

TSCA HEALTH & SAFETY STUDY COVER SHEET

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 <input checked="" type="checkbox"/> 8(d) <input checked="" type="checkbox"/> 8(e) <input type="checkbox"/> FYI <input type="checkbox"/> 4 <input type="checkbox"/> 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: # _____ <input type="checkbox"/> continuation sheet attached		
2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e); optional for §4, 8(d) & FYI) X - YES -NO	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID Cert# P 917006689 97-2-17	2.3 FOR EPA USE ONLY
3.0 CHEMICAL/TEST SUBSTANCE IDENTITY <input checked="" type="checkbox"/> Contains CBI <i>Reported Chemical Name (specify nomenclature if other than CAS name):</i> CAS#: Blend Purity _____ % X - Single Ingredient <input type="checkbox"/> Commercial/Tech Grade X - Mixture Trade Name: <u>Preventol WB</u> Common Name: _____		
4.0 REPORT/STUDY TITLE <input checked="" type="checkbox"/> Contains CBI Acute Oral Toxicity Study with Preventol WB in Rats <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>ORAL</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 Tox Laboratory, Stilwell, KS</u> Report/Study Date: <u>4/17/97</u> Source of Data/Study Sponsor (if different than submitter) _____ Number of pages <u>26</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 The substance is an experimental pesticide. <div style="text-align: center; font-size: 24px; font-weight: bold;">COMPANY SANITIZED</div> <input type="checkbox"/> continuation sheet attached		

8ENQ-05 97-13935 S

Confidential Information Has Been Sanitized

Submitter Signature: Donald W Lamb Date: 5/13/97

8ENQ-97-13935

88970000 185 S

5/13/97 11:03:01

9.0 CONTINUATION SHEET

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.

Submitter Tracking Number/Internal ID

P917006689

97-2-17

CONTINUED FROM COVER SHEET SECTION # 2.1 **Confidential Information Has Been Sanitized**

Contains CBI

The acute oral toxicity of Prevental WB was evaluated in young-adult Sprague-Dawley rats. Separate groups of six male and female rats were orally treated with nominal doses of 0 (control), 500, 1000, or 2000 mg/kg of the undiluted test substance. All surviving animals were observed for at least 14 days after treatment and body weights were recorded on days 0, 7, 14, and 17 (if appropriate), or when found dead. Gross necropsies were performed on animals found dead or at terminal sacrifice either 14 or 17 days following treatment.

Actual doses were based on individual animal weights and the dose volume each animal received. The actual doses were as follows:

Dose (mg/kg)	
Males	Females
0	0
580	650
1200	1300
2000	1800

Note: Groups showing 0 mg/kg were treated with deionized water.

Compound-related clinical signs were evident in males and females at all three dose levels. The number of signs and incidence generally increased with dose in both sexes. Signs that are ascribed to treatment with Prevental WB consisted of the following: dyspnea, hypoactivity, cool-to-touch, red discharge from the perigenital region, red staining on the thoracic region, salivation, spontaneous vocalization, convulsions, moribundity, diarrhea, ungroomed appearance, red or clear lacrimation, red or clear nasal staining, oral staining, urine staining, perianal staining, and tail lesions. These signs were first observed within hours after dosing on the day of treatment (day 0) and resolved in survivors by study termination.

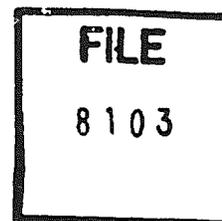
Males that survived treatment with 2000 mg/kg of the test substance had a significantly lower body weight gain, compared to controls, on days 7 and 14. There were no other differences in body weight gain for other groups of males or for females at any dose level.

No gross lesions were observed at necropsy for controls or treated animals sacrificed at term. Compound-related findings in animals found dead during the observation period consisted of the following: lacrimation, salivation, reddened lungs, nasal staining, ventrum staining, discolored glandular stomach mucosa, discolored urinary bladder fluid and bladder calculi. These lesions were generally observed for both sexes at all three dose levels.

The incidence of mortality increased with dose from 580 mg/kg to 1200 mg/kg for males (1 of 6 to 4 of 6) and from 650 mg/kg to 1300 mg/kg for females (1 of 6 to 4 of 6). There was no additional increase in mortality at the highest dose of 2000 and 1800 mg/kg for males and females, respectively (4 of 6 males and females). Based on these results, the LD50 estimate is 1100 mg/kg for males and 1200 mg/kg for females (95% confidence limits were incalculable for both males and females).

Since evidence of toxicity was evident at all dose levels, including the lowest dose, the present study did not establish a no-observed-effect level (NOEL). Based on these results, the NOEL is less than 580 mg/kg for males and is less than 650 mg/kg for females.

