TSCA HEALTH & SAFETY STUDY COVER SHEET

MR 11145

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 PDC: 88970000157

- Intial Submission **X**-Follow-up Submission - Final Report Submission

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

Follow up to 8EHQ-97-13907 8EHQ-1098-13907

☐ 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 917006751
98-2-21B

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 _____%

X - Single Ingredient

☐ Commerical/Tech Grade

☐-Mixture *Trade Name:* YRC 2894 *Common Name:* Chlornicotinyl

4.0 REPORT/STUDY TITLE - *Contains CBI*

Mechanistic Studies on Aromatase Induction in Mice (Feeding Study for 13 weeks) Study # T7061541, Tox # 8611

☐ Continuation sheet attached

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: BCHM SUBJECT ORGANISM (HE, EE only): MICE ROUTE OF EXPOSURE (HE only): Food VEHICLE OF EXPOSURE (HEonly)

Other: *Other:* *Other:* *Other:*

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

Laboratory Bayer Tox Lab, Wuppertal Germany Report/Study Date: 7/27/98

Source of Data/Study Sponsor (if different than submitter) _____ Number of pages 31

☐ 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*

These results are not directly reportable, but are being reported as supplementary data to aid in the evaluation of prior toxicological findings to previous submissions.

☐ continuation sheet attached

Submitter Signature: Donald W Lamb **Date:** 10/1/98

8EHQ-97-13907

8999000015

98 OCT 16 AM 11:23 OPPT INCIC

9.0 CONTINUATION SHEET

TSCA CBI STATUS:

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Submitter Tracking Number/Internal ID

P917006751
98-2-21B

CONTINUED FROM COVER SHEET SECTION #____2.1_____

TSCA 8(e) Evaluation

On 6/12/98 a chronic mouse study with "YRC 2894 Oncogenicity Stuidy in B6C3F1-Mice Administration in the Food over 2 Years" was submitted to the EPA. Based on liver necrosis and degeneration in males in the 1250 and 2500 ppm dose groups, cortical X-zone hypertrophy and vacuolization observed at the final necropsy in females in the 1250 and 2500 ppm dose groups, cortical X-zone hypertrophy and vacuolization observed at the final necropsy in females in the 1250 and 2500 ppm dose groups, and the increased number of luteromas in females in the 1250 and 2500 ppm dose groups. The present study was conducted in order to try to determine the mechanism of the findings in the females in the chronic study. This study does not require reporting to the EPA. however, it could be useful in evaluating the results from the chronic study with mice.

Abstract

The objective of this study was to determine the activity of aromatase in hepatic tissue and to study potential hormonal changes in female B6C3F1 mice fed YRC 2894 at dietary levels of 0, 10, 30, 250, and 2,500 ppm for 4 to 13 weeks. An additional group of female mice was treated with 2,500 ppm of YRC 2894 and also received 0.005% mecamylamine, a nicotinic antagonist, in their drinking water.

Clinical signs (changes in motility and reactivity) occurred at $\geq$ 250 ppm.

There were no treatment-related mortalities, no effect on water consumption or on body weight development, nor were there treatment-related gross pathological alterations.

Feed intake was reduced in the 2,500 ppm dose groups. The reduction was -22% in the 2,5000 ppm group without antidote, and -12% in the 2, 500 ppm group receiving the antidote (i.e., mecamylamine).

A dose-related increase in vacuolation of the X-zone located in the inner adrenal cortex was found at $\geq$ 250 ppm after 4 and 13 weeks of treatment. At 2,500 ppm, the marked vacuolation resulted in an enlargement of the X-zone after 13 weeks of treatment, 30 ppm was the histopathological NOEL..
Aromatase levels in hepatic tissue was slightly, but significantly and dose-related induced at $\geq$ 250 ppm after 13 weeks of treatment, while 30 ppm was the NOEL for this parameter.
Progesterone levels were increased and estradiol/progesterone ratio decreased at 2,500 ppm. Additional administration of mecamylamine did not abolish the effect of 2,500 ppm of YRC 2894 on estradiol/progesterone ratio. The NOEL for hormonal effects, defined as a change in estradiol/progesterone ratio, was 250 ppm.
The administration of mecamylamine did not abolish the effect of 2,500 ppm of YRC 2894 on estradiol/progesterone ratio or the decrement in feed intake produced by 2,500 ppm of YRC 2894 alone. This observation shows that YRC 2894 mediated effects on X-zone and hormone changes are not caused by central nervous events which can be counteracted by the nicotine antagonist, mecamylamine.

In summary, there was a clear NOEL of 30 ppm for all parameters studied. The most sensitive parameter in female mice was enzyme induction, exemplified by the hepatic enzyme aromatase which was already significantly induced at 250 pp. Vacuolation of the adrenal X-zone began at 250 ppm and caused X-zone enlargement at 2, 500 ppm. This latter treatment also resulted in slight hormonal changes which presented as a decrease in estrogen/progesterone ratio.

TX8611

STUDY TITLE

YRC 2894
Mechanistic Studies on Aromatase Induction in Mice
(Feeding Study for 13 Weeks)

DATA REQUIREMENT

US EPA-FIFRA Guideline No.: None

AUTHORS

Dr. P. Andrews, Dr. W. Bomann,
Dr. C. Ruhl-Fehlert and Dr. U. Schmidt

STUDY COMPLETION DATE

July 27, 1998

PERFORMING LABORATORY

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

LABORATORY PROJECT ID

Bayer AG Report No. PH-27716
Bayer AG Study No. T 7061541

STATEMENT OF DATA CONFIDENTIALITY

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(s), this study was conducted in compliance with the OECD Principles of Good Laboratory Practice (as revised in 1997) and with the Principles of Good Laboratory Practice (GLP) according to Annex 1 German Chemicals Act (Bundesgesetzblatt, Part I of the 29th of July 1994, and meets the FIFRA Good Laboratory Practice Standards (40 CFR Part 160) with the exception that recognized differences exist between the GLP principles/standards of OECD and FIFRA (for instance, authority granted Agency inspectors and certain record retention requirements).

The deviation(s) was/were as follows:
Determination of aromatase activity has not been done under GLP.

These deviations did not limit the assessment of results.

Dr. P. Andrews
(Study director)

July 15, 1998
Date

SPONSOR: **BAYER AG**

Dr. L. Machemer

10 August 1998
Date

SUBMITTER: BAYER CORPORATION

Dr. J.H. Thyssen
Vice President,
Toxicology

Date

Study no.: T 7061541

Flagging Statement

I have applied the critera of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of the attached study. This study neither meets nor exceeds any of the applied criteria.

SUBMITTER
BAYER CORPORATION

_____

Date _____

SPONSOR
BAYER AG

Dr. Machemer C. Machemer

Date 11th August 1998

STUDY DIRECTOR

Dr. Andrews Andrews

Date July 27, 1998

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1. Quality Assurance Statement

Test item: YRC 2894

Study no.: T 7061541

Study based inspections/audits were conducted by the 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
January 29, 1997	(study plan)	January 29, 1998
January 29, 1997	(study conduct)	January 29, 1997
February 10 1997		February 10, 1997
February 25, 1997		February 25, 1997
February 27 1997		February 27 1997
March 4, 1997		March 4, 1997
March 10, 1997		March 10, 1997
March 12, 1997		March 12, 1997
April 16, 1997		April 17, 1997
May 5, 1997		May 5, 1997
July 8 - 14, 1998	(first draft)	July 14, 1998
July 27, 1998	(final draft)	July 27, 1998

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

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

Date: July 27, 1998 Responsible: _____
(Dr. H. Lehn)

2. Signatures

Study director: (Dr. P. Andrews) July 27, 1998 (Date)

Co-author: (Dr. W. Bomann) July 27 1998 (Date)

Biochemistry: (Dr. U. Schmidt) July 27.1998 (Date)

Head of department of research toxicology (Dr. H.-J. Ahr) July 27, 1998 (Date)

3. Summary

The objective of the this mechanistic study was to determine the activity of aromatase in hepatic tissue and to study potential hormonal changes of female B6C3F1 mice fed YRC 2894 at dietary levels of 0, 10, 30, 250 and 2,500 ppm for 4 up to 13 weeks. An additional group of female mice was treated with 2,5000 ppm YRC 2894 and also received 0.005% mecamylamine, a nicotine mimicking agent, in their drinking water.

Clinical signs (changes in motility and reactivity) occurred at $\geq$ 250 ppm.

There were no treatment-related mortalities, no effect on water consumption or on body weight development, nor were there treatment-related gross pathological alterations.

Feed intake was reduced in the 2,500 ppm dose groups. The reduction was -22 % in the 2,500 ppm group without antidote, and -12 % in the 2,500 ppm group receiving the antidote mecamylamine.

A dose-related increase in vacuolation of the X-zone located in the inner adrenal cortex was found at $\geq$ 250 ppm after 4 and after 13 weeks of treatment. At 2,500 ppm, the marked vacuolation resulted in an enlargement of the X-zone after 13 weeks of treatment. 30 ppm was the histopathological no-observed-effect level.

Aromatase levels in hepatic tissue was slightly but significantly and dose-relatedly induced at $\geq$ 250 ppm after 13 weeks of treatment, while 30 ppm was the no-observed-effect level for this parameter.

Progesterone levels were increased and estradiol/progesterone ratio decreased at 2,500 ppm. Additional administration of mecamylamine did not abolish the effect of 2,500 ppm YRC 2894 on estradiol/progesterone ratio. The no-observed-effect level for hormonal effects, defined as a change in estradiol/progesteron ratio, was 250 ppm.

This additional administration of mecamylamine did not abolish the effect of 2,500 ppm YRC 2894 on estradiol/progesterone ratio or the decrement in feed intake produced by 2,500 ppm YRC 2894 alone. This observation shows that YRC 2894 mediated effects on X-zone and hormone changes are not caused by central nervous events which can be counteracted by the nicotine-like agent mecamylamine.

In summary, there was a clear no-observed-effect level of 30 ppm for all parameters studied. The most sensitive parameter in female mice was enzyme induction, exemplified by the hepatic enzyme aromatase which was already significantly induced at 250 ppm. Vacuolation of the adrenal X-zone began at 250 ppm and caused X-zone enlargement at 2,500 ppm. This latter treatment also resulted in slight hormonal changes which presented as a decrease in estrogen/progesterone ratio.

4. Introduction

This report describes the result of a special subchronic toxicity study in which YRC 2894 was administered to female mice in their diet for up to 13 weeks.

The objective of the this mechanistic study was to determine aromatase activity in the liver and to study potential hormonal changes of female mice after 4 and after 13 weeks of feeding YRC 2894.

This study was conducted in analogy to:
Method B 7, Directive 67/548/EEC of the Council of the European Communities of June 27, 1967 (Official Journal of the European Communities L 196/1 of August 1) in its current version as amended for the seventeenth time (Directive 92/69/EEC of the Commission of the European Communities of December 29, 1992; Official Journal of the European Communities L 383 A of December 29), and
OECD Guideline No. 407 (updated July 27, 1995; OECD Guidelines for Testing of Chemicals, Section 4, Health Effects).

5. General Information

5.1. Study Location

The study has been performed at the Institute of Toxicology, Bayer AG, D 42096 Wuppertal, Friedrich-Ebert-Straße 217 - 333.

5.2. Study Identification, Duration, Statements of Time

Unless otherwise indicated, the times stated in the report relate to weeks or days relative to the first day of treatment (= day 0) of the animal group in question. In the histopathology report, the first day of treatment is reckoned to be day 1. The first week on treatment is week 1.

Study number	T 7061541
Study initiation date	January 27, 1997
Experimental starting date	January 22, 1997
Study start date	February 3, 1997
Study termination date	May 16, 1997
Study completion date	see signature page
Scheduling of activities	
Animal delivery	January 22, 1997
Randomization	January 29, 1997
First day of treatment	February 3, 1997
Last day of treatment	May 16, 1997
Estrus cycle staging	February 24 - March 7 and April 28 - May 16, 1997
Necropsy and blood sampling for hormone determinations	March 3 - 7 and May 5 - 16, 1997
Liver for aromatase determination	May 5 - 16, 1997

5.3. Archiving

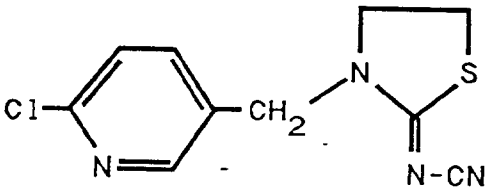
The study protocol, a copy of the report, study documentation, raw data, etc. are archived at the Institute of Toxicology, Bayer AG. Materials (test substance etc.) have been retained.

5.4. Persons Involved, Responsibilities

Study director	Dr. P. Andrews
Head of department	F. Mihail, M.Sc.
Analytical chemistry	Dr. W. Gau, Dr. W. Rüngeler
Aromatase determinations	Dr. U. Schmidt
Hormone determinations	McKnight Laboratories, Osterstraße 89, 20259 Hamburg, Germany
Macroscopic pathology	Dr. M. Rinke
Histopathology	Dr. C. Rühl-Fehlert
Archiving	Prof. Dr. G. Schlüter

6. Materials and Methods

6.1. Test Substance

Test substance:	YRC 2894
Manufacturer:	Bayer AG
Indication:	insecticide
Contents:	97.2 and 97 % (consecutive analyses)
Approval:	until August 20, 1997
Physical state:	solid
Appearance:	pale yellowish powder
Storage:	room temperature
Chemical name:	[3-(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene cyanamide
CAS Registry no.:	111988-49-9
Molecular weight:	252.5 g/mol
Molecular formula:	$C_{10}H_9ClN_4S$
Structural formula:	

6.2. Antidote

Antidote	mecamylamine
Supplier:	Sigma
Lot nos.	114H4049, 76H4060
Contents:	97.2 and 97 % (consecutive analyses)
Storage:	room temperature
Chemical name (C.A):	[N,2,3,3,-tetramethylbicyclo(2.2.1)-heptan-2-amine hydrochloride
Molecular weight:	203.8 g/mol
Molecular formula:	$C_{11}H_{21}N$ x HCl

6.3. Dietary Admixture and Analyses of the Test Substance

For treatment of the animals YRC 2894 was mixed into the diet intended for the following week in accordance with the dose scheme. A mixing granulator manufactured by Messrs. Loedige of Paderborn was used. The mixes contained 1% peanut oil to minimize dust formation (including 0 ppm).

Homogeneity and stability of the test substance were known from a previous study (T 0055541). Correct concentration in the feed mixture has been determined by analytical examination (see 9.4. in the Annex).

6.4. Dosage Form, Doses, Study Groups

At the start of the study, female mice were grouped by weight and assigned to dose groups using random lists. The cages were then numbered consecutively.

The test substance was administered in the feed from the start of the study until either spontaneous death or scheduled sacrifice of the animals.

The dose schedule and the distribution of the animals by group are shown in the following table:

group no.	dose [ppm]	no. of animals	animal no.
1	0	30	1 - 30
2	10	30	31 - 60
3	30	30	61 - 90
4	250	30	91 - 120
5	2,500	30	121 - 150
6	2,500 + mecamylamine	30	151 - 180
7	untreated control	10	181 - 190

Group 6 was given 0.005% mecamylamine, a nicotine mimicking agent, in the drinking water starting from day 1 of the study to check whether the nicotine-like effect of YRC 2894 was responsible for adrenal X-zone enlargement . Group 6 is also denoted as 2,500+ in the tables of the results section.

Group 7 was sacrificed at the start of the study. Some organs (e.g. pituitary, adrenals) were fixed and used for method development.

Random list were also used to determine the fate of the animals in groups 1- 6 (15 animals each for interim and terminal necropsy).

6.5. Rationale for Dose Selection

The dose range of 10 - 2,500 ppm for this mechanistic study was chosen because 50 ppm had resulted in enlargement of the x-zone of the inner cortex of the adrenals in a subchronic toxicity study (T 8055585) and doses > 1,250 ppm in vacuolation of the x-zone. The high dose of 2,500 ppm was chosen as this dose was the high dose in the mouse oncogenicity study (T 9059195). The low doses of 10 and 30 ppm were selected as putative no-observed-effect doses.

6.6. Test System (experimental animals) and Housing Conditions

6.6.1. Experimental Animals

The study was conducted on mice, a species recommended in guidelines for subacute toxicity studies.

The animals used were female SPF-bred B6C3F1 mice supplied by the breeder Charles Rivers. Animals of this strain have been used at Bayer AG for toxicological studies for many years. The state of health of the strain is routinely tested for the most important specific pathogens on a random basis. The results of these tests are held on file. Data on physiology and spontaneous changes in mice of this strain are also available.

After the arrival of the mice, the animals intended for this study were acclimatized to conditions in the animal room until start of treatment for at least 7 days. Their state of health was also monitored during this period.

Only healthy animals showing no clinical signs were used for the study. The animals were not vaccinated or treated with anti-infectives either before receipt or during the acclimatization or treatment periods. The females were nulliparous and not pregnant.

The mean group body weights at the first day of treatment are listed in table 7.6. On receipt, the age of the mice was 4 - 5 weeks. The scatter of the animal weights was less than 20% around the mean.

6.6.2. Housing Conditions

During the treatment period the animals were housed individually under conventional conditions in polycarbonate cages on low-dust wood granulate supplied by Ssniff Spezialdiäten GmbH of Soest/Westphalia. Throughout the acclimatization period mice were kept in groups.

Cages and bedding material were changed at least weekly. The wood granulate was randomly tested for contaminant contents. The results are retained on file. The results of analyses provided no indication of any effect on the study objective.

The cages containing the experimental animals were placed on racks, separated by groups, in ascending animal number order. All animals taking part in this study were kept in the same animal room.

6.6.2.1. Identification of the Experimental Animals

The animals were identified by means of ear taboos and cage cards stating the test substance, animal number, dose, sex and study number.

6.6.2.2. Cleaning, Disinfection, Pest Control

The animal room was cleaned once weekly and disinfected at least once a month with a 2.5% solution of Tegol 2000 provided from a centralized supply. 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.

The racks were cleaned at regular intervals. Drinking bottles, cage lids and feed containers were also replaced regularly. The entire cages were cleaned with hot water. A detergent was added to the final rinse, which was allowed to come into contact with the outside of the cages only.

6.6.2.3. Environmental Conditions

The environmental conditions in the animal room were standardized as follows:

room temperature:	22 ± 2°C
relative atmospheric humidity:	approx. 55 ± 5%
light/dark cycle:	12 hours, illumination from 6 a.m. to 6 p.m.
air changes:	approx. 15 - 20 changes per hour

Occasional deviations from these specifications occurred, e.g. as a consequence of cleaning the animal room. They had no identifiable influence on the course of the study.

6.6.2.4. Diet

The diet consisted of a fixed-formula standard diet (Altromin® 1321 powder supplied by Altromin GmbH of 32770 Lage, Germany) throughout acclimatization and treatment periods, and tap water. Feed and water were available ad libitum and were supplied in polycarbonate bottles and in stainless steel automatic feeders inside the cages, respectively.

The nutritive composition (9.2. in the Annex) and contaminant content of the standard diet were routinely checked and analyzed. The tap water complied with the German Drinking Water Ordinance [Trinkwasserverordnung] of December 5, 1990, Federal Law Gazette No. 66, issued on December 12, 1990, page 2612.

The results of analyses of the feed and water were stored. The available data provided no indication of any effect on the study objective.

6.7. General Investigations

Some of the values in the tables of individual body weights, feed or water intake may be missing. This may be the consequence of a technical defect which occurred during on-line data collection or of a value which cannot be listed (because of an error in weighing and a failure to meet printer format) or is unrealistic (indicated by "x" in the tables of the Annex).

6.7.1. Inspection of Experimental Animals

The experimental animals were inspected at least once a day. Any clinical signs (findings) and abnormalities were recorded. Body surfaces and orifices, posture, general behavior, breathing and excretory products were assessed. Findings and abnormalities were recorded either using a coding system or else uncoded.

If animals became ill, they were set apart, observed more frequently and sacrificed prematurely, if death seemed imminent.

6.7.2. Determination of Body Weight

The body weights of the individual experimental animals were determined before the beginning of the study and weekly thereafter up to the end of the study.

6.7.3. Determination of Feed and Test Substance Intake

The feed intake of each individual mouse was determined weekly. These primary data were then used to calculate the weekly means. The algorithm used for calculating intake of feed and test substance is described in the Annex (9.3.).

6.7.4. Determination of Water Consumption

Water consumption of each individual mouse was determined according to measurement of feed intake. These primary data were used to calculate mean and cumulative water consumption as described under 6.7.3.

6.7.5 Estrus Cycle Staging, Mating and Reproduction

Vaginal smears were taken from each female prior to mating, checked microscopically and classified as diestrus, proestrus or estrus.

6.8. Collection of Samples

Blood for hormone determinations was collected by cardiac puncture from ether anesthetized animals at the interim and the terminal necropsy (6.11.). Heparin plasma was prepared by centrifugation and kept deep frozen till analyzed (6.9.). However, hormone determinations were only performed on blood samples obtained at terminal necropsy.

At terminal necropsy, livers were removed in deep ether anesthesia, frozen on solid carbon dioxide and forwarded to the laboratory performing the aromatase determinations.

6.9. Hormone Determinations

Single determinations of estradiol and progesterone were performed by Mc Knight Laboratories GmbH, 20259 Hamburg, using radioimmune assays using sample volumes of 50 µl (no pre-extraction) and 100 µl (with pre-extraction), respectively. The methods employed are described in the Hormone Determination Report in the Annex (9.9)

6.10. Aromatase Determination

The method employed is described in the Aromatase Determination Report in the Annex (9.12.).

6.11. Necropsy

Animals were necropsied in the diestrus phase. 15 animals per group were necropsied during study days 28 - 32, the remaining animals during study days 91 - 102. Animals were necropsied after exsanguination under deep ether anesthesia. Animals that died spontaneously or were killed in a moribund state during the study were dissected at the earliest opportunity. The organs and tissues fixed and the methods of fixation are described in the pathology report in the Annex (9.11.).

6.12. Organ Weights

The following organs were weighed at necropsy:
brain, heart, kidneys, liver, spleen, thymus, adrenals, ovaries, uterus and pituitary.

6.13. Histopathology

The fixed material was retained (pathology no. 5006). Histological procedures are described in the pathology report in the Annex (9.11.).

The quantitative results for individual animals were used to calculate group means, medians and standard deviations. The results for the groups that received the test substance were compared with those for the control group and significant differences indicated by '+' for $p \leq 0.05$ and '++' for $p \leq 0.01$. In case of numbers of values too low to calculate test statistics this is indicated by '°' or '-' in the tables shown in the results section and by 'nc' (not calculated) or by '0' in the tables of the Annex. The individual results listed in the Annex to this report have been rounded off. Calculation of means and variances was based in part on the non-rounded original values.

Dunnett's test was used for body weight, feed and substance intake, water consumption and organ weight data (relative organ weights subsequent to logarithmic transformation). The statistical tests employed for other parameters are shown in the respective sections of the Annex together with mean and individual data.

Some of the values in the tables of individual body weights and feed intake may be missing. This may be the consequence of a technical defect which occurred during on-line data collection or of a value which cannot be listed (because of an error in weighing and a failure to meet printer format) or is unrealistic (e.g. negative feed intake) on account of a weighing error and deleted. Missing values for feed and water consumption are indicated by 'x' in the tables of the Annex.

