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Comparative Inhalation Toxicology of Selected Materials

Final Report for Phase II Studies

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Male and female F344/N rats were exposed nose-only to a respirable powder of Cu-Zn alloy. Air concentrations were 10 or 40 mg Cu-Zn/m^3, exposures were 1.5 or 3 hours/day, 2 or 4 days/week, for 4 weeks. Cumulative weekly exposures ranged from 0 to 480 mg. hr Cu-Zn/m^3, which included three pairs of exposure levels (60, 120, and 240 mg. hr Cu-Zn/m^3 per week) where comparisons could be made to evaluate exposure-response relationships among aerosol concentration, exposure duration, and exposure frequency. No rats died as a result of the exposures. Body weights were reduced relative to sham-exposed rats for rats exposed to 240 and 480 mg. hr Cu-Zn/m^3 per week. Hematological, immunological, and macrophage phagocytosis parameters were not significantly affected by inhaled Cu-Zn. All of the

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19. Abstract

additional observed biological responses to inhaled Cu-Zn were restricted to the respiratory tract. Lung weights were increased due to an inflammatory response for rats exposed to 120 mg. hr Cu-Zn/m^3 or more per week. Exposure to 240 mg. hr Cu-zn/m^3 per week caused restrictive pulmonary functional disorder, as evidenced by a reduced lung capacity, reduced quasistatic compliance, reduced carbon monoxide diffusing capacity, and increased percent forced vital capacity exhaled in 0.1 second. Exposure-related responses in lavage fluid indicators of lung damage included increased beta-glucuronidase, increased lactate dehydrogenase, and increases in inflammatory cells, total protein, and collagen. Histological lesions produced by Cu-Zn were (1) atrophy of the nasal olfactory epithelium and hyperplasia of goblet cells in the respiratory epithelium, (2) focal necrotizing alveolitis, (3) alveolar macrophage hyperplasia, and (4) goblet cell hyperplasia of bronchial and bronchiolar epithelium. The only significant biological responses that did not resolve during the 2-week recovery period were the nasal epithelial goblet cell hyperplasia, increased lung weight, and alveolar macrophage hyperplasia. These unresolved changes were associated with weekly cumulative exposures to at least 60 mg. hr Cu-Zn/m^3. The time required for full recovery was not determined, but the severity of the lesions and degree of recovery by 2 weeks suggested that recovery would likely be complete. In summary, within the spectrum of exposures used in this study, the inhaled Cu-Zn alloy caused exposure-related inflammatory and cytotoxic responses in the respiratory tract, but the inhaled Cu-Zn cleared rapidly and the responses largely resolved after cessation of exposures. While responses to Cu-Zn inhaled by F344/N rats were related to the weekly product of aerosol concentration multiplied by exposure time, and exposures 4 days per week generally produced larger responses than exposures 2 days per week for the same cumulative exposure, no relationship was detected for daily exposure duration (1.5 vs 3 hours/day) or exposure concentration (10 mg Cu-Zn/m^3 vs 40 mg Cu-Zn/m^3).

I. EXECUTIVE SUMMARY

This report describes Phase II of a project sponsored by the USABRDL to study biological effects produced by an inhaled powder of Cu-Zn alloy (Cu-Zn). Exposures were repeated, intermittent nose-only inhalation exposures of male and female F344/N rats. The study goal was to provide exposure-response data and evaluate the effects of aerosol concentration (mg Cu-Zn/m^3), exposure duration (hours/day), and exposure frequency (2 or 4 times/week) on biological effects produced by the inhaled Cu-Zn. Exposures were for 4 weeks, followed by a 2-week recovery period. Aerosol concentrations were 10 and 40 mg Cu-Zn/m^3. Exposures were defined in terms of cumulative weekly exposures, which were the product of aerosol concentration, exposure duration, and exposure frequency. Therefore, units of exposure were mg·hr Cu-Zn/m^3 per week. Cumulative weekly exposures were 0, 30, 60, 120, 240, and 480 mg·hr Cu-Zn/m^3. Within the 9 exposure groups were 3 pairs of groups that received the same cumulative weekly exposures in 2 or 4 days/weeks; these were 60, 120, and 240 mg·hr Cu-Zn/m^3 per week.

No rats died as a result of inhalation of Cu-Zn, but body weights were reduced for rats exposed to 240 and 480 mg·hr Cu-Zn/m^3 per week. Lung weights were increased relative to those of sham-exposed rats as a result of weekly exposures to 120 mg·hr Cu-Zn/m^3 or more, delivered over 4 days per week. This was due to an inflammatory response in the lung.

