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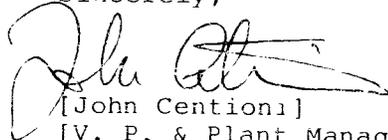
These effects are of questionable significance to humans who might be exposed to the test compound. Nevertheless, findings in the lung were not expected given that dosing was conducted by the gavage route and we are therefore filing this report with EPA's TSCA Section 8(e) office as a prudent measure.

It is relevant to note that additional histopathological analysis is being conducted on the recovery animals as well as the lymph tissues in the mid- and low-dose group animals. Once these findings are available they will be submitted to EPA.

Some of the information contained in this submission is deemed to be confidential and as such a confidential and a sanitized version of the report is enclosed. Please be aware, that our Washington, D.C. based consultant Mr. Robert Fensterheim is authorized to discuss and receive from EPA confidential information.

Do not hesitate to contact me or Mr. Fensterheim if we can provide you any additional information.

Sincerely,



[John Centioni]

[V. P. & Plant Manager]

Enclosure

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Bio/dynamics Inc.

Department of Toxicology

PROJECT NO. 90-3589

A SUBCHRONIC ORAL TOXICITY STUDY OF UVASORB HA-88 IN THE RAT
VIA ORAL GAVAGE ADMINISTRATION WITH A 4-WEEK RECOVERY PERIOD

Draft Final Report

VOLUME I OF II

Submitted to: RegNet, Inc.
1616 P Street, N.W.
Suite 412
Washington, DC 20036

Attn: Mr. Robert J. Fensterheim

Date: March 18, 1992



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PROJECT NO. 90-3589

A SUBCHRONIC ORAL TOXICITY STUDY OF UVASORB HA-88 IN THE RAT
VIA ORAL GAVAGE ADMINISTRATION WITH A 4-WEEK RECOVERY PERIOD

ABSTRACT

This study, conducted for 3-V Chemical Corporation, was designed to assess the potential subchronic toxicity of UVASORB HA-88 when administered orally, via gastric intubation to 80 Sprague-Dawley CD¹ rats [CD¹-CrI: CD¹ (SD)BR/1] (Groups II and III - 10/sex/group and Group IV - 20/sex) at dose levels of 25, 75, and 250 mg/kg/day. Control animals (20/sex) received the vehicle (i.e., 0.5% methylcellulose) at the same dose volume as administered to the treated animals. Physical observations, ophthalmoscopic examinations, body weight and food consumption measurements were done on all animals pretest and on all survivors at selected intervals during the study. Hematology, clinical chemistry, and urinalyses were performed on all survivors at selected intervals during the treatment and recovery periods. After at least 3 months of treatment, up to 10 animals/sex/group were sacrificed. Ten animals/sex/group in the control and high-dose groups were retained for a 4-week recovery period and sacrificed. Selected organs were weighed and organ/body and organ/brain weight ratios calculated at each sacrifice interval. Complete gross postmortem examinations were performed on all animals. Histopathological evaluations of selected tissues were conducted on all animals in the control and high-dose groups at terminal sacrifice. In addition, evaluations were performed on the lungs, liver and kidneys for all animals which were sacrificed at study termination in Groups II and III. There were no histopathological evaluations performed at recovery sacrifice.

Analysis of weekly dose suspension preparations confirmed that the test material concentrations were within the tolerances accepted for this study.

There were no treatment-related effects seen in the mortality, in-life physical observations and urinalysis values evaluated.

Administration of UVASORB HA-88 to rats for 90 days at a dose of 250 mg/kg/day produced transient decreases in body weight gains (males), reversible increases in numbers of segmented neutrophils and elevated absolute and relative lung weights which persisted in males through termination of the recovery period. Microscopic changes (granulomas and other evidence of foreign body reactions) in the lungs, mediastinal and mesenteric lymph nodes and nasal passages were also seen in animals in this group. Effects at the 75 mg/kg/day dose level consisted of elevated lung weights and the presence of microgranulomas in the lungs. The only effect at the 25 mg/kg/day dose level was the presence of granulomas in the lungs of a few animals.

Based on these observations, a no effect level for oral administration of UVASORB HA-88 to rats was not established in this study.

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I. INTRODUCTION:

This study, conducted for 3-V Chemical Corporation, was designed to assess the potential subchronic toxicity of UVASORB HA-88 when administered orally, via gastric intubation, to Sprague-Dawley CD¹ rats for 3 months and to evaluate reversibility of any effects during a 4-week recovery period.

This study was designed to meet or exceed the requirements of TSCA (Toxic Substance Control Act) of the U.S. Environmental Protection Agency, 40 CFR, Part 798.2650, Subchronic Oral Toxicity.

This study was also conducted in compliance with FDA, Part 58 of 21 CFR principles of Good Laboratory Practice and EPA Good Laboratory Practice Regulations - TSCA, Part 792 of 40 CFR.

Species and strain of test animal, method and route of test substance administration and dose levels were determined by the sponsor. This study was conducted at Bio/dynamics, Inc., Mettlers Road, East Millstone, New Jersey 08875. All raw data, specimens, the original study protocol, the original final report and a sample of the test substance and vehicle are stored in the Archives of Bio/dynamics, Inc.

II. MATERIALS AND METHODS:

A. Study Dates:

Study Initiation Date: 10 May 1991
(Date Study Director
Signs Protocol)

Experimental Start Date: 23 July 1991
(First Dose)

Study Completion Date: Date final report is signed by Study
Director.

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II. MATERIALS AND METHODS (cont.):

B. Test Substance: UVASORB HA-88

Supplier: 3-V Chemical Corporation
Penny Royal Road
Georgetown, South Carolina 29440

Lot No.: 03/A/0

Concentration: 98% Active Ingredient

Description: Off-white powder

Dates Received: 2 August 1990
17 August 1990
14 January 1991

Expiration Date: July 1992

Analysis: The identity, strength, purity and composition; and synthesis, fabrication, and/or derivation of the test substance is the responsibility of the sponsor.

