6-22-94

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 22 1994

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

6(a)2

MEMORANDUM

SUBJECT: EPA ID# 069001. Pyrethrins: Review of a series 82-4 subchronic (3-month) inhalation toxicity study in rats.

TOX CHEM No.: 715
PC No.: 069001
Barcode No.: D182966
Submission No.: S426040

FROM: John Doherty 6/15/94
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Bruce Sidwell/Alan Dixon KB 6/21/94
Product Manager #53
Special Review and Reregistration Division
(7508W)

THROUGH: Marion Copley, DVM, Section Head 6/21/94
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSION

The series 82-4 three month inhalation toxicity study with pyrethrin extract (MRID No.: 424782-01, Bio/Dynamics, September 14, 1992) was reviewed and classified as CORE MINIMUM. The NOEL and LEL for systemic effects was established as 0.03 and 0.1 mg/l based primarily on decreases in body weight gains in both sexes.

The study did not establish a NOEL for pathological changes in the respiratory tract as indicated by the presence of hyperplasia, metaplasia and hypertrophy in the mucosal seromucous glands of the larynx or pharynx. The need for an additional

onic inhalation toxicity study or a series 83-2
udy via the inhalation route of exposure have
the HED Science Analysis Branch. They have
to evaluate the findings of this study with
ict as well as other related information in order
n HED policy for inhalation toxicity studies not
particularly for hyperplastic, hypertrophy and/or
metal. esponses in the respiratory tract due to treatment.

6(a)2 status. No immediate regulatory action is required at this time. Regulatory action may be required pending the results of Science Analysis Branch's response to HED's referrals.

II. Action Requested

The Chemical Specialties Manufacturers Association (CSMA) on behalf of the Pyrethrin Joint Venture has submitted a series 82-4 three month inhalation toxicity study with pyrethrin extract as part of the data requirements for reregistration for pyrethrins (refer to letter from Ralph Engel dated September 16, 1992). This study was reviewed by the Clement International Corporation under contract to HED. A copy of the DER is attached. The study is identified under item IV below. The following comments apply.

III. Toxicology Branch Comments

1. The study was classified as CORE MINIMUM. The MINIMUM classification relates to the fact that although the study established a NOEL and LEL for systemic toxicity, no NOEL was established for responses in the respiratory tract. HED is currently trying to work out policy for such cases (see below).

A copy of the DER is attached.

2. The study did not establish a NOEL for pathological changes in the larynx as indicated by the presence of hyperplasia, metaplasia and/or hypertrophy in both sexes and in goblet cell hyperplasia of the nasopharynx. The data presented indicate that nearly all of the low dose treated animals have hyperplasia which was rarely reported in the controls. In particular, the following lesions in the larynx were noted in the low dose group (data for females only are illustrated, males were similar refer to the DER):

Lesion	Dose level mg/l: Control	2.2%	2.4	2.12	2.4
Larynx:					
-mucosa:seromucosal glands					
-hypertrophy/hyperplasia					
-ventral diverticulum	0/15	3/14(1.0)	4/14(1.5)	7/13(2.0)	6/13(1.7)
-ventral seromucous glands	0/15	12/13(2.0)	11/11(2.3)	9/10(2.4)	15/15(2.8)
-mucosa:pseudostratified ciliated/nonciliated cuboidal epithelium					
-squamous/squamoid metaplasia, hyperplasia-					
-ventral diverticulum	0/15	1/14(3.0)	2/14(2.0)	5/13(2.4)	13/13(2.2)
-ventral seromucosa glands	0/15	13/13(1.8)	11/11(2.5)	10/10(2.8)	15/15(2.9)

Data are incidence/number of examined mean score (= severity).

In males the incidence of "goblet cell hyperplasia" in the nasopharynx" was 12/15 (80%) in the low dose group versus only 7/15 (47%) in the control and the three higher dose levels were 86% to 100% affected.

3. As per discussion with Dr. Lucas Brennecke, hyperplasia is a common response in the mucosal glands in the larynx/pharynx to a aerosol that is an irritant. It is noted, however, that based on the acute toxicity studies, pyrethrum extract is not considered a dermal irritant.

The progression of the hyperplasia may but not definitely lead to neoplasia. Thus, TB-I is concerned with policy issues related to increases in hyperplasia especially when such as in this study with pyrethrum extract the LEL is not established.

This problem will be referred to the HED Science Analysis Branch (refer to memo from John Doherty to William Burnam dated May 16, 1994) for further discussion and evaluation. The issues presented were:

i. The need for a repeat series 82-4 subchronic inhalation toxicity study to establish the NOEL and LEL for hyperplasia and other lesions of the respiratory tract noted in the first study.

ii. The need for a series 83-2 carcinogenicity study via the inhalation route.

iii. How to use the endpoint of local toxicity of the

respiratory tract for regulatory purposes.

It is expected that resolution of these issues by the HED policy group will require up to six months.

4. The DER prepared by the contractor considered the statistically significant increases in brain (8.6% and 13.1% in females), kidney (9.9% and 14.2% in females and 11.9% in males) and lungs (18.4% in females and 12.2% in males) to body weight ratios (for the 0.1 or 0.35 mg/l dose groups respectively) to be related to the decreases in body weight rather than direct effects of the pyrethrum extract on these organs. TB-I notes that relatively small decreases in body weight were noted (i.e. 7.4 and 10.8% for females and 4.8 and 5.5% for males in the 0.1 and 0.35 dose groups for males and females respectively). In this regard, direct effects of pyrethrum extract exposure by the inhalation route cannot be ruled out. Moreover, in other studies such disproportionate increases in the organ to body weight ratio are not always seen when there are only minor decreases n body weight. Since no pathological changes were noted in the these organs, TB-I's interpretation that there may be direct effect on these organs remains only a possibility for further consideration. Since the NOEL and LEL are already covered by other toxicity endpoints, the speculation on the significance of these organ weight changes will not affect potential regulatory aspects of this study.

5. Note: The Clements reviewer classified the study as SUPPLEMENTARY. TB-I, however, has reclassified this study as MINIMUM because the study demonstrated a NOEL and LEL for systemic effects. The limiting factor for this study which precludes a higher classification is that the study did not establish a NOEL for effects in the respiratory tract but HED needs to establish policy for this situation (refer to item 3 above.

6. TB-I previously addressed the preliminary results of this study (refer to memo dated September 22, 1992 from J. Doherty to R. Mountfort and R. Brennis, Pm Team #10 under EPA ID# 004713-00001).