A measurement recorded on-line may occasionally have been identified as an outlier in tables of individual values and therefore have been excluded from further analysis, if it appeared implausible, i.e. in the event of an inexplicably large discrepancy compared with the expected or previously recorded value.

7. Results

The results of the investigations are summarized in the following sections. Abbreviations used are given in the Annex (9.1.).

7.1. Analysis of Test Substance in the Diet

The test substance was known to be homogeneously distributed (concentration range 10 - 2,500 ppm) and chemically stable for 14 days (s. 5.2.). Correct concentration in the feed mixes was ascertained analytically (9.4.).

7.2. Inspection of the Experimental Animals

Clinical signs attributable to the treatment were changes in motility and reactivity. Decreased reactivity was observed at 2,500 ppm starting from day 28, with 6/15 animals affected in the interim necropsy group and 5/15 in the terminal sacrifice group at 2,500 ppm affected, while only 2/15 and 3/15 were affected in the 250 ppm and the 2,5000 ppm plus antidote groups, respectively. Increased motility was observed in a total of 4/15 animals at 250 ppm, and in 1/15 or 2/15 animals of the 2,500 ppm groups from day 49. Reduced motility was observed in 2 animals of the 2,500 ppm group from day 57.

Other observations (animal trapped, empty water bottle, loss of hair) occurred throughout all groups and were not considered treatment related. For detailed results see 9.5. in the Annex.

7.3. Mortality

There were no treatment-related mortalities. 2 animals of the 10 ppm group died prematurely (animal no. 55 was trapped between cage and cage lid and was killed in a moribund conditions in week 1, animal no. 47 jumped from the cage in week 11 and was subsequently killed). All other animals survived to the end of the study.

7.4. Intake of Feed and Test Substance

Individual feed intake data and group means are shown in the Annex (9.6.). The table below summarizes mean daily feed consumption for 91days. There was no effect of treatment on feed uptake up to 250 ppm. Feed intake was reduced in the 2,500 ppm dose groups. The reduction (g/kg body weight) was -22 % in the 2,500 ppm group without antidote, and -12 % in the 2,500 ppm group receiving the antidote mecamylamine.

Mean feed intake				
dose	g/animal		g/kg body weight	
[ppm]	total	per day	total	per day
0	1129.4	12.4	51469.5	565.6
10	1136.7	12.5	50260.8	552.3
30	1162.3	12.8	53487.4	587.8
250	1100.9	12.1	50501.2	555.0
2,500	874.1	9.6	40067.0	440.3
2,500+	968.8	10.6	45271.9	497.5

Mean test substance intake for 91 days. The intake of test substance was proportional to the dietary concentration up to 250 ppm. Test substance intake was reduced at 2,500 ppm..

Mean test substance intake				
dose	g/animal		g/kg body weight	
[ppm]	total	per day	total	per day
28 days				
0	0	0	0	0.0
10	11	0	503	6
30	35	0	1605	18
250	275	3	12625	139
2,500	2185	24	100167	1101
2,500+	2422	27	113180	1244

7.5. *Water Consumption*

The results of individual determinations of water consumption are shown in the Annex (9.7.). The table below summarizes mean daily water consumption.

There was no toxicologically relevant effect of treatment on water consumption.

Mean water consumption				
dose	g/animal		g/kg body weight	
[ppm]]	total	per day	total	per day
0	479	5.3	21881	240.4
10	483	5.3	21359	234.7
30	490	5.4	22450	246.7
250	472	5.2	21567	237.0
2,500	466	5.1	21322	234.3
2,500+	473	5.2	22083	242.7

7.6. *Body Weights*

Individual body weights and group means with statistical data are shown in the Annex (9.8.). The table below summarizes mean body weights.

There was no toxicologically relevant effect of treatment on body weight development. The apparently statistically significant changes (elevated body weights at 10 ppm after 4 weeks of treatment and slight transient weight decrements in both 2,500 ppm groups in weeks 2 - 4) were considered spurious.

Body weight means [g]									
dose [ppm]	day 0	day 7	day 14	day 28	day 42	day 57	day 70	day 84	day 91
0	18.5	19.5	20.4	21.7	22.0	23.2	23.5	23.8	23.9
10	18.5	19.6	20.6	22.0	23.1++	24.6++	25.0++	25.0+	25.1+
30	18.3	19.2	20.0	21.2	22.0	23.4	23.7	24.2	23.9
250	18.4	19.3	20.1	21.3	22.1	23.5	23.9	24.1	23.9
2,500	18.4	19.4	19.8+	21.0+	22.2	23.8	23.9	24.3	24.0
2,500+	18.2	19.2	19.2	20.8++	21.5	23.0	23.4	23.6	23.5

7.7. *Necropsy*

The results of the gross pathology evaluation performed at necropsy are contained in the histopathology report in the Annex (9.11.).

There were no treatment-related gross pathological alterations in animals surviving up to scheduled necropsy. Animal no. 164 (2,500 ppm + mecamylamine) presented a clear cyst of 0.5 cm diameter at the right ovary, animal no. 176 (2,500 ppm + mecamylamine) presented some dark-red area of 0.2 cm diameter on the lungs.

7.8. *Hormone determinations*

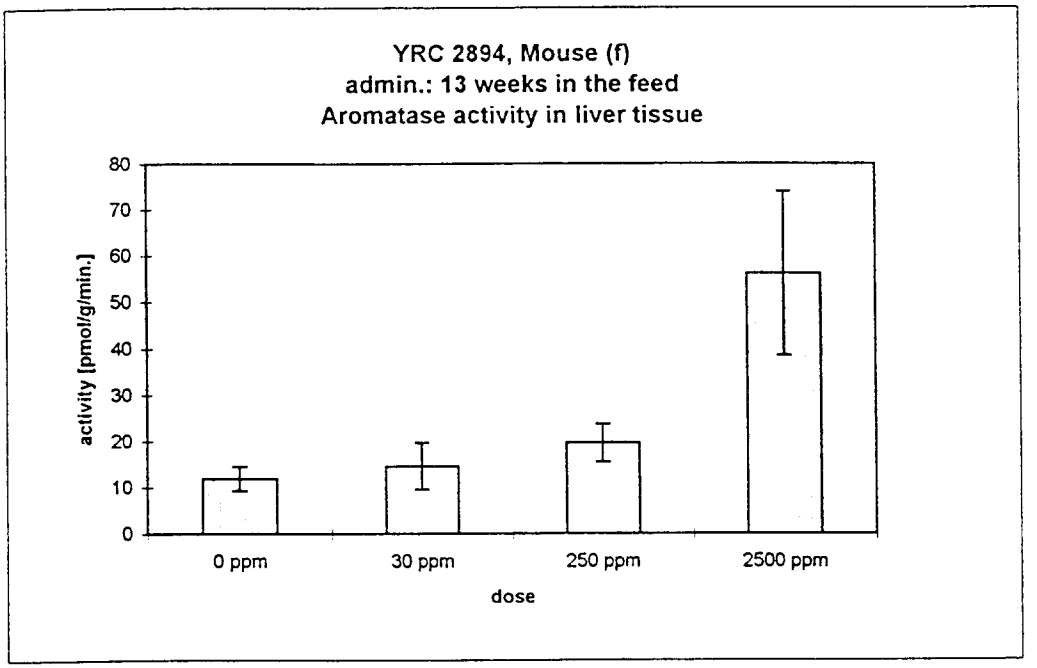
The concentration of estradiol and progesterone was determined in the diestrus phase of mice after 13 weeks of treatment. The table below shows the group means. Individual values and the results of estrus cycle staging are shown in the Annex (9.9.).

dose [ppm]	estradiol [pg/ml	progesterone [ng/ml	estradiol / progesterone ratio	number of values
0	35.2	1.48	26.1	15
10	37.8	1.57	28.8	14
30	37.5	1.43	28.0	15
250	32.3	1.45	32.0	14
2,500	31.5	2.02	17.4	14
2,500+	28.3	2.10	15.5	14

There was a considerable variation between the 14 - 15 individual animals per group. Progesterone levels were increased at 2,500 ppm. This resulted in a corresponding decrease in the estrogen/progesterone ratio at 2,500 ppm. At 250 ppm, estradiol levels were already slightly reduced, however, the estradiol/progesterone ratio remained unaffected. Additional administration of mecamylamine did not abolish the effect of 2,500 ppm YRC 2894 on estradiol/progesterone ratio. The no-observed-effect level for hormonal effects, defined as a change in estradiol/progesteron ratio, was 250 ppm.

7.9. Aromatase Activity

The determination of aromatase activity in hepatic tissue of 6 mice per group was performed in the 0, 30, 250 and 2,500 ppm groups. The results clearly show that aromatase is slightly but significantly induced at 250 and at 2,500 ppm after 13 weeks of treatment, while aromatase levels were not raised above the control level at 30 ppm. Individual data are shown in the Annex (9.12.).



7.10. Organ Weights

Individual results and group means with statistical data for absolute and relative organ weights determined during necropsy are shown in the Annex (9.10.).

The tables below summarize the group mean absolute and relative organ weights. The only organgravimetric effect observed was an increase in absolute and relative liver weights in both 2,500 ppm groups. This effect was already apparent after 4 weeks of treatment and was less pronounced in the 2,500 ppm group which was also given the antidote mecamylamine (+18/+25 % in absolute/relative weight at 4 weeks) than in the group only given 2,500 ppm YRC 2894 (+30/+32 %). A slight increase in relative liver weight at 250 ppm (+8 %) was observed after 4 weeks, but no longer at the termination of the study.

There were no organgravimetric effects on the uterus or the ovaries.

Absolute organ weights								
dose ppm	body weight [g]	brain [mg]	pituitary [mg]	adrenals [mg]	heart [mg]	liver [mg]	spleen [mg]	thymus [mg]
interim sacrifice								
0	22	473	2	8	118	1098	75	42
10	22	463	2	9	114	1087	78	48
30	21	468	2	9	116	1058	73	41
250	21	468	2	10	117	1166	72	44
2,500	21	463	2	8	120	1426++	73	45
2,500+	21++	462	2	10	115	1306++	71	43
terminal sacrifice								
0	24	484		10	127	1196	86	34
10	26++	492		10	133	1202	90	35
30	24	478		9	132	1140	85	32
250	24	479		9	134	1171	83	35
2,500	25	483		13	139	1508++	91	35
2,500+	24	479		11	136	1411++	87	34

Absolute organ weights				
dose ppm	body weight [g]	kidneys [mg]	ovaries [mg]	uterus [mg]
interim sacrifice				
0	22	339	23	240
10	22	338	24	278
30	21	326	19	245
250	21	330	27	257
2,500	21	321	22	250
2,500+	21++	319+	24	222
terminal sacrifice				
0	24	361	22	287
10	26++	383	25	278
30	24	364	23	285
250	24	361	23	269
2,500	25	359	23	269
2,500+	24	352	24	262

Relative organ weights								
dose ppm	body weight [g]	brain [mg/100g]	pituitary [mg/100g]	adrenals [mg/100g]	heart [mg/100g]	liver [mg/100g]	spleen [mg/100g]	thymus [mg/100g]
interim sacrifice								
0	22	2173	9	35	543	5039	343	194
10	22	2133	9	40	523	5000	356	219
30	21	2204	9	41	548	4974	342	194
250	21	2191	10	45	550	5444+	338	207
2,500	21	2172	9	40	559	6673++	342	212
2,500+	21++	2239	9	46	555	6305++	343	205
terminal sacrifice								
0	24	2013		43	531	4969	356	142
10	26++	1925+		39	521	4694	352	136
30	24	1970		36	545	4690	350	131
250	24	1971		38	552	4810	340	143
2,500	25	1968		52	566	6135++	371	141
2,500+	24	2028		45	575	5943++	365	144

Relative organ weights				
dose ppm	body weight [g]	kidneys [mg/100g]	ovaries [mg/100g]	uterus [mg/100g]
interim sacrifice				
0	22	1558	107	1104
10	22	1552	110	1284
30	21	1535	90	1158
250	21	1544	126	1197
2,500	21	1502	102	1168
2,500+	21++	1539	116	1062
terminal sacrifice				
0	24	1504	91	1195
10	26++	1498	99	1302
30	24	1500	94	1171
250	24	1487	96	1106
2,500	25	1459	95	1095
2,500+	24	1489	100	1104

7.11. Histopathology

Adrenals of all animals have been subjected to histopathology. A dose-related increase in vacuolation of the X-zone located in the inner adrenal cortex was found at ≥ 250 ppm after 4 and after 13 weeks of treatment. At 2,500 ppm, the marked vacuolation resulted in an enlargement of the X-zone after 13 weeks of treatment. The histopathological no-observed-effect level for this change was 30 ppm.

There was no effect of mecamylamine on the changes induced by 2,500 ppm YRC 2894 in the murine adrenal cortex.

Details of the histopathology investigations are shown in the pathology report in the Annex (9.11.).

8. Discussion and Evaluation of the Results

The objective of the this mechanistic study was to determine the activity of aromatase in hepatic tissue and to study potential hormonal changes of female B6C3F1 mice fed YRC 2894 at dietary levels of 0, 10, 30, 250 and 2,500 ppm for 4 up to 13 weeks. An additional group of female mice was treated with 2,5000 ppm YRC 2894 and also received 0.005% mecamylamine, a nicotine mimicking agent, in their drinking water.

Clinical signs (changes in motility and reactivity) occurred at $\geq$ 250 ppm.

There were no treatment-related mortalities, no effect on water consumption or on body weight development, nor were there treatment-related gross pathological alterations.

Feed intake was reduced in the 2,500 ppm dose groups. The reduction was -22 % in the 2,500 ppm group without antidote, and -12 % in the 2,500 ppm group receiving the antidote mecamylamine.

A dose-related increase in vacuolation of the X-zone located in the inner adrenal cortex was found at $\geq$ 250 ppm after 4 and after 13 weeks of treatment. At 2,500 ppm, the marked vacuolation resulted in an enlargement of the X-zone after 13 weeks of treatment. 30 ppm was the histopathological no-observed-effect level.

Aromatase levels in hepatic tissue was slightly but significantly and dose-relatedly induced at $\geq$ 250 ppm after 13 weeks of treatment, while 30 ppm was the no-observed-effect level for this parameter.

Progesterone levels were increased and estradiol/progesterone ratio decreased at 2,500 ppm. Additional administration of mecamylamine did not abolish the effect of 2,500 ppm YRC 2894 on estradiol/progesterone ratio. The no-observed-effect level for hormonal effects, defined as a change in estradiol/progesteron ratio, was 250 ppm.

This additional administration of mecamylamine did not abolish the effect of 2,500 ppm YRC 2894 on estradiol/progesterone ratio or the decrement in feed intake produced by 2,500 ppm YRC 2894 alone. This observation shows that YRC 2894 mediated effects on X-zone and hormone changes are not caused by central nervous events which can be counteracted by the nicotine-like agent mecamylamine.

In summary, there was a clear no-observed-effect level of 30 ppm for all parameters studied. The most sensitive parameter in female mice was enzyme induction, exemplified by the hepatic enzyme aromatase which was already significantly induced at 250 ppm. Vacuolation of the adrenal X-zone began at 250 ppm and caused X-zone enlargement at 2,500 ppm. This latter treatment also resulted in slight hormonal changes which presented as a decrease in estrogen/progesterone ratio.

9. Annex

9.1. List of Abbreviations

a.i.	active ingredient
a.m.	in the morning
approx.	approximately
b.w., body-w.	body weight
°C	degree Celcius
C.A.	Chemical Abstracts
CAS	Chemical Abstracts Service
c.n.	common name
cont.	continued
e.g.	for example
et al.	and others
etc.	et cetera, and so on
fl	femtoliter, 10^{-15} l
g	gram(me)
g	9.81 [m sec^{-2}], gravitational constant
i.e.	that is
kg	kilogram(me), 10^{3} g
l, L	liter
M	mean value
med	median
min	minimum
min, m	minute
max	maximum
µl	microliter, 10^{-6} l
mcmol, µmol	micromol(e), 10^{-6} mol(e)
mg	milligram(me), 10^{-3} gram(me)
ml	milliliter. 10^{-3} l
mmol	millimol(e), 10^{-3} mol(e)
n, N	number of values
nmol	nanomol(e), 10^{-9} mol(e)
no.	number
p	probability
pg	picogram(me), 10^{-12} g
p.m.	in the afternoon
p., pp.	page(s)
po, p.o.	per os
ppm	parts per million
s, sd, S.D.	standard deviation
sec, s	second
TS1%	significant at the 99 % level
TS5%	significant at the 95 % level
U	unit
%	per hundred, 10^{-2}
‰	per thousand, 10^{-3}

9.2. *Composition of Diet*

Altromin International, Standard diets, totally pathogen free TPF® 1321

Maintenance Diet Rats/Mice

Nutrients (*)	
crude protein	19.0
crude fat	4.0
crude fiber	6.0
ash	7.0
moisture	13.5
nitrogen-free extract	50.5
metabolizable energy (calculated)	
Kcal/kg	2,850.0
MJ/kg	11.9

Amino acids (*)	
lysine	0.90
methionine	0.30
cystine	0.30
phenylalanine	0.80
tyrosine	0.60
arginine	1.10
histidine	0.40
tryptophane	0.20
threonine	0.60
iosoleucine	0.80
leucine	1.30
valine	0.90

Minerals (*)	
calcium	0.9
phosphorus	0.7
magnesium	0.2
sodium	0.2
potassium	1.0

Trace elements (**)	
manganese	75.0
iron	180.0
copper	13.0
zinc	70.0
iodine	0.9
fluorine	15.0

Vitamins (***)	**Standard diet**	**Standard diet fortified**
Vitamin A	15,000.0 IU	25,000.0 IU
Vitamin D3	600.0 IU	1,000.0 IU
Vitamin E	75.0 mg	125.0 mg
Vitamin K3	3.0 mg	5.0 mg
Vitamin B1	18.0 mg	30.0 mg
Vitamin B2	12.0 mg	20.0 mg
Vitamin B6	9.0 mg	15.0 mg
Vitamin B12	24.0 µg	40.0 µg
nicotinic acid	36.0 mg	60.0 mg
pantothenic acid	21.0 mg	35.0 mg
folic acid	2.0 mg	3.0 mg
biotin	60. µmg	100.0 µg
choline	600.0 mg	1,000.0 mg
Vitamin C	36.0 mg	60.0 mg

(*) average % content in the diet
(**) average mg content in 1 kg diet
(***) additive in 1 kg diet

9.3. *Calculation of Feed and Water Consumption and Active Ingredient Intake*

The algorithms described below for the feed consumption are correspondingly applicable to the drinking water consumption. Body weights and the initial and final weights are measured in grams for the calculations.

1 Feed consumption (individual animal determination)

1.1 **Feed consumption per animal per day:** (I - F) : nT

I = weight of feed administered (if necessary, plus weight of feed container) at time of weighing (initial weight); F = weight of feed not consumed (if necessary, plus weight of feed container) at time of weighing back (final weight); nT = number of days between weighing and weighing back

1.2 **Mean feed consumption per animal per day (date-related):**

[sum of all values available (1.1) at a specific date] : [no. of values]

1.3 **Mean feed consumption per animal per day:** (1.1) : [no. of values]

1.4 **Cumulative feed consumption per animal:** (1.3) x ndays

ndays is established from the total number of feed consumption days

1.5 **Feed consumption per kg body weight per day:** (1.1) x 1000 [body weight of the animal]

The body weight value that was obtained within the time interval from the day of weighing back (final weight) to the day of "weighing back - 7" is taken as the basis for the mean body weight. If no determination was planned within this time, the time interval from the day of weighing back to the day of "weighing back + 6" is taken as the basis. If no body weight value is available within either of these two intervals, no feed consumption is calculated.

1.6 **Mean feed consumption per kg body weight per day (date-related):**

[sum of all values (1.5) at a specific date] : [no. of values]

1.7 **Mean feed consumption per kg body weight per day:** (1.5) : [no. of values]

1.8 **Cumulative feed consumption per kg body weight:** (1.7) x ndays

2. Active ingredient (AI) intake

The active ingredient intake is calculated from the feed consumption data by using a "dose factor". where: dose in ppm; feed consumption in g; AI intake in mg;dose factor = (dose) : 1000

2.1 **Mean AI intake per animal per day:** (1.3) x dose factor

2.2 **Cumulative AI intake per animal:** (1.4) x dose factor

2.3 **AI intake per kg body weight per day:** (1.5) x dose factor

2.4 **Mean AI intake per kg body weight per day (date-related):** (1.6) x dose factor

2.5 **Mean AI intake per kg body weight per day:** (1.7) x dose factor

2.6 **Cumulative AI intake per kg body weight:** (1.8) x dose factor

9.4. Analytical Certificates

Bayer AG
PF-PM/PPA

16.02.98

Approval of Active Ingredient Sample

Active Ingredient Sample TOX 3829

Sample: *YRC 2894*

Development-No.: *0085904*

Indication: *Insecticide*

Mixed Batch No.: *290894*

Origin of sample: *PF-E/FT*

Responsible Analyst: *Dr. Gau* Laboratory: *PB-A*

Analytical Methods: *HPLC, int. Std.*

Approvals:

TOX	Purity		Approved until	Date of Analysis	Comment
3829-01	*97.3*	*%*	*24.09.95*	*27.03.95*	*STANDMUSTER SIEHE TOX 3722-00*
3829-02	*97.2*	*%*	*01.03.96*	*01.09.95*	
3829-03	*97*	*%*	*20.08.96*	*20.02.96*	
3829-04	*97.2*	*%*	*20.02.97*	*21.08.96*	
3829-05	*97*	*%*	*20.08.97*	*21.02.97*	
3829-06	*97.1*	*%*	*19.02.98*	*20.08.97*	
3829-07	*96.2*	*%*	*12.08.98*	*12.02.98*	

(M. Haug, PF-PM/PPA)

A reserve sample will be retained.

PH-PDT Tox. Analytic
Dr. W. Rüngeler
ELB.; 514; ☎ 8278

Distribution:
Dr. Andrews

May 12, 1997

Analysis Certificate (Vers. 2)

Content Checks for Dose Verification in Rodent Ration

Test material:	**YRC 2894**
Mixed batch no.:	290894
Purity:	97.0%
Origin of sample:	Bayer AG, PF-E/FT
Stability approved until:	Aug. 20, 1997
Appearance:	pale yellow powder
Test material storage:	room temperature
Stability of analytical samples:	was ensured throughout the test period
Toxicology feed mixtures:	in Altromin 1321; mixed with 1% peanut oil DAB 10
Study director (Toxicology):	Dr. Andrews
Study No.	**T7061541**

The analytical method, its validation (HPLC) was formerly presented in the study no. T0055541 and was included in a separate report (D.I. Riegner, PF-E/RA; Report no. RA-0303/94; Sep. 8, 1994). A revalidation of the recovery was performed in the actual study.

