicative of metabolic load or hormonal adjustment, were completely reversible upon cessation of treatment. It was concluded that the no observable effect level (NOEL) for fenoxycarb when administered continuously in diet for a period of 3 months is 150 ppm, corresponding to a mean daily intake of 9.7 mg/kg bw in males and 10.1 mg/kg bw in females.
5.3	**Conclusion**	
5.3.1	LO(A)EL	LOAEL = 45 / 50 mg/kg bw/day (♂/♀)
5.3.2	NO(A)EL	NOAEL = 9.7 / 10.1 mg/kg bw/day (♂/♀)
5.3.3	Reliability	1
5.3.4	Deficiencies	The deviations (Section 2.3) are considered not to compromise the scientific validity of the study.

Section A6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 Thirteen-week dietary toxicity study in rats

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/08
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.4.1 Repeated dose toxicity

Annex Point IIA VI.6.4 6.4.1 Thirteen-week dietary toxicity study in rats

Table A6_4-1.1: Intergroup comparison of bodyweights (g) (selected timepoints)

	Dietary concentration of fenoxycarb (ppm)									
	Males					Females				
week	0	30	150	750	3000	0	30	150	750	3000
1	158.2	161.3	168.0+	161.4	156.8	135.2	134.0	134.6	137.0	137.8
13	457.1	467.1	491.7	460.2	436.9	294.0	289.5	292.1	290.1	265.7*
14	453.2	-	-	-	438.7	294.8	-	-	-	273.4
17	481.2	-	-	-	477.1	310.7	-	-	-	291.0

* Statistically significant difference from control group mean, p<0.01 (Lepage test)
+ Statistically significant difference from control group mean, p<0.01 (Jonckheere + test)

Table A6_4-1.2: Intergroup comparison of food consumption (g/rat/week) (selected timepoints)

	Dietary concentration of fenoxycarb (ppm)									
	Males					Females				
week	0	30	150	750	3000	0	30	150	750	3000
2	142.9	128.7	160.0	77.86	142.7	118.9	116.0	109.0	109.3	104.9*
5	179.6	178.1	188.6	178.6	169.3	135.8	135.4	124.1	130.7	115.2*
11	157.1	162.6	173.3*	159.5	156.8	118.2	127.6	113.0	112.7	108.9*

* Statistically significant difference from control group mean, p<0.05 (Jonckheere test)

Table A6_4-1.3: Intergroup comparison of selected blood biochemistry parameters

		Dietary concentration of fenoxycarb (ppm)									
		Males					Females				
Parameter	wk	0	30	150	750	3000	0	30	150	750	3000
Cholesterol	14	1.674	1.713	1.816	2.277*	2.524*	1.867	1.838	1.763	2.427*	3.070*
	18	1.787	-	-	-	2.087	2.210	-	-	-	2.506
Triglyceride	14	0.936	1.297	1.191	1.032	0.713*	0.814	0.753	0.901	0.818	0.840
	18	0.970	-	-	-	0.931	0.792	-	-	-	0.890
ALAT	14	40.00	39.18	40.95	46.60	62.59*	27.76	26.32	29.68	24.64	26.40
	18	36.62	-	-	-	49.92	29.92	-	-	-	32.66
ASAT	14	62.78	69.26	67.21	77.57	95.30*	60.17	57.08	62.46	58.65	52.06
	18	62.42	-	-	-	60.94	57.69	-	-	-	52.78
ALP	14	99.34	97.88	91.79	115.1	148.6*	64.34	53.79	63.82	62.39	88.97*
	18	96.63	-	-	-	87.38	55.57	-	-	-	66.56
A/G ratios	14	1.198	1.239	1.223	1.271*	1.343*	1.333	1.382	1.348	1.395	1.447*
	18	1.291	-	-	-	1.259	1.419	-	-	-	1.313*

* Statistically significant difference from control group mean, p<0.01 (Lepage and/or Jonckheere tests)

Table A6_4-1.4: Intergroup comparison of selected organ weights (g)

	Dietary concentration of fenoxycarb (ppm)									
	Males					Females				
Organ	**0**	**30**	**150**	**750**	**3000**	**0**	**30**	**150**	**750**	**3000**
Liver										
Main study – abs [g]	18.20	17.94	18.67	19.30	22.94 *	9.988	9.135	9.776	11.65	13.45 *
Relative to bw	40.89	40.02	39.71	43.64	55.11 *	36.40	33.30	35.68	42.49 *	55.29 *
Recovery – abs [g]	16.86	-	-	-	16.56	9.894	-	-	-	10.37
Relative to bw	36.56	-	-	-	36.47	33.97	-	-	-	37.61
Thyroid										
Main study – abs [g]	33.59	33.64	31.19	33.12	33.38	25.35	31.35	30.22	30.43	32.59
Relative to bw	0.075	0.076	0.066	0.076	0.081	0.093	0.114	0.109	0.112	0.136 *
Recovery - abs [g]	27.77	-	-	-	31.02	27.77	-	-	-	31.02
Relative to bw	0.061	-	-	-	0.068	28.60	-	-	-	29.70

* Statistically significant difference from control group mean, $p<0.01$ (Lepage and/or Jonckheere tests)

Table A6_4-1.5: Intergroup comparison of selected microscopic findings

	Dietary concentration of fenoxycarb (ppm)									
	Males					Females				
Organ	**0**	**30**	**150**	**750**	**3000**	**0**	**30**	**150**	**750**	**3000**
Animal examined										
Liver: Hepatocyte hypertrophy	0	0	0	0	10	0	0	0	8	10
Thyroid: hypertrophy of the follicular epithelium	0	0	0	0	3	0	0	0	7	10

Section 6.4.1	**Subchronic toxicity**	
Annex Point IIA VI.6.4	**90-day oral toxicity study in dogs**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	[redacted]	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/08/10	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

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

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

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]1992), Ro 13-5223/000:104-Week Oral (Dietary Administration) Carcinogenicity And Toxicity Study In The Rat With A 52-Week Interim Kill. [redacted], Report No. 5191-161/123R, 02 March 1992 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Syngenta	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes 87/302/EEC B.33 (1988) ≅ OECD 453 (1981) ≅ FIFRA §83-5	
2.2	**GLP**	Yes	
2.3	**Deviations**	Number of animals per group in the satellite group was lower than recommended (10/sex instead of 20/sex). Blood and urine samples from control and high dose animals were examined at weeks 25, 51, 78 and 102. Rectum was not examined.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Purity	[redacted]	
3.1.2.2	Stability	The stability and homogeneity of fenoxycarb in diet was confirmed before the start of the study.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley-derived (Crl:CD(SD)BR)	
3.2.3	Sex	♂ + ♀	
3.2.4	Number of animals per group		
3.2.4.1	at interim sacrifice	One-year sacrifice group: 10 rats/sex	
3.2.4.2	at terminal sacrifice	Two-year sacrifice group: 50 per sex	
3.2.5	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	102 weeks	X

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

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

3.3.2	Interim sacrifice(s)	After 51 weeks		X
3.3.3	Final sacrifice	After 102 weeks		X
3.3.4	Frequency of exposure	*ad libitum*		
3.3.5	Postexposure period	None		
		Oral		
3.3.6	Type	In food		
3.3.7	Concentration	nominal conc. in food actual dose in food	200, 600, 1800 ppm 8.1, 24.7, 74.4 mg/kg bw/day (males) 10.9, 33.1, 100.4 mg/kg bw/day (females)	
3.3.8	Controls	Plain diet		
3.4	**Examinations**	Clinical observations, bodyweights, food consumption, haematology and clinical biochemistry (blood and urine), were measured throughout the study. Ophthalmoscopic examinations were made on 10 rats/sex from control and the top dose groups pre-study and at weeks 51 and 102. At the end of the scheduled period the animals were killed and subjected to a full examination *post mortem*. Selected organs were weighed and specified tissues were taken for subsequent histopathological examination.		
3.5	**Further remarks**	–		
		4 RESULTS AND DISCUSSION		
4.1	**Body weight**	In week one there was a slight reduction in body weight for males fed 1800 ppm fenoxycarb and from week 40 to 96 females at this dose showed reduced bodyweight gain compared with controls. However, at study termination, the mean bodyweight in both sexes at this dose were 97% of the control weight. Bodyweights at 200 and 600 ppm were unaffected by treatment (see Table A6_7-1).		
4.2	**Clinical signs**	The survival rate for all groups was between 58 and 78% after 104 weeks of treatment. There were no treatment-related clinical or ophthalmoscopic changes.		
4.3	**Ophthalmoscopic examination**	No effects.		
4.4	**Haematology**	Red cell parameters (Hb and RBC) were below controls for both sexes at 1800 ppm at week 25, but reached statistical significance only in males. At 102 weeks, red blood cell values for females were reduced compared with control, primarily due to the low values recorded from one animal, but statistical significance was not achieved (see A6_7-2).		
4.5	**Clinical Chemistry**	Although glutamate oxaloacetate transaminase (GOT or ASAT), glutamate pyruvate transaminase (GPT or ALAT) and alkaline phosphatase levels were generally statistically significantly increased at 600 and/or 1800 ppm fenoxycarb, the mean values were still within the historical control range (see A6_7-3).		
4.6	**Urinalysis**	There were no treatment-related effects on any urine parameters.		
4.7	**Pathology**	There were no treatment-related gross pathology findings.		

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

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

4.8	**Organ Weights**	Liver weights adjusted for bodyweight were increased in animals fed 600 ppm fenoxycarb by 16 and 10% for males and females, respectively, at the interim kill; and by 11 and 13% for males and females, respectively, at terminal kill (see Table A6_7-4). Liver weights were increased in animals fed 1800 ppm fenoxycarb. At the interim kill the mean relative weight for males was 13% higher than controls. Female liver weights were increased by 26% when adjusted for final bodyweight. At study termination, adjusted mean liver weights were increased by 6% and 28%, respectively for males and females. Differences in other organ weights were considered not to be biologically significant. In animals fed 600 ppm fenoxycarb at the interim kill, the adjusted liver weight to final bodyweight was increased by 10% for females. The relative liver weight of the males was increased by 16% compared with control. At terminal kill the adjusted liver weight was increased by 11% and 13%, respectively for males and females.	
4.9	**Histopathology**	**Non-neoplastic lesions:** Histopathology showed an increased incidence of centrilobular hypertrophy of the liver, usually associated with focal necrosis and foci of pigmented histiocytes, the latter restricted to some animals in the 600 and 1800 ppm fenoxycarb males at terminal kill. The incidence of other lesions was comparable to controls (see Table A6_7-5). **Neoplastic lesions:** The most commonly seen tumours were pituitary tumours, which were responsible for 56 out of the 121 sporadic kill animals (see Table A6_7-6). Other common tumours included mammary tumours in females and skin tumours in males. There was no evidence of any treatment effect on the incidence of any tumour type and all types were consistent with the historical control range.	
4.10	**Other**	–	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of 60 male and 60 female Sprague Dawley-derived (Crl:CD(SD)BR) rats were fed diets containing nominal dose levels of 0 (control), 200, 600 or 1800 ppm fenoxycarb for up to 104 weeks. Of these, 10 male and 10 female rats per group were assigned for interim necropsy. Surviving animals were killed after 104 weeks and necropsied. The achieved concentration of fenoxycarb in the diets was analysed in week 1 and every 13 weeks thereafter. The stability and homogeneity of fenoxycarb in diet was confirmed before the start of the study. Clinical observations, bodyweights, food consumption, haematology and clinical biochemistry (blood and urine), were measured throughout the study. Ophthalmoscopic examinations were made on 10 rats/sex from control and the top dose groups pre-study and at weeks 51 and 102. At the end of the scheduled period the animals were killed and subjected to a full examination *post mortem.* Selected organs were weighed and specified tissues were taken for subsequent histopathological examination.	
5.2	**Results and discussion**	After 104 weeks of treatment, no toxicologically significant changes were seen in animals fed 200 ppm fenoxycarb and this was considered to be a no effect level. In addition, treatment for 104 weeks at a dose of 1800 ppm had no effect on the incidence or morphology of tumours.	X

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

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

5.3	**Conclusion**			
5.3.1	LO(A)EL	Non-neoplastic LOAEL: Neoplastic LOAEL:	24.7 / 33.1 mg/kg bw/day (♂ / ♀) –	X
5.3.2	NO(A)EL	Non-neoplastic NOAEL: Neoplastic NOAEL:	8.1 / 10.9 mg/kg bw/day (♂ / ♀) 74.4 / 100.4 mg/kg bw/day (♂ / ♀)	X
5.3.3	Other	–		
5.3.4	Reliability	1		
5.3.5	Deficiencies	The deviations (point 2.3) do not affect the overall validity of the study.		