In this study, hypoactivity was observed to last up to seven days in male rats.



Study Title

Acute Oral Toxicity Study
with Preventol WB in Rats

Data Requirement

40 CFR Part 158
US-EPA-FIFRA, Section 158.340, Guideline 81-1

Confidential Information Has Been Sanitized

Authors

L. P. Sheets and A. T. Halliburton

Study Completion Date

April 17, 1997

Test Facility

Bayer Corporation
Agriculture Division
Toxicology
17745 South Metcalf
Stilwell, Kansas 66085-9104

Study Number

97-012-LF

Bayer Corporation
97-012-LF

STATEMENT OF DATA CONFIDENTIALITY

Information claimed confidential on the basis of its falling within the scope of FIFRA Section 10(d)(1)(A), (B), or (C) has been removed to a confidential attachment, and is cited by cross-reference number in the body of the study.

Company: Bayer Corporation

Company Agent: J. H. Thyssen

Date: 4-17-97

Vice President, Toxicology


Signature

CROSS REFERENCE NUMBER 1

Confidential Information Has Been Sanitized

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with the FIFRA Good Laboratory Practice Standards of 40 CFR Part 160, TSCA Good Laboratory Practice Standards of 40 CFR Part 792 and the OECD Principles of Good Laboratory Practice, GD(92)32, (Paris, 1992).

Confidential Information Has Been Sanitized

SUBMITTED

BAYER CORPORATION

J.H. Thyssen:

J. H. Thyssen
Vice President, Toxicology

Date:

4-17-97

SPONSOR

INDUSTRIAL CHEMICALS DIVISION

J.H. Thyssen:

Vice President, Toxicology

Date:

J. H. Thyssen 4-17-97

STUDY DIRECTOR

L. P. Sheets:

L. P. Sheets

Date:

4/17/97

TABLE OF CONTENTS

Confidential Information Has Been Sanitized

	<u>Page No.</u>
Title Page	1
Statement of Data Confidentiality	2
Good Laboratory Practice Compliance Statement	3
Table of Contents	4
Sponsor, Test Facility, Dates, Personnel and Responsibilities	5
Quality Assurance Statement	6
Abstract	8
Materials	10
Introduction and Purpose, Test Guidelines	11
Methods	12
Results and Discussion	15
Summary and Conclusions	17
References	18
Tables	19
Appendices	25
Confidential Attachment	

Bayer Corporation
97-012-LF

SPONSOR

Bayer Corporation
Industrial Chemicals Division
100 Bayer Road
Pittsburgh, Pennsylvania 15205-9741

TEST FACILITY

Bayer Corporation
Agriculture Division
Toxicology
17745 South Metcalf
Stilwell, Kansas 66085-9104

Confidential Information Has Been Sanitized

DATES

Experimental Start Date: February 18, 1997
Experimental Termination Date: March 14, 1997

PERSONNEL AND RESPONSIBILITIES

Toxicology and Sponsor Representative:	J. H. Thyssen
Toxicology Laboratory:	G. K. Sangha
Study Direction:	L. P. Sheets
Study Conduct:	A. T. Hailiburton
Pathology Services:	B. P. Stuart
Animal Care:	R. E. Mueller
Necropsy:	H. E. Hoss
Quality Assurance:	D. M. Wallace

J. H. Thyssen
G. K. Sangha
L. P. Sheets
A. T. Hailiburton
B. P. Stuart
R. E. Mueller
H. E. Hoss
D. M. Wallace

QUALITY ASSURANCE STATEMENT

Audit reports have been submitted to the Study Director and Laboratory Management documenting the status of compliance with applicable departmental standard operating procedures, the study protocol, and Good Laboratory Practice regulations.

The quality assurance unit monitors at least one phase of this study, and at least annually, all phases of this study type including the functions of all support areas for this study type. The following are the audit dates, phases inspected, auditors, and report dates of Quality Assurance inspections of this study and, if applicable, of this study type as well as relevant support areas:

Confidential Information Has Been Sanitized

<u>Date</u>	<u>AUDITS</u>		<u>Auditor</u>	<u>REPORT TO STUDY DIRECTOR/ MANAGEMENT</u>
	<u>Phases</u>			
	<u>Phase of Study</u>			
02/17/97	Tailmarking		L.A. Berry	02/19/97
02/17/97	Test Material Use Log and Dose Preparation		L.A. Berry	02/19/97
02/17/97	Fasting		L.A. Berry	02/21/97
02/18/97	Dosing		L.A. Berry	02/21/97
03/04/97	Body Weights and Clinical Observations		L.A. Berry	03/05/97
03/10/97	Active Ingredient Date Check		L.A. Berry	03/11/97
03/11/97	Euthanasia, Gross Necropsy, and Test Animal inventory		L.A. Berry	03/11/97
03/27-28/97	Final Report Review		L.A. Berry	03/28/97
	<u>Phase of Study Type</u>			
06/03-04/96	Technician Training and Experience Records		L.A. Berry	06/04/96
	<u>Animal Care Support Functions</u>			
02/01/96	Eristrom Water Filter Changes/Checks		C.A. Cox	02/07/96
06/27/96	Rack Change		C.A. Cox	07/11/96

