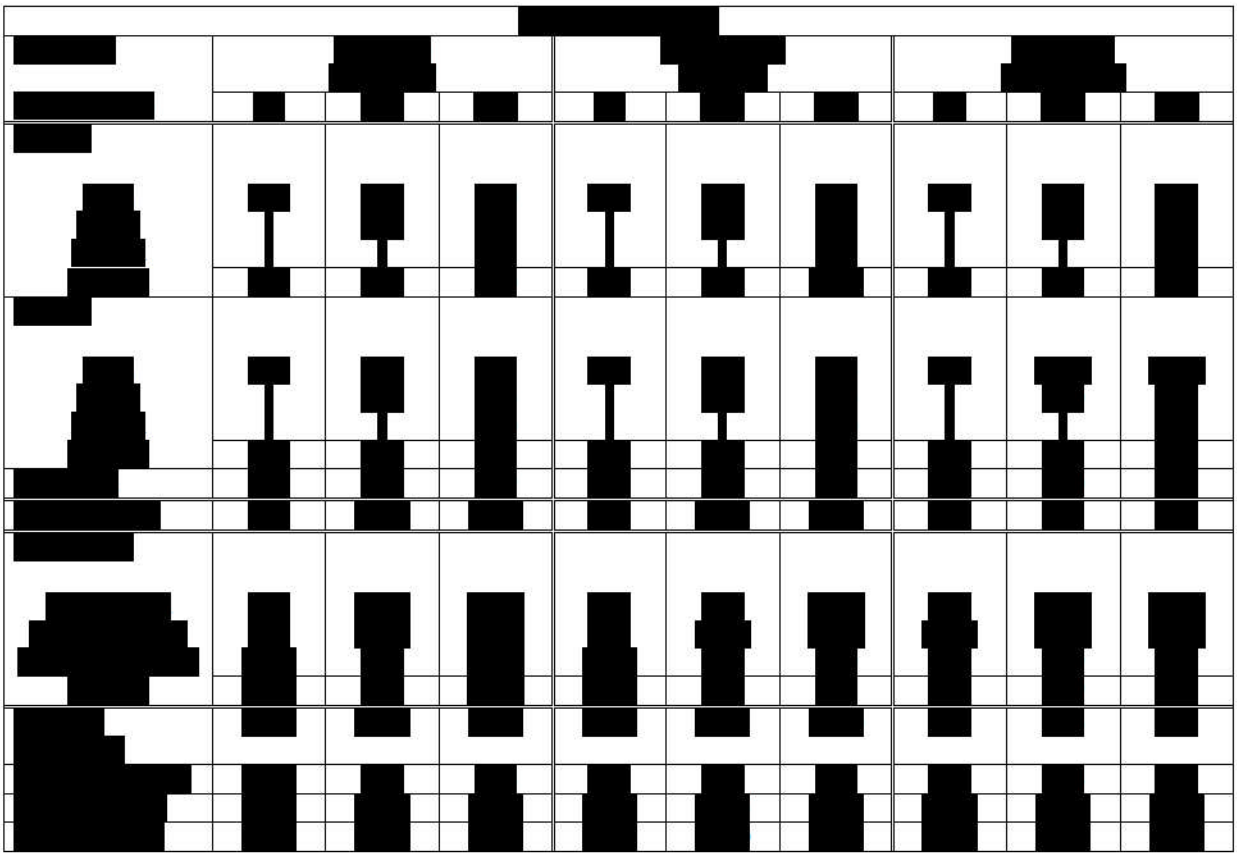
| Evaluation by Competent Authorities | |
|---|---|
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | 23.5.2005 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted]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

[redacted]

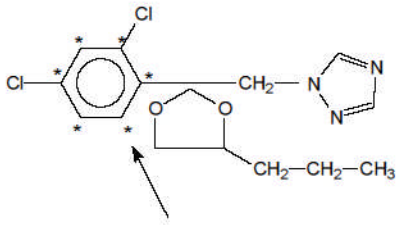


| | COMMENTS FROM ... |
|---|---|
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **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.** | **6.2/08** | **Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study** |
| **91/414 Annex Point addressed** | **II 5.1.1 / 08** | **Study on absorption, distribution, excretion and metabolism in mice** |

| | | |
|---|---|---|
| **1..2** | **Title** | The in vitro percutaneous absorption of [Phenyl-U-14] CGA 64250 formulated as TILT 250 EC (A-6097 K) through rat and human epidermis |
| **1.3** | **Report and/or project N° Syngenta File N° (SAM)** | 044AM02<br>64250/4276 |
| **1.4** | **Lab. Report N°** | 044AM02 |
| **1.5** | **91/414 Cross Reference to original study / report** | 5.1.1 / 08 |
| **1.6** | **Authors** | Report: [redacted] |
| **1.7** | **Date of report** | 4 January 2000 |
| **1.8** | **Published / owner** | no / SYNGENTA Ltd. |
| **2.1** | **Testing facility** | [redacted] |
| **2.2** | **Dates of experimental work** | 30 March 1999 to 4 January 2000 |
| **3.** | **Objectives** | To determine and compare the extent and rate of penetration of CGA 64250 formulated as TILT ® 250 EC (A-6097 K) through rat and human epidermis |
| **4.1** | **Test substance** | Formulation Name: TILT ® 250 EC (A-6097 K)<br>Common name of active substance: Propiconazole (company code CGA 64250)<br>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** | The homogeneity of the test substance in the application formulation was checked by TLC and was satisfactory |
| **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.<br>TILT ® 250 EC (A-6097 K) is a liquid |
| **7.1** | **Test method** | The method is outlined in the original report, and as described in the June 1996 (draft) OECD guideline for Dermal Delivery and Percutaneous Absorption *in vitro* method.<br>Radio labelled CGA 64250, formulated as TILT ® 250 EC (A-6097 K), was applied to in vitro epidermal membranes obtained from rats and humans. The membranes were maintained in diffusion flow-through cell apparatus with a donor and receptor cell. The receptor cell was connected to a peristaltic pump and the effluent was collected into vials at different time periods. The concentration applied to each cell was ($mg/cm^2$)<br>Rat 0.06 0.55 228<br>Human 0.06 0.56 231<br>The membranes were exposed for 6 hrs, and perfusates collected for up to 48 hours.<br>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** | OECD protocol |
| **9** | **Deviations** | Study conducted to OECD (draft) protocol |
| **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** | See 7.1 |
| **13 Findings** | | For the low and middle dose levels, 85% and 89%, respectively, of the dose of CGA 64250 penetrated through the rat epidermis after 12 hours. For the undiluted formulation (high dose) only 37% penetrated the skin. The calculated penetration rat (flux) for rat epidermis was $0.2ug/cm^2$, $2ug/cm^2$ and $76ug/cm^2$ at the low, middle and high dose.<br>Human epidermis was less permeable than rat skin at all three dose levels; at 12 hours only 14.2%, 6.2% and 2.2% of the applied dose penetrated through human epidermis at the low, middle and high doses and the corresponding calculated flux was $0.02ug/cm^2$, $0.1ug/cm^2$ and $7ug/cm^2$. Thus the species difference in respect to penetration rate (human to rat) was 1:10, 1:18 and 1:11 for the low, middle and high dose respectively.<br>In summary, CGA 64250 formulated as TILT(R) 250EC penetrated through rat epidermal membranes at a significantly faster rate and to a higher extent than through human epidermal membranes for both the diluted and undiluted formulations. |
| **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 |

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|---|---|
| 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] |