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

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

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/01/19
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_7-1: Intergroup comparison of bodyweight gain - selected timepoints (g)

	Dietary concentration of fenoxycarb (ppm)							
	Males				Females			
Week	**0**	**200**	**600**	**1800**	**0**	**200**	**600**	**1800**
0 - 13	316.4	299.7	309.0	287.5***	124.8	128.5	121.2	117.8** #
13 - 24	79.2	75.4	79.9	70.6*	24.4	26.4	26.2	24.6
40 - 52	37.4	40.1	40.1	27.5**	42.2	44.4	37.9	28.7**
0 - 52	489.3	477.5	493.5	446.4**	229.1	242.5	225.2	209.7* #
80 - 92	20.7	26.9	41.8*	34.8	32.6	29.0	-0.5**	31.3
0 - 104	566.6	537.5	579.9	545.7	326.4	352.8	317.5	311.4

* Statistically significant difference from control group mean, p<0.05
** Statistically significant difference from control group mean, p<0.01
*** Statistically significant difference from control group mean, p<0.001
# significant using the dose response test

Table A6_7-2: Intergroup comparison of selected haematology parameters

	Dietary concentration of fenoxycarb (ppm)			
	Males		Females	
Week:Parameter	**0**	**1800**	**0**	**1800**
25: Haemoglobin	16.3	15.7*	15.3	15.1
25: Red blood cells	8.52	8.17*	7.52	7.45

* Statistically significant difference from control group mean, p<0.05

Table A6_7-3: Intergroup comparison of selected clinical chemistry parameters

	Dietary concentration of fenoxycarb (ppm)							
	Males				Females			
Week:Parameter	**0**	**200**	**600**	**1800**	**0**	**200**	**600**	**1800**
25: Alkaline phosphatase	143	-	-	200**	73	-	-	107*
51: Alkaline phosphatase	158	-	-	243***	60	-	-	119**
78: Alkaline phosphatase	143	-	-	272**	84	-	-	131
102: Alkaline phosphatase	136	163	202	286***	72	74	94	104*
102: ASAT	78	90	197**	153*	85	79	107	104
102: ALAT	29	36	82**	73*	37	34	41	34

* Statistically significant difference from control group mean, p<0.05
** Statistically significant difference from control group mean, p<0.01
*** Statistically significant difference from control group mean, p<0.001

Table A6_7-4: Intergroup comparison of liver weights

	Dietary concentration of fenoxycarb (ppm)							
	Males				Females			
Study period	**0**	**200**	**600**	**1800**	**0**	**200**	**600**	**1800**
Interim kill: Adjusted (g)	-	-	-	-	8.094	8.816	8.943	10.190***
Interim kill: Relative (%)	2.388	2.208	2.774	2.688 #	-	-	-	-
Terminal kill: Adjusted (g)	15.287	14.577	17.009	16.213	9.978	9.754	11.268	12.743***

*** Statistically significant difference from control group mean, p<0.001
# significant using the dose response test
Adjusted – to terminal bodyweight (g) Relative – organ/bodyweight ratio (%)

Table A6_7-5: Intergroup comparison of microscopic liver findings

	Dietary concentration of fenoxycarb (ppm)							
	Males				Females			
Observation	**0**	**200**	**600**	**1800**	**0**	**200**	**600**	**1800**
Hypertrophy	0	0	8	22	0	0	0	10
Focal necrosis	1	6	18	19	2	2	6	0
Pigmented histiocytes	0	0	2	4	0	0	0	0

Table A6_7-6: Intergroup comparison of the incidence of pituitary tumours

	Dietary concentration of fenoxycarb (ppm)							
	Males				Females			
Observation	**0**	**200**	**600**	**1800**	**0**	**200**	**600**	**1800**
Adenoma	21	5	8	15	20	10	13	21
Carcinoma	1	0	0	3	11	6	4	5

The historical control range of adenoma was 30-70% in males and 58-89% in females
The historical control range of carcinoma was 1-2% in males and 0-28% in females

CA-Table 1: Intergroup comparison of the incidence of pituitary tumours – re-evaluation in males

	Dietary concentration of fenoxycarb (ppm)			
Observation	**0**	**200**	**600**	**1800**
Adenoma	25 (42 %)	14 (23 %)	17 (28 %)	23 (39 %)
Carcinoma	1 (2 %)	0	0	1 (2 %)

The historical control range of adenoma was 30-70 % in males.
The historical control range of carcinoma was 1-2 % in males.

Section A6.5 Chronic Toxicity

Annex Points IIA VI.6.5 6.5 One-year oral toxicity study in the dog

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1 REFERENCE

1.1	**Reference**	[redacted] (1988), Chronic Toxicity Study Following Oral Administration of Ro 13-5223/000, An Insect Growth Regulator, To Dogs For A Period Of One Year. [redacted], Report No. B-153778, 30 June 1988 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC B.30 (1988) ≅ OECD 452 (1981) ≅ FIFRA § 83-1 (b)
2.2	**GLP**	Yes
2.3	**Deviations**	Blood for haematology and clinical chemistry analysis was collected in weeks 0 (pre-treatment), 2, 6, 13, 26, 39 and 52. Urine was collected for urinalysis in weeks 5, 25 and 50. Urine volume was not recorded. Ornithine decarboxylase was not measured. Femur was not taken for histopathological examination. The amount of food consumed by the 4 dogs of each cage/group was measured on one or two days per week for the duration of the study. Food consumption values presented are totals eaten per group over 365 days and the value per animal derived from this.

3 MATERIALS AND METHODS

3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	Test substance analyses carried out on three occasions during the study demonstrated that the test substance was stable throughout the duration of the study with values of 95.1, 95.0 and 95.0% of nominal.
3.2	**Test Animals**	
3.2.1	Species	Dog
3.2.2	Strain	Beagle
3.2.3	Source	[redacted]
3.2.4	Sex	♂ + ♀
3.2.5	Age/weight at study initiation	♂: 10.8-12.6 kg, ♀: 9.3-11.3 kg
3.2.6	Number of animals per group	4/sex
3.2.7	Control animals	Yes

Section A6.5 Chronic Toxicity

Annex Points IIA VI.6.5 6.5 One-year oral toxicity study in the dog

3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	One year
3.3.2	Interim sacrifice(s)	No
3.3.3	Final sacrifice	All dogs
3.3.4	Frequency of exposure	Once daily
3.3.5	Postexposure period	None
		Oral
3.3.6	Type	Gelatine capsule
3.3.7	Concentration	0, 25, 80, 260 mg/kg bw/day
3.3.8	Controls	Empty capsules
3.4	**Examinations**	During the study, mortalities, clinical observations, body weights and food intake were recorded.
3.4.1	Ophthalmoscopic examination	Ophthalmoscopy was done at the beginning of the study and prior to termination.
3.4.2	Haematology	Yes,
3.4.3	Clinical Chemistry	Yes
3.4.4	Urinalysis	Yes
3.4.5	Pathology	Selected organs were weighed and specified tissues were taken for subsequent histopathology examination.
3.4.6	Histopathology	Yes
3.5	**Statistics**	Kruskal-Wallis ANOVA + Mann-Whitney u-tests (two-sided)
3.6	**Further remarks**	–
		4 RESULTS AND DISCUSSION
4.1	**Body weight**	There were no treatment-related effects on bodyweight or bodyweight gain in the 25 or 80 mg/kg groups compared with controls throughout the study. A reduction in bodyweight gain compared with controls was recorded for males and females in the 260 mg/kg group. The difference in bodyweight between dogs in the 260 mg/kg group and the controls was statistically significant for males from week 2 until the end of the study (see Table A6_5.1 and Table A6_5.2).
4.2	**Food consumption**	The calculated food consumption for four dogs of each sex in the 25 and 80 mg/kg groups and females in the 260 mg/kg group was similar to that of the controls. Reduced food consumption compared with controls was found in the 260 mg/kg males (see Table A6_5.3).
4.3	**Clinical signs**	No treatment-related clinical observations were recorded. Incidences of obesity in the 0, 25 and 80 mg/kg groups were considered to be the result of lack of physical exercise and other observations seen were the results of local infections of a general nature.
4.4	**Mortality**	No deaths occurred.
4.5	**Ophthalmoscopic examination**	No treatment-related effects.

Section A6.5	Chronic Toxicity	
Annex Points IIA VI.6.5	6.5 One-year oral toxicity study in the dog	
4.6	**Haematology**	No biologically or toxicologically meaningful differences were found between treated groups and controls in the haematological parameters measured at weeks 0, 2, 6, 13, 26, 39 or 52.
4.7	**Clinical Chemistry**	Plasma concentrations of inorganic phosphorus were statistically significantly reduced compared with controls in the 80 and 260 mg/kg males and 260 mg/kg females at week 52 and a similar trend was indicated by the week 39 results (see Table A6_5.4). Other clinical chemistry parameters measured generally remained within the physiological range for Beagle dogs of similar age and showed no treatment-related effects.
4.8	**Urinalysis**	No treatment-related effects.
4.9	**Pathology**	There were no treatment-related macroscopic findings.
4.10	**Organ Weights**	Absolute adrenal weights in the 260 mg/kg male group were statistically significantly lower than controls. The relative liver weight of male and female 260 mg/kg animals was statistically significantly increased compared with controls (see Table A6_5.5). Increases in relative testes weights and relative heart weight in 260 mg/kg males and relative kidney weight in 260 mg/kg females are considered not to be of toxicological importance, as they are not related to other findings.
4.11	**Histopathology**	There were no treatment related microscopic findings.
4.12	**Other**	–
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Fenoxycarb, an insect growth regulator, was orally administered for a period of at least one year to three groups of 8 Beagle dogs each (4 males and 4 females), at daily doses of 25, 80 or 260 mg/kg bw, by means of gelatine capsules. Eight further dogs were kept as controls and received empty gelatine capsules. During the study, mortalities, clinical observations, body weights and food intake were recorded. Clinical pathology parameters were measured from blood and urine samples taken at intervals during the study. Ophthalmoscopy was done at the beginning of the study and prior to termination. At the end of the scheduled period, the animals were killed and subjected to a full examination *post mortem*. Selected organs were weighed and specified tissues were taken for subsequent histopathology examination.
5.2	**Results and discussion**	From the results of this study, it can be concluded that fenoxycarb, an insect growth regulator, administered orally by gelatine capsule at daily doses of 0, 25, 80 or 260 mg/kg bw/day to male and female Beagle dogs over a period of at least 1 year, does not cause any adverse effect on the general state of health and behaviour of the dogs. There were no treatment related effects on haematology or clinical chemistry parameters, urinalysis, ophthalmoscopy, macroscopic or microscopic findings. Minor signs most probably due to reduced food consumption and adaptation of the liver to the test substance load, were apparent in both sexes in the 260 mg/kg group as reduced bodyweight gain compared with controls, reduced food consumption (males), reduced plasma concentration of inorganic phosphorus at week 52 (both sexes), increased relative liver weights (both sexes) and decreased adrenal

Section A6.5	Chronic Toxicity
Annex Points IIA VI.6.5	6.5 One-year oral toxicity study in the dog

		weight (males). The only change detected in the 80 mg/kg dose group was predominant in male dogs and consisted of decreased plasma levels of inorganic phosphorus at week 52. At the 25 mg/kg level no treatment related effects were seen and therefore a daily dose of 25 mg/kg bw/day is considered to represent the no-effect level (NOEL) in the Beagle dog for a chronic one-year study.
5.3	**Conclusion**	
5.3.1	LO(A)EL	LOAEL = 80 mg/kg bw/day (decreased blood phosphorus in ♂)
5.3.2	NO(A)EL	NOAEL = 25 mg/kg bw/day 0 mg/kg b.w./days
5.3.3	Other	–
5.3.4	Reliability	1
5.3.5	Deficiencies	The deviations (Section 2.3) are considered not to compromise the scientific validity of the study.

