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North America

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January 30, 2006

Via Federal Express
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US Environmental Protection Agency
OPPT Document Control Office Mail Code 7407M
Attention: Section 8(e) Submission
EPA East Building, Room 6428
1201 Constitution Avenue NW
Washington, DC 20460-0001

BEHQ-0106-16357

Sanitized

06 FEB 10 11:31

Confidential

Subject: TSCA 8(e) Notice – TKA 40318 (CGI 90)

Dear Section 8(e) Coordinator:

This letter contains Confidential Business Information. Confidential Information bracketed { }.

In accordance with EPA's March 16, 1978 Policy Statement on Section 8(e) reporting under the Toxic Substances Control Act (TSCA), the EPA's June, 1991 TSCA Section 8(e) Reporting Guide, Ciba Specialty Chemicals Corporation wishes to bring to the attention of the Environmental Protection Agency the results observed in an Acute Oral Toxicity Study in Rats. The IUPAC chemical name for CGI 90 is { }. The CAS number is: { }.

An acute oral toxicity study was conducted in female HanRcc:WIST (SPF) rats with TKA 40318. Three females were treated at a dosage of 2000 mg/kg and 6 females at 300 mg/kg of body weight. In the first group treated at a dosage level of 2000 mg/kg body weight, lateral recumbency and severe convulsions were noted in two animals 7 minutes after treatment just prior to death. In the remaining animal, hunched posture, slight sedation and uncoordinated movements were noted and severe convulsions were observed approximately 20 minutes after treatment followed by death.

No clinical signs were observed during the course of the study in four animals of the 300 mg/kg group. Slight to moderately ruffled fur as well as hunched posture, slight sedation and uncoordinated movements were observed in the remaining two animals prior to death.

The median lethal dose of TKA 40318 (CGI 90) is greater than 300 mg/kg body weight and less than 2000 mg/kg.

We are enclosing a copy of the study "TKA 40318 (CGI 90 – Acute Oral Toxicity Study in Rats". RCC Study Number A00325. Based upon current EPA guidelines, it is felt these results warrant reporting under TSCA 8(e). A sanitized copy of this letter and study report are also enclosed. A Confidential Business Information Substantiation for this product is also submitted pursuant to TSCA 8(e) requirements. Please call the undersigned if you have any questions concerning this submittal.

Respectfully,

Marie Paquette
Senior Regulatory Specialist



540 White Plains Road
Tarrytown, New York 10591

Tel. 914-785-4288
Fax 914-785-4147

292319

RCC Study Number A00325

TKA 40318 (CGI 90):

Acute Oral Toxicity Study in Rats

Report

Author: Dr. E. Straube

Sponsor: Ciba Specialty Chemicals Inc.
4002 Basel / Switzerland

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TKA 40318 (CGI 90)

Report

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1 PREFACE

1.1 GENERAL

Title	TKA 40318 (CGI 90): Acute Oral Toxicity Study in Rats
Sponsor	Ciba Specialty Chemicals Inc. 4002 Basel / Switzerland
Study Monitor	Dr. Mounq Sook Lee
Test Facility	RCC Ltd Toxicology Wölferstrasse 4 CH-4414 Füllinsdorf / Switzerland

1.2 RESPONSIBILITIES

Study Director	Dr. E. Straube
Deputy for Study Director	G. Arcelin
Technical Coordinator	M. Bernstein
Head of RCC Quality Assurance	I. Wüthrich

1.3 SCHEDULE

Experimental Starting Date	05-APR-2005
Experimental Completion Date	04-MAY-2005
Delivery of Animals	05-APR-2005 (females, 2000 mg/kg) 07-APR-2005 (females, 300 mg/kg) 13-APR-2005 (females, 300 mg/kg)
Acclimatization	05-APR-2005 to 11-APR-2005 (females, 2000 mg/kg) 07-APR-2005 to 13-APR-2005 (females, 300 mg/kg) 13-APR-2005 to 19-APR-2005 (females, 300 mg/kg)
Treatment	12-APR-2005 (females, 2000 mg/kg) 14-APR-2005 (females, 300 mg/kg) 20-APR-2005 (females, 300 mg/kg)
Observation	05-APR-2005 to 12-APR-2005 (females, 2000 mg/kg) 07-APR-2005 to 28-APR-2005 (females, 300 mg/kg) 13-APR-2005 to 04-MAY-2005 (females, 300 mg/kg)
Study Completion Date	20-JUL-2005

1.4 ARCHIVING

RCC Ltd (CH-4452 Itingen / Switzerland) will retain the study plan, raw data, a sample of test item(s) and the final report of the present study for at least ten years. No data will be discarded without the Sponsor's written consent.