IV. Studies Reviewed

Study Identification	Material	MRID No.:	Results	Classification
82-4. Subchronic (3-month) inhalation study - rats Bio/Dynamics, Study No.: 91-2535, September 14, 1992	Pyrethrum extract, lot #s3910 and 344 purity 57.57%	424782-01 (2-volumes)	LEL (respiratory system effects) < 0.03 mg/l. hypertrophy/hyperplasia of mucosal seromucous glands and pseudostratified ciliated/ non-ciliated columnar epithelium-squamous/squamoid metaplasia/ hyperplasia and epithelial hyperkeratosis of the larynx (both sexes) and goblet cell hyperplasia in the nasopharynx and nasoturbinates (males). At 0.35 mg/l: chronic inflammation and squamous cell hyperkeratosis/ hypertrophy of the nasoturbinates (males and females) and goblet cell hyperplasia of the nasopharynx (females). NOEL and LEL (systemic) = 0.03 and 0.1 mg/l. At 0.1 mg/l: decrease in body weight gain (both sexes); and tremor (females). At 0.35 mg/l: one death (male); tremors and labored breathing (both sexes, early weeks of study); increase liver body weight ratios (males and females); decrease in RBC parameters (hemoglobin, hematocrit and erythrocytes, to about 5%, males and females). Note: Increases in brain, kidney and lung weight at 0.10 or 0.35 mg/l noted but considered related to decrease in body weight in DER but other interpretations are possible.. Sprague-Dawley strain rat. Dose levels tested 0, 0.01, 0.03, 0.1 or 0.35 mg/l 5 d/week, 6 hrs/day for 13 weeks	MINIMUM

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DATA EVALUATION REPORT

Pyrethrum

Study Type:
Subchronic Inhalation Toxicity in Rats

Study Title:
A Subchronic (3-Month) Inhalation Toxicity Study of Pyrethrum Extract in the Rat Via Whole-Body Exposures

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

December 7, 1993

Principal Reviewer — Jay Meeks, B.S. — Date 12/7/93

Independent Reviewer — John Liccione, Ph.D. — Date 12/7/93

QA/QC Manager — Sharon Segal, Ph.D. — Date 12/7/93

Contract Number: 68D10075
Work Assignment Number: 2-35
Clement Number: 118
Project Officer: Caroline C. Gordon

[Guideline Series 82-6: Subchronic Inhalation Toxicity in Rats]

EPA Reviewer: John Bedden, M
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: [signature]
Date: 6/10/94

EPA Section [illegible] Marion Copley, D V M.
Review [illegible] I, Toxicology Branch I.
Health [illegible] Division

Signature: [signature]
Date: 6/10/94

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DATA EVALUATION REPORT

STUDY TYPE: Subchronic inhalation toxicity in rats

TEST MATERIAL: Pyrethrum Extract

P C Code: 069001

MRID Number: 424782-01

Tox Chem Number: 715

SYNONYMS: Pyrethrum

STUDY NUMBER: 91-8335

SPONSOR: Pyrethrin Joint Venture/Chemical Specialties Manufacturers Association, 1913 Eye Street, N.W., Washington, DC 20006

TESTING FACILITY: Bio/dynamics, Inc., Mettlers Road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: A Subchronic (3-Month), Inhalation Toxicity Study of Pyrethrum Extract in the Rat Via Whole-Body Exposures

AUTHOR: Paul E. Newton

REPORT ISSUED: September 14, 1992

CONCLUSIONS:

LEL (respiratory system effects, < 0.01 mg/L. Hypertrophy/hyperplasia of mucosal seromucous glands and pseudostratified ciliated/nonciliated columnar epithelium-squamous/squamoid metaplasia/hyperplasia of the mucosa and epithelial hyperkeratosis of the larynx (both sexes). Goblet cell hyperplasia in the nasopharynx and nasoturbinates (males) and epithelial intracytoplasmic eosinophilic material in the nasoturbinates. At 0.35 mg/L, chronic inflammation and squamous cell hyperplasia of the nasoturbinates (males and females) and goblet cell hyperplasia of the nasopharynx (females).

NOEL and LEL (systemic) = 0.03 and 0.1 mg/L. At 0.1 mg/L, decrease in body weight gain (both sexes) and tremors (females). At 0.35 mg/L, one death (male), tremors and labored breathing (both sexes, early weeks of

study, increase in liver weight males and females, and decrease in RBC parameters hemoglobin, hematocrit, and erythrocytes to about -5% in males and females.

Sprague-Dawley strain rat. Dose levels tested 0, 0.01, 0.03, 0.1 or 0.35 mg/L 5 days/week, 6 hours/day for 13 weeks

MINIMUM MR 6/10/94

CORE CLASSIFICATION: [redacted]. The study as presented did not establish a NOEL for hyperplasia in the larynx, nasoturbinates, and nasopharynx. The data indicate that nearly all the low dose treated animals may have hyperplasia which is not reported in controls. Hyperplasia is considered a more serious lesion and a NOEL or at least a minimal response at the LOEL should be established. [redacted]

At this time the requirement for a 82-4 study is satisfied

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Pyrethrum extract pyrethrins CAS #8003-34-7); and isoparaffinic petroleum solvent (CAS # 64742-47-8). A mixture prepared at Fairfield America Corporation of equal parts of three production runs:

Lot numbers: #3910 (supplied by McLaughlin Gormley King Co. #3944 supplied by Pyrethrum Board of Kenya. No lot number was provided for the third mixture that was supplied by Office du Pyrethria Rwanda.

Purity: 51.4% raw active ingredient inert ingredients not provided

Physical property: Dark viscous liquid

Stability: Reported by the sponsor to be stable

Storage: Frozen (<25°F), in the dark

2. Test Article Analyses and Stability

No information was provided by the sponsor regarding analysis for stability. The test substance was heated prior to aerosolization to decrease viscosity.

3. Exposure Conditions

Individually penned animals from wire mesh cages were exposed to the test material 6 hours/day, 5 days/week for 13 weeks, in a whole body exposure chamber (1000-liter glass volume).

Exposure atmospheres were generated by injecting room air or 0.01, 0.03, 0.1, or 0.35 mg/L of pyrethrum extract into an atomizer. The high exposure concentration was selected as 1/10 of the LC_{50} value of 3.4 mg/L determined from an acute inhalation study. The flow rate for animals exposed at 0.01 was 1.32 mL/hr. The flow rate for the remaining groups ranged from 0.4 to 1.35 mL/min. The flow rate was regulated by an FMI pump. The aerosols were generated into a PVC expansion chamber and then directed into the exposure chamber.

The concentrations of test material in the test atmospheres were determined gravimetrically and analytically by liquid chromatography. Air samples were filtered from the breathing zone of the chamber every 30 minutes for gravimetric determinations. Gravimetric concentrations were calculated by dividing the milligram weight difference of the test material by the total volume of air sampled. Analytical exposure concentrations were calculated by dividing the test substance weight (in milligrams) by the total volume of air sampled. Sample analysis for analytical determinations was performed once per exposure; however, four samples per exposure were analyzed for 16 days because of discrepancies between the gravimetric and analytical exposure values. The nominal concentrations were calculated by dividing the total amount of pyrethrum extract injected into the atomizer by the total air flow through the chamber. The daily aerosol exposure concentrations are presented in Table 1.

The number of air changes per hour in the exposure chamber ranged from 12 to 13. The airflow rate of the exposure chamber ranged from 201 to 215 L per minute. Although oxygen content was not measured the air flow rate should have been sufficient to maintain adequate oxygen levels. Temperature and relative humidity were recorded approximately every 30 minutes during exposure. The temperature of the exposure chamber ranged from 19°C to 28°C, while the mean relative humidity ranged from 21% to 35%. The weekly temperature and humidity means with standard deviations are presented in Table 1. The occasional daily deviations from the Guideline ranges are considered to be minor.

Particle size distribution was determined once daily per exposure for each concentration using a TSI Aerodynamic Particle Sizer. Particle size distribution measurements are presented in Table 1. The mass median aerodynamic diameter of the aerosol particles for all exposure groups ranged from 2.4 to 3.3 µm indicating that particles were in the respirable range. The geometric standard deviation was 1.7 µm. The percentage of particles that were ≤10 µm ranged from 98.0% to 100.0%, while the percentage of particles ≤1.0 ranged from 1.4% to 4.6%.

Animals

Six-week-old CD-Crl: (CD) BR Sprague-Dawley rats were received from Charles River Breeding Laboratories, Inc. (Kingston, New York)

2 weeks prior to the first exposure. Following acclimation, 75 males (257-313 g) and 75 females (187-219 g) were randomly assigned to study groups (5 groups, 15 rats/sex/group) via a computer-generated randomization procedure such that body weight means of each group were comparable.