Stability: The stability of the test substance is the responsibility of the sponsor.

Storage: Room temperature, in a temperature monitored room.

Sampling: An archival sample of approximately 10 grams of the test substance is stored in the Archives of Bio/dynamics, Inc.

Disposition: All remaining containers of the test substance will be returned to the sponsor after completion of the study.

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II. MATERIALS AND METHODS (cont.):

C. Vehicle: Methylcellulose (prepared as a 0.5% aqueous suspension).

Supplier: Dow Chemical
Midland, Michigan 48640

Description: Fine white powder.

Date Received: 27 July 1984

Lot No.: M83092611A

Storage: Room temperature, keep dry.

Sampling: An archival sample of approximately 10 grams of the vehicle is stored in the Archives of Bio/dynamics, Inc.

D. Test Animals: Albino Rats (outbred)

Strain: CD⁰ (Sprague-Dawley derived)
[CD⁰ - Cr1: CD⁰ (SD)BR]

Justification for Animal Selection: The rat is a rodent animal model commonly utilized in toxicity studies as recommended in the referenced guidelines. In addition, a historical data base is available for comparative evaluation.

Number of Animals:

Received: 155 total (77 males, 78 females)

Placed on Test: 120 total (60 males, 60 females)

Supplier: Charles River Breeding Laboratories, Inc.
Kingston, New York 12484

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II. MATERIALS AND METHODS (cont.):

D. Test Animals (cont.):

Date Received: 8 July 1991

Age at Receipt: 28 days old

Age at Initiation of Treatment: 43 days old

Weight at Initiation of Treatment (grams):	Mean	Range
Males:	260	234-288
Females:	182	164-199

Acclimation Period: Animals were acclimated for 14 days (8 to 22 July 1991). All animals were examined by the staff veterinarian during the acclimation period.

E. Selection: More animals than required for the study were purchased and equilibrated. Animals considered unsuitable for the study on the basis of pretest physical examinations, outlying body weight data and/or ophthalmoscopic examinations were eliminated prior to random selection for group assignment.

F. Group Assignment: Animals considered suitable for study were first distributed into 6 groups of 10 animals/group by a computerized random sort program so that body weight means for each group were comparable. Those groups were then randomly combined to form the four permanent dose groups (i.e., Groups I and IV - 20/sex/group and Groups II and III - 10/sex/group). Individual weights of animals placed on test did not exceed 20% of the mean weight for each sex.

G. Animal Identification: Each rat was identified with a metal ear tag bearing its unique Bio/dynamics, Inc. animal number. If the tag was lost, it was replaced. In addition, each cage was provided with a cage card which was color coded for dose level identification and contained the project number, animal number, sex and dose-group information.

II. MATERIALS AND METHODS (cont.):

H. Experimental Outline:

Group	Test Substance	Dose Level (mg/kg/day)	Number of Animals											
			Total		Clinical Laboratory Studies ^b				Necropsy ^c				Histopathology ^d	
					(Termination)		(Recovery)		(Termination)		(Recovery)			
			M	F	M	F	M	F	M	F	M	F		
I	Control ^a	0	20	20	10	10	9	9	10	10	9	9	10	10
II	UVASORB HA-88	25	10	10	10	10	-	-	10	10	-	-	10	10
III	UVASORB HA-88	75	10	10	10	10	-	-	10	10	-	-	10	10
IV	UVASORB HA-88	250	20	20	9	10	10	10	9	10	10	10	10	10

^aControl animals received the vehicle (0.5% methylcellulose) at the same dose volume administered to the test animals.

^bHematology, clinical chemistry and urinalysis were performed on the first 10 animals/sex/group which survived to the termination of dosing and on all surviving animals in Groups I and IV at the recovery sacrifice.

^cGross necropsy examinations were performed on all animals, including those animals which died prior to their scheduled sacrifice.

^dHistopathological examinations of selected tissues were performed on all animals in the control and high-dose groups which were scheduled for sacrifice at termination of dosing (includes one Group IV male which died prior to sacrifice). In addition, the lungs, liver and kidneys were examined for all animals in Groups II and III. Tissues from animals sacrificed at the recovery interval were not evaluated.

I. Husbandry:

Housing:

Animals were doubly housed in elevated stainless steel wire mesh cages during the first week of the acclimation period and individually housed thereafter.

Food:

ad libitum; standard laboratory diet (Purina Certified Rodent Chow[®] Brand Animal Diet #5002 - mash-type). Fresh food presented weekly.

Analysis of Feed:

Analysis of each feed lot used during this study was performed by Purina Mills, Inc. prior to receipt at Bio/dynamics, Inc. Results are maintained on file at Bio/dynamics.

II. MATERIALS AND METHODS (cont.):

I. Husbandry (cont.):

Water: ad libitum; by automated watering system (Elizabethtown Water Company)

Analysis of Water: Water analysis was provided by Elizabethtown Water Company, Westfield New Jersey (Raritan-East Millstone Plant). Results are maintained on file at Bio/dynamics.

Environmental Conditions: 12 hour light/dark cycle (7 AM to 7 PM and 7 PM to 7 AM) via automatic timer; temperature was monitored and recorded twice daily, humidity was monitored and recorded once daily.

Temperature: Desired: 67-76°F (19-24°C)
Actual: 67-75°F (19-24°C)

Humidity: Desired: 40-60%
Actual: 32-84%

2. Test Substance Administration:

Route: Oral, via intubation (oral gavage).

Justification of Route of Administration: The oral route is one of the potential routes of human exposure to this test substance and is the route specified in the referenced guidelines.