Inhalation of 240 mg·hr Cu-Zn/m^3 per week caused reduced total lung capacity, reduced quasistatic lung compliance, reduced carbon monoxide diffusing capacity, and increased percent forced vital capacity exhaled in 0.1 second. These alterations were consistent with a restrictive functional disorder, with no evidence of airflow obstruction. The respiratory functional changes were resolved during the 2-week recovery period.

Bronchoalveolar lavage fluid analyses at the end of exposure indicated that the inhaled Cu-Zn produced an inflammatory response in the lung if exposures were to 60 mg·hr Cu-Zn/m^3 or more per week. Exposure-related increases were noted for: (1) beta-glucuronidase, (2) lactate dehydrogenase, (3) polymorphonuclear leukocytes, (4) total protein, and (5) airway collagen. Alkaline phosphatase, an important indicator of damage to type II cells of the lung, had no exposure-related trend. The numbers of pulmonary alveolar macrophages were increased with exposures to 60 mg·hr Cu-Zn/m^3 or more per week, but there was no exposure-related trend. These changes in lavage fluid indicators of damage resolved by the end of the 2-week recovery period.

Hematological parameters were unaffected at all exposure levels. Immunological results for rats exposed to Cu-Zn were not significantly different from those of sham-exposed rats at the end of exposure or after the recovery period. Trend analyses, however, indicated slight exposure-related increases in total cells and total numbers of antibody-forming cells in lung-associated lymph nodes. Although total cells were slightly elevated, there was no clear pattern indicating the lung immune system was at risk as a result of inhalation of the powdered Cu-Zn. The phagocytic ability of pulmonary alveolar macrophages was not significantly affected by these exposures to Cu-Zn.

Atrophy of the nasal olfactory epithelium occurred at all exposure levels, and both the incidence and severity of the lesion were exposure-related. This lesion completely resolved during the 2-week recovery period for rats exposed to 120 mg·hr Cu-Zn/m^3 per week, or less. Goblet cell hyperplasia and hypertrophy were prominent in the ciliated epithelium lining the anterior portion of the nasal septum and occasionally the epithelium lining the anterior portion of the nasal septum and occasionally the epithelium lining the anterior portion of the maxilloturbinate. The lesions resolved after 2 weeks recovery if exposures were less than the equivalent of 120 mg·hr Cu-Zn/m^3 per week for 4 weeks.

Other histopathological effects were focal necrotizing alveolitis and goblet cell hyperplasia of bronchial and bronchiolar epithelium for all rats exposed to 120 mg·hr Cu-Zn/m^3 or more per week. The incidence and severity were exposure-related. Both of these lesions represented significant responses to exposures to relatively high levels of the Cu-Zn, but completely resolved during the 2 weeks recovery period.

Alveolar macrophage hyperplasia was observed in 3 of 10 rats exposed to 30 mg·hr Cu-Zn/m^3 per week and was present in all rats exposed to levels higher than 30 mg·hr/m^3 per week. This lesion only partially resolved during the recovery period and persisted in most rats exposed to 60 mg·hr Cu-Zn/m^3 per week or more. Alveolar macrophage hyperplasia was the most persistent histopathological response observed in lungs of these rats.

In summary, the Cu-Zn produced exposure-related responses in the respiratory tracts of the F344/N rats but did not accumulate in the lung, indicating a rapid clearance for this inhaled powder. Biological responses were most apparent for bronchoalveolar lavage fluid indicators of damage and inflammation, increased lung weight, and histopathological changes. Exposures to at least 60 mg·hr Cu-Zn/m^3 per week were needed to produce significant responses. Responses to a given cumulative weekly exposure were generally more marked when exposures were delivered during 4 days per week instead of during 2 days per week. While responses were related to the weekly product of aerosol concentration multiplied by exposure time, and exposures 4 days per week generally produced larger responses than exposures 2 days per week for the same cumulative exposure, no relationship was detected for daily exposure duration (1.5 vs. 3 hours/day) or exposure concentration (10 mg Cu-Zn/m^3 vs. 40 mg Cu-Zn/m^3). This was probably a consequence of the relatively small difference between 1.5 hours and 3 hours per day, and the fact that the total amount of Cu-Zn deposited per day was more important than either the exposure time or the aerosol concentration.

