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09/12/88	09/03/97	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-

TSCA CBI STATUS:

-CHECK IF THIS PAGE CONTAINS CONFIDENTIAL BUSINESS INFORMATION (CBI)

Clearly mark the confidential information with bracketing and check the box in the appropriate section (☐ *Contains CBI*).
Submit a sanitized cover sheet with CBI deleted. Mark the sanitized copy, "Public Display Copy" in the heading.

1.0 SUBMISSION TYPE - *Contains CBI*

☐ 8(d) X 8(e) ☐ FYI ☐ 4 ☐ OTHER: Specify_____

X- Initial Submission -Follow-up Submission -Final Report Submission

Previous EPA Submission Number or Title if update or follow-up: Docket Number, if any: #

☐ continuation sheet attached

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(f)	2.3 FOR EPA USE ONLY 8EHQ-0997-14045

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY -*Contains CBI*

Reported Chemical Name (specify nomenclature if other than CAS name):

CAS#: N/A (2,3,5,6-tetrafluorophenyl)-methyl-(1R-trans)-3-(2,2-dichloroethenyl)-2,

Purity 94.5 % 2-dimethylcyclopropane carboxylate

☐ - Single Ingredient

X - Technical Active Ingredient

☐ -Mixture *Trade Name:* NAK 4455 *Common Name:*

4.0 REPORT/STUDY TITLE - *Contains CBI*

NAK 4455 Technical - Study for Acute Intraperitoneal Toxicity to Rats, Report # 17139

☐ Continuation sheet attached

8EHQ-97-14045

5.1 STUDY/TSCATS INDEXING TERMS

[CHECK ONE]

HEALTH EFFECTS (HE): X ENVIRONMENTAL EFFECTS (EE): ENVIRONMENTAL FATE (EF):

5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes)

STUDY TYPE: ATOX	SUBJECT ORGANISM (HE, EE only): RATS	ROUTE OF EXPOSURE (HE only): INTP	VEHICLE OF EXPOSURE (HEonly)
Other:	*Other:*	*Other:*	*Other:*

6.0 REPORT/STUDY INFORMATION ☐ *Contains CBI* ☐ Study is GLP

Laboratory Bayer AG -Wuppertal Report/Study Date: 9/12/88

Source of Data/Study Sponsor (if different than submitter) Bayer AG Number of pages 52

☐ continuation sheet attached

7.0 SUBMITTER INFORMATION ☐ *Contains CBI*

Submitter: Donald W. Lamb, Ph.D Title: V. P., Prod. Safety & Reg. Affrs Phone: 412-777-7431

Company Name: Bayer Corporation Company Address: 100 Bayer Road

Pittsburgh, PA 15205-9741 Submitter Address (if different):

Technical Contact: Donald W. Lamb, Ph.D Phone: (412)777-7431

☐ continuation sheet attached

8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS ☐ *Contains CBI*

Substance is a developmental pyrethroid and the report indicates some impact on neurotoxicity.

Contains No CBI

☐ continuation sheet attached

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

97 SEP -3 AM 7:18

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OPPT CMIC

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

Report no. 17139

Date 12.09.1988

NAK 4455 techn.

STUDY FOR ACUTE INTRAPERITONEAL TOXICITY TO RATS

by

Dr. F. Krötlinger

FILE
8135

Study number: T 2025122

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1. QUALITY ASSURANCE/GLP DECLARATIONS

Test substance: NAK 4455 techn.

Study no.: T 2025122

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/inspection	Date of issue of inspection report
25.03.1987	25.03.1987
25.03.1987	30.03.1987

The results of the study and the methods used have been correctly reported.

Quality Assurance
PH-AQ-S/GLP, Bayer AG

Date: 07.09.88 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 11.04.1988

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2. SIGNATURES

Study director: (Dr. F. Krötlinger)

Head of Department: (Dr. W. Flucke)

C. J. Marshall MA
Translator
17.02.1989

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3. SUMMARY

A study for acute intraperitoneal toxicity to the rat was conducted with the active ingredient NAK 4455 techn.