RCC STUDY NUMBER A00325
TKA 40318 (CGI 90)

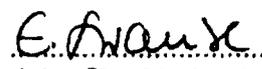
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1.5 SIGNATURE PAGE

Study Director:

Dr. E. Straube


date: 20-JUL-2005

Management:

 Dr. H. Fankhauser


date: 19-JUL-2005

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TKA 40318 (CGI 90)

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1.6 QUALITY ASSURANCE GLP TOXICOLOGY

RCC Ltd, Toxicology, CH-4452 Itingen / Switzerland

STATEMENT

RCC STUDY NUMBER : A00325
TEST ITEM : TKA 40318 (CGI 90)
STUDY DIRECTOR : Dr. E. Straube
TITLE : TKA 40318 (CGI 90):
Acute Oral Toxicity Study in Rats

The general facilities and activities are inspected periodically and the results are reported to the responsible person and the management.

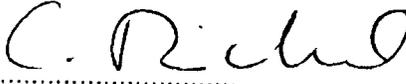
Study procedures, with exception of the formulation trials, were periodically audited. The study plan and this report were audited by the Quality Assurance. The dates are given below.

Dates and Types of QA Inspections	Dates of Reports to the Study Director and Test Facility Management
21-MAR-2005 Study Plan	21-MAR-2005
05-APR-2005 Process Based (Test System, Treatment, Raw Data)	05-APR-2005
20-MAY-2005 Report	20-MAY-2005

This statement also confirms that this final report reflects the raw data.

Quality Assurance:

L. Michel


date: 20-JUL-2005

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GOOD LABORATORY PRACTICE

1.7 STATEMENT OF COMPLIANCE

RCC STUDY NUMBER : A00325
TEST ITEM : TKA 40318 (CGI 90)
STUDY DIRECTOR : Dr. E. Straube
TITLE : TKA 40318 (CGI 90):
Acute Oral Toxicity Study in Rats

The purity of the test item is unknown. The formulation trials were performed before the study initiation date. Therefore, they are excluded from this statement.

This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted February 2nd, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final].

These principles are consistent with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA) and Japan (MHLW, MAFF and METI).

Study Director:

Dr. E. Straube

E. Straube
date: 20-JUL-2005

1.8 TEST GUIDELINES

The study procedures described in this report meet or exceed the requirements of the following guidelines:

Directive 2004/73/EC, B.1 tris "Acute Oral Toxicity-Acute Toxic Class Method", April 29, 2004.

OECD Guidelines for the Testing of Chemicals, Number 423 "Acute Oral Toxicity – Acute Toxic Class Method", adopted 17th December 2001.

1.9 ANIMAL WELFARE

This study will be performed in an AAALAC-approved laboratory in accordance with the Swiss Animal Protection Law under license no. 34.

2 SUMMARY

Three groups, each of three female HanRcc:WIST (SPF) rats, were treated with TKA 40318 (CGI 90) by oral gavage administration at a dosage of 2000 or 300 mg/kg body weight, respectively. The test item was diluted in vehicle (PEG 300) at a concentration of 0.2 or 0.03 g/mL and administered at a volume dosage of 10 mL/kg.

The animals were examined daily during the acclimatization period and mortality, viability and clinical signs were recorded. All animals were examined for clinical signs at approximately 30 minutes, 1, 2, 3 and 5 hours after treatment on day 1 and once daily during test days 2-15. Mortality/viability was recorded at approximately 30 minutes, 1, 2, 3 and 5 hours after administration on test day 1 (with the clinical signs) and twice daily during days 2-15. Body weights were recorded on day 1 (prior to administration) and on days 8 and 15. All animals were necropsied and examined macroscopically.

