13 Findings

Animal observations: No treatment-realated findings were noted on appearance and behaviour.

Absorption: Renal elimination after oral gavage suggested that at least 50% of the dose was absorbed from the intestinal tract. The high amount of radioactivity found in feces after intravenous administration suggests that the enteral absorption is significantly higher.

Excretion: The mean excretion data in the different groups were as follows:

	Group A 0.5 mg/kg i.v.		**Group B** 0.5 mg/kg oral		**Group C** 0.5 mg/kg oral (pretr.)		**Group D** 50 mg/kg oral	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Urine								
12 hrs	35.8	39.5	27.6	39.1	26.4	38.2	20.2	35.7
24 hrs	5.0	4.6	8.9	3.7	9.7	5.3	13.7	9.3
48 hrs	1.8	1.7	1.9	0.7	4.0	1.7	4.4	3.4
72 hrs	0.2	0.3	0.2	0.1	0.3	0.2	0.8	0.2
120 hrs	0.1	0.1	0.1	0.1	ND	0.1	0.1	ND
168 hrs	ND	ND	ND	ND	--	--	ND	ND
Total	**42.9**	**46.3**	**38.7**	**43.8**	**40.6**	**45.6**	**39.2**	**48.7**
Feces								
12 hrs	11.4	17.6	25.3	19.9	8.4	14.0	10.5	11.2
24 hrs	23.7	11.7	11.8	11.9	26.6	16.9	20.6	14.2
48 hrs	5.1	7.3	11.4	4.9	12.0	8.2	13.9	9.7
72 hrs	1.3	1.3	1.2	0.6	1.2	0.7	2.6	1.7
120 hrs	0.2	0.8	0.3	0.1	0.2	0.1	0.4	0.1
168 hrs	ND	0.2	0.2	ND	--	--	ND	ND
Total	**41.8**	**39.0**	**50.2**	**37.4**	**48.4**	**39.9**	**47.9**	**37.0**
Air (total)	**n.d.**	**n.d.**	**n.d.**	**n.d.**	**n.d.**	**n.d.**	**n.d.**	**n.d.**
Cage wash	**5.0**	**8.6**	**7.0**	**12.5**	**6.5**	**9.8**	**5.6**	**8.4**
Tissue Residues	**0.1%**	**0.1%**	**0.1%**	**0.1%**	**0.1%**	**1.1%**	**0.1%**	**0.2%**
Total Recovery	**89.8%**	**94.0%**	**96.0%**	**94.3%**	**95.6%**	**96.4%**	**94.2%**	**94.3%**

With the phenyl labelled compound, elimination was similar in urine and feces. Excretion was rapid at both dose levels with around 70% of the administered radioactivity excreted after 24 hours and around 95% within 48 hours. Fecal elimination was similar after oral and intravenous administration, indicating that a significant amount is eliminated with the bile. In females, urinary elimination was slightly higher than in males.

Tissue residues: The following table outlines the mean residues found in selected tissues 168 hours after the administration. The values were given in ppm propiconazole equivalents.

	Group A		Group B		Group C		Group D	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Adrenal	0.003	0.006	LD	LD	0.002	0.010	0.56	0.264
Blood	0.001	0.004	LD	0.001	LD	0.002	0.076	0.161
Bone marr.	0.051	0.008	LD	0.006	LD	0.036	LD	0.144
Bone	LD	LD	LD	LD	LD	0.002	LD	LD
Brain	LD	LD	LD	LD	LD	0.001	LD	LD
Carcass	LD	LD	LD	LD	LD	0.006	LD	0.151
Fat	0.002	0.004	0.006	0.002	0.002	0.008	0.141	0.326
Gonads	LD	0.003	LD	0.002	LD	0.012	0.043	0.256
Heart	0.001	LD	LD	LD	LD	0.002	0.037	0.038
Kidney	0.006	0.005	0.004	0.005	0.006	0.007	0.345	0.366
Lung	0.003	LD	LD	0 001	0.001	0.003	0.081	0.085
Liver	0.021	0.010	0.012	0.008	0.022	0.018	0.938	0.784
Muscle	LD	LD	0.001	0.001	LD	0.002	0.019	LD
Spleen	0.013	0.009	LD	0.001	LD	0.003	0.057	0.085
Uterus		0.001		0.001		0.003		0.144
LD = Detection limit 0.0011 - 0.0064 ppm (low), 0.015 - 0.15 ppm (high dose)								

Reflecting the rapid elimination of the radioactivity, residues in tissues were very low. Pretreatment with the non-labeled compound had no influence on the residual radioactivity.

Metabolite pattern: Only the Group A animals showed significant amounts of unchanged CGA 64'250 in the urine. In this group, there was no unchanged CGA 64'250 detected in the feces. In all orally dosed groups, urinary elimination was exclusively in form of metabolites and around 7-15 % of the administered radioactivity was excreted with the feces as the parent molecule. Comparison with analytical standards showed that propiconazole was extensively metabolized with possible side-chain oxidation and the loss of the dioxolane ring occurring.

Conclusion: Propiconazole absorbed from the intestinal tract to a high extent and rapidly excreted with urine and feces. In females, urinary elimination was slightly higher than in males where a higher amount of radioactivity was found in the feces. Seven days after a single dose residues in tissues were generally low, being highest in the liver.

The metabolite pattern in the urine was similar in both sexes and in both dose groups with only slight, quantitative differences.