RESULTS: CONTENT CHECKS

The analytical data (HPLC) verify that the test material content in the toxicology test mixtures agreed with the target concentrations (except the 10 ppm sample) (Tab. 1). Additionally a stability test of these samples was performed. The samples were stored for 7 days under conditions comparable to those in the actual study, and then quantified. The stability was assured.
The concentration of two 10 ppm samples (prep. dates: Jan. 31 and Feb. 7, 1997) were above the defined limit.
Further investigtions showed, that the extraction method was not valid for the low 10 ppm concentration. Therefore a new validated extraction method was established. These later results of another two diet preparations (see analysis certificate from May 12, 1997), produced consistent results between the diet preparation and the analytical values.

For calculations integrator values from each sample were based on the external standard calibration curve of the active ingredient. The analytical results of the test material were expressed in weight units [ppm]. For assessment of content checks the percentage of active ingredient in the original test material was not included for calculations.

Table 1 presents analytical results from sequential evaluations of the feed mixture concentrations. These values were means of two individual samples for each concentration.
The calculation [%] of target concentration based on the analytical result on day 0!
In analyzed control samples amounts of active ingredient were not detected.

Table 1: Content (in [%] of target concentration and actual weight units [ppm])
date of preparation {I} / freezing {II}
samples thawed and date of measurement {III}

sample	10 ppm	30 ppm	250 ppm	2500 ppm
I+II: Jan. 31, 1997 **(stab. test-start)**	**143.4%** (14.34 ppm)	**111.2%** (33.37 ppm)	**102.6%** (256.45 ppm)	**103.0%** (2575.02 ppm)
I: Jan. 31, 1997 II: Feb. 7, 1997 III: Feb. 21, 1997 **(stab. 7 days)**	**111.3%** (15.96 ppm) based on day 0	**97.8%** (32.63 ppm) based on day 0	**97.0%** (248.73 ppm) based on day 0	**100.5%** (2588.70 ppm) based on day 0

Table 2: Content - 10 ppm reserve sample of the next preparation date (in [%] of target concentration and actual weight units [ppm])

sample	10 ppm
I+II: Feb. 7, 1997 III: March 3, 1997 **reserve sample**	**140.8%** (14.08 ppm)

Head of Analytical Laboratory: _____signed_____ May 12, 1997
Dr. W. Rüngeler Date

PH-PDT Tox. Analytic
Dr. W. Rüngeler
ELB.; 514; ☎ 8278

Distribution:
Dr. Andrews

May 12, 1997

Analysis Certificate (Vers. 1)

Content Checks for Dose Verification in Rodent Ration

Test material:	**YRC 2894**
Mixed batch no.:	290894
Purity:	97.0%
Origin of sample:	Bayer AG, PF-E/FT
Stability approved until:	Aug. 20, 1997
Appearance:	pale yellow powder
Test material storage:	room temperature
Stability of analytical samples:	was ensured throughout the test period
Toxicology feed mixtures:	in Altromin 1321; mixed with 1% peanut oil DAB 10
Study director (Toxicology):	Dr. Andrews
Study No.	**T7061541**

The analytical method, its validation (HPLC) was formerly presented in the study no. T0055541 and was included in a separate report (D.I. Riegner, PF-E/RA; Report no. RA-0303/94; Sep. 8, 1994). A revalidation of the recovery was performed in the actual study.

RESULTS: CONTENT CHECKS

The analytical data (HPLC) verify that the test material content in the toxicology test mixtures agreed with the target concentrations (Tab. 1). Additionally a stability test of these samples was performed. The samples were stored for 7 days under conditions comparable to those in the actual study, and then quantified. The stability was assured.

For calculations integrator values from each sample were based on the external standard calibration curve of the active ingredient. The analytical results of the test material were expressed in weight units [ppm]. For assessment of content checks the percentage of active ingredient in the original test material was not included for calculations.
Table 1 presents analytical results from sequential evaluations of the feed mixture concentrations. These values were means of two individual samples for each concentration.
The calculation [%] of target concentration based on the analytical result on day 0!
In analyzed control samples amounts of active ingredient were not detected.

Table 1: Content (in [%] of target concentration and actual weight units [ppm])
date of preparation {I} / freezing {II}
samples thawed and date of measurement {III}

sample	10 ppm	30 ppm	250 ppm	2500 ppm
I+II: April 25, 1997 **(stab. test-start)**	**102%** (10 ppm)	**91%** (27 ppm)	**98%** (244 ppm)	**95%** (2374 ppm)
I: April 25, 1997 III: May 2, 1997 **(stab. 7 days)**	**96%** (10 ppm) based on day 0	**96%** (26 ppm) based on day 0	**94%** (229 ppm) based on day 0	**100%** (2379 ppm) based on day 0
I+II: May 2, 1997 **(stab. test-start)**	**88%** (9 ppm)	**91%** (27 ppm)	**89%** (222 ppm)	**96%** (2408 ppm)
I: May 2, 1997 III: May 9, 1997 **(stab. 7 days)**	**100%** (9 ppm) based on day 0	**98%** (27 ppm) based on day 0	**98%** (217 ppm) based on day 0	**96%** (2305 ppm) based on day 0

Head of Analytical Laboratory: _____signed_____ May 12, 1997
Dr. W. Rüngeler Date

9.5. Clinical Signs

Befunde und Vorfaelle / findings and occurrences

von Tag 2 bis Tag 91 / from day 2 to day 91

Dosis/ dose (PPM)		10	30	250	2500	2500 #
Sex/ sex		w/f	w/f	w/f	w/f	w/f
Appl/ adm		PO	PO	PO	PO	PO
n		30	30	30	30	30
TIER EINGEKLEMMT ANIMAL CLAMPED	C	3		1		1
WASSERFLASCHE AUSGELAUFEN WATER BOTTLE EMPTIED	C	1	1			
HAARAUSFALL LOSS OF HAIR	C	1	1		1	1
MOTILITAET VERMINDERT REDUCED MOTILITY	C				2	
MOTILITAET GESTEIGERT INCREASED MOTILITY	C			4	1	2
REAKTIVITAET VERMINDERT REACTIVITY DECREASED	C			2	13	3

C = Anzahl der Tiere, bei denen der Befund oder Vorfall innerhalb des Zeitbereiches mindestens einmal aufgetreten ist/ number of animals with at least one finding or occurrence within the specified time interval
n = Anzahl eingesetzter Tiere/ number of animals used

= + mecamylamine

E i n z e l b e f u n d / i n d i v i d u a l f i n d i n g

TIER EINGEKLEMMT / ANIMAL CLAMPED

von Tag 2 bis Tag 91 / from day 2 to day 91

Dosis/ dose (PPM)	Sex sex	Appl adm	n		Tag / day 2	7	15	22	28	35	42	49	57	63	70	77	84	91
					4										72			
10	w/f	PO	30	B	1	1									1			
				A	30	29									15			
250	w/f	PO	30	B		1												
				A		30												
2500	w/f	PO	30	B				1										
				A				30										

n = Anzahl eingesetzter Tiere/ number of animals used
B = Anzahl Tiere mit Befund oder Vorfall/
number of animals with finding or occurrence
A = Anzahl lebender Tiere zum Befundungstermin/
number of live animals at day scheduled

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E i n z e l b e f u n d / i n d i v i d u a l f i n d i n g

WASSERFLASCHE AUSGELAUFEN / WATER BOTTLE EMPTIED

von Tag 2 bis Tag 91 / from day 2 to day 91

Dosis/ dose (PPM)	Sex sex	Appl adm	n		Tag / day 2 4	7	15	22	28	35	42	49	57	63	70 72	77	84	91
10	w/f	PO	30	B			1											
				A			29											
30	w/f	PO	30	B	1													
				A	30													

n = Anzahl eingesetzter Tiere/ number of animals used
B = Anzahl Tiere mit Befund oder Vorfall/
number of animals with finding or occurrence
A = Anzahl lebender Tiere zum Befundungstermin/
number of live animals at day scheduled

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E i n z e l b e f u n d / i n d i v i d u a l f i n d i n g

HAARAUSFALL / LOSS OF HAIR

von Tag 2 bis Tag 91 / from day 2 to day 91

Dosis/ dose (PPM)	Sex sex	Appl adm	n		Tag / day 2 4	7	15	22	28	35	42	49	57	63	70 72	77	84	91
10	w/f	PO	30	B												1	1	
				A												14	14	
30	w/f	PO	30	B										1	1	1	1	
				A										15	15	15	15	
2500	w/f	PO	30	B										1	1	1	1	1
				A										15	15	15	15	13
2500 #	w/f	PO	30	B									1	1				
				A									15	15				

n = Anzahl eingesetzter Tiere/ number of animals used
B = Anzahl Tiere mit Befund oder Vorfall/
number of animals with finding or occurrence
A = Anzahl lebender Tiere zum Befundungstermin/
number of live animals at day scheduled

= + mecamylamine

Studien-Nr./ study no.: T7061541
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Einzelbefund / individual finding

MOTILITAET VERMINDERT / REDUCED MOTILITY

von Tag 2 bis Tag 91 / from day 2 to day 91

Dosis/ dose (PPM)	Sex sex	Appl adm	n		Tag / day 2 4	7	15	22	28	35	42	49	57	63	70 72	77	84	91
2500	w/f	PO	30	B									2	2	2	2		
				A									15	15	15	15		

n = Anzahl eingesetzter Tiere/ number of animals used
B = Anzahl Tiere mit Befund oder Vorfall/
number of animals with finding or occurrence
A = Anzahl lebender Tiere zum Befundungstermin/
number of live animals at day scheduled

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E i n z e l b e f u n d / i n d i v i d u a l f i n d i n g

MOTILITAET GESTEIGERT / INCREASED MOTILITY

von Tag 2 bis Tag 91 / from day 2 to day 91

Dosis/ dose (PPM)	Sex sex	Appl adm	n		Tag / day 2 4	7	15	22	28	35	42	49	57	63	70 72	77	84	91
250	w/f	PO	30	B								2	3	2	2	1	1	1
				A								15	15	15	15	15	15	13
2500	w/f	PO	30	B								1	1	1	1	1		1
				A								15	15	15	15	15		13
2500 #	w/f	PO	30	B									1	1			1	1
				A									15	15			15	9

n = Anzahl eingesetzter Tiere/ number of animals used
B = Anzahl Tiere mit Befund oder Vorfall/
number of animals with finding or occurrence
A = Anzahl lebender Tiere zum Befundungstermin/
number of live animals at day scheduled

= + mecamylamine

Studien-Nr./ study no.: T7061541 YRC2894
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E i n z e l b e f u n d / i n d i v i d u a l f i n d i n g

REAKTIVITAET VERMINDERT / REACTIVITY DECREASED

von Tag 2 bis Tag 91 / from day 2 to day 91

Dosis/ dose (PPM)	Sex sex	Appl adm	n		Tag / day 2	4	7	15	22	28	35	42	49	57	63	70	72	77	84	91
250	w/f	PO	30	B							2	1	1	1	1	1		1		
				A							15	15	15	15	15	15		15		
2500	w/f	PO	30	B						9	5	6	3	2	2	2		2	4	3
				A						27	15	15	15	15	15	15		15	15	13
2500 #	w/f	PO	30	B						2		1	1	1						
				A						24		15	15	15						

n = Anzahl eingesetzter Tiere/ number of animals used
B = Anzahl Tiere mit Befund oder Vorfall/
number of animals with finding or occurrence
A = Anzahl lebender Tiere zum Befundungstermin/
number of live animals at day scheduled

= + mecamylamine

individual clinical findings

all findings

from week 0 to 20

anim. no.	finding	day
10 PPM female PO		
33	ANIMAL CLAMPED	7
47	ANIMAL CLAMPED	72
50	WATER BOTTLE EMPTIED	16
55	ANIMAL CLAMPED	4
60	LOSS OF HAIR	77 - 84
30 PPM female PO		
75	LOSS OF HAIR	63 - 84
89	WATER BOTTLE EMPTIED	2
250 PPM female PO		
98	INCREASED MOTILITY	49
101	REACTIVITY DECREASED	35 - 77
107	INCREASED MOTILITY	57 - 70
108	REACTIVITY DECREASED	35
112	INCREASED MOTILITY	57
117	INCREASED MOTILITY	49 - 91
119	ANIMAL CLAMPED	7
2500 PPM female PO		
127	REACTIVITY DECREASED	35 - 91
129	LOSS OF HAIR	63 - 92
	REACTIVITY DECREASED	28 - 91
130	REDUCED MOTILITY	57 - 77
131	REACTIVITY DECREASED	28 - 42; 84 - 91
133	REACTIVITY DECREASED	42
135	REACTIVITY DECREASED	42

individual clinical findings

all findings

from week 0 to 20

anim. no.	finding	day
2500 PPM female PO cont.		
136	REACTIVITY DECREASED	28
137	REACTIVITY DECREASED	28
138	REACTIVITY DECREASED	28
140	REDUCED MOTILITY	57 - 77
	REACTIVITY DECREASED	35
142	REACTIVITY DECREASED	28
143	REACTIVITY DECREASED	28 - 49; 84
146	INCREASED MOTILITY	49 - 77; 91
149	REACTIVITY DECREASED	28
150	REACTIVITY DECREASED	28
2500 PPM female PO #		
155	REACTIVITY DECREASED	28
157	INCREASED MOTILITY	84 - 91
160	LOSS OF HAIR	57 - 63
162	REACTIVITY DECREASED	42 - 57
176	ANIMAL CLAMPED	22
	INCREASED MOTILITY	57 - 63
178	REACTIVITY DECREASED	28

= + mecamylamine

9.6. Feed Intake

Food Consumption

(g/d)

022765/98.001

	Day 7	14	21	28	35	42	49	57	63	70	77	84	91
0 ppm Female PO													
Mean	9.73	13.5	12.8	10.7	11.3	12.6	12.2	11.4	15.0	13.6	14.1	13.8	13.7
Med.	10.1	13.7	13.1	10.9	12.0	12.9	12.7	11.9	15.5	14.2	14.0	13.5	14.5
S.D.	2.24	1.70	2.20	1.53	1.92	1.46	2.38	1.49	2.95	1.96	1.74	2.05	1.77
Min.	4.89	8.94	5.76	6.70	6.50	9.37	6.71	8.86	9.72	9.43	11.3	9.01	10.5
Max.	13.7	16.0	15.2	13.0	13.2	14.6	15.4	13.4	18.8	16.2	16.5	16.6	16.2
N	30	30	30	30	15	15	15	15	15	15	15	15	15
10 ppm Female PO													
Mean	10.5	13.8	13.5	10.7	11.6	12.5	13.2	11.5	14.5	13.0	13.4	13.2	12.4
Med.	10.3	14.1	13.8	10.9	12.4	12.6	13.8	12.2	15.6	13.3	13.8	13.2	13.9
S.D.	2.58	1.35	1.85	1.31	2.01	1.60	2.31	1.85	3.04	1.72	2.51	1.44	2.80
Min.	6.09	10.1	9.00	7.39	5.94	8.57	7.80	6.40	7.72	10.2	7.79	11.1	6.79
Max.	15.0	15.8	16.8	12.3	13.5	14.7	16.1	13.1	17.7	16.3	16.9	15.1	15.3
N	29	29	29	29	15	15	15	15	15	15	14	14	14
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-
30 ppm Female PO													
Mean	11.0	14.3	13.6	11.4	13.1	12.2	13.6	11.8	14.9	13.5	13.2	12.4	11.7
Med.	10.9	14.4	13.7	11.8	13.0	12.1	14.1	12.3	15.9	14.3	13.6	13.9	11.6
S.D.	2.61	1.19	1.67	1.52	.818	1.28	1.92	1.65	3.05	2.32	2.77	3.06	2.88
Min.	5.66	11.6	8.69	6.87	11.9	9.03	7.79	7.61	8.25	8.17	7.01	6.51	7.27
Max.	15.5	15.9	16.5	13.4	14.7	14.0	15.8	13.6	18.0	16.6	16.7	16.4	15.9
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	+	+	-	-	-	-	-	-	-	-
250 ppm Female PO													
Mean	11.7	13.6	13.5	11.7	11.5	11.3	11.7	10.7	13.1	11.8	11.8	11.3	11.3
Med.	12.2	14.5	14.1	12.3	12.9	12.2	12.3	11.2	14.5	13.4	11.7	11.3	12.6
S.D.	2.97	2.16	2.26	2.02	2.66	2.35	2.98	2.64	4.00	3.36	3.06	3.55	3.18
Min.	5.79	6.94	6.14	5.69	5.99	6.17	5.77	6.95	6.15	6.09	6.53	6.07	5.99
Max.	15.9	16.0	16.2	14.2	14.0	13.9	15.2	14.0	18.3	16.2	15.7	16.0	15.7
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	+	-	-	+	-	-	-	-	-	-	-	-	-

Food Consumption

(g/d)

022765/98.002

	Day												
	7	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO													
Mean	8.66	10.0	9.27	9.38	9.71	10.2	9.68	8.93	10.1	10.1	9.34	10.9	9.65
Med.	8.74	10.1	9.29	9.83	9.93	9.80	8.43	8.51	9.35	9.36	9.04	10.7	9.56
S.D.	1.77	2.09	2.16	1.98	1.95	1.83	2.29	1.82	2.61	2.91	2.40	3.14	2.38
Min.	5.77	4.83	4.94	5.10	6.56	7.16	6.41	6.44	6.53	6.03	5.21	5.79	6.84
Max.	11.6	13.3	12.0	12.4	12.2	12.4	13.1	12.6	15.6	14.8	14.4	16.6	13.1
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	++	++	-	-	++	-	++	++	++	++	-	++
TS 5%	-	+	+	+	-	+	+	+	+	+	+	-	+
+ MECAMYLAMINE 2500 ppm Female PO													
Mean	9.32	10.5	10.1	9.50	10.1	10.5	11.4	11.1	12.8	11.2	11.4	12.0	11.5
Med.	9.00	11.2	10.1	9.59	11.0	11.2	12.2	11.5	13.1	11.0	12.3	11.3	12.2
S.D.	1.72	2.16	2.04	1.82	2.69	2.27	2.43	2.31	3.38	2.39	3.05	2.70	2.73
Min.	5.17	4.40	4.70	5.46	4.86	5.24	5.44	5.68	5.92	6.31	5.97	7.83	5.81
Max.	12.5	13.9	13.5	12.8	14.6	13.5	15.0	14.1	17.3	15.0	15.7	15.9	15.6
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	++	++	-	-	-	-	-	-	-	-	-	-
TS 5%	-	+	+	+	-	+	-	-	-	+	+	-	+

Food Consumption

(g/d)

022765/98.001

Anim. No.	Day 7	14	21	28	35	42	49	57	63	70	77	84	91
0 ppm Female PO													
1	9.5	14.1	12.4	11.0	13.1	13.9	12.9	13.0	17.3	15.0	16.1	13.5	15.1
2	11.1	13.8	12.8	12.2									
3	10.1	12.5	11.5	10.6	12.4	12.3	13.1	11.0	10.2	9.4	11.6	9.0	10.5
4	7.2	12.8	8.7	8.4	9.9	9.4	7.8	8.9	12.5	11.9	13.1	13.4	14.8
5	9.3	14.5	13.5	11.5									
6	5.2	11.3	5.8	6.7	8.6	11.0	6.7	8.9	12.7	14.8	14.0	14.3	14.1
7	7.0	9.9	11.0	7.7	6.5	14.4	9.6	9.3	9.7	11.7	11.4	12.2	14.5
8	12.3	15.8	15.0	12.3	12.7	14.1	13.6	12.5	17.6	14.7	15.3	15.3	16.2
9	11.5	14.5	13.8	11.8	12.2	13.1	13.4	12.6	17.4	14.2	14.9	15.3	14.6
10	8.9	13.4	14.8	10.1									
11	10.0	13.0	12.1	10.4									
12	10.3	16.0	15.0	11.5									
13	6.7	10.2	10.8	9.1									
14	12.0	14.5	15.1	10.6									
15	7.9	12.0	10.4	10.1									
16	4.9	8.9	9.6	8.0	9.6	12.2	12.0	11.9	15.5	14.2	13.3	12.3	12.9
17	8.2	13.8	13.0	12.3	10.9	12.9	12.4	10.7	13.8	10.2	13.6	13.0	11.4
18	7.1	13.2	13.2	10.6									
19	9.8	14.1	14.5	10.8									
20	10.5	14.1	14.7	11.2									
21	11.9	15.0	14.2	11.7	13.2	12.9	14.6	12.6	18.6	15.0	16.5	15.4	15.1
22	13.7	15.8	15.0	12.1									
23	10.1	13.6	13.1	10.6	12.0	12.7	12.4	11.3	12.7	13.5	11.3	11.4	10.5
24	10.6	13.6	11.2	11.1	13.1	13.1	12.2	13.4	17.7	16.2	16.2	15.7	14.7
25	9.3	13.7	12.9	11.8									
26	13.0	15.6	13.7	11.9	12.4	14.6	12.7	12.6	18.8	15.8	15.3	16.6	15.2
27	9.2	13.7	11.8	8.9	12.0	12.6	13.6	12.0	14.5	13.8	13.9	13.0	12.6
28	10.3	14.2	15.2	11.7									
29	11.6	12.5	13.2	13.0	10.9	10.4	15.4	10.8	15.7	13.4	15.2	15.9	13.6
30	12.8	14.8	15.1	10.1									

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Food Consumption

(g/d)

022765/98.002

Anim. No.	Day 7	14	21	28	35	42	49	57	63	70	77	84	91
10 ppm Female PO													
31	10.3	13.8	12.5	12.1									
32	11.2	13.9	14.3	12.2									
33	9.7	13.3	14.4	10.4	12.3	11.2	10.3	12.2	10.0	10.3	7.8	12.2	11.4
34	8.6	12.1	9.0	9.0									
35	14.5	14.7	15.1	11.9	13.5	12.9	14.2	11.7	17.2	13.8	13.8	14.6	15.3
36	14.1	15.0	14.2	11.6	12.5	12.3	13.2	12.5	16.7	13.4	15.5	15.1	14.2
37	10.8	14.3	13.6	10.4	11.6	12.1	15.8	12.2	15.6	14.0	14.9	14.6	15.0
38	8.0	12.2	13.7	9.8									
39	10.2	13.3	13.8	9.8									
40	10.7	15.4	14.8	10.9									
41	7.5	11.9	13.4	7.4	5.9	8.6	7.8	6.4	7.7	13.0	9.7	11.6	6.8
42	10.3	14.7	12.9	10.5									
43	13.8	14.8	13.2	10.1									
44	14.5	14.1	14.2	10.3									
45	7.5	13.2	14.6	10.4									
46	9.4	13.8	13.1	10.9	13.2	12.4	16.1	12.3	16.2	13.3	15.0	14.0	15.3
47	15.0	15.0	14.3	12.3	12.6	13.1	15.6	13.1	17.6	14.9	X		
48	6.8	12.4	13.9	11.9	12.5	13.9	15.3	12.8	17.7	12.0	15.0	14.4	14.0
49	11.8	14.4	12.9	11.3									
50	12.6	15.1	16.8	11.5									
51	10.7	12.0	9.7	7.8	8.2	13.7	11.8	9.9	11.9	16.3	10.5	11.1	10.2
52	10.4	14.4	16.4	11.9	11.2	14.5	14.4	13.0	16.3	13.9	15.2	13.5	14.5
53	12.2	15.8	15.8	11.9	12.7	14.7	11.2	9.2	13.3	12.3	13.7	12.4	11.3
54	10.2	14.3	12.5	9.1									
55	X												
56	7.8	10.1	9.4	8.7	11.0	12.4	11.9	9.9	11.7	10.5	16.9	11.3	8.6
57	6.1	13.0	11.0	11.4									
58	9.5	15.5	14.5	11.4	12.7	12.6	13.9	12.9	14.6	13.3	12.7	13.0	13.8
59	6.7	12.6	13.5	11.3	12.2	10.2	12.4	12.2	13.8	10.2	12.6	12.0	9.3
60	14.3	15.2	14.4	11.5	12.4	13.0	13.8	11.8	17.2	14.4	13.7	15.0	14.3

