

CODING FORMS FOR SRC INDEXING

Microfiche No.		OTS0573778	
New Doc ID	89970000286	Old Doc ID	8EHQ-0997-14044
Date Produced	09/14/88	Date Received	09/03/97
		TSCA Section	8E
Submitting Organization		BAYER CORP	
Contractor		BAYER AG - WUPPERTAL	
Document Title	SUPPORT: ACUTE TOXICITY OF (2,3,5,6-TETRAFLUOROPHENYL)-METHYL-(1R-TRANS)-3-(2,2-DICHLORO-ETHENYL)-2,2-DIMETHYLCYCLOPROPANE CARBOXYLATE W/TSCA COVER SHEET DATED 05/08/97		
Chemical Category	(2,3,5,6-TETRAFLUOROPHENYL)-METHYL-(1R-TRANS)-3-(2,2-DICHLORO-		

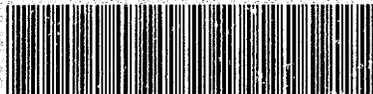
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2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e); optional for §4, 8(d) & FYI) - YES X - NO	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID Cert# P 917006688 97-2-12(e)	2.3 FOR EPA USE ONLY
3.0 CHEMICAL/TEST SUBSTANCE IDENTITY - Contains CBI <i>Reported Chemical Name (specify nomenclature if other than CAS name):</i> CAS#: N/A (2,3,5,6-tetrafluorophenyl)-methyl-(1R-trans)-3-(2,2-dichloroethyl)-2, Purity <u>94.5</u> % 2-dimethylcyclopropene carboxylate <input type="checkbox"/> - Single Ingredient <input checked="" type="checkbox"/> - Technical Active Ingredient <input type="checkbox"/> - Mixture Trade Name: <u>NAK 4455</u> Common Name: _____		
4.0 REPORT/STUDY TITLE - Contains CBI NAK 4455 Technical - Study for Acute Dermal Toxicity to Rats, Report # 17155 <input type="checkbox"/> Continuation sheet attached		
5.1 STUDY/TSCATS INDEXING TERMS [CHECK ONE] HEALTH EFFECTS (HE): <input checked="" type="checkbox"/> ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____		
5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes) STUDY SUBJECT ROUTE OF VEHICLE OF TYPE: <u>ATOX</u> ORGANISM (HE, EE only): <u>RATS</u> EXPOSURE (HE only): <u>DERM</u> EXPOSURE (HE only): _____ Other: _____ Other: _____ Other: _____		
6.0 REPORT/STUDY INFORMATION <input type="checkbox"/> Contains CBI <input type="checkbox"/> Study is GLP Laboratory <u>Bayer AG -Wuppertal</u> Report/Study Date: <u>9/14/88</u> Source of Data/Study Sponsor (if different than submitter) <u>Bayer AG</u> Number of pages <u>28</u> <input type="checkbox"/> continuation sheet attached		
7.0 SUBMITTER INFORMATION <input type="checkbox"/> Contains CBI Submitter: <u>Donald W. Lamb, Ph.D</u> Title: <u>V. P., Prod. Safety & Reg. Affrs</u> Phone: <u>412-777-7431</u> Company Name: <u>Bayer Corporation</u> Company Address: <u>100 Bayer Road</u> <u>Pittsburgh, PA 15205-9741</u> Submitter Address (if different): _____ Technical Contact: <u>Donald W. Lamb, Ph.D</u> Phone: <u>(412)777-7431</u> <input type="checkbox"/> continuation sheet attached		
8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS <input type="checkbox"/> Contains CBI Substance is a developmental neurotoxic and the report indicates some impact on neurotoxicity.		



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Submitter Signature: Donald W Lamb Date: 5/8/97

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BAYER AG
Fachbereich Toxikologie
(Toxicology Unit)
Friedrich-Ebert-Str. 217 - 333
D-56 Wuppertal 1

Report no. 17155
Date of report: 14.09.1988

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NAK 4455 techn.

STUDY FOR ACUTE DERMAL TOXICITY TO RATS

by
Dr. F. Krötlinger

BAYER AG

FILE
8141

Study number: T 5025026

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may only be used with the approval of BAYER AG. Further repro-
duction of all or part of this report is not permissible.

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1. QUALITY ASSURANCE / GLP DECLARATIONS

Test substance: NAK 4455 techn.

Study no.: T 5025026

1.1 Quality assurance declaration

The study was inspected by Quality Assurance on the dates given below. The results of the checks and inspections are conveyed in writing to the study director and, if necessary, also the Head and Director of the Institute, or other persons affected.

Date of
check/inspectionDate of issue of
inspection report7.5.1987
21/26.5.19877.5.1987
21.5.1987Quality Assurance
PH-AQ-S/GLP, Bayer AG

Date: 8.9.1988

Responsible: (Dr. H.P. Schulz)

1.2 Study director's GLP declaration

The study conformed to the OECD principles of Good Laboratory Practice (GLP) of 4.2.1983, published in Bundesanzeiger No. 42a of 2.3.1983.