<u>Date</u>	<u>AUDITS</u>		<u>Auditor</u>	<u>REPORT TO STUDY DIRECTOR/ MANAGEMENT</u>
	<u>Phases</u>			
	<u>Animal Care Support Functions (continued)</u>			
08/27/96	1996 Training Records		C.A. Cox	08/27/96
08/27/96	Data Review of Water Analysis		C.A. Cox	08/27/96
08/27/96	1996 Rack Check Documentation		C.A. Cox	08/27/96
08/27/96	Data Review of Vermin Control		C.A. Cox	08/27/96
08/27/96	Equipment Maintenance and Cage Wash Repair		C.A. Cox	08/27/96
01/08/97	Rat Cage Rack Preparation (Wire Mesh)		C.A. Cox	01/09/97
01/08/97	Rat Room Filter Check/Change		C.A. Cox	01/09/97
01/27/97	Rat Room Bedding Change and Room Maintenance		C.A. Cox	01/27/97
01/28/97	Rat Room Disinfection		C.A. Cox	01/28/97
02/10/97	Animal Examination and Release		L.A. Berry	02/10/97
02/03/97	Acute Rats: Animal Receipt, Shipment Exam, Animal Inventory, AM Observations, Feeding/Feed Check, Cage Identification (Cage Cards), Randomization, Quarantine		C.A. Cox	02/04/97
02/19-20/97	Cleaning of Rat Wire Mesh Racks, Cages and Trays		C.A. Cox	02/20/97

In compliance with the Good Laboratory Practice regulations, this final report for study number 97-012-LF has been reviewed by the Quality Assurance Unit. The results presented in this report accurately describe the methods and standard operating procedures and reflect the raw data collected during the conduct of the study.



L. A. Berry, Quality Assurance

4-16-97

Date

ABSTRACT

The acute oral toxicity of Preventol WB was evaluated in young-adult Sprague-Dawley rats. Separate groups of six male and female rats were orally treated with nominal doses of 0 (control), 500, 1000, or 2000 mg/kg of the undiluted test substance. All surviving animals were observed for at least 14 days after treatment and body weights were recorded on days 0, 7, 14, and 17 (if appropriate), or when found dead. Gross necropsies were performed on animals found dead or at terminal sacrifice, either 14 or 17 days following treatment.

Since the test substance was administered undiluted, it was not necessary to analyze doses to establish concentration and homogeneity. Furthermore, doses were not analyzed for stability, since the undiluted test substance was used within several hours following removal from the freezer.

Actual doses were based on individual animal weights and the dose volume each animal received. The actual doses were as follows:

<u>Dose (mg/kg)</u>	
<u>Males</u>	<u>Females</u>
0	0
580	650
1200	1300
2000	1800

Note: Groups showing 0 mg/kg were treated with deionized water.

Compound-related clinical signs were evident in males and females at all three dose levels. The number of signs and incidence generally increased with dose in both sexes. Signs that are ascribed to treatment with Preventol WB consisted of the following: dyspnea, hypoactivity, cool-to-touch, red discharge from the perigenital region, red staining on the thoracic region, salivation, spontaneous vocalization, convulsions, moribundity, diarrhea, ungroomed appearance, red or clear lacrimation, red or clear nasal staining, oral staining, urine staining, perianal staining, and tail lesions. These signs were first observed within hours after dosing on the day of treatment (day 0) and resolved in survivors by study termination.

Males that survived treatment with 2000 mg/kg of the test substance had a significantly lower body weight gain, compared to controls, on days 7 and 14. There were no other differences in body weight gain for other groups of males or for females at any dose level.

No gross lesions were observed at necropsy for controls or treated animals sacrificed at term. Compound-related findings in animals found dead during the observation period consisted of the following: lacrimation, salivation, reddened lungs, nasal staining, ventrum staining, discolored glandular stomach mucosa, discolored urinary bladder fluid and bladder calculi. These lesions were generally observed for both sexes at all three dose levels.