Group	Target Concentration (mg/L)	Number of Animals (males)	(females)
Air control	0	15	15
Low dose	0.01	15	15
Mid dose 1	0.03	15	15
Mid dose 2	0.10	15	15
High dose	0.35	15	15

Rats were caged in pairs segregated by sex and study group in suspended wire mesh cages during the first week of the quarantine period and individually thereafter. The nonexposure temperature and relative humidity (measured twice per day) ranged from 17°C to 24°C and from 4% to 32%, respectively. A 12-hour light/dark cycle was maintained. Purina Mills Rodent Laboratory Chow #5002 and water were provided ad libitum during the nonexposure period.

5. Statistical Analyses

Body weight, food consumption, hematology, clinical chemistry, organ weights, organ-to-body-weight ratio, and organ-to-brain-weight ratios were analyzed for statistically significant differences from control values. One-way analysis of variance was used to determine significant differences among mean values. Bartlett's test was performed to determine equal variance among groups. If significance was noted, Dunnett's test was used to determine statistical significance from control values. If variances were not equal, nonparametric procedures (Kruskal-Wallis) were performed. Differences among control values were determined by a summed rank test (Dunn). A Jonckheere's test for dose-trend significances was also performed.

6. Observations

a. Mortality/moribundity/survival

Animals were observed twice daily for mortality/moribundity. Two high-concentration animals died during the study. One female died on day 3 accidentally and was replaced. The second death that occurred in a male rat on day 15 may have been the result of test material exposure since labored breathing was noted prior to death.

b. Clinical observations

Animals were initially observed every week for adverse clinical signs; however, beginning on day 28, animals were observed daily (as a group) in the exposure chamber. These in-chamber observations were performed because adverse signs of toxicity were noted at weekly examinations.

Selected in-life clinical observations at weeks 1, 3, 5, 7, 9, 11, and 13 are presented in Table 2. Clinical observations noted in all groups included secretory signs such as dried red nasal discharge, mucoid nasal discharge, and dried red material on the face. The number of animals displaying these observations began to increase after week 3 and persisted in most animals until study termination. Other clinical observations noted predominantly in the animals exposed to the two highest concentrations (0.1 and 0.35 mg/L) included matted hair coats, and dried yellow material on the face. Labored breathing was observed in six male rats in the high-concentration group (0.35 mg/L) at week 1 and persisted in one rat until study termination. Tremors were observed in 2/15 females in the high-exposure group at week 1; however, these signs were reversible by week 3. One male in the high-exposure group displayed tremors at week 5 which persisted until week 13. The one male that died in the high-exposure group displayed labored breathing until death on day 15. This death was considered to be treatment related.

In-chamber clinical observations were similar to the in-life observations and included secretory signs, labored respiration, tremors, hyperactivity, and matted coat, which were predominantly seen in the high-concentration animals. No abnormalities were noted in the low-concentration animals.

c. Body weights/food consumption

Body weights--All animals were weighed three times pretest, and weekly during exposure and at termination.

Mean body weights at selected intervals are presented in Table 3A, while mean body weight gains are presented in Table 3B. There were no statistically significant differences in the body weights of the treated males when compared to those of controls. At week 13, there was a 4.7% decrease in mean body weights for males of the 0.1 and 0.35 mg/L exposure groups when compared to the mean body weights of the control animals. In the females exposed to 0.1 or 0.35 mg/L, statistically significant body weight reductions were noted as early as week 3 and persisted until week 13. At week 13, mean body weight reductions were 5.6% and 8.9% in the females exposed to 0.1 and 0.35 mg/L, respectively, when compared to that of the controls. Additionally, mean body weight gains after 13 weeks of exposure were reduced by 13% and 17% in the females exposed to 0.1 and

0.35 mg/L, respectively, when compared to the concurrent controls. No other significant body weight reductions were observed.

Significant decreases in mean body weight gains (from week 0) were noted at week 1 among the males exposed to 0.1 (19%) and 0.35 mg/L (17%) when compared to the controls. Body weight gains (weeks 0-3) were decreased 17% among the males exposed to 0.1 mg/L when compared to the controls. Significant body weight changes were noted in the females exposed to 0.1 and 0.35 mg/L at weeks 3, 5, 7, 11, and/or 13 (13-19%) when compared to the controls.

Food consumption--Food consumption was measured every week beginning 1 week prior to test material exposure. Although there was an approximate 10% decrease in food consumption among the males exposed to 0.1 or 0.35 mg/L compared to controls during week 1, there were no significant food consumption reductions that could be attributed to test material exposure.

(d) Ophthalmoscopic examination

Ophthalmoscopic examinations were performed prior to exposure and prior to sacrifice by a veterinarian. No ocular abnormalities were noted that could be attributed to test material exposure.

7. Clinical Pathology

Hematology and blood chemistry analyses were performed on all animals at study termination. Blood samples were taken from fasted rats from the orbital sinus. The parameters checked in below were examined.

(a) Hematology

(X) Hematocrit (HCT)*
(X) Hemoglobin (HGB)*
(X) Leukocyte count (WBC)*
(X) Erythrocyte count (RBC)*
(X) Erythrocyte morphology
(X) Platelet count*
(X) Reticulocyte count (RETIC)
(X) Leukocyte differential count*
(X) Mean corpuscular HGB (MCH)
(X) Mean corpuscular HGB concentration (MCHC)
(X) Mean corpuscular volume (MCV)
(X) Activated prothrombin time (APT)
(X) Activated partial thromboplastin time (APTT)

* Recommended by Subdivision F (November 1984) Guidelines

Selected hematology parameters are presented in Table 4. Decreases in several parameters indicative of anemia were observed in the pyrethrum-treated male and female rats at the three highest concentration levels. These included statistically significant decreases in hemoglobin and hematocrit levels at 0.03 and 0.35 mg/L.

and in PLT count at 0.03, 0.1, and 0.35 mg/L for the males and decreases in hemoglobin and hematocrit in females at 0.35 mg/L. The slight decreases (<5%) in RBC parameters at exposure levels below 0.35 mg/L in males do not demonstrate a true dose response and are not considered to be a toxicologically meaningful effect of the test chemical. The LEL for effects on the RBC parameters is set at 0.35 mg/L because both sexes are decreased. However, the effect is considered to be a marginal effect. An increase in white blood cell count was also noted in the high-exposure females only when compared to controls.

(b) Blood (clinical) chemistry

Electrolytes
(X) Calcium*
(X) Chloride*
(X) Phosphorus*
(X) Potassium*
(X) Sodium*

Enzymes

(X) Alkaline phosphatase (ALP)
(X) Serum aspartate aminotransferase*
(X) Serum alanine aminotransferase*

Other

(X) Albumin*
(X) Albumin/globulin ratio
(X) Blood creatine*
(X) Blood urea nitrogen*
Cholesterol
(X) Globulin
(X) Glucose*
(X) Total bilirubin*
(X) Total protein*
Triglycerides
Lactic acid dehydrogenase

* = Recommended by Subdivision F (November 1984) Guidelines

Selected clinical chemistry parameters are presented in Table I. Statistically significant differences in serum glutamic pyruvic transaminase, creatinine, glucose, total protein, globulin, and albumin/globulin ratio were noted predominantly in the high-exposure group. Statistically significant decreases in the serum glutamic pyruvic transaminase levels were noted in the females exposed to 0.1 and 0.35 mg/L (28% and 21%, respectively when compared to the controls. Decreases in SGPT [illegible] not recognized

as being toxicologically significant. Because there is not a dose response, the effects on this enzyme are not considered to be related to the test compound. Additionally, there was a 22% reduction in the glucose levels of the high-exposure (0.35 mg/L) animals when compared to the concurrent controls. The changes in clinical chemistry parameters in the high dose group were not consistent between males and females, nor of sufficient magnitude or direction to conclude that they were toxic responses to the test material.