14	**Statistics**	not applicable
15 (published)	**References**	none
16 data	**Unpublished**	none
17	**Reliability Indicator**	1

Data Protection Claim	Yes

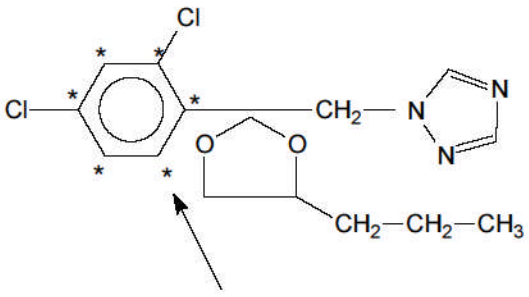
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18.5.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

	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	

PP 2.504 / WM / 27. 10. 1994

98/8 Doc IIIA section No.	6.2/03	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
91/414 Annex Point addressed	II 5.1.1 / 03	Absorption, distribution and excretion in rats

1.2	Title	Biliary excretion, absorption and distribution kinetics of [U-^{14}C]phenyl-CGA 64'250 in the rat after oral administration.
1.3	Report and/or project N° Syngenta File N° (SAM)	11PT01 64250/1988
1.4	Lab. Report N°	11PT01
1.5	91/414 Cross Reference to original study / report	5.1.1 / 03
1.6	Authors	Report: [redacted] Summary:
1.7	Date of report	January 14, 1992
1.8	Published / owner	no / SYNGENTA Ltd.
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	May 17 to October 31, 1991
3.	Objectives	To determine the absorption of the test compound given by the oral route based on biliary and urinary excretion and the amount remaining in the animals. To determine the blood level of radioactivity after different time points. To determine the pattern of tissue distribution of radioactivity at different time points. To determine the rate and route of excretion. To establish an overall balance of radioactivity in bile-duct cannulated rats. To investigate the metabolite pattern in urine, bile and feces extracts.
4.1	Test substance	Common name: Propiconazole Label: Phenyl-^{14}C-Propiconazole



Phenyl Label = Φ-^{14}C-CGA 64'250

4.2	Specification	[redacted]
4.3	Storage stability	not applicable
4.4	Stability in vehicle	The stability was checked by TLC at the time of dosing.
4.5	Homogeneity in vehicle	not applicable
4.6	Validity	not applicable

5	**Vehicle / solvent**	ethanol / polyethyleneglycol 200 / water (1 / 2 / 2)
6	**Physical form**	viscous liquid
7.1	**Test method**	The method is outlined in the original report. The study was conducted to fulfill the Agricultural Chemicals Laws and Regulations, Japan, Testing Guidelines of Toxicological Studies. Measurement of radioactivity was done using standard scintillation mixtures. Feces, tissues and carcass were homogenized. Homogenized feces, tissues and blood were combusted before scintillation. Characterization of urinary, biliary and fecal radioactivity was done by two-dimensional TLC on silica gel using the following solvent systems: ethyl acetate ethyl acetate / 2-propanol (75 / 25) ethyl acetate / 2-propanol /water / formic acid (65 / 25 / 10 / 2) chloroform / methanol / formic acid / water (75 / 20 / 4 / 2)
7.2	**Justification**	Standard methods
7.3	**Copy of method**	The original report contains all relevant information.
8	**Choice of method**	not applicable
9	**Deviations**	Deviations from 87/302/EEC: None
10.1	**Certified laboratory**	yes
10.2	**Certifying authority**	Swiss Federal Department of Interior and the Intercantonal Office for the Control of Medicaments.
10.3	**GLP**	yes
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12 Test system

Animals:

Strain: Male Rat, Sprague Dawley derived, Tif RAIf (SPF)

Source: [redacted]

Age: 7 - 8 weeks

Weight: 200 - 260 g

Doses and administration

Test substance was suspended in the vehicle.
Doses of 0.5 mg/kg bw were used in all groups.

Each animal received a single administration of about 1 ml with an activity of 4-5 µCi.

Group	animals	µCi.	Sample collection
E1	3 males	3.9	Blood after 0.25, 0.5, 1, 2, 4, 8, 12, 24 32 and 48 h
F1 1 and 8 h 14 and 20h	6 males 6 males	4.0 4.0	Tissues at Tcmax, Tcmax/2, Tcmax/4 and Tcmax/8, i.e. 1, 8, 14 and 20 h after the oral gavage
G1	5 males	5.0	Urine feces, bile, gastroinstestinal tract, carcass

Tcmax = time of maximal blood concentration of radioactivity

13 Findings

Animal observations: No treatment-realated findings were noted on appearance and behaviour. One bild-duct cannulated rat was excluded due to bad general condition and extremely low bile flow.

Absorption: Calculated on the basis of urinary and biliary excretion and on the amount remaining in the carcass, the mean absorption was 86.16% (range: 75.06 - 90.80%) of the administered dose in group G1.

Excretion: The mean excretion data calculated as % of the administered radioactivity were as follows:

Group G1						
Sample	**Urine**	%	**Feces**	%	**Bile**	%
	0 - 24 hrs	15.34	0 - 24 hrs	4.17	0 - 4 hrs	27.14
	24 - 48 hrs	4.61	24 - 48 hrs	1.77	4 - 8 hrs	10.93
					8 - 24 hrs	19.22
					24 - 48 hrs	7.93
	Total	**19.95**	**Total**	**5.94**	**Total**	**64.61**
Cage wash	**2.72 %**					
Carcass	**1.60 %**					
Total Recovery	**96.44 %**					

Blood Kinetics: The determination of blood residues at different time points in **Group E1** resulted in the following values:

Time of maximal blood concentration of radioactivity: Tcmax 1 hour
Tcmax/2 8 hours
Tcmax/4 14 hours
Tcmax/8 20 hours

Tissue residues: The following table outlines the mean residues found in selected tissues at different time points after the administration. The values are given in ppm propiconazole equivalents.