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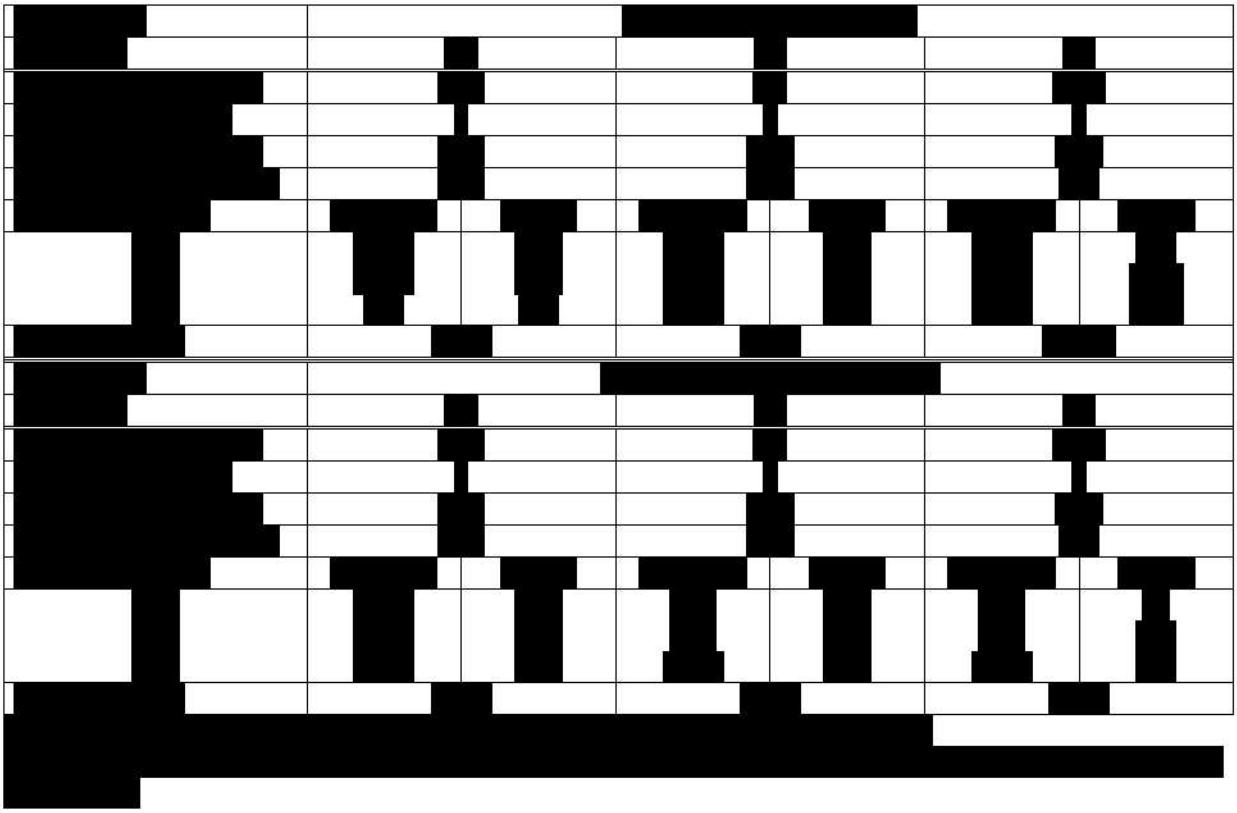

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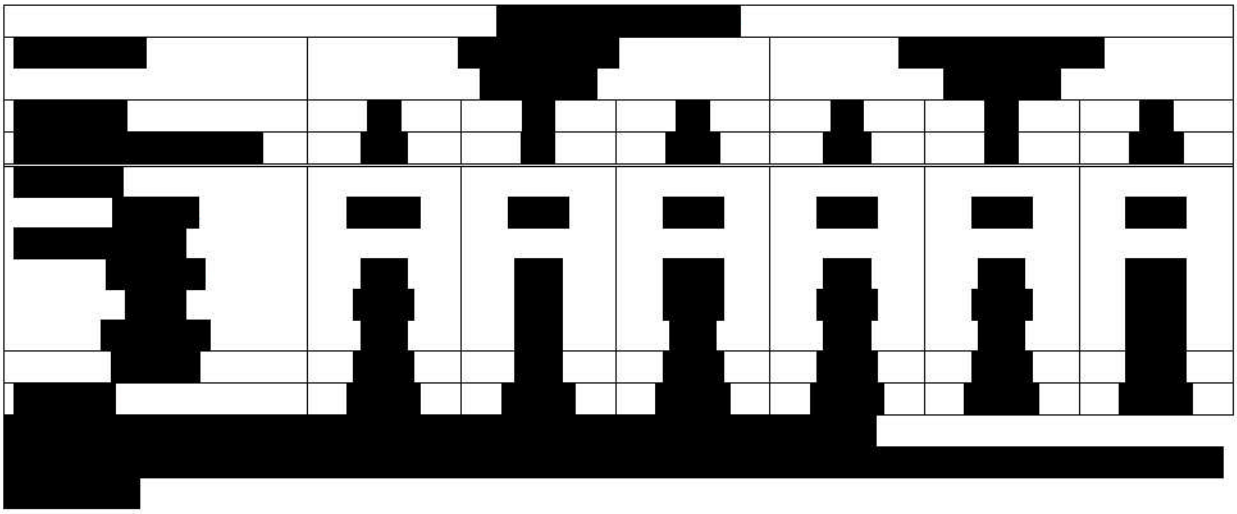

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| | COMMENTS FROM ... |
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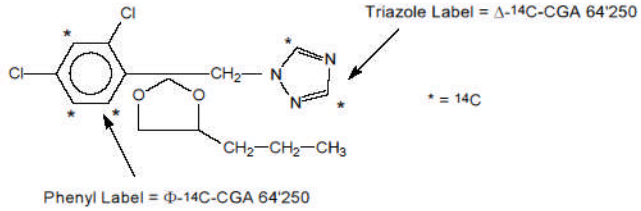
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **Results and discussion** | *Discuss 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. | 6.2/09 | Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study |
|---|---|---|
| 91/414 Annex Point addressed | II 5.1.2 / 01 | Metabolism |

| | | |
|---|---|---|
| 1.2 | Title | Characterization of urinary and fecal metabolites of rats after oral application of CGA 64'250 |
| 1.3 | Report and/or project N° Syngenta File N° (SAM) | 35 / 79<br>64250/1547 |
| 1.4 | Lab. Report N° | 35 / 79 |
| 1.5 | 91/414 Cross Reference to original study / report | 5.1.2 / 01 |
| 1.6 | Authors | Report: [redacted]<br>Summary: |
| 1.7 | Date of report | August 31, 1979 |
| 1.8 | Published / owner | no / SYNGENTA Ltd. |
| 2.1 | Testing facility | [redacted] |
| 2.2 | Dates of experimental work | not specified |
| 3. | Objectives | To gain some preliminary information on the character of the metabolites in urine and feces of rats after a single oral dose of triazole or phenyl labeled propiconazole. |
| 4.1 | Test substance | Common name: Propiconazole<br>Label: Triazole-$^{14}$C-Propiconazole<br>Phenyl- $^{14}$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** | water / ethanol / polyethyleneglycol 200 (50 / 30 / 20)<br>Concentration of the a.i.: 5.5 mg/ml |
| **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.<br><br>Measurement of radioactivity was done using standard scintillation mixtures. Feces and tissues were combusted before scintillation.<br><br>Characterization of urinary radioactivity was done by two-dimentional TLC on silica gel. Co-chromatography with reference substances CGA 91'305 and 91'304 (1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazole-1-yl)-ethanone and -ethanol). Solvent systems:<br>ethyl acetate<br>ethyl acetate / isopropanol / water / formic acid (65 / 25 / 10 / 2 v/v)<br>chloroform / methanol / water / formic acid (75 / 20 / 2 / 4 v/v)<br>acetonitrile<br>Chloroform / isopropanol (90 / 10 v/v)<br><br>High voltage electrophoresis was conducted on chromatography paper at 70 V/cm for 30 minutes using acetic acid / pyridine / water (0.6 / 50 / 950 (v/v) as buffer (pH 6.9) |
| **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 regulations were not enacted. |
| **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]

**Weight:** 167-186 g

**Doses and administration**

Test substance was suspended in the vehicle.
Doses around 30 mg/kg were used.