8. Sacrifice and Pathology

Following the collection of blood samples, all of the animals were sacrificed via exsanguination under carbon dioxide anesthesia and subjected to gross necropsy. Animals that died during the study prior to termination were also necropsied. Tissue samples for all animals were retained in 10% buffered formalin (the eyes, testes, and epididymides were preserved in Bouin's solution for the first 48-72 hours). Histological examinations were performed on all animals in the control and high-exposure group for those organs checked (X) below. The larynx, nasopharyngeal tissues, lungs, and any gross lesions were examined histopathologically in animals of all groups. The larynx was divided into two parts for analyses: the ventral diverticulum and the ventral seromucous glands at the base of the epiglottis. The nasoturbinates were divided into five sections for analyses. The first section included the area between the upper incisor tooth and the incisive papilla, the second included the area between the incisive papilla and the first palatal ridge, the third included the area between the second palatal ridge and the first upper molar, the fourth included the area between the first upper molar and the nasopharynx, and the fifth section included the nasopharynx. Weights were recorded for those organs double-checked (XX) below. Paired organs were weighed individually. Histopathology was not performed on musculature and oviducts. This is a minor deviation.

Digestive System

X Salivary glands*
X Esophagus*
X Stomach*
X Duodenum*
X Jejunum*
X Ileum*
X Cecum*
X Colon*
X Rectum*
XX Liver*
X Pancreas*

Respiratory

X Trachea*
XX Lung*
X Larynx
X Nasopharyngeal tissue*

Cardiovascular/Hematologic

X Aorta*
X Heart*
X Bone marrow*
X Lymph nodes*
X Spleen*
Thymus*

Urogenital

XX Kidneys*
X Urinary bladder*
XX Testes*
XX Epididymides
XX Ovaries
X Uterus*
Prostate
Seminal vesicles

Neurologic

XX Brain*
X Peripheral nerve*
Spinal cord (cervical, thoracic, lumbar)
Pituitary*
Eyes (optic nerve*)

Glandular

XX Adrenals*
X Mammary gland*
X Thyroids*
X Parathyroids*
Lacrimal gland

Other

X Skin
X Any gross lesions*
X Bone (sternum with marrow and rib*)

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic

Selected necropsy findings are presented in Table 6. Discolored, matted, or moist hair coat were noted in the high-exposure males and females. Additionally discoloration of the lungs was seen in males of all exposure groups, but this finding was more pronounced in males (10/15 animals) exposed to the highest concentration of test material. No other treatment-related lesions were noted.

(b) Organ weights

Mean absolute liver weights (data not presented, of the females exposed at 0.35 mg/L were significantly increased (7%, over the concurrent control mean absolute liver weights. All other absolute organ weights were comparable among groups.

Table 7 summarizes data on selected organ-to-body-weight ratios. Statistically significant kidney-, liver-, and lung-to-body-weight increases (11-15%, were noted among the male animals exposed to 0.35 mg/L. Brain-, kidney-, liver-, and lung-to-body weight values were significantly increased among the females exposed at 0.1 and/or 0.35 mg/L when compared to the control values. With the exception of the effects on liver weight changes in the organ-to-body weight ratios for the kidney, lung,

and brain were considered to reflect decreases in terminal body weight rather than a toxic effect of the test material. This conclusion is supported by the absence of an effect on the organ-to-brain weight data for these organs.

c. Microscopic examination

Tables 3a and 3b present microscopic findings of selected tissues. Microscopic findings suggestive of exposure-related irritation were observed in the larynx, nasoturbinates, and nasopharynx from all groups. The incidence and severity of findings in these organs were greater with increasing exposure concentrations.

Microscopic abnormalities noted in the larynx included hypertrophy/hyperplasia of the mucosal seromucous glands, squamous metaplasia/hyperplasia of the pseudostratified ciliated and nonciliated columnar epithelium, metaplastic epithelial hyperkeratosis, and hypertrophy and hyperplasia of the nonkeratinized stratified squamous epithelium. Many of these effects were increased at the lowest concentration tested (0.01 mg/L). Both incidence and severity increased with dose.

Subchronic/acute inflammation and squamous cell hyperplasia/hyperkeratosis in the vestibular region of the nasoturbinates were observed predominantly in the animals exposed to the highest concentration (0.35 mg/L). Goblet cell hyperplasia was also noted in all groups but was more pronounced in the animals exposed to the highest concentration with severity grades of 3 occurring predominantly in the animals exposed to concentrations of 0.1 and 0.35 mg/L. Goblet cell hyperplasia in the epithelial lining of the nasopharynx was more pronounced in the high-concentration animals. Epithelial intracytoplasmic eosinophilic material was observed in all treated groups in a dose-related manner.

Microscopic analyses also showed exposure-related effects in the lung in the 0.35 mg/L group of both males and females. These effects were epithelial hypertrophy and hyperplasia of the terminal bronchioles which occurred in 9 males and 5 females, and congestion and edema which were seen in 3 males. Although subacute/chronic pulmonary inflammation and alveolar/intraalveolar macrophages were observed in both controls and treated animals, the severity was increased in the animals exposed to the highest concentration.

3 QUALITY ASSURANCE

A signed Good Laboratory Compliance Statement, a signed Quality Assurance Statement, and a list of Quality Assurance Inspections were included.

DISCUSSION

The overall design and conduct of the study were adequate. There were a few minor deviations from Guideline requirements (minor deviations outside the Guideline recommendations for temperature and humidity; stability data were not presented; no histopathology was performed on skeletal muscle or the oviducts), but none that would comprise the acceptance of this study as Core Guideline.

Treatment-related clinical observations noted in the animals exposed to concentrations of 0.03, 0.1, and 0.35 mg/L included dried yellow material surrounding the face and labored respiration. With the exception of one male animal (0.35 mg/L) displaying labored breathing until study termination, the treatment-related clinical observations noted were reversible. Tremors were also seen in the high-exposure animals (9 females, 1 males); however they were reversible in the females and persisted in one male. One male rat exposed to 0.35 mg/L of the material died on day 15. This animal displayed labored respiration prior to death which may have been a result of test material exposure.

Microscopic abnormalities were noted in respiratory tissues. At the lowest concentration, effects observed included hypertrophy/hyperplasia of the seromucous glands, squamous/squamoid metaplasia/hyperplasia of the pseudostratified ciliated/nonciliated columnar epithelium, and epithelial keratosis in the mucosa of the larynx of both sexes; goblet cell hyperplasia in the epithelial mucosa of the nasopharynx in males; and goblet cell hyperplasia and intracytoplasmic eosinophilic material in the nasoturbinates of both sexes. At higher concentrations, goblet cell hyperplasia in the epithelial mucosa of the nasopharynx of females, hyperplasia and hyperkeratosis in the nonkeratinized stratified squamous epithelium of the larynx in both males and females, subacute/chronic inflammation and squamous cell hyperplasia in the nasoturbinates of both males and females, hypertrophy/hyperplasia in the epithelium of the terminal bronchioles of the lungs in both males and females, edema and congestion in the lungs of males, and increased severity of subacute/chronic inflammation and alveolar/intraalveolar macrophages in the lungs of both males and females were observed.