The incidence of mortality increased with dose from 580 mg/kg to 1200 mg/kg for males (1 of 3 to 4 of 6) and from 650 mg/kg to 1300 mg/kg for females (1 of 6 to 4 of 6). There was no additional increase in mortality at the highest dose of 2000 and 1800 mg/kg for males and females, respectively (4 of 6 males and females). Based on these results, the LD50 estimate is 1100 mg/kg for males and 1200 mg/kg for females (95% confidence limits were incalculable for both males and females).

Since evidence of toxicity was evident at all dose levels, including the lowest dose, the present study did not establish a no-observed-effect level (NOEL). Based on these results, the NOEL is less than 580 mg/kg for males and is less than 650 mg/kg for females.

Confidential information has been sanitized

MATERIALS

- I. The test substance was supplied by the sponsor with the following information:

Test Substance:

Identification:	Preventol WB
Physical Appearance:	Dark Brown Liquid
Batch Number:	Pa. 16
Composition:	See Confidential Attachment CROSS REFERENCE NUMBER 1

Confidential Information Has Been Sanitized

Percent Active Ingredient:	4-Chloro-3-methylphenolate:	29.7%
	2-Phenylphenolate:	13.1%
	1,2-Propanediol:	14.1%

Stability under Storage Conditions:	Test substance was stored frozen. The active ingredients have been shown to be stable for the duration of use.
--	--

CAS Registry Numbers:	4-Chloro-3-methylphenolate:	015733-22-9
	2-Phenylphenolate:	000132-27-4
	1,2-Propanediol:	000057-55-6

- II. The test substance was stored under freezer conditions. Doses were prepared for use on the day administered.

INTRODUCTION AND PURPOSE

The purpose of this study was to provide an estimate of the LD50 and to evaluate the toxicologic consequences of acute oral exposure to Preventol WB. A previous study established acute oral toxicity in rats [1]. The present study was conducted due to Agency (U.S. EPA) concerns that the use of a vehicle in that study may have reduced the toxicity of the test substance.

TEST GUIDELINES

This study was conducted in accordance with:

- 1) US-EPA-FIFRA, Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Guideline 81-1, November 1984.
- 2) US-EPA-TSCA, Health Effects Testing Guidelines, 40 CFR Section 798.1175.
- 3) OECD Guidelines for Testing of Chemicals, Section 4, Guideline 401, February 1987.
- 4) Japan, Ministry of Agriculture, Forestry and Fisheries, Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration, 59 NohSan No. 4200, January 1985.

Confidential Information Has Been Sanitized

METHODS

Animal Information

Source, Number, Weight and Age

Young-adult male and female (nulliparous and non-pregnant) Sprague-Dawley rats (Sas:CD(SD)BR), a commonly used laboratory strain obtained from Sasco Inc., Kingston NY, were used in this study. A total of 48 rats (24 males and 24 females) were used. Body weights just prior to dosing ranged from 203 to 267 g for males and from 180 to 210 g for females. These rats were approximately eight to eleven weeks of age when the dose was administered.

Examination and Acclimation

Rats were examined upon receipt and held for at least six days prior to use. During the holding period, each rat was examined daily for changes in general appearance, behavior and gross external abnormalities. Animals with abnormalities were not used.

Care and Housing

Prior to and following the dosing period, animals were housed individually in stainless steel wire-mesh cages suspended over a bedding of Deotized Animal Cage Board (DACB). Bedding was changed three times weekly and rats were transferred to clean cages every two weeks. The environmental conditions were set for a room temperature of 18 to 26 °C, a relative humidity (RH) of 30 - 70%, and a photoperiod with 12 hours of light alternating with 12 hours of darkness. Environmental conditions were continuously monitored. Potable municipal tap water and Purina Rodent Laboratory Chow (Formulation #5001-4) were available for *ad libitum* consumption with one exception - animals were denied access to food overnight prior to dosing on day 0.

Identification

Each animal was identified by a tail mark and cage card with a unique number.

Randomization

Animals were assigned to sequentially numbered cages using a list of random numbers generated using SAS software [2]. Rats were assigned to dosing groups in numerical order after randomization.

Experimental Design

Route, Dose and Number of Animals

The test substance was administered neat (undiluted) as a single dose by oral gavage to separate groups of male and female rats at nominal dose levels of 0, 500, 1000 or 2000 mg/kg (6 rats/sex/dose level). A vehicle was not used because of Agency (U.S. EPA) concerns that this might reduce the toxicity of the test substance. Although a vehicle was not used, controls were treated by gavage with deionized water as a reference for effects associated with the administration of an innocuous material by gavage. All animals were fasted overnight prior to dosing and dose volumes were individually adjusted for the body weight of each animal.

Analytical Chemistry

Doses were not analyzed for content of the active ingredient or for homogeneity and stability since the test substance was administered undiluted and removed from the freezer only shortly before use.