Each animal received a single administration of about 1 ml of the described dose suspension orally by gavage.

| Label | Group size | Dose mg/kg | Sample collection |
|---|---|---|---|
| Triazole | 20 | 31.4 | Urine and feces and were collected in 24 hour intervals |
| Phenyl | 3 | 32.5 | over 72 hours. Separation of urine and fecal metabolites |

**13** **Findings**

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

**Excretion:** The mean excretion data in the different groups were as follows. All values are given in % of the administered radioactivity:

| Group | Triazole label | Phenyl label |
|---|---|---|
| Dose (mg/kg) | 31.4 | 32.5 |
| No of animals | 20 | 3 |
| **Urine** | | |
| - 0-24 hrs | 44.5 | 48.5 |
| - 24 - 48 hrs | 6.8 | 2.6 |
| - 48 - 72 hrs | 1.0 | 0.3 |
| **Subtotal** | **52.3** | **51.4** |
| **Feces** | | |
| - 0-24 hrs | 36.2 | 44.2 |
| - 24 - 48 hrs | 6.5 | 3.4 |
| - 48 - 72 hrs | 0.6 | 0.6 |
| **Subtotal** | **43.3** | **48.2** |
| **TOTAL** | **95.6** | **99.6** |

Urine was the major route of exretion. Excretion was rapid at both dose levels with around 78% of the administered radioactivity excreted after 24 hours and around 95% within 48 hours.

**Characterization**: The following table outlines the quantitation and characterization of urinary metabolite fractions separated by two-dimensional TLC from rats treated with the triazole labeled compound. All values are given in % of total urinary radioactivity.

| Fraction | % of activity | Remarks |
|---|---|---|
| 1 | - | |
| 2 | - | Emerging from fractions 15 and 17 after treatment with |
| 3 | - | arylsulfatase and β-glucuronidase, respectively. |
| 4 | - | |
| 5 | 8 | co-chromatographs with CGA 91'305 (partially) |
| 6 | 4 | co-chromatographs with CGA 91'304 |
| 7 | 3 | |
| 8 | 24 | anionic at pH 6.9 (HVE) |
| 9 | 2 | |
| 10 | 10 | |
| 11 | 3 | |
| 12 | 6 | Not present in rats treated with the phenyl label |
| 13 | 5 | |
| 14 | 3 | |
| 15 | 12 | |
| 16 | 8 | |
| 17 | 9 | Susceptible to β-glucuronidase |

No unchanged parent was found in the urine. With the exception of fraction 12, all major fractions were detected in similar quantity also in rats treated with the phenyl label. Fraction 15 and 17 represent conjugates of the same metabolites (fractions 1 to 4).

Most of the metabolites (about 80%) were found to be acidic in nature.

The extraction and characterization of fecal metabolites gave the following results. All values are given in % of total fecal radioactivity:

| | Triazole label | Phenyl label |
|---|---|---|
| Extractability | | |
| Methanol / water (80 / 20 v/v) | 60 | 60 |
| Distribution | | |
| Ether extract pH 9 | 17 | 17 |
| Ether extract pH 7 | 11 | 8 |
| Ether extract pH 2 | 10 | 16 |
| Aqueous phase | 22 | 19 |
| Non-extractable | 40 | 40 |

The extractability and distribution of fecal metabolites was the same for both labels. Two-dimensional electrophoresis revealed at least 8 metabolite fractions, which were less polar than most of the urinary metabolites. The unchanged parent represented 5% of the radioactivity in the feces. About 35% of the extracted radioactivity was anionic at pH 6.9.

**Conclusion:** Propiconazole was extensively metabolized by the rats. About 20 metabolite fractions were found in the urine, 5 of them accounting for more than 5% of the urinary radioactivity. No unchanged parent was found in the urine. Metabolite patterns showed only slight differences between the phenyl- or triazole label. This observation indicates that the bridge between the phenyl and the triazole ring of the parent molecule is cleaved only to a minor extent. With both labels, the presence of reference compounds CGA 91'304 and CGA 91'305 confirmed that the major metabolic pathway involves the cleavage of the dioxolane ring.

About 60% of the radioactivity eliminated with feces was extractable. The extract consisted of at least 8 fractions, which were generally less polar than the major urinary metabolites.

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

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|---|---|
| Data Protection Claim | Yes |

| Evaluation by Competent Authorities | |
|---|---|
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | 27.5.2005 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | [redacted] |

| | **COMMENTS FROM ...** |
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| **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.*<br>*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. | 6.2/10 | Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study |
|---|---|---|
| 91/414 Annex Point addressed | II 5.1.2 / 02 | Metabolism |

| | | |
|---|---|---|
| 1.2 | Title | The metabolism of CGA 64'250 in the rat |
| 1.3 project N° Syngenta File N° (SAM) | Report and/or | 24 / 83<br>64250/1550 |
| 1.4 | Lab. Report N° | 24 / 83 |
| 1.5 Reference to original study / report | 91/414 Cross | 5.1.2 / 02 |
| 1.6 | Authors | Report: [redacted]<br>Summary: |
| 1.7 | Date of report | September 1, 1979 |
| 1.8 owner | Published / | no / SYNGENTA Ltd. |
| 2.1 | Testing facility | [redacted] |
| 2.2 experimental work | Dates of | not specified |
| 3. | Objectives | To elucidate the metabolic transformations and the metabolic pathways of propiconazole in the rat and to identify the structures of the metabolites.<br>The analyses were performed with 0-24 hours urine and feces from rats treated with triazole labeled propiconazole as described in section 5.1.2 /01. |
| 4.1 | Test substance | Common name: Propiconazole<br>Label: Triazole-$^{14}$C-Propiconazole |
| 4.2 | Specification | [redacted] |
| 4.3 stability | Storage | not applicable |
| 4.4 vehicle | Stability in | not applicable |
| 4.5 vehicle | Homogeneity in | not applicable |
| 4.6 | Validity | not applicable |
| 5 solvent | Vehicle / | For a summary, see section 5.1.2 / 01. The original report contains all information. |
| 6 | Physical form | viscous liquid |

| | | |
|---|---|---|
| **7.1** | **Test method** | The methods are outlined in detail in the original report.<br><br>Urine was extracted in 4 steps with ether at different pH levels and treated with arylsulfatase and β-glucuronidase. Final separation steps were conducted with LC on a servachrom column using water and methanol as eluent. Extracts were further separated and purified by HPLC using different columns (LiChrosorb RP18, Servachrom XAD-4, Sephadex A25 or $SiO_2$) and eluents (amminium formate / methanol (gradient), water / methanol (grad.), ammonium formate (0 to 0.3M grad.).<br><br>Feces were lyophilized and extracted with methanol / water and ether. Metabolites were separated by LC and HPLC using RP18 and $SiO_2$ columns and different eluents.<br><br>Several metabolites were derivatised by methylation, ethylation or silylation, 1-fluoro-2,4-dinitrobenzene or phenoboroic acid conjugation before spectroscopy.<br><br>Spectroscopy was conducted using MS, HR-MS and NMS techniques. |
| **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 regulations were not enacted. |
| **11.1** | **GEP** | not applicable |
| **11.2** | **Type of facility (official or officially recognised)** | [redacted] |
| **11.3** | **Justification** | not applicable |
| **12** | **Test system** | For a summary, see section 5.1.2 / 01. The original report contains all information.<br><br>0-24 hours samples from urine and feces of rats were used which were orally treated with 31.4 mg/kg triazole labeled propiconazole. |

**13 Findings:** Numerous metabolites were isolated from urine and feces. Their identification revealed a wide variety of metabolic pathways being operative in the degradation of propiconazole:

The major sites of enzymatic attack are the propyl side chain and the dioxolane ring of the parent molecule.

The 2,4-dichlorophenyl ring is attacked in various ways including the formation of a cyclohexadiene ring system, hydroxylation, replacement of the chlorine substituent by a hydroxy group and by introduction of a methylthio group, most probably a degradation product derived from glutathion conjugation.

Also the 1,2,4-triazole ring is oxidized leading to hydroxy derivatives.