Section A6.5 Chronic Toxicity

Annex Points IIA VI.6.5 6.5 One-year oral toxicity study in the dog

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/10
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.5 Chronic Toxicity

Annex Points IIA VI.6.5 6.5 One-year oral toxicity study in the dog

Table A6_5.1: Intergroup comparison of bodyweights (kg) - (selected timepoints)

	Dose level of fenoxycarb (mg/kg bw/day)							
	Males				Females			
Week	**0**	**25**	**80**	**260**	**0**	**25**	**80**	**260**
0	12.6	10.9	12.0	10.8	9.3	10.5	11.3 #	10.7
2	12.6	11.3	12.3	10.5 #	9.4	10.5	11.3 #	10.3
12	14.2	12.7	13.5	11.3 #	10.6	11.3	12.6	10.5
24	17.1	13.8	14.7	11.8 #	11.2	12.4	13.2	11.1
36	17.4	14.7	15.3	11.9 #	11.7	12.6	13.9	11.3
48	19.1	15.5	16.2	11.8 #	12.6	13.4	15.7	11.2
53	19.3	15.1	16.1	11.5 #	12.3	13.6	14.9	11.1

Statistically significant difference from control group mean

Table A6_5.2: Bodyweight gain as % of initial weight during 365 days

Sex	**Dose level of fenoxycarb (mg/kg bw/day)**			
	0	**25**	**80**	**260**
Males	53	39	34	6
Females	32	30	32	4

Table A6_5.3: Calculated total food consumption for 365 days per group (kg) and daily per dog (g/day)

	Dose level of fenoxycarb (mg/kg bw/day)			
Sex	**0**	**25**	**80**	**260**
Males:				
per group 365 days (kg)	481.3	443.0	456.4	416.7
per dog (g/day)	330	303	313	285
Females:				
per group 365 days (kg)	405.2	399.8	426.0	405.1
per dog (g/day)	278	274	292	278

Table A6_5.4: Intergroup comparison of blood clinical chemistry – selected parameter, selected weeks

		Dose level of fenoxycarb (mg/kg bw/day)							
		Males				Females			
Parameter	**Wk**	**0**	**25**	**80**	**260**	**0**	**25**	**80**	**260**
Inorganic phosphorus	39	1.31	1.24	1.09	0.99	1.28	1.15	1.11	0.96
	52	1.23	0.93	0.84*	0.67*	1.09	0.92	0.71	0.54*

* Statistically significant difference from control group mean, p<0.05 Kruskal-Wallis ANOVA + Mann-Whitney u-tests (two-sided)

Table A6_5.5: Intergroup comparison of mean selected organ weights

		Dose level of fenoxycarb (mg/kg bw/day)							
		Males				Females			
Organ		**0**	**25**	**80**	**260**	**0**	**25**	**80**	**260**
Adrenal	Absolute (g)	1.3500	1.0425	1.0800*	0.8850*	1.2625	1.2150	1.2450	1.3525
	Relative [%]	0.0070	0.0072	0.0070	0.0078	0.0107	0.0095	0.0085	0.0128
Liver	Absolute (g)	414.925	358.775	414.825	311.000	236.098	327.668	345.260	327.983
	Relative [%]	2.156	2.395	2.561	2.715*	1.931	2.521	2.347	3.033*
Testes	Absolute (g)	16.878	13.875	17.933	15.130	-	-	-	-
	Relative [%]	0.088	0.097	0.115	0.131*	-	-	-	-
Heart	Absolute (g)	91.725	89.050	88.800	82.275	68.223	69.130	71.915	69.203
	Relative [%]	0.479	0.612	0.567	0.718*	0.574	0.540	0.493	0.649
Kidney	Absolute (g)	72.215	61.808	71.168	64.853	44.718	53.390	53.738	48.105
	Relative [%]	0.378	0.430	0.454	0.565	0.386	0.410	0.364	0.444*

* Statistically significant difference from control group mean, p<0.05 (two-sided)

Section A6.6.1 Genotoxicity in vitro

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

Official use only

1 REFERENCE

1.1	**Reference**	Gocke E (1988), Mutagenicity evaluation of fenoxycarb (Ro 13-5223/000) in the Ames assay. F. Hoffmann-La Roche & Co. Ltd., Basel, Switzerland, Report No. B-153'219, 08 November 1988 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No guidelines specified. The study was performed according to the methods described by Ames et al., 1975 and Yahagi et al. 1975. It is in accordance with OECD Guideline 471 (1983) and 87/302/EEC B13/14 (1988).
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	Not reported
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	S. typhimurium: TA 1535, TA 1537, TA 1538, TA 97, TA 98, TA 100 and TA 102
3.2.2	Deficiencies / Proficiencies	Histidine auxotrophic
3.2.3	Metabolic activation system	S9 from liver of rats (treated with phenobarbital and beta-naphthoflavone) and co-factors
3.2.4	Positive control	see Table A6_6_1-1
3.3	**Application of test substance**	
3.3.1	Concentrations	Original test (standard plate incorporation method): 0, 15.8, 50.0, 158, 500 and 1580 µg/plate; Confirmatory test (liquid preincubation assay): 0, 10, 31.6, 100, 316 1000 µg/plate
3.3.2	Vehicle	DMSO
3.3.3	Way of application	Plate incorporation + pre-incubation
3.4	**Examinations**	See tables in appendix for examinations and results.

Section A6.6.1 Genotoxicity in vitro

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

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No, see Table A6_6_1-2
4.1.2	with metabolic activation	No, see Table A6_6_1-2
4.2	**Cytotoxicity**	The test material did not induce growth inhibiting effects at the concentrations tested in the original experiment, but slight reduction in background growth was observed occasionally in the confirmatory experiment (preincubation assay)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The mutagenic potential of fenoxycarb was tested in the Salmonella/Mammalian Microsome Reverse Mutation Assay.

The metabolic activation mixture contained S9 from liver of rats (treated with phenobarbital and beta-naphthoflavone) and co-factors. The toxicity of the test material was determined in a preliminary toxicity assay with strain TA 100. The concentration of 1580 µg/plate produced a milky suspension in the aqueous medium and small droplets remained in the soft agar. It was selected as highest concentration in the standard plate incorporation assay. 1000 µg/plate was used as highest concentration in the preincubation assay. The mutagenicity assays were performed with the following concentrations: Original test (standard plate incorporation method): 0, 15.8, 50.0, 158, 500 and 1580 µg/plate; confirmatory test (liquid preincubation assay): 0, 10, 31.6, 100, 316 1000 µg/plate. Positive controls were included to demonstrate the sensitivity of the strains and the activation mixture.

Autoclaved tubes containing 2 mL of 0.6% agar medium were supplemented with 0.2 mL histidine/biotin, 0.1 mL test compound solution at different concentrations or solvent or positive control, 0.1 mL of overnight culture of the *Salmonella* strains and 0.5 mL S9 mixture or sodium phosphate buffered saline. The contents of the tubes were mixed and poured immediately onto Vogel-Bonner minimal agar plates. After preparation, the plates (4 plates per concentration or negative control, 2 plates per positive control) were incubated for 2 days, upside down, at 37°C. Thereafter, they were evaluated by counting the number of colonies. Representative plates were examined microscopically for micro colony growth and the absence of a confluent lawn of bacteria. Inhibition of growth was attributed to toxic effects of the substance. A reproducible concentration-related increase in the numbers of revertants by a factor of 2 for strains TA 1535, TA 1537, TA 1538 and TA 98 or by a factor of 1.5 for strains TA 97, TA 100 and TA 102 was considered indicative of a positive result.

Section A6.6.1		Genotoxicity in vitro
Annex Point IIA VI.6.6.1		6.6.1 Mutagenicity testing in bacteria – Salmonella/microsome test
5.2	**Results and discussion**	In the original and confirmatory experiments performed without and with metabolic activation mixture, there was no increased incidence of back mutations, indicative of a mutagenic response in any strain. The test material did not induce growth inhibiting effects at the concentrations tested in the original experiment, but slight reduction in background growth was observed occasionally in the confirmatory experiment (preincubation assay).
5.3	**Conclusion**	**Based on the results of this study and on standard evaluation criteria, it is concluded that fenoxycarb did not lead to an increase in the incidence of mutants in the *S. typhimurium* strains TA 1535, TA 1537, TA 1538, TA 97, TA 98, TA 100 and TA 102. Fenoxycarb was devoid of any mutagenic activity in this test system.**
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.6.1 Genotoxicity in vitro

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

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/04
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.1 Genotoxicity in vitro

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

Table A6_6_1-1: Positive controls to demonstrate the specificity of the Salmonella typhimurium strains

:			
Strain	***Mutagen***	***Concentrations***	***Metabolic activation***
TA 1535, TA 100	Sodium azide	1.0 µg/plate	no
TA 1537, TA 97	ICR 191	1.0 µg/plate	no
TA 102	Mitomycin-C (MMC)	0.4 µg/plate	no
TA 1538, TA 98	2-AAF	4.0 µg/plate	no/yes
Positive controls to demonstrate the activity of the S9 mix:			
Strain	*Mutagen*	*Concentrations*	*Metabolic activation*
All strains	2-Aminoanthracene	4.0 µg/plate	no/yes

Table A6_6_1-2: Gene mutation assay with fenoxycarb in *S. typhimurium* strains - Number of revertant colonies (mean of 4 or 2 plates)

Original experiment (standard plate incorporation assay)														
Strain	**TA 1535**		**TA 1537**		**TA 1538**		**TA 97**		**TA 98**		**TA 100**		**TA 102**	
Metabolisation	-	+	-	+	-	+	-	+	-	+	-	+	-	+
Solvent control	11	12	13	13	8	22	150	178	23	29	96	95	295	283
Fenoxycarb														
15.8 µg/plate	10	7	14	13	10	22	156	180	25	33	88	103	288	298
50.0 µg/plate	13	8	10	13	12	21	167	166	33	29	81	100	296	273
158 µg/plate	15	7	14	9	14	24	160	178	29	26	106	95	255	292
500 µg/plate	9	8	11	8	17	28	151	165	24	23	102	92	166	236
1580 µg/plate	10	12	8	10	13	17	153	181	32	26	97	87	114	160
Positive control														
Sodium azide	408										405			
ICR 191			616				1326							
MMC													918	
2-AAF					10	361			21	152				
2-Aminoanthr.	6	591	11	517	17	2417	173	1098	48	1797	105	1882	210	894
Confirmatory experiment (liquid preincubation assay)														
Strain	**TA 1535**		**TA 1537**		**TA 1538**		**TA 97**		**TA 98**		**TA 100**		**TA 102**	
Metabolisation	-	+	-	+	-	+	-	+	-	+	-	+	-	+
Solvent control	6	10	12	11	19	24	167	214	20	26	106	105	179	248
Fenoxycarb														
10.0 µg/plate	9	10	14	12	13	26	174	203	21	25	116	106	196	265
31.6 µg/plate	8	10	12	14	16	24	165	226	19	28	116	112	177	247
100 µg/plate	10	8	6[t]	13	6[t]	25	165	221	14	26	54[t]	106	163	239
316 µg/plate	10	9	2[t]	12	5[t]	29	155	221	13[t]	23	40[t]	105	108	137
1000 µg/plate	9	8	2[t]	7	4[t]	10[t]	160	233	13[t]	20	42[t]	81	111	118
Positive control														
Sodium azide	266										642			
ICR 191			2087				2620							
MMC													1616	
2-AAF					17	218			20	239				
2-Aminoanthr.	10	73	13	237	20	1790	217	2031	25	2407	120	2481	118	789