Clinical Signs and Body Weight Measurements

Observations were conducted at least twice daily (once daily on weekends and holidays) for mortality, moribundity and clinical signs of toxicity. Detailed examinations were conducted following treatment and until terminal sacrifice or death. The detailed clinical examination was performed in a systematic fashion, proceeding from the least to most manipulative with respect to the animal. First, the animal was observed in its home cage for overt signs, such as unusual posture, coarse tremors, gross muscle fasciculations, activity level, and stereotypic or highly-unusual behaviors. The bedding material was inspected to assess consistency of feces. Second, the cage was opened for an unobstructed view and the animal was observed for signs including clonic or tonic movements, response to stimuli, piloerection, gait abnormalities, respiratory abnormalities and level of activity. Next, the animal was retrieved and inspected for general appearance, evidence of injury, areas of coloration or alopecia, and for the presence and color of stains and secretions. The eyes were examined for evidence of palpebral closure and if needed an inspection was conducted for broken teeth or malocclusion. The location, color and approximate size of gross lesions were also noted if present. Lastly, the animal is encouraged to move about for further observance of gait abnormalities, responses to stimuli, or for evidence of clonic or tonic movements. Individual body weights were performed at the time of treatment (day 0) and again on days 7 and 14 following treatment or at terminal sacrifice.

Study Length

The post-treatment observation period was extended from 14 days to 17 days for the 2000 mg/kg males due to the persistence of compound-related clinical signs and lower body weight gain compared to controls on day 14. The study was terminated on day 17 when clinical signs were no longer present in survivors.

Gross Pathology

All surviving rats were sacrificed at term (days 14 or 17) by CO₂ asphyxiation. A complete gross necropsy was performed on each rat sacrificed or that died during the course of the study. This involved an examination of all organs, body cavities, cut surfaces, external orifices, and surfaces. All gross abnormalities were recorded.

Statistical Analysis

Group mean body weight changes were evaluated with Univariate Analysis of Variance test and, where significant differences were detected, the Dunnett's t-statistic was calculated to determine whether specific groups were significantly different from controls. Statistical procedures were conducted using SAS software [2]. Lotus 1-2-3 software [3] was used to compute the mean and standard deviation of groups of values as needed.

In all cases, a p-value less than or equal to 0.05 was considered to be statistically significant.

Archival Procedures

The protocol, raw data, a sample of the test substance, and the final report are archived at locations specified by Bayer Corporation, Agriculture Division, Toxicology, 17745 South Metcalf, Stilwell, Kansas 66085-9104.

RESULTS AND DISCUSSION

Animal Care: Housing and Contaminants

Continuous monitoring of the animal quarters during this study showed deviations from the desired ranges for temperature (18 - 26 °C) and RH (30 - 70%). These deviations were minimal and of short duration and therefore are not considered to have affected the results obtained from this study. Levels of possible contaminants found in commercially available food and municipal water are not expected to affect the outcome of this study.

Analytical Chemistry

The homogeneity and concentration of active ingredient in the doses were not verified by analytical methods, since the test substance was administered undiluted. Likewise, it was not necessary to verify stability, since the undiluted material was administered within hours of removal from the freezer.

Actual and Nominal Doses

A disparity is expected and typically exists between the actual versus the nominal dose. This disparity is directly related to the precision of the measured dose to each animal and is considered unavoidable. Consequently, dose levels are referred to in the text on the basis of the actual dose and in tables as nominal dose.

Clinical Observations

Clinical observations for males and females are summarized in Tables 1 and 2, respectively. The incidence and occurrence of compound-related clinical signs increased with dose in both sexes. Signs that are ascribed to treatment consisted of the following: dyspnea, hypoactivity, cool-to-touch, red discharge from perigenital region, red stain on the thoracic region (males only), salivation, spontaneous vocalization (1 female only), convulsions (1 female only), moribundity (females only), diarrhea (1 male only), ungroomed appearance (1 male only), red or clear lachrimation, red or clear nasal staining, oral staining, urine staining, perianal staining (males only), and tail lesion (1 male). These signs were generally common to both sexes, with the exceptions noted. Compound-related signs were first observed on the day of treatment (day 0) and persisted in surviving animals until study termination.

One additional sign was observed in two males that was not considered to be compound-related. This consisted of scabs under the chin of one low dose male (days 3-9) and one high-dose male (days 13-16). These lesions were not ascribed to treatment, due the combination of (1) low incidence, (2) no apparent relationship with dose level, and (3) no relationship between the time when the lesion appeared and the administration of the test substance.