Food Consumption

(g/d)

022765/98.003

Anim. No.	Day 7	14	21	28	35	42	49	57	63	70	77	84	91
30 ppm Female PO													
61	13.7	13.4	13.3	9.3									
62	14.0	15.3	15.2	11.5									
63	10.4	13.4	13.7	9.7	13.1	11.3	13.8	10.2	16.3	14.6	14.2	15.0	11.2
64	5.7	11.6	8.7	6.9									
65	9.5	13.4	14.9	12.2	12.3	13.0	15.0	13.0	17.2	14.2	14.3	14.7	14.5
66	12.4	13.4	13.6	10.4									
67	11.6	15.3	14.3	11.7	13.8	12.7	14.7	13.1	15.8	15.0	14.8	14.1	15.9
68	7.0	15.3	13.7	12.1	13.5	12.3	13.3	12.7	15.4	13.7	12.6	13.9	13.4
69	9.2	13.8	11.5	12.3	12.8	11.3	11.3	10.6	13.6	13.6	13.2	13.2	11.6
70	9.7	12.2	14.8	11.6	12.1	12.1	14.4	12.3	15.9	11.4	12.0	10.9	9.4
71	14.4	15.7	15.7	12.6	13.8	12.9	14.1	13.2	17.3	14.4	15.2	14.8	13.9
72	8.9	13.2	10.9	7.8									
73	7.4	12.2	12.7	10.8									
74	13.2	15.8	16.5	13.1	14.4	14.0	14.7	13.6	18.0	16.6	16.3	16.4	15.7
75	11.5	15.7	13.4	12.9	13.0	11.7	13.2	12.0	16.8	14.3	13.6	12.5	10.5
76	12.9	15.7	13.1	12.8									
77	12.7	14.4	13.8	12.0	14.7	12.0	15.8	13.4	17.7	15.2	15.8	14.6	14.3
78	8.9	15.2	14.3	11.2	12.5	13.9	13.7	11.6	14.3	14.7	12.9	8.4	7.3
79	7.7	13.6	13.7	12.0									
80	11.3	13.7	12.9	11.1									
81	7.2	13.2	10.3	9.8									
82	10.1	13.6	14.6	12.8									
83	9.8	14.4	11.9	11.4									
84	9.8	15.2	14.4	12.5	12.7	13.6	14.8	12.8	16.8	14.8	16.7	14.0	11.9
85	12.1	14.8	13.7	13.0									
86	14.9	15.9	13.5	10.7									
87	13.8	15.5	15.7	12.0	13.6	11.8	14.4	10.0	9.8	12.0	12.0	10.4	10.4
88	14.0	14.7	14.7	11.2	12.7	9.0	7.8	7.6	8.3	8.2	7.0	6.5	7.3
89	15.5	14.9	14.9	13.4									
90	10.0	14.3	14.8	12.1	11.9	10.9	13.3	11.1	10.5	9.1	7.8	7.2	8.3

Food Consumption

(g/d)

022765/98.004

Anim. No.	Day 7	14	21	28	35	42	49	57	63	70	77	84	91
250 ppm Female PO													
91	14.4	13.5	14.6	9.7									
92	15.3	15.2	14.7	11.8									
93	14.7	16.0	15.9	13.5									
94	9.4	12.7	13.1	12.3	10.4	8.7	10.2	9.6	15.5	10.0	11.2	7.1	6.6
95	13.7	11.4	13.4	9.1									
96	5.8	6.9	6.1	5.7	6.0	6.2	5.8	7.0	6.2	6.1	6.6	6.1	6.0
97	9.2	14.7	15.0	14.2									
98	15.9	15.2	14.1	12.5	11.8	10.4	6.8	7.3	7.3	7.0	7.9	8.1	7.4
99	11.9	14.7	14.6	13.5	13.7	11.9	12.3	12.5	18.3	14.4	14.9	16.0	14.7
100	10.7	14.9	15.0	13.7	13.5	12.5	15.2	13.7	17.8	14.7	14.7	15.5	14.1
101	7.4	10.8	10.2	7.5	8.7	13.9	10.3	9.4	11.1	9.9	11.7	10.9	9.8
102	9.8	14.4	8.6	9.9	6.1	7.6	9.4	7.4	9.0	8.4	9.7	7.5	10.1
103	13.2	15.5	14.1	14.1									
104	11.3	14.6	14.6	11.9									
105	8.9	14.8	12.4	10.3									
106	15.6	13.9	16.2	13.2	13.4	12.2	13.7	11.2	14.5	13.6	13.4	15.3	12.7
107	7.6	9.5	10.1	10.5	10.9	9.7	10.1	7.8	10.1	7.6	6.5	6.7	8.7
108	15.9	15.4	14.7	13.4	13.5	12.9	14.5	13.3	11.0	12.2	13.2	10.0	12.6
109	12.6	15.4	14.1	11.5									
110	13.1	13.9	14.0	12.5									
111	15.2	15.3	14.8	13.7									
112	13.6	15.3	15.7	12.5	13.0	13.1	15.0	13.2	17.2	16.2	14.8	13.7	14.6
113	13.4	15.0	13.8	11.4	12.9	13.2	13.5	14.0	15.6	15.1	14.6	13.7	13.6
114	12.5	13.2	14.9	12.0									
115	11.5	13.9	11.6	9.2									
116	11.5	13.2	13.9	12.3	14.0	12.8	14.3	12.8	16.5	14.7	15.7	15.2	15.7
117	7.5	11.9	14.0	10.7	11.7	10.2	10.3	8.7	10.5	13.4	10.7	11.3	9.7
118	8.2	11.1	13.6	12.6	13.4	13.5	14.1	12.9	16.2	14.4	11.5	12.5	13.3
119	13.8	15.6	15.9	13.1									
120	7.3	10.1	12.0	13.3									

Food Consumption

(g/d)

022765/98.005

Anim. No.	Day 7	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO													
121	8.9	10.3	7.5	6.9	7.2	9.1	8.4	8.2	9.2	12.8	10.7	13.1	10.6
122	11.4	11.4	11.7	10.0									
123	6.1	6.8	5.9	7.5									
124	7.5	9.3	6.5	6.8									
125	7.5	8.3	7.1	7.0									
126	7.5	8.6	9.2	8.5	8.1	8.6	8.2	9.2	7.7	9.4	9.0	10.2	9.6
127	7.5	11.1	11.2	10.4	11.8	12.4	12.1	9.8	13.4	14.4	12.9	12.5	13.1
128	7.8	9.6	10.7	9.9	9.4	8.8	8.2	7.6	9.4	7.8	7.8	7.5	8.6
129	6.2	10.0	6.6	6.9	9.8	9.6	8.3	8.5	14.0	6.0	5.2	5.8	6.9
130	9.6	12.6	9.3	11.6	9.9	12.3	11.7	12.0	8.8	9.0	9.7	9.3	7.6
131	10.0	11.1	9.3	9.8	11.5	11.6	11.2	12.6	15.6	13.7	12.0	12.5	12.5
132	9.0	13.3	10.2	11.0									
133	9.0	7.7	7.8	10.7	7.1	7.2	6.9	7.7	9.7	7.5	8.1	9.1	7.4
134	8.6	9.8	10.4	11.2									
135	9.6	12.2	9.3	11.8	12.2	11.5	10.9	9.8	11.0	12.3	7.7	10.7	10.7
136	6.5	9.4	8.5	7.5									
137	10.8	12.2	12.0	12.4									
138	8.6	8.3	5.8	6.9									
139	6.1	6.7	7.9	8.8									
140	7.5	8.4	6.9	7.8	6.6	9.8	6.4	6.8	8.0	11.1	7.3	14.2	7.5
141	7.1	9.7	9.5	9.7	10.9	11.1	13.1	7.2	10.0	8.2	9.2	11.1	11.8
142	7.6	12.2	11.2	9.4									
143	11.5	12.3	11.6	12.2	10.2	9.3	7.2	6.4	6.5	7.2	7.3	7.2	6.8
144	11.6	13.3	11.3	11.2									
145	8.9	10.8	11.6	10.5									
146	9.4	7.8	8.7	7.2	7.7	7.2	8.2	8.0	7.5	7.1	8.4	7.8	7.0
147	10.1	11.5	11.6	10.6	11.8	12.2	12.6	10.0	12.2	14.8	14.4	15.0	13.1
148	11.4	10.8	12.0	10.8	11.4	12.2	11.7	10.2	9.3	10.2	10.4	16.6	11.5
149	10.9	10.8	12.0	11.3									
150	5.8	4.8	4.9	5.1									

Food Consumption

(g/d)

022765/98.006

Anim. No.	Day 7	14	21	28	35	42	49	57	63	70	77	84	91
+ MECAMYLAMINE 2500 ppm Female PO													
151	11.4	11.4	10.6	9.4									
152	8.2	9.4	11.8	9.0	9.3	11.2	12.6	12.7	14.3	12.0	13.2	15.1	12.6
153	9.9	12.0	10.7	8.7	8.2	11.7	12.8	11.3	11.4	10.0	11.7	11.2	13.5
154	10.1	11.5	11.9	10.9	11.7	11.3	12.7	12.3	16.8	8.8	13.0	15.9	15.6
155	9.1	6.9	6.6	6.2	6.0	7.7	10.4	10.9	13.1	11.0	10.7	15.3	7.4
156	7.8	9.0	11.4	10.6									
157	11.8	10.4	10.0	8.5	11.0	9.7	9.5	9.7	8.8	9.2	8.0	11.0	10.3
158	11.4	13.2	13.5	11.0									
159	8.3	10.9	12.9	7.9									
160	7.8	11.0	10.1	8.5	9.1	10.9	12.2	8.9	12.3	14.0	8.4	8.9	10.3
161	11.0	12.5	12.6	11.2	14.6	12.3	12.8	12.3	12.5	10.8	8.7	10.5	9.2
162	12.5	10.1	10.3	11.3	11.7	13.1	15.0	14.1	17.3	15.0	15.7	14.0	14.2
163	8.9	7.8	8.9	10.4									
164	9.4	11.4	10.7	11.2	10.2	10.4	11.6	11.5	14.8	12.7	14.2	14.0	13.6
165	7.8	11.8	10.3	11.9									
166	9.8	13.0	12.0	11.1									
167	11.0	11.3	9.9	8.8									
168	8.8	11.4	9.5	10.9									
169	7.5	7.3	8.8	8.2	7.0	7.0	7.6	8.1	9.0	9.6	7.1	7.8	8.9
170	12.1	13.9	12.0	10.5	12.0	11.2	12.2	12.5	13.1	11.2	12.3	11.3	11.9
171	7.3	9.4	6.4	7.9									
172	8.5	11.6	9.0	9.8	11.9	11.6	10.5	9.7	9.5	10.0	12.3	9.6	12.2
173	9.2	11.0	10.1	6.0									
174	11.6	13.0	13.3	12.8	11.8	13.5	13.0	14.0	16.2	14.3	14.8	13.5	12.8
175	7.9	10.1	9.9	9.1									
176	10.3	11.9	10.0	11.0	12.7	11.4	13.1	12.9	16.6	13.7	14.4	14.0	13.5
177	8.4	10.4	8.0	7.4									
178	5.2	4.4	4.7	5.5	4.9	5.2	5.4	5.7	5.9	6.3	6.0	8.1	5.8
179	8.0	6.8	8.1	8.9									
180	8.9	11.7	9.5	10.7									

Food Consumption Difference

(g/d)

022725/98.001

	Day 7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
0 ppm Female PO												
Mean	3.76	-.72	-2.1	0.88	1.36	-.47	-.75	3.55	-1.4	0.53	-.36	-.03
Med.	3.56	-.76	-2.0	1.50	0.86	-.46	-.82	3.89	-1.5	0.64	0.04	-.27
S.D.	1.30	1.49	1.47	1.48	2.10	2.33	1.64	1.97	1.86	1.41	1.15	1.34
Min.	0.87	-5.5	-5.0	-2.2	-.50	-4.9	-4.6	-.80	-3.6	-2.3	-2.6	-2.3
Max.	6.07	1.34	0.94	3.10	7.91	4.94	2.15	6.15	2.02	3.39	1.30	2.34
N	30	30	30	15	15	15	15	15	15	15	15	15
10 ppm Female PO												
Mean	3.29	-.30	-2.8	0.89	0.88	0.67	-1.7	3.01	-1.4	0.45	-.16	-.76
Med.	3.51	-.70	-3.1	0.94	0.54	0.97	-1.9	3.42	-2.4	1.13	-.31	-.79
S.D.	1.91	1.35	1.50	1.01	1.91	1.99	1.40	2.02	2.91	2.98	2.21	1.69
Min.	-.33	-3.1	-6.0	-1.4	-2.0	-3.5	-3.9	-2.2	-5.6	-5.8	-5.6	-4.8
Max.	6.89	1.93	0.37	2.23	5.46	3.73	1.90	5.48	5.31	6.39	4.44	1.27
N	29	29	29	15	15	15	15	15	15	14	14	14
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-
30 ppm Female PO												
Mean	3.32	-.65	-2.2	1.17	-.96	1.45	-1.8	3.08	-1.4	-.23	-.79	-.75
Med.	3.26	-.36	-2.2	1.27	-1.1	1.46	-2.0	3.60	-1.7	-.33	-.60	-.66
S.D.	2.10	1.40	1.25	1.04	1.34	1.28	1.12	1.88	1.64	.962	1.43	1.40
Min.	-.51	-2.9	-4.0	-.24	-3.7	-1.2	-4.4	-.59	-4.5	-1.8	-4.5	-3.8
Max.	8.26	2.64	0.83	3.43	1.33	3.79	-.17	6.11	2.21	1.96	1.30	1.79
N	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	++	-	-	-	-	-	-	-
TS 5%	-	-	-	-	+	+	-	-	-	-	-	-
250 ppm Female PO												
Mean	1.91	-.09	-1.8	0.09	-.27	0.44	-.98	2.39	-1.3	-.04	-.49	-.00
Med.	1.84	-.01	-1.8	0.30	-.94	0.53	-1.2	2.33	-1.1	0.46	-.49	-.10
S.D.	2.02	1.67	1.45	1.37	1.77	1.82	1.10	2.28	2.01	1.43	1.62	1.55
Min.	-2.3	-5.8	-5.0	-3.7	-1.9	-3.6	-2.5	-2.3	-5.5	-2.9	-4.0	-2.6
Max.	5.86	2.53	1.31	1.67	5.19	2.71	1.18	5.92	2.88	1.79	1.86	2.57
N	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	++	-	-	-	-	-	-	-	-	-	-	-
TS 5%	+	-	-	-	+	-	-	-	-	-	-	-

Food Consumption Difference

(g/d)

022725/98.002

	Day											
	7	14	21	28	35	42	49	57	63	70	77	84
	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO												
Mean	1.38	-.77	0.11	0.05	0.50	-.52	-.75	1.21	-.04	-.76	1.51	-1.2
Med.	1.26	-.52	0.21	0.43	0.23	-.51	-.28	1.22	0.62	-.31	0.61	-.63
S.D.	1.58	1.51	1.20	1.65	1.20	1.22	1.84	2.19	2.86	1.72	2.32	2.23
Min.	-1.6	-3.5	-1.8	-3.6	-.96	-3.4	-5.9	-3.2	-8.0	-4.6	-.60	-6.7
Max.	4.56	1.20	2.83	2.94	3.24	1.99	1.43	5.52	3.62	1.33	6.91	1.10
N	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	++	-	++	-	-	-	-	-	-	-	-	-
TS 5%	+	-	+	-	-	-	-	+	-	-	-	-
+ MECAMYLAMINE 2500 ppm Female PO												
Mean	1.22	-.42	-.62	0.59	0.41	0.89	-.34	1.67	-1.5	0.14	0.65	-.56
Med.	1.71	-.56	-.74	0.34	0.14	1.07	-.11	1.62	-1.9	0.76	0.50	-.34
S.D.	1.68	1.47	1.66	1.39	1.55	.999	1.03	1.68	2.27	2.30	2.05	2.51
Min.	-2.4	-3.0	-5.0	-1.2	-2.3	-1.1	-3.3	-.91	-8.0	-5.6	-2.8	-7.9
Max.	3.96	2.43	1.59	3.40	3.46	2.74	0.98	4.53	1.67	4.14	4.61	2.67
N	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	++	-	++	-	-	-	-	-	-	-	-	-
TS 5%	+	-	+	-	-	-	-	+	-	-	-	-

Food Consumption Difference

(g/d)

022725/98.001

Anim. No.	Day 7-14	14-21	21-28	28-35	35-42	42-49	49-57	57-63	63-70	70-77	77-84
0 ppm Female PO											
1	4.6	-1.7	-1.3	2.0	0.9	-1.0	0.1	4.3	-2.3	1.1	-2.5	1.6
2	2.7	-1.0	-0.6									
3	2.5	-1.0	-0.9	1.8	-0.1	0.8	-2.1	-0.8	-0.7	2.2	-2.6	1.5
4	5.7	-4.1	-0.3	1.5	-0.5	-1.5	1.1	3.6	-0.6	1.2	0.3	1.4
5	5.2	-0.9	-2.1									
6	6.0	-5.5	0.9	1.9	2.4	-4.3	2.1	3.9	2.0	-0.8	0.4	-0.3
7	3.0	1.1	-3.4	-1.2	7.9	-4.9	-0.3	0.4	2.0	-0.3	0.8	2.3
8	3.5	-0.8	-2.7	0.3	1.4	-0.5	-1.1	5.1	-2.9	0.6	0.0	0.8
9	3.0	-0.7	-2.0	0.4	1.0	0.3	-0.8	4.8	-3.2	0.6	0.4	-0.6
10	4.5	1.3	-4.7									
11	3.0	-0.9	-1.8									
12	5.7	-1.0	-3.4									
13	3.5	0.7	-1.7									
14	2.5	0.6	-4.4									
15	4.1	-1.6	-0.3									
16	4.1	0.7	-1.6	1.5	2.7	-0.2	-0.1	3.5	-1.3	-0.8	-1.0	0.6
17	5.5	-0.7	-0.8	-1.4	2.1	-0.5	-1.7	3.1	-3.6	3.4	-0.6	-1.6
18	6.1	0.0	-2.6									
19	4.3	0.4	-3.7									
20	3.6	0.6	-3.5									
21	3.1	-0.8	-2.5	1.5	-0.3	1.7	-2.1	6.0	-3.5	1.5	-1.2	-0.2
22	2.0	-0.8	-2.9									
23	3.4	-0.5	-2.5	1.4	0.7	-0.3	-1.1	1.4	0.8	-2.3	0.1	-0.8
24	3.0	-2.4	-0.2	2.0	0.0	-0.9	1.2	4.3	-1.5	0.0	-0.5	-1.1
25	4.4	-0.8	-1.1									
26	2.5	-1.9	-1.7	0.4	2.2	-1.9	-0.1	6.1	-3.0	-0.5	1.3	-1.3
27	4.5	-1.8	-3.0	3.1	0.7	1.0	-1.6	2.5	-0.7	0.1	-0.9	-0.4
28	4.0	0.9	-3.4									
29	0.9	0.7	-0.2	-2.2	-0.5	4.9	-4.6	5.0	-2.4	1.9	0.7	-2.3
30	2.0	0.3	-5.0									

Food Consumption Difference

(g/d)

022725/98.002

Anim. No.	Day 7 - 14	14 - 21	21 - 28	28 - 35	35 - 42	42 - 49	49 - 57	57 - 63	63 - 70	70 - 77	77 - 84	84 - 91
10 ppm Female PO												
31	3.4	-1.3	-0.4									
32	2.7	0.4	-2.1									
33	3.6	1.0	-4.0	1.9	-1.1	-0.9	1.9	-2.2	0.4	-2.5	4.4	-0.9
34	3.5	-3.1	0.0									
35	0.3	0.4	-3.3	1.7	-0.6	1.3	-2.5	5.5	-3.3	-0.1	0.8	0.7
36	0.9	-0.8	-2.6	0.9	-0.2	1.0	-0.8	4.2	-3.2	2.0	-0.3	-0.9
37	3.5	-0.8	-3.2	1.2	0.5	3.7	-3.7	3.4	-1.6	0.9	-0.3	0.4
38	4.2	1.5	-3.9									
39	3.2	0.5	-4.0									
40	4.6	-0.6	-3.9									
41	4.4	1.5	-6.0	-1.4	2.6	-0.8	-1.4	1.3	5.3	-3.3	1.8	-4.8
42	4.4	-1.8	-2.4									
43	1.0	-1.6	-3.2									
44	-0.3	0.1	-3.9									
45	5.7	1.4	-4.1									
46	4.5	-0.7	-2.2	2.2	-0.7	3.7	-3.9	3.9	-2.9	1.7	-0.9	1.3
47	0.1	-0.7	-2.1	0.3	0.5	2.4	-2.4	4.5	-2.7	X	X	
48	5.7	1.5	-2.0	0.5	1.5	1.3	-2.5	4.9	-5.6	3.0	-0.7	-0.4
49	2.6	-1.5	-1.6									
50	2.5	1.8	-5.3									
51	1.3	-2.2	-2.0	0.4	5.5	-1.9	-1.9	2.0	4.4	-5.8	0.6	-0.9
52	4.1	1.9	-4.5	-0.7	3.3	-0.1	-1.4	3.3	-2.4	1.3	-1.8	1.1
53	3.6	-0.1	-3.9	0.9	2.0	-3.5	-1.9	4.1	-1.0	1.4	-1.3	-1.1
54	4.1	-1.8	-3.4									
55	X											
56	2.4	-0.8	-0.6	2.2	1.4	-0.5	-2.0	1.8	-1.2	6.4	-5.6	-2.7
57	6.9	-1.9	0.4									
58	5.9	-0.9	-3.1	1.3	-0.1	1.3	-1.0	1.7	-1.3	-0.6	0.3	0.8
59	5.8	0.9	-2.2	0.9	-2.0	2.1	-0.2	1.6	-3.7	2.4	-0.6	-2.6
60	0.9	-0.9	-2.9	1.0	0.6	0.8	-2.0	5.3	-2.8	-0.6	1.3	-0.7

Food Consumption Difference

(g/d)

