PDCN: 88940000229

8EHQ-0295-12987

(1)

Olin

ENVIRONMENTAL HYGIENE AND TOXICOLOGY DEPARTMENT
91 SHELTON AVENUE, P.O. BOX 30-9643, NEW HAVEN, CONNECTICUT 06511
(203) 781-5400

8EHQ-94-12987
SP001 02/01/95

January 25, 1995

Document Processing Center (7407)
ATTN: TSCA 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M. Street, S.W.
Washington, D.C. 204060-0001

(B)

Contains No CBI

ORIGINAL

95 FEB -1 AM 8:19

RECEIVED

Gentlemen:

Re: 8EHQ-94-12987 - 8(e) "Substantial Risk Notification" Acute Inhalation Toxicity Evaluation in Rats with Copper, N-Hydroxypyridine-(1H)-Thione, (CAS# 14915-37-8)

As a follow up to Olin's previous submission of draft results from the Nose-Only Acute Inhalation Toxicity Study in Rats with Copper, N-Hydroxypyridine-(1H)-Thione to EPA TSCA under section 8(e) "Substantial Risk Notification", one copy of the final report is attached.

Olin has incorporated these findings into the MSDS. We have indicated it is an inhalation hazard and have included the warning statement "May Be Fatal If Inhaled". Olin is in the process of developing an internal worker exposure standard for an 8 hr. TWA. In the interim a 30-minute short term exposure limit of 0.40 mg/m^3 will be recommended.

If you have any questions or require more information, please call me at (203) 495-8550, ext. 5779.

Very truly yours,

Nicholas P. Skoulis

Nicholas P. Skoulis, Ph.D.
Manager, Toxicology

89950000106

cc: S. J. Barbee
N. J. Barone
K. J. Christy
D. A. Farmer, Jr.
R. J. Martin
G. B. Schifilliti

RECEIVED 2/8/95

CUOM8e.195

Contains no CBI

Nose-Only Acute Inhalation Toxicity Evaluation on Copper Omadine® [Copper, N-Hydroxypyridine-(1H)-Thione] in Rats

TEST ARTICLE: Copper Omadine®

PERFORMING LABORATORY: IRDC
500 North Main Street
Mattawan, MI 49071
616/668-3336

LABORATORY PROJECT IDENTIFICATION: 397-062

DATA REQUIREMENTS: Guideline 81-3

PURCHASE ORDER RELEASE: FP-CS-NH-009-1809

AUTHOR: Roger J. Hilaski, M.A.

RECEIVED
95 FEB -1 AM 9:20

SPONSOR: Olin Corporation
Environmental Hygiene and Toxicology Department
91 Shelton Avenue
New Haven, CT 06511

DATE OF STUDY COMPLETION: October 27, 1994

IRDC

STATEMENT OF NO DATA CONFIDENTIALITY CLAIM

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

Sponsor _____ 1/25/95
Olin Corporation

Sponsor's Agent _____ Date 12/9/94
Nick Skoulis, Ph.D.

397-062

IRDC

STATEMENT OF COMPLIANCE

This study meets the requirements for 40 CFR Part 160.

Study Director: Roger Hilaski Date 10-26-94
Roger J. Hilaski, M.A.

Sponsor/Submitter: Nicholas P. Skoulis Date 12/9/94
Nick Skoulis, Ph.D.
Sponsor's Representative for
Scientific Purposes

Submitter: G B Schiefelbein 1/25/95

397-062

TABLE OF CONTENTS

1. Quality Assurance Statement. 6
2. Synopsis 7
3. Study Summary. 8
   3.1. Objective 8
   3.2. Study Schedule. 8
4. Materials and Methods. 8
   4.1. Test Article. 8
   4.2. Experimental Design 8
   4.3. Test System 9
   4.4. Test Material Administration 10
   4.5. Determination of Exposure Concentrations 10
   4.6. Appearance, Behavior and Mortality 11
   4.7. Body Weights. 11
   4.8. Necropsy. 12
   4.9. Data Retention 12
5. Results 13
   5.1. Exposure Atmosphere Characterization. 13
   5.2. Environment 14
   5.3. Behavior and Mortality. 14
   5.4. Body Weights 16
   5.5. Necropsy 16
6. Signatures. 17
7. Study Director's Statement 18
8. Glossary 19

Table No.
   1. Actual Aerosol Concentrations of Copper Omadine® Determined Analytically 20
   2. Particle Size Distribution Data 21
   3. Body Weights for Animals "Found Dead" 22

Figure No.
   1. Diagram of the Generation and Exposure System 23
   2-11. Numerical Data and Graph of Particle Size Distribution 24-33

TABLE OF CONTENTS

Supplementary Information	Appendix
Test Material Information	A
Individual Pharmacotoxic Signs	B
Individual Body Weights	C
Macroscopic Findings	D
Analytical Methods	E
Comments on Study Data	F

1. QUALITY ASSURANCE STATEMENT

Below are the inspections conducted by the IRDC Quality Assurance department and the dates that any findings were reported to the Study Director and Management:

Date(s) of Inspection	Study Phase Inspected	Date(s) Reported to Study Director/Management
04-29-94	Protocol Review for Compliance with GLP Regulations	a
05-09-94	Body Weight Measurement	
05-27-94	Body Weight Measurement	a
08-19-94	Data Review	a
08-19-94	Report Review	a
10-25-94	Report Review	a

Approved By: Theresa A Stewart 10/27/94

Theresa A. Stewart, B.Sc.
Manager, Quality Assurance

Date

[a]There were no Quality Assurance findings to report to the Study Director and Management.

2. SYNOPSIS

Five groups of 5-male and 5-female albino rats were exposed for four hours, using nose-only exposure methods, to aerosol concentrations of 0.8, 0.4, 0.11, 0.01 and 0.04 mg/L (Groups I, II, III, IV and V, respectively) of Copper Omadine®. The mass median aerodynamic diameter ranged from 1.4 to 2.8 micrometers with a mean of 1.8 micrometers for the five groups. The significant pharmacotoxic signs noted immediately post-exposure were death, labored breathing, rales, rapid respiration, tremors, abnormal gait, increased salivation and excessive lacrimation. During the two week post-exposure observation period the significant pharmacotoxic signs noted were death, labored breathing, rapid respiration, rales, tremors, cold to touch and decreased activity. All animals from Groups I and II died prior to the first post-exposure body weight collection. All males from Group III died prior to the first post-exposure body weight collection. The body weight gain for the one surviving female from Group III was normal for the entire two-week post-exposure period. Body weight gain for the Group IV animals was normal for both sexes during the entire two-week post-exposure period. Group V males (four surviving) exhibited a reduced body weight gain during the first post-exposure week but returned to normal during the second post-exposure week. Group V females showed a normal body weight gain during the post-exposure period. At necropsy the significant findings noted were red discoloration of the lungs.

Based on these results, the LC50 for Copper Omadine was considered to be 0.07 mg/L with 95% confidence limits of 0.05 to 0.09 mg/L.

3. STUDY SUMMARY

3.1. OBJECTIVE

The purpose of this study was to evaluate the acute toxicity of Copper Omadine® [Copper, n-hydroxypyridine-(1H)-thione] when administered via the inhalation route according to the Guidelines of Environmental Protection Agency: Human and Domestic Animals....Section 81-3. EPA 540/9-28-025, November 1984 and the Guidelines of the Organization for Economic Cooperation and Development (Acute Inhalation Toxicity, No. 403) issued May, 1981.

3.2. STUDY SCHEDULE

Group Number	Study Initiated	Date of Exposure	Date of Final Observation
I	4-20-94	5-09-94	5-09-94
II	4-20-94	5-17-94	5-17-94
III	4-20-94	5-20-94	6-03-94
IV	4-20-94	6-08-94	6-22-94
V	4-20-94	6-14-94	6-28-94

4. MATERIALS AND METHODS

4.1. TEST ARTICLE

The test material was received from the Olin Research Center on April 19, 1994. The pertinent test material information is located in Appendix A.

4.2. EXPERIMENTAL DESIGN

Five groups of five male and five female albino rats were exposed to dust aerosol atmospheres of Copper Omadine® for four hours using nose-only exposure methods. After exposure, surviving animals were held for a 14-day observation period. Animals were observed for mortality and pharmacotoxic signs upon removal from the exposure chamber and once for mortality and once for pharmacotoxic signs daily thereafter. Body weights were obtained weekly. All animals dying on study received a complete necropsy. At the end of the observation period, surviving animals were euthanized and received a complete necropsy. The following summarizes the experimental design of this study:

Table 4.2

Group Number	Desired Concentration (mg/L)	Number of Animals MALE	Number of Animals FEMALE
I	1.0	5	5
II	0.4	5	5
III	0.1	5	5
IV	0.01	5	5
V	0.04	5	5

4.3. TEST SYSTEM

4.3.1. Species

Rat

4.3.2. Strain

Crl:CD® BR VAF/Plus®
Sprague-Dawley derived

4.3.3. Source

Charles River Laboratories
9801 Shaver Road
Portage, Michigan 49081

4.3.4. Reason for Selection

The rat was selected as the test system because it is a universally used model for evaluating acute toxicity.

4.3.5. Body Weight Range

Male weights ranged from 247 - 292 grams and females ranged from 186 - 224 grams on day the of exposure.

4.3.6. Age at Start of Study

Approximately 53 to 64 days of age.

4.3.7. Method of Identification

Ear tag

4.3.8. Quarantine

Acclimated for a period of at least 11 days prior to exposure.

4.3.9. Housing

Individual stainless steel wire mesh cages.