Confidential Information Has Been Sanitized

Bayer Corporation
97-012-LF

Body Weights

Summaries of body weight data are presented in Tables 3 and 4. Individual body weights for all animals are presented in Appendices I and II.

All body weights prior to dosing were within 20% of the mean for each sex, except for one high-dose male that exceeded the body weight range by 4 g. This exception is not considered to affect the outcome of this study.

Males treated with 2000 mg/kg of the test substance had a significantly lower body weight gain, relative to controls, on days 7 and 14. No significant difference or apparent trend toward a difference in body weight gain were evident in other surviving males or in females at any dose level, relative to controls.

Gross Pathology

All lesions observed during gross pathological examination are presented in Tables 5 and 6 for males and females, respectively.

There were no lesions in control or treated animals that were sacrificed at term. In males and females that died during the observation period, the following findings were considered to be compound-related: lacrimation (females only), salivation, nasal staining, reddened lungs (one male only), urine staining, discolored glandular stomach mucosa, discolored urinary bladder fluid and calculi in the bladder.

Estimates for LD50 and NOEL

LD50

The incidence of mortality for each group of males and females is summarized in Tables 3 and 4, respectively. All deaths were considered to be compound-related, with mortality occurring on days 1 - 16. The incidence of mortality increased with dose in both sexes as the dose was raised from 580 to 1200 mg/kg for males and from 650 to 1300 mg/kg for females, with no further increase in mortality at a dose of 2000 mg/kg for males and 1800 for females. Based on these results, the LD50 is estimated to be 1100 mg/kg for males and 1200 mg/kg for females (95% confidence limits were incalculable for both sexes).

No-Observed-Effect Level (NOEL)

A NOEL for Preventol WB was not established in either sex, since compound-related clinical signs and mortality were evident in all dose groups, including the lowest dose. Thus, the NOEL for males is less than 580 mg/kg and is less than 650 mg/kg for females.

SUMMARY AND CONCLUSIONS

Separate groups of young-adult male and female rats were treated by oral gavage with a single dose of undiluted Preventol WB at dose levels of 0, 580, 1200 or 2000 mg/kg for males and 650, 1300, or 1800 mg/kg for females (6 rats/dose level).

Compound-related signs of intoxication, including mortality, were evident in males and females at all three dose levels, with the incidence and occurrence of toxic signs increasing with dose in both sexes. The incidence of mortality increased from 1 of 6/sex at the low dose to 4 of 6/sex at the middle dose, there was no further increase in the incidence of mortality at the highest dose level. Body weight gain was reduced, relative to controls, in high-dose (2000 mg/kg) males, but was not affected in males at lower dose levels or in females at any dose level. Necropsy findings generally increased with dose and were only noted in animals that died during the course of the 14-17 day observation period.

Based on the incidence of mortality at these dose levels, the LD50 estimate for Preventol WB is 1100 mg/kg for males and 1200 mg/kg for females (95% confidence limits were incalculable for both sexes). Since compound-related effects were evident at all dose levels, the present results indicate the NOEL is less than 580 mg/kg for males and is less than 650 mg/kg for females.

Original information Has Been Sanitized

REFERENCES

1. Bomhard, E., "PREVENTOL WB acute oral toxicity study in male and female wistar rats", Bayer Corp., Agriculture Division Report Number 22330, EPA MRID No. 429412-01, 1993.
2. SAS Institute Inc., Cary, North Carolina.
3. Lotus Development Corp., Cambridge, Massachusetts.

Confidential Information Has Been Sanitized

Table 1

Incidence of Clinical Signs from Males During an Acute Oral
Toxicity Study with Praxventol WB

Confidential information Has Been Sanitized

Sign	Incidence ¹ (Day of First Onset-Last Conclusion)			
	Nominal Dose (mg/kg)			
	0	500	1000	2000
Dyspnea	0	0	3 (1-3)	2 (1-15)
Hypoactive	0	1 (0-2)	3 (0-7)	4 (0-1)
Cool to touch	0	1 (1-2)	2 (1-4)	0
Red Discharge from perigenital region	0	0	2 (1-6)	4 (0-6)
Red Stain from thoracic region	0	0	2 (1-4)	1 (2-6)
Salivation	0	0	0	4 (0-15)
Diarrhea	0	0	0	1 (13-15)
Ungroomed Appearance	0	0	0	1 (13-16)
Red Lacrimation	0	0	1 (3-4)	0
Red Nasal Stain	0	0	4 (0-7)	3 (1-13)
Clear Nasal Stain	0	0	0	1 (14-16)
Oral Stain	0	3 (0-2)	5 (0-7)	4 (0-16)
Urine Stain	0	3 (0-6)	3 (0-7)	4 (0-16)
Perianal Stain	0	1 (1-2)	1 (1-2)	0
Lesions on tail	0	1 (1-9)	0	0
Scab under chin	0	1 (3-9)	0	1 (13-16)

0 = No signs observed.