Analyses of Dose Suspensions: Analyses to determine stability, homogeneity and concentration of the test substance with a carrier under the conditions of this study were performed by the Metabolism and Analytical Chemistry Department at Bio/dynamics, Inc. Results of these analyses are presented in Appendix K.

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II. MATERIALS AND METHODS (cont.):

J. Test Substance Administration (cont.):

Method: Appropriate amounts of test substance were suspended in the vehicle weekly to yield dose levels of 25, 75, and 250 mg/kg/day (which are concentrations of 5, 15 and 50 mg/ml, respectively) at a constant dose volume of 5 ml/kg/dose. Individual doses were adjusted by most recent weekly body weight. Control animals were administered the vehicle at the same dose volume as one of the dose groups.

Dose Volume: 5 ml/kg/dose
Frequency: Once daily, (7 days per week) through the day prior to necropsy.
Duration: 90 or 91 days (depending on day of sacrifice).
Dates of Treatment: 23 July to 20 or 21 October 1991 (depending on day of sacrifice).

K. Recovery Period:

Duration: 28 days
Dates of Recovery: 22 October to 18 November 1991

L. Observations:

For Mortality and Gross Signs of Toxicologic or Pharmacologic Effects: Twice daily, once in the morning and once in the afternoon.

Detailed Physical Examination for Signs of Local or Systemic Toxicity, Pharmacologic Effects and Palpation for Tissue Masses: (Methodology and References, Appendix A)
Pretest and weekly thereafter.

II. MATERIALS AND METHODS (cont.):

M. Ophthalmoscopic Examination: (Methodology and References, Appendix A)

Time Intervals

Pretest: 12 July 1991
Termination: 17 October 1991
Recovery: 15 November 1991

N. Body Weight: (Methodology and References, Appendix A)

Twice pretest, weekly during the study period and terminally (after fasting).

O. Food Consumption: (Methodology and References, Appendix A)

Once pretest and weekly throughout the study.

P. Laboratory Studies: (Methodology and References, Appendix A)

Blood was obtained via venipuncture of the orbital sinus (retrobulbar venous plexus) while animals were lightly anesthetized with a mixture of carbon dioxide and oxygen. Rats were fasted overnight prior to blood collections.

Number of Animals: Performed on up to 10 animals/sex/group at terminal sacrifice and on all remaining animals (up to 10 animals/sex/group) in Groups I and IV at the recovery sacrifice.

Parameters Evaluated:

Hematology:

Time Intervals

hemoglobin concentration	Termination: 21, 22 October 1991
hematocrit	Recovery: 18 November 1991
erythrocyte count	
reticulocyte count	
platelet count	
mean corpuscular volume	
mean corpuscular hemoglobin	
mean corpuscular hemoglobin concentration	
prothrombin time	
activated partial thromboplastin time	
total and differential leukocyte counts	
erythrocyte morphology	

II. MATERIALS AND METHODS (cont.):

P. Laboratory Studies (cont.):

Parameters Evaluated (cont.):

Clinical Chemistry:

Time Intervals

aspartate aminotransferase	Termination: 21, 22 October 1991
alanine aminotransferase	Recovery: 18 November 1991
alkaline phosphatase	
blood urea nitrogen	
creatinine	
blood urea nitrogen/ creatinine ratio (calculated)	
fasting glucose	
cholesterol	
triglycerides	
total protein	
albumin	
globulin (calculated)	
A/G ratio (calculated)	
total bilirubin	
sodium	
potassium	
chloride	
calcium	
inorganic phosphorus	
gamma glutamyl transpeptidase	

Urinalysis:

Time Intervals

gross appearance	Termination: 17, 18 October 1991
specific gravity	Recovery: 15 November 1991
pH	
protein	
nitrite	
glucose	
ketones	
bilirubin	
occult blood	
urobilinogen	
16-hour volume	
microscopic analysis	

II. MATERIALS AND METHODS (cont.):

0. Postmortem:

Animals Found Dead or Killed at Scheduled Sacrifice Intervals:

Complete gross postmortem examinations were performed on all animals. External surface, all orifices, the cranial cavity, carcass, the external surfaces of the brain and spinal cord, the thoracic, abdominal and pelvic cavities and their viscera and cervical tissues and organs were examined for all animals. Animals were fasted prior to scheduled sacrifices.

Terminal Sacrifice: 21 and 22 October 1991

Number of Animals: 79 animals total

Recovery Sacrifice: 18 November 1991

Number of Animals: 38 animals total

Sacrifice Method: Exsanguination under ethyl ether anesthesia.

Organs Weighed and Organ/Body Weight, Organ/Brain Weight Ratios Calculated:

(Methodology and References, Appendix A)

The following organs were weighed for all animals at the scheduled sacrifice intervals. Paired organs were weighed together.

- adrenals
- brain
- heart
- kidneys
- liver
- lungs
- pituitary
- spleen
- testes with epididymides
- thymus
- thyroid/parathyroids
- ovaries

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II. MATERIALS AND METHODS (cont.):

Q. Postmortem (cont.):

Tissues Preserved:¹

adrenals (2)
 aorta (thoracic)
 bone (sternum)
 bone marrow (sternum)
 brain (medulla/pons, cerebrum and cerebellum)
 epididymides (2)
 esophagus
 eyes with optic nerve (2)
 femur (including articular surface)
 heart
 intestine
 cecum
 colon
 duodenum
 ileum
 jejunum
 rectum
 kidneys (2)
 lacrimal gland (2)
 liver (2 lobes)
 lungs (with mainstem bronchi - 2)
 lymph nodes (mesenteric, mediastinal)
 mammary gland
 nasopharyngeal (4)
 nerve (sciatic)
 ovaries (10 sections/ovary)
 pancreas
 pituitary
 prostate
 salivary gland (mandibular)
 seminal vesicles (2)
 skeletal muscle (biceps femoris)
 skin
 spinal cord (cervical, thoracic, lumbar)
 spleen
 stomach (3)
 testes (2 sections/testis)
 thymus
 thyroid/parathyroids (2)
 trachea
 urinary bladder
 uterus (body/horns) with cervix
 gross lesions

¹Number in parentheses indicates number of organs/sections preserved.