The following animals were treated and percentage of mortality was observed:

3 females treated at 2000 mg/kg	100 %
6 females treated at 300 mg/kg	16.7 %

In the first group treated at a dosage level of 2000 mg/kg body weight, lateral recumbency and severe convulsions were noted in two animals 7 minutes after treatment prior to their spontaneous death. In the remaining animal, hunched posture, slight sedation and uncoordinated movements were noted at this observation and severe convulsions were observed approximately 20 minutes after treatment in this animal prior to its spontaneous death.

No clinical signs were observed during the course of the study in four animals of the second and third treated group (300 mg/kg body weight). Slightly to moderately ruffled fur as well as hunched posture from the 0.5- to 5-hour reading and slight sedation at the 3-hour reading was noted in another animal. Uncoordinated movements, slight sedation, hunched posture, slightly ruffled fur from the 0.5- to 1-hour reading and moderated convulsions at the 0.5-hour reading were observed in the remaining animal prior to its spontaneous death.

The body weight of the animals was within the range commonly recorded for this strain and age.

Liquid contents in the stomach were noted in all animals of the first treated group at unscheduled necropsy after their spontaneous death. Congestion in the lungs, liquid contents in stomach, duodenum, jejunum, ileum and caecum as well as a dry abdominal cavity were recorded after the spontaneous death of one animal dosed 300 mg/kg body weight. No macroscopic findings were recorded at necropsy of the remaining animals.

3 CONCLUSION

The median lethal dose of TKA 40318 (CGI 90) after single oral administration to female rats, observed over a period of 14 days is:

300 mg/kg body weight < LD₅₀ (female rat) < 2000 mg/kg body weight

4 PURPOSE

The purpose of this study was to assess the acute toxicity of TKA 40318 (CGI 90) when administered by a single oral gavage to rats, followed by an observation period of 14 days.

This study provides information for both hazard assessment and hazard classification purposes.

5 MATERIALS AND METHODS

5.1 TEST SYSTEM

Test system	Rat, HanRcc:WIST (SPF)
Rationale	Recognized by the international guidelines as a recommended test system.
Source	RCC Ltd, Laboratory Animal Services CH-4414 Füllinsdorf / Switzerland
Number of animals per group	3 females
Total number of animals	9 females
Age when treated	11 to 13 weeks
Identification	Unique cage number and corresponding color-coded spots on the tail. The animals were marked at acclimatization start.
Randomization	Selected by hand at time of delivery. No computer generated randomization program.
Acclimatization	Under laboratory conditions, after health examination. Only animals without any visible signs of illness were used for the study.

5.2 HUSBANDRY

Room no.	0105 / RCC Ltd, Füllinsdorf
Conditions	Standard Laboratory Conditions. Air-conditioned with 10-15 air changes per hour, and continuously monitored environment with ranges for room temperature 22 ± 3 °C and for relative humidity between 30-70 % (values above 70 % during cleaning process possible), automatically controlled light cycle of 12 hours light and 12 hours dark, music during the daytime light period.
Accommodation	In groups of three in Makrolon type-4 cages with wire mesh tops and standard softwood bedding ('Lignocel' Schill AG, CH-4132 Muttenz/Switzerland).

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Diet	Pelleted standard Provimi Kliba 3433 rat/mouse maintenance diet, batch no. 4/05 (Provimi Kliba AG, CH-4303 Kaiseraugst/Switzerland) <i>ad libitum</i> . Results of analyses for contaminants are archived at RCC Ltd.
Water	Community tap water from Füllinsdorf <i>ad libitum</i> . Results of bacteriological, chemical and contaminant analyses are archived at RCC Ltd.