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2 6.6.2 *In-vitro* mammalian chromosome aberration test in CHO cells

Official use only

		1 REFERENCE
1.1	**Reference**	Ogorek B (1998) Cytogenetic test on Chinese hamster cells in vitro. CGA 114597 tech. Genetic Toxicology, Novartis Crop Protection AG, Basel, Switzerland, Report No. 972169, 18 June 1998 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	OECD 473 (1983), 92/69/EEC B.10, EPA OPPTS 870.5375 (1998)
2.2	**GLP**	Yes
2.3	**Deviations**	Deviations to 2000/32/EC B.10 (2000): none
		3 MATERIALS AND METHODS
3.1	**Test material**	Fenoxycarb (CGA 114597 tech.
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	Formulations analysis indicated that the achieved concentration was within acceptable limits (±20% of intended concentration), confirming a sufficient stability of the test material in the vehicle used.
3.2	**Study Type**	*In-vitro* mammalian chromosome aberration test
3.2.1	Organism/cell type	Chinese hamster ovary (CHO)
3.2.2	Metabolic activation system	Rat liver S9
3.2.3	Positive control	–S9: Mitomycin C (0.2 µg/mL) +S9: Cyclophosphamide (20.0 µg/mL)
3.3	**Application of test substance**	
3.3.1	Concentrations	–S9: 6.3, 9.4, 12.5, 18.8, 25.0 µg/mL +S9: 9.8, 19.5, 30.0, 39.1, 40.0, 60.0 µg/mL
3.3.2	Way of application	Dissolved in DMSO
3.3.3	Exposure times	+S9: 3 h –S9: 21 and 45 h
3.3.4	Harvest times	21 h after initiation of exposure (45 h in a confirmatory experiment –S9)
3.4	**Examinations**	
3.4.1	Number of cells evaluated	Mitotic index: at least 2000 cells from each slide. Whenever possible Chromosomal aberrations: 100 metaphases per replicate culture (50 in positive controls)

Section A6.6.2	Genotoxicity in vitro
Annex Point IIA VI.6.6.2	6.6.2 *In-vitro* mammalian chromosome aberration test in CHO cells

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No
4.1.2	with metabolic activation	No
4.2	**Cytotoxicity**	In the original experiment, distinct cytotoxicity was observed at the concentrations of 50.0 µg/mL and above. In the confirmatory study without metabolic activation, marked cytotoxicity was observed at the concentrations of 25 µg/mL and above. In the part with metabolic activation, cytotoxicity occurred at 60 and 80 µg/mL.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The effect of fenoxycarb on the induction of chromosomal aberrations and in cultured CHO cells was studied.

Test article solutions were prepared by dissolving fenoxycarb in dimethyl sulfoxide (DMSO). 125 µg/mL was chosen as the maximum concentration. It resulted in a tolerable homogenous turbidity when added to the culture medium. Lower concentrations were prepared by serial dilution of the stock solution with DMSO.

Chinese hamster ovary cells (ATCC CCL61) were incubated *in situ* on glass slides in culture dishes (Quadriperm) with several concentrations of the test article. Mitomycin C (0.2 µg/mL), a mutagen not requiring metabolic activation, and cyclophosphamide (20.0 µg/mL), which requires metabolic activation, were used as positive controls. Two hours prior to harvesting, the cultures were treated with 0.4 µg/mL colcemid to arrest cells in metaphase. The experiments were terminated by hypotonic treatment of the cultures. Thereafter the cells were fixed, air dried and stained. A cytotoxicity test was performed as an integral part of the mutagenicity test. The percentage of mitotic suppression was determined by evaluating at least 2000 cells from each slide. Whenever possible two hundred well spread metaphase figures with 19 to 21 centromeres from two cultures (100 metaphases per replicate culture) in the vehicle control and in the treated groups were scored for chromosomal aberrations. At least fifty metaphases were scored in the positive controls (25 per replicate culture). The slides were examined for specific and unspecific structural aberrations. The occurrence of polyploid metaphases was registered in addition.

5.2 Results and discussion

The results of the cytotoxicity test are given in Table A6_6-2.1. In the original experiment, distinct cytotoxicity was observed at the concentrations of 50.0 µg/mL and above. In the confirmatory study without metabolic activation, marked cytotoxicity was observed at the concentrations of 25 µg/mL and above. In the part with metabolic activation, cytotoxicity occurred at 60 and 80 µg/mL. The concentrations with frame were selected for chromosome analysis.

In the mutagenicity experiments performed without and with metabolic activation at all harvest times no statistically significant increase in the number of metaphases with specific chromosomal aberrations was detected at any concentration tested. The number of specific and unspecific chromosomal aberrations was within the historical control range and did not fulfil the criteria for a positive response. The results

Section A6.6.2		Genotoxicity in vitro
Annex Point IIA VI.6.6.2		6.6.2 *In-vitro* mammalian chromosome aberration test in CHO cells
		are listed in Table A6_6-2.2. Treatment of CHO cells with the positive control compounds mitomycin-C and cyclophosphamide resulted in a high incidence of specific chromosomal aberrations, demonstrating the sensitivity of the test system.
5.3	**Conclusion**	**Based on the results of this study it is concluded that fenoxycarb has no clastogenic activity.**
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2 6.6.2 *In-vitro* mammalian chromosome aberration test in CHO cells

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/07
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.2 Genotoxicity in vitro

Annex Point IIA VI.6.6.2 6.6.2 *In-vitro* mammalian chromosome aberration test in CHO cells

Table A6_6-2.1: Mitotic Index (% of control) of CHO cells treated with fenoxycarb

	Original study			Confirmatory study			
Experiment	**1**	**2**	**Experiment**	**1**	**2**	**3**	**4**
Metabolic activation	**-**	**+**	**Metabolic activation**	**-**	**+**	**-**	**+**
Treatment (h)	**21**	**3**	**Treatment (h)**	**21**	**3**	**45**	**3**
Recovery (h)	**0**	**18**	**Recovery (h)**	**0**	**18**	**0**	**42**
Fenoxycarb			**Fenoxycarb**				
0.8 µg/mL	a	--	9.4 µg/mL	99.0	--	73.7	--
1.6 µg/mL	a	--	10.0 µg/mL	--	a		a
3.1 µg/mL	109.52	--	12.5 µg/mL	72.1	--	37.2	--
6.3 µg/mL	96.03	--	15.0 µg/mL	--	a	--	a
9.8 µg/mL	--	65.78	18.8 µg/mL	76.8	--	35.8	--
12.5 µg/mL	89.68	--	20.0 µg/mL	--	84.7		105.6
19.5 µg/mL	--	49.78	25.0 µg/mL	25.3	--	7.4	--
25.0 µg/mL	50.79	--	30.0 µg/mL	--	86.4	--	107.5
39.1 µg/mL	--	93.78	37.5 µg/mL	8.4	--	8.1	--
50.0 µg/mL	0.79	--	40.0 µg/mL	--	77.0	--	97.7
78.1 µg/mL	--	10.67	50.0 µg/mL	b	--	b	--
100.0 µg/mL	b	--	60.0 µg/mL	--	33.2	--	37.9
156.3 µg/mL	--	b	80.0 µg/mL	--	9.4	--	b

2000 cells were scored
concentrations with frame (☐) were used for chromosome analysis
-- no cultures at this concentration
a when three subsequent concentrations with a frequency of 70% mitosis or more in relation to the solvent control are found, the evaluation of the lower concentrations is omitted.
b no cells scored due to toxicity.

Table A6_6-2.2: Percent incidence of specific chromosomal aberrations in CHO cells treated with fenoxycarb

Experiment	Original 1	Confirmatory 1	Confirmatory 3	Experiment	Original 2	Confirmatory 2	Confirmatory 4
	Without metabolic activation				With metabolic activation		
Treatment (h)	21	21	45	Treatment (h)	3	3	3
Recovery (h)	0	0	0	Recovery (h)	18	18	42
Neg. control	2.5	4.0	2.5	Neg. control	2.0	2.5	3.0
Fenoxycarb 6.3 µg/mL	3.5			Fenoxycarb 9.8 µg/mL	2.5		
9.4 µg/mL			3.5	19.5 µg/mL	2.0		
12.5 µg/mL	1.0	4.5	4.0	30.0 µg/mL		4.0	4.0
18.8 µg/mL		3.5	3.5	39.1 µg/mL	3.0		
25.0 µg/mL	3.5	3.5		40.0 µg/mL		4.0	1.0
				60.0 µg/mL		5.5	5.0
Pos. control	74.0*** [a]	68.0*** [a]		Pos. control	72.0*** [b]	56.0*** [b]	

200 cells with well spread metaphase figures were scored, except for positive controls where 50 cells were scored
-- not scored
[a] Mitomycin-C, 0.2 µg/mL
[b] Cyclophosphamide, 20 µg/mL
*** $p \leq 0.001$ (Chi-square test)

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 HGPRT-forward-mutation assay in CHO cells

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1 REFERENCE

1.1	**Reference**	Strobel R (1982), Mutagenicity evaluation of the insect growth regulator Ro 13-5223/000 in Chinese hamster cells in vitro in the absence and presence of a mouse liver homogenate metabolic activation system. F. Hoffmann-La Roche & Co. Ltd., Basel, Switzerland, Report No. B-96728, 11 June 1982 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No guidelines specified but in general accordance with EC Method B.17.
2.2	**GLP**	Yes
2.3	**Deviations**	Deviations from 2000/32/EC B.17: Only three instead of four concentrations were tested. There was only one culture per concentration used. The spacing of concentrations was somewhat too large.