Group F1					
	1 hour	8 hours	14 hours	20 hours	T_{50} 0 - 20 hours
Adrenal	0.1374	0.1085	0.0323	0.0267	7.2
Blood	0.0487	0.0390	0.0131	0.0119	8.3
Bone	0.0129	0.0097	0.0034	0.0026	7.6
Brain	0.0169	0.0118	0.0040	0.0024	6.4
Fat	0.0417	0.0310	0.0108	0.0109	8.6
Heart	0.0361	0.0309	0.0098	0.0085	8.0
Kidney	0.2528	0.2316	0.0747	0.0190	9.5
Liver	0.6838	0.5776	0.1455	0.1433	7.2
Lung	0.1133	0.0991	0.0472	0.0346	10.2
Muscle	0.0188	0.0128	0.0046	0.0036	7.3
Plasma	0.0831	0.0665	0.0223	0.0209	8.4
Spleen	0.0201	0.0178	0.0069	0.0044	8.0
Testes	0.0177	0.0139	0.0055	0.0042	8.4
Carcass	0.5779	0.3935	0.1353	0.1395	8.2

Reflecting the rapid elimination of the radioactivity, residues in tissues were relatively low. Highest residues were found in the excretory organs liver and kidney.

Metabolite pattern: In the urine of the Group G animals one major metabolite was detected, which accounted for 31% of the urinary radioactivity. It was identified as the α-hydroxy-carboxy acid of propiconazole. Further metabolites identified by co-chromatography were CGA 91'305 and CGA 91'304, which confirmed the results of a previous metabolism study (This study is summarized in Point 5.1.2)

Group G animals showed significant amounts of unchanged CGA 64'250 in the feces accounting for 66% of the fecal radioactivity.

In the bile, about 10 metabolited were separated. The unpolar fraction of the pattern was similar to the corresponding urinary metabolite fractions. Around 10% of the biliary radioactivity co-chromatographed with CGA 91'305 and CGA 91'304. Three polar fractions (accounting for 22% of the biliary radioactivity or 11% of the administered dose) were not present in the urine.

Conclusion: Propiconazole was to about 85% absorbed from the intestinal tract. A significant amount of the administered radioactivity was eliminated with the bile (65% in bile cannulated rats).

A detailed determination of tissue depletion confirmed the low level of residual radioactivity in tissues which was already detemined in earlier studies. Calculated half life times for the depuration were in the range of 6 to 10 hours (assuming first order kinetics).

The metabolite patterns in urine and bile were similar in the middle and unpolar regions. The polar fractions in bile were not detected in urine.

14	**Statistics**	not applicable
15 (published)	**References**	none
16 data	**Unpublished**	none
17	**Reliability Indicator**	1

Data Protection Claim	Yes

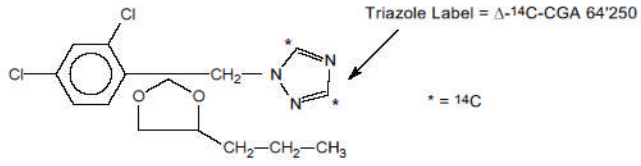
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18.5.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

	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	

PP 2.504 / WM / 27. 10. 1994

98/8 Doc IIIA section No.	6.2/04	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
91/414 Annex Point addressed	II 5.1.1 / 04	Absorption, distribution and excretion in rats

1.2	Title	Dermal absorption of triazole-^{14}C-CGA 64'250 by rats
1.3	Report and/or project N° Syngenta File N° (SAM)	M5-62-2A 64250/1551
1.4	Lab. Report N°	M5-62-2A
1.5	91/414 Cross Reference to original study / report	5.1.1 / 04
1.6	Authors	Report: [redacted] Summary:
1.7	Date of report	May 11, 1983
1.8	Published / owner	no / SYNGENTA Ltd.
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	not specified
3.	Objectives	To determine skin absorption rates of propiconazole when applied in form of an EC-formulation at doses of 1.0 and 10.0 mg a.i. /kg body weight. Determination of blood and tissue levels of radioactivity and of balance data at selected time intervals. Compare urinary metabolites after dermal administration to those found after oral gavage.
4.1	Test substance	Common name: Propiconazole Label: Triazole-^{14}C-Propiconazole



4.2	Specification	[redacted]
4.3	Storage stability	not applicable
4.4	Stability in vehicle	not applicable
4.5	Homogeneity in vehicle	not applicable
4.6	Validity	not applicable
5	Vehicle / solvent	An experimental EC formulation was made, which was similar to a sales formulation marketed at that time in the U.S.A.

^{14}C-CGA 64'250:	41.8% (w/w)
Tenneco T-500-100	56.2% (w/w)
Toximul S-HF	1.6 % (w/w)
Polyfoc 8240	0.4% (w/w)