5.3 TEST ITEM

The following information was provided by the sponsor:

Identification	TKA 40318 (CGI 90)
Description	White to bluish solid
Batch number	[]
Purity / Formulation	Unknown; is excluded from the Statement of Compliance.
Stability of test item	Stable under storage conditions.
Expiry date	16-FEB-2008
Stability of test item dilution	At least one hour in PEG 300 at room temperature.
Storage conditions	At room temperature (range of 20 ± 5 °C), light protected.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

5.4 VEHICLE

The following information was provided by RCC Ltd:

Identification	Polyethylene glycol 300 (PEG 300)
Description	Colorless viscous liquid
Lot number	1078164 12004034
Source	FLUKA Chemie GmbH, CH-9471 Buchs
Stability of vehicle	Stable under storage conditions; expiration date: 13-JUL-2005
Storage conditions	At room temperature (range of 20 ± 5 °C), light protected.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

PEG 300 was found to be a suitable vehicle.

The vehicle was chosen after a non-GLP solubility trial which was performed before the study initiation date. This formulation trial is excluded from the GLP statement of compliance.

5.5 DOSE FORMULATION

Dose levels are in terms of the test item as supplied by the sponsor.

The dose formulations were made shortly before each dosing occasion using a spatula and a magnetic stirrer as homogenizers.

The test item was reduced into a fine powder using a mortar and a pestle. Thereafter, the test item was weighed into a tared glass beaker on a suitable precision balance and the vehicle added (weight:volume). The glass beaker was wrapped with aluminium foil to protect the test item solution against light.

Homogeneity of the test item in the vehicle was maintained during administration using a magnetic stirrer.

5.6 TREATMENT

The animals received a single dose of the test item by oral gavage administration at 2000 or 300 mg/kg body weight after being fasted for approximately 18 to 19 hours (access to water was permitted). Food was provided again 3 hours after dosing.

The application volume was 10 mL/kg body weight.

Rationale: Oral administration was considered to be an appropriate application method as it is a possible route of humane exposure during manufacture, handling and use of the test item.

5.7 OBSERVATIONS

Mortality / Viability	Daily during the acclimatization period, during the first 30 minutes and at approximately 1, 2, 3 and 5 hours after administration on test day 1 (with the clinical signs) and twice daily during days 2-15.
Body weights	On test days 1 (prior to administration), 8 and 15.
Clinical signs	Daily during the acclimatization period, during the first 30 minutes and at approximately 1, 2, 3 and 5 hours after administration on test day 1. Once daily during days 2-15.

6 PATHOLOGY

6.1 NECROPSY

All animals which died spontaneously during the observation period were necropsied as soon as they were found dead.

All surviving animals were killed at the end of the observation period by an intraperitoneal injection of Vetanarcol at a dose of at least 2.0 mL/kg body weight (equivalent to at least 324 mg sodium pentobarbitone/kg body weight) and discarded after macroscopic examinations were performed. No organs or tissues were retained.

7 STATISTICAL ANALYSIS

No statistical analysis was used.

8 DATA COMPILATION

Body weights were recorded on-line.

Clinical signs were recorded on data sheets.

Mortality/viability were compiled into the RCC Tox Computer System during recording and/or recorded on data sheets.

Macroscopic findings were compiled into the RCC Tox Computer System during recording or recordings were carried out on data sheets and the data were transcribed later for compilation and analysis.

The RCC Tox Computer System (RCC-Tox-Lims) had been validated with respect to data collection, storage and retrievability.

9 RESULTS

9.1 MORTALITY

All females treated at a dosage level of 2000 mg/kg body weight died 10 or 30 minutes after application, respectively. One female treated at a dosage level of 300 mg/kg body weight was found dead 2 hours after application. The remaining animals (administered 300 mg/kg body weight) survived until the end of the observation period.

9.2 CLINICAL SIGNS

In the first group treated at a dosage level of 2000 mg/kg body weight, lateral recumbency and severe convulsions were noted in two animals seven minutes after treatment prior to their spontaneous death. In the remaining animal, hunched posture, slight sedation and uncoordinated movements were noted at this observation and severe convulsions were observed approximately 20 minutes after treatment in this animal prior to its spontaneous death.

No clinical signs were observed during the course of the study in four animals of the second and third treated group (300 mg/kg body weight). Slightly to moderately ruffled fur as well as hunched posture from the 0.5- to 5-hour reading and slight sedation at the 3-hour reading was noted in another animal. Uncoordinated movements, slight sedation, hunched posture, slightly ruffled fur from the 0.5- to 1-hour reading and moderated convulsions at the 0.5-hour reading were observed in the remaining animal prior to its spontaneous death.