II. MATERIALS AND METHODS (cont.):

Q. Postmortem (cont.):

Tissues Examined
Histopathologically:²

All tissues listed below and on the following page were examined for all animals in the control and high-dose groups which were scheduled for sacrifice at termination of dosing (includes one Group IV male which died prior to sacrifice). In addition, kidneys, lungs, and liver were examined for all animals in Groups II and III. Tissues from animals sacrificed at the recovery interval were not evaluated.

adrenals (2)
aorta (thoracic)
bone (sternum)
bone marrow (sternum)
brain (medulla/pons, cerebrum and cerebellum)
epididymides (2)
esophagus
eyes with optic nerve (2)
femur (including articular surface)
heart
intestine
 cecum
 colon
 duodenum
 ileum
 jejunum
 rectum
kidneys (2)
lacrimal gland (2)
liver (2 lobes)
lungs (with mainstem bronchi - 2)
lymph nodes (mesenteric, mediastinal)
mammary gland
nasopharyngeal (4)
nerve (sciatic)
ovaries (10 sections/ovary)
pancreas
pituitary
prostate
salivary gland (mandibular)
seminal vesicles (2)
skeletal muscle (biceps femoris)

²Number in parentheses indicates number of organs/sections examined.

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II. MATERIALS AND METHODS (cont.):

Q. Postmortem (cont.):

Tissues Examined
Histopathologically
(cont.):³

skin
spinal cord (cervical, thoracic, lumbar)
spleen
stomach (3)
testes (2 sections/testis)
thymus
thyroid/parathyroids (2)
trachea
urinary bladder
uterus (body/horns) with cervix
gross lesions

Preservatives:

10% neutral buffered formalin (eyes, testes and epididymides were initially placed in Bouin's solution, transferred to 70% Synosol[®], and then preserved in formalin).

Stain:

(Methodology and References, Appendix A)
Hematoxylin and Eosin

R. Statistical Analysis:

(Methodology and References, Appendix A)

Body weight, body weight change (week to week), body weight change from Week 0, food consumption, hematology and clinical chemistry parameters, terminal organ and body weights and organ/body and organ/brain weight ratios were analyzed. Mean values of all dose groups were compared to control at each time interval. Statistically significant differences from control are indicated on mean tables of appendices.

³Number in parentheses indicates number of organs/sections examined.

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II. MATERIALS AND METHODS (cont.):

S. Protocol Deviations:

The following protocol deviations occurred during the study period. These deviations were not considered to have had an adverse effect on the study purpose or results.

1. Humidity values were outside of the desired range on several occasions.
2. Due to a calculation error at Week 9, control Female No. 1503 received 1.4 ml/kg/day rather than 1.3 ml/kg/day and high-dose Male No. 4006 received 2.4 ml/kg/day (240 mg/kg/day) rather than 2.3 ml/kg/day (250 mg/kg/day) during this week.

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III. RESULTS AND DISCUSSION:

A. Mortality (Appendix B):

In the treatment phase of this study, the only death was a high-dose (Group IV) male in Week 2. Based on the results of gross and microscopic evaluations, this death can not be clearly attributed to the test material. During the recovery phase of this study two control animals (one male and one female) died.

B. In-Life Physical Observations (Appendix C):

All of the noted observations are common to laboratory rats and not test material-related.

C. Ophthalmoscopic Examinations (Appendix D):

There were no indications of treatment-related effects in the eyes.

D. Body Weights (Appendix E):

The body weight values of the low- and mid-dose groups (II and III) and high-dose (Group IV) females were similar to the control group. Body weight gains for Group IV males were statistically significantly decreased compared to values for the control group from Week 3 to 8 and tended to remain decreased during the remainder of the dosing period. However, mean weights for this group were within two percent of the control mean at study termination, and Group IV males had body weight gains similar to or greater than the control group during the recovery period.

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III. RESULTS AND DISCUSSION (cont.):

E. Food Consumption (Appendix E):

The high-dose (Group IV) and occasionally the mid-dose (Group III) food consumption values were statistically significantly greater than the control group values. Though these differences appear to be test material-related, increased food consumption values are generally not considered to be an adverse effect. This difference was not seen in the recovery animals.

F. Hematology (Appendices F and G):

At termination, there was a treatment-related increase in the white blood cell counts in the high-dose (Group IV) animals when compared to the control group; this effect was more evident in the females. The increases were due to an increase in the segmented neutrophil portion of the white blood cell population. Although these differences appear to represent an effect of test material administration, white blood cell counts in all of the groups were within the range of Bio/dynamics' normal control values. This effect was not evident at the end of the recovery period.

G. Clinical Chemistry (Appendix H):

Slight, statistically significant, elevations in serum alanine aminotransferase (SGPT) values and decreases in total protein and serum albumin values were seen in high-dose males at study termination. SGPT values for mid- and high-dose females were also slightly higher than control values, but differences were not statistically significant. Similar differences were not evident at termination of the recovery period. Most individual values were within Bio/dynamics' historical control ranges and, in the absence of microscopic liver pathology, these slight, reversible differences are considered to be of questionable toxicological significance.

III. RESULTS AND DISCUSSION (cont.):

H. Urinalysis (Appendix I):

There were no treatment-related effects evident in the urinalysis values.

I. Terminal Organ and Body Weight, Organ/Body Weight and Organ/Brain Weight Ratios (Appendix J):

Lung weights and/or lung/body and lung/brain weight ratios tended to increase with increasing dose and the increases were greatest in the mid- and high-dose females. This treatment-related increase was consistent with microscopic observations of granuloma formation and edema in the lungs of treated animals. This effect persisted through the recovery period in the high-dose group males, but not in the females.