6	**Physical form**	viscous liquid
7.1	**Test method**	The method is outlined in the original report. Testing guidelines were not available at the time when the study was conducted. The study was divided into three parts: Balance study: Single dermal treatment, sacrifice after 72 hours. Collection of urine and feces every 24 hours. Kinetic study: Single treatment, sacrifice after 2, 4, 8, 24, 48 and 72 hours. Determination of plateau levels of radioactivity in blood and tissues as a function of dose and time. Characterization of urinary metabolites: Single treatment, characterization of urinary metabolites in 24 hours and 48 hours urine. Measurement of radioactivity was done using standard scintillation mixtures. Feces and tissues were homogenized and combusted before scintillation. Skin was soaked overnight in methanol and solubilized with a commercial reagent (Beckman BTS-450) before scintillation. A preliminary experiment with two rats showed that no radiolabelled CO_2 was expired. Characterization of urinary radioactivity was done by two-dimentional TLC on silica gel using two solvent systems (ethyl acetate / isopropanol / water / formic acid 65 / 25 / 10 / 2 and chloroform / methanol / formic acid / water 75 / 20 / 4 / 2).
7.2	**Justification**	The procedures followed are in-line with sound scientific principles.
7.3	**Copy of method**	The original report contains all relevant information.
8	**Choice of method**	not applicable
9	**Deviations**	not applicable. The design of the study was specifically adjusted to its objectives. Sound scientific principles were observed.
10.1	**Certified laboratory**	no
10.2	**Certifying authority**	not applicable
10.3	**GLP**	no
10.4	**Justification**	When the study was conducted, GLP regulations were not enacted in the laboratory.
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12	**Test system**	**Animals:**	**Strain:**	Rat, Sprague Dawley
			Source:	[redacted]
			Weight:	around 200 g
		Doses and administration		Test formulation was applied to the clipped back skin of the rats (1.5 x 1.5 cm). Doses of 1 mg/kg bw and 10 mg/kg b.w. were used (doses relate to the active ingredient). The rear legs of the rats were tied together and the animals were housed individually to prevent scratching or oral uptake. The treated area was left uncovered.
		Group size:		4 males and 4 females per dose or sacrifice group were used for all parts of the study.

13 Findings

Absorption: Estimated on the basis of urinary excretion and on the amount remaining in the carcass, the absorption was higher than 60% of the administered dose in all groups. Assuming first order kinetics, half life times of absorption were around 24 hours for the low dose group and around
31 hours for the high dose group animals.

Balance data: The balance of radioactivity in the different groups was as follows:

	1 mg/kg		10 mg/kg	
	Males	**Females**	**Males**	**Females**
Source				
Cage wash	4.35	3.07	7.45	6.76
Tissues	2.79	1.44	2.28	1.80
Blood	0.13	0.09	0.12	0.09
Urine	33.68	38.30	23.70	32.74
Feces	31.04	27.34	20.87	20.65
Skin wash*	19.93	19.07	22.33	22.13
Skin residue	0.30	0.26	0.24	0.27
Carcass	10.72	10.34	12.33	20.75
Recovery	**102.96**	**99.88**	**91.14**	**105.20**
* Radioactivity recovered from skin after overnight soaking with methanol.				

Irrespective of the applied dose and of the sex of the animals, the balance data were similar in all groups. Approximately 20% of the applied dose was found in the treated skin 72 hours after the administration whith the bulk of the material removable by treatment with methanol. Although this cannot be regarded as a skin wash, this result indicates that most of the residual radioactivity may lie unaltered on the epidermal layer of the skin. Only a marginal portion of the skin radioactivity was more tightly bound.

Retention in the tissues was low, indicating that the absorbed material is rapidly excreted.

The half-life time of excretion (combined urine und feces) was calculated to be around 48 hours for the low dose group and 72 hours for the high dose group rats, regardless of the sex.

Kinetic data: The values found in the high dose group are summarized in the following table:

	2 hours	4 hrs	8 hrs	24 hrs	48 hrs	72 hrs
Males						
RBC	0.6	0.05	0.14	0.21	0.18	0.15
Plasma	0.11	0.08	0.25	0.32	0.28	0.21
Fat	LD	LD	LD	LD	LD	LD
Muscle	0.07	0.10	0.14	0.21	0.16	0.12
Lung	0.21	0.10	0.39	0.35	0.33	0.19
Heart	0.14	0.07	0.33	0.29	0.28	0.18
Kidney	0.42	0.29	0.96	0.79	0.70	0.46
Liver	0.56	0.48	1.81	1.19	1.51	0.95
Skin	83%	82%	73%	59%	23%	22%
Females						
RBC	0.11	0.10	0.11	0.16	0.15	0.10
Plasma	0.11	0.06	0.20	0.27	0.23	0.17
Fat	LD	LD	LD	LD	LD	LD
Muscle	0.08	0.06	0.11	0.13	0.10	0.07
Lung	0.27	0.15	0.30	0.29	0.28	0.15
Heart	0.18	0.21	0.22	0.26	0.20	0.11
Kidney	0.61	0.46	1.00	1.19	0.95	0.45
Liver	0.93	1.04	1.66	1.97	1.51	0.91
Skin	79%	80%	86%	51%	24%	22%
Values are given in ppm propiconazole equivalents except for skin (% of dose)						

Apparently, a equilibrium was established between skin absorption and excretion. In general, the radioactivity in tissues reached a plateau 24 hours after the adiministration. Thereafter, linear excretion patterns were found in all groups with half live times of excretion around 48 hours for liver and kidney. Lung, red blood cells and plasma showed longer half life times, however, the short observation period precluded the calculation of exact values.

Metabolite pattern: The metabolite pattern in the urine showed that an extensive metabolization: TLC patterns were the same in all groups, regardless of the sex or the administered dose. Patterns were very similar to those observed after oral administration of the test substance.

Conclusion: Propiconazole was slowly absorbed from the skin with a half life time of absorption around 24 to 30 hours.

Retention in the tissues was low, indicating that the absorbed material is rapidly excreted. The half-life time of excretion (combined urine und feces) was calculated to be around 48 hours for the low dose group and 72 hours for the high dose group rats, regardless of the sex.