The majority of the alcoholic and phenolic metabolites are excreted via the kidney in form of sulfuric acid or glucuronic acid conjugates.

| | | |
|---|---|---|
| **14** | **Statistics** | not applicable |

| | | |
|---|---|---|
| **15 (published)** | **References** | Details about test substance, test system and treatment are outlined in the Tier I document 5.1.2 / 01 (see pages 13 - 15).<br>The original report 5.1.2 / 02 contains all these details, which were omitted in the summary in order to avoid unnecessary repetition. |
| **16 data** | **Unpublished** | none |
| **17** | **Reliability Indicator** | 1 |

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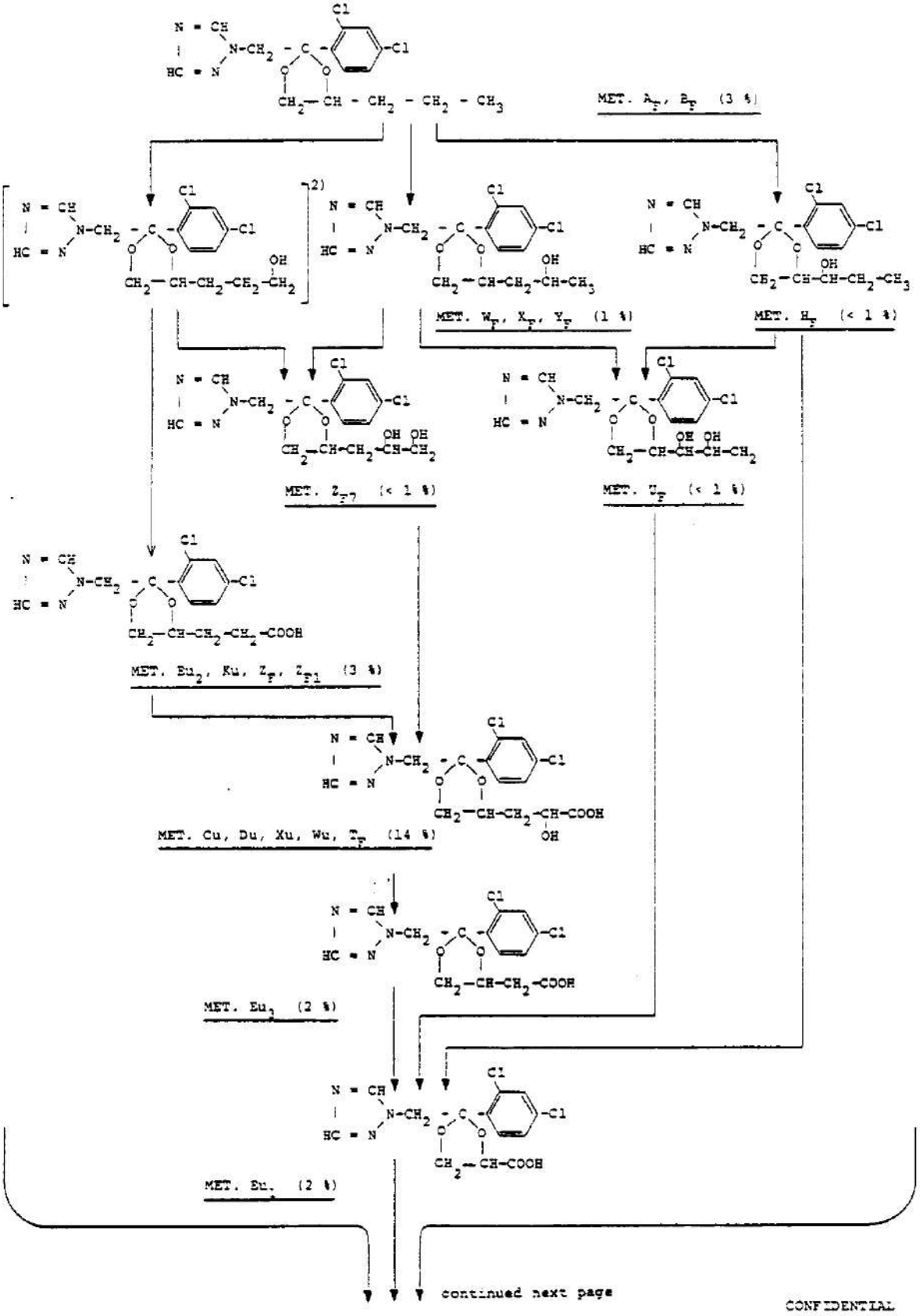
| Data Protection Claim | Yes |