With the exception of the decreased body weight, all of the observed biological responses to inhaled Cu-Zn were restricted to the respiratory tract. Goblet cell hyperplasia in respiratory epithelium and alveolar macrophage hyperplasia were caused by exposures to 30 mg·hr Cu-Zn/m^3 per week. All other statistically significant responses required exposures to 60 mg·hr Cu-Zn/m^3 or more per week. Most differences in biological responses between sham-exposed rats and rats exposed to Cu-Zn had resolved by the end of a 2-week recovery period. The only significant unresolved changes were the nasal epithelial goblet cell hyperplasia, increased lung weight, and alveolar macrophage hyperplasia. These unresolved changes were associated with weekly cumulative exposures to at least 60 mg·hr Cu-Zn/m^3. The time required for full recovery was not determined, but the severity of the lesions and degree of recovery by 2 weeks suggest that recovery would likely be complete. Within the spectrum of exposures used in this study, the Cu-Zn alloy caused exposure-related inflammatory and cytotoxic responses in the respiratory tract, but the inhaled Cu-Zn cleared rapidly and the responses largely resolved after cessation of exposure.

II. FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U. S. Army.

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______In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

Morris B. [signature] 12-Aug-88

PI Signature Date

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V. EXPERIMENTAL METHODS

A. Test Material

We obtained Atlantic Brass Richgold fine 1800 from Atlantic Powdered Metals, Inc., New York, NY. This powdered metal alloy was from lot number T-7464. We mixed the bulk material in a plastic-lined 55 gallon drum, then transferred part of the powder to 9 approximately 2 liter sub-lots in Teflon bottles for convenience of storage and use in this project. The remainder of the bulk material was returned to its shipping containers. This metal powder contained approximately 2/3 Cu and 1/3 Zn by weight. In Phase I of this project we determined the projected area diameter of bulk and aerosolized powder (Snipes et al., 1986). Results indicated that most of the particles in this powder were flakes, having projected area diameters in the range 0.6 to 16.4 µm. We also approximated the thickness of the flakes to be one-thirtieth to one-fourtieth of the projected area diameter. Aerosols generated using this powder typically had mass median aerodynamic diameters approximately 0.9 to 1.2 µm, with geometric standard deviations in the range 3.1 to 3.5.

B. Experimental Design

Fischer-344/N rats were used in this study to allow comparisons with specific results from other related studies and to make general comparisons with the growing inhalation toxicology data base for rats. This laboratory animal species was suitable for pulmonary function evaluations during and after exposure to the test material and procedures for evaluating specific endpoints have been well defined for rats. Previous observations in Phase I of this project and by others (Thomson et al., 1986) indicated the most likely responses in Phase II would involve the nasopharynx and pulmonary region of the respiratory tract. In addition to possible physical disruption of function related to inhaling the metal powder, there were potential biological and biochemical effects to consider which might result from exposure to the Cu and/or Zn constituents of the test material. The respiratory tract was the most likely physiological region of the rats which might be affected by inhalation exposure to the powdered Cu-Zn alloy (Cu-Zn). Observations and endpoints of interest therefore emphasized the respiratory tract. The measurements and endpoints we included in this study were selected to determine changes in important indicators of general health, the respiratory tract or other specific organ function as a consequence of the exposures. Specific categories of endpoint evaluations included hematology, clinical chemistry, pulmonary biochemistry, immunology, and histopathology.

Our observations and data collections also included indicators of morbidity. Rats were observed daily, their body weights were recorded twice per week, and pulmonary function measurements were made after the exposures to the test material as indicators of morbidity.

After the last exposures, rats were necropsied and examined using histopathology procedures to determine tissue responses to the inhaled material. Hematology, lavage fluid biochemistry, immunology, and phagocytosis evaluations were also collected at that time.

Exposures were nose-only and designed to evaluate effects of exposure concentration, exposure duration, and exposure frequency. Exposure concentrations were 10 mg Cu-Zn/m^3 and 40 mg Cu-Zn/m^3, exposure durations were 1.5 hr/day and 3.0 hr/day, and exposure frequencies were 2 times or 4 times per week. Exposures 4 times per week were conducted Monday thru Thursday or Tuesday thru Friday; exposure 2 days per week were conducted on Monday and Thursday, or on Tuesday and Friday.