3 MATERIALS AND METHODS

3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	Not reported
3.1.2.2	Stability	Not reported
3.2	**Study Type**	*In-vitro* mammalian cell gene mutation test (HGPRT test)
3.2.1	Organism/cell type	Chinese hamster V79 lung fibroblasts
3.2.2	Metabolic activation system	Rat liver S9 mix
3.2.3	Positive control	–S9: ethylmethanesulphonate (EMS), 200 µg/mL +S9: 2-acet-aminofluorene (2AAF), 200 µg/mL
3.3	**Application of test substance**	
3.3.1	Concentrations	–S9: 0, 1, 5, 25 µg/mL +S9: 0, 25, 50, 100 µg/mL
3.3.2	Way of application	Dissolved in DMSO
3.3.3	Exposure time	–S9: 16 h +S9: 5 h
3.3.4	Other modifications	–

Section A6.6.3		**Genotoxicity in vitro**
Annex Point IIA VI.6.6.3		6.6.3 HGPRT-forward-mutation assay in CHO cells
3.4	**Examinations**	At the end of the expression period the cultures were harvested and from each culture 10^5 cells were plated on 4 dishes and incubated at 37°C in presence of 20 µg/mL 8-azaguanine for the mutant selection (Ag^r cells). After two weeks, the cultures were fixed and stained. Survival of the cells was determined at the beginning as well as at the end of the phenotypic expression phase because of recovering of the cells during the period of time. Clones were scored macroscopically.
		4 RESULTS AND DISCUSSION
4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No, see Table A6_6-3.1
4.1.2	with metabolic activation	No, see Table A6_6-3.2
4.2	**Cytotoxicity**	Cytotoxicity after treatment was observed at 1 µg/mL without and 50 µg/mL with metabolic activation.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Fenoxycarb was tested for the induction of forward mutations in the HPRT locus in Chinese hamster V79 cells. Culture flasks cells were plated with 10^6 cells and incubated in growth medium for 24 hours. Thereafter the cells were treated using Hank's BSS containing the test compound, positive control or solvent only (DMSO) as treatment medium. In the non-activated part of the experiment, the positive control was the ultimate mutagen ethyl methanesulfonate (EMS) at a concentration of 200 µg/mL. In the part with metabolic activation the positive control was the promutagen 2-acet-aminofluorene (2AAF) at a concentration of 200 µg/mL. The exposure period was 5 hours (with metabolic activation) or 16 hours (without metabolic activation). For phenotypic expression, cells were incubated in growth medium for five days and subcultured after 2 to 3 days to keep them in logarithmic phase. At the end of the expression period the cultures were harvested and from each culture 10^5 cells were plated on 4 dishes and incubated at 37°C in presence of 20 µg/mL 8-azaguanine for the mutant selection (Ag^r cells). After two weeks, the cultures were fixed and stained. Survival of the cells was determined at the beginning as well as at the end of the phenotypic expression phase because of recovering of the cells during the period of time. Clones were scored macroscopically.
5.2	**Results and discussion**	Mutagenicity test: In the experiments performed with and without microsomal activation comparison of the number of 8-azaguanine resistant cells (Ag^r cells) revealed no significant deviations between cultures treated with fenoxycarb and negative solvent controls. Cytotoxicity after treatment was observed at 1 µg/mL without and 50 µg/mL with metabolic activation. The positive control substances showed clear mutagenic effects with and without metabolic activation (Table A6_6-3.1, Table A6_6-3.2).
5.3	**Conclusion**	
5.3.1	Reliability	2
5.3.2	Deficiencies	The deviations (point 2.3) are not considered to affect the validity of the study.

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 HGPRT-forward-mutation assay in CHO cells

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/07
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.3 Genotoxicity in vitro

Annex Point IIA VI.6.6.3 6.6.3 HGPRT-forward-mutation assay in CHO cells

Table A6_6-3.1: V 79-HGPRT assay with fenoxycarb: Summary of the results of the mutagenicity experiments without metabolic activation (16 hours treatment)

Original experiment				Confirmatory experiment			
	Cell survival [a]		Ag^r cells [b]		Cell survival [a]		Ag^r cells [b]
	Day 2	Day 7			Day 2	Day 7	
Solvent Control	151.0	118.0	0.5	Solvent Control	182.3	130.5	1.3
Fenoxycarb				**Fenoxycarb**			
1 µg/mL	113.3	128.3	3.3	1 µg/mL	149.5	153.3	1.5
5 µg/mL	112.3	-- *	2.0	5 µg/mL	107.8	151.3	0.5
25 µg/mL	39.0	104.0	2.0	25 µg/mL	50.0	144.8	0.8
Positive control: EMS 200 µg/Ml	77.0	85.5	32.3	Positive control: EMS 200 µg/mL	103.8	94.8	36.3

[a] - 200 cells seeded per dish [b] - 10^5 cells seeded per dish * - no growth, experimental error

Table A6_6-3.2: V79-HGPRT assay with fenoxycarb: Summary of the results of the mutagenicity experiments with metabolic activation (5 hours treatment)

Original experiment				Confirmatory experiment			
	Cell survival [a]		Ag^r cells [b]		Cell survival [a]		Ag^r cells [b]
	Day 2	Day 7			Day 2	Day 7	
Solvent Control	178.8	154.5	0.5	Solvent Control	146.8	161.8	2.8
Fenoxycarb				**Fenoxycarb**			
25 µg/mL	179.0	155.0	1.0	25 µg/mL	140.0	136.3	2.5
50 µg/mL	86.3	187.3	2.0	50 µg/mL	110.0	128.0	1.0
100 µg/mL	8.8	160.8	0	100 µg/mL	26.5	134.8	0.5
Positive control: 2AAF 200 µg/mL	89.3	114.0	6.5	Positive control: 2AAF 200 µg/mL	109.3	124.3	5.5

[a] - 200 cells seeded per dish [b] - 10^5 cells seeded per dish

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.5 *In vivo* micronucleus test in murine bone marrow

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1996) Micronucleus test, mouse, *in vivo* study. CGA 114597 tech. - (Fenoxycarb). [redacted], Report No. 962052, 29 November 1996 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Syngenta	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes 2000/32/EEC B.12 (2000);OECD 474 (1997), OPPTS 870.5395 (1998)	
2.2	**GLP**	Yes	
2.3	**Deviations**	Deviations from 2000/32/EC B.12: none.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Fenoxycarb (CGA 114597 tech.)	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Purity	[redacted]	
3.1.2.2	Stability	The analytical values (HPLC/UV) were in agreement with the nominal concentrations, thus indicating sufficient stability of the test substance in the vehicle used.	
3.1.2.3	Maximum tolerable dose	> 5000 mg/kg bw, based on acute oral toxicity study	
3.2	**Test Animals**		
3.2.1	Species	Mouse	
3.2.2	Strain	Tif:MAGf (SPF)	
3.2.3	Sex	♂ + ♀	
3.2.4	Number of animals per group	Control + high dose: 8 /sex/group Low dose + medium dose + pos. control: 5 /sex/group	X
3.2.5	Control animals	Yes	
3.3	**Administration/ Exposure**		
3.3.1	Number of applications	1	
3.3.2	Postexposure period	16, 24, 48 h (16, 48 h: control and high dose only)	
		Oral	
3.3.3	Type	Gavage	
3.3.4	Concentration	1250, 2500, 5000 mg/kg bw	

Section A6.6.4		Genotoxicity in vivo	
Annex Point IIA VI.6.6.4		6.6.5 *In vivo* micronucleus test in murine bone marrow	
3.3.5	Vehicle	Arachis oil	
3.3.6	Total volume applied	10 mL/kg bw	
3.3.7	Substance used as positive control	Cyclophosphamide (CPA): 64 mg/kg bw	
3.3.8	Controls	Vehicle	
3.4	**Examinations**		
3.4.1	Clinical signs	Yes	
3.4.2	Tissue	Bone marrow	
	Number of animals:	All animals	
	Number of cells:	2000/animal	
	Time points:	16, 24, 48 h after treatment (16, 48 h: control and high dose only)	
	Type of cells	Erythrocytes	
	Parameters:	Incidence of micronuclei, ratio of polychromatic to normochromatic erythrocytes	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	The animals treated at all doses of fenoxycarb showed no symptoms of toxicity.	
4.2	**Genotoxicity**	None. See Table 6_6-4.1	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In the micronucleus test, a high dose (5000 mg/kg bw) and a negative control were administered once to 3 groups of 8 male and 8 female Tif:MAGf (SPF) mice (oral, gavage, 10 mL/kg). Each group of animals was killed after 16, 24, or 48 hours. To three further groups of 5 male and 5 female mice, a low (1250 mg/kg) or an intermediate dose (2500 mg/kg) of fenoxycarb or the positive control substance (cyclophosphamide) were given. These groups were killed 24 hours after administration. The animals were killed by CO_2 gas. Bone marrow was harvested and smears prepared on microscope slides. Prior to analysis the slides were coded. The slides of five animals/sex/dose, showing good differentiation between mature and polychromatic erythrocytes (PCE), were scored. In order to detect any disturbance of erythropoiesis, the ratio of polychromatic to normochromatic erythrocytes was determined and 2000 polychromatic erythrocytes were scored for micronuclei from each animal.	X
5.2	**Results and discussion**	At all sampling times (16, 24, and 48 hours), no significantly increased incidence of micronucleated polychromatic erythrocytes were noted after treatment of the animals with the various doses of fenoxycarb (Table A6_6-4.1). In contrast, a significant increase in the number of micronucleated polychromatic erythrocytes was noted in the positive control group. The ratio of polychromatic to normochromatic erythrocytes after treatment with fenoxycarb indicated no cytotoxic effects on blood forming cells. The animals treated at all doses of fenoxycarb showed no symptoms of	

Section A6.6.4		**Genotoxicity in vivo**
Annex Point IIA VI.6.6.4		6.6.5 *In vivo* micronucleus test in murine bone marrow
		toxicity.
5.3	**Conclusion**	**Under the conditions of this assay, fenoxycarb did not show any clastogenic or aneugenic activity in this test system *in vivo*.**
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.5 *In vivo* micronucleus test in murine bone marrow

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/07
Materials and Methods	[redacted]
Results and discussion	[redacted]
	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.5 *In vivo* micronucleus test in murine bone marrow

Table A6_6-4.1: Mouse micronucleus test on bone marrow cells: Percentage of micronucleated PCE

		Time to sacrifice		
Test article and concentration	**Sex**	**16 hours**	**24 hours**	**48 hours**
Negative control	males	0.09	0.05	0.05
Vehicle (arachis oil)	females	0.07	0.07	0.06
	mean	**0.08**	**0.06**	**0.06**
Fenoxycarb 1250 mg/kg bw	males		0.09	
	females		0.06	
	mean		**0.08**	
Fenoxycarb 2500 mg/kg bw	males		0.09	
	females		0.07	
	mean		**0.08**	
Fenoxycarb 5000 mg/kg bw	males	0.08	0.09	0.09
	females	0.06	0.03	0.09
	mean	**0.07**	**0.06**	**0.09**
Positive control	males		2.07*	
Cyclophosphamide 64 mg/kg bw	females		1.62*	
	mean		**1.85***	

* $p \leq 0.05$ (Chi-Square Test)

Section A6.6.4 Genotoxicity in vivo

Annex Point IIA VI.6.6.4 6.6.5 *In vivo* micronucleus test in murine bone marrow

Organ	Dose group	Tail length [µm, mean* ± SD]		
		3 h	8 h	24 h
Liver	Neg. control	34.17 ± 3.24	34.58 ± 2.33	34.77 ± 1.80
	OPP			
	250 mg/kg	40.02 ± 0.84	32.63 ± 3.56	35.30 ± 4.51
	2000 mg/kg	35.93 ± 3.70	31.98 ± 2.14	36.80 ± 3.33
	EMS 400 mg/kg	48.60 ± 4.58	48.72 ± 3.57	45.30 ± 1.87
Kidney	Neg. control	23.23 ± 1.99	23.48 ± 0.87	20.56 ± 0.45
	OPP			
	250 mg/kg	20.93 ± 1.11	21.76 ± 1.02	21.65 ± 2.57
	2000 mg/kg	19.71 ± 1.00	21.54 ± 1.35	23.27 ± 3.37
	EMS 400 mg/kg	34.60 ± 2.25	33.90 ± 2.11	32.75 ± 4.05

* 100 cells evaluated

Table A6_6_4-2. Table for Cytogenetic In-Vivo-Test: Cytotoxicity

State mean ± standard deviation *state individual numbers for critical findings*		**negative control**	**250**	**2000**	**positive control**
Number of cells evaluated		**100**			
Cytotoxicity: Liver cells					
Sacrifice Time: 3h	**Absolute Viability[a]**	**79.0 ± 8.04**	**77.6 ± 5.04**	**76.2 ± 5.06**	**74.9 ± 3.16**
	Relative Viability[b] [%]	100	**98.1**	**96.4**	**94.8**
Sacrifice Time: 8h	**Absolute Viability[a]**	**81.0 ± 5.48**	**77.0 ± 2.27**	**73.5 ± 1.30**	**78.1 ± 4.68**
	Relative Viability[b] [%]	100	**95.1**	**90.8**	**96.4**
Sacrifice Time: 24h	**Absolute Viability[a]**	**82.9±3.61**	**77.7 ± 4.96**	**74.2 ± 1.72**	**72.3 ± 9.77**
	Relative Viability[b] [%]	100	**93.7**	**89.5**	**87.2**
Cytotoxicity: Kidney cells					
Sacrifice Time: 3h	**Absolute Viability[a]**	**92.3 ± 1.56**	**91.6 ± 2.758**	**86.2 ± 6.37**	**89.9 ± 2.53**
	Relative Viability[b] [%]	100	**99.2**	**93.4**	**97.4**
Sacrifice Time: 8h	**Absolute Viability[a]**	**92.7 ± 2.86**	**91.3 ± 2.11**	**90.1 ± 2.69**	**93.9 ± 2.31**
	Relative Viability[b] [%]	100	**98.5**	**97.2**	**101.3**
Sacrifice Time: 24h	**Absolute Viability[a]**	**92.5 ± 1.63**	**92.5 ± 1.73**	**90.0 ± 1.87**	**93.3 ± 2 43**
	Relative Viability[b] [%]	100	100	**97.3**	**100.9**

[a] = mean viability of cell preparation per dose group after perfusion
[b] = relative to negative control animals

Section A6.7 Carcinogenicity

Annex Point IIA VI.6.7 6.7 Carcinogenicity study in the mouse

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1 REFERENCE

1.1	**Reference**	[redacted] (1995), 18-Month Oncogenicity Study In Mice. CGA 114597 tech. [redacted], Report No. 922117, 9 January 1995 (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes 87/302/EEC B.32 (1988) ≅ OECD 451 (1981) ≅ FIFRA § 83-2
2.2	**GLP**	Yes
2.3	**Deviations**	A differential blood count, together with measurement of numerous other haematological parameters, was performed on blood samples collected from 10 male and 10 female mice per group at 12 and 18 months. The 10 animals per group designated for haematology were not examined histopathologically.