The test compound was formulated with polyethylene glycol E 400.

LD50 intraperitoneal

Rat male: 2413 (2022 - 2881) mg/kg bw
Rat female: 1496 (1340 - 1670) mg/kg bw

Assessment

The test compound proved to be slightly toxic to rats after acute intraperitoneal administration. The symptoms observed pointed to an action on the nervous system, as is familiar after dosage of pyrethroids of this class.

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4. INTRODUCTION

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

The purpose of the study was to permit estimation of the acute health hazard after intraperitoneal administration, in comparison to oral and dermal administration. Conclusions as to the bioavailability or absorption after oral or dermal administration may also be drawn from the results of such a comparison.

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

5. STUDY IDENTIFICATION AND RESPONSIBILITY

5.1. Study number

Acute intraperitoneal toxicity:	T 2025122

5.2. Responsibility

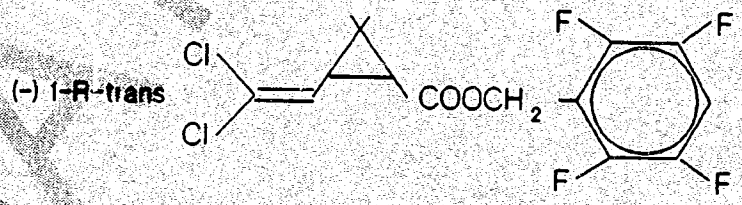
Head of Institute of Toxicology Agrochemicals:	Dr. L. Machemer
Head of Department:	Dr. W. Flucke
Study director:	Dr. K. G. Heimann (until 31.12.1987) Dr. F. Krötlinger (from 01.01.1988)
Analysis:	Dr. K. Wohlers / R. Stugh
Quality assurance:	Dr. H. P. Schulz
Filing of study data:	Dr. E. A. Löbbecke

6. MATERIAL AND METHODS

6.1. Test compound

Test compound designation:	NAK 4455 technical active ingred.
Manufacturer:	Bayer AG
Batch no.:	130187
Purity:	94.5 % (analytical finding, APF of 27.01.87, see Appendix, page 52)
Approval:	until 27.07.1987
State of aggregation:	solid/liquid (melting point 50° C)
Appearance:	dark brown
pH	4.4 (2 % in water)
Storage:	in laboratory cabinet at 20.5° C to 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:	$C_{15}H_{12}Cl_2F_4O_2$

6.2. Laboratory animals

6.2.1. Species

The study was conducted with SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb), from Versuchstierzucht Winkelmann, Borchen, Kreis Paderborn. Animals of this strain have been used for many years for toxicological studies at BAYER AG. Historical data on their physiology and spontaneous alterations 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 study the animals had a mean initial weight of 183 g (males 163 to 191 g, females 170 to 192 g). This is equivalent to an age of seven to twelve weeks.

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6.3. Animal husbandry

6.3.1. Accommodation of animals

During the acclimatisation period the animals were conventionally kept in Makrolon(R) cages type III (five per cage/sex), and during the test period individually in Makrolon(R) 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 a week with cages containing clean litter.

The litter used was low-dust wood granules (manufacturer: Bogner GmbH, Solingen-Ohligs). The granules were spot-checked for contaminants. The documentation on the results of the checks is filed at BAYER AG. The analytical results did not provide any indications of an effect on the objective of the study.

6.3.2. Rooms

All the animals in this study were in one room. 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 room, but in a separate laboratory.

6.3.3. Cleaning, disinfection

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.

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, from 6 to 18 hrs CET artificial lighting
Air throughput:	approx. 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(R) 1324 diet for rats and mice", which corresponds in content to "Altromin(R) 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 51 in Appendix) and the contaminant content of the standard diet were routinely spot-checked and analysed.