J. Analyses of Dosing Suspensions (Appendix K):

The analysis results confirmed that the test material dosing suspensions were homogeneous and stable during the dosing period. Weekly analyses confirmed that the dosing solutions were prepared within acceptable tolerances.

K. Pathology (Appendix L, Volume II):

Gross postmortem examination revealed changes which occurred sporadically, or otherwise showed similar incidences between the control and the treated groups.

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III. RESULTS AND DISCUSSION (cont.):

K. Pathology (cont.):

Microscopically, microgranulomas in the lungs were seen in all treated groups, with the incidence greatest in the high-dose group. Edema in the lungs, microgranulomas in the mediastinal lymph nodes and acute inflammation, purulent exudate, and proteinaceous exudate in the nasal passages were also seen in the high-dose animals (these tissues were only examined for high-dose animals). Although no evidence of intratracheal intubation was seen, these changes suggest that small amounts of the test material entered the respiratory tract during dosing and/or that excretion of the test material by the respiratory system occurred. Microgranuloma formation with focal necrosis and plasma cell hyperplasia in the mesenteric lymph nodes of high-dose males and females were deemed to be associated with the absorption of the test material from the gastrointestinal tract. These changes were considered treatment-related. No effects of the test material were seen in the testes, ovaries or any of the other tissues examined.

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IV. CONCLUSION:

Oral administration of UVASORB HA-88 to rats for 90 days at doses of 25, 75 and 250 mg/kg/day was associated with granulomas in the lungs of some animals in all dose groups and elevated lung weights, primarily in mid- and high-dose animals. Other signs of toxicity were seen in the high-dose group only. However, based on the presence of lung granulomas in some animals at the lowest dose administered, a no effect level was not established in this study.

John M. Mitchell, M.S.
Study Director
Toxicologist

Date

Ira W. Daly, Ph.D., D.A.B.T.
Senior Vice-President and
Director of Toxicology

Date

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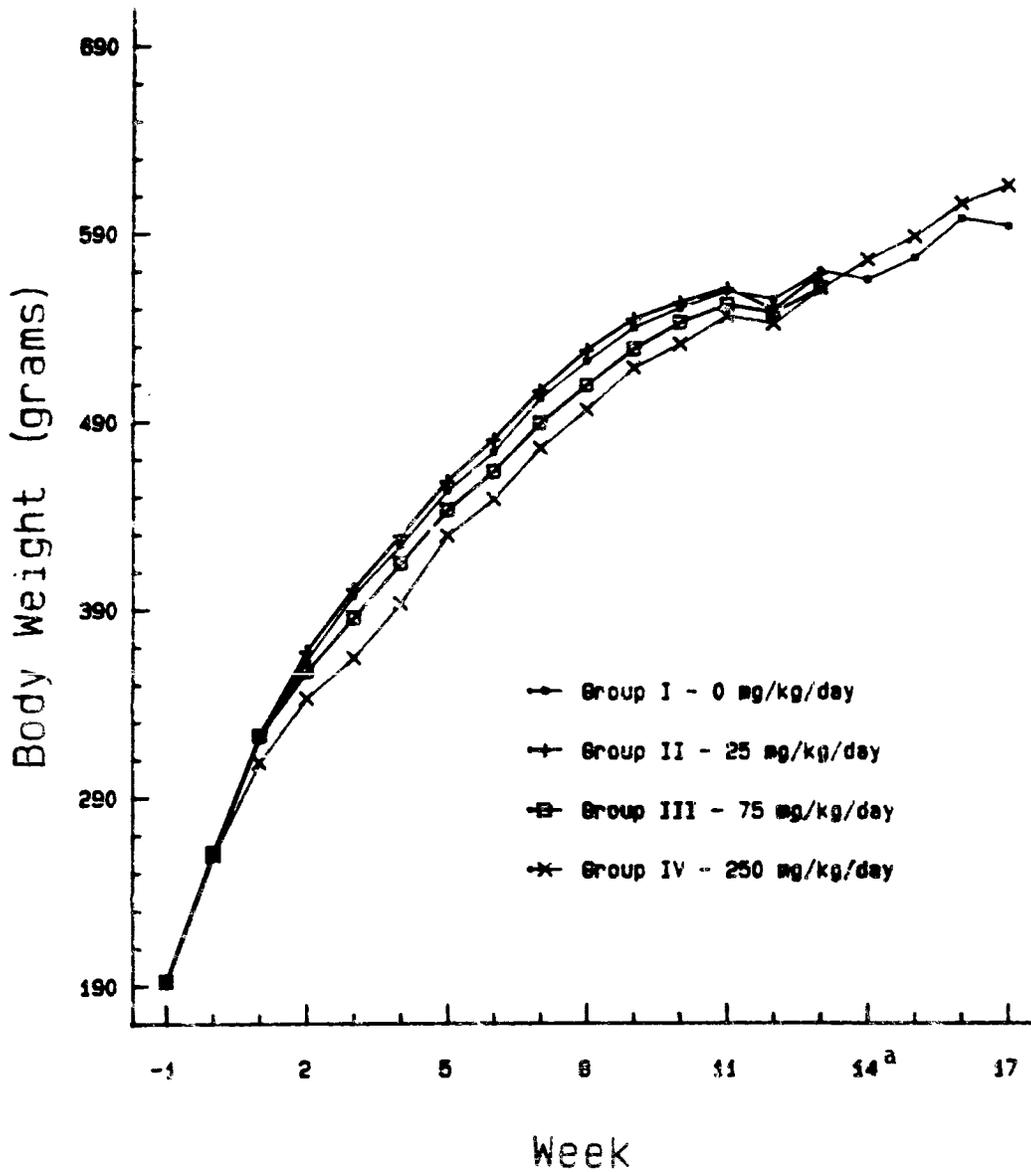
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Figure 1

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Group Mean Body Weights - Males



^aRecovery period initiated Week 14 (Groups I and IV).