The metabolite pattern in the urine was similar in both sexes and in both dose groups with only slight, quantitative differences. No unchanged parent was found.

14	**Statistics**	not applicable
15 (published)	**References**	none
16 data	**Unpublished**	none
17	**Reliability Indicator**	1

Data Protection Claim	Yes

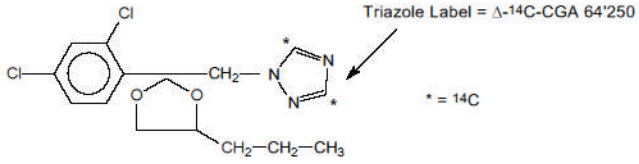
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18.5.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

	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	

PP 2.504 / WM / 27. 10. 1994

98/8 Doc IIIA section No.	6.2/05	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
91/414 Annex Point addressed	II 5.1.1 / 05	Absorption, distribution and excretion in rats

1.2	Title	Dermal absorption of ^{14}C-Propiconazole in rats after a ten-hour exposure period
1.3	Report and/or project N° Syngenta File N° (SAM)	ABR-86053 and ABR-86064 (Addendum) 64250/1552
1.4	Lab. Report N°	ABR-86053 and ABR 86064 (Addendum)
1.5	91/414 Cross Reference to original study / report	5.1.1 / 05
1.6	Authors	Report: [redacted] Summary:
1.7	Date of report	ABR- 86053: August 4, 1986, ABR-86064: September 30, 1986
1.8	Published / owner	no / SYNGENTA Ltd.
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	not specified
3.	Objectives	To estimate skin absorption rates of propiconazole when applied in form of an EC-formulation at doses of 0.1, 1.0 and 10.0 mg a.i. / rat by measuring the dose absorbed, excreted and the amount remaining on the skin Determination of balance data.
4.1	Test substance	Common name: Propiconazole Label: Triazole-^{14}C-Propiconazole
4.2	Specification	[redacted]
4.3	Storage stability	not applicable
4.4	Stability in vehicle	not applicable
4.5	Homogeneity in vehicle	not applicable
4.6	Validity	not applicable
5	Vehicle / solvent	An experimental EC formulation was made, [redacted] ^{14}C-CGA 64'250: [redacted] Before administration, an appropriate volume of water was added to allow for an even distribution on the treated skin (50 µl suspension /10 cm^2 skin area, high dose 100 µl).



6	**Physical form**	viscous liquid
7.1	**Test method**	The method is outlined in the original report. There is no standard protocol available for the specific aim of the study. After the administration the treated area was covered with a non-occlusive dressing and the animals were housed individually until sacrifice after 2, 4 or 10 hours. An additional asssay used an exposure period of 10 or 24 hours followed by a skin wash (see below) and a 72 hours depletion period. One further group of rats was sacrificed immediately afer 24 hour of exposure. The treated skin was washed twice with soap solution and once with deionized water. Wash solution, skin samples from treated and surrounding area, collected urine, feces, blood, the remaining carcass and the skin cover were measured for radioactivity using standard methods.
7.2	**Justification**	The procedures followed are in-line with sound scientific principles.
7.3	**Copy of method**	The original report contains all relevant information.
8	**Choice of method**	not applicable
9	**Deviations**	not applicable. The design of the study was specifically adjusted to its objectives. Sound scientific principles were observed.
10.1	**Certified laboratory**	no
10.2	**Certifying authority**	not applicable
10.3	**GLP**	no
10.4	**Justification**	When the study was conducted, GLP regulations were not enacted in the laboratory.
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12	**Test system**	**Animals:**	**Strain:**	Male rat, Sprague Dawley
			Source:	[redacted]
			Weight:	200 - 250 g
		Doses and administration		Test formulation was applied to the shaved back skin of the rats (4.0 x 2.5 cm). Doses of 0.1, 1.0 and 10 mg were used (doses relate to the active ingredient), equivalent to 0.01, 0.1 and 1 mg/cm^2. The treated area was covered but not occluded.
		Group size:		4 males per dose and sacrifice group were used, i.e. 24 animals per dose group.

13 Findings

Absorption: The absorption was inversely related to the administered dose.

The following table gives a survey on the results. The values are given as % of the administered radioactivity at different dose levels, exposure periods and depletion periods.

Treatment group	Absorbed*	+ Skin**	Unabsorbed***	Recovery
0.01 mg/cm²				
- 2 hours exposure	14.68	20.06	77.87	112.61
- 4 hours	12.79	36.73	58.02	107.54
- 10 hours	39.67	14.03	43.63	97.33
- 24 hours	47.44	9.69	48.17	105.30
- 10 hrs, 72 hrs depletion	42.37	48.25	59.79	108.04
- 24 hrs, 72 hrs depletion	54.71	59.41	42.33	101.74
1 mg/cm²				
- 2 hours exposure	2.70	23.45	79.07	105.22
- 4 hours	20.65	15.47	69.22	105.34
- 10 hours	11.20	24.99	62.51	98.70
- 24 hours	10.22	16.92	55.70	82.84
- 10 hrs, 72 hrs depletion	21.46	25.16	61.49	86.65
- 24 hrs, 72 hrs depletion	29.83	35.36	59.92	95.28
10 mg/cm²				
- 2 hours exposure	1.42	28.68	72.88	102.98
- 4 hours	1.34	29.73	64.76	95.83
- 10 hours	4.81	24.48	57.32	86.61
- 24 hours	1.42	28.68	72.88	102.98
- 10 hrs, 72 hrs depletion	30.97	37.02	58.37	95.39
- 24 hrs, 72 hrs depletion	29.83	42.39	48.49	90.88

* Total radioactivity in blood, urine, feces and carcass.
** Including radioactivity extracted from the skin at the site of treatment.
*** Sum of skin soap rinse, gauze and bandage rinse, cage wash.