In addition to the respiratory effects slight but significant decreases in hemoglobin and hematocrit levels in the males and females exposed to 0.35 mg/L and decreases in RBC in males at 0.35 mg/L were suggestive of anemia.

Body weights were reduced (when compared to controls) in the males exposed to 0.35 mg/L of the test material. Statistically significant body weight reductions were noted in the females exposed to 0.1 and 0.35 mg/L of the test material at week 3 that persisted until week 13. These changes were reflected in decreases in body weight gains of both males and females at 0.1 mg/L and above. Increases in the liver weight and liver-to-body weight ratios were observed for both males and females at 0.35 mg/L.

Based on in the decreases in body weight gain in male and females and tremors in females exposed to 0.1 mg/L, the LOEL for systemic toxicity is considered to be 0.1 mg/L. The NOEL for systemic toxicity is 0.03 mg/L. Based on microscopic findings noted in the larynx and nasopharynx, the LOEL for respiratory toxicity is considered to be <0.01 mg/L for male and female rats. A NOEL for respiratory toxicity was not determined.

MINIMUM

This study is classified as [redacted] because of the failure of the study to establish a NOEL or less serious LOEL for respiratory toxicity. Hyperplasia (observed at the lowest concentration tested) is considered to be a more serious lesion. [redacted]

MC 6/10/94

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TABLE 1. Characteristics of Exposure Atmospheres for a 13-Week Study with Pyrethrum Extract in Sprague-Dawley Rats[a]

	Air Control	Target Concentration			
		0.01 mg/L	0.03 mg/L	0.1 mg/L	0.35 mg/L
Gravimetric Concentration (mg/L)[b]	0.0	0.009±0.002	0.026±0.003	0.089±0.018	0.316±0.041
Analytical Concentration (mg/L)[b]	0.0	0.011±0.002	0.030±0.005	0.100±0.022	0.356±0.061
Nominal Concentration (mg/L)[b]	N/A	0.038±0.00?	0.068±0.038	0.230±0.090	0.827±0.421
Median Particle Size (microns)[b]	N/A	2.4±0.2	2.4±0.3	2.3±0.2	3.3±0.2
Geometric Standard Deviation (μm)	N/A	1.7	1.7	1.7	1.7
Average % of Particles ≤1.0 μm[b,c]	N/A	4.6±3.7	4.4±1.4	2.0±0.9	1.4±1.1
Average % of Particles ≤10.0 μm[b,c]	N/A	100.0±1.0	10 .0±3.0	99.0±1.0	98.0±1.0
Mean Chamber Temperature (°C)[b]	24.0±1.0	24.0±2.0	24.0±2.0	24.0±1.0	24.0±2.0
Mean Relative Humidity (%)[b]	47.0±11.0	48.0±10.0	50 ±11.0	53.0±15.0	53.0±12.0

[a]Data extracted from study no. 91-8335, Appendix B, pp. 67-83
[b]Mean ± standard deviation
[c]Mean median particle size of 2.7 calculated by the reviewers (average of median particle sizes for the four exposure levels)
N/A = Not applicable

Table 2. Selected In-Life Clinical Observations at Alternating Intervals from Rats Exposed to Pyrethrum Extract-Containing Atmosphere[a]

Observation	Group	Incidence of Clinical Observations at Study Week						
		1	3	5	7	9	11	13
				Males[b]				
Tremors								
	Air Control	0/15	0/15	0/15	0/15	0/15	1/15	0/15
	0.01 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.03 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.10 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.35 mg/L	0/15	0/15	1/14	1/14	1/14	1/14	1/14
Labored breathing								
	Air Control	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.01 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.03 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.10 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.35 mg/L	6/15	2/15	1/14	1/14	1/14	1/14	1/14
Dried yellow material on the face								
	Air Control	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.01 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.03 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.10 mg/L	0/15	0/15	0/15	0/15	1/15	0/15	1/15
	0.35 mg/L	0/15	0/15	5/14	8/14	12/14	6/14	9/14

[a] Data extracted from Study No. 91-8335, Appendix D, p. 87-154.
[b] One rat was found dead on Day 15.

Table 2-cont. Selected In-Life Clinical Observations at Alternating Intervals from Rats Exposed to Pyrethrum Extract-Containing Atmosphere[a]

Observation	Group	Incidence of Clinical Observations at Study Week: 1	3	5	7	9	11	13
				Females				
Tremors								
	Air Control	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.01 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.03 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.10 mg/L	2/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.35 mg/L	9/15	0/15	0/15	0/15	0/15	0/15	0/15
Labored breathing								
	Air Control	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.01 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.03 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.10 mg/L	4/15	3/15	0/15	0/15	0/15	0/15	0/15
	0.35 mg/L	6/15	2/15	0/15	0/15	0/15	0/15	0/15
Dried yellow material on face								
	Air Control	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.01 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.03 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.10 mg/L	0/15	0/15	0/15	0/15	0/15	0/15	0/15
	0.35 mg/L	0/15	0/15	2/15	1/15	7/15	0/15	1/15

[a] Data extracted from study no. 91-8335, Appendix D, pp. 87-154

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Table 3A. Mean Body Weights at Selected Intervals in Sprague-Dawley Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a]

Exposure Group (mg/L)	Mean Body Weight (g ± S.D.) at Study Week: 1	3	5	7	9	11	13
				Males			
Air Control	341.3±17.3	406.2±29.3	459.6±33.6	500.5±39.1	531.1±40.7	550.3±41.1	581.5±41.7
0.01 mg/L	340.7±21.1	406.0±31.8	458.4±36.5	493.3±34.8	527.3±46.5	546.3±47.7	572.9±49.0
0.03 mg/L	340.0±21.1	402.7±25.3	456.2±33.6	496.1±41.5	529.7±44.8	551.3±50.4	576.1±53.4
0.10 mg/L	330.2±13.7	358.3±26.0	435.6±27.1	475.7±30.5	507.4±29.6	525.7±35.8	554.0±40.3
0.35 mg/L	330.2±18.3	386.6±28.3	436.2±35.7	473.4±44.3	505.3±48.2	530.6±57.7	553.9±60.5
				Females			
Air Control	241.2±10.5	282.5±12.8	312.2±17.8	333.2±22.3	347.9±28.2	363.2±33.5	375.9±34.6
0.01 mg/L	238.1±10.9	273.6±13.2	300.9±17.8	319.1±17.8	332.7±19.6	34[illegible].2±21.1	358.7±25.0
0.03 mg/L	238.9±11.3	278.0±12.4	307.1±15.0	327.0±16.8	343.6±19.2	359.1±21.9	369.1±22.2
0.10 mg/L	235.0±14.8	268.0±13.8*	299.5±16.1	317.5±19.4	330.4±21.5	340.7±21.7*	351.1±23.9*
0.35 mg/L	233.5± 9.4	265.1±13.0**	293.1±19.1*	308.8±20.9*	323.9±22.3*	333.1±22.8**	342.3±23.0**

[a] Data extracted from study no. 91-8335, Appendix F, pp. 140-147

* Significantly different from control value, $p \leq 0.05$
** Significantly different from control value, $p \leq 0.01$

Table 3B. Mean Body Weights at Selected Intervals in Sprague-Dawley Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a]