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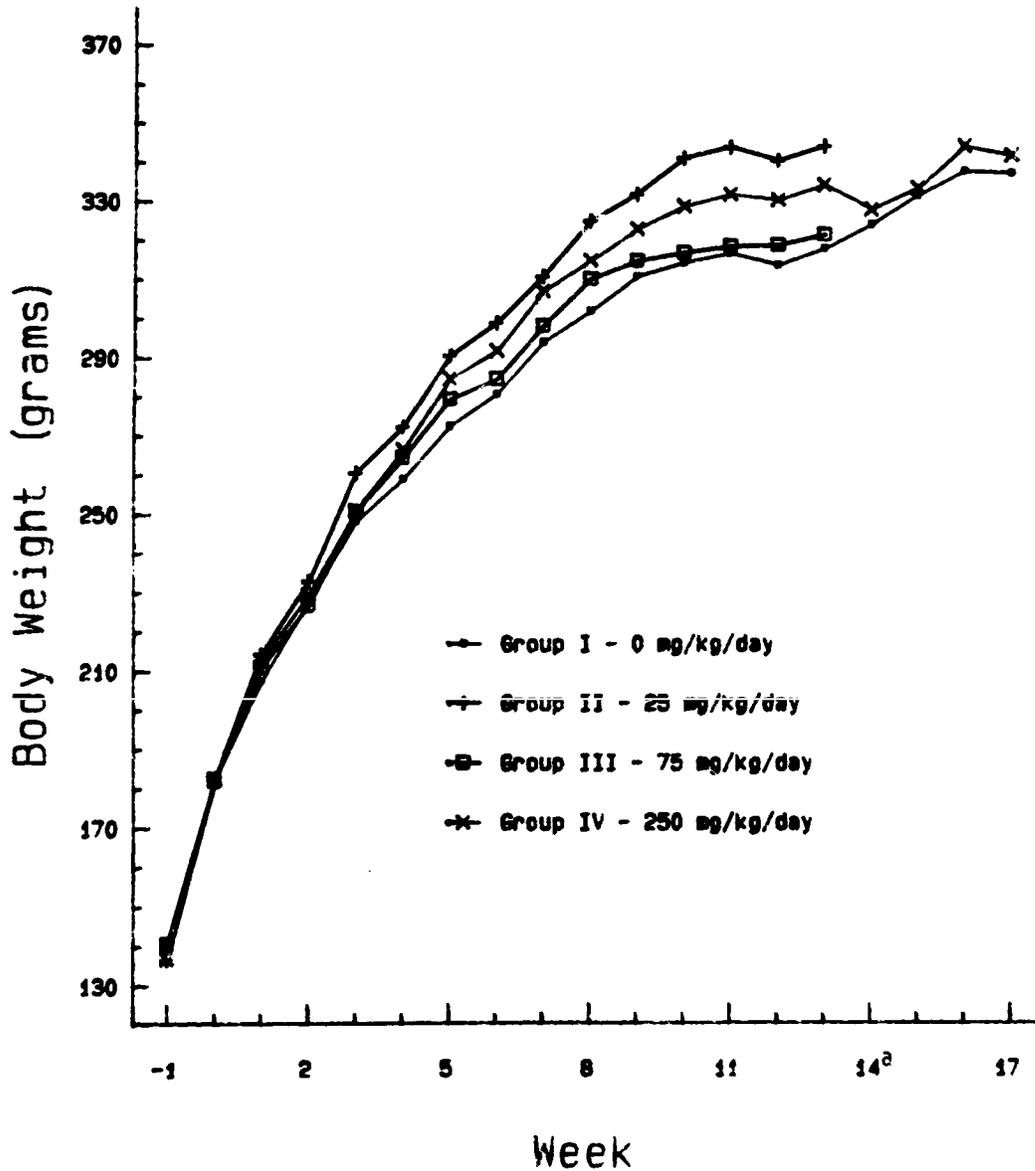
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Figure 1 (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Group Mean Body Weights - Females



^aRecovery period initiated Week 14 (Groups I and IV).

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Appendix G

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

90-3589

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Preface

Differential leukocytes are expressed as percent total leukocytes (WBC) and as absolute values.

The following cells are identified and counted:

<u>Abbreviation</u>	<u>Type of Cell</u>
Mono	Monocyte
Lymph	Lymphocyte
Seg	Mature (segmented) neutrophil
Band	Band cell
Meta	Metamyelocyte
Myel	Myelocyte
Eosin	Mature (segmented) eosinophil
Baso	Mature (segmented) basophil
Atyp. Lymph.	Atypical lymphocyte
Blast	Blast
Prolymph	Prolymphocyte

Remarkable erythrocyte or leukocyte morphology and any other comments are noted under "Other". Abbreviations used are:

<u>Abbreviation</u>	<u>Cell Morphology</u>
Aniso.	Anisocytosis
NRBC	Nucleated erythrocyte
Polychr.	Polychromia
Poik.	Poikilocytosis
Sph.	Spherocytes

Range

1+ = slight
2+ = moderate
3+ = marked
4+ = extreme

NOTE: A key to statistical symbols is presented in Appendix A, Methodology and References - Statistical Analyses, pages A-9 through A-12.