022725/98.003

Anim. No.	7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
30 ppm Female PO												
61	-0.4	0.0	-4.0									
62	1.3	-0.1	-3.6									
63	3.0	0.3	-4.0	3.4	-1.8	2.5	-3.5	6.1	-1.7	-0.5	0.8	-3.8
64	5.9	-2.9	-1.8									
65	3.8	1.5	-2.7	0.0	0.7	2.0	-2.0	4.2	-3.0	0.1	0.4	-0.3
66	1.0	0.2	-3.2									
67	3.7	-0.9	-2.6	2.1	-1.1	2.0	-1.6	2.7	-0.8	-0.2	-0.7	1.8
68	8.3	-1.5	-1.6	1.4	-1.3	1.1	-0.7	2.7	-1.7	-1.0	1.3	-0.5
69	4.6	-2.3	0.8	0.5	-1.5	0.0	-0.7	2.9	0.1	-0.4	0.0	-1.6
70	2.5	2.6	-3.2	0.5	0.0	2.3	-2.1	3.6	-4.5	0.6	-1.2	-1.5
71	1.3	0.0	-3.0	1.1	-0.9	1.2	-0.9	4.1	-2.9	0.8	-0.4	-0.9
72	4.3	-2.3	-3.0									
73	4.8	0.5	-1.9									
74	2.6	0.8	-3.4	1.3	-0.4	0.7	-1.0	4.4	-1.4	-0.3	0.1	-0.7
75	4.1	-2.3	-0.4	0.1	-1.3	1.5	-1.2	4.8	-2.5	-0.8	-1.1	-2.0
76	2.8	-2.6	-0.2									
77	1.7	-0.6	-1.8	2.7	-2.7	3.8	-2.4	4.3	-2.5	0.6	-1.2	-0.3
78	6.3	-0.9	-3.1	1.4	1.3	-0.2	-2.0	2.7	0.4	-1.8	-4.5	-1.1
79	5.9	0.1	-1.7									
80	2.4	-0.8	-1.8									
81	6.0	-2.8	-0.6									
82	3.5	1.0	-1.8									
83	4.6	-2.5	-0.5									
84	5.4	-0.8	-1.9	0.2	0.8	1.3	-2.1	4.0	-2.0	2.0	-2.7	-2.2
85	2.7	-1.1	-0.7									
86	1.1	-2.4	-2.8									
87	1.7	0.1	-3.7	1.6	-1.8	2.6	-4.4	-0.2	2.2	-0.1	-1.6	0.0
88	0.8	0.0	-3.6	1.5	-3.7	-1.2	-0.2	0.6	-0.1	-1.2	-0.5	0.8
89	-0.5	0.0	-1.5									
90	4.3	0.4	-2.6	-0.2	-1.0	2.4	-2.2	-0.6	-1.4	-1.3	-0.6	1.0

Food Consumption Difference

(g/d)

022725/98.004

Anim. No.	Day 7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
250 ppm Female PO												
91	-0.8	1.1	-5.0									
92	-0.2	-0.5	-2.8									
93	1.3	-0.1	-2.3									
94	3.3	0.3	-0.8	-1.9	-1.7	1.4	-0.5	5.9	-5.5	1.1	-4.0	-0.5
95	-2.3	2.0	-4.2									
96	1.2	-0.8	-0.5	0.3	0.2	-0.4	1.2	-0.8	-0.1	0.5	-0.5	-0.1
97	5.5	0.3	-0.7									
98	-0.7	-1.1	-1.6	-0.7	-1.4	-3.6	0.5	0.0	-0.3	0.9	0.2	-0.6
99	2.7	0.0	-1.2	0.2	-1.9	0.4	0.2	5.8	-3.9	0.5	1.1	-1.3
100	4.2	0.2	-1.4	-0.2	-0.9	2.7	-1.5	4.0	-3.1	-0.1	0.8	-1.4
101	3.4	-0.7	-2.6	1.1	5.2	-3.5	-0.9	1.7	-1.2	1.8	-0.7	-1.2
102	4.6	-5.8	1.3	-3.7	1.4	1.8	-2.0	1.6	-0.6	1.3	-2.2	2.6
103	2.4	-1.4	-0.1									
104	3.4	-0.1	-2.7									
105	5.9	-2.4	-2.1									
106	-1.7	2.3	-3.0	0.2	-1.3	1.5	-2.5	3.3	-0.8	-0.2	1.9	-2.6
107	1.9	0.6	0.4	0.4	-1.1	0.3	-2.3	2.3	-2.5	-1.1	0.2	2.0
108	-0.5	-0.7	-1.2	0.0	-0.5	1.6	-1.2	-2.3	1.2	0.9	-3.1	2.5
109	2.8	-1.3	-2.6									
110	0.9	0.0	-1.5									
111	0.0	-0.5	-1.1									
112	1.7	0.4	-3.3	0.5	0.1	1.9	-1.7	4.0	-1.1	-1.3	-1.1	0.9
113	1.6	-1.2	-2.4	1.5	0.3	0.3	0.4	1.7	-0.5	-0.4	-0.9	-0.1
114	0.8	1.7	-3.0									
115	2.4	-2.3	-2.4									
116	1.7	0.7	-1.5	1.7	-1.2	1.5	-1.5	3.6	-1.8	1.0	-0.5	0.5
117	4.4	2.1	-3.2	1.0	-1.5	0.1	-1.6	1.8	2.9	-2.7	0.6	-1.5
118	2.9	2.5	-1.0	0.8	0.2	0.5	-1.1	3.3	-1.8	-2.9	1.0	0.9
119	1.8	0.4	-2.8									
120	2.8	1.9	1.3									

Food Consumption Difference

(g/d)

022725/98.005

Anim. No.	Day 7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
2500 ppm Female PO												
121	1.4	-2.8	-0.6	0.3	2.0	-0.7	-0.3	1.0	3.6	-2.1	2.4	-2.5
122	0.0	0.3	-1.7									
123	0.7	-0.8	1.5									
124	1.8	-2.9	0.3									
125	0.8	-1.1	-0.1									
126	1.1	0.5	-0.6	-0.5	0.6	-0.4	0.9	-1.5	1.7	-0.3	1.1	-0.6
127	3.7	0.1	-0.8	1.4	0.6	-0.3	-2.3	3.6	1.0	-1.6	-0.4	0.6
128	1.8	1.2	-0.9	-0.4	-0.7	-0.6	-0.6	1.8	-1.5	0.0	-0.3	1.1
129	3.8	-3.5	0.3	2.9	-0.2	-1.4	0.3	5.5	-8.0	-0.8	0.6	1.1
130	3.0	-3.3	2.3	-1.6	2.4	-0.6	0.3	-3.2	0.2	0.6	-0.4	-1.7
131	1.2	-1.8	0.5	1.7	0.1	-0.4	1.4	3.0	-1.9	-1.7	0.5	-0.1
132	4.3	-3.1	0.8									
133	-1.3	0.1	2.8	-3.6	0.1	-0.3	0.9	2.0	-2.2	0.6	1.0	-1.7
134	1.1	0.6	0.8									
135	2.6	-2.9	2.5	0.4	-0.7	-0.6	-1.2	1.2	1.3	-4.6	3.0	-0.1
136	2.9	-0.9	-1.0									
137	1.4	-0.2	0.4									
138	-0.3	-2.4	1.1									
139	0.6	1.2	0.9									
140	1.0	-1.5	0.9	-1.3	3.2	-3.4	0.3	1.2	3.2	-3.8	6.9	-6.7
141	2.7	-0.3	0.3	1.2	0.2	2.0	-5.9	2.7	-1.7	0.9	2.0	0.7
142	4.6	-0.9	-1.8									
143	0.9	-0.8	0.6	-1.9	-1.0	-2.0	-0.8	0.1	0.6	0.1	-0.1	-0.4
144	1.7	-2.1	0.0									
145	1.9	0.8	-1.1									
146	-1.6	0.8	-1.4	0.5	-0.5	0.9	-0.2	-0.5	-0.4	1.3	-0.6	-0.8
147	1.4	0.1	-1.0	1.2	0.4	0.4	-2.7	2.2	2.6	-0.4	0.6	-1.9
148	-0.5	1.1	-1.2	0.6	0.8	-0.5	-1.5	-1.0	0.9	0.2	6.3	-5.1
149	-0.1	1.2	-0.7									
150	-0.9	0.1	0.2									

Food Consumption Difference

(g/d)

022725/98.006

Anim. No.	Day 7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
+ MECAMYLAMINE 2500 ppm Female PO												
151	0.0	-0.8	-1.2									
152	1.2	2.4	-2.8	0.3	1.9	1.4	0.0	1.6	-2.3	1.2	1.9	-2.5
153	2.0	-1.3	-2.0	-0.4	3.5	1.1	-1.5	0.1	-1.4	1.7	-0.5	2.3
154	1.4	0.4	-1.0	0.8	-0.4	1.4	-0.5	4.5	-8.0	4.1	3.0	-0.3
155	-2.2	-0.3	-0.4	-0.2	1.7	2.7	0.4	2.2	-2.1	-0.3	4.6	-7.9
156	1.2	2.4	-0.9									
157	-1.4	-0.4	-1.5	2.5	-1.3	-0.2	0.2	-0.9	0.4	-1.1	3.0	-0.8
158	1.8	0.3	-2.5									
159	2.6	2.1	-5.0									
160	3.2	-0.9	-1.6	0.6	1.8	1.3	-3.3	3.4	1.7	-5.6	0.5	1.4
161	1.5	0.1	-1.5	3.4	-2.3	0.5	-0.5	0.2	-1.7	-2.0	1.8	-1.3
162	-2.4	0.2	1.0	0.3	1.4	2.0	-0.9	3.2	-2.4	0.8	-1.7	0.2
163	-1.1	1.1	1.5									
164	2.0	-0.7	0.5	-1.0	0.1	1.2	-0.1	3.3	-2.1	1.5	-0.3	-0.3
165	4.0	-1.5	1.6									
166	3.2	-1.0	-0.9									
167	0.3	-1.4	-1.0									
168	2.6	-1.9	1.3									
169	-0.2	1.5	-0.6	-1.2	0.0	0.6	0.5	0.9	0.7	-2.5	0.7	1.1
170	1.8	-1.9	-1.5	1.5	-0.8	1.0	0.3	0.6	-1.9	1.1	-1.0	0.6
171	2.0	-3.0	1.5									
172	3.1	-2.5	0.8	2.1	-0.3	-1.1	-0.7	-0.3	0.5	2.4	-2.8	2.7
173	1.8	-0.9	-4.1									
174	1.4	0.3	-0.5	-1.0	1.6	-0.5	1.0	2.3	-1.9	0.5	-1.3	-0.7
175	2.2	-0.1	-0.9									
176	1.6	-1.9	1.0	1.7	-1.3	1.7	-0.2	3.7	-2.9	0.8	-0.4	-0.5
177	1.9	-2.4	-0.6									
178	-0.8	0.3	0.8	-0.6	0.4	0.2	0.2	0.2	0.4	-0.3	2.2	-2.3
179	-1.1	1.3	0.8									
180	2.8	-2.3	1.2									

9.7. Water Consumption

Water Consumption

(g/d)

022755/98.001

	Day 7/8	14	21	28	35	42	49	57	63	70	77	84	91
0 ppm Female PO													
Mean	4.88	4.96	5.16	5.86	5.24	5.37	5.34	5.24	5.34	5.16	5.11	5.31	5.64
Med.	4.92	4.96	5.16	5.91	5.33	5.50	5.29	5.35	5.47	5.19	5.21	5.29	5.73
S.D.	.363	.338	.363	.670	.456	.403	.420	.424	.515	.488	.450	.465	.593
Min.	3.70	3.99	4.49	4.54	4.57	4.64	4.60	4.44	4.25	4.16	4.17	4.50	4.71
Max.	5.34	5.59	5.97	7.26	5.87	5.94	5.99	5.75	6.03	5.91	5.66	6.06	6.64
N	30	30	30	30	15	15	14	15	15	15	15	15	15
10 ppm Female PO													
Mean	4.94	5.12	5.25	5.83	5.32	5.37	5.29	5.32	5.31	5.16	5.11	5.31	5.69
Med.	4.99	5.07	5.34	5.71	5.31	5.33	5.19	5.28	5.23	4.97	5.09	5.30	5.86
S.D.	.345	.315	.359	.704	.303	.274	.271	.354	.413	.400	.422	.420	.554
Min.	4.06	4.36	4.47	4.80	4.63	4.90	4.89	4.69	4.60	4.71	4.46	4.51	4.27
Max.	5.59	5.63	5.99	7.29	5.97	5.99	5.89	5.81	6.20	6.04	5.91	5.90	6.50
N	29	29	28	29	15	15	15	15	15	15	14	14	14
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-
30 ppm Female PO													
Mean	4.77	5.29	5.17	5.85	5.35	5.46	5.49	5.48	5.38	5.29	5.33	5.52	5.95
Med.	4.81	5.15	5.17	5.88	5.19	5.41	5.56	5.56	5.40	5.23	5.21	5.44	6.09
S.D.	.316	1.11	.352	.511	.556	.665	.428	.395	.423	.562	.470	.560	.611
Min.	4.00	4.43	4.46	4.66	4.47	4.50	4.83	4.91	4.75	4.47	4.57	4.37	4.86
Max.	5.29	10.9	5.90	6.60	6.50	6.69	6.19	6.14	6.22	6.20	6.24	6.56	6.73
N	29	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-
250 ppm Female PO													
Mean	4.64	4.93	5.16	5.74	5.09	5.28	5.26	5.19	5.24	5.03	4.97	5.23	5.88
Med.	4.60	4.86	5.11	5.73	5.03	5.26	5.39	5.05	5.27	5.01	4.77	5.34	5.83
S.D.	.345	.377	.436	.715	.451	.444	.427	.388	.435	.393	.486	.559	.459
Min.	3.89	4.17	4.53	4.73	4.67	4.66	4.61	4.54	4.43	4.44	4.36	3.89	5.10
Max.	5.43	5.73	6.23	7.21	6.30	6.40	5.97	5.89	6.08	5.69	5.90	5.97	6.79
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	+	-	-	-	-	-	-	-	-	-	-	-	-

Study No. T7061541 YRC2894
SUBCHRTOX B6C3F1 MICE

Water Consumption

(g/d)

022755/98.002

	Day												
	7/8	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO													
Mean	5.06	4.76	4.89	5.54	5.09	5.02	5.13	4.92	5.07	4.97	5.12	5.16	5.99
Med.	5.09	4.84	4.94	5.64	5.11	5.03	5.17	4.93	5.08	4.99	5.11	5.13	5.86
S.D.	.490	.414	.413	.592	.479	.573	.553	.460	.547	.554	.574	.608	.632
Min.	3.89	3.81	4.03	4.34	4.17	4.16	4.27	4.19	4.12	3.86	4.10	4.39	5.19
Max.	6.09	5.51	5.56	6.51	5.76	6.03	6.21	5.79	6.25	5.79	6.21	6.24	7.50
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-
+ MECAMYLAMINE 2500 ppm Female PO													
Mean	4.91	4.90	5.25	5.20	5.17	5.08	5.69	4.95	5.20	5.31	5.16	5.47	5.74
Med.	4.99	4.89	5.16	5.14	5.10	5.07	5.59	5.06	5.17	5.31	5.27	5.46	5.61
S.D.	.757	.418	.609	.359	.433	.391	.377	.328	.346	.311	.343	.419	.496
Min.	1.41	3.58	4.67	4.59	4.60	4.44	5.19	4.31	4.53	4.77	4.57	4.84	4.96
Max.	5.70	5.88	8.00	6.17	6.10	5.77	6.36	5.38	5.70	5.87	5.63	6.29	6.63
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	++	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	+	-	-	-	-	-	-	-	-	-

Water Consumption

(g/d)

022755/98.001

Anim. No.	Day 7/8	14	21	28	35	42	49	57	63	70	77	84	91
0 ppm Female PO													
1	4.9	4.8	5.1	5.8	4.7	5.1	5.0	5.0	5.5	5.0	5.2	5.1	5.7
2	5.3	5.3	5.5	6.4									
3	5.2	5.6	5.2	6.3	5.4	5.8	5.3	5.7	5.6	5.6	5.4	5.6	5.6
4	4.9	5.1	5.4	6.3	5.6	5.9	5.6	5.6	5.9	5.5	5.5	5.9	6.2
5	5.2	5.4	5.4	6.2									
6	4.9	4.8	4.9	5.3	5.0	5.0	5.2	5.2	5.2	5.1	4.9	4.7	4.8
7	4.5	4.9	4.7	5.0	5.3	5.2	5.7	5.8	6.0	5.9	5.6	6.1	6.3
8	5.0	5.4	5.7	6.3	5.7	5.6	5.6	5.6	5.5	5.3	5.3	5.3	5.9
9	5.2	5.2	5.1	5.6	5.9	5.7	5.6	5.5	5.6	5.2	5.4	5.6	6.2
10	5.3	5.1	5.2	5.8									
11	4.7	5.0	4.7	6.3									
12	4.9	4.6	4.9	6.7									
13	4.5	4.7	5.0	5.4									
14	5.0	4.6	5.2	6.0									
15	4.5	4.6	5.0	5.6									
16	3.7	4.0	4.5	4.6	4.7	5.0	4.8	4.7	4.8	4.5	4.8	4.5	5.3
17	4.9	5.0	5.6	5.4	5.3	5.5	5.0	4.9	5.1	4.9	4.8	5.0	4.9
18	5.1	5.1	5.4	6.2									
19	5.3	5.0	5.7	7.3									
20	5.1	5.0	5.1	6.3									
21	4.9	5.1	5.4	5.6	5.7	5.9	6.0	5.6	5.8	5.8	5.7	5.8	6.6
22	4.8	4.8	4.9	6.1									
23	4.6	4.9	5.5	5.5	5.8	5.6	5.9	5.6	5.9	5.4	4.8	5.6	5.7
24	4.7	4.8	5.0	5.4	5.5	5.7	X	5.4	5.4	5.2	5.5	5.6	5.9
25	5.2	4.9	4.9	6.6									
26	4.1	4.4	4.5	4.5	4.9	5.0	5.1	5.0	5.1	5.1	5.1	5.3	5.5
27	5.1	5.0	5.3	5.0	4.7	4.9	5.2	4.7	4.6	4.5	4.4	4.9	5.1
28	4.9	5.2	5.5	6.2									
29	4.9	4.9	4.7	4.8	4.6	4.6	4.6	4.4	4.3	4.2	4.2	4.8	4.7
30	5.2	5.5	6.0	7.0									

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Water Consumption

(g/d)

022755/98.002

Anim. No.	Day 7/8	14	21	28	35	42	49	57	63	70	77	84	91
10 ppm Female PO													
31	4.4	4.6	4.5	4.9									
32	5.0	5.2	5.9	6.6									
33	4.1	5.5	5.5	5.6	4.6	5.6	5.2	5.3	5.4	5.0	4.7	5.1	5.7
34	4.8	4.8	4.7	5.5									
35	5.5	5.0	5.4	5.5	5.6	5.3	5.4	5.7	5.7	5.3	5.8	5.3	6.1
36	5.2	5.3	5.5	5.8	5.6	5.6	5.6	5.8	5.5	5.5	5.2	5.2	6.1
37	5.0	5.1	4.8	5.2	5.0	4.9	5.0	5.0	5.0	4.8	5.0	4.7	6.0
38	5.0	5.2	5.4	5.7									
39	4.9	5.2	5.7	6.2									
40	5.5	5.6	6.0	6.6									
41	4.7	5.0	5.0	4.9	5.1	5.2	5.2	5.1	4.6	5.0	5.2	5.3	5.2
42	5.0	4.9	5.5	6.8									
43	5.2	5.6	5.4	6.2									
44	4.9	5.0	5.3	6.8									
45	4.7	4.9	5.1	5.9									
46	4.6	5.0	4.9	5.1	5.3	5.3	5.2	5.6	4.8	4.9	5.2	5.8	6.0
47	4.8	5.1	5.3	5.3	5.4	5.3	5.2	5.0	5.2	5.1	X		
48	5.4	5.2	5.3	5.6	5.1	5.6	5.6	5.6	6.2	6.0	5.9	5.8	6.5
49	4.8	4.9	5.6	7.2									
50	4.6	4.8	X	6.1									
51	4.7	4.8	5.0	5.4	5.4	5.3	5.2	5.0	4.9	4.7	4.5	4.5	4.3
52	5.6	5.4	5.4	5.4	5.4	5.4	5.5	5.8	5.6	5.3	4.8	5.7	6.0
53	4.8	4.4	4.9	5.2	5.3	5.2	5.1	4.7	5.2	5.0	4.8	5.0	5.3
54	5.0	5.0	5.5	6.7									
55	X												
56	5.2	5.3	4.7	4.8	5.3	5.3	5.0	5.3	5.4	4.8	5.0	5.4	5.3
57	5.1	5.4	5.4	7.3									
58	5.2	5.6	5.4	5.9	5.3	5.4	5.4	5.2	5.2	5.4	5.4	5.6	5.9
59	4.7	4.9	4.9	5.1	5.3	4.9	4.9	5.0	5.2	4.8	4.6	5.0	5.4
60	5.3	5.6	5.3	6.0	6.0	6.0	5.9	5.7	5.8	5.9	5.4	5.9	5.9

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Water Consumption

(g/d)

022755/98.003

Anim. No.	Day 7/8	14	21	28	35	42	49	57	63	70	77	84	91
30 ppm Female PO													
61	4.8	4.9	5.2	5.9									
62	4.0	4.5	4.7	5.8									
63	5.0	5.4	5.6	6.1	6.1	6.7	6.1	5.8	5.6	5.9	5.6	5.9	6.2
64	4.6	4.9	5.1	6.3									
65	4.7	4.8	5.0	5.6	5.2	5.1	5.0	5.2	5.2	4.8	4.6	4.4	5.3
66	5.1	5.4	5.7	6.1									
67	5.0	4.9	4.9	5.8	5.3	5.4	5.6	5.3	5.3	5.2	5.2	5.5	6.1
68	4.7	5.2	5.2	5.6	5.6	5.4	5.6	5.1	5.4	5.4	5.4	5.3	5.6
69	4.0	4.4	4.5	4.7	4.5	4.5	5.0	5.0	5.0	4.7	4.8	4.8	4.9
70	5.0	5.2	5.6	5.9	5.3	5.7	5.6	5.8	5.5	5.5	5.4	5.7	6.6
71	4.6	4.8	4.6	5.4	5.2	4.9	5.1	5.5	4.9	4.6	4.9	5.2	5.6
72	4.8	4.9	5.1	6.6									
73	4.8	5.2	5.6	6.5									
74	4.5	4.9	5.2	5.4	4.9	4.9	5.3	4.9	5.1	5.0	5.1	5.4	5.8
75	4.7	5.2	5.7	6.5	6.3	6.3	6.2	6.1	6.2	6.2	6.2	6.6	6.6
76	5.3	5.2	5.1	6.6									
77	4.8	5.1	5.0	5.7	5.0	5.7	5.5	5.6	5.4	5.0	5.1	5.3	4.9
78	4.6	10.9	4.9	5.0	4.9	4.7	4.8	5.0	4.9	5.0	5.1	5.4	6.2
79	4.6	5.1	5.3	6.0									
80	4.5	5.1	4.8	5.6									
81	5.0	5.0	5.0	6.1									
82	4.8	5.1	5.3	5.7									
83	4.9	5.3	5.3	6.4									
84	4.4	4.5	4.8	5.1	5.2	5.0	5.1	5.6	4.8	4.5	5.1	5.1	5.6
85	4.9	5.6	5.6	5.9									
86	5.1	5.3	5.2	6.3									
87	5.1	5.6	5.9	6.5	6.5	6.7	6.1	6.1	5.8	5.5	5.9	5.9	6.7
88	5.1	5.3	5.0	5.1	5.0	5.3	5.6	5.6	5.9	6.2	6.1	6.1	6.5
89	X	5.3	5.4	6.1									
90	5.3	5.7	5.0	5.2	5.2	5.6	5.7	5.6	5.7	5.8	5.4	6.2	6.6