Conclusion: Although not all results obtained are conclusive and the recovery of radioactivity was not satisfactory in all cases, the study gives a good survey on the dermal absorption behaviour of propiconazole when administered in form of a typical EC formulation.

After 10 hours of exposure, an average of 54, 36 and 29% of the applied dose was absorbed in the low, intermediate and high dose group, respectively. After 24 hours, these values were only slightly higher, indicating that a significant part of the absorbed radioactivity is tightly bound to the skin and only slowly released into general circulation.

In all cases and even after 24 hours of exposure, approximately half of the applied dose could be removed by washing the treated area with soap and water.

It is justified to conclude that dermal absorption of propiconazole in rats does generally not exceed 50% of the administered dose.

14 Statistics not applicable

15 References (published) none

16 Unpublished data none

17 Reliability Indicator 1

Data Protection Claim	Yes

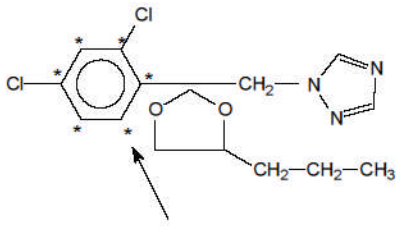
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	23.5.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

	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	

PP 2.504 / WM / 27. 10. 1994

98/8 Doc IIIA section No.	6.2/06	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
91/414 Annex Point addressed	II 5.1.1 / 06	Study on absorption, distribution, excretion and metabolism in mice

1.2	**Title**	The metabolism of [U-^{14}C]-phenyl-CGA 64'250 in mice after pretreatment with unlabelled CGA 64'250
1.3	**Report and/or project N° Syngenta File N° (SAM)**	12RB01, 12RB02 and 12RB03 64250/1554
1.4	**Lab. Report N°**	6 / 86
1.5	**91/414 Cross Reference to original study / report**	5.1.1 / 06
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	May 20, 1986
1.8	**Published / owner**	no / SYNGENTA Ltd.
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	June 1985 to March 1986
3.	**Objectives**	To compare excretion data, tissue residues and urinary metabolite pattern in mice between both sexes and three dose levels. To characterize and identify metabolites showing interesting differences. To compare the results to those obtained with rats.
4.1	**Test substance**	Common name: Propiconazole Label: Phenyl-^{14}C-Propiconazole



Phenyl Label = Φ-^{14}C-CGA 64'250

4.2	**Specification**	[redacted]
4.3	**Storage stability**	The stability of the non-labeled test material was confirmed by analysis. No degradation was detected during 28 days at room temperature.
4.4	**Stability in vehicle**	The stability of the test material in the dosing solution was checked by TLC at the time of dosing. It was found to be stable.
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable

5	**Vehicle / solvent**	ethanol / polyethyleneglycol 200 / water (7 / 9 / 4) (v/v) Final solutions were 0.250, 4.974 and 116.048 mg/ml (male rats and mice) and 0.261, 4.996 and 116.563 mg/ml (female mice) in the low, intermediate and high dose group, respectively.
6	**Physical form**	viscous liquid
7.1	**Test method**	The method is outlined in the original report. Measurement of radioactivity was done using standard scintillation mixtures. Feces and tissues were homogenized combusted before scintillation. Characterization of urinary radioactivity was done by two-dimentional TLC on silica gel using two solvent systems (ethyl acetate / 2-propanol / water / formic acid 65:25:10:2 and chloroform / methanol / water / formic acid 75:20:2:4, all given as v/v). Purification of urinary metabolites was done by standard methods using LC and HPLC. Identification of metabolites was done by NMR and MS using standard methods.
7.2	**Justification**	The procedures followed are in-line with sound scientific principles.
7.3	**Copy of method**	The original report contains all relevant information.
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	no
10.2	**Certifying authority**	not applicable
10.3	**GLP**	no
10.4	**Justification**	When the study was conducted, GLP was not yet certified to the laboratory. However, SOP's were operative and the study was conducted under Quality Assurance.
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12	**Test system**	**Animals:**	**Strain:**	Mouse: CD-1 Rat, Sprague Dawley derived, Tif RAIf (SPF)
			Source:	[redacted]
			Weight:	Mice: around 26 g (males) and 22 g (females) 4 weeks old Rats: around 200 g, 7 weeks old

Doses and administration

Male and female mice were treated with non-labeled propiconazole for 21 days at dietary concentrations of 5, 100 and 2'500 ppm followed by a single oral dose of the labeled test material.

For comparison, three female mice and 2 male rats received a single oral doses of the radiolabeled test material without pretreatment.

Test radiolabeled substance was suspended in the vehicle as described above. Doses of 0.1 ml were administered to the pretreated mice, resulting in average doses corresponding to dietary concentrations of 5, 100 and 2'500 ppm.

The rats and mice receiving single treatments (comparison groups) received only the high concentration corresponding to 100 ppm (mice 0.1 ml, rats 0.4 ml of the high concentration dose solution).