The tap water was of drinking quality (Statute for Drinking Water and Water for Foodstuff Factories of 22.05.1986, BGBl I page 760).

Documentation on the analyses regarding the adherence to specification of the 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.

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

6.4. Conduct of study

6.4.1. Test compound formulation

The test compound was formulated with polyethylene glycol E 400 before administration.

Its stability in the administered formulations over the period of use was analytically confirmed before administration. Since the formulations were genuine solutions, no test for homogeneity was needed (for analytical certificate see Appendix page 50).

6.4.2. Grouping and identification of animals

All the animals were allocated to the treatment groups before administration 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 also by cage cards giving test compound, animal number, dose, sex and study number. Five animals were used per dose and sex.

6.4.3. Administration and dosage

The test compound was injected once into the abdominal cavities of male and female rats.

The volume administered was 5 ml/kg or 10 ml/kg body weight.

In addition to the test compound groups, a control group was also used, in which the animals were administered 5 ml/kg bw polyethylene glycol E 400.

6.4.4. Examinations

6.4.4.1. Clinical observation

Appearance and behaviour were recorded several time on the day of administration, and then at least once per day. If symptoms occurred, their type, duration and intensity were compiled as group findings. In the case of mortalities the time of death was registered. The times given refer to the administration day (first test day) at administration. 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 present for the full previous test day. If symptoms occur for the first time after such an observation-free period, it is assumed that they were already present on the previous test day.

Similarly mortalities occurring in this observation-free period (e.g. overnight) are allocated to the previous test day.

6.4.4.2. Observation period

The observation period lasted fourteen days.

6.4.4.3. Body weights

The rats' body weights were noted before administration and then daily. The administration day is defined as 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.

6.4.4.4. Autopsy

The animals were sacrificed at the end of the observation period with diethyl ether and, like the animals which died intercurrently, subjected to gross pathological examination.

6.4.5. 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).

6.4.6. 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 is filed in the Toxicology Division, BAYER AG (archive).

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7. RESULTS

7.1. Acute intraperitoneal toxicity (rat)

7.1.1. Dose-effect table (LD50)

The results of the tests for acute intraperitoneal toxicity to the rat, stating the LD50, are compiled in the following Table 1. The graphs for the LD50 determination are shown on page 20 in the Appendix.

Table 1

Dosis (mg/kg Kgw.) / Dose (mg/kg b.w.)	Toxikol. Ergebnis* / Toxicol. results*	Symptomdauer / Duration of signs	Todeszeitpunkt / Time of death	Mortalitaet(%) / Mortality (%)
Ratte/rat - ♂				
0.0	0/ 5/ 5	50´-1d	--	0
1.0	0/ 5/ 5	25´-1d	--	0
10.0	0/ 5/ 5	175´-1d	--	0
100.0	0/ 5/ 5	40´-2d	--	0
1000.0	0/ 5/ 5	55´-7d	--	0
1600.0	0/ 5/ 5	20´-5d	--	0
2000.0	1/ 5/ 5	50´-4d	2d	20
2500.0	4/ 5/ 5	20´-9d	1d-2d	80
3550.0	4/ 5/ 5	15´-5d	1d-2d	80
5000.0	5/ 5/ 5	20´-2d	1h30´-2d	100
5000.0 **	3/ 5/ 5	45´-4d	2h38´-4d	60
LD50 = 2413 mg/kg Kgw. Vertrauensbereich (95%) = 2021.9 - 2880.9 mg/kg Kgw. Steigung = 3.31				
Ratte/rat - ♀				
0.0	0/ 5/ 5	45´-1d	--	0
1.0	0/ 5/ 5	20´-1d	--	0
10.0	0/ 5/ 5	175´-4d	--	0
100.0	0/ 5/ 5	50´-2d	--	0
1000.0	0/ 5/ 5	55´-7d	--	0
1400.0	2/ 5/ 5	55´-8d	2d-6d	40
1600.0	3/ 5/ 5	45´-8d	1d-4d	60
1800.0	4/ 5/ 5	20´-7d	1d-3d	80
2000.0	5/ 5/ 5	50´-2d	2d	100
2500.0 **	5/ 5/ 5	15´-2d	2d	100
LD50 = 1496 mg/kg Kgw. Vertrauensbereich (95%) = 1340.4 - 1669.7 mg/kg Kgw. Steigung = 5.48				