Table 1 summarizes the matrix of exposures. The result was a low level exposure (30 mg·hr Cu-Zn/m^3 per week), a high level exposure (480 mg·hr Cu-Zn/m^3 per week), and three pairs of exposure levels (60, 120, and 240 mg·hr Cu-Zn/m^3 per week). The pairs of exposure levels allowed comparisons between different conditions which produced the same total exposure to the test material. These exposure groups are referred to as 30-2, 60-2, 60-4, 120-2, 120-4, 240-2, 240-4, and 480-4, respectively; this terminology was used consistently throughout this report to identify the groups of rats. Filtered-air exposed rats are referred to as "shams," and identified as sham-4, indicating they were exposed 4 times per week; their exposures were 3 hours per day.

Rats were 17 ± 1 weeks old at the start of their exposures. The rats were weighed during the week prior to exposure and those weights were used to randomize them for assignment to their study groups. The randomization procedure made use of the ITRI Path/Tox Data System (Xybion Medical Systems, Inc., Cedar Knolls, NJ) and RS/1 (BBN Research Systems, Cambridge, MA). The result of the randomization procedure was assignment of rats to the 9 experimental groups indicated in Table 1.

Animal assignments for endpoint evaluations are specified in Table 2. This table indicates the degree to which rats were shared for most of the endpoint evaluations. There were 70 rats (30 females and 40 males) in all groups except the lowest exposure group (30-2) and highest exposure group (480-4), which had 20 rats each (10 females and 10 males). The reason for the unequal numbers of females and males was that only males were subjected to the pulmonary function evaluations. Equal numbers of females and males were used for all other evaluations. Rats were randomly assigned for endpoint

Table 1

Exposure Groups for Phase II

mg Cu-Zn per m^3	2 days/week 1.5 hr/day	2 days/week 3.0 hr/day	4 days/week 1.5 hr/day	4 days/week 3.0 hr/day
10	30[a] (20)[b,c]	60 (70)	60 (70)	120 (70)
40	120 (70)	240 (70)	240 (70)	480 (20)[c]
0 (Sham)				0 (70)

[a]Accumulated weekly exposure (mg·hr Cu-Zn/m^3).

[b]Numbers of rats are indicated in parentheses.

[c]These animals, 10 males and 10 females, were subjected only to histopathology evaluations. Half the animals at the end of the 4 week exposure, the other half two weeks later.

Table 2

Use of Animals Having Cumulative Exposures of 0, 30, 60, 120, 240, and 480 mg·hr Cu-Zn Alloy/m^3

Evaluation	Number of Rats per Group[a]	Total Rats
Histopathology	20	180
Respiratory Function	10	70
Shared for Endpoints:	24	168
Biochemistry	24	
Hematology	12	
Connective Tissue	12	
Phagocytosis	16	
Shared for Endpoints:	16	112
Immunology	16	
Tissue Distribution	12	
Overall Total		530

[a]Half of the rats evaluated after the 4 week exposure, the other half evaluated two weeks later. With the exception of respiratory function evaluations, which used only male rats, all groups had equal numbers of males and females. Rats exposed to 30 or 480 mg·hr Cu-Zn/m^3 per week were evaluated only for histopathology.

evaluations and whether they would be evaluated at the end of the exposure or after the 2-week recovery period. The first groups of rats were killed three days after their last exposure to the Cu-Zn, the rest were killed exactly two weeks later. The exceptions to this schedule were the rats used for pulmonary function evaluations; the same rats were evaluated at the end of the exposure series and again after the 2-week recovery period.

C. Animals: Identification and Housing

Rats were obtained from Charles River Laboratories, Kingston, NY. They were shipped from a viral-antibody-free facility in filter crates and were 4 weeks old when they arrived at the LITRI. Prior to the animal's arrival, the room selected for their housing was disinfected. This was accomplished by sponging or mopping all surfaces of the room with diluted Johnson's Expose® (National Sanitary Supply Co., Albuquerque, NM), then fumigating the room with AN-FA-CIDE-S® (Pharmaceutical Research Laboratories, Greenwich, CT). Thereafter, anyone entering the room followed quarantine procedures for themselves, food, cages, bedding, and equipment taken into the room. The rats were maintained under quarantine conditions throughout the study.

Upon arrival at the Institute, cellophane tape preparations were done on 10 rats (5 females and 5 males) to examine for pinworm ova. Serology was performed when the rats were 10 to 12 weeks old, after maternal antibodies had decreased. This procedure is described below, under the section "Routine Animal Surveillance."

All animals assigned to the project had unique individual identification numbers. The numbers were affixed to the animal's ears in the form of permanent metal ear tags. The ear tags were attached during the week before inhalation exposures were started. Occasionally, these ear tags were lost; they were replaced as necessary to maintain positive identification of each animal.