Exposure Group (mg/L)	Mean Body Weight Gain (g ± S.D.) at Study Week: 1	3	5	7	9	11	13
				Males			
Air Control	59.0±10.1	123.9±25.0	177.3±28.0	218.1±33.3	248.8±33.7	268.0±35.3	299.2±35.7
0.01 mg/L	58.5± 9.3	123.8±22.7	176.2±28.7	211.1±27.9	245.1±40.3	264.1±43.0	290.7±43.1
0.03 mg/L	58.3± 8.4	121.1±16.1	174.5±25.2	214.4±32.7	248.0±37.8	269.7±43.4	294.4±46.8
0.10 mg/L	47.9± 9.5**	103.0±21.4*	153.1±21.8	193.3±24.8	225.1±24.5	243.4±31.0	271.7±35.1
0.35 mg/L	48.8±10.8*	107.3±23.6	154.9±30.7	192.1±40.1	224.0±43.4	249.4±52.6	272.6±56.1
				Females			
Air Control	40.7±38.4	81.9± 8.1	111.7±12.9	132.7±19.2	147.4±24.2	162.7±29.4	175.4±30.5
0.01 mg/L	38.4± 8.3	73.9±10.7	101.3±16.2	119.5±14.9	133.1±17.6	143.5±19.5	159.1±22.8
0.03 mg/L	39.0± 7.2	78.1± 9.5	107.3±13.9	127.1±14.5	143.7±18.0	159.3±21.0	169.3±21.9
0.10 mg/L	35.7±12.3	68.7±12.5**	100.3±13.4	118.2±17.1	131.1±18.9	141.4±19.1*	151.8±21.5*
0.35 mg/L	35.2± 7.4	66.3±10.3**	95.8±16.1*	111.0±17.6*	126.6±19.1*	135.6±19.8**	145.1±19.6**

[a] Data extracted from study no. 91-8335, Appendix F, pp. 140-147

* Significantly different from control value, $p \leq 0.05$
** Significantly different from control value, $p \leq 0.01$

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Table 4. Selected Hematology Data (±S.D.) from Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a,b]

	Males				Females			
Group	Hemoglobin (g/dL)	Hematocrit (%)	RBC (%)	WBC (%)	Hemoglobin (g/dL)	Hematocrit (%)	RBC (%)	WBC (%)
Air Control	15.7 ±0.70	47.4 ±2.50	9.0 ±0.30	12.1 ±3.13	15.4 ±0.60	45.8 ±2.20	8.3 ±0.40	8.5 ±2.96
0.01 mg/L	15.7 ±0.80	47.4 ±2.50	9.0 ±0.49	11.7 ±2.36	15.6 ±0.60	46.1 ±1.70	8.4 ±0.27	7.9 ±1.61
0.03 mg/L	15.1 ±0.40*	45.3 ±1.80*	8.6 ±0.29*	12.3 ±2.99	15.5 ±0.0.35	46.1 ±1.70	8.4 ±0.31	8.5 ±2.48
0.10 mg/L	15.3 ±0.40	45.8 ±1.50	8.6 ±0.34**	10.5 ±1.95	15.1 ±0.80	44.5 ±2.80	8.1 ±0.48	8.4 ±1.71
0.35 mg/L	14.9 ±0.40**	44.7 ±1.30**	8.4 ±0.34**	12.8 ±3.14	14.6 ±0.60**	43.3 ±2.10**	8.0 ±0.33	11.3 ±3.57*

[a] Data extracted from study no. 91-8335, Appendix G, pp. 325-339.
[b] N-15 for all groups except the males at 0.35 mg/L, where N-14

* Significantly different from control value, p ≤ 0.01
** Significantly different from control value, p ≤ 0.05

Table 5. Selected Clinical Chemistry Parameters (±S.D.) from Rats Exposed to Pyrethrum Extract By Whole-Body Inhalation for 90 Days[a,b]

Group	Males						Females					
	SGPT IU/L	Creat mg/dL	Glu mg/dL	T Prot g/dL	Glob g/dL	A/G ...	SGPT IU/L	Creat mg/dL	Glu mg/dL	T Prot g/dL	Glob g/dL	A/G ...
Air Control	29.0 ± 4.0	0.5±0.1	155.0 ±30.0	6.5±0.2	2.5±0.3	1.6±0.2	29.0 ±7.0	0.6±0.1	147.0 ±19.0	7.0±0.4	2.2±0.3	2.3±0.4
0.01 mg/L	33.0 ±24.0	0.6±0.1	169.0 ±28.0	6.4+0.4	2.5±0.3	1.6±0.2	25.0 ±6.0	0.6±0.1	146.0 ±24.0	6.9±0.4	2.4±0.3	1.9±0.3
0.03 mg/L	29.0 ± 7.0	0.5±0.1	151.0 ±29.0	6.3+0.3	2.4±0.2	1.6±0.2	25.0 ±5.0	0.6±0.1	157.0 ±30.0	6.7±0.3	2.3±0.2	1.9±0.3*
0.10 mg/L	28.0 ± 6.0	0.5±0.1	143.0 ±21.0	6.2+0.3	2.3±0.2**	1.7±0.2	21.0 ±4.0**	0.6±0.1	133.0+21.0	6.7+0.4	2.2±0.3	2.0±0.3
0.35 mg/L	27.0 ± 5.0	0.6±0.1	148.0 ±33.0	6.2+0.2*	2.2±0.2**	1.8±0.2*	23.0 ±4.0*	0.7±0.1*	114.0 ±24.0**	7.0±0.4	2.3±0.3	2.1±0.5

[a] Data extracted from study no. 91-8335, Appendix 1, pp. 345-369.
[b] N=15 for all groups except the males at 0.35 mg/L, where N=14.

* Significantly different from control value, p ≤ 0.01
** Significantly different from control value, p ≤ 0.05

SGPT - serum glutamic oxaloacetic transaminase
Creat - creatine
Glu - fasting glucose
T Prot - total protein
Glob - globulin
A/G - albumin/globulin ratio

Table 6. Incidence of Selected Necropsy Observations for Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a]

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Observation	Group (mg/L)				
	0	0.01	0.03	0.10	0.35
Males					
Lung					
Discolored	3/15	4/15	5/15	5/15	10/15
Edema	0/15	0/15	0/15	0/15	1/15
Emphysema	0/15	1/15	0/15	0/15	1/15
Hair Coat					
Discolored	0/15	0/15	0/15	0/15	2/15
Moist	0/15	0/15	0/15	0/15	1/15
Matted	0/15	0/15	0/15	0/15	1/15
Females					
Lung					
Discolored	1/15	1/15	1/15	4/15	0/15
Edema	0/15	0/15	0/15	0/15	0/15
Emphysema	0/15	0/15	0/15	1/15	0/15
Hair Coat					
Discolored	0/15	0/15	0/15	0/15	5/15
Moist	0/15	0/15	0/15	0/15	0/15
Matted	0/15	0/15	0/15	0/15	4/15

[a] Data extracted from study no. 91-8335, Appendix K, Table II, pp. 438-441.