¹ = Conclusion represents complete recovery or death.

Results presented are from 6 treated animals per group.

Note = Date of dosing is denoted as day 0.

Table 2

Incidence of Clinical Signs from Females During an Acute Oral
Toxicity Study with Preventol WB

Confidential Information Has Been Sanitized

Incidence¹(Day of First Onset-Last Conclusion)

Sign	Nominal Dose (mg/kg)			
	0	500	1000	2000
Dyspnea	0	2 (0-3)	1 (2-2)	1 (0-1)
Hypoactive	0	2 (0-2)	6 (0-3)	5 (0-2)
Cool to touch	0	1 (1-2)	4 (1-3)	2 (1-2)
Red Discharge from perigenital region	0	1 (0-0)	2 (0-1)	3 (0-2)
Salivation	0	1 (0-0)	2 (1-2)	4 (0-2)
Spontaneous Vocalization	0	1 (1-1)	0	0
Convulsions	0	1 (0-0)	0	0
Moribund	0	0	1 (2-2)	4 (0-1)
Clear Lacrimation	0	0	5 (0-3)	1 (0-2)
Red Nasal Stain	0	2 (0-3)	2 (0-2)	3 (0-5)
Oral Stain	0	5 (0-6)	2 (1-1)	3 (0-3)
Urine Stain	0	3 (0-3)	4 (0-3)	3 (0-6)

0 = No signs observed.

¹ = Conclusion represents complete recovery or death.

Results presented are from 6 treated animals per group.

Note = Date of dosing is denoted as day 0.

Confidential Information Has Been Sanitized

Bayer Corporation
97-012-LF

Table 3

Summary of Body Weight and Mortality Data from Males During
an Acute Oral Toxicity Study with Preventol WB

Nominal Dose (mg/kg)	Initial Body Weight Range (g)		Body Weight (g)			Mortality	
			Days of Study ^a			No. Dead/ No. Exposed	Day of Death
			0	7	14		
0	204-218	Mean	209	283	319	0/6	NA
		SD	6	9	16		
		MC		74	110		
		MC-SD		9	14		
500	203-218	Mean	209	264	290	1/6	1; day 2
		SD	7	34	51		
		MC		54	80		
		MC-SD		28	46		
1000	203-232	Mean	210	260	305	4/6	1; day 1 1; day 2 1; day 4 1; day 7
		SD	11	25	18		
		MC		52	97		
		MC-SD		26	19		
2000	229-267	Mean	248	261	237	4/6	1; day 0 2; day 1 1; day 16
		SD	14	29	86		
		MC		6*	-18*		
		MC-SD		22	78		

SD = Standard deviation.

MC = Mean change of surviving animals from day 0.

NA = Not applicable

MC-SD = Standard deviation of the mean change.

^a = Date of dosing is denoted as day 0.

* Significant difference - Indicates that the group mean weight is statistically different from that of the control group ($p \leq 0.05$)

Confidential Information Has Been Sanitized

Bayer Corporation
97-012-LF

Table 4

Summary of Body Weight and Mortality Data from Females During
an Acute Oral Toxicity Study with Preventol WB

Nominal Dose (mg/kg)	Initial Body Weight Range (g)		Body Weight (g)			Mortality	
			Days of Study ^a			No. Dead/ No. Exposed	Day of Death
			0	7	14		
0	181-207	Mean	193	222	231	0/6	NA
		SD	10	15	11		
		MC		30	38		
		MC-SD		7	3		
500	180-194	Mean	187	210	218	1/6	1; day 2
		SD	6	16	16		
		MC		22	31		
		MC-SD		11	13		
1000	182-202	Mean	193	215	230	4/6	3; day 2 1; day 3
		SD	8	12	1		
		MC		19	34		
		MC-SD		4	8		
2000	191-210	Mean	199	229	247	4/6	1; day 0 1; day 1 2; day 2
		SD	7	17	28		
		MC		26	44		
		MC-SD		8	19		

SD = Standard deviation.

MC = Mean change of surviving animals from day 0.

NA = Not applicable

MC-SD = Standard deviation of the mean change.

^a = Date of dosing is denoted as day 0.