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Termination - Males

Group mg/kg/day	An. No.	Absolute Values			Neutrophils					Other	
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin	Baso		
		STAT SYMBOL:	A-L	A-L-	KJ+						
I 0	1001		13.12	10102	2362	4	77	18	1	0	1+ Aniso.; 1 NRBC; 1+ Poik.; 1+ Polychr.; 1+ Sph.
	1002		11.67	10386	1050	2	89	9	0	0	
	1003		12.06	9286	2653	1	77	22	0	0	
	1004		11.60	9048	2436	1	78	21	0	0	1+ Poik.
	1005		10.63	9142	1382	1	86	13	0	0	
	1006		6.32	4993	1074	3	79	17	1	0	1+ Poik.
	1007		9.93	8043	1390	3	81	14	2	0	1+ Poik.; 1+ Polychr.
	1008		8.41	6812	1514	1	81	18	0	0	
	1009		13.01	6505	6245	1	50	48	1	0	
	1010		12.52	9515	2629	2	76	21	1	0	
	Mean		10.93	8383	2274						
	S.D.		2.18	1754	1534						
	N		10	10	10						

CONTAINS NO GRI



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G-3

Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Termination - Males (cont.)

Group mg/kg/day	An. No.	Absolute Values			Neutrophils					Other
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin	Baso	
	S.AT SYMBOL:	A-L	A-L-	KJ+						
II 25	2001	11.85	10784	356	4	91	3	2	0	
	2002	10.30	8137	2060	1	79	20	0	0	
	2003	11.76	10466	1176	1	89	10	0	0	
	2004	15.69	12866	1883	3	82	12	3	0	1 NRBC; 1+ Poik.
	2005	11.47	8602	2638	2	75	23	0	0	
	2006	11.88	9148	2257	3	77	19	1	0	
	2007	11.34	8845	2381	1	78	21	0	0	
	2008	7.43	6018	1114	3	81	15	1	0	
	2009	9.90	8415	1287	1	85	13	1	0	1+ Polychr.
	2010	10.79	7877	2698	2	73	25	0	0	
	Mean	11.24	9116	1785						
	S.D.	2.06	1873	770						
	N	10	10	10						

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CONTAINS NO GRI

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery PeriodTotal and Differential Leukocyte Count
and Erythrocyte Morphology
Termination - Males (cont.)

Group mg/kg/day	An. No.	Absolute Values			Neutrophils					Other	
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin	Baso		
		STAT SYMBOL:	A-L	A-L-	KJ+						
III 75	3001		18.42	13631	4237	3	74	23	0	0	1+ Poik.; 1+ Polychr.; 1+ Sph.
	3002		8.76	7709	876	2	88	10	0	0	
	3003		7.17	5019	2008	1	70	28	1	0	
	3004		9.30	7254	1674	4	78	18	0	0	1+ Poik.
	3005		11.00	8470	2200	2	77	20	1	0	
	3006		11.45	8358	2862	2	73	25	0	0	1+ Poik.
	3007		18.10	14118	3620	2	78	20	0	0	2+ Poik.
	3008		9.14	4753	3930	4	52	43	1	0	1+ Poik.; 1+ Polychr.
	3009		11.77	10122	1177	3	86	10	1	0	
	3010		10.55	8124	2110	3	77	20	0	0	
	Mean		11.57	8756	2469						
	S.D.		3.79	3133	1154						
	N		10	10	10						

CONTAINS NO CBI

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Termination - Males (cont.)

Group mg/kg/day	An. No.	Absolute Values			Neutrophils					Other
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin	Baso	
	STAT SYMBOL:	A-L	A-L-	KJ+						
IV 250	4001	15.30	11628	3366	2	76	22	0	0	
	4002	23.86	10498	12884	2	44	54	0	0	1+ Polychr.
	4003	10.62	6372	3717	3	60	35	1	0	1 Band
	4005	11.86	8302	3321	1	70	28	1	0	
	4006	9.46	5487	3784	1	58	40	1	0	
	4007	12.84	6163	6163	4	48	48	0	0	1+ Poik.; 1+ Sph.
	4008	12.53	9773	2631	1	78	21	0	0	1+ Polychr.
	4009	15.57	11522	3581	3	74	23	0	0	
	4010	10.62	8708	1805	1	82	17	0	0	1+ Poik.; 1+ Polychr.
					*					
	Mean	13.63	8717	4584						
	S.D.	4.35	2325	3324						
	N	9	9	9						

CONTAINS NO CBI

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Termination - Females

Group mg/kg/day	An. No.	Absolute Values			Neutrophils			Other		
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg Eosin Baso			
	STAT SYMBOL:	AL+	A-L-	A+L+						
I	1501	6.61	5024	1322	2	76	20	2	0	
0	1502	9.32	7642	1491	1	82	16	1	0	1+ Poik.
	1503	3.75	2625	975	2	70	26	2	0	1+ Polychr.
	1504	8.89	7112	1334	2	80	15	3	0	1+ Poik.
	1505	5.26	4524	579	3	86	11	0	0	1+ Poik.
	1506	9.94	8648	1093	1	87	11	1	0	
	1507	6.05	5324	605	1	88	10	1	0	1+ Poik.
	1508	10.73	9335	1180	2	87	11	0	0	1+ Poik.
	1509	7.01	4907	2103	0	70	30	0	0	1+ Poik.
	1510	10.37	7155	2592	4	69	25	1	0	1 Atyp. Lymph.; 1+ Poik.; 1+ Polychr.
	Mean	7.79	6230	1327						
	S.D.	2.39	2083	625						
	N	10	10	10						

CONTAINS NO CBI

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Termination - Females (cont.)

Group mg/kg/day	An. No.	Absolute Values			Neutrophils					Other
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin	Baso	
		STAT SYMBOL:	AI+	A-L-	A+L+					
11	2501	10.55	8546	950	5	81	9	3	0	2 Atyp. Lymph.;
	2502	11.17	6702	3910	3	60	35	2	0	1+ Poik.
	2503	10.54	9697	527	2	92	5	1	0	1+ Poik.
	2504	13.98	11883	1817	2	85	13	0	0	1+ Poik.
	2505	7.31	5702	1096	1	78	15	6	0	1+ Poik.;
	2506	11.33	8384	2832	0	74	25	1	0	1+ Polychr.
	2507	9.43	7355	1980	1	78	21	0	0	1+ Poik.
	2508	5.54	3712	1662	3	67	30	0	0	1+ Poik.;
	2509	7.00	6230	560	3	89	8	0	0	1+ Polychr.
	2510	10.41	7703	2290	2	74	22	2	0	1+ Poik.
										1+ Poik.;
										1+ Polychr.
	Mean	9.73	7591	1762						
	S.D.	2.48	2254	1063						
	N	10	10	10						

CONTAINS NO CBI

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Termination - Females (cont.)