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Table 7. Liver Weight Data for Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a,b]

Organ	Liver Weight (g) Data (Mean ± S.D.) by Exposure Concentration (mg/L)				
	0	0.01	0.03	0.10	0.35
			Males		
Liver					
absolute weight	14.82 ± 1.57	14.99 ± 1.68 (101)	14.81 ± 1.68 (100)	14.33 ± 1.49 (97)	16.38 ± 2.02 (111)
body weight ratio	2.69 ± 0.15	2.73 ± 0.17 (101)	2.69 ± 0.18 (100)	2.73 ± 0.19 (101)	3.16 ± 0.37** (117)
brain weight ratio	6.64 ± 0.70	6.81 ± 0.77 (103)	6.72 ± 0.78 (101)	6.44 ± 0.84 (97)	7.41 ± 1.09 (112)
			Females		
Liver					
absolute weight	9.23 ± 0.81	8.98 ± 0.82 (97)	8.98 ± 0.87 (97)	9.14 ± 0.82 (99)	10.99 ± 1.08** (119)
body weight ratio	2.68 ± 0.19	2.74 ± 0.19 (102)	2.68 ± 0.26 (100)	2.86 ± 0.22 (107)	3.57 ± 0.28** (133)
brain weight ratio	4.48 ± 0.45	4.39 ± 0.44 (98)	4.25 ± 0.49 (95)	4.39 ± 0.41 (98)	5.27 ± 0.54** (118)

[a] Data was extracted from study no. 91 8335, Appendix I, pp. 370-406.
[b] Values in parentheses indicate percent control.

** Significantly different from control value, $p \leq 0.01$

Table 7. Selected Mean Organ-to-Body Weight Data (g)
for Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a,b] (continued)

Organ	Exposure Concentration (mg/L) 0	0.01	0.03	0.10	0.35
			Females		
Brain	6.02 (0.59)	6.28 (0.46)	6.34 (0.44)	6.54* (+8.7%) (0.53)	6.81** (+13.1%) (0.52)
Kidneys	7.26 (0.52	7.70 (0.69)	7.51 (0.54)	7.98** (+9.9%) (0.47)	8.29** (+14.2%) (0.53)
Liver	2.68 (0.19)	2.74 (0.19)	2.68 (0.26)	2.86 (0.22)	3.57** (+33.2%) (0.28)
Lungs	4.14 (0.46)	4.45 (0.35)	4.54 (0.46)	4.55 (0.48)	4.90** (+18.4%) (0.46)
Body Weight	345.3 ± 31.6	327.9 ± 23.0	335.2 ± 29.1	319.7 ± 22.7 -7.4%	307.7 ± 22.0 -10.8%

[a] Data was extracted from study no. 91 8335, Appendix J, pp. 370-406.

* Significantly different from control value, $0.01 < p < 0.05$
** Significantly different from control value, $p < 0.01$

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Table 7. Selected Mean Organ-to-Body Weight Data (g) for Rats Exposed to Pyrethrum Extract[a,b]

Organ	Exposure Concentration (mg/L) 0	0.01	0.03	0.10	0.35
Males					
Kidneys	1.47 (0.51)	1.43 (0.95)	1.57 (1.10)	1.77 (0.54)	8.36* (0.74) (+11.9%)
Liver	2.69 (0.15)	2.73 (0.17)	2.69 (0.18)	2.73 (0.19)	3.16** (0.37) (+17.5%)
Lungs	3.43 (0.36)	3.48 (0.54)	3.33 (0.31)	3.53 (0.32)	3.85* (0.34) (+12.2%)
Body Weight	538.5±40.8	548.6±52.3	551.1±52.7	524.3±31.9 -4.8%	520.3±21.8 -5.5%

a Data was extracted from study no. 91-8335, Appendix J, pp. 370-406.

b Values in parentheses are standard deviations
* Significantly different from control value, $0.01 < p \leq 0.05$
** Significantly different from control value, $0.05 < p \leq 0.05$

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TABLE 8a. Incidence of Selected Microscopic Observations for Male Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a,b]

	0			0.01			0.03			0.10			0.35		
	I.		A.S.	I.		A.S.	I.		A.S.	I.		A.S.	I.		A.S.
Larynx															
-mucosa:seromucosal glands															
-hypertrophy/hyperplasia															
-ventral diverticulum	0/13			7/15	(47)	1.1	6/11	(55)	1.7	5/13	(38)	2.0	5/15	(33)	2.4
-ventral seromucous glands	0/14			9/10	(90)	2.0	11/11	(100)	2.5	8/8	(100)	2.3	15/15	(100)	2.8
-mucosa:pseudostratified ciliated/ nonciliated columnar epithelium															
-squamous/squamoid metaplasia/ hyperplasia															
-ventral diverticulum	0/13			2/15	(13)	3.0	4/11	(36)	2.0	11/13	(85)	2.1	15/15	(100)	2.8
-ventral seromucous glands	2/14	(14)	1.0	9/10	(90)	2.1	11/11	(100)	2.7	8/8	(100)	3.5	15/15	(100)	3.4
-mucosa:metaplastic epithelial hyperkeratosis															
-ventral diverticulum	0/13			1/15	(7)	2.0	3/11	(27)	1.0	9/13	(69)	1.0	15/15	(100)	1.9
-ventral seromucous glands	0/14			6/10	(60)	1.2	10/11	(91)	1.7	8/8	(100)	1.8	15/15	(100)	2.1
-mucosa:nonkeratinized stratified squamous epithelium (normally present)															
-hyperplasia															
-ventral diverticulum	0/13			0/15			4/11	(36)	1.3	11/13	(85)	2.1	14/15	(93)	2.6
-ventral seromucous glands	0/14			1/10	(10)	1.0	7/11	(64)	1.4	6/8	(75)	2.0	13/15	(87)	2.3
-hyperkeratosis															
-ventral diverticulum	0/13			0/15			4/11	(36)	1.3	11/13	(85)	1.3	14/15	(93)	1.8
-ventral seromucous glands	0/14			1/10	(10)	1.0	4/11	(36)	1.0	5/8	(63)	1.8	13/15	(87)	1.7
Nasopharynx															
-mucosa:epithelium															
-goblet cell hyperplasia	7/15	(47)	1.0	12/15	(80)	1.3	12/14	(86)	1.2	15/15	(100)	1.3	14/15	(93)	1.6
Nasoturbinates															
-mucosa (chronic active):subacute/ chronic inflammation															
section 1	1/15	(7)	1.0	1/15	(7)	1.0	1/14	(7)	1.0	2/15	(13)	1.0	14/15	(93)	1.4
2	0/15			0/15			1/14	(7)	2.0	0/15			12/15	(80)	1.2
3	0/15			0/15			0/14			0/15			3/15	(20)	1.0
4	NE														
5	NE														

TABLE 8a. (continued)

	0		0.01		0.03		0.10		0.35	
	I.	A.S.	I.	A.S.	I.	A.S.	I.	A.S.	I.	A.S.
Nasoturbinates (continued)										
-mucosa:squamous cell hyperplasia										
section 1	0/15		0/15		0/14		0/15		9/15 (60)	1.6
2	0/15		0/15		1/14 (7)	2.0	1/15 (7)	1.0	13/15 (87)	1.1
3	0/15		0/15		0/14		0/15		3/15 (20)	1.0
4	NE									
5	NE									
-mucosa:goblet cell hyperplasia										
section 1	15/15 (100)	1.4	15/15 (100)	2.1	14/14 (100)	2.2	15/15 (100)	2.4	14/15 (93)	2.8
2	8/15 (53)	1.5	12/15 (80)	1.3	14/14 (100)	1.1	15/15 (100)	1.4	15/15 (100)	2.3
3	5/15 (33)	1.0	9/15 (60)	1.2	12/14 (86)	1.4	11/15 (73)	1.3	14/15 (93)	1.6
4	3/15 (20)	1.0	0/15		0/14		0/15		11/15 (73)	1.6
5	0/15		0/11		0/7		0/7		9/15 (60)	1.1
-mucosa:epithelium										
-intracytoplasmic eosinophilic material										
section 1	0/15		12/15 (80)	1.1	12/14 (86)	1.2	13/15 (87)	1.2	14/15 (93)	1.5
2	0/15		0/15		2/14 (14)	1.0	3/15 (20)	1.0	8/15 (53)	1.3
3	0/15		4/15 (27)	2.5	8/14 (57)	1.8	9/15 (60)	2.3	9/15 (60)	2.0
4	0/15		6/15 (40)	1.8	10/14 (71)	2.0	10/15 (67)	2.4	12/15 (80)	2.3
5	0/15		0/11		1/7 (14)	2.0	0/7		10/15 (67)	2.3
Lungs										
-interstitium: subacute/chronic -inflammation	15/15 (100)	1.5	15/15 (100)	1.5	15/15 (100)	1.5	15/15 (100)	1.7	15/15 (100)	3.1
-alveolar/intraalveolar -macrophages	15/15 (100)	1.4	15/15 (100)	1.3	15/15 (100)	1.3	15/15 (100)	1.7	15/15 (100)	2.8
-terminal bronchioles:										
-epithelium										
-hypertrophy/hyperplasia	0/15		0/15		0/15		0/15		9/15 (60)	1.0
-congestion	0/15		0/15		0/15		0/15		3/15 (20)	2.0
-edema (alveolar/peribronchiolar /perivascular)	0/15		1/15 (7)	2.0	0/15		0/15		3/15 (20)	2.0