* Significant difference - Indicates that the group mean weight is statistically different from that of the control group ($p \leq 0.05$)

Table 5

**Gross Observations of Males in an
Acute Oral Study with Preventol WB**

<u>DOSE (mg/kg)</u> <u>FATE</u>	<u>Nominal Dose (mg/kg)</u>						
	<u>CONTROL</u>	<u>500</u>		<u>1000</u>		<u>2000</u>	
	<u>6/6 SAC</u>	<u>6/6 SAC</u>	<u>1/6 FD</u>	<u>2/6 SAC</u>	<u>4/6 FD</u>	<u>2/6 SAC</u>	<u>4/6 FD</u>
NO GROSS LESIONS	6	5		2		2	
SALIVATION					1		1
VENTRUM STAIN, URINE					2		2
GLANDULAR STOMACH, MUCOSA DISCOLORED			1		4		4
NASAL STAIN			1		2		1
DISCOLORED BLADDER FLUID					2		1
BLADDER CALCULI							1
LUNGS REDDENED					1		

SAC = Sacrificed on day 14.
FD = Found Dead.

Confidential information Has Been Sanitized

Table 6

Gross Observations of Females in an
Acute Oral Study with Preventol WB

<u>DOSE (mg/kg)</u> <u>FATE</u>	<u>Nominal Dose (mg/kg)</u>						
	<u>CONTROL</u> <u>6/6 SAC</u>	<u>500</u>		<u>1000</u>		<u>2000</u>	
		<u>5/6 SAC</u>	<u>1/6 FD</u>	<u>2/6 SAC</u>	<u>4/6 FD</u>	<u>2/6 SAC</u>	<u>4/6 FD</u>
NO GROSS LESIONS	6	5		2		2	
GLANDULAR STOMACH, MUCOSA DISCOLORED			1		4		4
SALIVATION			1		1		2
VENTRUM STAIN, URINE					3		
NASAL STAIN			1				
DISCOLORED BLADDER FLUID							1
BLADDER CALCULI					1		
LACRIMATION					1		1

SAC = Sacrificed on day 14.

FD = Found Dead.

Confidential Information Has Been Sanitized

Confidential Information Has Been Sanitized

Bayer Corporation
97-012-LF

Appendix I

Individual Body Weights (g) from Males in an Acute Oral Toxicity
Study with Preventol WB

<u>Nominal Dose (mg/kg)</u>	<u>Animal Number</u>	<u>Day 0</u>	<u>Day 7</u>	<u>Day 14</u>
0	85	206	278	314
	86	214	277	309
	87	204	273	302
	88	218	292	340
	104	205	285	310
	90	207	295	339
500	91	206	229	273
	92	206	272	308
	93	217	298	336
	94	204	228	210
	95	218	294	324
	96	203		
1000	97	205		
	98	209	242	292
	99	232		
	105	208	278	318
	101	203		
	102	204		
2000	110	244	252	218
	111	255	238	163
	112	235		
	113	229		
	114	255		
	115	267	293	331

Date of dosing is denoted as day 0.
Blanks indicate animal death.

Confidential Information Has Been Sanitized

Bayer Corporation
97-012-LF

Appendix II

Individual Body Weights (g) from Females in an Acute Oral Toxicity
Study with Preventol WB

<u>Nominal Dose (mg/kg)</u>	<u>Animal Number</u>	<u>Day 0</u>	<u>Day 7</u>	<u>Day 14</u>
0	121	192	222	231
	122	192	211	230
	123	207	249	250
	124	200	230	235
	125	184	214	218
	126	181	208	221
500	127	188	205	226
	128	192	218	223
	129	194	230	225
	130	185		
	131	182	209	226
	132	180	186	190
1000	134	190	206	229
	135	186		
	136	202	223	230
	138	182		
	139	193		
	140	202		
2000	146	191		
	147	204		
	148	200		
	149	197	217	227
	150	191		
	151	210	241	267

Date of dosing is denoted as day 0.
Blanks indicate animal death.

Confidential Information Has Been Sanitized

**Bayer Corporation
97-012-LF**

Confidential Attachment

Study Title

**Acute Oral Toxicity Study
with Preventol WB in Rats**

Data Requirement

**40 CFR Part 158
US-EPA-FIFRA, Section 158.340, Guideline 81-1**

Authors

L. P. Sheets and A. T. Halliburton

Study Completion Date

April 17, 1997

Test Facility

**Bayer Corporation
Agriculture Division
Toxicology
17745 South Metcalf
Stilwell, Kansas 66085-9104**

Study Number

97-012-LF

CROSS REFERENCE NUMBER 1

DELETED INFORMATION:

Formulation:

INGREDIENTS

% W/W

Confidential Information Has Been Sanitized

<u>PAGE</u>	<u>LINES</u>	<u>REASON FOR THE DELETION</u>	<u>FIFRA REFERENCE</u>
9	16-24	Identity of Ingredients	Section 10(d)(1)(c)

Best Available Copy