**Proposed metabolic pathways of propiconazole in rats**
**(All values are given in % of the administered dose)**

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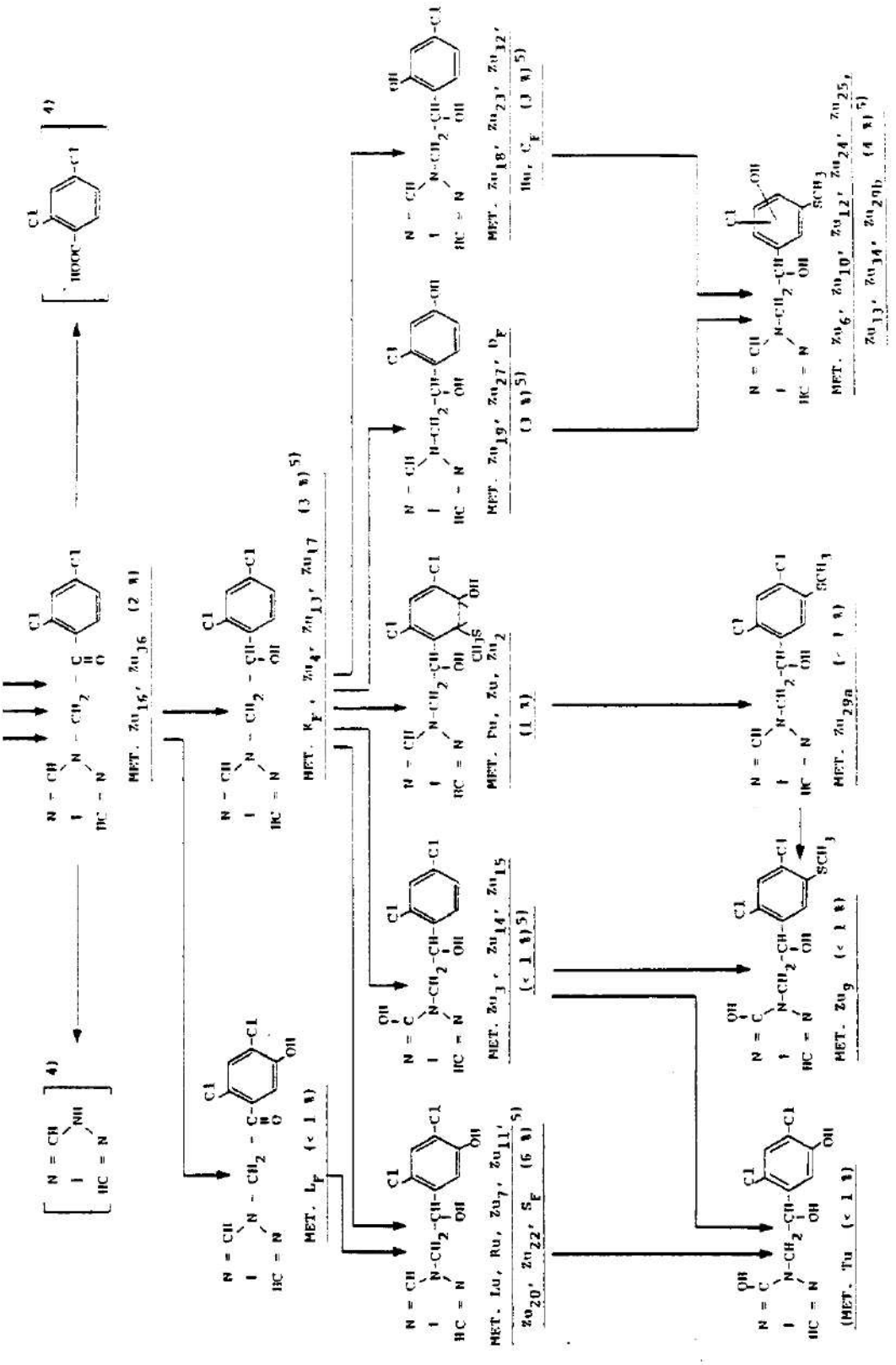
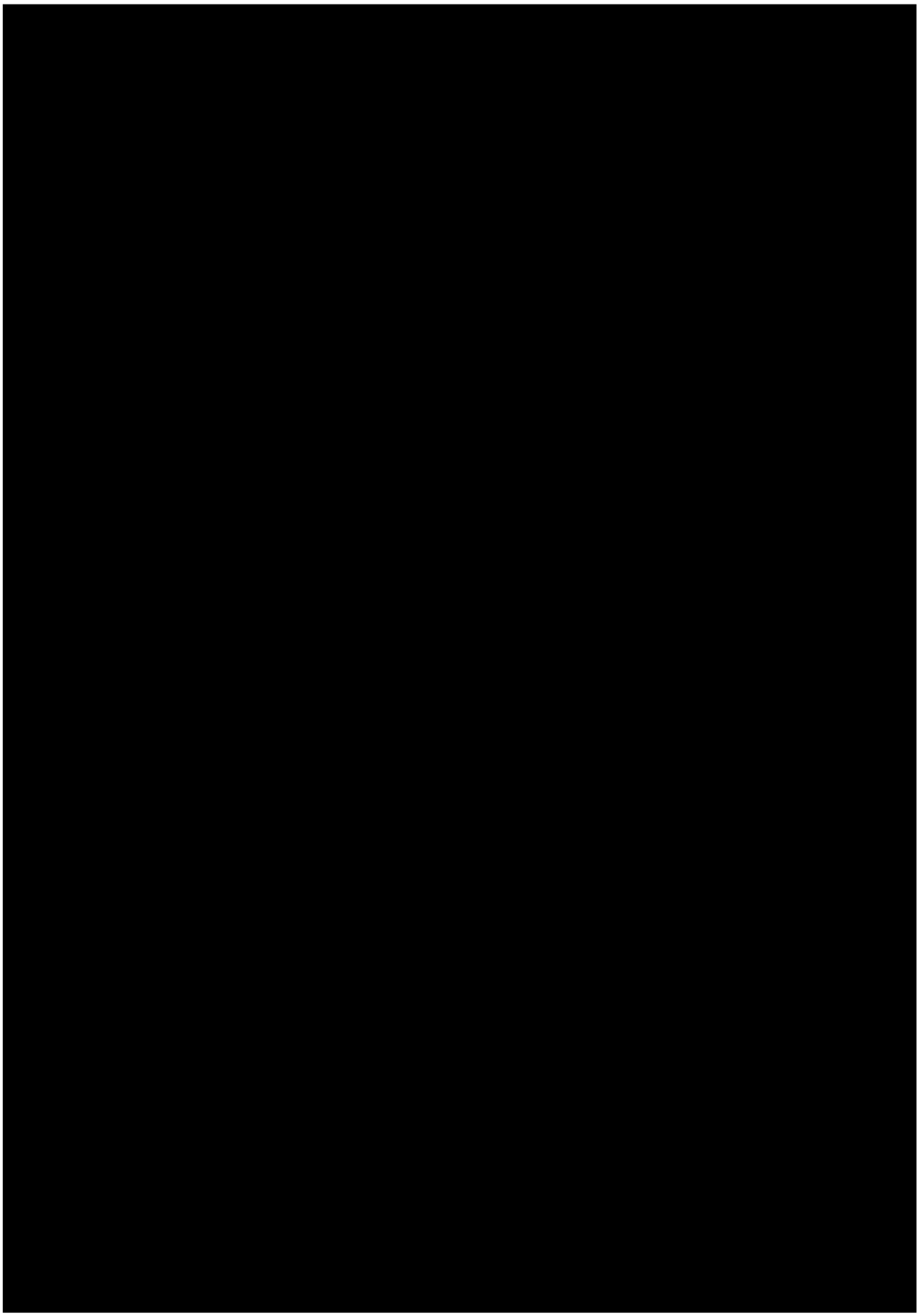
**cont.: Proposed metabolic pathways of propiconazole in rats**
**(All values are given in % of the administered dose)**



| Evaluation by Competent Authorities | |
|---|---|
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | 23.6.2005 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **Remarks** | [redacted] |

[redacted]

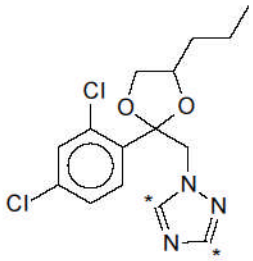


| | COMMENTS FROM ... |
|---|---|
| **Date** | *Give date of comments submitted* |
| **Materials and Methods** | *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*<br>*Discuss if deviating from view of rapporteur member state* |
| **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. | 6.2/11<br>6.2/12<br>6.2/13 | Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study |
| 91/414 Annex Point addressed | II<br>5.1.3 / 01a<br>5.1.3 / 01b<br>5.1.3 / 01c | Biokinetics and metabolism in farm animals |

| | | |
|---|---|---|
| 1.2 | Title | **Part A: Biological Report for the Metabolism of [Triazole-$^{14}$C]Propiconazole in a Lactating Goat**<br>**Part B: Balance and Metabolism of [Triazole-$^{14}$C]Propiconazole in a Lactating Goat**<br>**Part C: Characterization of Metabolites in Urine, Milk and Liver of a Goat treated with [Triazole-$^{14}$C]Propiconazole** |
| 1.3 | Report and/or project N°<br>Syngenta File N° (SAM) | Biol-80004 (Part A), ABR-80036 (Part B), ABR 81007 (Part C)<br>64250/1935 (Part A), 64250/1558 (Part B), 64250/1559 (Part C) |
| 1.4 | Lab. Report N° | |
| 1.5 | 91/414 Cross Reference | 6.3 / 03 (A - C) |
| 1.6 | Authors | Report: [redacted]<br>Summary: |
| 1.7 | Date of report | July 29, 1980 (Part A)<br>September 18, 1980 (Part B)<br>March 27, 1981 (Part C) |
| 1.8 | Published / Owner | no / Syngenta Limited |
| 2.1 | Testing facility | [redacted] |
| 2.2 | Dates of experimental work | September 18, 1980 (Completion of balance study)<br>March 27, 1981 (Completion of characterization study) |
| 3. | Objectives | Part B: Determination of 1) total balance of radioactivity, 2) urinary and fecal excretion radioactivity and 3) uptake and tissue deposition.<br>Part C: 1) Compare the autoradiographic pattern of rat and goat urines, 2) characterize the metabolites in milk and liver, 3) determine whether the same metabolites are in goat urine, milk and liver and 4) to characterize the common metabolites in milk and liver present in the highest amount. |
| 4.1 | Test substance | ISO common name: Propiconazole<br>Trade name:<br>Batch:<br>$^{14}$C-labeled test substance: Yes [ x ] No [ ]<br>Specific activity: [redacted]<br>Radiochemical purity of the test substance:<br>Structural formula: [U-$^{14}$C-triazole]CGA 64250<br>(position of label) |
| 4.2 | Specification | [redacted] |