4.3.10. Environmental Conditions (Quarantine and Post-Exposure Periods)

Animal room with controlled temperature, humidity and light (12 hours light and 12 hours dark). Maintained in accordance with the recommendations contained in the D.H.H.S. Publication entitled "Guide for the Care and Use of Laboratory Animals".

4.3.11. Selection for Study

Selected from a colony maintained for acute work based on body weight and the appearance of good health.

4.3.12. Diet and Water

Certified Rodent Chow® #5002, Purina Mills, Inc., St. Louis, Missouri. Diet and water were freely available except during exposure.

4.4 TEST MATERIAL ADMINISTRATION

4.4.1. Animal Exposure

The animals were exposed to an aerosol atmosphere of Copper Omadine® for four hours (as measured from the end of the 7 minute chamber equilibration time) in a 60 L stainless steel and acrylic nose-only exposure chamber. Chamber ventilation air was provided by the aerosol generation system supplied from a compressed air system. The mean chamber airflow rate was 38 L/min.

4.4.2. Generation of Exposure Atmospheres

Exposure atmospheres were generated with the system similar to that shown in Figure 1. Test material was delivered to an air-micronizer (Fluid Energy model 00) at a constant rate with an auger dust feeder of in-house design. The test material, mixed with air, passed through the micronizer into the chamber. The aerosol exited via chamber exhaust to a fume hood. Presented in the following table are the generation system operation parameters.

Table 4.4.2

Group Number	Auger Size (cm)	Air-Micronizer RPM	Air-Micronizer Input Pressure (psig)	Air-Micronizer Grinding Pressure (psig)	Total Airflow (L/min)
I	1.27	0.6	36	38	38
II	0.95	1.0	36	38	38
III	0.64	4.6[a]	36	38	38
IV	0.64	0.8[b]	36	38	38
V	0.64	1.1	36	38	38

[a] increased from 0.3 rpm after 64 minutes.
b decreased from 1.5 rpm after 76 minutes

4.5. DETERMINATION OF EXPOSURE CONCENTRATIONS

4.5.1. Nominal Exposure Concentrations

The nominal exposure concentration for each group was calculated by dividing the total amount of test material used during the generation of test material (exposure time plus T_{99} time) by the total volume of air passed through the chamber.

4.5.2. Actual Exposure Concentrations

Actual exposure concentrations were determined using a Sponsor provided quantitative procedure for Copper Pyrithione in the test material. Samples of the aerosol atmosphere were collected on pre-weighed 25 mm glass-fiber filters (Gelman Catalog No. 61630), held in open-faced filter holders and positioned near the breathing zone of the animals. Chamber atmospheres were drawn through filter pads using the following parameters:

Table 4.5.2.

Group Number	Sampling Air Flow Rate (L/min)	Duration (Minutes)	Fisher-Porter Flow Meter Number
I	1.0	5	F/P-1/8-25-G-5/81
II	1.0	10	F/P-1/8-25-G-5/81
III	6.0	5	F/P-1/4-25-G-5/81
IV	6.0	30	F/P-1/4-16-G-5/81
V	6.0	15	F/P-1/4-16-G-5/81

The filters were placed into amber bottles for analytical analysis. Refer to Appendix E for the analytical methods employed.

4.5.3. Particle Size Determinations

The aerosol particle size distribution in the exposure atmosphere was determined with a cascade impactor (Andersen® 8-stage) two times during each exposure. The chamber was sampled at 28.3 L/min for five minutes for Groups I and II, twenty minutes for Group III, ninety minutes for Group IV and sixty minutes for Group V. The amount of aerosol collected on each stage was determined gravimetrically for Groups I, II, III and V and analytically for Group IV. The cumulative percentages, by weight, of particles with aerodynamic diameters smaller than the cutoffs for the individual stages of the impactor were derived and plotted by computer. Figures 2 thru 11 are numerical data and graphical representations of the particle size distributions. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated by a method similar to that of Raabe (Environ. Sci. Technol., 12: 1162-1167, 1978).

4.6. APPEARANCE, BEHAVIOR AND MORTALITY

Observed for pharmacotoxic signs and mortality following exposure; two times daily during 14 day post-exposure period, once for pharmacotoxic signs and once for mortality. The use of a computerized data collection system (Xybion) required body weights and observations to be defined in such a manner that day 1 is the day of exposure and days 2-15 are post-exposure days 1-14.

4.7. BODY WEIGHTS

Body weights were recorded just prior to the exposure and at 7 and 14 days post-exposure. Animals were also weighed when found dead.

4.8. NECROPSY

All animals underwent a complete necropsy. Surviving animals were euthanized by intraperitoneal injection of sodium pentobarbital with subsequent exsanguination from the abdominal aorta. All major organs in abdominal and thoracic cavities were observed for gross abnormalities by veterinary pathologists. No tissues were saved.

4.9. DATA RETENTION

All raw data, documentation, records, protocols, and final reports generated as a result of this study will be retained at IRDC and will be made available for inspection upon request by authorized personnel of the Sponsor for a period of 5 years following study completion (final report issue date).

5. RESULTS

5.1 EXPOSURE ATMOSPHERE CHARACTERIZATION

5.1.1. Nominal Exposure Concentration

Presented below is the nominal exposure concentration for Copper Omadine®.

Table 5.1.1

Group Number	Nominal Exposure Concentration (mg/L)
I	3.9
II	1.6
III	0.32
IV	0.11
V	0.21

5.1.2. Actual Exposure Concentrations

Actual Exposure Concentrations (See Table 1): Actual exposure concentration results, determined analytically, are presented as follows:

Table 5.1.2

Group Number	Total Formulation Concentration (mg/L) Mean	S.D.
I	0.8	0.22
II	0.4	0.86
III	0.11	0.029
IV	0.01	0.005
V	0.04	0.013

S.D.= Standard Deviation

Based on these results, the four hour LC_{50} for Copper Omadine® in rats was considered to be 0.07mg/L with 95% confidence limits of 0.05 to 0.09 mg/L.

5.1.3. Particle Size Distribution

Graphical representations and numerical data of the aerosol partical size distribution in the exposure atmosphere are presented in Figures 2 through 11. The individual mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) for each group are presented in Table 2 and a mean of these values are presented as follows:

Table 5.1.3

Group Number	MMAD (micrometers)	GSD
I	2.5	1.98
II	2.0	1.96
III	1.6	2.05
IV	1.3	1.85
V	1.6	2.03

5.2 ENVIRONMENT

Temperature, relative humidity and chamber airflow were monitored continuously during the exposure and recorded at 30 minute intervals. In addition, the oxygen content of the exposure atmosphere was measured once during the exposure. The results of these measurements are summarized as follows:

Table 5.2

Group Number	Temperature C°		Relative Humidity (%)		Chamber Air Flow Rate (L/min)		Oxygen Content (%)
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
I	22	0.5	20	2.9	38	0.00	20.8
II	23	0.6	10	0.8	38	0.00	21.0
III	23	0.5	14	1.6	38	0.00	20.8
IV	22	0.5	11	1.9	38	0.00	20.9
V	21	1.1	12	1.0	38	0.00	20.9

S.D. - Standard Deviation

The low humidity resulted from the dry compressed air used to generate the aerosol.

5.3. BEHAVIOR AND MORTALITY (See Appendix B):

The significant pharmacotoxic signs noted during the study are listed below:

Group I
All dead immediately post-exposure

Group II
All dead immediately post-exposure

Group III
- Immediately post-exposure
  - Labored Breathing: 5 males, 5 females
  - Decreased Activity: 5 males, 5 females
  - Tremors: 1 male, 1 female
  - Increased Salivation: 5 males, 3 females
  - Excessive Lacrimation: 1 female
  - Death: 5 males, 3 females
- Post-Exposure period:
  - Death: 1 female
  - Labored Breathing: 1 female
  - Decreased Activity: 1 female
  - Rapid Respiration: 1 female

Group IV
- Immediately post-exposure
  - Rapid Respiration: 5 males and 4 females
  - Increased Salivation: 4 males
  - Decreased Activity: 4 males and 5 females
- Post-Exposure Period:
  - Rapid Respiration: 5 males and 2 females
  - Decreased Activity: 3 males

Group V
- Immediately post-exposure
  - Labored Breathing: 2 males and 3 females
  - Decreased Activity: 5 males and 4 females
  - Cold to Touch: 1 female and 1 male
  - Rapid Respiration: 3 males and 2 females
  - Increased Salivation: 2 males and 3 females
  - Excessive Lacrimation: 1 female
  - Tremors: 1 male
  - Rales: 1 male
  - Abnormal gait: 1 female
- Post-Exposure Period
  - Rapid Respiration: 4 males and 5 females
  - Death: 1 male
  - Tremors: 1 male
  - Cold to Touch: 1 male and 1 female
  - Labored Breathing: 1 male

The following summarizes the mortality data:

Table 5.3a

Group Number	Total Formulation Concentration (mg/L)	Number of Deaths/Number Exposed Male	Female
I	0.8	5/5	5/5
II	0.4	5/5	5/5
III	0.11	5/5	4/5
IV	0.01	0/5	0/5
V	0.04	1/5	0/5

Individual pharmacotoxic sign tables appear in Appendix B.

