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Document Title	INITIAL SUBMISSION: YRC 2894, STUDY FOR ACUTE ORAL TOXICITY IN RATS, W/TSCA HLTH & SFTY STUDY COVER SHEET DATED 2/1/1999		
Chemical Category	(CYANAMIDE, (3-(6-CHLORO-3-PYRIDINYL)METHYL)-2)THIAZOLINDIN*		

TSCA HEALTH & SAFETY STUDY COVER SHEET

TSCA CBI STATUS:

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2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e); optional for 8(d) & FYI) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID Cert# P 917006757 99-2-12	2.3 FOR EPA USE ONLY
3.0 CHEMICAL/TEST SUBSTANCE IDENTITY -Contains CBI Reported Chemical Name (specify nomenclature if other than CAS name): (Cyanamide, [3-(6-chloro-3-pyridinyl)methyl]-2)thiazolidinylidene], CAS#: 111988-49-9 Purity _____ % <input checked="" type="checkbox"/> Single Ingredient <input type="checkbox"/> Commercial/Tech Grade <input type="checkbox"/> Mixture Trade Name: <u>YRC 2894</u> Common Name: <u>Chlornicotinyl</u>		99 FEB -4 AM 11:37 RECEIVED OPPT CBI
4.0 REPORT/STUDY TITLE - Contains CBI Study for Acute Oral Toxicity in Rats, Report # PH 25376 <input type="checkbox"/> Continuation sheet attached		
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6.0 REPORT/STUDY INFORMATION L Contains CBI X- Study is GLP Laboratory: <u>Bayer Toxicology, Wuppertal, Germany</u> Report/Study Date: <u>8/26/96</u> Source of Data/Study Sponsor (if different than submitter): _____ Number of pages: <u>41</u> <input type="checkbox"/> continuation sheet attached		
7.0 SUBMITTER INFORMATION L Contains CBI Submitter: <u>Donald W. Lamb, Ph.D</u> Title: <u>V. P., Prod. Safety & Reg. Affirs</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 L Contains CBI This compound is a developmental insecticide. <div style="text-align: right;">  8EHQ-99-14393 </div> <input type="checkbox"/> continuation sheet attached		

Submitter Signature: Donald W. Lamb Date: 2/1/99

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The clinical signs of reactivity decreased, decreased motility, poor reflexes, and spasmodic state occurred in more than two animals with the duration of the signs being greater than two days. As the signs occurred in more than two non-moribund animals with the signs lasting for more than two days, these findings are a trigger for reporting.

Abstract

The acute oral toxicity of YRC 2894 was evaluated in male and female Wistar rats.

At a dose of 100 mg/kg and above, the main clinical signs were piloerection, constipation, decreased motility and reactivity, poor reflexes, spasmodic state, tremor, labored breathing, narrowed palpebral fissure, and red excretion from the nose. The signs observed occurred within 25 minutes and 8 days after administration. The majority of signs usually lasted until 2 to 8 days after dosing.

There were no compound-related effects on body weight.

Gross pathology investigations, performed at the end of the 14 day post-dosing observation period, did not afford any findings indicative of a compound-related effect.

The LD50 for males was approximately 836 mg/kg and for females the LD50 was approximately 444 mg/kg. A dose of 62.5 mg/kg was tolerated by males and females without signs of toxicity or mortality.

Accordingly, YRC 2894 was of moderate toxicity to Wistar rats following acute oral administration.

A 05

STUDY TITLE

YRC 2894
Study for Acute Oral Toxicity in Rats

DATA REQUIREMENT

US EPA-FIFRA Guideline No. 81-1

108854

AUTHOR

Dr. F. Krotlinger

FILE

8759

STUDY COMPLETION DATE

August 26, 1996

PERFORMING LABORATORY

BAYER AG
DEPARTMENT OF TOXICOLOGY
Friedrich-Ebert-Strasse 217-233
D-42096 Wuppertal
Germany

LABORATORY PROJECT ID

Bayer AG Report No. PH 25376
Bayer AG Study No. T3059270

STATEMENT OF DATA CONFIDENTIALITY

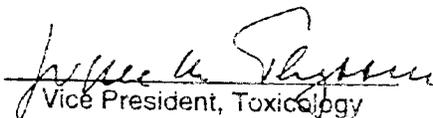
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The following statement supercedes the above statement of confidentiality that may occur elsewhere in this report:

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10(d)(1)(A), (B), or (C).