9.3 BODY WEIGHTS

The body weight of the animals was within the range commonly recorded for this strain and age.

9.4 MACROSCOPIC FINDINGS

Liquid contents in the stomach were noted in all animals of the first treated group at unscheduled necropsy after their spontaneous death. Congestion in the lungs, liquid contents in stomach, duodenum, jejunum, ileum and caecum as well as a dry abdominal cavity were recorded after the spontaneous death of one animal dosed 300 mg/kg body weight. No macroscopic findings were recorded at necropsy of the remaining animals.

9.5 MEDIAN LETHAL DOSE

The median lethal dose of TKA 40318 (CGI 90) after single oral administration to female rats, observed over a period of 14 days is:

300 mg/kg body weight < LD₅₀ (female rat) < 2000 mg/kg body weight

10 INDIVIDUAL FINDINGS**10.1 MORTALITY / CLINICAL SIGNS**

Dose mg/kg	Ani- mal No.	Sex	Signs	Test days																		
				1					2	3	4	5	6	7	8	9	10	11	12	13	14	15
				0.5*	1*	2*	3*	5*														
2000	1	F	No clinical signs	+																		
			Hunched posture	√																		
			Sedation	1																		
			Uncoordinated movements	1																		
			Convulsions	3																		
	2	F	No clinical signs	+																		
			Lateral recumbency	√																		
			Convulsions	3																		
	3	F	No clinical signs	+																		
			Lateral recumbency	√																		
Convulsions			3																			

Key: 1 slight, 3 marked, + found dead, √ noted

* Examinations were performed approximately 7 minutes (animals nos. 1 to 3), 22 minutes (animal no 1 only), 0.5, 1, 2, 3 and 5 hours after treatment.

10.3 MACROSCOPIC FINDINGS

Dose mg/kg	Animal No.	Sex	Mode of death	Findings
2000	1	F	D	Liquid contents in the stomach
	2	F	D	Liquid contents in the stomach
	3	F	D	Liquid contents in the stomach
300	4	F	S	No macroscopic findings
	5	F	S	No macroscopic findings
	6	F	S	No macroscopic findings
300	7	F	S	No macroscopic findings
	8	F	S	No macroscopic findings
	9	F	D	Congestion in the lungs, liquid contents in stomach, duodenum, jejunum, ileum and caecum, dry abdominal cavity

S: scheduled necropsy, D: found dead

11 GLP – CERTIFICATION

The Swiss GLP Monitoring Authorities



Swiss Federal
Office of
Public Health



Swiss Agency for the
Environment, Forests
and Landscape

swissmedic

Swissmedic
Swiss Agency for
Therapeutic Products

Statement of GLP Compliance

It is hereby confirmed that

during the period of

November 18 – 22, 2002

the following Test Facilities of

RCC Ltd
4452 Itingen
Switzerland

were inspected by the Federal Office of Public Health, the Swiss Agency for Therapeutic Products and the Swiss Agency for the Environment, Forests and Landscape with respect to the compliance with the Swiss legislation on Good Laboratory Practice.

Test Facilities

Areas of expertise *

- Toxicology

TOX, ACC, MUT,
OTH (Safety Pharmacology)

- Environmental Chemistry and
Pharmanalytica

ACC, ECT, ENF, EMN, PCT,
RES, OTH (Animal metabolism)

The inspections were performed in agreement with the OECD Guidelines for National GLP Inspections and Audits. It was found that the aforementioned test facilities were operating in compliance with the Swiss Ordinance relating to Good Laboratory Practice [RS 813.016.5] at the time they were inspected.

Federal Office of Public Health
The Director

Bern, March 2003

Prof. Th. Zellner

* TOX = Toxicology ; ACC = Analytical and Clinical Chemistry ; ECT = Environmental toxicity on aquatic and terrestrial organisms ; ENF = Behaviour in water, soil and air. Bioaccumulation ; EMN = Studies on effects on mesocosms and natural ecosystems ; MUT = Mutagenicity ; PCT = Physical-chemical testing ; RES = Residue studies ; OTH = Other, to be specified.