Dr. F. Krötlinger
(Study director)

Date 6.9.1988

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2. SIGNATURES

Study director:

(Dr. F. Krötlinger)

Head of Department:

(Dr. W. Flucke)

Translator:


.....
G.J. Marshall MA
24.4.89

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3. SUMMARY

A study of acute dermal toxicity to rats was conducted with the test compound NAK 4455 techn.

The methods used conformed to the OECD Guideline for Testing of Chemicals, Section 4: Health Effects, No. 402 - "Acute Dermal Toxicity", adopted: 12th May 1981.

The test compound was mixed to a paste with cellulose powder.

LD50 dermal

Rat male (exposure 24 h): > 5000 mg/kg bw
Rat female (exposure 24 h): > 5000 mg/kg bw

Evaluation:

The test compound proved to have little toxicity after acute dermal application to rats. The slight systemic effect observed on the animals did not appear until a high dose range was reached (from 1000 mg/kg body weight). No mortalities occurred up to and including the dose of 5000 mg/kg body weight. The no-effect level was 100 mg/kg body weight.

4. INTRODUCTION

A study for acute dermal toxicity to the rat was conducted with NAK 4455 techn.

The purpose of the study was to permit product classification and estimation of the acute health hazard.

The study took place from May to June 1987 at the Institute of Toxicology Agrochemicals, Toxicology Division, BAYER AG Wuppertal, Friedrich-Ebert-Str. 217-333.

5. STUDY IDENTIFICATION AND RESPONSIBILITY5.1. Study number

Acute dermal toxicity:

T 5025026

5.2. Responsibility

Head of Institute of Toxicology Agrochemicals:

Dr. L. Macheimer

Head of Department:

Dr. W. Flucke

Study Director:

Dr. K.G. Heinemann
(until 31.12.1987)
Dr. F. Krötlinger
(from 1.1.1988)

Analysis:

Dr. K. Wohlers/
Dr. Köhler

Quality assurance:

Dr. M.P. Schulz

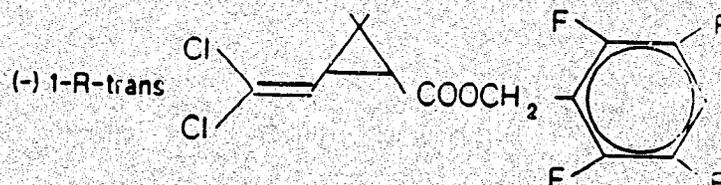
Filing of study data:

Dr. E.A. Löbbecke

6. MATERIAL AND METHODS**6.1. Test compound**

Test compound designation: NAK 4455 techn. active ingredient
Manufacturer: Bayer AG
Batch no.: 130187
Purity: 94.5 % (analytical finding, APF of 27.1.87, see Appendix, page 28)
Approval: until 27.7.1987
State of aggregation: solid/liquid (melting point 50°C)
Appearance: dark brown
pH: 4.4 (2 % in water)
Storage: laboratory cabinet at 22-24°C
Chemical name: (2,3,5,6-tetrafluorophenyl)-methyl-(1R-trans)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate (CA)

Structural formula:



Molar mass:

371.2 g/mol

Molecular formula:

C₁₅H₁₂Cl₂F₄O₂

6.2. Laboratory animals

6.2.1. Species and species rationale

The study was conducted with rats - a species recommended in the test guidelines.

SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb) from Versuchstierzucht Winkelmann, Borcheln, Kreis Paderborn, were used. Animals of this strain have been used for toxicological studies at BAYER AG for many years. Historical data of control groups for the parameters investigated in this study is available. The breed's state of health is routinely spot-checked for the main specific pathogens. The results of these examinations are filed at BAYER AG.

6.2.2. Acclimatisation

After receipt the animals intended for this study were acclimatised to the conditions of husbandry for at least seven days until the start of treatment.

6.2.3. State of health

Only healthy, symptom-free animals were used for the study. The animals were not vaccinated or treated against infection either before delivery, or during the acclimatisation or study periods. The females were nulliparous and not pregnant.

6.2.4. Age and body weight

At start of test the males had a mean starting weight of 223 g (209 to 239 g), and the females 233 g (217 g to 258 g). These body weights correspond to an animal age of approx. nine to sixteen weeks.

6.3. Animal husbandry

6.3.1. Accommodation of animals

During the acclimatisation period the animals were kept, individually and conventionally, in Makrolon® cages type III (five per cage/sex), and during the test period in Makrolon® cages type II (SPIEGEL, A., GÖNNERT, R., Zschr. Versuchstierkunde 1, 38, 1961, and MEISTER, G., Zschr. Versuchstierkunde 7, 144-153, 1965). The cages were replaced at least once per week with cages containing clean litter.