Group 21 d pretreatment	animals	radiolabeled dose	Sample collection (all groups)
5 ppm	mice 5m + 5f	m: 0.81 mg/kg f: 1.02 mg/kg	Urine and feces at 24 hours intervals. Carcass and tissues at sacrifice.
100 ppm	mice 5m + 5f	m: 16.8 mg/kg f: 21.5 mg/kg	
2'500 ppm	mice 5m + 5f	m: 434 mg/kg f: 475 mg/kg	
	mice 3 f	597 mg/kg	
-	rats 2 m	9.4 mg/kg	

-

13 Findings

Animal observations: All three mice treated with 597 mg/kg without previous dietary exposure to the active ingredient showed signs of severe intoxication. Two animals died spontaneously soon after the administration. With regard to the severely impaired condition, balance data were not obtained from this group. The surviving female was only used for urinary metabolite profiling.

Excretion: The mean excretion data in the low and the high dose groups were as follows. All values are given in % of the administered radioactivity:

Species	Mouse						Rat
	Male			Female			Male
Pretreatment (ppm)	5	100	2'500	5	100	2'500	-
Dose (mg/kg)	0.81	16.8	434	1.02	21.5	475	9.4
Feces							
- 0-24 hrs	35.42	32.92	25.72	34.54	15.15	20.40	48.48
- 24 - 48 hrs	1.84	1.68	5.36	6.69	4.89	7.78	4.79
- 48 - 72 hrs	0.44	0.21	0.66	1.06	1.57	2.67	0.26
- 72 - 96 hrs	0.16	0.10	0.15	0.21	0.42	0.25	0.10
Subtotal	**37.86**	**34.91**	**31.89**	**42.50**	**22.03**	**31.10**	**53.63**
Urine							
- 0-24 hrs	46.52	57.44	56.61	39.36	71.84	43.91	45.26
- 24 - 48 hrs	4.26	1.97	9.27	2.43	4.08	5.90	2.65
- 48 - 72 hrs	2.13	0.46	1.07	2.16	3.37	1.90	0.36
- 72 - 96 hrs	0.62	0.19	0.37	0.64	1.54	0.44	0.11
Subtotal	**53.53**	**60.06**	**67.32**	**44.59**	**80.83**	**52.15**	**48.38**
Tissues + Carcass	0.45	0.13	0.20	0.20	0.16	0.27	0.31
Recovery	93.14	95.71	100.27	91.43	105.81	87.83	102.57

Within 24 hours 64% to 94% of the administered dose were eliminated by mice and rats, respectively. Mice eliminated the major portion with the urine while the rats eliminated about equal amounts of radioactivity with urine and feces. After 96 hours the administered radioactivity was nearly totally excreted in both species.

Tissue residues: The following table outlines the mean residues found in selected tissues 96 hours after the administration. The values were given in ppm propiconazole equivalents.

Species	Mouse						Rat
	Male			Female			Male
Pretreatment (ppm)	5	100	2'500	5	100	2'500	-
Dose (mg/kg)	0.81	16.8	434	1.02	21.5	475	9.4
Blood	LD	0.0181	0.203	LQ	0.0348	0.316	0.0139
Liver	0.0064	0.1390	2.262	0.0106	0.1935	2.956	0.2245
Kidneys	0.0143	0.0767	0.848	0.0025	0.0412	0.871	0.0498
Lungs	LD	0.0254	0.273	LD	0.0357	0.393	0.0181.
Carcass	0.0029	0.0111	0.639	0.0018	0.0247	1.162	0.0122
LD around 0.0015 ppm in all tissues. LQ = 0.0025 ppm							

Residual radioactivity was dependent from the administered dose. In the low dose groups, residues remained at or below the limit of quantification in blood and lungs and did not exceed 0.015 ppm propiconazole equivalents in other tissues including the excretory organs liver and kidney. Except for the kidneys, residues tended to be slightly higher in females than in males. The ratio of tissue residues at higher doses compared generally well with the feeding levels.

The residiues in mice (100 ppm group) were similar to those found in rats treated at a comparable dose level.

Metabolite pattern: In the urine (0-24 hrs) of all groups, 15 - 30 metabolite fractions were separated by two-dimensional TLC. Comparing their quantitative distribution, significant differences were found between the sexes and between mice and rats.

After the elimination of the dioxolan ring of the molecule, the alcohol CGA 91'305 (1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazole-1-yl)-ethanol) is formed, which is ultimately conjugated to glucuronic acid. This metabolite represented 30% of the administered dose in males but only 15% in female mice. Further, the 2-hydroxy-carboxy acid of propiconazole represented up to 15% of the applied dose in females but only 1 to 3% in males.

In rats, the quantitative metabolite pattern is similar to that found in female mice.

Conclusion: The excretion pattern of propiconazole in mice was only slightly influenced by the sex of the animals. Urine was the major route of excretion. The residual radioactivity in tissues and organs was generally low with highest values detected in the liver.

The administered substance was efficiently degraded to various metabolites which showed quantitative differences between males and females.

14	**Statistics**	not applicable
15 (published)	**References**	none
16 data	**Unpublished**	For comparison, the metabolite pattern in rats is cited from Ref. 5.1.2. / 02 (see below)
17	**Reliability Indicator**	1

Data Protection Claim	Yes

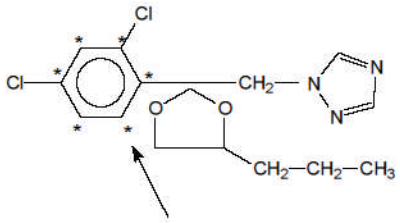
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	23.5.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

	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	

PP 2.504 / WM / 27. 10. 1994

98/8 Doc IIIA section No.	6.2/07	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
91/414 Annex Point addressed	II 5.1.1 / 07	Study on absorption, distribution, excretion and metabolism in mice