[a] Data extracted from study no. 91-8335, Appendix K, Table IV (pp. 593-604) and Table VI (pp. 740-746).
[b] Numbers in parentheses indicate percent incidence.

NE = not examined
I = incidence
AS = average severity score

TABLE 8b. Incidence of Selected Microscopic Observations for Female Rats Exposed to Pyrethrum Extract by Whole-Body Inhalation for 90 Days[a,b]

	0			0.01			0.03			0.10			0.35		
	I.		A.S.	I.		A.S.	I.		A.S.	I.		A.S.	I.		A.S.
Larynx															
-mucosa:seromucosal glands															
-hypertrophy/hyperplasia															
-ventral diverticulum	0/15			3/14	(21)	1.0	4/14	(29)	1.5	7/13	(54)	2.0	6/13	(46)	1.7
-ventral seromucous glands	0/15			12/13	(92)	2.0	11/11	(100)	2.3	9/10	(90)	2.4	15/15	(100)	2.5
-mucosa:pseudostratified ciliated/ nonciliated columnar epithelium															
-squamous/squamoid metaplasia/ hyperplasia															
-ventral diverticulum	0/15			1/14	(7)	3.0	2/14	(14)	2.0	5/13	(38)	2.4	13/13	(100)	2.2
-ventral seromucous glands	0/15			13/13	(100)	1.8	11/11	(100)	2.5	10/10	(100)	2.8	15/15	(100)	2.9
-mucosa:metaplastic epithelial hyperkeratosis															
-ventral diverticulum	0/15			1/14	(7)	1.0	2/14	(14)	1.0	5/13	(38)	1.4	13/13	(100)	1.4
-ventral seromucous glands	0/15			4/13	(31)	1.0	10/11	(91)	1.5	9/10	(90)	1.7	15/15	(100)	1.9
-mucosa:nonkeratinized stratified squamous epithelium (normally present)															
-hyperplasia															
-ventral diverticulum	0/15			2/14	(14)	1.0	0/14			5/13	(38)	1.8	13/13	(100)	2.3
-ventral seromucous glands	0/15			0/13			9/11	(82)	1.8	9/10	(90)	2.1	12/15	(80)	2.4
-hyperkeratosis															
-ventral diverticulum	0/15			1/14	(7)	1.0	0/14			4/13	(31)	1.5	13/13	(100)	1.8
-ventral seromucous glands	0/15			0/13			7/11	(64)	1.4	9/10	(90)	1.4	12/15	(80)	1.9
Nasopharynx															
-mucosa:epithelium															
-goblet cell hyperplasia															
-ventral diverticulum	5/14	(36)	1.2	6/15	(40)	1.0	9/15	(60)	1.2	6/14	(43)	1.2	14/15	(93)	1.7
Nasoturbinates															
-mucosa (chronic active):subacute/ chronic inflammation															
section 1	0/15			1/15	(7)	2.0	0/15			0/14			13/15	(87)	1.2
2	0/15			0/15			1/15	(7)	1.0	0/14			12/15	(80)	1.3
3	0/15			0/15			0/15			0/14			3/15	(20)	1.3
4	NE														
5	NE														

TABLE 8b. (continued)

	0			0.01			0.03			0.10			0.35		
	I.		A.S.	I.		A.S.	I.		A.S.	I.		A.S.	I.		A.S.
Nasoturbinates (continued)															
-mucosa:squamous cell hyperplasia															
section 1	0/15			0/15			0/15			1/14	(7)	1.0	6/15	(40)	1.2
2	0/15			0/15			1/15	(7)	1.0	0/14			8/15	(53)	1.3
3	0/15			0/15			0/15			0/14			2/15	(13)	1.0
4	NE														
5	NE														
-mucosa:goblet cell hyperplasia															
section 1	12/15	(80)	1.8	12/15	(80)	1.3	15/15	(100)	1.7	13/14	(93)	2.0	15/15	(100)	2.4
2	4/15	(27)	1.0	10/15	(67)	1.0	10/15	(67)	1.2	10/14	(71)	1.2	14/15	(93)	2.1
3	6/15	(40)	1.0	9/15	(60)	1.0	10/15	(67)	1.2	10/14	(71)	1.3	15/15	(100)	1.6
4	4/15	(27)	1.0	0/14			0/15			2/14	(14)	1.5	13/15	(87)	1.3
5	2/14	(14)	1.0	0/6			0/9			0/5			7/15	(47)	1.3
-mucosa:epithelium															
-intracytoplasmic eosinophilic material															
section 1	1/15	(7)	1.0	8/15	(53)	1.0	9/15	(60)	1.2	9/14	(64)	1.2	10/15	(67)	1.5
2	3/15	(20)	1.0	1/15	(7)	1.0	1/15	(7)	1.0	1/14	(7)	1.0	4/15	(27)	1.5
3	1/15	(7)	1.0	3/15	(20)	1.3	2/15	(13)	2.0	5/14	(36)	2.4	6/15	(40)	1.8
4	2/15	(13)	1.0	4/14	(29)	1.5	7/15	(47)	1.7	10/14	(71)	2.6	9/15	(60)	2.3
5	2/14	(14)	1.0	0/6			1/9	(11)	1.0	0/5			11/15	(73)	2.1
Lungs															
-interstitium: subacute/chronic -inflammation	15/15	(100)	1.3	15/15	(100)	1.3	15/15	(100)	1.3	15/15	(100)	1.6	15/15	(100)	2.2
-alveolar/intraalveolar -macrophages	15/15	(100)	1.3	15/15	(100)	1.2	15/15	(100)	1.2	15/15	(100)	1.5	15/15	(100)	1.9
-terminal bronchioles:															
-epithelium													5/15	(33)	1.0
-hypertrophy/hyperplasia	0/15			0/15			0/15			0/15			0/15		
-congestion	0/15			0/15			0/15			0/15					
-edema (alveolar/peribronchiolar /perivascular)	0/15			0/15			0/15			1/15	(7)	1.0	0/15		

[a] Data extracted from study no. 91-8335, Appendix K, Table IV (pp. 593-604) and Table VI (pp. 740-746).
[b] Numbers in parentheses indicate percent incidence.

NE = not examined
I = incidence
AS = average severity score