Rats were housed two or three per cage in polycarbonate cages 20 cm H x 25 cm W x 45 cm L. Cages had polyester filter caps to reduce possible spread of disease and parasites. Cages and filter caps for the sham group were kept separate from cages and filter caps used for the rats exposed to the Cu-Zn powder. Also, the cages used for this study were not mixed with similar cages being used in the same housing area for other studies. Normal cage washing procedures were used, but control and exposed cages were washed separately and independently relative to other cages in the building.

Cages had hardwood chip bedding which was changed twice weekly. Certified Rodent Blox pellets (Allied Mills, Chicago, IL) and water were available ad libitum in the housing area. Food was analyzed by the Continental Grain Company, Libertyville, IL and was not analyzed at the LITRI for contaminants as they were not likely to be present in amounts which would influence results of the study. Data sheets from analysis of Lot P06185-1 of this feed by the Continental Grain Company are included in the Appendix. This analysis was representative of the feed used during Phase II.

Light was provided on a 12-hour daily cycle (0600-1800) at 50 ft candles or less. Room temperature was maintained at 20 to 24°C, and relative humidity was 30 to 50 percent.

D. Routine Animal Surveillance

Rats were received from Charles River Laboratories, Kingston, NY on October 22, 1985. They were 4 weeks old and placed directly into a quarantine room where they were maintained throughout the study.

On October 23, 1985, cellophane tape preparations were done on 10 randomly selected rats (5 males and 5 females) to determine if pinworms (*Syphacia muris*) were present. All 10 rats were negative for pinworm ova.

When the rats were 12 weeks old, serum samples were collected from 5 male and 5 female rats as part of the ITRI disease surveillance program. This surveillance included gross necropsy, parasitology screening, and serology. Samples of the serum were sent to Microbiological Associates, Inc. (Bethesda, MD) for serologic testing for the following diseases: pneumonia virus of mice (PVM), kilham rat virus (KRV), Toolan's H-1 virus (H-1), sendai virus, rat coronavirus-sialodacryoadeniti virus (RCV-SDA), lymphocytic choriomeningitis virus (LCM), reovirus type 3 (Reo3), mouse adenovirus (MAD), GDVII, and *Mycoplasma pulmonis*. A cellophane tape preparation was also done on each of the 10 rats to examine for pinworm ova. A pooled fecal sample was submitted from the 5 males and another pooled fecal sample was submitted from the 5 females for fecal flotation analysis.

The same disease surveillance procedures were performed on an additional 5 female and 5 male rats during the week prior to beginning exposures, and on another 5 female and 5 male rats at the conclusion of the study. No gross lesions were observed on any of the rats. At the conclusion of the study, one rat was positive for pinworm ova in the fecal flotation analysis, and pinworm ova were observed on cellophane preparations from 4 of the 10 rats. All 10 rats were negative for *Mycoplasma* and all viruses tested.

E. Aerosol Generation and Exposure Systems

1. Aerosol Generation and Delivery Systems

One requirement for this project was to minimize changes in physical and chemical characteristics of the powdered Cu-Zn. This required using an aerosol generator which would not grind or otherwise alter the size and shape of the powder. In addition, a suspension of the powder was not possible, since this would require a solvent which might alter the test material physically or alter the exposure patterns for the rats. Testing in Phase I of this project indicated that the Model 0101-C6S Jet-O-Mizer® aerosol generator (Fluid Energy Corp., Hatfield, PA) would be appropriate for this study (Snipes et al., 1986). Figure 1 is a schematic diagram of the aerosol generation system with its bulk materials feeder. The Jet-O-Mizer produced aerosols of the Cu-Zn having the desired exposure concentrations, stability, and volume production for this project.

Each daily operation of this aerosol generation system started with a fresh supply of bulk Cu-Zn alloy powder. The bulk powder was stored in 2-liter Teflon containers. Containers were physically mixed by turning them end over end 25 times prior to transfer of the bulk material. This procedure was done to obviate daily variations in aerosols due to differential settling of particles in the storage containers.

In all cases where aerosols of the Cu-Zn were used, the aerosol generation systems were enclosed to protect the operator(s) from exposure. These enclosures were made of 1.3 cm thick plexiglas and were equipped with glove ports and pass boxes. The enclosures were maintained at a relative negative internal pressure of 0.5-0.75 inches (1.3-1.9 cm) of hydrostatic pressure. This ensured that any leaks in the system would result in room air being drawn into the enclosure rather than test material escaping from the enclosure to contaminate the work environment and result in personnel exposures.