1.2	Title	Dermal absorbtion of [Phenyl-U-14C] CGA 64250 formulated as Tilt 250 EC (A-6097 K) in the rat
1.3	Report and/or project N° Syngenta File N° (SAM)	044AM01; 64250/4292
1.4	Lab. Report N°	044AM01
1.5	91/414 Cross Reference to original study / report	5.1.1 / 07
1.6	Authors	Report: [redacted]
1.7	Date of report	9 February 2000
1.8	Published / owner	no / SYNGENTA Ltd.
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	February 1999 to February 2000
3.	Objectives	To determine the absorption of CGA 64250 formualted as TILT ® 250 EC (A-6097 K) through rat skin after dermal application.
4.1	Test substance	Formulation Name: TILT ® 250 EC (A-6097 K) Common name of active substance: Propiconazole (company code CGA 64250) Label: Phenyl-^{14}C-Propiconazole
4.2	Specification	[redacted]
4.3	Storage stability	The non-radio-labelled material was used within the stated expiry date (February 2005)
4.4	Stability in vehicle	The stability of the test substance in the application formulation was checked by TLC and was stable
4.5	Homogeneity in vehicle	not applicable
4.6	Validity	not applicable
5	Vehicle / solvent	For the low and middle dose levels, blank formulation was added to the labelled CGA 64250 and the test substance diluted with water. For the high dose level, non-radiolabeled CGA 64250 was mixed with radiolabeld CGA 64250 and then dissolved in blank formulation.



Phenyl Label = Φ-^{14}C-CGA 64'250

6	**Physical form**	CGA 64250 is a colourless, clear liquid. TILT ® 250 EC (A-6097 K) is a liquid
7.1	**Test method**	The method is outlined in the original report. Radio labelled CGA 64250, formulated as TILT ® 250 EC (A-6097 K), was dermally applied to groups of 12 male rats; three doses of CGA 64250 were used, 0.0006, 0.006 and 2.3 mg/cm^2. Exposures were for 6 hours, after which the skin was washed. Subgroups were sacrificed at 6, 24 and 48 hours after treatment. Excreta and blood samples were taken; samples were taken of skin wash, 'O' rings, cage washings and treated skin area. Radioactivity was measured by liquid scintillation countering; the pattern of radioactivity was measured on TLC using a Packard Instant Imager or a Bio-Imaging Analyser
7.2	**Justification**	The procedures followed are in-line with sound scientific principles.
7.3	**Copy of method**	The original report contains all relevant information.
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	Yes
10.2	**Certifying authority**	Switzerland – Swiss Federal Department of the Interior and the Intercantonal Office for the Control of Medicants
10.3	**GLP**	Yes – see 10.2
10.4	**Justification**	Not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12 Test system

Animals:

Strain: Rat, Sprague Dawley derived, Tif RAIf (SPF)

Source: [redacted]

Weight: Rats: around 250 g, 8 weeks old

Doses and administration

On the day prior to dosing, a dorsal area was shaved and a double 'O' ring glued to the skin using cyanoacrylate adhessve. Rats were dosed at three levels (see below) and the 'O' ring covered with permeable tape. After 6 hours exposure, the cover was removed and retained for analysis. The skin was washed with a mild soap solution. Subgroups of 4 animals were sacrificed after 6, 24 or 48 hours from the strat of treatment.

Group	Formualtion (ug/cm^2)	radiolabeled dose (kBq/animal)
P1	0.6	16
P2	6	171
P3	2327	921

13 Findings

The formulated test substance was stable at the time of application

In the skin was, more than 96% of the radioactivity was unchanged CGA 64250.

Blood Kinetics: for the low dose level, all analyses of blood residues were below the limit of determination. In the middle dose, maximum residues were seen 2 hours after exposure (0.0103ppm) after which levels remained fairly constant at about 0.008ppm until the end of the exposure period. At the end of the exposure, residue levels were below the limit of determination within 18 hours. At the high dose level, blood residues increased throughout the exposure period, reaching a max of 0.828ppm. Residues decreased after the exposure period and were below the limit of determination by the end of the study.

Absorption and Excretion: the low dose was moderately absorbed; systemic absorption was calculated to be 12% of the applied dose after the absorption period, which increased to 17% within 42 hours following washing. At the middle and high dose, absorption was moderate. During the exposure period, 17 and 7% of the test substance was absorbed through the skin at the middle and high dose respectively; this increase to 21% for the middle dose within the 42 h wash period whilst for the high dose level, the absorption did not increase during this period.

The majority of the test material was washed off the skin (70-93%) with 10, 9 and 4% remaining in the skin of the low, middle and high dose animals. The mass balance showed that within 48hs, the mean amounts absorbed were 0.1ug/cm^2, 1.3ug/cm^2, and 130ug/cm^2 for the low, middle and high dose.

Material that was absorbed was excreted in equal parts in the urine and the faeces.

Terminal Residues; at the low dose, detectable residues were only seen at the 6 h exposure period, at very low levels. Significant residues were determined at the high dose 6 h after exposure, with the highest residue in plasma (1.515ppm CGA54250 equivalents). Skin had 1.127 ppm residue which declined rapidly at the end of the exposure period.

In summary, it was concluded that CGA 64250 formulated as TILT ® 250 EC (A-6097 K) penetrated moderately through the rat skin at all dose levels. The systemic absorbed dose was rapidly excreted.

14 Statistics

Methods are described in the report

15 References (published)

Currie LA Limits of Qualitative Detection and Quantitative Determination . Application to Radiochemistry . Analytical Chemistry, 40, 586 (1968)

16 References (unpublished)

not applicable

17 Reliability Indicator

1

Data Protection Claim	Yes