The following table presents the mortalities by study day:

Table 5.3b

Group Number	Number Died on Study Day 0	1	2 - 14
I	10	NA	NA
II	10	NA	NA
III	8	1	0
IV	0	0	0
V	0	1	0

NA - Not applicable

5.4. BODY WEIGHTS (See Appendix C)

All animals for Groups I and II died prior to the first post-exposure body weight collection. The body weight gain for the one surviving female from Group III was normal for the entire 14-day post-exposure. The body weight gain for the Group IV animals was normal for both sexes during the entire two-week post-exposure period.The body weight gain for the four surviving males from Group V was decreased during the first post-exposure week but returned to normal during the second week. Body weight gain for the Group V females was normal during the entire two-week post-exposure period.The body weight data is summarized as follows:

Table 5.4

Mean Body Weight (g) at Indicated Interval

Group Number	Sex	Pre-Exposure	Days Post-Exposure 7	14
I	M	278	NA	NA
	F	193	NA	NA
II	M	286	NA	NA
	F	203	NA	NA
III	M	255	NA	NA
	F	208*	232	266
IV	M	287	313	345
	F	220	240	264
V	M	276	290	340
	F	204	232	249

* NA- Not applicable
one surviving female

Body weights for animals "found dead" are located in Table 3.

5.5. NECROPSY (See Appendix D)

At necropsy the finding of discolored lungs appeared in 10 of 10 animals exposed to 0.4 mg/L and 1 of 10 animals exposed to 0.04 mg/L. Discolored lungs were not observed in the animals exposed to 0.01 mg/L.

IRDC

6. SIGNATURES

Prepared By: _____ 10/26/94
David A. Lewis, B.A.
Senior Inhalation Technologist,
Inhalation Toxicology
Date

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Benjie A. Culp
Department Manager,
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Date

Reviewed By: _____ 10/26/94
Richard Thelemann, B.S.
Chemist
Inhalation Toxicology
Date

Reviewed By: C.E. Ulrich Oct. 26, 94
Charles E. Ulrich, B.S.
Director
Inhalation Toxicology
Date

7. STUDY DIRECTOR'S STATEMENT

There were no significant deviations from the Good Laboratory Practice Standards which affected the quality or integrity of the study. This study was conducted in conformance with the Good Laboratory Practice Standards. Comments on Study Data are presented in Appendix F. This report accurately reflects the raw data obtained during the performance of the study.

Roger Hilaski

Roger J. Hilaski, M.A.
Staff Toxicologist
Inhalation Toxicology
Study Director

10-27-94
Date

8. GLOSSARY

Actual concentration - An independent measure of the amount of test material (per sample volume, e.g., mg/L) present in the exposure chamber. It is based upon analytical determination (usually gravimetric or instrumental) of the test material.

Concentration - Amount of a given material in a given volume of air (or gas); e.g., mg/L, mg/m^3 or ppm.

Desired concentration - The target exposure level of test material (per volume unit, e.g., mg/L) selected for each exposure group.

Exposure atmosphere types -

Vapors:	The gas form of any substance which is usually a liquid or solid at room temperature.
Gases:	A substance which is neither liquid nor solid at room temperature, has a very low density and viscosity, relatively great expansion and contraction with changes in pressure and temperature, diffuses readily and spontaneously distributes uniformly throughout any container.
Aerosols:	Solid or liquid particles dispersed or suspended in air or a gas, e.g., mist, spray, fog, smoke, etc.

Exposure day - Defined as the day or days when an exposure was conducted for a study.

Exposure duration - The time interval during which the animals were exposed to the test material, e.g., 1 hour, 4 hours, etc.

Geometric standard deviation (GSD) - A number defining the dispersion of the aerosol size distribution.

Inhalable particles - Those materials that are deposited anywhere in the respiratory tract.

Mass median aerodynamic diameter (MMAD) - A measurement of aerosol size based on the inertial/aerodynamic properties of the particles. The measurements are usually made with a cascade impactor.

Nominal concentration - A gross estimate of exposure concentration based upon test material usage. The total amount of test material used during a given exposure day divided by the total volume of air passed through the chamber during the exposure.

Respirable particles - Those materials that are deposited in the gas-exchange region of the lung.

Respiratory tract - Composed of the conducting airway including the nose, mouth, pharynx, trachea, bronchi, bronchioles and alveoli.

Saturated vapor concentration - The concentration (usually in ppm) of a vapor in equilibrium with its liquid at a given temperature.

psig - Pounds per square inch, gauge

psia - Pounds per square inch absolute

T_{99} - The time required for an exposure system to change from an equilibrated state to attain 99% of a new concentration level. This time interval is referred to as "chamber equilibrium time", is usually expressed in minutes and is calculated as follows:

$$T_{99} = 4.60 \times \frac{\text{Chamber volume}}{\text{Chamber flow rate}}$$

Table 1. Actual Aerosol Concentrations of Copper Omadine® Determined Analytically

Group Number	Sample Number	Concentration (mg/L)
I	1	1.1
	2	0.8
	3	0.7
	4	0.6
II	1	0.44
	2	0.35
	3	0.49
	4	0.30
III	1	0.10
	2	0.09
	3	0.09
	4	0.15
IV	1	0.01
	2	0.02
	3	0.01
	4	0.01
V	1	0.05
	2	0.04
	3	0.03
	4	0.02

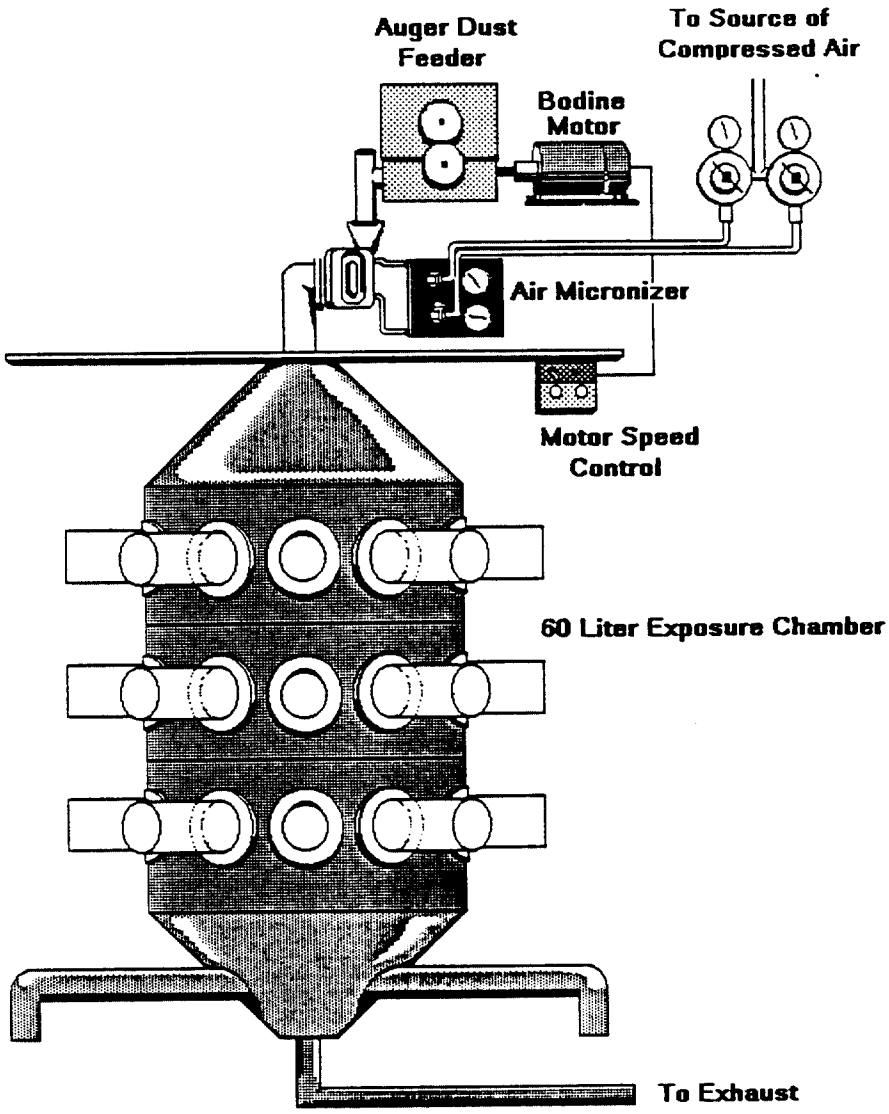
Table 2. Particle Size Distribution Data

Group Number	Mass Median Aerodynamic Diameter (micrometers)	Geometric Standard Deviation
I	2.2	1.92
	2.8	2.04
II	1.9	1.92
	2.0	1.99
III	1.8	2.12
	1.4	1.98
IV	1.3	1.85
	1.6	2.09
V	1.6	1.98
	1.6	2.07

Table 3. Body Weights for Animals "Found Dead"

Group Number	Animal Number	Sex	Study Day	Body Weight (g)
I	88031	M	0	270
	88032	M	0	273
	88033	M	0	266
	88034	M	0	275
	88035	M	0	262
	88036	F	0	179
	88037	F	0	190
	88038	F	0	190
	88039	F	0	185
	88040	F	0	189
II	88051	M	0	278
	88052	M	0	279
	88053	M	0	277
	88054	M	0	282
	88055	M	0	274
	88056	F	0	210
	88057	F	0	193
	88058	F	0	192
	88059	F	0	193
	88060	F	0	191
III	88071	M	0	243
	88072	M	0	246
	88073	M	0	230
	88074	M	0	237
	88075	M	0	232
	88076	F	1	197
	88077	F	0	195
	88078	F	0	197
	88080	F	0	182
V	88124	M	1	255