Figure 1. Schematic Diagram of Jet-O-Mizer® Aerosol Generation System and AccuRate® Materials Feeder

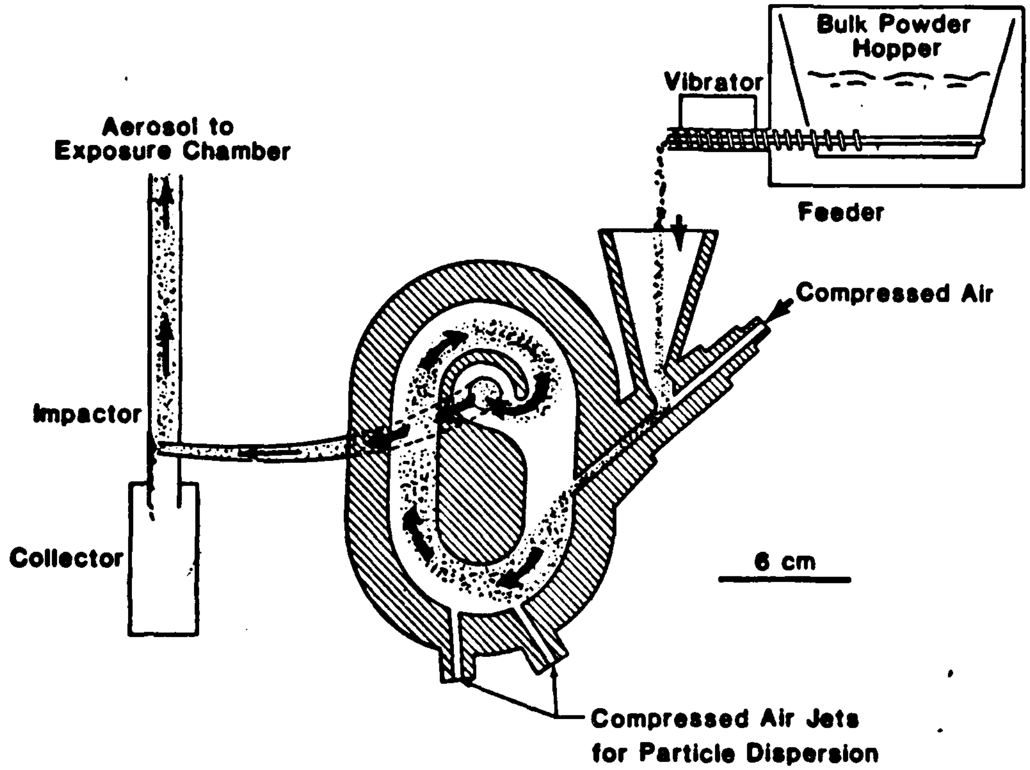


Figure 2 indicates the relationship of the aerosol generation, delivery, and animal exposure systems in the exposure room. The figure also indicates the location of control and sampling apparatus requisite to generation and handling of aerosol samples.

2. Control of Relative Humidity

Aerosols were produced by the Jet-O-Mizer aerosol generation system using dry, filtered air. This aerosol might have caused dehydration of the rats during the 1.5 and 3.0 hour exposures. To obviate this potential problem, the aerosols of Cu-Zn were humidified by mixing them with filtered air which was saturated with water vapor. The saturated air was filtered prior to mixing with the aerosols. The filtration procedure eliminated water droplets from the aerosol; water droplets could cause problems with aerosol stability, primarily clumping of individual aerosol particles. By adjusting the amount of water-saturated air used, this procedure achieved a relative humidity of 30-50 percent which was stable over the duration of the exposures. Figure 3 shows a schematic diagram of the humidification system.

After being humidified, aerosols were passed through the exposure chambers or through a bypass as excess aerosol. Excess aerosol flow was drawn through a high efficiency particulate air (HEPA) filter via the room air exhaust system; the exposure chambers were exhausted through a separate HEPA filtered chamber exhaust system.