BAYER CORPORATION

Dr. J.H. Thyssen:


Vice President, Toxicology

Date:



GLP COMPLIANCE STATEMENT

Except for the following deviation, this study was conducted in compliance with the OECD Principles of Good Laboratory Practice (GLP)¹ and with the Principles of Good Laboratory Practice according to Annex 1 ChemG² and meets the FIFRA Good Laboratory Practice Standards (40 CFR Part 160), with the exception that recognized differences exist between GLP principles/standards of OECD and FIFRA (for instance, authority granted Agency inspectors and certain record retention requirements).

The deviation was as follows: The analytical investigations were performed for the concentration range of 1.0 wt% to 30.0 wt%. The concentration of 0.625 wt% (= 62.5 mg/kg) was not verified.


Dr. F. Krötlinger
(Study director)

Sept. 27, 1995
Date

**Sponsor:
BAYER AG**


Dr. L. Machemer

March 25, 1996
Date

**Submitter:
BAYER CORPORATION**


Dr. J.H. Thyssen
Vice President, Toxicology

Jan. 26, 99
Date

¹ Bundesanzeiger No. 42a (March 2, 1983) (German version)

² Bundesgesetzblatt Part I (July 29, 1994)

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YRC 2894

T3059270

1. Quality Assurance Statement

Test substance: YRC 2894

Study no.: T3059270

The study was audited by Quality Assurance on the dates given below. Audit reports have been submitted in writing to the study director and, if necessary, also to the laboratory management, or other persons affected.

Date of audit

Date of report to study
director/management

May 31, 1995 (study plan)
June 8, 1995

May 31, 1995
June 8, 1995

To the best of my knowledge, the results of the study and the methods used have been correctly reported.

Quality Assurance Unit
PH-QA-C/GLP, Bayer AG

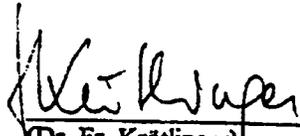
Date: March 22, 1996

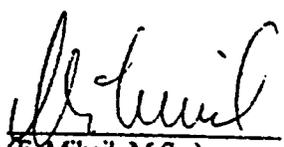
Responsible:

Niemers

(Dr. E. Niemers)

2. Signatures

Study director:  August 25, 1996
(Dr. Fr. Krötlinger) (Date)

Head of department:  Aug. 26, 1996
(F. Mihail, M.Sc.) (Date)

3. Summary

A study for acute oral toxicity in male and female Wistar rats was conducted with the test substance YRC 2894.

The method used complied with the OECD - Guideline for Testing of Chemicals; Section 4: Health Effects, No. 401 - "Acute Oral Toxicity"; adopted: 24 February, 1987 (Third Addendum to the 1981 OECD Guidelines for Testing of Chemicals, OECD Publication Service, Paris 1987) and the Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Humans and Domestic Animals, Series 81-1 Acute Oral Toxicity Study (Revised Edition, November 1984), U.S. Environmental Protection Agency, Washington D.C., 20460, National Technical Information Service, US Department of Commerce, Springfield, VA. and Annex V, Part B.1. (acute toxicity oral) to Directive 67/548/EEC of the Council of the European Communities of 27 June, 1967 (*) in its current version as amended for the seventeenth time by Directive 92/69/EEC of the Commission of the European Communities of 31 July, 1992 (**).

*) Official Journal of the European Communities L196/1 of 16th August 1967.