Water Consumption

(g/d)

022755/98.004

Anim. No.	Day 7/8	14	21	28	35	42	49	57	63	70	77	84	91
250 ppm Female PO													
91	5.0	5.1	5.7	6.5									
92	4.5	5.3	5.1	5.5									
93	4.2	5.3	4.7	5.4									
94	5.1	5.3	5.4	5.7	5.1	5.7	5.6	5.9	5.7	5.5	5.5	5.8	6.3
95	4.8	4.8	5.5	6.4									
96	4.3	4.2	4.5	4.7	4.7	5.3	4.9	4.9	5.0	4.7	4.6	5.4	5.6
97	4.6	4.8	5.2	5.9									
98	5.4	5.5	6.2	6.8	6.3	6.4	5.9	5.9	6.1	5.7	5.9	6.0	6.8
99	4.4	4.2	4.7	4.8	4.8	4.9	4.6	4.5	4.8	4.4	4.4	4.5	5.8
100	4.4	5.0	4.6	5.0	4.7	4.7	4.7	5.0	4.8	5.0	4.4	5.3	5.8
101	4.5	4.2	5.1	5.1	5.3	5.4	5.5	5.4	5.4	5.6	5.5	5.2	6.4
102	4.9	5.0	4.9	4.8	4.7	4.7	4.8	4.8	5.3	5.1	5.5	5.7	6.1
103	4.7	4.7	5.2	6.5									
104	4.3	4.7	4.9	5.9									
105	4.4	4.8	5.0	5.8									
106	4.8	5.1	5.3	5.4	5.1	5.2	5.2	5.0	5.1	4.8	4.7	5.0	5.1
107	4.8	4.9	4.8	5.2	5.0	5.2	5.1	5.1	5.4	4.8	4.6	3.9	5.5
108	5.0	4.7	5.2	5.7	4.8	5.3	5.4	5.3	5.1	4.7	4.8	5.3	6.2
109	4.5	4.9	5.4	6.3									
110	5.1	5.7	6.0	7.2									
111	5.0	5.2	5.1	6.1									
112	4.2	4.7	5.0	4.9	5.0	5.5	5.4	5.0	4.9	4.8	4.6	5.1	6.3
113	4.6	4.8	4.6	5.1	5.2	5.3	5.5	5.2	5.3	5.0	5.1	5.6	5.5
114	4.5	5.1	5.3	6.5									
115	4.8	5.2	5.7	6.9									
116	3.9	4.7	4.5	4.8	4.7	4.8	4.8	4.9	4.4	4.5	4.5	4.6	5.3
117	5.1	4.8	5.4	5.8	5.8	5.7	6.0	5.4	5.7	5.5	5.2	5.7	5.7
118	4.4	5.0	4.8	5.3	5.2	5.3	5.6	5.7	5.7	5.3	5.2	5.5	5.9
119	4.4	5.7	5.9	6.8									
120	4.6	4.7	4.9	5.4									

Water Consumption

(g/d)

022755/98.005

Anim. No.	Day 7/8	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO													
121	5.3	5.2	5.6	5.0	5.1	5.0	4.9	4.9	5.1	5.1	5.6	5.7	6.0
122	5.1	4.4	5.2	5.8									
123	4.9	5.1	5.5	6.3									
124	6.1	5.3	5.3	6.5									
125	5.5	5.1	5.3	6.2									
126	4.6	4.6	4.7	5.2	5.1	5.0	4.8	4.7	5.0	4.9	4.7	5.2	6.0
127	3.9	3.8	4.6	4.6	4.5	4.2	4.4	4.4	4.1	3.9	4.1	4.4	5.4
128	5.6	4.9	4.9	4.9	5.4	5.3	5.6	5.7	6.3	5.8	6.2	6.2	6.8
129	4.5	4.4	4.3	4.7	4.4	4.4	4.3	4.3	4.3	4.3	4.5	4.4	5.2
130	5.3	5.1	5.2	6.0	5.7	6.0	6.2	5.8	5.3	5.1	5.1	4.9	6.6
131	4.4	4.2	4.1	4.3	4.2	4.3	4.4	4.2	4.3	4.1	4.2	4.5	5.2
132	5.0	4.4	4.6	5.7									
133	5.1	4.6	4.6	4.7	4.9	4.8	4.8	4.6	4.9	4.9	5.0	5.3	5.6
134	5.2	4.7	4.6	5.9									
135	5.5	5.1	5.0	5.5	5.5	5.7	5.8	4.9	5.1	5.7	5.6	5.5	7.5
136	4.0	4.0	4.0	5.2									
137	4.7	4.2	4.5	5.7									
138	4.7	4.7	4.9	6.2									
139	5.0	4.9	5.2	6.4									
140	5.6	5.0	5.0	5.6	5.2	5.6	5.3	5.1	5.5	5.4	5.7	5.1	5.7
141	4.8	4.4	4.8	5.1	4.8	5.0	5.1	4.8	5.1	5.0	5.0	5.0	5.7
142	5.3	5.5	5.4	6.0									
143	5.3	5.0	5.2	5.6	5.5	5.4	5.6	5.3	5.6	5.5	5.5	6.2	6.1
144	5.1	4.4	4.3	5.0									
145	5.1	4.8	4.9	6.0									
146	5.5	5.3	5.5	5.4	5.8	4.2	5.3	5.1	5.5	5.3	5.2	5.7	6.4
147	4.8	4.9	4.8	5.7	4.9	5.2	5.3	5.0	5.0	4.9	5.1	4.9	5.7
148	4.9	4.9	4.6	4.9	5.4	5.3	5.2	5.1	5.0	4.7	5.2	4.5	5.9
149	5.6	4.8	5.1	5.8									
150	5.7	5.1	5.0	6.2									

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Water Consumption

(g/d)

022755/98.006

Anim. No.	Day 7/8	14	21	28	35	42	49	57	63	70	77	84	91
+ MECAMYLAMINE 2500 ppm Female PO													
151	4.5	4.8	5.0	5.0									
152	4.7	4.4	4.7	4.7	4.6	4.6	5.2	4.6	5.1	5.2	4.9	5.2	5.1
153	4.8	4.7	5.4	5.2	5.5	5.3	5.8	5.2	5.6	5.9	5.3	5.6	5.9
154	4.9	5.0	5.4	5.3	4.8	4.8	5.3	4.4	4.9	4.8	4.6	4.9	5.4
155	4.8	4.5	4.7	4.7	4.7	4.5	5.2	4.3	4.5	4.9	4.7	4.8	5.3
156	4.8	4.7	4.7	4.6									
157	5.0	5.0	8.0	5.1	5.1	5.3	6.4	5.2	5.7	5.5	5.5	5.8	6.2
158	4.9	4.9	5.1	5.0									
159	5.7	5.9	5.6	5.4									
160	5.5	5.3	5.1	5.3	4.8	4.8	5.4	4.7	5.0	4.9	4.6	5.0	5.0
161	4.4	4.7	4.7	5.1	4.8	5.4	5.5	5.0	5.4	5.6	5.5	5.5	5.5
162	5.7	3.6	6.1	6.2	6.1	5.8	6.2	5.4	5.6	5.3	5.4	6.2	6.2
163	4.8	4.9	5.0	5.0									
164	4.7	4.9	5.1	5.8	5.1	5.1	6.0	5.1	5.0	5.5	5.4	5.3	6.6
165	1.4	5.1	5.2	4.9									
166	4.3	4.7	4.8	4.6									
167	5.3	5.3	5.4	5.3									
168	5.1	4.8	5.2	5.3									
169	5.5	5.5	5.4	5.6	5.4	5.3	6.1	5.3	5.6	5.8	5.5	5.5	6.1
170	5.6	5.6	5.6	5.9	5.7	5.6	6.0	5.2	5.4	5.2	5.1	5.2	5.8
171	5.2	5.0	5.2	5.1									
172	5.4	4.9	4.8	5.3	5.5	4.4	5.5	5.1	5.2	5.4	5.3	5.8	5.6
173	5.0	5.4	5.4	5.2									
174	5.0	4.6	5.3	5.1	5.3	5.0	5.5	4.8	4.9	5.2	5.3	5.5	5.5
175	5.1	5.0	5.1	5.1									
176	5.0	4.7	4.9	5.0	4.8	5.0	5.6	4.9	4.8	5.2	5.0	5.4	5.3
177	4.6	4.6	4.8	5.0									
178	5.1	4.7	5.3	5.6	5.3	5.1	5.7	5.1	5.3	5.4	5.6	6.3	6.5
179	5.4	4.9	5.1	5.0									
180	4.9	5.0	5.2	5.4									

9.8. Body Weights

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.001

	Day 0	7	14	21	28	35	42	49	57	63	70	77	84	91
0 ppm Female PO														
Mean	18.5	19.5	20.4	21.3	21.7	21.6	22.0	22.6	23.2	23.4	23.5	23.9	23.8	23.9
Med.	18.7	19.6	20.4	21.5	21.8	21.8	22.3	22.8	23.5	23.4	23.6	24.2	23.7	24.1
S.D.	.839	.762	.646	.730	.803	.707	.871	.770	.994	.932	.863	.888	1.12	.953
Min.	16.8	18.0	18.4	19.6	19.6	20.0	20.0	21.0	21.4	21.3	21.2	21.6	21.4	21.6
Max.	20.4	20.7	21.5	22.6	23.1	22.6	22.8	23.6	24.7	25.0	24.5	24.9	25.4	24.9
N	30	30	30	30	30	15	14	15	15	15	15	15	15	15
10 ppm Female PO														
Mean	18.5	19.6	20.6	21.6	22.0	22.6	23.1	23.8	24.6	24.8	25.0	25.2	25.0	25.1
Med.	18.4	19.7	20.3	21.4	21.8	22.5	23.0	23.7	24.5	24.9	24.7	24.8	24.8	24.9
S.D.	1.01	1.27	.873	.969	1.04	.885	1.07	.843	.938	1.06	1.41	1.27	1.20	1.21
Min.	16.7	15.3	19.4	20.3	20.3	21.1	21.6	22.7	23.4	23.3	23.4	23.8	23.5	23.5
Max.	21.8	23.2	23.4	24.0	24.4	25.1	25.3	25.6	26.8	27.1	28.3	27.9	27.4	27.9
N	30	29	29	29	29	15	15	15	15	15	15	14	14	14
TS 1%	-	-	-	-	-	++	++	++	++	++	++	-	-	-
TS 5%	-	-	-	-	-	+	+	+	+	+	+	+	+	+
30 ppm Female PO														
Mean	18.3	19.2	20.0	21.1	21.2	21.7	22.0	22.6	23.4	23.7	23.7	24.1	24.2	23.9
Med.	18.2	19.3	20.0	21.2	21.4	21.8	22.1	22.6	23.6	23.9	24.1	24.1	23.9	24.0
S.D.	.739	.647	.745	.813	.780	.893	.625	.843	1.17	1.08	1.14	1.13	1.12	.953
Min.	17.0	17.6	18.2	18.9	19.7	20.3	20.8	21.2	20.9	21.0	20.8	21.4	22.1	21.6
Max.	19.8	20.6	21.1	22.7	22.3	23.9	22.9	24.0	24.8	25.2	25.1	25.4	26.0	25.2
N	30	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
250 ppm Female PO														
Mean	18.4	19.3	20.1	21.2	21.3	21.8	22.1	22.7	23.5	23.8	23.9	24.1	24.1	23.9
Med.	18.5	19.5	20.1	21.2	21.1	21.6	22.3	22.7	23.5	23.7	23.9	23.8	24.0	23.6
S.D.	.874	.895	.603	.765	.953	.763	.933	.902	.894	.951	.978	.797	1.05	1.11
Min.	17.2	16.5	19.0	19.9	19.9	20.8	20.2	21.1	22.2	22.2	22.4	23.1	22.8	22.5
Max.	20.4	20.9	21.6	23.0	23.4	23.3	23.6	24.4	25.1	25.6	25.8	25.4	25.8	25.5
N	30	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.002

	Day													
	0	7	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO														
Mean	18.4	19.4	19.8	21.1	21.0	21.6	22.2	22.8	23.8	24.1	23.9	24.7	24.3	24.0
Med.	18.4	19.3	19.9	21.2	20.9	21.6	22.6	23.1	24.1	24.4	24.1	25.0	24.4	24.0
S.D.	.692	.818	.804	.836	.702	.904	.923	.865	1.06	1.16	1.20	1.46	1.16	1.13
Min.	16.4	17.5	17.4	18.9	19.4	19.1	19.9	21.1	21.5	21.3	21.3	22.4	21.9	21.6
Max.	19.5	20.7	21.1	22.9	22.1	22.8	23.2	24.4	25.4	25.4	25.8	28.1	26.3	26.5
N	30	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	+	-	+	-	-	-	-	-	-	-	-	-
+ MECAMYLAMINE 2500 ppm Female PO														
Mean	18.2	19.2	19.2	20.8	20.8	21.4	21.5	22.1	23.0	23.4	23.4	23.7	23.6	23.5
Med.	18.2	19.3	19.2	20.9	20.8	21.4	21.7	22.2	22.9	23.4	23.7	23.6	23.5	23.6
S.D.	.874	.913	1.02	.926	1.19	.849	.831	1.04	1.05	1.12	1.07	1.11	1.24	1.13
Min.	16.6	17.0	16.9	19.2	17.7	19.9	19.7	20.2	21.4	21.3	21.9	22.0	21.7	21.5
Max.	19.9	20.5	20.7	22.8	23.6	22.7	23.0	23.9	25.0	25.1	24.7	25.6	25.8	25.4
N	30	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	++	-	++	-	-	-	-	-	-	-	-	-
TS 5%	-	-	+	+	+	-	-	-	-	-	-	-	-	-

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.001

Anim. No.	Day 0	7	14	21	28	35	42	49	57	63	70	77	84	91
0 ppm Female PO														
1	16.8	18.1	18.4	19.6	19.6	20.0	20.0	21.0	21.4	21.8	21.2	21.6	21.4	21.6
2	17.9	19.9	20.5	21.4	21.5									
3	16.8	18.5	20.1	20.5	20.4	21.1	21.6	22.0	23.1	23.6	24.0	24.2	23.7	24.1
4	18.3	18.9	19.6	20.4	20.5	21.1	21.2	22.0	22.2	23.3	23.4	23.2	23.3	23.4
5	18.8	19.8	21.1	22.5	21.4									
6	18.8	20.2	20.7	22.3	22.1	21.8	22.8	23.3	24.7	23.2	23.6	24.2	23.6	23.3
7	18.4	19.5	20.3	20.9	21.8	22.2	22.8	23.2	24.3	25.0	24.5	24.7	24.8	24.9
8	19.4	20.5	20.6	21.7	23.1	22.4	22.8	23.2	23.7	24.3	23.9	24.3	24.7	24.8
9	18.9	20.7	20.4	21.2	22.2	21.9	22.7	22.8	23.5	23.9	23.7	24.0	24.2	24.3
10	20.4	19.9	20.9	22.1	21.6									
11	17.4	18.7	20.6	21.2	20.8									
12	17.9	19.5	20.1	20.7	20.6									
13	18.6	19.1	20.3	21.2	20.9									
14	19.0	19.3	20.2	21.7	21.7									
15	18.5	20.3	20.7	22.1	21.7									
16	17.6	20.0	19.9	20.3	21.8	21.1	21.0	21.5	22.2	23.2	23.0	23.4	22.9	23.3
17	19.0	19.5	20.3	21.7	22.4	22.1	22.5	23.6	24.2	23.7	24.3	24.8	25.0	24.8
18	19.8	20.1	20.6	21.8	21.8									
19	18.8	20.4	21.5	22.6	22.3									
20	19.2	20.7	21.5	21.6	22.4									
21	17.3	18.0	19.1	19.9	21.1	20.6	21.6	21.8	22.0	21.3	22.2	22.6	21.9	22.4
22	17.7	18.7	19.8	21.1	21.1									
23	18.6	18.9	20.1	21.7	22.2	21.8	21.2	22.6	22.1	22.7	23.5	23.9	23.6	23.7
24	18.1	19.1	20.3	21.6	21.8	22.1		22.6	22.9	23.3	23.6	23.6	23.6	23.7
25	18.7	19.5	20.7	21.2	21.2									
26	18.2	18.5	19.6	20.5	22.1	21.6	22.2	23.4	23.5	23.4	23.5	24.9	23.8	24.1
27	19.3	19.6	20.2	21.7	22.9	22.6	22.7	23.1	23.6	23.6	23.8	24.2	24.8	24.6
28	19.2	20.4	21.1	21.8	22.3									
29	19.3	19.6	20.5	21.4	22.6	21.7	22.3	22.8	24.1	24.3	24.5	24.5	25.4	24.8
30	18.9	20.3	20.8	21.5	22.5									

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.002

Anim. No.	Day 0	7	14	21	28	35	42	49	57	63	70	77	84	91
10 ppm Female PO														
31	16.7	18.5	19.8	20.3	20.3									
32	19.0	20.1	20.3	20.8	22.2									
33	17.8	15.3	19.8	20.9	23.3	22.4	24.9	24.7	24.5	26.1	28.3	27.0	26.8	27.9
34	18.0	19.7	21.3	21.7	22.0									
35	18.1	19.1	20.2	21.7	21.3	22.6	23.0	23.1	24.3	23.8	23.8	24.5	23.6	24.2
36	18.6	19.1	20.2	21.2	21.2	22.3	22.1	23.3	23.9	23.3	23.5	23.8	24.2	23.8
37	18.7	20.0	20.8	21.3	21.8	22.3	22.5	23.9	25.1	25.0	24.7	25.9	25.9	25.0
38	19.5	20.3	20.6	22.1	22.8									
39	18.5	19.7	20.1	21.7	21.3									
40	21.8	23.2	23.4	24.0	24.3									
41	17.5	18.6	19.4	20.4	20.4	21.1	21.6	22.9	23.4	23.8	23.9	24.0	23.6	24.4
42	18.5	20.2	20.5	21.2	21.4									
43	18.0	20.2	20.9	21.7	22.0									
44	17.9	18.9	20.1	20.7	20.8									
45	17.5	18.5	20.2	21.3	21.1									
46	19.0	19.7	21.0	22.4	22.8	22.5	23.1	23.9	26.8	25.3	25.2	24.9	25.0	25.6
47	17.6	18.9	20.0	21.6	21.8	21.7	21.8	23.1	24.3	24.7	24.6			
48	19.7	20.2	21.4	22.8	23.0	22.9	23.5	24.2	24.8	25.1	25.5	25.8	25.7	26.1
49	18.1	18.9	19.5	20.5	20.8									
50	18.4	19.6	20.7	20.9	21.7									
51	17.3	19.3	20.2	21.4	21.7	22.5	22.2	22.7	23.5	23.4	23.4	24.2	23.5	23.5
52	18.2	19.0	19.8	21.0	21.4	22.2	22.6	23.1	23.7	23.8	23.7	23.8	24.5	24.3
53	18.9	19.9	20.3	21.1	21.8	22.3	22.4	23.0	24.2	24.4	24.2	24.0	24.3	24.9
54	18.4	19.5	20.4	21.6	21.9									
55	17.5													
56	19.3	20.1	21.2	22.2	22.7	23.2	23.5	23.7	24.6	25.6	26.0	24.7	24.6	24.9
57	18.2	19.8	20.0	20.7	21.3									
58	19.0	20.5	21.4	23.2	23.4	23.3	23.8	24.9	25.4	25.4	25.6	26.0	25.7	24.8
59	19.9	20.0	20.7	22.7	22.7	23.1	23.6	24.2	24.6	24.9	25.0	25.9	25.3	25.1
60	20.1	21.8	22.7	23.9	24.4	25.1	25.3	25.6	26.1	27.1	27.3	27.9	27.4	27.0

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.003

Anim. No.	Day 0	7	14	21	28	35	42	49	57	63	70	77	84	91
30 ppm Female PO														
61	17.2	18.8	18.9	19.8	19.9									
62	17.2	18.4	19.3	20.9	20.6									
63	18.0	19.6	19.9	21.1	21.1	21.9	22.1	22.6	23.7	23.5	23.3	23.9	23.6	23.5
64	18.4	19.7	21.1	22.5	21.7									
65	18.4	19.6	20.0	20.6	20.6	21.8	22.1	22.1	23.4	24.1	24.4	24.1	23.9	24.3
66	17.8	18.8	20.1	21.2	21.3									
67	19.8	20.6	21.0	21.7	22.2	22.6	22.8	24.0	24.8	25.2	25.1	25.3	25.4	25.0
68	18.7	19.2	20.4	21.2	21.8	23.9	22.9	23.9	24.3	24.1	24.2	25.1	24.7	24.1
69	17.9	18.4	19.3	20.8	20.8	21.8	22.0	22.8	24.6	24.7	24.1	24.9	24.6	23.8
70	19.0	19.3	19.7	20.5	21.5	21.3	21.3	22.3	23.0	23.3	22.9	23.4	23.2	24.8
71	17.0	17.6	18.2	18.9	19.7	20.4	20.8	21.8	21.2	22.1	22.4	22.7	22.6	22.4
72	17.1	18.3	19.2	20.6	19.7									
73	18.1	19.4	20.6	21.7	21.1									
74	17.2	18.1	18.8	19.8	20.1	20.8	21.3	21.2	20.9	21.0	20.8	21.4	22.1	21.6
75	17.9	18.9	19.7	20.9	21.6	21.3	21.4	21.8	22.4	23.0	22.8	23.0	23.4	23.7
76	18.2	19.2	19.9	21.2	22.2									
77	18.4	19.7	21.1	22.2	22.3	21.9	22.5	22.8	24.5	24.7	24.9	25.4	25.6	24.4
78	18.2	19.4	19.5	20.4	21.0	21.9	21.9	22.6	23.4	23.9	23.6	23.8	23.9	24.0
79	19.4	19.9	20.7	21.8	22.1									
80	19.4	19.6	20.7	21.5	21.6									
81	17.8	18.9	19.1	20.9	20.6									
82	18.5	19.8	20.6	22.0	21.3									
83	18.0	19.0	20.5	21.6	20.6									
84	17.7	18.6	19.4	20.3	20.3	20.3	21.4	22.1	23.6	23.0	23.1	23.7	23.7	23.1
85	18.6	19.7	20.9	22.7	22.1									
86	18.7	19.1	20.4	21.3	21.4									
87	18.2	19.1	20.3	21.3	22.0	21.8	22.3	22.3	23.0	23.8	24.6	25.3	24.6	24.3
88	19.4	19.6	20.0	20.8	22.0	22.2	22.4	24.0	24.5	24.3	24.2	24.1	26.0	24.0
89	18.5	19.7	20.0	21.0	21.5									
90	19.2	20.1	20.6	21.7	21.9	22.3	22.6	23.2	23.6	24.2	24.5	24.7	25.2	25.2