3. Animal Exposure Chambers

Two 96-port nose-only exposure chambers were used for exposing rats to the Cu-Zn; an 80-port nose-only chamber was used to expose the shams. These multiport small animal exposure systems were similar to those described by Raabe _et al_. (1973). During exposures, rats were in polycarbonate

Figure 2. Schematic Diagram of Room Used for Aerosol Generation, Sampling, and Animal Exposures

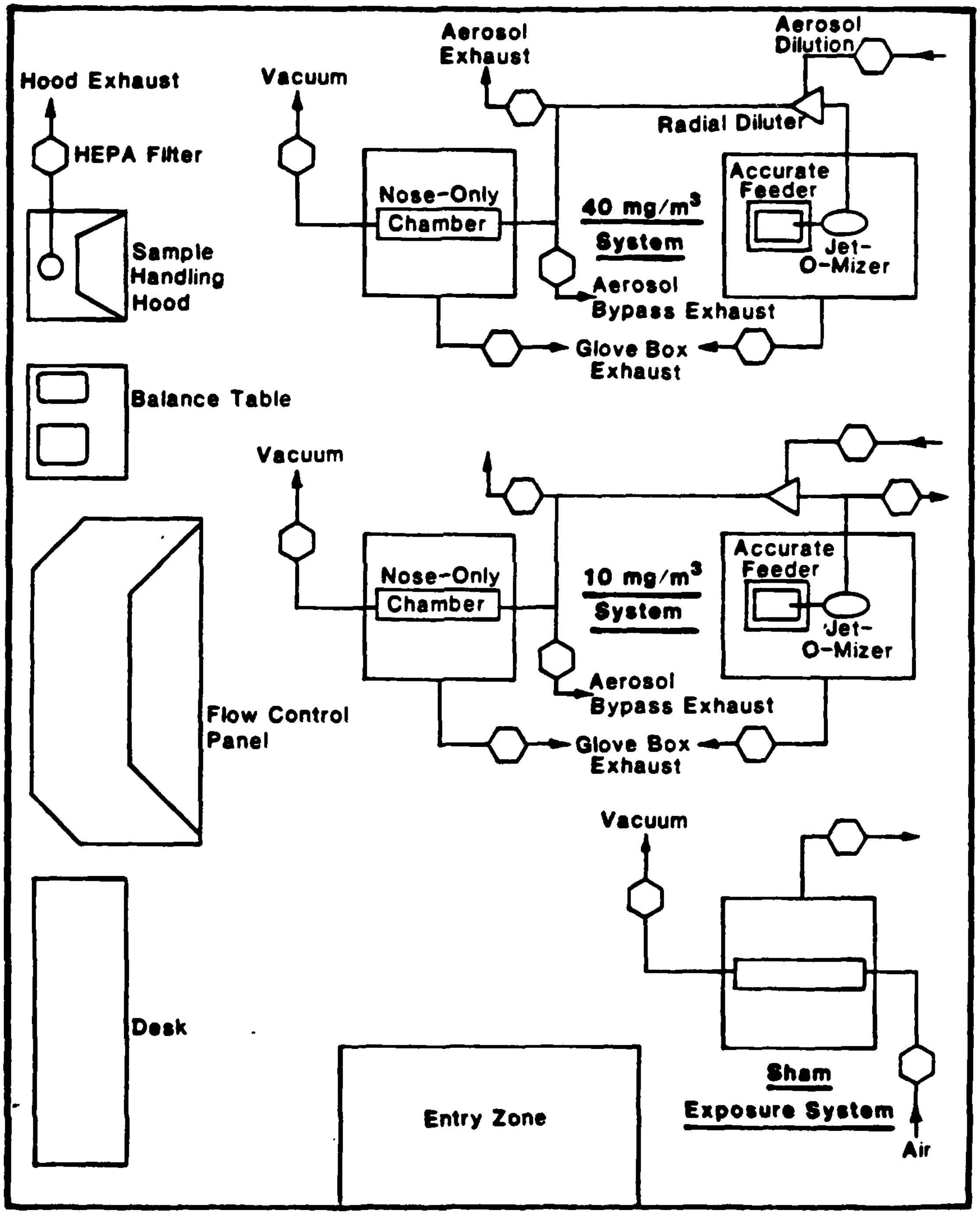
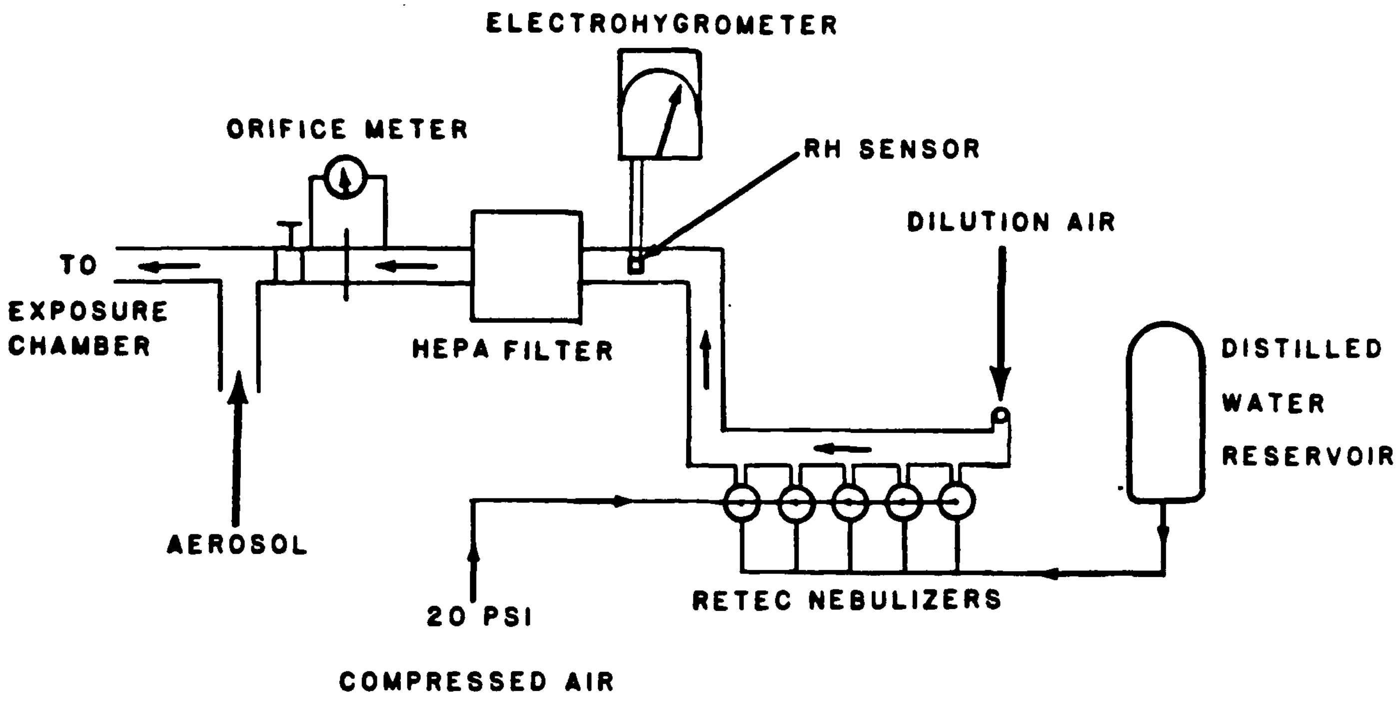