***) Official Journal of the European Communities L383/113 of 29th December 1992.

The results can be summarized as follows:

LD50:	rat, male:	836 mg/kg body weight (approximative)
	rat, female:	444 mg/kg body weight (approximative)

At a dose of 100 mg/kg body weight and above the main clinical signs were piloerection, constipation, decreased motility and reactivity, poor reflexes, spasmodic state, tremor, labored breathing, narrowed palpebral fissure and red excretion of the nose. The signs observed occurred within 25 minutes and 8 days after administration. The majority of signs usually lasted until day 2 to 8 of the study.

There were no toxicological effects on body weights in male and female rats.

The gross pathology investigations performed at the end of the follow-up period did not afford any findings indicative of a specific test compound effect.

A LD50 of approx. 836 mg/kg body weight was determined for male rats and of approx. 444 mg/kg body weight for female rats. 62.5 mg/kg body weight were tolerated by male and female rats without signs and mortalities.

Accordingly, the test substance was of moderate toxicity to Wistar rats following acute oral administration.

4. Introduction

A study for acute oral toxicity in the rat was performed with YRC 2894.

The purpose of the study was to enable the product to be classified (labeling), and to assess the potential oral acute health hazard when handling the test substance.

The study was performed at BAYER AG, Toxicology, Department of Short-term Rodent Studies and Neurotoxicology, 42096 Wuppertal, Friedrich-Ebert-Strasse 217 - 333. The study data is archived at BAYER AG.

5. Study Identification and Responsibilities

5.1. Study Identification

Study number: T3059270
Duration of study: June 08, 1995 - August 09, 1995

5.2. Responsibilities

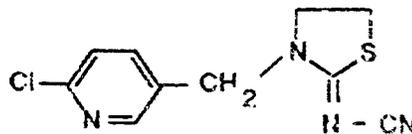
Head of department: F. Mihai, M.Sc.
Study director: Dr. F. Krötlinger
Analysis: Dr. W. Gau
Dr. W. Rüngeier
Quality assurance: Dr. H. Lehn
Archiving of study data: Prof. Dr. G. Schlüter

6. Materials and Methods

6.1. Test Substance

Test substance:	YRC 2894 Synonyma: NTN 33894
Manufacturer:	Bayer AG
Indication:	insecticide
Batch no.:	Mixed batch no.: 290894
Contents a.i.:	97.3%
Approval:	until September 24, 1995 (see page 38 in the annex)
Physical state:	solid
Appearance:	pale yellow powder
Storage:	room temperature
Chemical name (C.A.):	3-(2-Chlor-5-pyridylmethyl)-2-cyanimino=thiazolidin
Molecular weight:	252.5 g/mole
Molecular formula:	C ₁₀ H ₉ CLN ₄ S

Structure:



6.2. Experimental Animals

6.2.1. Species and Strain

SPF-bred Wistar rats of the strain Hsd Cpb:WU from the laboratory animal breeder Harlan Winkelmann GmbH, District of Paderborn were used. Animals of this strain have been used at BAYER AG for toxicological studies for many years. Historical data on their physiology and spontaneous alterations is available. The state of health of the breeding colony is routinely spot-checked for the main specific pathogens. The results of these examinations are archived.

6.2.2. Acclimatization

On delivery, the animals were acclimatized to the animal room conditions for at least 7 days before commencing treatment.

6.2.3. State of Health

Only healthy animals free of signs were used for the study. The animals were not vaccinated or treated against infection either before delivery, or during the acclimatization or study periods. The females were nulliparous and not gravid.

6.2.4. Age and Body Weight

The male animals had starting weights of 159 - 184 g and the female animals of 167 - 178 g. This corresponds to an age of approx. 7 - 8 weeks for males and 10 weeks for females.

6.3. Animal Care

6.3.1. Animal Accommodation

During the acclimatization period the animals were kept conventionally in polycarbonate cages type III (five animals per cage). The cages were changed at least three times a week.

During the test period the animals were kept conventionally in polycarbonate cages type III (five animals per cage) on the first study day and in type IIA cages (one animal per cage) afterwards. The cages were changed at least once a week.