The litter used was low-dust wood granules (Bogner GmbH, Solingen-Ohligs). The wood granules were spot-checked for contaminant content. The documentation of these examinations is filed at BAYER AG. The results of the analyses did not provide any indications of an influence on the objective of the study.

6.3.2. Rooms

All the animals in this study were in one room. For capacity reasons, rats in other toxicological studies were temporarily kept in the same room. Adequate spatial separation and suitable organisation of procedures ensured that the animals were not confused. The animals were not treated in the animal room, but in a separate laboratory.

6.3.3. Cleaning, disinfecting

The animal room was cleaned and disinfected once weekly. It was ensured that the food was not contaminated and there was no contact with the animals.

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6.3.4. Climatic conditions

The room climate was set as follows.

Room temperature:	22 ± 2° C
Humidity (relative):	approx. 50 %
Light/dark rhythm:	12-hour, artificial lighting
Air throughput:	at least 10 times per hour

Occasional variations from this standard, for instance due to room cleaning, occurred. They had no apparent effect on the course of the study.

6.3.5 Feeding

The diet consisted of "Altromin® 1324 diet for rats and mice", which corresponds in content to the components of "Altromin® 1320" (manufacturer Altromin GmbH, Lage), and tap water (watering bottles). Food and water were available for ad-libitum consumption.

The nutritive composition (for specification see page 27 in Appendix) and the contaminant content of the standard diet were routinely spot-checked and analysed.

The tap water was of drinking quality (Statute on Drinking Water and on Water for Foodstuff Factories of 22.5.1986, BGBI. I page 760).

Documentation on the analyses regarding the adherence to specification of food and water is filed at BAYER AG. The data available did not provide any indications of an effect on the objective of the study.

Polycarbonate bottles containing approx. 300 ml were used for the water during the study (SPIEGEL, A., GÖNNERT, R., Zschr. Versuchstierkunde 1, 38, 1961, and MEISTER, G., Zschr. Versuchstierkunde 7, 144-153, 1965).

6.4. Test methods

Guidelines

- OECD Guideline for Testing of Chemicals, Section 4: Health Effects, No. 402 - "Acute Dermal Toxicity", adopted: 12th May 1981.

6.5. Conduct of test

6.5.1. Test compound formulation

The test compound was mixed to a paste before application with four per cent by weight cellulose powder, for better adhesion to the skin.

The test compound was stable in cellulose powder over the treatment period (for analytical findings see Appendix page 26). G

6.5.2. Grouping and identification of animals

All the animals were allocated before administration to the treatment groups with the aid of random number tables (van der Gulden, Dr. W.J.I. et al.: Versuchstiere und Versuchstechnik, Band II, 325-327 (1975)). The animals were identified by individual marks using aqueous picric acid solution, and by cage cards giving test compound, animal number, dose, sex and study number. G

6.5.3. Administration and dosage

The tests were made with male and female rats. The test compound doses were individually weighed on the aluminium foil intended for covering the skin areas, and mixed to a paste with cellulose powder. The foil was placed on the intact dorsal skin, shorn on the previous day, of five rats per dose and sex, and fastened to the skin with an occlusive dressing. The exposure lasted twenty-four hours. After removal of the dressings, the treated skin areas were cleaned with soap and water.

6.5.4. Examinations

6.5.4.1. Clinical observation

Appearance and behaviour were recorded several times on the day of administration, and then at least once per day. If symptoms occurred, their type, duration and intensity were noted as group findings. In the case of mortalities the time of death was registered. The times given refer to the application time on the administration day (first test day). For clearer presentation these times may be adjusted by five and ten minutes, and to quarter, half and full hours. The figures in days represent test days. If symptoms no longer occur after an observation-free period between two test days (e.g. overnight), it is assumed that they were apparent for the full previous test day. B A R

If symptoms occur for the first time after such an interval, it is assumed that they were already apparent on the previous day. Similarly mortalities which occurred in this observation-free period (e.g. overnight) are allocated to the previous test day.

6.5.4.2. Observation period

The observation period lasted for 14 days.

6.5.4.3. Body weights

The rats' body weights were recorded before administration and then daily. The day of administration is designated day 0. The body weight determination on day 0 took place before administration. The days given represent calendar days relative to the day of administration.

6.5.4.4. Autopsy

The animals were sacrificed at the end of the observation period with diethylether and subjected to gross pathological examination.

6.5.5. LD50 calculation

If it was possible to calculate the median lethal dose (LD50), this was done with computer assistance (HP 3000) by A.P. ROSIELLO, J.M. ESSIGMANN and G.N. WOGAN's method (1977) as modified by J. PAULUHN (1983).

This procedure is based on C.I. BLISS' maximum likelihood method (1938).