Figure 1. Diagram of the Generation and Exposure System



397-062

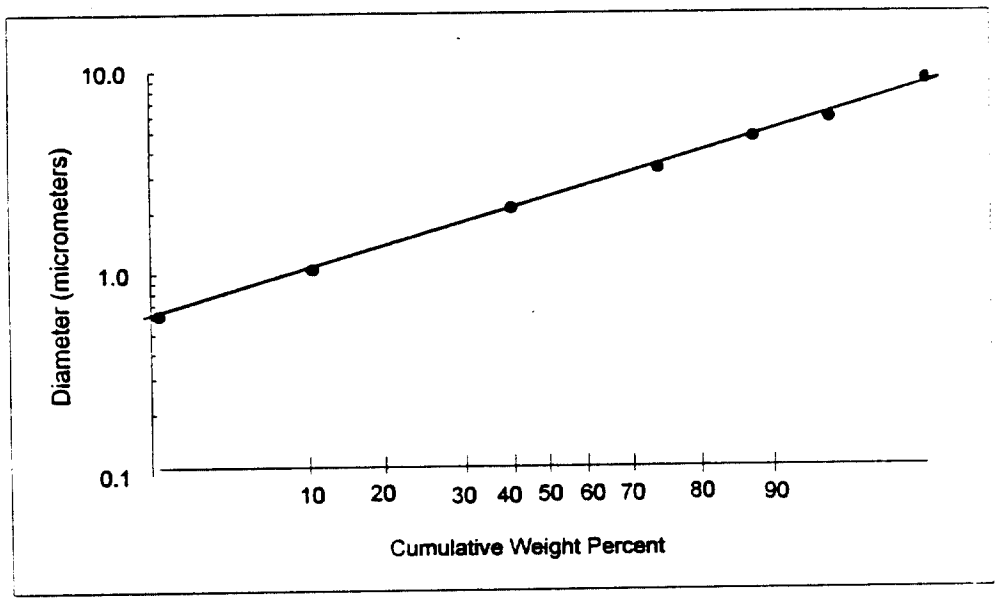
Figure 2. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 1

Particle Size Distribution for Copper Omadine

Sample Collected on 5/9/94 12:31pm

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	2.2	97.8
1	5.8	4.3	93.5
2	4.7	6.6	86.9
3	3.3	13.5	73.4
4	2.1	28.9	44.5
5	1.05	32.2	12.2
6	0.62	9.7	2.5
7	0.44	2.5	0.0
Filter	<0.44	0.0	0.0



The mass median aerodynamic diameter is 2.2

The geometric standard deviation is 1.92

ECD = Effective Cutoff Diameter

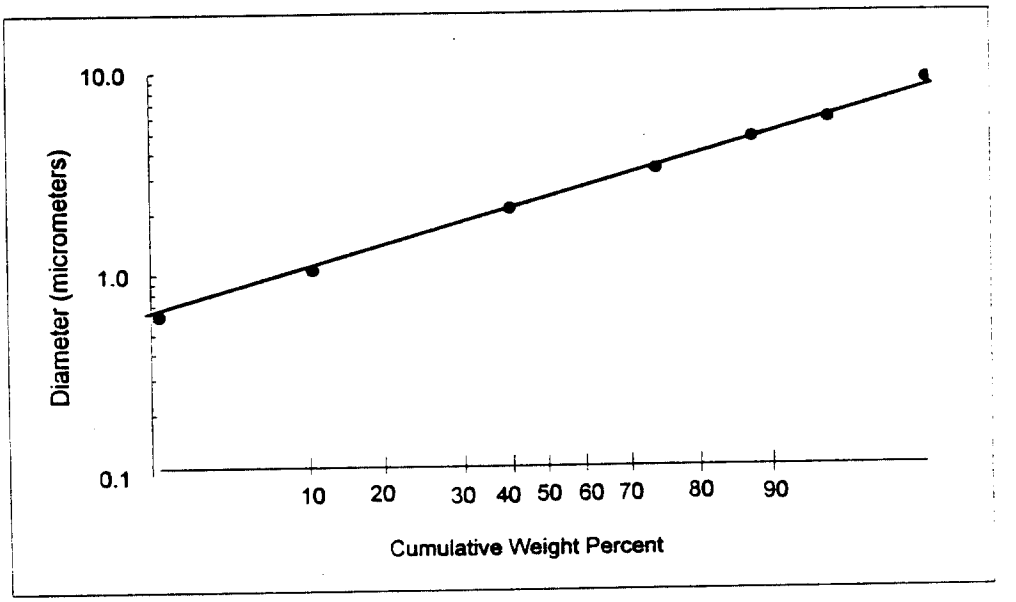
Figure 3. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 1

Particle Size Distribution for Copper Omadine

Sample Collected on 5/9/94 12:31pm

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	2.2	97.8
1	5.8	4.3	93.5
2	4.7	6.6	86.9
3	3.3	13.5	73.4
4	2.1	28.9	44.5
5	1.05	32.2	12.2
6	0.62	9.7	2.5
7	0.44	2.5	0.0
Filter	<0.44	0.0	0.0



The mass median aerodynamic diameter is 2.2

The geometric standard deviation is 1.92

ECD = Effective Cutoff Diameter

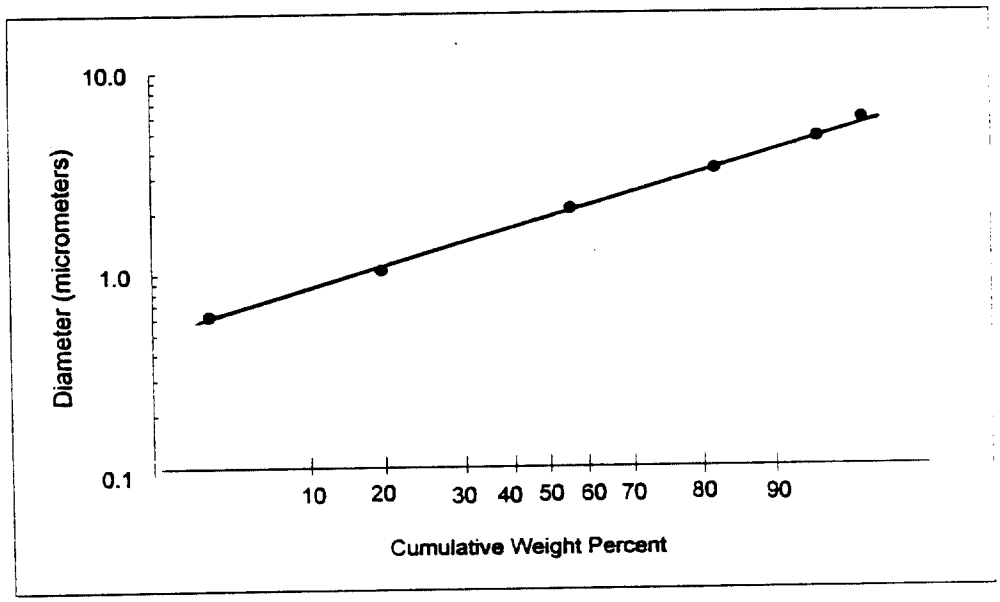
Figure 4. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 2

Particle Size Distribution for Copper Omadine

Sample Collected on 5/17/94 11:23am

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	1.6	98.4
1	5.8	3.0	95.3
2	4.7	2.7	92.6
3	3.3	10.7	81.9
4	2.1	25.3	56.6
5	1.05	35.7	20.9
6	0.62	16.5	4.4
7	0.44	4.1	0.3
Filter	<0.44	0.3	0.0



The mass median aerodynamic diameter is 1.9

The geometric standard deviation is 1.92

ECD = Effective Cutoff Diameter

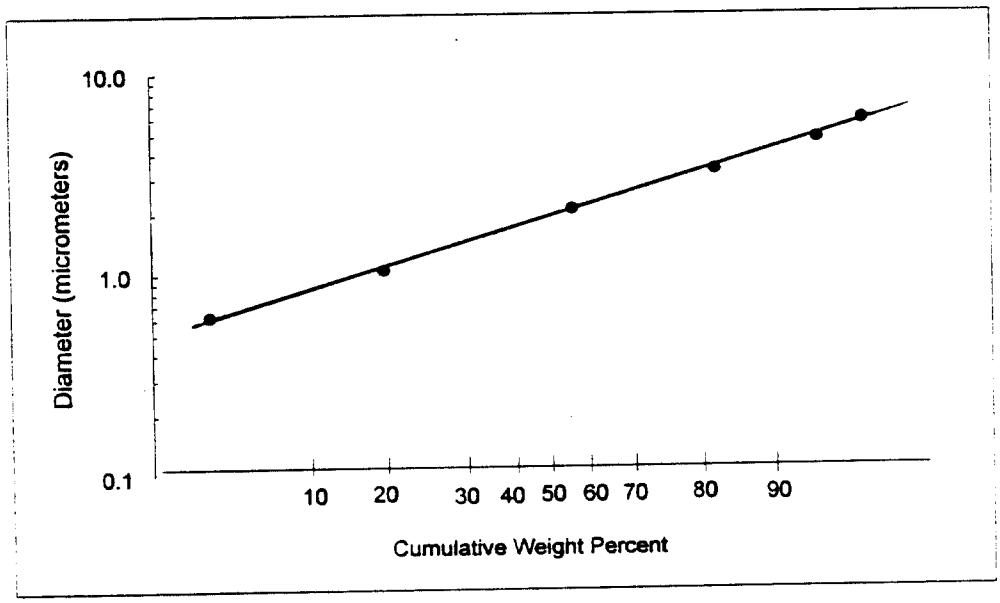
Figure 5. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 2