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.004

Anim. No.	Day 0	7	14	21	28	35	42	49	57	63	70	77	84	91
250 ppm Female PO														
91	17.4	19.2	19.8	20.5	20.9									
92	17.2	18.2	19.7	21.1	20.6									
93	17.6	18.9	20.2	21.0	21.1									
94	19.1	19.5	20.4	21.9	22.6	22.7	22.5	23.1	23.5	24.3	24.0	24.1	24.1	24.2
95	18.8	19.5	20.3	21.5	20.7									
96	17.7	19.0	19.8	20.3	20.6	21.3	22.3	21.8	22.3	22.5	22.4	23.2	23.4	22.7
97	17.9	18.6	19.5	20.6	20.2									
98	19.0	20.1	20.6	21.9	22.8	22.5	22.6	23.6	24.4	25.1	24.9	25.4	25.8	25.5
99	18.8	20.2	20.4	21.6	21.8	22.3	23.6	24.4	24.9	24.5	24.6	25.4	25.4	25.5
100	19.0	19.9	20.8	21.3	22.0	22.1	22.7	23.3	24.4	24.0	25.8	24.1	24.9	24.9
101	17.4	17.8	19.0	20.6	20.2	20.8	21.1	22.2	23.2	23.3	23.2	23.8	23.2	23.2
102	17.7	18.2	19.6	20.8	20.5	20.8	20.9	21.1	22.2	22.2	22.5	23.5	22.9	22.5
103	18.8	19.8	20.1	20.8	21.0									
104	18.1	19.7	20.0	20.6	20.8									
105	18.1	19.3	20.2	21.4	22.1									
106	18.4	19.7	20.0	21.2	21.6	22.4	22.5	22.8	23.2	24.6	23.9	24.4	24.4	24.4
107	17.2	19.6	20.7	21.7	21.2	21.6	21.6	22.5	23.6	23.3	23.7	24.7	23.5	22.8
108	19.7	20.2	20.7	21.9	22.7	23.3	23.4	24.1	25.1	25.6	25.5	25.3	25.7	25.5
109	19.1	20.0	20.9	22.8	22.2									
110	20.4	20.9	21.6	23.0	23.4									
111	17.5	18.8	19.5	20.0	20.2									
112	17.9	18.2	19.1	20.3	19.9	20.8	20.2	22.0	22.3	22.6	23.9	23.1	22.8	22.5
113	17.3	18.8	19.7	19.9	20.0	21.1	21.2	21.8	23.5	23.7	23.5	23.5	23.5	23.1
114	19.5	20.0	20.6	21.7	21.9									
115	18.2	19.6	20.1	21.1	20.8									
116	18.6	19.0	20.0	21.8	21.1	21.8	22.2	23.0	23.6	23.5	24.2	23.7	24.0	23.6
117	18.5	19.7	19.8	20.5	20.4	21.5	21.7	22.3	23.0	23.6	23.3	23.4	23.0	23.5
118	18.8	19.4	20.1	21.2	21.5	21.6	22.3	22.7	23.7	23.8	23.3	23.5	25.2	24.4
119	19.6	16.5	19.6	20.6	20.4									
120	19.9	20.3	21.4	22.2	22.6									

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.005

Anim. No.	Day 0	7	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO														
121	18.2	18.7	19.9	20.5	20.2	21.0	21.2	22.0	23.2	23.1	23.1	23.3	23.4	22.7
122	18.1	18.7	19.2	20.1	20.0									
123	19.5	20.0	20.4	22.1	22.1									
124	18.9	20.5	21.1	22.3	21.9									
125	17.6	18.6	19.5	20.8	20.8									
126	18.9	19.9	19.9	21.5	21.2	22.1	23.1	23.5	24.7	24.9	25.8	25.5	24.6	25.0
127	18.7	20.3	20.4	21.5	21.3	22.2	22.6	23.4	25.0	25.2	24.6	25.8	25.2	24.2
128	18.9	19.7	19.5	20.1	20.1	21.0	21.9	22.7	23.1	23.3	24.1	24.4	24.2	24.0
129	18.8	20.4	20.7	21.9	21.7	22.1	23.0	23.5	24.8	25.2	24.0	25.6	25.4	25.0
130	19.1	20.7	20.8	21.8	21.8	22.4	23.1	24.4	25.4	24.8	25.1	25.2	24.9	24.3
131	17.1	18.7	18.6	19.7	19.9	21.5	22.0	22.2	22.7	23.5	23.4	23.3	23.2	23.5
132	17.9	18.4	19.3	20.7	20.6									
133	18.2	19.3	19.8	20.6	20.6	21.3	21.9	21.8	23.0	23.1	23.3	23.0	22.9	22.9
134	18.6	19.3	19.8	21.0	20.8									
135	18.7	20.3	20.1	21.5	21.6	22.1	22.9	23.6	24.3	24.4	24.2	25.5	25.0	24.2
136	17.9	19.6	19.9	21.2	21.0									
137	18.4	18.9	19.7	21.3	20.7									
138	18.4	19.1	19.9	21.5	21.0									
139	18.8	20.0	20.3	21.9	21.8									
140	19.0	20.4	20.7	22.2	21.9	22.8	23.2	23.1	24.2	25.4	25.8	28.1	26.3	26.5
141	16.4	17.5	17.4	18.9	19.4	19.1	19.9	21.1	21.5	21.3	21.3	22.4	21.9	21.6
142	17.3	18.3	19.1	20.6	20.8									
143	17.7	18.1	18.7	20.3	20.7	21.4	21.2	22.2	22.7	23.1	22.4	23.5	23.7	23.5
144	18.4	19.6	19.2	20.9	20.6									
145	18.4	18.3	19.0	20.8	20.2									
146	18.2	19.3	20.4	21.3	20.9	20.9	22.1	22.5	23.7	23.9	23.2	25.0	25.4	24.0
147	18.4	19.7	20.1	21.4	21.3	22.4	22.6	23.2	24.1	24.5	24.3	24.3	23.6	24.4
148	19.0	19.1	20.3	21.2	21.2	21.6	22.8	23.4	24.2	25.3	24.1	25.7	24.4	23.6
149	17.9	19.1	19.3	20.8	20.5									
150	19.5	20.0	21.1	22.9	22.1									

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weights

(g)

022715/98.006

Anim. No.	Day 0	7	14	21	28	35	42	49	57	63	70	77	84	91
+ MECAMYLAMINE 2500 ppm Female PO														
151	16.6	17.3	16.9	19.2	17.7									
152	17.0	18.2	18.0	19.8	19.5	19.9	19.7	20.2	22.0	21.3	21.9	22.0	21.8	21.5
153	17.6	17.8	17.6	19.3	19.9	20.8	21.2	20.9	21.4	22.2	21.9	22.7	22.7	22.8
154	17.9	18.9	19.0	21.1	21.0	21.9	21.8	22.1	22.7	23.4	23.7	23.2	23.4	23.6
155	18.6	19.2	19.4	20.3	20.7	21.6	21.9	22.4	22.8	23.1	23.2	23.5	23.4	23.9
156	18.6	19.8	20.1	21.3	21.2									
157	18.1	19.0	19.1	20.9	21.1	20.9	20.7	21.7	22.2	22.4	22.6	23.7	23.5	23.2
158	18.2	19.1	19.0	21.5	20.4									
159	19.6	19.8	20.3	22.2	22.0									
160	19.9	20.2	20.5	22.8	22.9	22.7	23.0	23.9	25.0	24.5	24.7	25.6	25.4	25.4
161	18.5	19.6	19.8	21.1	21.6	21.4	21.9	22.4	23.1	23.4	24.3	24.4	23.8	23.6
162	18.3	18.8	19.5	20.5	20.8	21.4	21.3	21.7	22.9	23.3	24.0	23.7	23.0	23.0
163	17.7	19.6	19.1	20.9	20.7									
164	18.1	19.8	19.5	21.1	22.5	22.6	22.2	23.7	24.9	25.1	24.5	25.1	25.8	25.1
165	19.5	20.1	20.6	21.7	20.8									
166	17.8	18.0	18.3	20.1	19.7									
167	18.4	19.8	19.2	20.8	20.6									
168	19.7	20.4	20.7	22.1	23.6									
169	19.5	19.9	20.6	21.8	22.7	21.8	21.7	22.6	23.9	25.1	24.7	25.3	25.8	25.0
170	18.8	20.5	20.2	21.0	21.2	22.6	22.4	22.5	23.9	24.8	24.4	23.6	23.9	24.2
171	18.8	20.2	20.2	21.5	21.2									
172	18.3	19.0	19.6	20.4	21.0	21.4	21.6	22.2	23.0	23.5	23.4	23.6	23.8	23.6
173	17.6	18.9	18.8	19.8	20.8									
174	18.2	18.7	17.9	19.2	20.2	20.4	20.8	21.0	22.3	23.1	22.1	22.9	22.9	23.0
175	16.6	17.0	17.9	19.2	19.4									
176	16.9	18.1	17.9	20.4	19.4	20.4	20.6	20.9	22.0	22.1	21.9	22.1	21.7	21.6
177	18.2	19.3	18.8	20.9	20.0									
178	18.0	19.6	19.1	21.0	21.1	21.9	22.1	22.9	23.6	23.5	23.7	24.8	23.8	23.5
179	18.8	20.1	19.5	21.1	21.4									
180	17.4	18.7	17.9	20.0	20.1									

Body Weight Gain

(g)

022735/98.001

	Day												
	0	7	14	21	28	35	42	49	57	63	70	77	84
	7	14	21	28	35	42	49	57	63	70	77	84	91
0 ppm Female PO													
Mean	1.02	0.81	0.98	0.35	-.17	0.39	0.64	0.57	0.21	0.14	0.36	-.09	0.07
Med.	1.05	0.80	0.90	0.10	-.30	0.45	0.50	0.50	0.40	0.20	0.40	0.00	0.10
S.D.	.649	.473	.399	.693	.511	.447	.395	.505	.684	.453	.358	.534	.294
Min.	-.50	-.30	0.10	-1.1	-.90	-.60	0.10	-.50	-1.5	-.60	-.20	-1.1	-.60
Max.	2.40	1.90	1.60	1.60	0.70	1.00	1.40	1.40	1.10	0.90	1.40	0.90	0.50
N	30	30	30	30	15	14	14	15	15	15	15	15	15
10 ppm Female PO													
Mean	1.05	0.98	1.04	0.37	0.39	0.43	0.69	0.86	0.17	0.20	0.16	-.16	0.10
Med.	1.10	0.90	1.00	0.30	0.50	0.40	0.60	0.60	0.20	0.10	0.30	-.15	0.15
S.D.	.831	.791	.449	.533	.583	.634	.486	.684	.735	.589	.746	.447	.624
Min.	-2.5	0.20	0.20	-.40	-.90	-.30	-.20	-.20	-1.5	-.30	-1.3	-.90	-.90
Max.	2.20	4.50	2.00	2.40	1.30	2.50	1.40	2.90	1.60	2.20	1.20	0.70	1.10
N	29	29	29	29	15	15	15	15	15	15	14	14	14
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	+	-	-	-	-	-	-	-	-
30 ppm Female PO													
Mean	0.94	0.79	1.10	0.12	0.49	0.24	0.65	0.76	0.27	0.00	0.39	0.11	-.29
Med.	1.00	0.80	1.10	0.10	0.40	0.20	0.70	0.70	0.30	-.10	0.50	0.00	-.30
S.D.	.386	.419	.313	.585	.677	.440	.479	.668	.434	.351	.333	.615	.799
Min.	0.20	0.10	0.60	-1.0	-.40	-1.0	-.10	-.60	-.60	-.60	-.30	-.70	-2.0
Max.	1.60	1.50	1.80	1.20	2.10	1.10	1.60	1.80	0.90	0.80	0.90	1.90	1.60
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	++	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	+	-	-	-	-	-	-	-	-
250 ppm Female PO													
Mean	0.85	0.85	1.05	0.07	0.51	0.28	0.66	0.81	0.25	0.14	0.16	0.05	-.23
Med.	0.95	0.85	1.10	0.20	0.60	0.10	0.60	0.80	0.20	-.10	0.20	0.00	-.30
S.D.	.898	.549	.398	.474	.400	.471	.498	.378	.493	.677	.739	.674	.356
Min.	-3.1	0.10	0.20	-.80	-.30	-.60	-.50	0.30	-.40	-.70	-1.7	-1.2	-.80
Max.	2.40	3.10	1.90	0.90	1.10	1.30	1.80	1.70	1.40	1.80	1.00	1.70	0.50
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	++	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	+	-	-	-	-	-	-	-	-

Body Weight Gain

(g)

022735/98.002

	Day												
	0	7	14	21	28	35	42	49	57	63	70	77	84
	7	14	21	28	35	42	49	57	63	70	77	84	91
2500 ppm Female PO													
Mean	0.99	0.45	1.31	-.15	0.67	0.64	0.61	0.93	0.29	-.15	0.79	-.43	-.31
Med.	1.05	0.45	1.35	-.15	0.70	0.70	0.60	1.00	0.20	-.10	1.10	-.30	-.30
S.D.	.493	.441	.340	.286	.451	.394	.411	.370	.468	.638	.849	.578	.590
Min.	-.10	-.40	0.60	-.80	-.30	-.20	-.10	0.40	-.60	-1.2	-.30	-1.8	-1.4
Max.	1.70	1.20	1.80	0.50	1.60	1.20	1.30	1.60	1.20	0.90	2.30	0.40	0.80
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	-	++	++	++	-	-	-	-	-	-	-	-
TS 5%	-	+	+	+	+	-	-	-	-	-	-	-	-
+ MECAMYLAMINE 2500 ppm Female PO													
Mean	0.94	-.01	1.60	0.07	0.41	0.08	0.55	0.97	0.34	0.01	0.35	-.10	-.11
Med.	0.95	-.05	1.60	0.10	0.40	0.20	0.50	1.10	0.30	0.10	0.30	-.10	-.10
S.D.	.492	.467	.497	.716	.610	.278	.432	.406	.515	.514	.573	.455	.348
Min.	0.20	-.80	0.80	-1.5	-.90	-.40	-.30	0.40	-.70	-1.0	-.80	-1.0	-.80
Max.	1.90	0.90	2.50	1.50	1.40	0.50	1.50	1.80	1.20	0.90	1.10	0.70	0.50
N	30	30	30	30	15	15	15	15	15	15	15	15	15
TS 1%	-	++	++	-	-	-	-	-	-	-	-	-	-
TS 5%	-	+	+	-	+	-	-	-	-	-	-	-	-

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weight Gain

(g)

022735/98.001

Anim. No.	Day 0 7	7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
0 ppm Female PO													
1	1.3	0.3	1.2	0.0	0.4	0.0	1.0	0.4	0.4	-0.6	0.4	-0.2	0.2
2	2.0	0.6	0.9	0.1									
3	1.7	1.6	0.4	-0.1	0.7	0.5	0.4	1.1	0.5	0.4	0.2	-0.5	0.4
4	0.6	0.7	0.8	0.1	0.6	0.1	0.8	0.2	1.1	0.1	-0.2	0.1	0.1
5	1.0	1.3	1.4	-1.1									
6	1.4	0.5	1.6	-0.2	-0.3	1.0	0.5	1.4	-1.5	0.4	0.6	-0.6	-0.3
7	1.1	0.8	0.6	0.9	0.4	0.6	0.4	1.1	0.7	-0.5	0.2	0.1	0.1
8	1.1	0.1	1.1	1.4	-0.7	0.4	0.4	0.5	0.6	-0.4	0.4	0.4	0.1
9	1.8	-0.3	0.8	1.0	-0.3	0.8	0.1	0.7	0.4	-0.2	0.3	0.2	0.1
10	-0.5	1.0	1.2	-0.5									
11	1.3	1.9	0.6	-0.4									
12	1.6	0.6	0.6	-0.1									
13	0.5	1.2	0.9	-0.3									
14	0.3	0.9	1.5	0.0									
15	1.8	0.4	1.4	-0.4									
16	2.4	-0.1	0.4	1.5	-0.7	-0.1	0.5	0.7	1.0	-0.2	0.4	-0.5	0.4
17	0.5	0.8	1.4	0.7	-0.3	0.4	1.1	0.6	-0.5	0.6	0.5	0.2	-0.2
18	0.3	0.5	1.2	0.0									
19	1.6	1.1	1.1	-0.3									
20	1.5	0.8	0.1	0.8									
21	0.7	1.1	0.8	1.2	-0.5	1.0	0.2	0.2	-0.7	0.9	0.4	-0.7	0.5
22	1.0	1.1	1.3	0.0									
23	0.3	1.2	1.6	0.5	-0.4	-0.6	1.4	-0.5	0.6	0.8	0.4	-0.3	0.1
24	1.0	1.2	1.3	0.2	0.3			0.3	0.4	0.3	0.0	0.0	0.1
25	0.8	1.2	0.5	0.0									
26	0.3	1.1	0.9	1.6	-0.5	0.6	1.2	0.1	-0.1	0.1	1.4	-1.1	0.3
27	0.3	0.6	1.5	1.2	-0.3	0.1	0.4	0.5	0.0	0.2	0.4	0.6	-0.2
28	1.2	0.7	0.7	0.5									
29	0.3	0.9	0.9	1.2	-0.9	0.6	0.5	1.3	0.2	0.2	0.0	0.9	-0.6
30	1.4	0.5	0.7	1.0									

Body Weight Gain

(g)

022735/98.002

Anim. No.	0 7	7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
10 ppm Female PO													
31	1.8	1.3	0.5	0.0									
32	1.1	0.2	0.5	1.4									
33	-2.5	4.5	1.1	2.4	-0.9	2.5	-0.2	-0.2	1.6	2.2	-1.3	-0.2	1.1
34	1.7	1.6	0.4	0.3									
35	1.0	1.1	1.5	-0.4	1.3	0.4	0.1	1.2	-0.5	0.0	0.7	-0.9	0.6
36	0.5	1.1	1.0	0.0	1.1	-0.2	1.2	0.6	-0.6	0.2	0.3	0.4	-0.4
37	1.3	0.8	0.5	0.5	0.5	0.2	1.4	1.2	-0.1	-0.3	1.2	0.0	-0.9
38	0.8	0.3	1.5	0.7									
39	1.2	0.4	1.6	-0.4									
40	1.4	0.2	0.6	0.3									
41	1.1	0.8	1.0	0.0	0.7	0.5	1.3	0.5	0.4	0.1	0.1	-0.4	0.8
42	1.7	0.3	0.7	0.2									
43	2.2	0.7	0.8	0.3									
44	1.0	1.2	0.6	0.1									
45	1.0	1.7	1.1	-0.2									
46	0.7	1.3	1.4	0.4	-0.3	0.6	0.8	2.9	-1.5	-0.1	-0.3	0.1	0.6
47	1.3	1.1	1.6	0.2	-0.1	0.1	1.3	1.2	0.4	-0.1			
48	0.5	1.2	1.4	0.2	-0.1	0.6	0.7	0.6	0.3	0.4	0.3	-0.1	0.4
49	0.8	0.6	1.0	0.3									
50	1.2	1.1	0.2	0.8									
51	2.0	0.9	1.2	0.3	0.8	-0.3	0.5	0.8	-0.1	0.0	0.8	-0.7	0.0
52	0.8	0.8	1.2	0.4	0.8	0.4	0.5	0.6	0.1	-0.1	0.1	0.7	-0.2
53	1.0	0.4	0.8	0.7	0.5	0.1	0.6	1.2	0.2	-0.2	-0.2	0.3	0.6
54	1.1	0.9	1.2	0.3									
55													
56	0.8	1.1	1.0	0.5	0.5	0.3	0.2	0.9	1.0	0.4	-1.3	-0.1	0.3
57	1.6	0.2	0.7	0.6									
58	1.5	0.9	1.8	0.2	-0.1	0.5	1.1	0.5	0.0	0.2	0.4	-0.3	-0.9
59	0.1	0.7	2.0	0.0	0.4	0.5	0.6	0.4	0.3	0.1	0.9	-0.6	-0.2
60	1.7	0.9	1.2	0.5	0.7	0.2	0.3	0.5	1.0	0.2	0.6	-0.5	-0.4

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Body Weight Gain

(g)

022735/98.003

Anim. No.	0 7	7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
30 ppm Female PO													
61	1.6	0.1	0.9	0.1									
62	1.2	0.9	1.6	-0.3									
63	1.6	0.3	1.2	0.0	0.8	0.2	0.5	1.1	-0.2	-0.2	0.6	-0.3	-0.1
64	1.3	1.4	1.4	-0.8									
65	1.2	0.4	0.6	0.0	1.2	0.3	0.0	1.3	0.7	0.3	-0.3	-0.2	0.4
66	1.0	1.3	1.1	0.1									
67	0.8	0.4	0.7	0.5	0.4	0.2	1.2	0.8	0.4	-0.1	0.2	0.1	-0.4
68	0.5	1.2	0.8	0.6	2.1	-1.0	1.0	0.4	-0.2	0.1	0.9	-0.4	-0.6
69	0.5	0.9	1.5	0.0	1.0	0.2	0.8	1.8	0.1	-0.6	0.8	-0.3	-0.8
70	0.3	0.4	0.8	1.0	-0.2	0.0	1.0	0.7	0.3	-0.4	0.5	-0.2	1.6
71	0.6	0.6	0.7	0.8	0.7	0.4	1.0	-0.6	0.9	0.3	0.3	-0.1	-0.2
72	1.2	0.9	1.4	-0.9									
73	1.3	1.2	1.1	-0.6									
74	0.9	0.7	1.0	0.3	0.7	0.5	-0.1	-0.3	0.1	-0.2	0.6	0.7	-0.5
75	1.0	0.8	1.2	0.7	-0.3	0.1	0.4	0.6	0.6	-0.2	0.2	0.4	0.3
76	1.0	0.7	1.3	1.0									
77	1.3	1.4	1.1	0.1	-0.4	0.6	0.3	1.7	0.2	0.2	0.5	0.2	-1.2
78	1.2	0.1	0.9	0.6	0.9	0.0	0.7	0.8	0.5	-0.3	0.2	0.1	0.1
79	0.5	0.8	1.1	0.3									
80	0.2	1.1	0.8	0.1									
81	1.1	0.2	1.8	-0.3									
82	1.3	0.8	1.4	-0.7									
83	1.0	1.5	1.1	-1.0									
84	0.9	0.8	0.9	0.0	0.0	1.1	0.7	1.5	-0.6	0.1	0.6	0.0	-0.6
85	1.1	1.2	1.8	-0.6									
86	0.4	1.3	0.9	0.1									
87	0.9	1.2	1.0	0.7	-0.2	0.5	0.0	0.7	0.8	0.8	0.7	-0.7	-0.3
88	0.2	0.4	0.8	1.2	0.2	0.2	1.6	0.5	-0.2	-0.1	-0.1	1.9	-2.0
89	1.2	0.3	1.0	0.5									
90	0.9	0.5	1.1	0.2	0.4	0.3	0.6	0.4	0.6	0.3	0.2	0.5	0.0

Body Weight Gain

(g)