Group mg/kg/day	An. No.	Absolute Values			Neutrophils					Other
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin	Baso	
	STAT SYMBOL:	AL+	A-L-	A+L+						
III 75	3501	9.02	7126	1804	1	79	20	0	0	1+ Poik.; 1+ Polychr.; 1+ Sph.
	3502	6.94	5136	1319	4	74	19	2	1	1+ Poik.; 1+ Polychr.
	3503	10.20	8160	1530	3	80	15	1	0	1 Atyp. Lymph.; 1+ Poik.
	3504	6.97	5088	1255	3	73	18	4	0	2 Atyp. Lymph.; 1+ Poik.
	3505	11.78	8835	2356	3	75	20	1	0	1 Atyp. Lymph.; 1+ Polychr.
	3506	8.16	5875	2203	1	72	27	0	0	
	3507	8.90	6230	2581	1	70	29	0	0	2+ Poik.
	3508	10.35	6728	3105	4	65	30	1	0	1+ Poik.
	3509	7.04	5702	1267	1	81	18	0	0	1+ Poik.
	3510	9.91	8820	991	1	89	10	0	0	1+ Poik.
	Mean	8.93	6770	1841						
	S.D.	1.66	1424	692						
	N	10	10	10						

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat
via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count
and Erythrocyte Morphology
Recovery - Males

Group mg/kg/day	An. No.	Absolute Values			Neutrophils				Other	
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin		Baso
	STAT SYMBOL:	F-	F-	F-						
I 0	1011	10.23	9514	614	1	93	6	0	0	
	1012	15.16	12583	2274	1	83	15	1	0	
	1014	15.21	13385	1825	0	88	12	0	0	
	1015	11.18	10062	1006	1	90	9	0	0	
	1016	13.51	9862	3107	2	73	23	2	0	
	1017	18.11	12858	5071	1	71	28	0	0	1+ Polychr.
	1018	18.41	14360	3682	2	78	20	0	0	2+ Poik.; 1+ Polychr.
	1019	14.66	12021	2346	1	82	16	1	0	1+ Polychr.
	1020	10.12	8804	1113	2	87	11	0	0	
		Mean	14.07	11494	2338					
	S.D.	3.10	1968	1431						
	N	9	9	9						
IV 250	4011	19.06	14087	3612	2	78	20	0	0	1+ Poik.
	4012	15.05	10084	4515	1	67	30	2	0	1+ Poik.
	4013	17.77	12617	4798	1	71	27	1	0	1+ Polychr.
	4014	10.55	6858	3692	0	65	35	0	0	1+ Polychr.
	4015	13.40	10988	2010	2	82	15	1	0	1+ Polychr.
	4016	14.85	11880	2822	1	80	19	0	0	1+ Polychr.
	4017	10.95	7118	3723	1	65	34	0	0	
	4018	11.37	8641	2729	0	76	24	0	0	1+ Poik.
	4019	11.41	9128	2054	2	80	18	0	0	1+ Poik.
	4020	10.01	8809	1101	1	88	11	0	0	
	Mean	13.34	10021	3106						
	S.D.	2.97	2363	1173						
	N	10	10	10						

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Appendix G (cont.)

A Subchronic Oral Toxicity Study of UVASORB HA-88 in the Rat via Oral Gavage Administration with a 4-Week Recovery Period

Total and Differential Leukocyte Count and Erythrocyte Morphology Recovery - Females

Group mg/kg/day	An. No.	Absolute Values			Neutrophils					Other
		WBC thous/ μ l	Lymph	Seg	Mono	Lymph	Seg	Eosin	Basc	
STAT SYMBOL:										
		F-	F-	F-						
I 0	1511	6.45	4966	1419	1	77	22	0	0	
	1512	10.03	9328	602	1	93	6	0	0	
	1513	7.71	7170	463	1	53	6	0	0	1+ Poik.
	1514	10.12	9310	607	1	92	6	1	0	1+ Poik.
	1515	6.92	5398	1522	0	78	22	0	0	1+ Poik.; 1+ Polychr.
	1516	10.48	8594	1677	1	82	16	1	0	
	1517	5.67	5160	454	1	91	8	0	0	1+ Poik.; 1+ Polychr.
	1518	5.90	4956	885	0	84	15	1	0	1+ Poik.
	1519	6.72	5040	1478	1	75	22	1	0	1 Atyp. Lymph.; 1+ Polychr.
		Mean	7.78	6658	1012					
	S.D.	1.92	1949	506						
	n	9	9	9						
IV 250	4511	9.03	6953	2077	0	77	23	0	0	
	4512	12.20	10004	1952	1	82	16	1	0	1+ Poik.
	4513	11.66	7346	4198	1	63	36	0	0	
	4514	6.32	5688	569	0	90	9	1	0	1+ Poik.
	4515	8.82	7762	970	1	88	11	0	0	
	4516	9.69	7655	1938	1	79	20	0	0	1+ Poik.
	4517	9.05	5882	3077	1	65	34	0	0	
	4518	9.28	7053	1856	2	76	20	2	0	1+ Poik.
	4519	6.53	4898	1557	1	75	24	0	0	
	4520	3.40	2584	782	1	76	23	0	0	
				*						
	Mean	8.60	6583	1899						
	S.D.	2.60	1981	1090						
	N	10	10	10						