6.5.6. Adherence to GLP principles

The study conformed to the OECD principles of Good Laboratory Practice (GLP), Bundesanzeiger No. 42a, 3-16, 2nd March 1983. For the GLP declarations see page 3.

In accordance with these principles all the study documentation was filed in the Toxicology Division, BAYER AG (archive).

7. RESULTS**7.1. Acute dermal toxicity (rat)****7.1.1. Dose-effect table (LD50)**

The results of the study for acute dermal toxicity to the rat, with information on the LD50, are compiled in the following Table 1.

Table 1

Dosis mg/kg Kgw.	Toxikol. Ergebnis*	Symptom- dauer	Todes- zeitpunkt	Mor a- lität(%)
Dose mg/kg b.w.	Toxicol. results*	Duration of signs	Time of death	Morta- lity (%)
Ratte/rat ♂				
100.0	0/ 0/ 5	--	--	0
1000.0	0/ 5/ 5	165'-1d	--	0
2500.0	0/ 5/ 5	235'-1d	--	0
5000.0	0/ 5/ 5	70'-3d	--	0
LD50 = > 5000 mg/kg Kgw.				
Ratte/rat ♀				
100.0	0/ 0/ 5	--	--	0
1000.0	0/ 5/ 5	80'-1d	--	0
2500.0	0/ 5/ 5	225'-1d	--	0
5000.0	0/ 5/ 5	60'-3d	--	0
LD50 = > 5000 mg/kg Kgw.				

- * 1. Zahl = Anzahl der gestorbenen Tiere
 2. Zahl = Anzahl der Tiere mit Symptomen
 3. Zahl = Anzahl der eingesetzten Tiere

1st figure = number of dead animals
 2nd figure = number of animals with signs
 3rd figure = number of animals in the group

7.1.2. Clinical findings

The dose of 100 mg/kg was tolerated by animals of both sexes without symptoms. From the dose of 1000 mg/kg body weight, males and females exhibited apathy, which was apparent at higher doses up to a maximum of three days after administration. In addition female animals from the dose of 1000 mg/kg body weight exhibited vocalization on the first day. In the 5000 mg/kg body weight group, both sexes exhibited spasmodic posture and tremor.

The group findings are listed in the Appendix on page 19.

7.1.3. Local findings

No gross alterations were observed in any of the dose groups in the treatment area.

7.1.4. Body weights

The males' and females' body weight development in all the dose groups was unaffected by the treatment. The lower body weights in the first test days are assessed as a result of reduced food intake, due to the restriction and the stress caused by the occlusive dressing. During the rest of the observation period this effect was made good (for individual and mean figures see page 20 to 23 in the Appendix).

7.1.5. Gross pathological findings

Animals sacrificed at end of observation period: no indications of treatment-induced grossly apparent organ damage.

The individual autopsy findings are listed in the Appendix on pages 24 and 25.

8. DISCUSSION AND EVALUATION

The test compound NAK 4455 techn. was evaluated in male and female rats for acute dermal toxicity. An LD50 greater than 5000 mg/kg body weight was established for male and female rats.

The symptoms occurring in the dose groups from 1000 mg/kg body weight (e.g. spasmodic posture, tremor and vocalization, which only occurred in the case of the females) point to an effect of the test compound of weak intensity on the nervous system, which was reversible. No mortalities occurred. No skin alterations were observed in any of the dose groups. The dose of 100 mg/kg body weight was tolerated without symptoms by male and female rats.

The test compound therefore proved to have little toxicity after acute dermal administration.

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9. LITERATUR / REFERENCES

OECD-Guideline for Testing of Chemicals; Section 4: Health Effects, No. 402: "Acute Dermal Toxicity", adopted: 12th May 1981.

BLISS, C.I.

The determination of the dosage-mortality curve from small numbers.

Q.J. Pharm. Pharmacol. 11, 192-216 (1938).

PAULUHN, J.

Über die computergestützte Abschätzung der LD50/LC50
BAYER AG Bericht-Nr.: 11835 vom 18.5.1983
(unveröffentlicht).

ROSIELLO, A.P., J.M. ESSIGMANN und G.N. WOGAN

Rapid and accurate determination of the median lethal dose (LD50) and its error with small computer.

J. Tox. and Environ. Health 3, 797-809 (1977).

NOAKES und SANDERSON

Wickelmethode

Brit. J. Ind. Med. 26, 59, (1969).

10. ABKÜRZUNGSVERZEICHNIS / KEY TO ABBREVIATIONS

Kgw.	Körpergewicht / body weight
Nr.	Nummer / number
o.b.B.	ohne besonderen Befund / no special finding
Toxikol. Ergebnis	Toxikologisches Ergebnis / toxicological result
Expos.	Exposition / exposure
b.w.	body weight
Toxicol. results	Toxicological results