3 MATERIALS AND METHODS

3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	Analysis of the diets showed that the achieved concentrations of fenoxycarb technical in the diet were satisfactory with concentrations of 81-106% of the nominal values. The results indicated that fenoxycarb is stable in the diet for at least 5 weeks at room temperature and that the prepared diets were homogenous.
3.2	**Test Animals**	
3.2.1	Species	Mouse
3.2.2	Strain	Tif:MAGf (SPF)
3.2.3	Sex	♂ + ♀
3.2.4	Initial bodyweights	29.6–30.4 g (♂); 24.0–24.5 g (♀)
3.2.5	Number of animals per group	60 per sex
3.2.6	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	78 weeks
3.3.2	Interim sacrifice(s)	None

Section A6.7		Carcinogenicity	
Annex Point IIA VI.6.7		6.7 Carcinogenicity study in the mouse	
3.3.3	Final sacrifice	After 78 weeks	
3.3.4	Frequency of exposure	*ad libitum*	
3.3.5	Postexposure period	None	
		Oral	
3.3.6	Type	In food	
3.3.7	Concentration	nominal conc. in food actual dose in food	10, 50, 500, 2000 ppm 1.1, 5.9, 60.8, 247 mg/kg bw/day (males) 1.0, 5.5, 56.5, 224 mg/kg bw/day (females)
3.3.8	Controls	Plain diet	
3.4	**Examinations**	Clinical observations, bodyweights, food consumption and haematology parameters were measured throughout the study. At the end of the scheduled period the animals were killed and subjected to a full examination *post mortem*. Terminal blood and bone marrow samples were taken, selected organs were weighed and specified tissues were taken for subsequent histopathology examination.	
3.5	**Further remarks**	–	

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	The clinical signs observed during the study were typical for mice of this colony on long-term feeding studies. The incidences recorded showed no treatment-related influences. An exceptionally low mortality was recorded for control females (4 out of 60) whereas for treated females the usual level of mortality was recorded for all groups. As mortality among treated male groups was similar to that of the male controls it was concluded that treatment had not influenced the survival of the mice.
4.2	**Body weight**	Bodyweight gains for the treated male groups were similar to those of the control group throughout the study (see Table A6_7-1). Mean bodyweights for females given 500 and 2000 ppm were reduced compared with controls from about week 18 and by the end of the study were 9% and 13% lower than the control value, respectively.
4.3	**Food consumption**	Higher mean food consumption values were recorded for males of groups fed 500 and 2000 ppm during the last 6 months of the study. Food consumption by females was not affected (see Table A6_7-2).
4.4	**Haematology**	There were no treatment-related haematological changes.
4.5	**Organ Weights**	The liver/bodyweight ratio was increased for males and females given 500 and 2000 ppm. The kidney/bodyweight ratio was increased for females at 2000ppm and the adrenal/bodyweight ratio was increased for males at 2000 ppm (see Table A6_7-3).

Section A6.7		Carcinogenicity
Annex Point IIA VI.6.7		6.7 Carcinogenicity study in the mouse
4.6	Pathology	Gross necropsy revealed an increased incidence of nodules/masses in the lungs of males at 500 and 2000 ppm and females at 2000 ppm (see Table A6_7-4). Enlarged livers were present in both sexes at 2000 ppm with an increased incidence of hepatic masses in males at 500 and 2000 ppm. Enlarged spleens were seen in males at all dose levels in an apparently dose-related manner. The incidence of macroscopically enlarged ovaries was decreased in females at 2000 ppm, which microscopically showed an increased incidence of ovarian atrophy.
4.7	Histopathology	**Non-neoplastic lesions:** Male and female animals at 2000 ppm showed a slightly increased incidence of hepatic foci of cellular change (see Table A6_7-5). In males at 500 and 2000 ppm the incidence of hepatic fatty change was slightly decreased. The incidence of naturally occurring adrenal cortical atrophy was decreased in males at 2000 ppm and as this was associated with an increase in mean adrenal weight, it probably represented a mild functional change related to an unspecific stress. In treated females a variety of non-neoplastic changes (including decreased incidence of fatty atrophy of bone marrow and hepatic fatty change at 500 and 2000 ppm, and of pancreatic fatty atrophy at 2000 ppm as well as increased incidence of ovarian atrophy at 2000 ppm) reflected a suppression of bodyweight gain. **Neoplastic lesions:** The incidence of pulmonary neoplasia (adenomas and carcinomas, considered to originate from the "bronchiolo-alveolar" parenchyma) was increased in both sexes at 500 and 2000 ppm and was considered to be treatment-related (see Table A6_7-6). The incidence of hepatocellular neoplasia was increased in males at 500 and 2000 ppm. These were classified as benign hepatoma or hepatocellular carcinoma. The occurrence of a few hepatoblastomas in a few mice across the groups was considered not to represent a treatment-related effect. The incidence of benign hepatoma was within the historical control range. The tumour incidence (hepatocellular neoplasia) in the males fed 50 ppm was considered incidental and unrelated to treatment.
4.8	Other	–

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	Materials and methods	Groups of 60 male and 60 female Tif:MAGf (SPF), albino mice were fed diets containing 0 (control), 10, 50, 500 or 2000 ppm fenoxycarb for 18 months. Of these, 10 male and 10 female mice were assigned for evaluation of haematological parameters and the remaining animals were assigned for evaluation of the carcinogenic potential and survival analysis. Samples from all dietary levels (including controls) were taken at intervals throughout the study and analysed for achieved concentration. Stability for a period of up to 5 weeks was determined in a concurrent 3 month study in rats (using an identical procedure and the same batch of fenoxycarb) and homogeneity at all doses was measured. Fresh diet was prepared at 4-week intervals. Clinical observations, bodyweights, food consumption and haematology parameters were measured throughout the study. At the end of the scheduled period the animals were killed and subjected to a full examination *post mortem*. Terminal blood and bone marrow samples were taken, selected organs were weighed and specified tissues were

Section A6.7		Carcinogenicity		
Annex Point IIA VI.6.7		6.7 Carcinogenicity study in the mouse		
		taken for subsequent histopathology examination.		
5.2	**Results and discussion**	Dietary administration of fenoxycarb up to dose levels of 2000 ppm was tolerated by the mice without overt clinical signs or effects on survival. However, the dietary level of 2000 ppm was considered to represent the maximum tolerated dose, producing mean bodyweights 13% lower in females by the end of the treatment period. Males treated at this dietary level were not similarly affected.		
		Dietary levels of 500 and 2000 ppm resulted in increased incidences of pulmonary tumours in males and females and hepatic tumours in males.		X
5.3	**Conclusion**			
5.3.1	LO(A)EL	Non-neoplastic LOAEL: Neoplastic LOAEL:	60.8 / 56.5 mg/kg bw/day (♂ / ♀) 60.8 / 56.5 mg/kg bw/day (♂ / ♀)	
5.3.2	NO(A)EL	Non-neoplastic NOAEL: Neoplastic NOAEL:	5.9 / 5.5 mg/kg bw/day (♂ / ♀) 5.9 / 5.5 mg/kg bw/day (♂ / ♀)	
5.3.3	Other	–		
5.3.4	Reliability	1		
5.3.5	Deficiencies	The deviations (point 2.3) do not affect the overall validity of the study.		

Section A6.7 Carcinogenicity

Annex Point IIA VI.6.7 6.7 Carcinogenicity study in the mouse

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/04/04
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_7-1: Intergroup comparison of bodyweights - selected timepoints (g)

	Dietary concentration of fenoxycarb (ppm)									
	Males					Females				
Week	0	10	50	500	2000	0	10	50	500	2000
1	29.63	29.89	30.16	30.12	30.43	24.51	24.00	24.17	24.17	24.27
18	47.82	47.97	48.33	48.84	48.28	41.19	40.83	41.58	40.11	39.39
26	50.44	50.44	51.06	51.26	50.50	45.73	45.21	46.18	44.09	42.95
50	52.94	53.08	54.20	53.88	53.50	51.97	50.74	52.64	49.12	48.11*
62	52.24	53.40	53.86	53.61	52.50	52.95	51.88	51.57	49.84	47.31$*
78	52.70	51.79	53.03	52.91	51.05	53.47	50.18	49.26*	48.54$*	46.72$*

$ Statistically significant difference from control group mean, p<0.01 (Lepage test)
* Statistically significant difference from control group mean, p<0.01 (Jonckheere test)

Table A6_7-2: Intergroup comparison of food consumption - selected timepoints (g/animal/week)

	Dietary concentration of fenoxycarb (ppm)									
	Males					Females				
Week	0	10	50	500	2000	0	10	50	500	2000
1	22.52	23.16	23.16	22.28	25.06	23.73	24.22	24.32	23.07	24.61
18	41.89	40.81	41.51	43.36	40.25	31.85	34.24	32.69	33.46	31.63
26	40.19	40.19	41.43	41.88	40.83	31.31	31.94	31.25	33.31	29.96
50	43.05	43.62	42.28	43.27	43.66	35.30	35.48	33.61	34.47	34.28
62	37.60	38.54	39.56	40.76$*	42.33$*	31.55	32.48	32.20	33.95	33.41
78	38.75	38.43	39.82	43.16$*	44.72$*	32.87	34.10	32.01	36.50	35.53

$ Statistically significant difference from control group mean, p<0.01 (Lepage test)
* Statistically significant difference from control group mean, p<0.01 (Jonckheere test)

Table A6_7-3: Intergroup comparison of selected organ weight/bodyweight ratios

	Dietary concentration of fenoxycarb (ppm)									
	Males					Females				
Organ	0	10	50	500	2000	0	10	50	500	2000
Liver	59.67	56.98	57.35	64.80*	90.77$*	50.24	46.75	49.03	53.06*	70.70$*
Kidney (both)	15.85	15.70	15.93	16.10	16.35	10.09	10.15	10.59	10.71	12.16$*
Adrenal (both)	0.135	0.137	0.144	0.149	0.161$*	0.336	0.327	0.357	0.345	0.353

$ Statistically significant difference from control group mean, p<0.01 (Lepage test)
* Statistically significant difference from control group mean, p<0.01 (Jonckheere test)