The bedding consisted of low-dust wood granules type S 8/15 (supplier: Ssniff, Spezialdiäten GmbH, Soest/Westphalia). The wood granules were spot-checked for contaminants and the data archived. The results of these analyses did not indicate that the objective of the study had been influenced.

6.3.2. Animal Rooms

During the study, all animals were kept in one animal room. For reasons of capacity, rats being used for other toxicological studies were temporarily kept in the same room. Adequate spatial separation and suitable organization of working procedures ensured that animals were not mixed up. The animals were treated in a separate room.

6.3.3. Cleaning, Disinfection

The animal room was cleaned once a week and disinfected at least once a month with Zephirol® 10% (10 g benzalkonium chloride/100 g; applied as a 2% dilution, i.e. 20 ml Zephirol® 10% to 1 L water). At the same time it was ensured that the diet was not contaminated, and that there was no contact with the test animals. No pest control measures were carried out in the animal rooms.

6.3.4. Climatic Conditions

The animal room climate was set as follows:

Room temperature:	22° ± 3°C (drifting higher when ambient temperature above 25.0°C)
Relative humidity:	approx. 40% - 70%
Light/dark cycle:	approx. 12-hour artificial lighting from 6 a.m. to 6 p.m.
Air exchange rate:	at least 10 times per hour

Occasional deviations from this standard occurred, e.g. during clearing of the animal room. This had no apparent influence on the course of the study.

6.3.5. Diet

The animals were given "Altromin® 1324 Diet for Rats and Mice" (manufacturer: Altromin GmbH and Co. KG, Lage), and tap water (drinking bottles). Food (2 hours after administration) and water were available for ad-libitum consumption.

The nutritive composition (for specification see page 41 in the annex) and contaminant content of the standard diet were routinely spot-checked and analyzed.

Drinking water (in accordance with the German Trinkwasserverordnung of December 5, 90, Bundesgesetzblatt No.66, part 1, issued on December 12, 90, pages 2612-2629) was supplied from polycarbonate bottles which were changed weekly. The results of the water analyses are archived at BAYER AG. The available data did not indicate that the objective of the study had been influenced.

6.4. Test Methods

The study was performed in accordance with the following guidelines:

OECD - Guideline for Testing of Chemicals; Section 4: Health Effects, No. 401 - "Acute Oral Toxicity"; adopted: 24 February, 1987 (Third Addendum to the 1981 OECD Guidelines for Testing of Chemicals, OECD Publication Service, Paris 1987).

Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Humans and Domestic Animals, Series 81-1 Acute Oral Toxicity Study (Revised Edition, November 1984), U.S. Environmental Protection Agency, Washington D.C., 20460, National Technical Information Service, US Department of Commerce, Springfield, VA. 22161.

Annex V, Part B.1. (acute toxicity [oral]) to Directive 67/548/EEC of the Council of the European Communities of 27 June, 1967 (*) in its current version as amended for the seventeenth time by Directive 92/69/EEC of the Commission of the European Communities of 31 July, 1992 (**).

*) Official Journal of the European Communities L196/1 of 16th August 1967.

***) Official Journal of the European Communities L383/113 of 29th December 1992.

6.5. Performance of Test

6.5.1. Grouping and Identification of the Test Animals

Before administration, the animals were assigned to treatment groups on the basis of pre-arranged weight classes. When using several groups per administration day and sex, the animals were allocated to their treatment groups according to randomization lists created with a computer program run on an HP 3000 computer.

The animals were identified using cage cards recording the test substance, animal number, dose, sex and study number as well as by individual markings using a saturated aqueous picric acid solution and by numbering the tails of the animals with a waterproof felt-tip pen.

6.5.2. Test Substance Formulation

The test substance was formulated in demineralized water with Cremophor EL 2% v/v before administration. The applied formulations were well mixed by stirring on a magnetic mixer before and during administration, and by pumping the syringe several times.