* = $^{14}$C

| | | |
|---|---|---|
| **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** | Gelatin capsules with ground corn cobs |
| **6** | **Physical form** | see 5 |
| **7.1** | **Test method** | In house method. Guidelines were not available at the time the test was performed. |
| **7.2** | **Justification** | Report was accepted by several European Authorities and by EPA |
| **7.3** | **Copy of method** | Description of the test method is included in the report |
| **8** | **Choice of method** | Not applicable |
| **9** | **Deviations** | Not applicable |
| **10.1** | **Certified laboratory** | Not applicable |
| **10.2** | **Certifying authority** | Not applicable |
| **10.3** | **GLP** | No |
| **10.4** | **Justification** | When the study was performed, GLP was not required |
| **11.1** | **GEP** | Not applicable |
| **11.2** | **Type of facility (official or officially recognized)** | [redacted] |
| **11.3** | **Justification** | Not applicable |

| | | | |
|---|---|---|---|
| **12** | **Test system** | **Test species**: | lactating goats |
| | | Source: | [redacted] |
| | | Age/weight (at time of dosing): | Age: 2-5 years/34-38 kg |
| | | **Application**<br>Dose levels: | oral application<br>one goat received 1 gelatin capsule containing 5 mg (0.125 mCi) of propiconazole per day for 10 consecutive days |
| | | vehicles or solvents used/concentration: | see application, 5 and 6 |
| | | Group size: | 3 goats, one goat was used for the test |
| | | Analytical methods: | The goat was acclimatized for 3 days prior to dosing. Excreta, milk and $CO_2$ were collected daily. 27 hours after the last dose, the goat was sacrificed, blood and tissue samples were collected. Quantitation of the radioactivity in tissues and extracts was by combustion with subsequent LSC-measurement or direct LSC-measurement, respectively. |
| | | Radioactive areas on plates: | Autoradiography |
| | | Non-radioactive standards: | Fluorescence quenching under short wavelength ultraviolet light |
| | | Radioassay: | Liquid scintillation counting |
| **13** | **Findings** | | |

Part B:

The metabolism of [triazole-$^{14}$C]propiconazole was determined utilizing the in-life [redacted]. A lactating goat was dosed daily with 5 mg of [triazole-$^{14}$C]propiconazole (4.53 ppm in feed based on averaged feed/day intake) in a gelatin capsule for 10 consecutive days.

Milk, urine, feces and volatiles were collected during the dosing phase. 27 hours after the last dose, the goat was sacrificed and tissues were exercised. Most of the administered $^{14}$C-dose was eliminated in the urine and feces: 68.59 % and 20.96 %, respectively. Edible tissues and milk were found to contain the following levels of $^{14}$C-residues, calculated as [triazole-$^{14}$C]propiconazole equivalents: blood (0.019 ppm), liver (0.096 ppm), kidney (0.01 ppm), fat (<0.008 ppm), muscle (0.0094 ppm) and milk (maximum 0.013 to 0.016 ppm after day 3).

Ninety-two percent of the excreted radioactivity was shown to contain both the triazole and benzene rings with the alkyl bridge intact. Characterization of the urinary radioactivity showed that parent triazole-$^{14}$C-CGA 64250 was not present. Partitioning and chromatographic data showed degradation to acidic products. At least 75 % of the metabolites contain the basic structure of CGA 64250, i.e. all three rings attached to an alkyl bridge.

The metabolism of [triazole-$^{14}$C]propiconazole by goat resulted in the formation of polar products, which are rapidly excreted.

Part C:

Based on the 2D-TLC, the urinary goat metabolites could be divided into four groups, nonpolar, acidic, more polar and conjugated metabolites.

The major metabolite in goat urine is less polar than the main metabolite of CGA 64250 in rat urine. The sulfate conjugates found in rat urine are missing in goat urine, while one metabolite in goat urine is not seen in rat urine. The other metabolites in rat and goat urines exhibit the same pattern on 2D-TLC. The acidic metabolites result from the oxidation of the n-propyl side chain of the dioxolane ring to carboxylic acid.

Only 19 % of the total radioactivity in milk and liver contain both the triazole and phenyl rings of CGA 64 250. This indicates the cleavage of the alkyl chain and major metabolites in milk and liver are associated with the triazole ring only. Most of the radioactivity (89 %) in milk and (38 %) liver could be converted to $^{14}$C-triazole (CGA 71019).

Carter (2) reported the formation of 3-amino-1,2,4-triazolyl-alanine by the condensation of 3-amino-1,2,4-triazole and serine. The structure of the most probable conjugated metabolite in milk is postulated as a triazole conjugate of alanine with the amino group acetylated. This major metabolite accounts for more than 50 % of the metabolites of the more polar groups in milk. The pattern of the radioactive metabolites in milk and liver are very similar. They are common to those metabolites in urine, but they differ quantitatively.

For tables see next page

| | | |
|---|---|---|
| **14** | **Statistics** | Not applicable |
| **15 (published)** | **References** | (1) Prosser, C.L. and Brown, Jr., F.A. 1961, In: Comparative Animal Physiology, 2nd Edition by Sounders Co., page 388.<br>(2) Carter, M.C., Physiol. Plant., 18, 1054 (1965). |
| **16 (unpublished)** | **References** | No unpublished data cited in this summary |
| **17** | **Reliability Indicator** | 1 |

| | |
|---|---|
| Data Protection Claim | Yes |

**Table 1: Residual radioactivity in tissues of goats after oral administration of 4.53 ppm for ten consecutive days**

| Tissue: | [U-$^{14}$C-triazole]CGA 64250[1] | |
|---|---|---|
| | ppm | % of total dose |
| Liver | 0.096 | 0.014 |
| Brain | <0.009 | <0.01 |
| Kidney | 0.029 | 0.01 |
| Heart | 0.014 | <0.01 |
| Tenderloin Muscle | 0.011 | 0.01 |
| Leg Muscle | 0.009 | 0.01 |
| Omental Fat | <0.008 | <0.01 |
| Skeletal Fat | <0.008 | <0.01 |
| Rumen Fluid | 0.134 | 0.85 |
| Intestinal Contents | 0.379 | 1.17 |
| $CO_2$ | <0.01 | |
| Volatiles | <0.01 | |

[1] as ppm propiconazole equivalent

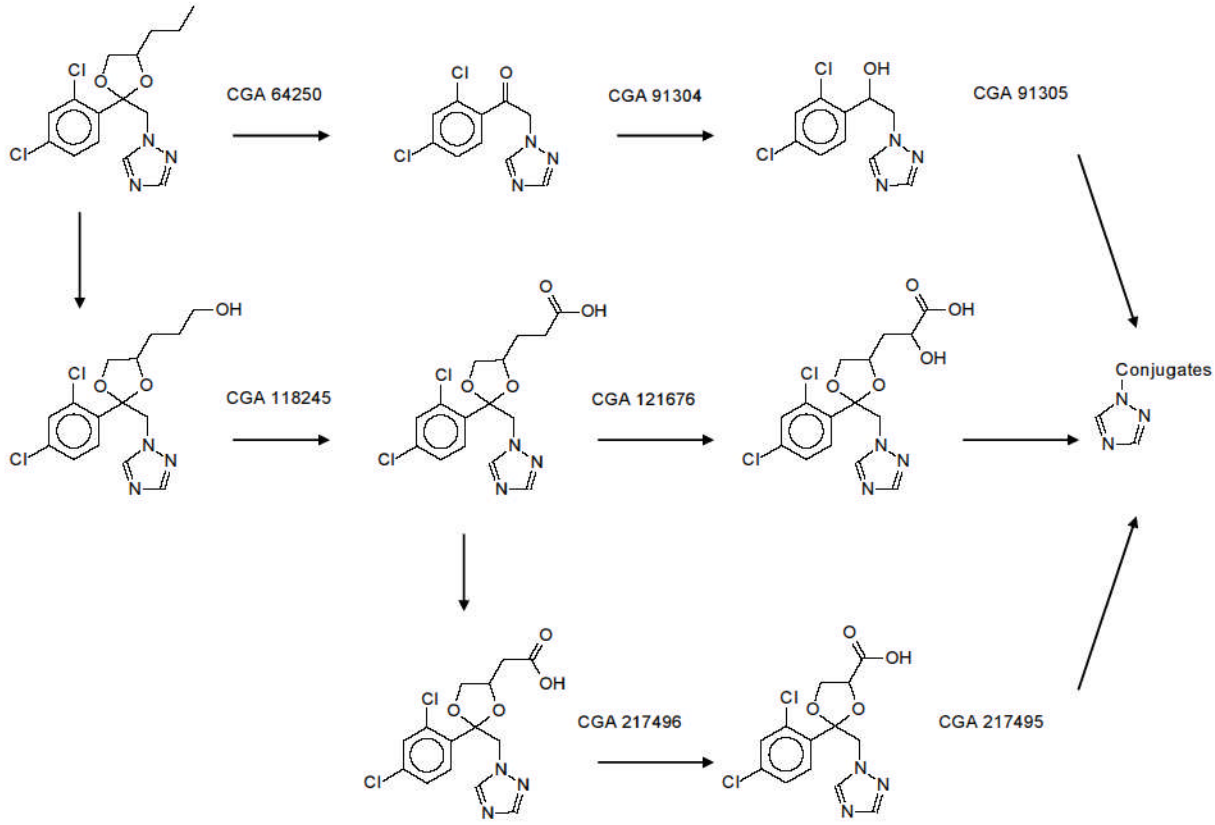
**Table 2: Residual radioactivity in milk, blood, urine and excreta of a goat after oral administration of 4.53 ppm of [U-$^{14}$C-triazole]CGA 64250 for ten consecutive days**