Table A6_7-4: Intergroup comparison of incidence of selected macroscopic findings

		Dietary concentration of fenoxycarb (ppm)									
		Males					Females				
Findings		**0**	**10**	**50**	**500**	**2000**	**0**	**10**	**50**	**500**	**2000**
Lung	nodules	7	8	3	12	17	1	4	6	4	8
	masses	0	3	3	4	4	1	3	1	2	4
Liver	enlarged	2	1	4	6	16	4	3	6	5	14
	masses	18	13	20	26	38	4	2	6	5	5
Spleen	enlarged	8	12	19	24	26	34	31	29	33	32
Ovaries	enlarged	-	-	-	-	-	7	6	3	5	1

Table A6_7-5: Intergroup comparison of incidence of selected non-neoplastic microscopic findings

		Dietary concentration of fenoxycarb (ppm)									
		Males					Females				
Findings		**0**	**10**	**50**	**500**	**2000**	**0**	**10**	**50**	**500**	**2000**
Number of tissues examined		50	50	50	50	50	50	50	49	50	50
Liver	**Focus of cellular change**	5	1	7	2	9	2	4	3	3	7
	Fatty change	39	33	39	26	30	42	34	28	15	8
Adrenal	**Cortical atrophy**	33	25	19	26	15	0	0	0	0	0
Bone Marrow	**Fatty atrophy**	0	0	0	0	0	36	30	26	23	16
Pancreas	**Fatty atrophy**	0	0	1	0	0	6	3	2	2	0
Ovary	**Atrophy**	-	-	-	-	-	19	18	22	26	31

Table A6_7-6: Intergroup comparison of incidence of selected neoplastic microscopic findings

		Dietary concentration of fenoxycarb (ppm)									
		Males					Females				
Findings		**0**	**10**	**50**	**500**	**2000**	**0**	**10**	**50**	**500**	**2000**
Number of tissues examined		50	50	50	50	50	50	50	49	50	50
Lung	**Adenoma**	8	8	4	14	16	1	5	4	6	11
	Carcinoma	1	3	1	10	10	2	2	2	3	9
	adenoma or carcinoma	9	11	5	21	22	3	7	6	9	20
Liver	**benign hepatoma**	11	12	9	13	16	2	2	3	1	3
	hepatocellular carcinoma	8	4	12	17	21	1	0	2	0	2
	benign hepatoma or hepatocellular carcinoma	16	13	17	25	29	3	2	5	1	4

CA-Table 1: Intergroup comparison of incidence of neoplastic microscopic findings in males

		Dietary concentration of fenoxycarb (ppm)					
Findings		**hist. contr.**	**0**	**10**	**50**	**500**	**2000**
Number of tissues examined		**300**	50	50	50	50	50
Lung	**Adenoma**	57 19 %	8 16 %	8 16 %	4 8 %	14 28 %	16 32 %
	Carcinoma	17 6 %	1 2 %	3 6 %	1 2 %	10 20 %**	10 20 %**
	adenoma or carcinoma	72 24 %	9 18 %	11 22 %	5 10 %	21 42 %**	22 44 %**
Liver	**benign hepatoma**	83 28 %	11 22 %	12 24 %	9 18 %	13 26 %	16 32 %
	hepatocellular carcinoma	25 8 %	8 16 %	4 8 %	12 24 %	17 34 %*	21 42 %**
	benign hepatoma or hepatocellular carcinoma	91 30 %	16 32 %	13 26 %	17 34 %	25 50 %**	29 58 %**

p<0.05, ** p < 0.01

CA-Table 2: Intergroup comparison of incidence of neoplastic microscopic findings in females

		Dietary concentration of fenoxycarb (ppm)					
Findings		**hist. contr.**	**0**	**10**	**50**	**500**	**2000**
Number of tissues examined		300	50	50	49	50	50
Lung	**Adenoma**	21 7 %	1 2 %	5 10 %	4 8 %	6 12 %	11 22 %**
	Carcinoma	13 4 %	2 4 %	2 4 %	2 4 %	3 6 %	9 18 %*
	adenoma or carcinoma	33 11 %	3 6 %	7 14 %	6 12 %	9 18 %	20 40 %**

p<0.05, ** p < 0.01

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Developmental toxicity study in rabbits

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1984), Embryotoxicity Study In Rabbits With Oral Administration Of Ro 13-5223/000. Segment II – Teratological Study. [redacted], Report No. B-104700, 13 February 1984. (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Syngenta	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	87/302/EEC B.31 (1988) ≅ OECD 414 (1981) ≅ FIFRA § 83-3 The study was performed prior to the above guideline but has been checked for compliance with the above.	
2.2	**GLP**	Yes	
2.3	**Deviations**	Purity of the test substance was not reported. There was no day 0. The day that mating was observed was designated Day 1 and the animals were dosed on days 7 to 19 rather than 8 to 20. Bodyweights were measured on gestation days 1, 7, 20 and 30. Food consumption was not measured in this study. The sex of the foetuses and individual foetal weights were determined and the mean foetal weight derived but weights per sex were not identified. No historical data has been presented in this report.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Purity	Not reported	
3.1.2.2	Stability	A fresh formulation of the test compound in the vehicle was prepared weekly. High shear mixing was used during formulation and the suspension was kept homogenous during dosing by the use of a magneto stirrer.	X
3.2	**Test Animals**		
3.2.1	Species	Rabbits	
3.2.2	Strain	Swiss hare	
3.2.3	Sex	Females	
3.2.4	Number of animals per group	20	
3.2.5	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	

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3.3.1	Duration of exposure	Day 7-19 post mating	X
3.3.2	Postexposure period	11 days	
		Oral	
3.3.3	Type	Gavage	
3.3.4	Concentration	Initial study: 30, 100 and 300 mg/kg bw/day Supplementary study: 200 mg/kg bw/day	
3.3.5	Vehicle	4% carboxymethylcellulose, 0.9% NaCl, 0.5% benzyl alcohol, 0.4% Tween 80 in H_2O dest.	X
3.3.6	Controls	Vehicle	
3.4	**Examinations**		
3.4.1	Body weight	Yes, does were weighed on days 1, 7, 20 and 30 of gestation	
3.4.2	Food consumption	Not reported	
3.4.3	Clinical signs	Yes, daily	
3.4.4	Examination of uterine content	Yes corpora lutea, implantation sites	
3.4.5	Examination of foetuses	Foetuses were removed, tested for viability over 24 hours and examined for macroscopic, skeletal and soft tissue anomalies.	
3.4.5.1	General	Yes	
3.4.5.2	Skeleton	Yes	
3.4.5.3	Soft tissue	Yes	

4 RESULTS AND DISCUSSION

4.1 Maternal toxic effects

There were no deaths and no treatment-related clinical abnormalities were seen. Females in the 200 and 300 mg/kg/day groups showed moderately reduced bodyweight gain compared with the respective controls during the treatment period, but subsequently, the females in the 300 mg/kg/day group showed a slightly increased bodyweight gain up to the end of the study (see Table A6_8-1.1).

The number of pregnant females, average number of *corpora lutea* and average number of implantation sites were within normal limits for all groups. There were no discernable effects at any dose level on the measured reproductive parameters.

4.2 Teratogenic / embryo toxic effects

In study A, macroscopic examination of the foetuses in the control group showed one foetus with a hypoplastic tail. One litter in the 30 mg/kg/day group had a foetus with a hypoplastic tail and 2 litter mates with missing tails. In the 100 mg/kg/day group, one foetus had open eyes and another had *spina bifida*. At 300 mg/kg/day, there were 2 foetuses with *spin bifida* and hypoplastic tails, one with *spina bifida* alone, one with open eyes, two with hypoplastic tails alone and one foetal resorption with omphalocoele.

In study B, the only malformation observed at macroscopic examination in the 200 mg/kg/day group, was in a foetal resorption showing open eyes and a reduction malformation of the right foreleg. The control group of study B contained malformations analogous in type and incidence to those seen in the 300 mg/kg/day group. These included 2 foetuses with ectopy, one of which had a missing tail, one foetus with an eye open, one foetus with omphalocoele and one foetus with a

hypoplastic tail.

4.3 Other effects –

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Initially, groups of twenty mated, female Swiss hare rabbits were treated orally by gavage with fenoxycarb at doses of 30, 100 and 300 mg/kg/day from days 7 to 19 of gestation (the day of mating was designated day 1 of gestation). A control group received the standard solvent vehicle alone. The rabbits were observed daily for changes in behaviour, general condition and signs of pharmacological action. They were weighed on days 1, 7, 20 and 30 of gestation. All females were sacrificed on day 30 of gestation. Foetuses were removed, tested for viability over 24 hours and examined for macroscopic, skeletal and soft tissue anomalies.

Interpretation of the findings from this principle study was inconclusive and a supplementary study was conducted with increased numbers of females using a dose of 200 mg/kg. The same treatment schedule was used as in the principle study and included a separate control group. The studies are referred to as A and B for the principle and supplementary study, respectively.

5.2 Results and discussion

Maternal findings: There were no deaths and no treatment-related clinical abnormalities were seen. Females in the 200 and 300 mg/kg/day groups showed moderately reduced bodyweight gain compared with the respective controls during the treatment period, but subsequently, the females in the 300 mg/kg/day group showed a slightly increased bodyweight gain up to the end of the study.

The number of pregnant females, average number of *corpora lutea* and average number of implantation sites were within normal limits for all groups. There were no discernable effects at any dose level on the measured reproductive parameters.

Foetal data: There were no discernable effects at any dose level on the measured litter parameters and no effect on survival of the neonates.

In study A, macroscopic examination of the foetuses in the control group showed one foetus with a hypoplastic tail. One litter in the 30 mg/kg/day group had a foetus with a hypoplastic tail and 2 litter mates with missing tails. In the 100 mg/kg/day group, one foetus had open eyes and another had *spina bifida*. At 300 mg/kg/day, there were 2 foetuses with *spin bifida* and hypoplastic tails, one with *spina bifida* alone, one with open eyes, two with hypoplastic tails alone and one foetal resorption with omphalocoele.

In study B, the only malformation observed at macroscopic examination in the 200 mg/kg/day group, was in a foetal resorption showing open eyes and a reduction malformation of the right foreleg. The control group of study B contained malformations analogous in type and incidence to those seen in the 300 mg/kg/day group. These included 2 foetuses with ectopy, one of which had a missing tail, one foetus with an eye open, one foetus with omphalocoele and one foetus with a hypoplastic tail.

Examination of the foetal heads in both studies showed similar incidences and variations in soft tissue structure between treatment groups and controls. The low incidence of abnormalities seen in study A has previously been seen in the historical controls for the rabbit strain used in this study.