Vertrauensbereich - confidence range
Steigung - slope

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

** = dose was not used for calculation of LD50

0.0 = control dose (5 ml/kg bw polyethylene glycol E 400)

7.1.2. Clinical findings

The group findings are listed in the Appendix on pages 21 to 24.

As the table and the group findings indicate, animals of both sexes in the control group showed apathy and bristling coats on the first day, which were later no longer apparent. These symptoms attributable to the vehicle (polyethylene glycol E 400) were also noted in animals in the 1 mg/kg bw dose group (both sexes), and are therefore not to be regarded as induced by the test compound.

In the case of the animals from the 10 mg/kg bw dose group onwards, both sexes exhibited in addition spasmodic posture. From 100 mg/kg bw onwards tremor was also observed in the male and female rats, and in higher dose groups in addition spasmodic tremor, spastic gaits, dyspnoea and accelerated respiration, prostration on side and stomach, and in isolated cases soft stool and moist anuses. The symptoms were sometimes apparent for up to nine days after administration.

Mortalities occurred in the case of the males from 2000 mg/kg bw, and in the case of the females from 1400 mg/kg bw. The animals died between the first to the sixth day of observation.

7.1.3. Body weights

In isolated cases a temporary effect on body weight development was noted during the observation period. This had been made good by the end of the observation (for individual and mean figures see pages 25 to 36 in the Appendix).

7.1.4. Gross pathological findings

- Animals dying during observation: lung patchy, distended, in isolated cases up to dark red and with fluid in tissue; liver sometimes patchy; liver lobes adherent to each other and to diaphragm and other abdominal organs; whitish to yellowish deposits on all abdominal organs; in isolated cases spleen patchy, pale, covered with whitish skin; in isolated cases kidneys patchy; sometimes ulceroid foci in glandular stomach; yellowish brownish to almost black mucous contents in gastro-intestinal tract.

- Animals sacrificed at end of observation: liver swollen, liver lobes fused or adherent to each other and to abdominal wall and abdominal organs; spleen covered with whitish skin. These findings were also made for the controls, and are attributed to the local effect of the vehicle polyethylene glycol E 400.

The individual autopsy findings are listed in the Appendix on pages 37 to 49.

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8. DISCUSSION AND ASSESSMENT

The test compound NAK 4455 was evaluated in male and female rats for acute intraperitoneal toxicity. An LD50 of 2413 mg/kg bw was established for male rats, and 1496 mg/kg bw for females.

The symptoms observed (tremor, spasmodic tremor, spasmodic posture, spastic gaits) point to an action of the test compound on the nervous system, as is familiar after dosage with pyrethroids of this class. The symptoms disappeared during the second week of observation, and were therefore completely reversible. The female animals were more susceptible than the males. In isolated cases a slight body weight reduction was observed in the higher dose groups, which however had been made good by the end of the observation period. The alterations noted in the abdominal cavity (adhesions and fusions) are attributable to a local irritant effect or reaction of the pleura to foreign bodies. The dose of 1 mg/kg bw is to be regarded as without treatment-induced symptoms.

The test compound therefore proved to be slightly toxic to rats after acute intraperitoneal administration.

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9. REFERENCES

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).

10. KEY TO ABBREVIATIONS

Kgw./bw	body weight
Nr./no.	number
Toxikol. Ergebnis/ toxicol. results	toxicological results
ip	intraperitoneal

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