Homogeneity and stability of the test substance in the administered formulations was confirmed by analytical examinations of the study T9055423 (for certificate(s) see page 39 - 40 in the annex).

6.5.3. Administration and Dose

The test substance was administered in a single dose orally by stomach tube oral to fasted male and female rats (fasted for approx. 17 hours \pm 1 hour; 5 animals respectively per group).

A volume of 10 ml/kg body weight was administered.

The animals were allowed to feed two hours after administration.

6.5.4. Examinations**6.5.4.1. Clinical Observation**

Appearance and behavior were recorded several times on the day of treatment, and at least once a day thereafter. Where signs occurred, the type, period and intensity (1 = weak, 2 = moderate, 3 = strong) were determined individually. In the annex they are shown as individual group and summary findings. Where mortalities occurred, the time recorded was the time the dead animal was first noted.

On the day of administration, the times reported relate to the time of administration (day 1 of the test). In order to obtain a clearer picture reported times over one hour have been rounded to the nearest full hour. Reported times less than one hour have been rounded to the nearest five minutes. The times reported are the time when the sign first appeared and the time when the sign was last observed. The days recorded are test days.

During clinical observation all abnormal findings were registered and particular attention is paid to the following organ systems, localizations and physiological functions:

Appearance:	fur, skin color, edemas, eyes, lacrimation, nasal discharge, salivation etc.
Behavior:	grooming, vocalization, excitement, aggression, digging and preening movements, cannibalism etc.
Nervous system:	reactivity, motility, reflexes, gait, paralysis, spasms, tremors etc.
Respiration:	where assessable, e.g. frequency etc.
Cardiovascular system:	where assessable, e.g. heart rate, pallor etc.
Posture:	ventral, lateral recumbency etc.
Gastrointestinal functions:	appearance of feces etc.

6.5.4.2. Post-treatment Observation

The post-treatment observation period lasted 14 days.

6.5.4.3. Body Weights

The body weights of the rats are recorded on day 1 before administration and then weekly. Additionally, all animals that died or are sacrificed are weighed.

6.5.4.4. Necropsy

At the end of the post-treatment observation period the animals are anesthetized by inhaling diethyl ether and sacrificed. They are then subjected to a gross pathology examination, as are any animals which may have died intercurrently.

6.5.5. LD50 Calculation

Where it was possible to calculate the mean (median) lethal dose (LD50) this was done by computer (HP 3000) according to BLISS, C.I., "The calculation of the dosage-mortality curve", *Ann. Appl. Biol.* 22, 134 (1935) and "The determination of the dosage-mortality curve from small numbers", *Q. J. Pharm. Pharmacol.* 11, 192-216 (1938) in the manner described by ROSIELLO, A.P., J.M. ESSIGMANN and G.N. WOGAN "Rapid and accurate determination of the median lethal dose (LD50) and its error with a small computer", *J. Toxicol. Environ. Health* 3, 797-809 (1977) and BAIRD, J.B. and R.L. BALSTER "Analysis of Nominal Dose-Effect Data with an Advanced Programmable Calculator", *Neurobehavior. Tox.* 1, 73-77 (1979).

The approximate LD50 value is assessed without slope and confidence interval where only 2 dose groups were used in the mortality range >0% and <100% and where at least one dose of 0% or 100% mortality was present. The procedure was performed by computer in a manner similar to the LD50 calculation (according to PAULUHN, J. "Über die computergestützte Abschätzung der LD50/LC50", BAYER AG, Report: 11835 (1983)).

Where computation using an HP 3000 or an assessment of the LD50 was not possible or meaningful, an assessment was made based on the dose-response curve.

7. Results

7.1. Dose-response Table (LD50)

The results of the study for acute oral toxicity in the fasted rat, including the LD50, are summarized in the table below.