| | Milk | | Blood[2] | | Urine | | Feces | |
|---|---|---|---|---|---|---|---|---|
| | ppm[1] | % of total dose | ppm | % of total dose | ppm | % of total dose | ppm | % of total dose |
| Day 1 | 0.007 | 0.01 | 0.008 | 0.04 | 5.273 | 6.11 | 0.242 | 0.24 |
| Day 2 | 0.011 | 0.01 | | | 5.818 | 6.86 | 1.927 | 1.83 |
| Day 3 | 0.013 | 0.02 | 0.014 | 0.08 | 4.643 | 7.22 | 1.871 | 1.87 |
| Day 4 | 0.014 | 0.02 | | | 4.013 | 6.26 | 2.095 | 1.89 |
| Day 5 | 0.014 | 0.02 | 0.018 | 0.01 | 4.270 | 6.32 | 2.556 | 1.92 |
| Day 6 | 0.016 | 0.02 | | | 4.297 | 6.36 | 2.508 | 3.01 |
| Day 7 | 0.015 | 0.02 | 0.015 | 0.09 | 5.034 | 6.74 | 1.940 | 3.88 |
| Day 8 | 0.016 | 0.02 | | | 5.320 | 6.17 | 1.540 | 1.69 |
| Day 9 | 0.016 | 0.02 | 0.016 | 0.09 | 5.347 | 6.42 | 1.935 | 2.52 |
| Day 10 | 0.015 | 0.02 | 0.019 | 0.12 | 4.333 | 10.13 | 1.507 | 2.11 |
| Total | | 0.18 | | | | 68.59 | | 20.96 |

[1] as ppm propiconazole equivalent

[2] Blood comprises an estimated 7.3 % of body weight (1)

**Figure 1: Proposed metabolic pathway for propiconazole in goats**



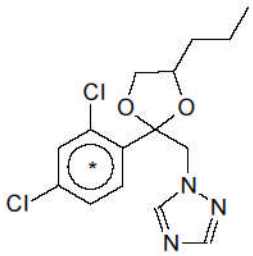
| Evaluation by Competent Authorities | |
|---|---|
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | 27.6.2005 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **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.*<br>*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.** | **6.2/14 6.2/15** | **Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study** |
| **91/414 Annex Point addressed** | **II 5.1.3 / 02a 5.1.3/ 02b** | **Biokinetics and metabolism in farm animals** |

| | | |
|---|---|---|
| **1.2** | **Title** | **Part A: Biological Report for the Metabolism of [Phenyl-$^{14}$C]Propiconazole in a Lactating Goat**<br>**Part B: Metabolism of [Phenyl-$^{14}$C]Propiconazole in Goats** |
| **1.3** | **Report and/or project N° Syngenta File N° (SAM)** | Biol-89012 (Part A) and F-00052 (Part B)<br>64250/2469 (Part A) 64250/2021 (Part B) |
| **1.4** | **Lab. Report N°** | |
| **1.5** | **91/414 Cross Reference** | 6.3 / 04 (A,B) |
| **1.6** | **Authors** | Report: [redacted]<br>Summary: [redacted] |
| **1.7** | **Date of report** | September 30, 1989 (Part A)<br>July 7, 1990 (Part B) |
| **1.8** | **Published / Owner** | no / Syngenta Limited |
| **2.1** | **Testing facility** | [redacted] |
| **2.2** | **Dates of experimental work** | May 30, 1989 (Application)<br>April 30, 1990 (Completion of analytical work) |
| **3.** | **Objectives** | This metabolism study was conducted to determine the qualitative nature of propiconazole residues in edible tissues. |
| **4.1** | **Test substance** | ISO common name: Propiconazole<br>Trade name:<br>Batch: [redacted]<br>$^{14}$C-labeled test substance: Yes [ x ] No [ ]<br>Specific activity: [redacted]<br>Radiochemical purity:<br>Structural formula: [U-$^{14}$C-phenyl]CGA 64250<br>(position of label) |




* = $^{14}$C

| | | |
|---|---|---|
| **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** | Gelatin capsules with granular cellulose filler |
| **6** | **Physical form** | see 5 |

| | | |
|---|---|---|
| **7.1** | **Test method** | US EPA Guideline: 40 CFR Part 158 Subdivision O: 171-4 |
| **7.2** | **Justification** | - |
| **7.3** | **Copy of method** | Description of the test method is included in the report |
| **8** | **Choice of method** | Not applicable |
| **9** | **Deviations** | Not applicable |
| **10.1** | **Certified laboratory** | Not applicable |
| **10.2** | **Certifying authority** | Not applicable |
| **10.3** | **GLP** | according to the FIFRA § 10 Guidelines |
| **10.4** | **Justification** | - |
| **11.1** | **GEP** | Not applicable |
| **11.2** | **Type of facility (official or officially recognized)** | [redacted] |
| **11.3** | **Justification** | Not applicable |

| | | | |
|---|---|---|---|
| **12** | **Test system** | **Test species**: | lactating goats (alpine crosses) |
| | | Source: | [redacted] |
| | | Age/weight (at time of dosing): | Age: 1.5 years/39.7 respectively 41.4 kg |
| | | **Application**<br>Dose levels: | oral application<br>each goat received 1 gelatin/cellulose capsule containing 125 mg (5 mCi) of propiconazole per day for 4 consecutive days |
| | | vehicles or solvents used/concentration: | see application, 5 and 6 |
| | | Group size: | 2 goats |
| | | Analytical methods: | The goats were acclimatized for 7 days prior to dosing. Excreta and milk were collected daily. 5.9 and 6.8 hours respectively after the last dose, the goats were sacrificed, blood and tissue samples were collected. Quantitation of the radioactivity in tissues and extracts was by combustion with subsequent LSC-measurement or direct LSC-measurement, respectively. |
| | | Radioactive areas on plates: | Ambis Radioanalytic Imaging System |
| | | Non-radioactive standards: | Not used |
| | | Radioassay: | Liquid scintillation counting |

**13 Findings**

The metabolism of [phenyl-$^{14}$C]propiconazole was determined utilizing the in-life [redacted]. Two lactating goats were dosed daily with 125 mg of [phenyl-$^{14}$C]propiconazole (62-92 ppm in feed based on averaged feed/day intake) in a gelatin capsule for 4 consecutive days.

Milk, urine and feces were collected during the dosing phase. Six hours after the last dose, the goats were sacrificed and tissues were exercised. Most of the administered $^{14}$C-dose was eliminated in the urine and feces: 48.1 - 56.5 % and 37.8 - 39.3 %, respectively. Edible tissues and milk were found to contain the following levels of $^{14}$C-residues, calculated as [phenyl-$^{14}$C]propiconazole equivalents (averaged for two goats): liver (3.83 ppm), kidney (2.53 ppm), fat (0.08 ppm), muscle (0.08 ppm) and milk (maximum 0.22 ppm on day 4).