Particle Size Distribution for Copper Omadine

Sample Collected on 5/17/94 12:33pm

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	1.6	98.4
1	5.8	3.0	95.3
2	4.7	2.7	92.6
3	3.3	10.7	81.9
4	2.1	25.3	56.6
5	1.05	35.7	20.9
6	0.62	16.5	4.4
7	0.44	4.1	0.3
Filter	<0.44	0.3	0.0



The mass median aerodynamic diameter is 1.9

The geometric standard deviation is 1.92

ECD = Effective Cutoff Diameter

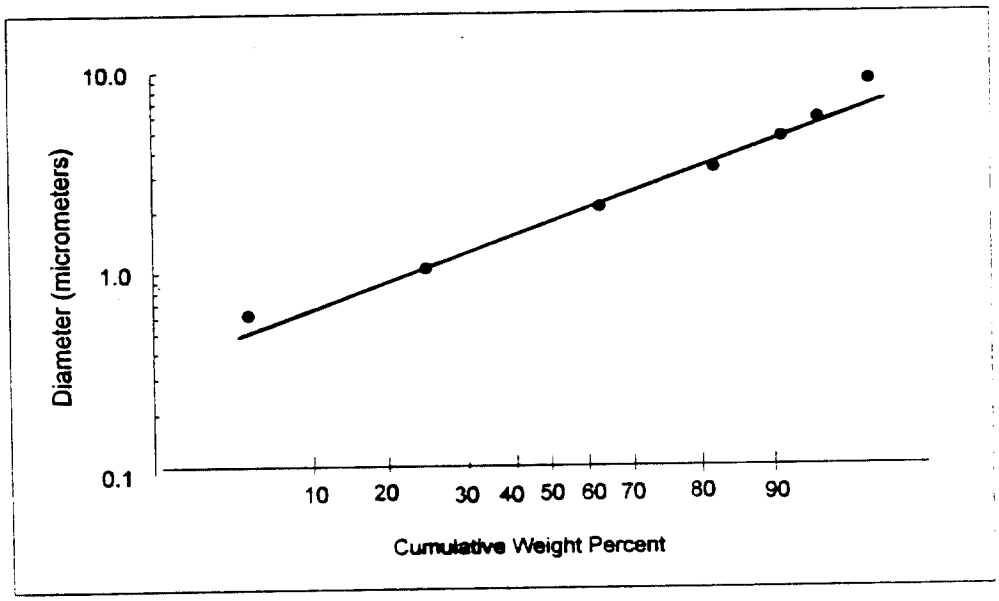
Figure 6. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 3

Particle Size Distribution for Copper Omadine

Sample Collected on 5/20/94 11:31am

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	4.3	95.7
1	5.8	3.0	92.7
2	4.7	3.0	89.7
3	3.3	7.8	82.0
4	2.1	19.5	62.4
5	1.05	34.8	27.6
6	0.62	21.1	6.5
7	0.44	6.0	0.5
Filter	<0.44	0.5	0.0



The mass median aerodynamic diameter is 1.8

The geometric standard deviation is 2.12

ECD = Effective Cutoff Diameter

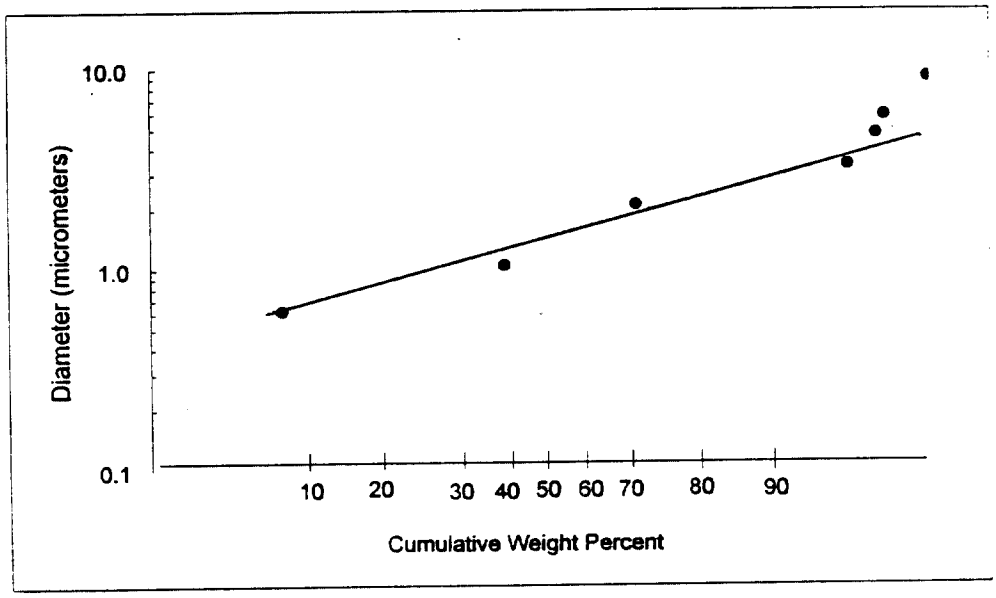
Figure 7. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 3

Particle Size Distribution for Copper Omadine

Sample Collected on 5/20/94 1:19pm

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	2.2	97.8
1	5.8	1.4	96.4
2	4.7	0.4	96.1
3	3.3	1.4	94.6
4	2.1	25.1	69.5
5	1.05	26.2	43.4
6	0.62	34.1	9.3
7	0.44	7.9	1.4
Filter	<0.44	1.4	0.0



The mass median aerodynamic diameter is 1.4

The geometric standard deviation is 1.98

ECD = Effective Cutoff Diameter

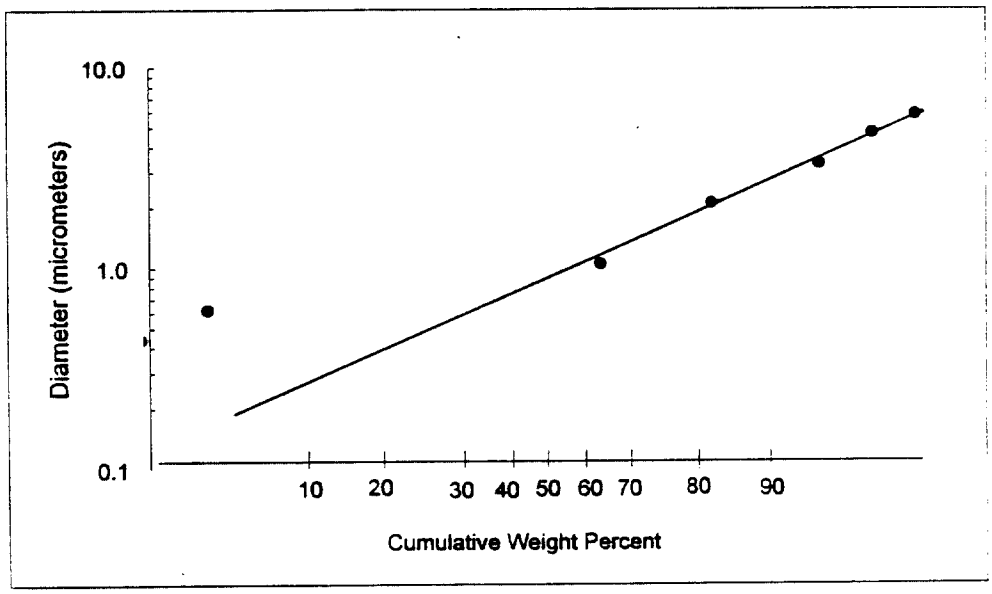
Figure 8. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 4

Particle Size Distribution for Copper Omadine

Sample Collected on 6/8/94 10:26am

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	0.7	99.3
1	5.8	1.6	97.6
2	4.7	1.6	96.1
3	3.3	3.0	93.0
4	2.1	11.1	82.0
5	1.05	19.1	62.9
6	0.62	58.4	4.4
7	0.44	2.4	2.0
Filter	<0.44	2.0	0.0



The mass median aerodynamic diameter is 1.3

The geometric standard deviation is 1.85

ECD = Effective Cutoff Diameter

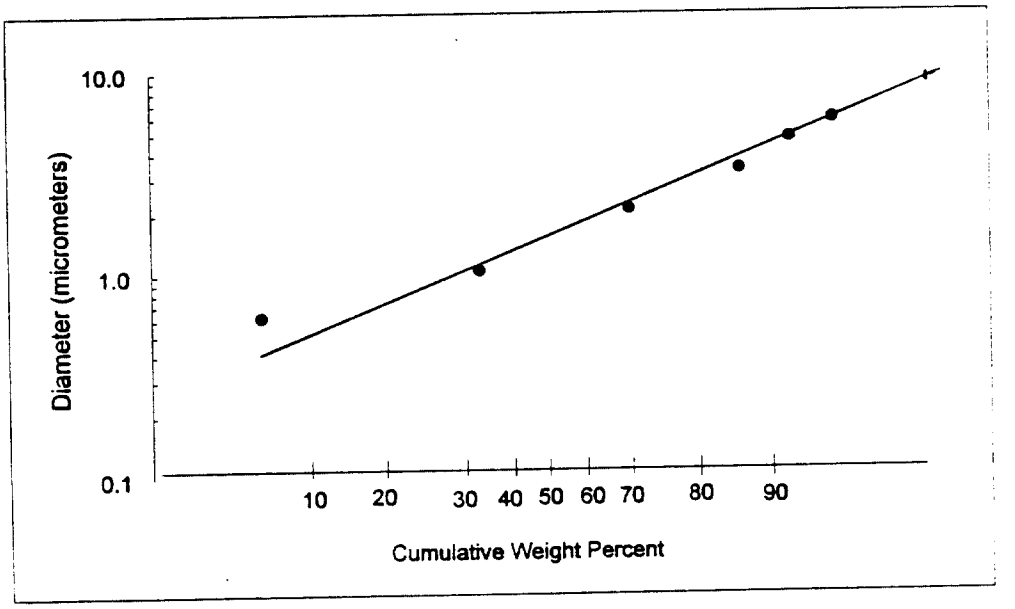
Figure 9. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 4