022735/98.004

Anim. No.	Day 0 7	7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
250 ppm Female PO													
91	1.8	0.6	0.7	0.4									
92	1.0	1.5	1.4	-0.5									
93	1.3	1.3	0.8	0.1									
94	0.4	0.9	1.5	0.7	0.1	-0.2	0.6	0.4	0.8	-0.3	0.1	0.0	0.1
95	0.7	0.8	1.2	-0.8									
96	1.3	0.8	0.5	0.3	0.7	1.0	-0.5	0.5	0.2	-0.1	0.8	0.2	-0.7
97	0.7	0.9	1.1	-0.4									
98	1.1	0.5	1.3	0.9	-0.3	0.1	1.0	0.8	0.7	-0.2	0.5	0.4	-0.3
99	1.4	0.2	1.2	0.2	0.5	1.3	0.8	0.5	-0.4	0.1	0.8	0.0	0.1
100	0.9	0.9	0.5	0.7	0.1	0.6	0.6	1.1	-0.4	1.8	-1.7	0.8	0.0
101	0.4	1.2	1.6	-0.4	0.6	0.3	1.1	1.0	0.1	-0.1	0.6	-0.6	0.0
102	0.5	1.4	1.2	-0.3	0.3	0.1	0.2	1.1	0.0	0.3	1.0	-0.6	-0.4
103	1.0	0.3	0.7	0.2									
104	1.6	0.3	0.6	0.2									
105	1.2	0.9	1.2	0.7									
106	1.3	0.3	1.2	0.4	0.8	0.1	0.3	0.4	1.4	-0.7	0.5	0.0	0.0
107	2.4	1.1	1.0	-0.5	0.4	0.0	0.9	1.1	-0.3	0.4	1.0	-1.2	-0.7
108	0.5	0.5	1.2	0.8	0.6	0.1	0.7	1.0	0.5	-0.1	-0.2	0.4	-0.2
109	0.9	0.9	1.9	-0.6									
110	0.5	0.7	1.4	0.4									
111	1.3	0.7	0.5	0.2									
112	0.3	0.9	1.2	-0.4	0.9	-0.6	1.8	0.3	0.3	1.3	-0.8	-0.3	-0.3
113	1.5	0.9	0.2	0.1	1.1	0.1	0.6	1.7	0.2	-0.2	0.0	0.0	-0.4
114	0.5	0.6	1.1	0.2									
115	1.4	0.5	1.0	-0.3									
116	0.4	1.0	1.8	-0.7	0.7	0.4	0.8	0.6	-0.1	0.7	-0.5	0.3	-0.4
117	1.2	0.1	0.7	-0.1	1.1	0.2	0.6	0.7	0.6	-0.3	0.1	-0.4	0.5
118	0.6	0.7	1.1	0.3	0.1	0.7	0.4	1.0	0.1	-0.5	0.2	1.7	-0.8
119	-3.1	3.1	1.0	-0.2									
120	0.4	1.1	0.8	0.4									

Body Weight Gain

(g)

022735/98.005

Anim. No.	0 7	7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
2500 ppm Female PO													
121	0.5	1.2	0.6	-0.3	0.8	0.2	0.8	1.2	-0.1	0.0	0.2	0.1	-0.7
122	0.6	0.5	0.9	-0.1									
123	0.5	0.4	1.7	0.0									
124	1.6	0.6	1.2	-0.4									
125	1.0	0.9	1.3	0.0									
126	1.0	0.0	1.6	-0.3	0.9	1.0	0.4	1.2	0.2	0.9	-0.3	-0.9	0.4
127	1.6	0.1	1.1	-0.2	0.9	0.4	0.8	1.6	0.2	-0.6	1.2	-0.6	-1.0
128	0.8	-0.2	0.6	0.0	0.9	0.9	0.8	0.4	0.2	0.8	0.3	-0.2	-0.2
129	1.6	0.3	1.2	-0.2	0.4	0.9	0.5	1.3	0.4	-1.2	1.6	-0.2	-0.4
130	1.6	0.1	1.0	0.0	0.6	0.7	1.3	1.0	-0.6	0.3	0.1	-0.3	-0.6
131	1.6	-0.1	1.1	0.2	1.6	0.5	0.2	0.5	0.8	-0.1	-0.1	-0.1	0.3
132	0.5	0.9	1.4	-0.1									
133	1.1	0.5	0.8	0.0	0.7	0.6	-0.1	1.2	0.1	0.2	-0.3	-0.1	0.0
134	0.7	0.5	1.2	-0.2									
135	1.6	-0.2	1.4	0.1	0.5	0.8	0.7	0.7	0.1	-0.2	1.3	-0.5	-0.8
136	1.7	0.3	1.3	-0.2									
137	0.5	0.8	1.6	-0.6									
138	0.7	0.8	1.6	-0.5									
139	1.2	0.3	1.6	-0.1									
140	1.4	0.3	1.5	-0.3	0.9	0.4	-0.1	1.1	1.2	0.4	2.3	-1.8	0.2
141	1.1	-0.1	1.5	0.5	-0.3	0.8	1.2	0.4	-0.2	0.0	1.1	-0.5	-0.3
142	1.0	0.8	1.5	0.2									
143	0.4	0.6	1.6	0.4	0.7	-0.2	1.0	0.5	0.4	-0.7	1.1	0.2	-0.2
144	1.2	-0.4	1.7	-0.3									
145	-0.1	0.7	1.8	-0.6									
146	1.1	1.1	0.9	-0.4	0.0	1.2	0.4	1.2	0.2	-0.7	1.8	0.4	-1.4
147	1.3	0.4	1.3	-0.1	1.1	0.2	0.6	0.9	0.4	-0.2	0.0	-0.7	0.8
148	0.1	1.2	0.9	0.0	0.4	1.2	0.6	0.8	1.1	-1.2	1.6	-1.3	-0.8
149	1.2	0.2	1.5	-0.3									
150	0.5	1.1	1.8	-0.8									

Body Weight Gain

(g)

022735/98.006

Anim. No.	0 7	7 14	14 21	21 28	28 35	35 42	42 49	49 57	57 63	63 70	70 77	77 84	84 91
+ MECAMYLAMINE 2500 ppm Female PO													
151	0.7	-0.4	2.3	-1.5									
152	1.2	-0.2	1.8	-0.3	0.4	-0.2	0.5	1.8	-0.7	0.6	0.1	-0.2	-0.3
153	0.2	-0.2	1.7	0.6	0.9	0.4	-0.3	0.5	0.8	-0.3	0.8	0.0	0.1
154	1.0	0.1	2.1	-0.1	0.9	-0.1	0.3	0.6	0.7	0.3	-0.5	0.2	0.2
155	0.6	0.2	0.9	0.4	0.9	0.3	0.5	0.4	0.3	0.1	0.3	-0.1	0.5
156	1.2	0.3	1.2	-0.1									
157	0.9	0.1	1.8	0.2	-0.2	-0.2	1.0	0.5	0.2	0.2	1.1	-0.2	-0.3
158	0.9	-0.1	2.5	-1.1									
159	0.2	0.5	1.9	-0.2									
160	0.3	0.3	2.3	0.1	-0.2	0.3	0.9	1.1	-0.5	0.2	0.9	-0.2	0.0
161	1.1	0.2	1.3	0.5	-0.2	0.5	0.5	0.7	0.3	0.9	0.1	-0.6	-0.2
162	0.5	0.7	1.0	0.3	0.6	-0.1	0.4	1.2	0.4	0.7	-0.3	-0.7	0.0
163	1.9	-0.5	1.8	-0.2									
164	1.7	-0.3	1.6	1.4	0.1	-0.4	1.5	1.2	0.2	-0.6	0.6	0.7	-0.7
165	0.6	0.5	1.1	-0.9									
166	0.2	0.3	1.8	-0.4									
167	1.4	-0.6	1.6	-0.2									
168	0.7	0.3	1.4	1.5									
169	0.4	0.7	1.2	0.9	-0.9	-0.1	0.9	1.3	1.2	-0.4	0.6	0.5	-0.8
170	1.7	-0.3	0.8	0.2	1.4	-0.2	0.1	1.4	0.9	-0.4	-0.8	0.3	0.3
171	1.4	0.0	1.3	-0.3									
172	0.7	0.6	0.8	0.6	0.4	0.2	0.6	0.8	0.5	-0.1	0.2	0.2	-0.2
173	1.3	-0.1	1.0	1.0									
174	0.5	-0.8	1.3	1.0	0.2	0.4	0.2	1.3	0.8	-1.0	0.8	0.0	0.1
175	0.4	0.9	1.3	0.2									
176	1.2	-0.2	2.5	-1.0	1.0	0.2	0.3	1.1	0.1	-0.2	0.2	-0.4	-0.1
177	1.1	-0.5	2.1	-0.9									
178	1.6	-0.5	1.9	0.1	0.8	0.2	0.8	0.7	-0.1	0.2	1.1	-1.0	-0.3
179	1.3	-0.6	1.6	0.3									
180	1.3	-0.8	2.1	0.1									

9.9. *Hormone Determinations*

Determination of Estradiol und Progesterone in Murine Plasma

Analytical Report

MKL: 2704
Bayer: T 7061541

Mc Knight Laboratories GmbH

Hamburg, June 29, 1998

Prof. Dr. K. Bührens
(President)

30.6.98

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30/06/98

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1 SYNOPSIS

Protocol approval:	July 03, 1997
Samples receipt:	June 23, 1997
Analytics:	July 9 -16, 1997
Report:	June 29, 1998

The concentrations of estradiol and progesterone were determined in 89 Li-heparin plasma samples. The analyses of both parameters were performed with RIA using ^{125}I-labelled tracers and specific antibodies. The separation of free and bound antigen was carried out by precipitation with a second antibody/PEG reagent.

To save sample material for determination of other parameters in the future the analysis was performed as single determination only. This was agreed by the sponsor. The standards were processed in duplicate.

2 ASSAYS

2.1 ESTRADIOL

Producer:	ICN (USA)
Range of standard curve:	10 - 3000 pg/ml
Sample volume used:	50 µl
Quality Controls:	Lyphochek 60000 in original dilution
Incubation:	90 min/37 °C

2.2 PROGESTERONE

Producer:	ICN (USA) - tracer BFU (CZ) - 1-st Ab (*) MKL - standards and 2-nd Ab
Range of standard curve:	0.2 - 100 ng/ml
Sample volume used:	extract from 50 µl serum
Quality Controls:	Lyphochek 60000 in original dilution
Incubation:	overnight at + 6 °C

(*) In comparison to the antibody used in the original assay, this antibody shows a significantly lower cross-reactivity to some compounds in mouse plasma, resulting in lower concentrations of progesterone when identical standards are used.

3 EQUIPMENT

Instrument	Parameter	Value
Berthold-Gamma-Counter (Multi-Crystal-Counter LB 2104)	time	1 min
	window	16-84 keV LCF-procedure
Evaporator centrifuge UNIVAPO 150 H	temperature	40 °C
Shaker REAX 2 (Heidolph)	min^{-1}	30
Centrifuge: Heraeus Varifuge AH	g	3600

Additionally usual laboratory equipment was used. Before starting the analytical work, variable pipettes were checked with respect to accuracy and precision.

4 METHOD

Estradiol and progesterone were analysed in all samples as single determination.

4.1 SAMPLE TREATMENT

The samples were received frozen on dry ice and were stored at -20 °C immediately after receipt. Immediately before the analysis the samples were thawed in a cold water bath (approx. 10° C) and aliquots were taken for the analyses. The remainder was frozen again.

4.1.1 Estradiol

The assays of estradiol were performed according to the instructions for use as supplied by the producer.

According to the assay manual 50 µl aliquots of each sample were pipetted into 11 x 70 mm plastic tubes. Afterwards, 500 µl of ^{125}I-tracer and 500 µl of first antibody were added to each tube except those for Total and NSB, antibody was omitted here. The assay was incubated at 37 °C for 90 minutes. Afterwards, 500 µl of second antibody were added to each tube and the incubation continued at 22 °C for 30 minutes. After centrifugation and decantation of the supernatant the pellets were counted in a gamma-counter.

4.1.2 Progesterone

Sample aliquots of 50 µl plasma, standards and QCs were pipetted for the extraction into 12*100 mm screw-capped glass tubes. To each tube 250 µl

of saline were added and progesterone was extracted on a „Rotavator" with 4 ml of hexane.

The water phase was frozen and the hexane extracts were decanted in 11*100 mm glass tubes, evaporated to dryness and dissolved in 100 µl of the PBS-gelatine buffer.

200 µl each of the tracer and the antiserum solution in RIA-buffer were added to each sample. The assay was allowed to incubate at 6°C for 16 h. The bound radioactivity was separated using the second antibody method. After centrifugation the pellet was counted in a gamma-counter.

4.2 Standards and Quality Controls

4.2.1 Standards

For estradiol the standards delivered with the kit were used.

Standards for progesterone (extractive assay) were prepared by spiking a 6 % BSA solution with concentrated solutions of progesterone in 50 % methanol.

4.2.2 Quality Controls

Lyphocheck control sera (lot no. 60000) were used as quality control samples for estradiol.

5 REVALIDATION, QUALITY CONTROLS AND ASSAY PARAMETERS

Prior to the start of the analysis the methods were revalidated. The results for the quality control samples are given in the tables below. The range of the Lyphocheck sera as given by the producer is displayed in brackets.

5.1 ESTRADIOL

Calibration Samples - Percentage Binding

Concentration	Sequence	
(pg/ml)	Revalidation	Study
10	89.4	87.3
30	77.2	76.9
100	52.5	53.4
300	25.0	26.4
1000	10.6	11.2
3000	4.5	5.8

QC-Samples - Recalculated Concentrations (pg/ml)

Concentration Range	Sequence	
	Revalidation (n=5)	Study (n=3)
LQC	65.8 ± 2.54	64.5 ± 6.6
[28-64]	[63.6 - 69.1]	[57.8 - 71.0]
MQC	240.7 ± 28.5	223.5 ± 14.7
[156-283]	[196.3 - 270.6]	[206.9 - 234.8]
HQC	714.0 ± 30.8	695 ± 33
[600-988]	[678.2 - 753.8]	[674 - 733]

The LOQ was validated to 10.0 pg/ml by analysis of ten independent samples of this standard in one sequence (mean = 11.72 pg/ml; s.d. = 1.22; CV = 10.4 %; Inaccuracy = + 17.2 %).

5.2 PROGESTERONE

Calibration Samples - Percentage Binding		
Concentration	Sequence	
(ng/ml)	Revalidation	Study
0.5	81.3	83.8
1	72.9	76.7
2	61.0	65.9
5	47.4	49.0
10	37.8	38.1
20	27.8	28.3
50	17.3	18.2
100	10.9	11.9

The LOQ was validated to 0.5 ng/ml by analysis of ten independent extracted samples of this standard in one sequence (mean = 0.586 ng/ml; s.d. = 0.101; CV = 17.2 %; Inaccuracy = + 17.2 %). The standard 0.2 ng/ml has not fulfilled the validation criteria.

QC-Samples - Recalculated Concentrations (ng/ml)		
Concentration	Revalidation (n=5)	Study (n=3)
LQC	1.55 ± 0.12 [1.42 - 1.65]	1.40 ± 0.17 [1.21 - 1.49]
MQC	10.23 ± 0.33 [9.83 - 10.66]	11.80 ± 1.11 [10.92 - 13.05]
HQC	16.17 ± 0.64 [15.29 - 16.74]	18.10 ± 1.76 [16.35 - 19.87]

6 ANALYTICAL RESULTS

Study-No. T 7061541

MKL-No.	Animal-No.	Sampling-Date	Estradiol (pg/ml)	Progesteron (ng/ml)
1	4	05.05.97	35,3	1,24
2	7	-	32,9	1,20
3	8	-	35,0	1,26
4	23	-	34,4	1,23
5	48	-	45,3	1,87
6	56	-	30,8	0,71
7	71	-	39,7	1,89
8	75	-	33,8	1,41
9	90	-	43,6	1,93
10	98	-	34,8	0,98
11	143	-	35,4	1,74
12	147	-	27,0	1,56
13	153	-	30,5	3,03
14	154	no sample	-	-
15	164	-	26,2	2,61
16	172	-	31,4	2,99
17	174	-	31,6	3,82
18	176	-	27,2	3,18
19	94	-	33,1	2,51
20	17	06.05.97	39,8	2,32
21	21	-	36,4	1,24
22	24	-	34,6	0,83
23	26	-	31,5	1,66
24	29	-	35,3	0,90
25	36	-	31,1	1,79
26	51	-	32,8	3,05
27	58	-	31,9	2,63
28	68	-	37,4	1,54
29	69	-	33,0	1,38
30	77	-	42,8	1,57
31	84	-	40,2	2,55
32	96	-	36,3	1,43
33	99	-	34,7	1,32
34	101	-	30,3	1,44
35	102	-	33,4	1,96
36	113	-	31,2	2,50
37	121	-	20,6	1,09
38	128	-	31,3	1,59
39	129	-	28,4	3,99
40	135	-	29.2	1.16
41	141	-	33.9	1.94
42	146	-	34.5	1.17
43	160	-	34.2	1.73
44	178	-	31.5	2.37
45	3	07.05.97	38.4	1.61
46	6	07.05.97	35.0	2.35
47	33	-	34.3	1.53
48	35	-	33.7	1.67
49	37	-	37.6	0.91

Determination of Estradiol und Progesterone in Murine Plasma
BAYER AG, Wuppertal T 7061541

Study-No. T 7061541				
MKL-No.	Animal-No.	Sampling-Date	Estradiol (pg/ml)	Progesteron (ng/ml)
50	41	"	44.1	1.58
51	52	"	44.5	1.54
52	67	"	39.2	1.35
53	74	"	40.5	1.48
54	87	"	40.7	1.10
55	107	"	33.7	1.26
56	112	"	38.6	2.07
57	116	"	25.1	1.30
58	130	"	41.2	3.21
59	133	"	31.7	1.98
60	152	"	28.5	1.67
61	1	09.05.97	32.9	1.18
62	27	"	34.7	1.15
63	140	"	26.8	1.72
64	162	"	25.2	1.78
65	60	"	39.6	0.68
66	65	"	32.0	0.78
67	70	"	34.5	1.21
68	78	"	30.8	1.31
69	100	"	24.9	1.12
70	9	12.05.97	35.7	2.19
71	16	"	36.3	1.77
72	126	"	31.2	2.64
73	131	"	30.6	1.65
74	127	"	25.3	24.72
75	155	"	21.1	1.38
76	169	"	28.2	1.34
77	170	"	26.5	1.29
78	46	"	42.2	1.00
79	53	"	38.1	1.57
80	63	"	38.6	1.09
81	88	"	35.7	0.89
82	106	"	26.4	0.94
83	108	"	38.8	0.25
84	117	"	28.3	15.97
85	118	"	31.3	1.14
86	157	13.05.97	27.3	1.11
87	59	14.05.97	43.6	1.48
88	148	"	38.8	2.89
89	161	16.05.97	26.3	1.11

9.10. Organ Weights

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Absolute Organ Weights
1st Interim Sacrifice

034985/98.001

	Body W.	Brain	Pituitary	Adrenals	Heart	Liver	Spleen	Thymus
	G	mg	mg	mg	mg	mg	mg	mg
0 ppm Female PO								
Mean	22	473	2	8	118	1098	75	42
Med.	22	471	2	8	119	1119	74	42
S.D.	0.7	13.6	1.2	3.2	8.0	70.1	6.3	10.8
Min.	21	448	1	2	100	966	63	25
Max.	23	494	5	13	131	1178	84	63
N	15	15	15	15	15	15	15	15
10 ppm Female PO								
Mean	22	463	2	9	114	1087	78	48
Med.	22	469	2	8	114	1100	77	47
S.D.	1.0	20.1	0.7	3.8	5.9	79.9	9.6	11.7
Min.	20	423	1	4	103	945	64	30
Max.	25	489	3	20	128	1216	99	75
N	14	14	14	14	14	14	14	14
TS 1%	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-
30 ppm Female PO								
Mean	21	468	2	9	116	1058	73	41
Med.	22	467	2	8	115	1061	71	41
S.D.	0.7	17.2	0.8	3.0	6.5	56.2	7.7	6.1
Min.	20	441	1	4	108	898	57	28
Max.	22	505	4	14	129	1130	88	52
N	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-
250 ppm Female PO								
Mean	21	468	2	10	117	1166	72	44
Med.	21	471	2	9	116	1122	72	47
S.D.	1.1	15.4	0.9	2.8	8.8	161.7	6.2	8.5
Min.	20	435	1	3	106	1014	61	28
Max.	24	486	5	13	134	1700	83	58
N	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-
2500 ppm Female PO								
Mean	21	463	2	8	120	1426	73	45
Med.	21	464	2	8	119	1469	74	45
S.D.	0.7	17.5	0.6	2.2	12.5	147.2	7.7	7.1
Min.	20	433	1	5	103	1193	57	35
Max.	23	508	3	12	142	1789	87	61
N	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	++	-	-
TS 5%	-	-	-	-	-	+	-	-

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Absolute Organ Weights
1st Interim Sacrifice

034985/98.002

	Body W.	Brain	Pituitary	Adrenals	Heart	Liver	Spleen	Thymus
	G	mg	mg	mg	mg	mg	mg	mg
+ MECAMYLAMINE 2500 ppm Female PO								
Mean	21	462	2	10	115	1306	71	43
Med.	21	464	2	10	116	1331	72	40
S.D.	1.3	15.1	0.6	2.7	7.3	130.6	8.6	8.4
Min.	18	433	1	5	99	1089	53	27
Max.	24	481	3	16	125	1493	85	64
N	15	15	15	15	15	15	15	15
TS 1%	-	-	-	-	-	++	-	-
TS 5%	+	-	-	-	-	+	-	-

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Absolute Organ Weights
1st Interim Sacrifice

034985/98.003

	Kidneys	Ovaries	Uterus
	mg	mg	mg
0 ppm Female PO			
Mean	339	23	240
Med.	345	24	230
S.D.	17.3	5.5	58.0
Min.	306	16	147
Max.	362	32	375
N	15	15	15
10 ppm Female PO			
Mean	338	24	278
Med.	340	21	274
S.D.	20.3	10.6	80.3
Min.	303	11	136
Max.	369	41	428
N	14	14	14
TS 1%	-	-	-
TS 5%	-	-	-
30 ppm Female PO			
Mean	326	19	245
Med.	325	19	256
S.D.	18.1	5.2	67.8
Min.	296	9	148
Max.	377	28	365
N	15	15	15
TS 1%	-	-	-
TS 5%	-	-	-
250 ppm Female PO			
Mean	330	27	257
Med.	328	25	236
S.D.	24.2	13.2	78.6
Min.	290	6	138
Max.	370	49	374
N	15	15	15
TS 1%	-	-	-
TS 5%	-	-	-
2500 ppm Female PO			
Mean	321	22	250
Med.	326	21	245
S.D.	18.5	5.2	47.5
Min.	295	13	146
Max.	346	31	320
N	15	15	15
TS 1%	-	-	-
TS 5%	-	-	-

Study No. T7061541
SUBCHRTOX

YRC2894
B6C3F1 MICE

Absolute Organ Weights
1st Interim Sacrifice

034985/98.004

	Kidneys	Ovaries	Uterus
	mg	mg	mg
+ MECAMYLAMINE 2500 ppm Female PO			
Mean	319	24	222
Med.	316	26	216
S.D.	26.5	7.6	82.5
Min.	263	8	110
Max.	358	33	404
N	15	15	15
TS 1%	-	-	-
TS 5%	+	-	-