Dose [mg/kg b.w.]	Toxicological results *			Duration of signs		Time of death			Mortality [%]
male									
62.5	0	0	5	-		-			0
300	0	5	5	4h	-	2d	-		
700	1	5	5	1h	-	5d	2d	-	2d
1000	4	5	5	25m	-	3d	2d	-	3d
LD50: 836 mg/kg b.w. (approximative)									
female									
62.5	0	0	5	-		-			0
100	0	5	5	6h	-	2d	-		
300	1	5	5	2h	-	8d	8d	-	8d
500	3	5	5	1h	-	6d	2d	-	6d
LD50 : 444 mg/kg b.w. (approximative)									

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

Mortality-dose curves see page 20.

7.2. Clinical Findings

62.5 mg/kg body weight were tolerated without signs by male and female rats. At the dose of 100 mg/kg body weight and above clinical signs were observed. They were as follows: piloerection, constipation, decreased motility and reactivity, poor reflexes, spastic gait, spasmodic state, convulsions, tremor, tachypnea, dyspnea, labored breathing, diarrhea, increased salivation, narrowed palpebral fissure, closed eyelids, red excretion out of the nose and red incrustated snout.

The signs observed occurred within 25 minutes and 8 days after administration. The majority of signs usually lasted until day 2 through 8 of the study.

For summary, group and individual animal lists see pages 21 - 28 in the annex.

7.3. Body Weights

With exception of one female rat of the 300 mg/kg b.w.-group, which showed a transient depression in body weight, no effects on body weights were observed in the remaining groups. Thus, this depression is not regarded as toxicological relevant.

For individual and mean values see pages 29 - 32 in the annex.

7.4. Gross Pathology Findings

In animals that died during the observation period the following changes were detected:

Esophagus: change-in-contents, full of shavings (animal no. 8)
Lungs: spotted discoloration/s (animal no. 3), dark-red
Liver: dark-red, spotted discoloration/s,
distinct lobulation (animal no.6)
Spleen: pale and/or partly dark-red; discoloration/s
Kidneys: pale and/or red discoloration/s
Stomach: glandular stomach area/s, up to, 1, mm, discoloration/s (animal no.19);
Adrenal glands: discoloration/s
Intestine: change-in-contents (animal no. 8, no. 19); discoloration partly black; partly empty; partly mucous

No gross pathologic changes were observed in animals killed at the end of the study period.

For individual gross necropsy lists see pages 33 - 37 in the annex.

8. Discussion and Assessment

A study for acute oral toxicity in male and female Wistar rats was conducted with the test substance YRC 2894.

A dose of 62.5 mg/kg body weight was tolerated by male and female rats without signs and mortalities

At a dose of 100 mg/kg body weight and above the main clinical signs were piloerection, constipation, decreased motility and reactivity, poor reflexes, spasmodic state, tremor, labored breathing, narrowed palpebral fissure and red excretion out of the nose. The signs observed occurred within 25 minutes and 8 days after administration. The majority of signs usually lasted until day 2 to 8 of the study.

There was no toxicological effects on body weight development in male and female rats.

The gross pathology investigations performed at the end of the follow-up period did not afford any findings indicative of a specific test compound effect.

A LD50 of approx. 836 mg/kg body weight was determined for male rats and one of approx. 444 mg/kg body weight for female rats.

Accordingly, the test substance was of moderate toxicity to Wistar rats following acute oral administration.

9. List of abbreviations

a.i.	active ingredient
approx.	approximately
b.w.	body weight
C.A.	Chemical Abstracts
CAS	Chemical Abstracts Service
c.n.	common name
conc.	concentration
cont.	continuation
contd	continued
d	day(s)
d.	death
E	terminal sacrifice
e.g.	for example
etc.	et cetera
Fig	figure
Fl.	Formulation
g, G	gram(me)(s)
h	hour(s)
i.e.	that is
intens.	intensity
kg	kilogram(me)(s)
l, L	litre(s)
m	minute(s), mean
max.	maximum
mg	milligram(me)(s)
ml	millilitre(s)
n.a.o.	nothing anomalous observed
no.	number
PO	per os
s, sd	standard deviation
T	death during the study period
tab.	table
toxicol.	toxicological
vol.	volume