Particle Size Distribution for Copper Omadine

Sample Collected on 6/8/94 12:21pm

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	2.0	98.0
1	5.8	4.1	93.9
2	4.7	3.2	90.7
3	3.3	5.1	85.6
4	2.1	17.1	68.4
5	1.05	30.5	37.9
6	0.62	30.4	7.5
7	0.44	6.8	0.8
Filter	<0.44	0.8	0.0



The mass median aerodynamic diameter is 1.6

The geometric standard deviation is 2.09

ECD = Effective Cutoff Diameter

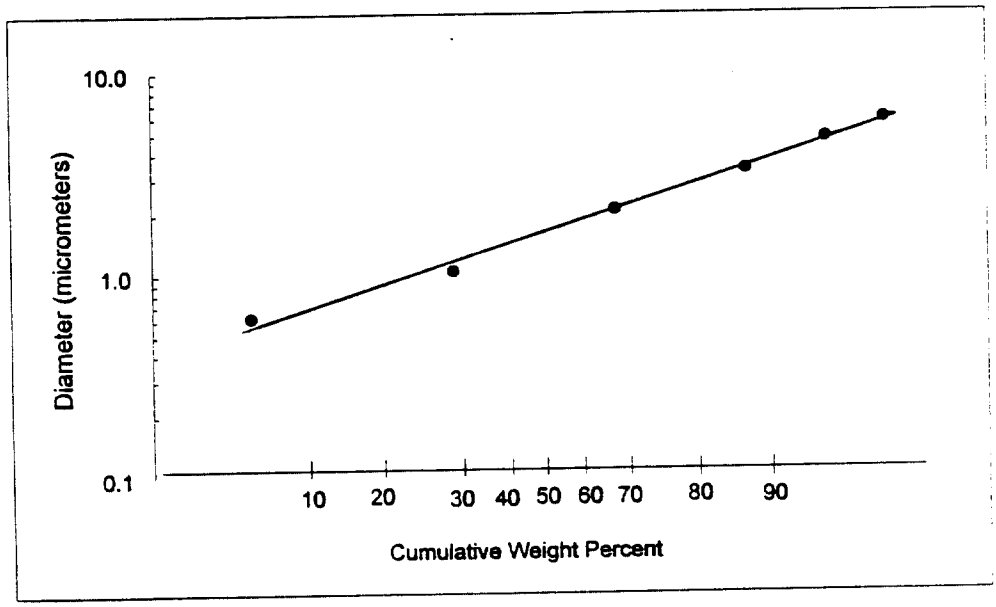
Figure 10. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 5

Particle Size Distribution for Copper Omadine

Sample Collected on 6/14/94 10:26am

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	1.5	98.5
1	5.8	2.0	96.5
2	4.7	3.0	93.5
3	3.3	7.1	86.3
4	2.1	20.1	66.3
5	1.05	32.8	33.4
6	0.62	26.6	6.8
7	0.44	6.1	0.8
Filter	<0.44	0.8	0.0



The mass median aerodynamic diameter is 1.6

The geometric standard deviation is 1.98

ECD = Effective Cutoff Diameter

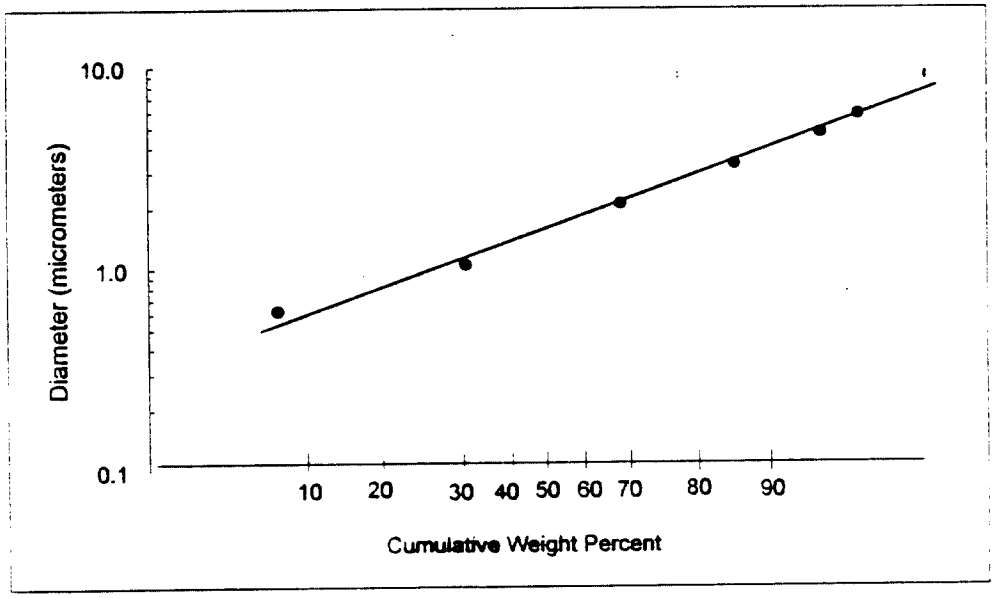
Figure 11. Numerical Data and Graph of Particle Size Distribution

Study Number: 397-062 Group 5

Particle Size Distribution for Copper Omadine

Sample Collected on 6/14/94 12:30pm

Stage Number	ECD (microns)	Weight Percent	Cumulative Weight Percent
0	9	2.0	98.0
1	5.8	2.6	95.4
2	4.7	2.2	93.1
3	3.3	8.1	85.1
4	2.1	18.0	67.1
5	1.05	31.3	35.8
6	0.62	26.7	9.1
7	0.44	8.1	1.0
Filter	<0.44	1.0	0.0



The mass median aerodynamic diameter is 1.6

The geometric standard deviation is 2.07

ECD = Effective Cutoff Diameter

APPENDIX A
Test Material Information

The test material was received from the Olin Research Center on April 19, 1994. Presented below is the pertinent information on the test material.

Amount Received:	Approximately 5 kg
Label Identification:	Copper Omadine®
Batch No.:	9311104351
Lot No.:	Not provided
Purity:	99.5%
Physico-Chemical Properties:	Olive Green powder
Stability:	Stable through end of study
Storage Conditions:	Refrigerate, protect from light
IRDC Number:	10214C

The Sponsor assumes responsibility for defining the identity, stability, strength, purity, and composition (or other characteristics) of the test material.

APPENDIX B
Individual Pharmacotoxic Signs

INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Males - Group number: 1		Day First Seen	Day Last Seen
88031	Died prior to first observation,	1	1
88032	Died prior to first observation,	1	1
88033	Died prior to first observation,	1	1
88034	Died prior to first observation,	1	1
88035	Died prior to first observation,	1	1

397-062

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Females - Group number: 1		Day First Seen	Day Last Seen
88036	Died prior to first observation,	1	1
88037	Died prior to first observation,	1	1
88038	Died prior to first observation,	1	1
88039	Died prior to first observation,	1	1
88040	Died prior to first observation,	1	1

397-062

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Males - Group number: II		Day First Seen	Day Last Seen
88051	Died prior to first observation,	1	1
88052	Died prior to first observation,	1	1
88053	Died prior to first observation,	1	1
88054	Died prior to first observation,	1	1
88055	Died prior to first observation,	1	1

397-062

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Females - Group number: II		Day First Seen	Day Last Seen
88056	Died prior to first observation,	1	1
88057	Died prior to first observation,	1	1
88058	Died prior to first observation,	1	1
88059	Died prior to first observation,	1	1
88060	Died prior to first observation,	1	1

397-062

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Males - Group number: III		Day First Seen	Day Last Seen
88071	*Dead,	1	1
	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Left shoulder,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1
88072	*Dead,	1	1
	Decreased activity,	1	1
	Tremors,	1	1
	Test Material Staining, Nose,	1	1
	Test Material Staining, Right shoulder,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1
88073	*Dead,	1	1
	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1
88074	*Dead,	1	1
	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Left shoulder,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1
88075	*Dead,	1	1
	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Nose,	1	1
	Test Material Staining, Right shoulder,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1

397-062 *- Animal found dead study day 0 upon comletion of post-exposure observations

INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Females - Group number: III		Day First Seen	Day Last Seen
88076	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
88077	*Dead,	1	1
	Decreased activity,	1	1
	Tremors,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1
	Excessive lacrimation, Both eyes,	1	1
88078	*Dead,	1	1
	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Nose,	1	1
	Test Material Staining, Right shoulder,	1	1
	Labored breathing,	1	1
88079	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1
88080	*Dead,	1	1
	Decreased activity,	1	1
	Body surface stained, Ventral surface,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1