Beside the parent compound, the following metabolites were identified in goats:

- 1-{[2-(2,4-dichlorophenyl)-4-(2-hydroxypropyl)-1,3-dioxolan-2yl]methyl}-1H-1,2,4-triazole (CGA 118 244)
- 1-{[2-(2,4-dichlorophenyl)-2-(2-hydroxyethyl}-1H-1,2,4-triazole (CGA 91 305)

Parent and metabolites accounted for most of the $^{14}$C-residues found in tissues and milk. In addition to these, milk was found to contain several other more polar $^{14}$C-residues, which were characterized as aryl sulfate conjugates.

| | | |
|---|---|---|
| **14** | **Statistics** | Not applicable |
| **15 (published)** | **References** | No publications cited in this summary |
| **16 (unpublished)** | **References** | No unpublished data cited in this summary |
| **17** | **Reliability Indicator** | 1 |

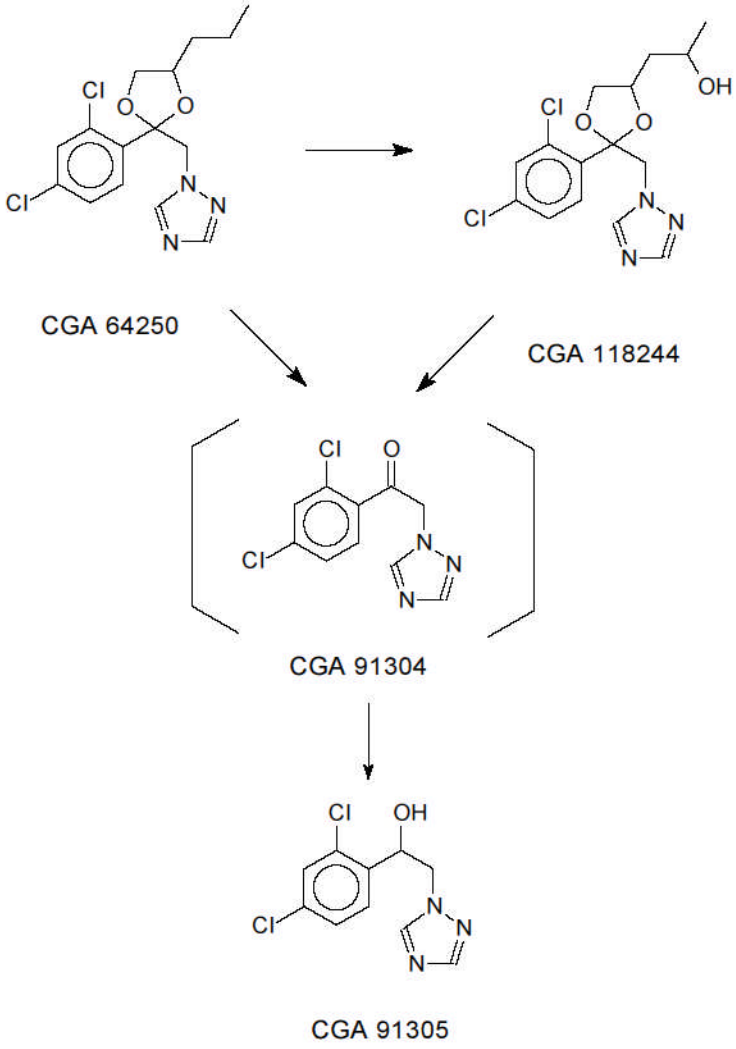
| | |
|---|---|
| Data Protection Claim | Yes |

**Table 1: Summary of distribution of the radioactivity in tissue and milk of lactating goats dosed with of [U-$^{14}$C-phenyl]CGA 64250**

| Animal Goat #73 | Residues [ppm] | Acetonitrile Extract [% of total residues] | | | | | Water Extracts [%] | N.E. [%] | Recovery [%] |
|---|---|---|---|---|---|---|---|---|---|
| tissue | | total | CGA 64250 | CGA 118244 | CGA 91305 | un-known | | | |
| Liver | 4.52 | 65.9 | 13.9 | 21.0 | 15.9 | 14.8 | 17.8 | 4.8 | 88.5 |
| Kidney | 2.67 | 78.7 | 4.5 | 9.4 | 17.6 | 31.1 | 17.4 | 1.3 | 97.4 |
| Tenderloin | 0.08 | 92.2 | 1.7 | 13.4 | 30.3 | 19.2 | 23.3 | 1.1 | 117.3 |
| | | Hexane Extract [% of total residues] | | | | | AcCN % | | |
| Omental fat | 0.07 | 88.7 | 20.3 | 34.0 | 31.3 | | 7.9 | 1.5 | 98.1. |
| Milk day 4 | 0.23 | 35.1 | - | 23.3 | 24.3 | [1]29.0 | 58.5 | 7.3 | 100.9 |

[1] Metabolites appear to be aryl sulfate conjugates based on their chromatographic behavior after treatment with aryl sulfatase.

**Figure 1: Proposed metabolic pathway for propiconazole in goats[1]**




[1] Metabolites detected with the phenyl labelled propiconazole

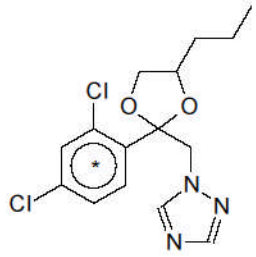
| Evaluation by Competent Authorities | |
|---|---|
| | **EVALUATION BY RAPPORTEUR MEMBER STATE** |
| **Date** | 27.6.2005 |
| **Materials and Methods** | [redacted] |
| **Results and discussion** | [redacted] |
| **Conclusion** | [redacted] |
| **Reliability** | [redacted] |
| **Acceptability** | [redacted] |
| **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.*<br>*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. | 6.2/16<br>6.2/17 | Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study |
| 91/414 Annex Point addressed | II<br>5.1.3 / 03a<br>5.1.3 / 03b | Biokinetics and metabolism in farm animals |

| | | |
|---|---|---|
| 1.2 | Title | **Part A: Biological Report for the Metabolism of Phenyl and Triazole $^{14}$C-Labeled CGA 64250 in Laying Hens, 50 ppm of Feed**<br>**Part B: Distribution, Extraction and Partitioning Characteristics of Phenyl and Triazole Labeled Propiconazole in Chickens** |
| 1.3 | Report and/or project N° Syngenta File N° (SAM) | BIOL-83011 (Part A) and ABR-85043 (Part B)<br>64250/1564 (Part A), 64250/1566 (Part B) |
| 1.4 | Lab. Report N° | |
| 1.5 | 91/414 Cross Reference | 6.3 / 01 (A, B) |
| 1.6 | Authors | Report: [redacted]<br>Summary: [redacted] |
| 1.7 | Date of report | January 6, 1984 (Part A)<br>June 25, 1985 (Part B) |
| 1.8 | Published / Owner | No / Syngenta Limited |
| 2.1 | Testing facility | [redacted] |
| 2.2 | Dates of experimental work | August 13, 1983 (Application) |
| 3. | Objectives | see findings |

| | | |
|---|---|---|
| 4.1 | Test substance | ISO common name: Propiconazole<br>Trade name:<br>Batch: [redacted]<br>$^{14}$C-labelled test substance: Yes [ x ] No [ ]<br>Specific activity of [U-$^{14}$C-phenyl]CGA 64250: [redacted]<br>Radiochemical purity of the test substance: [redacted]<br>Structural formula: [U-$^{14}$C-phenyl]CGA 64250<br>(position of label)<br>  <br>* = 14C<br>Batch: [redacted]<br>$^{14}$C-labelled test substance: Yes [ x ] No [ ]<br>Specific activity of [U-$^{14}$C-triazole]CGA 64250: [redacted]<br>Radiochemical purity of the test substance: [redacted] |