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		In the supplementary study (B) using a dose of 200 mg/kg/day, it was assumed that a pattern of the same types of malformations would appear if the effects seen in the 300 mg/kg/day group were relevant. However, the results from this study show that no pattern or associated malformation was established between the two doses and only one malformation was present, which was localised in a foetal resorption. Furthermore, in contrast to the single malformation from the control group of study A, the malformations seen in the control group of study B appeared more frequently and were analogous in type and incidence to the malformations seen in the 300 mg/kg/day group. Therefore considering the high incidence of malformations in the study B controls in particular, all malformations seen in the 300 mg/kg/day group are considered to be arbitrary findings and not compound–related. Skeletal examination of the neonates by radiography and/or Alizarin Red staining revealed no compound-related effects on any of the measured ossification parameters and all findings from the treatment groups of both studies were comparable with the respective controls.
5.3	**Conclusion**	**It was concluded that considering the results overall, fenoxycarb when administered orally at a dose of up to 300 mg/kg/day in rabbits is neither embryotoxic, teratogenic nor has any effect on the course and outcome of pregnancy.**
5.3.1	LO(A)EL maternal toxic effects	LOAEL = 200 mg/kg bw/day (maternal decreased bodyweight gain)
5.3.2	NO(A)EL maternal toxic effects	NOAEL = 100 mg/kg bw/day
5.3.3	LO(A)EL embryo toxic / teratogenic effects	LOAEL > 300 mg/kg bw/day
5.3.4	NO(A)EL embryo toxic / teratogenic effects	NOAEL = 300 mg/kg bw/day
5.3.5	Reliability	2
5.3.6	Deficiencies	No

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	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/07/26
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_8-1.1: Intergroup comparison of maternal bodyweight gain (g)

	Dose level of mg fenoxycarb/kg/day					
	Study A				Study B[a)]	
Gestation days	**0**	**30**	**100**	**300**	**0**	**200**
1 – 7 (before treatment)	85.9	128.8	133.5	132.8	60	70
7-20 (during treatment)	171.8	198.2	218.2	137.2	170	130
20-30 (after treatment)	223.5	213.8	283.5	326.1	270	220
1-30 (overall)	481.2	558.8	635.3	596.1	500	450

a) values are median

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 6.8.1 Developmental toxicity study in rats

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1983), Embryotoxicity Study In Rats With Oral Administration Of Ro 13-5223/000. Segment II – Teratological Study With Post-Natal Evaluations. [redacted], Report No. B-104875, 12 May 1983 (unpublished)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Syngenta	
1.2.2	Company with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	87/302/EEC B.31 (1988) ≅ OECD 414 (1981) ≅ FIFRA § 83-3 The study was performed prior to the above guideline but has been checked for compliance with the above.	
2.2	**GLP**	Yes	
2.3	**Deviations**	The purity of the test substance was not reported. There were 36 mated females rats per group. On 21st day of gestation the animals were allocated to 2 groups - a necropsy group for teratological examination of the foetuses and a group where the dams were allowed to rear their offspring for 23 days *post partum*. No maternal toxicity was seen in this study with a top dose of 500 mg/kg/day. Food consumption was not measured in this study. The sex of the foetuses and individual foetal weights were determined and the mean foetal weight derived but weights per sex were not identified. Individual foetus skeletal examination was done on 1/2 of each of 15 litters per dose group and the second half of each of the 15 litters were examined for visceral abnormalities. No historical data has been presented in this report.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2 of dossier.	
3.1.2.1	Purity	Not reported	
3.1.2.2	Stability	The test compound was formulated once per 10 days of treatment in the vehicle and stored in a refrigerator. High shear mixing was used during formulation and the suspension was kept homogenous during dosing by the use of a magneto stirrer.	X
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Fü-albino outbred strain	
3.2.3	Sex	Females	

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3.2.4	Number of animals per group	36	
3.2.5	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of exposure	Day 7-16 of gestation	X
3.3.2	Postexposure period	5 days	
		Oral	
3.3.3	Type	Gavage	
3.3.4	Concentration	50, 150, 500 mg/kg bw/day	
3.3.5	Vehicle	4% carboxymethylcellulose, 0.9% NaCl, 0.5% benzyl alcohol, 0.4% Tween 80 in H_2O dest.	
3.3.6	Controls	Vehicle	
3.4	**Examinations**		
3.4.1	Body weight	Dams were weighed at the start of the study, daily during the treatment period, and on days 17 and 21 of gestation.	
3.4.2	Food consumption	Not reported	
3.4.3	Clinical signs	The rats were observed daily for changes in behaviour, general condition and signs of pharmacological action.	
3.4.4	Examination of uterine content	Yes corpora lutea, implantation sites	
3.4.5	Examination of foetuses	The foetuses were weighed and examined macroscopically. One half of the foetuses of 15 litters per group were eviscerated, macerated, and stained for subsequent skeletal examination. The second half of the litters were fixed and subsequently examined for visceral abnormalities.	
3.5	**Further remarks**	On day 21 of gestation, the rats were allocated to 2 subgroups, a necropsy subgroup and a rearing subgroup. The dams of the necropsy sub group were killed on day 21 of gestation and their uteri examined for the number and location of implantations and resorptions. The dams of the rearing subgroup were allowed to litter spontaneously and to rear their young up to weaning. On lactation days 1, 4, 12 and 23, the litter size was recorded and the young and mothers were weighed. On day 23 *post partum*, the offspring were examined externally, killed and discarded. All females were killed after 23 days *post partum* and their uteri examined for implantation sites. Any females, which did not litter within a week of the expected end of gestation were killed and their uteri examined for implantation sites.	
		4 RESULTS AND DISCUSSION	
4.1	**Maternal toxic effects**	There were no deaths in the 50 or 500 mg/kg/day groups. One pregnant female in the 150 mg/kg/day group died from unknown reasons on day 10 of gestation. Females from the 500 and 150 mg/kg/day groups became slightly nervous following treatment from the 11th and 13th day of gestation, respectively, with the effects persisting up to the end of treatment on day 16 of gestation. Body weight development of the dams receiving treatment did not show appreciable deviations from the	X

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concurrent control group.

4.2 Teratogenic / embryo toxic effects

There were no adverse effects on any of the measured reproductive or litter parameters for the 50, 150 and 500 mg/kg/day groups, except for a slightly increased mortality rate between lactation days 1 and 4 for the pups in the 150 mg/kg/day group compared with the controls. The finding was not dose-related and probably not of biological significance, as the mortality of the pups in this group between days 1 and 23 was comparable to controls and no effect was seen at the higher dose level. A slight increase in the number of embryonic resorptions was recorded in the 500 mg/kg/day necropsy sub group. This increase was not statistically significant, was within the historical control data range available at the laboratory and was not seen in the comparable dose level of the rearing sub group. It was therefore considered not to be of biological significance.

Macroscopic and soft tissue examination from treated and control groups found one foetus oedematous with ectopia of the viscera in the control group and one foetus oedematous with various skeletal aberrations in the 50 mg/kg/day group. Skeletal examinations of all other foetuses showed no teratological findings in any dose group.

4.3 Other effects

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5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Female Fü-albino rats, of a closed, randomised outbred strain, were mated (1:1) overnight with males of the same strain. Successful mating (designated day 1 of gestation) was determined the next morning by the presence of a vaginal plug. The mated females were then allocated to groups. Groups of 36 mated females were dosed by gavage with 0 (control), 50, 150 or 500 mg fenoxycarb /kg bodyweight daily on days 7 to 16 of gestation. The control group was given the vehicle (Standard Solvent Vehicle: 4% carboxymethylcellulose, 0.9% NaCl, 0.5% benzyl alcohol, 0.4% Tween 80 in H_2O dest.). The rats were observed daily for changes in behaviour, general condition and signs of pharmacological action. They were weighed at the start of the study, daily during the treatment period, and on days 17 and 21 of gestation. On day 21 of gestation, the rats were allocated to 2 subgroups, a necropsy subgroup and a rearing subgroup.

The dams of the necropsy sub group were killed on day 21 of gestation and their uteri examined for the number and location of implantations and resorptions. The number of *corpora* lutea was determined. The foetuses were weighed and examined macroscopically. One half of the foetuses of 15 litters per group were eviscerated, macerated, and stained for subsequent skeletal examination. The second half of the litters were fixed and subsequently examined for visceral abnormalities.

The dams of the rearing subgroup were allowed to litter spontaneously and to rear their young up to weaning. On lactation days 1, 4, 12 and 23, the litter size was recorded and the young and mothers were weighed. On day 23 *post partum*, the offspring were examined externally, killed and discarded. All females were killed after 23 days *post partum* and their uteri examined for implantation sites. Any females, which did not litter within a week of the expected end of gestation were killed and their uteri examined for implantation sites.

5.2 Results and discussion

Maternal findings: There were no deaths in the 50 or 500 mg/kg/day groups. One pregnant female in the 150 mg/kg/day group died from

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Annex Point IIA VI.6.8.1 6.8.1 Developmental toxicity study in rats

		unknown reasons on day 10 of gestation. Females from the 500 and 150 mg/kg/day groups became slightly nervous following treatment from the 11th and 13th day of gestation, respectively, with the effects persisting up to the end of treatment on day 16 of gestation. Body weight development of the dams receiving treatment did not show appreciable deviations from the concurrent control group. **Foetal data:** There were no adverse effects on any of the measured reproductive or litter parameters for the 50, 150 and 500 mg/kg/day groups, except for a slightly increased mortality rate between lactation days 1 and 4 for the pups in the 150 mg/kg/day group compared with the controls. The finding was not dose-related and probably not of biological significance, as the mortality of the pups in this group between days 1 and 23 was comparable to controls and no effect was seen at the higher dose level. A slight increase in the number of embryonic resorptions was recorded in the 500 mg/kg/day necropsy sub group. This increase was not statistically significant, was within the historical control data range available at the laboratory and was not seen in the comparable dose level of the rearing sub group. It was therefore considered not to be of biological significance. Macroscopic and soft tissue examination from treated and control groups found one foetus oedematous with ectopia of the viscera in the control group and one foetus oedematous with various skeletal aberrations in the 50 mg/kg/day group. Skeletal examinations of all other foetuses showed no teratological findings in any dose group.
5.3	**Conclusion**	**It can be concluded that under the conditions of the present study fenoxycarb when orally dosed to pregnant rats up to a dose of 500 mg/kg/day is neither embryotoxic, teratogenic nor impairs the postnatal development of the offspring.**
5.3.1	LO(A)EL maternal toxic effects	LOAEL = 150 mg/kg bw/day (maternal signs of nervousness)
5.3.2	NO(A)EL maternal toxic effects	NOAEL = 50 mg/kg bw/day
5.3.3	LO(A)EL embryo toxic / teratogenic effects	LOAEL > 500 mg/kg bw/day
5.3.4	NO(A)EL embryo toxic / teratogenic effects	NOAEL = 500 mg/kg bw/day
5.3.5	Reliability	2
5.3.6	Deficiencies	The guideline deviations (point 2.3) do not impair the overall validity of the study.

Section A6.8.1 Teratogenicity Study

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	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/07/26
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.8.2 Multigeneration Reproduction Toxicity Study

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

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1 REFERENCE

1.1	**Reference**	[redacted] (1986). Ro 13-5223/000: 2 Generation Oral (Dietary Administration) Reproduction Study In The Rat. [redacted]., Report No. 4623-161/124, September 1986 (main report), April 1992 (amendment), April 1992 (supplement), (unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	Syngenta
1.2.2	Company with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	87/302/EEC B.35 (1988) ≅ OECD 416 (1983) ≅ FIFRA § 83-4 The study was performed prior to the above guideline but has been checked for compliance with the above.
2.2	**GLP**	Yes
2.3	**Deviations**	One male was housed with one female for up to 21 days but if mating did not occur within the first 10 days of the cohabitation period, the male was replaced with a 'proven' male from the same group. Food consumed by each cage of the F0 and selected F1 animals was recorded at weekly intervals during the pre-mating (maturation) periods only. The uterus was preserved for possible microscopic examination but the report dose not state whether the cervix was taken. Coagulating gland and pituitary were not taken from F0 and F1 animals selected for mating. The tissues and organs taken from F0 and F1 males or females that failed to mate or conceive at both pairings were not examined histopathologically. The uterus of females that failed to litter was examined for evidence of implantation. The deviations are considered not to compromise the scientific validity of the study.

3 MATERIALS AND METHODS

3.1	**Test material**	Fenoxycarb (Ro 13-5223/000)
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in Section 2 of dossier.
3.1.2.1	Purity	[redacted]
3.1.2.2	Stability	Analysis of the diets showed that the achieved concentrations, homogeneity and stability of fenoxycarb in the diet were satisfactory.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Sprague-Dawley-derived albino rats (Crl:CD (SD)BR)
3.2.3	Sex	♂+♀
3.2.4	Age/weight at	♂: 184-187 g bw, ♀: 141-145 g bw