*- Animal found dead study day 0 upon completion of post-exposure observations

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Males - Group number: IV		Day First Seen	Day Last Seen
88091	Rapid Respiration,	1	1
	Increased salivation,	1	1
	Red/brown material around nose,	1	1
88092	Decreased activity,	1	1
	Test Material Staining, Nose,	1	1
	Rapid Respiration,	1	1
	Increased salivation,	1	1
88093	Decreased activity,	1	1
	Rapid Respiration,	1	1
	Increased salivation,	1	1
	Red/brown material around nose,	1	1
88094	Decreased activity,	1	1
	Rapid Respiration,	1	1
	Red/brown material around nose,	1	1
88095	Decreased activity,	1	1
	Rapid Respiration,	1	1
	Increased salivation,	1	1
	Red/brown material around nose,	1	1

397-062

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Females - Group number: IV		Day First Seen	Day Last Seen
88096	Decreased activity,	1	1
	Rapid Respiration,	1	1
	Red/brown material around nose,	1	1
88097	Decreased activity,	1	1
	Rapid Respiration,	1	1
88098	Decreased activity,	1	1
	Rapid Respiration,	1	1
	Red/brown material around nose,	1	1
88099	Decreased activity,	1	1
	Rapid Respiration,	1	1
	Red/brown material around nose,	1	1
88100	Decreased activity,	1	1
	Red/brown material around nose,	1	1

397-062

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Males - Group number: V		Day First Seen	Day Last Seen
88121	Decreased activity,	1	1
	Tremors,	1	1
	Test Material Staining, Nose,	1	1
	Rapid Respiration,	1	1
88122	Decreased activity,	1	1
	Labored breathing,	1	1
	Red/brown material around nose,	1	1
88123	Decreased activity,	1	1
	Cold to touch,	1	1
	Labored breathing,	1	1
	Rales,	1	1
88124	Decreased activity,	1	1
	Test Material Staining, Nose,	1	1
	Rapid Respiration,	1	1
	Increased salivation,	1	1
	Red/brown material around nose,	1	1
88125	Decreased activity,	1	1
	Test Material Staining, Nose,	1	1
	Rapid Respiration,	1	1
	Increased salivation,	1	1

397-062

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INDIVIDUAL PHARMACOTOXIC SIGNS
Immediately Post-Exposure

Females - Group number: V		Day First Seen	Day Last Seen
88126	Decreased activity,	1	1
	Labored breathing,	1	1
	Red/brown material around nose,	1	1
88127	Abnormal gait,	1	1
	Cold to touch,	1	1
	Test Material Staining, Nose,	1	1
	Rapid Respiration,	1	1
	Increased salivation,	1	1
88128	Decreased activity,	1	1
	Test Material Staining, Nose,	1	1
	Rapid Respiration,	1	1
	Increased salivation,	1	1
	Excessive lacrimation, Right eye,	1	1
88129	Decreased activity,	1	1
	Test Material Staining, Nose,	1	1
	Labored breathing,	1	1
88130	Decreased activity,	1	1
	Labored breathing,	1	1
	Increased salivation,	1	1
	Red/brown material around nose,	1	1

397-062

IRDC

INDIVIDUAL PHARMACOTOXIC SIGNS
(Study Days 2-15 Represent Post-Exposure Days 1-14)

Females - Group number: III		Day First Seen	Day Last Seen	Days Sign Present
88076	Dead,	2	2	1
88079	Normal/no visible abnormalities	12	15	4
	Decreased activity,	2	11	10
	Body surface stained, Both forelimbs,	3	3	1
	Body surface stained, Ventral surface,	2	4	3
	Labored breathing,	2	2	1
	Rapid Respiration,	3	11	9
	Red/brown material around nose,	2	4	3
	Staining around mouth,	2	4	3

397-062

0047

IRDC

INDIVIDUAL PHARMACOTOXIC SIGNS
(Study Days 2-15 Represent Post-Exposure Days 1-14)

Males - Group number: IV		Day First Seen	Day Last Seen	Days Sign Present
88091	Normal/no visible abnormalities	5	15	11
	Rapid Respiration,	2	4	3
88092	Normal/no visible abnormalities	5	15	11
	Decreased activity,	2	3	2
	Body surface stained, Ventral surface,	2	3	2
	Rapid Respiration,	2	4	3
	Red/brown material around nose,	2	3	2
	Staining around mouth,	2	2	1
88093	Normal/no visible abnormalities	5	15	11
	Rapid Respiration,	2	4	3
	Red/brown material around nose,	2	3	2
	Staining around mouth,	2	2	1
88094	Normal/no visible abnormalities	5	15	11
	Decreased activity,	2	3	2
	Body surface stained, Dorsal head,	2	4	3
	Rapid Respiration,	2	4	3
	Red/brown material around nose,	2	2	1
88095	Normal/no visible abnormalities	5	15	11
	Decreased activity,	2	4	3
	Body surface stained, Dorsal head,	2	3	2
	Body surface stained, Ventral surface,	2	3	2
	Rapid Respiration,	2	4	3
	Red/brown material around nose,	2	2	1

397-062

IRDC

INDIVIDUAL PHARMACOTOXIC SIGNS
(Study Days 2-15 Represent Post-Exposure Days 1-14)

Females - Group number: IV		Day First Seen	Day Last Seen	Days Sign Present
88096	Normal/no visible abnormalities	5	15	11
	Rapid Respiration,	2	4	3
88097	Normal/no visible abnormalities	2	15	14
88098	Normal/no visible abnormalities	5	15	11
	Body surface stained, Dorsal head,	2	3	2
	Rapid Respiration,	2	4	3
88099	Normal/no visible abnormalities	2	15	14
88100	Normal/no visible abnormalities	2	15	14

397-062

IRDC

INDIVIDUAL PHARMACOTOXIC SIGNS
(Study Days 2-15 Represent Post-Exposure Days 1-14)

Females - Group number: V		Day First Seen	Day Last Seen	Days Sign Present
88126	Normal/no visible abnormalities	7	15	9
	Decreased activity,	2	6	5
	Body surface stained, Anogenital region,	2	5	4
	Body surface stained, Dorsal head,	3	6	4
	Rapid Respiration,	2	6	5
	Red/brown material around nose,	2	6	5
88127	Normal/no visible abnormalities	7	15	9
	Decreased activity,	2	6	5
	Body surface stained, Dorsal head,	3	6	4
	Body surface stained, Ventral surface,	2	4	3
	Cold to touch,	2	6	5
	Rapid Respiration,	2	6	5
	Red/brown material around nose,	2	6	5
	Red/brown material mouth,	2	6	5
88128	Normal/no visible abnormalities	7	15	9
	Decreased activity,	2	6	5
	Body surface stained, Anogenital region,	2	4	3
	Rapid Respiration,	2	6	5
	Red/brown material around nose,	2	2	1
88129	Normal/no visible abnormalities	7	15	9
	Decreased activity,	2	6	5
	Body surface stained, Anogenital region,	2	4	3
	Body surface stained, Dorsal head,	2	6	5
	Body surface stained, Ventral surface,	2	6	5
	Rapid Respiration,	2	6	5
	Red/brown material around nose,	2	2	1
	Red/brown material mouth,	2	2	1
88130	Normal/no visible abnormalities	7	15	9
	Decreased activity,	2	6	5
	Body surface stained, Anogenital region,	2	2	1
	Body surface stained, Ventral surface,	2	2	1
	Rapid Respiration,	2	6	5
	Red/brown material around nose,	2	2	1
	Red/brown material mouth,	2	2	1

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IRDC

APPENDIX C
Individual Body Weights

INDIVIDUAL BODY WEIGHTS (g)

Animal Number	Sex	Day of Study Pre-Exposure
Group: I		
88031	M	279
88032	M	281
88033	M	274
88034	M	283
88035	M	274
	(N)	5
	Means	278
	S.D.	4.1
88036	F	186
88037	F	197
88038	F	195
88039	F	192
88040	F	195
	(N)	5
	Means	193
	S.D.	4.3

397-062

All animals died prior to post exposure day 7.
S.D. = standard deviation
N = number of animals

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INDIVIDUAL BODY WEIGHTS (g)

Animal Number	Sex	Pre-Exposure	Day of Study
Group: II			
88051	M		285
88052	M		289
88053	M		283
88054	M		290
88055	M		281
	(N)		5
	Means		286
	S.D.		3.8
88056	F		221
88057	F		199
88058	F		200
88059	F		198
88060	F		198
	(N)		5
	Means		203
	S.D.		10.0

397-062

All animals died prior to post exposure day 7.
S.D. = standard deviation
N = number of animals

IRDC

INDIVIDUAL BODY WEIGHTS (g)

Animal Number	Sex	Pre-Exposure	Day of Study 8	15
Group: III				
88071	M	261	---	---
88072	M	262	---	---
88073	M	247	---	---
88074	M	255	---	---
88075	M	250	---	---
	(N)	5	0	0
	Means	255	0	0
	S.D.	6.6	0	0
88076	F	213	---	---
88077	F	209	---	---
88078	F	216	---	---
88079	F	205	232	266
88080	F	199	---	---
	(N)	5	1	1
	Means	208	232	266
	S.D.	6.7	0	0

397-062

- = Animal died prior to body weight collection
S.D. = standard deviation
N = number of animals

0055
IRDC

INDIVIDUAL BODY WEIGHTS (g)

Animal Number	Sex	Pre-Exposure	Day of Study 8	15
Group: IV				
88091	M	289	314	347
88092	M	284	305	334
88093	M	288	319	350
88094	M	281	307	338
88095	M	292	318	356
	(N)	5	5	5
	Means	287	313	345
	S.D.	4.3	6.3	8.9
88096	F	224	242	267
88097	F	223	245	276
88098	F	223	240	266
88099	F	217	243	267
88100	F	215	231	245
	(N)	5	5	5
	Means	220	240	264
	S.D.	4.1	5.4	11.5

397-062

S.D. = standard deviation
N = number of animals

0059

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INDIVIDUAL BODY WEIGHTS (g)

Animal Number	Sex	Pre-Exposure	Day of Study 8	15
Group: V				
88121	M	279	311	359
88122	M	277	316	374
88123	M	280	251	314
88124	M	275	---	---
88125	M	271	280	314
	(N)	5	4	4
	Means	276	290	340
	S.D.	3.6	30.2	30.9
88126	F	196	216	229
88127	F	202	241	258
88128	F	209	249	260
88129	F	203	222	245
88130	F	211	233	251
	(N)	5	5	5
	Means	204	232	249
	S.D	6.0	13.5	12.5

397-062

- = Animal died prior to body weight collection
S.D. = standard deviation
N = number of animals

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APPENDIX D
Macroscopic Findings

Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 1				
88031	M	D	MACROSCOPIC: Lung Nasal Tissues	- Discoloration, red, multiple lobes, diffuse, severe. - Foreign material, green, bilateral, trace.
88032	M	D	MACROSCOPIC: Kidney Lung Nasal Tissues	- Dilatation, pelvic, right, mild. - Small, left, moderate; Approximately one-quarter normal size. - Discoloration, red, multiple lobes, diffuse, severe. - Within normal limits.
88033	M	D	MACROSCOPIC: Lung Nasal Tissues	- Discoloration, red, multiple lobes, diffuse, severe. - Within normal limits.
88034	M	D	MACROSCOPIC: Lung Nasal Tissues	- Discoloration, red, multiple lobes, diffuse, severe. - Within normal limits.
88035	M	D	MACROSCOPIC: Lung Nasal Tissues	- Discoloration, red, multiple lobes, diffuse, severe. - Within normal limits.

397-062

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 1				
88036	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
88037	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
88038	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
88039	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
88040	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 2				
88051	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88052	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88053	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88054	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88055	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 2				
88056	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88057	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88058	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88059	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.
88060	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
			Tongue	- Discoloration, green, dorsal, focal, mild.

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0062
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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 3				
88071	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, shoulder, hair, left, mild.
				- Corresponds to ante mortem observation.
88072	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, shoulder, hair, right, mild.
				- Corresponds to ante mortem observation.
88073	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, trace.
				- Corresponds to ante mortem observation.
88074	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, shoulder, hair, left, mild.
				- Corresponds to ante mortem observation.
88075	M	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, shoulder, hair, right, mild.
				- Corresponds to ante mortem observation.

397-062

[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 3				
88076	F	D	MACROSCOPIC:	
			Liver	- Focus/foci, red, left lateral lobe, multifocal, mild; 2 - 5 mm diameter.
			Lung	- Discoloration, red, multiple lobes, diffuse, moderate.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
				- Corresponds to ante mortem observation.
			Stomach, Glandular	- Focus/foci, red, mucosa, focal, trace; 2 mm diameter.
88077	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
				- Corresponds to ante mortem observation.
88078	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, shoulder, hair, right, mild.
				- Corresponds to ante mortem observation.
			Stomach, Glandular	- Focus/foci, red, mucosa, focal, trace, pinpoint.
88079	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.

397-062

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 3				
88080	F	D	MACROSCOPIC:	
			Lung	- Discoloration, red, multiple lobes, diffuse, severe.
			Nasal Tissues	- Within normal limits.
			Skin	- Discoloration, green, nose/muzzle, hair, mild.
				- Corresponds to ante mortem observation.

397-062

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 4				
88091	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88092	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88093	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88094	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88095	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.

397-062

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 4				
88096	F	S	MACROSCOPIC:	
			Lung	- Focus/foci, red, multiple lobes, multifocal, trace.
			Nasal Tissues	- Within normal limits.
88097	F	S	MACROSCOPIC:	
			Lymph Node, Mandibular	- Enlarged, bilateral, mild; 2X normal size.
			Nasal Tissues	- Within normal limits.
88098	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88099	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88100	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.

397-062

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 5				
88121	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88122	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88123	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88124	M	D	MACROSCOPIC:	
			Eye	- Neovascularization, bilateral, trace.
			Lung	- Discoloration, red, multiple lobes, diffuse, moderate.
			Nasal Tissues	- Within normal limits.
88125	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.

397-062

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Individual Animal Data Record: Pathology
0 to Termination: RAT

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Group 5				
88126	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88127	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88128	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88129	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.
88130	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Nasal Tissues	- Within normal limits.

397-062

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APPENDIX E
Analytical Methods

Analytical Method for Copper Omadine

A. Method of Analysis

The test article, copper omadine (IRDC NO. 10214C), was analyzed using a sponsor provided compound specific high performance liquid chromatographic (HPLC) method. The copper omadine (CuOM) was derivatized using a solution of 4-chloro-7-nitrobenzofurazan (NBD-Cl) and ethylenediaminetetraacetic acid, tetrasodium salt (EDTA). The derivatized extracts were injected into an HPLC and separated by gradient elution over a 25 cm standard C-8 column. Quantitation was by ultraviolet light absorbance at 263 nanometers and reported on an electronic integrator. The linear regression analysis of peak area vs. concentration of known purity copper omadine was used to determine the test article concentration in the exposure chamber.

B. Instrumentation

A Waters model 6000A HPLC pump with a WISP-712 autosampler were used to inject the sample onto the J. T. Baker C-8 standard chromatoraphy column. A Kratos analytical spectraflow 773 absorbance detector connected to a Hewlett-Packard 3396B series II integrator was used to produce and collect the peak area data. Specific integrator conditions were listed per chromatogram.

C. Operational Parameters

Pump: Waters model 6000A
Flowrate = 1 ml/min
Backpressure approximately 1000 psig with 70:30 water:acetonitrile
approximately 600 psig 100% acetonitrile

Autosampler: Waters WISP-712
Injection volume = 200 microliters

Detector: Kratos / Spectraflow 773
wavelength = 263 nanometers
runtime = 10 minutes
absorbance range = 0.300
rise time = 0.5 seconds

Integrator: Hewlett-Packard 3396B series II
zero = 0
attenuation = 2 to the 3rd
area rejection = 0
peak width = 0.04 minutes

Column: J.T. Baker C-8, 5 micron, standard
250 mm x 4.6 mm on Bakerbond narrow bore

Guard column: Waters micro porasil silica 5 micron

Chart speed: 0.5 cm/min

C. Operational Parameters (continued):
Gravimetric filter pad analysis

Mobile Phase: Gradient run time 30 minutes

Time	% water	% acetonitrile
0.0	70.0	30.0
10.0	0.0	100.0
20.0	70.0	30.0

Mobile phase for the particle size filter pad analysis was done isocratically with a 70% water / 30% acetonitrile solution.

Retention times:

Omadine/NBD	8 minutes
Excess EDTA	3 minutes
Excess NBD-Cl	20 minutes

D. Reagents

Derivatizing reagent preparation:

To a 25.0 ml volumetric flask 0.5 grams of NBD-Cl was added and dilute to mark with acetonitrile. To a separate 25.0 mL volumetric flask 0.25 grams of EDTA was added and dilute to the mark with distilled water. This solution was sonicated for 20 minutes to ensure total dissolution. To a separate 50.0 ml volumetric flask pipette 5.0 ml NBD-Cl stock solution, add 125 microliters EDTA solution and dilute to the mark with 25/75 acetonitrile/ water.

Copper Omadine Stock Solution:

To a 50.0 ml amber volumetric flask, weigh approximately 25 (+/- 0.1) mg of CuOM and dilute to the mark with DMSO. Sonicate this material in the dark for approximately 30 minutes. Transfer it to a properly labelled amber screw capped bottle and store at room temperature in the dark. This is the stock CuOM standard.

Dilution scheme:

Standard solutions were prepared by transferring aliquots of CuOM stock solution to individual amber volumetric flasks and diluting them with DMSO. The concentrations were approximately 25, 20 and 5 ppm CuOM for the final calibration solutions. Two milliliters of each solution were then derivatized for subsequent HPLC analysis. Two milliliters of DMSO were derivatized as the blank.

Derivatization procedure for samples and standards :

Gravimetric filter pad samples were transported to analytical laboratory in 30 cc amber screw capped bottles. To each bottle, 25.0 mls of DMSO was added and the samples were sonicated for 30 minutes in the dark. To ensure no volume change due to thermal expansion of the DMSO, a 25.0 ml volumetric filled with DMSO was sonicated concurrently as a reference. The samples were allowed to cool to room temperature prior to derivatization. This took approximately 30 minutes. 3.0mls of the extract was further diluted to 50.0 ml in DMSO as the final dilution. 2.0 mls of this dilution was added to 5.0 mls of the derivatizing solution and swirled to mix. This was allowed to stand for 30 minutes at room temperature in order for the derivative to develop.

Standard solutions were prepared by transferring 2.0 mls of each diluted CuOM stock solutions to 5.0 mls of the derivatizing agent and allowed to sit for 30 minutes to develop.

An aliquot, approximately 3.8 mls, of derivatized material is then filtered through a 0.45 micron PTFE filter into individual amber autosampler vials for subsequent analysis.

APPENDIX F
Comments on Study Data

Comments on Study Data

This study was conducted in conformance with the protocol, IRDC Standard Operating Procedures and in compliance with the Good Laboratory Practice Standards.

The exposure was conducted in an acrylic and stainless steel chamber rather than a glass and stainless steel chamber.

In the opinion of the study director, any minor deviations that occurred did not affect the quality or integrity of the study.