Figure 3. Schematic Diagram of Humidification System for Exposure Atmospheres



nose-only exposure tubes. These tubes were designed to allow the animal's nose to project into the aerosol passing through the exposure chamber, while minimizing external contamination of the animals. The wall thickness of the lexan tubes was 2.3 mm and the tube diameter was adequate to allow the rats space for thorax expansion during breathing, but not large enough for the rat to turn around in the tube. The front end of each tube was tapered internally to conform to the shape of the rat's head and the rear end of the tube was closed by an adjustable plunger. The rats were secured in these tubes during exposure, with their noses projecting slightly past the end of the exposure tube and into the aerosol passing through the exposure chamber.

4. Aerosol Physical Characterization

Three types of aerosol samples were collected. Filter samples were collected to determine aerosol concentrations, Lovelace Multijet (LMJ) cascade impactors were used to collect samples for aerosol size determinations, and point-to-plane electrostatic precipitator (ESP) samples were collected for routine aerosol morphology evaluations.

A RAM-S® real-time aerosol monitor (GCA Corporation, Bedford, MA) was used to continuously monitor the aerosol concentrations during testing and exposures. The primary use of this measuring device was to provide real-time indications of the functional state of the aerosol generation and delivery systems. This information was used by the exposure technician to make any necessary adjustments within the systems to maintain the desired exposure conditions.

Our previous experience with RAM-S monitors indicated that continuously monitoring high concentration aerosols would necessitate routine servicing the RAM-S every few days. The servicing procedures were time consuming and require having an extra RAM-S unit for backup use. The main problems were (1) aerosol accumulation on optical surfaces and (2) clogging of the downstream filter, which made it impossible to maintain a constant flow rate through the RAM-S.

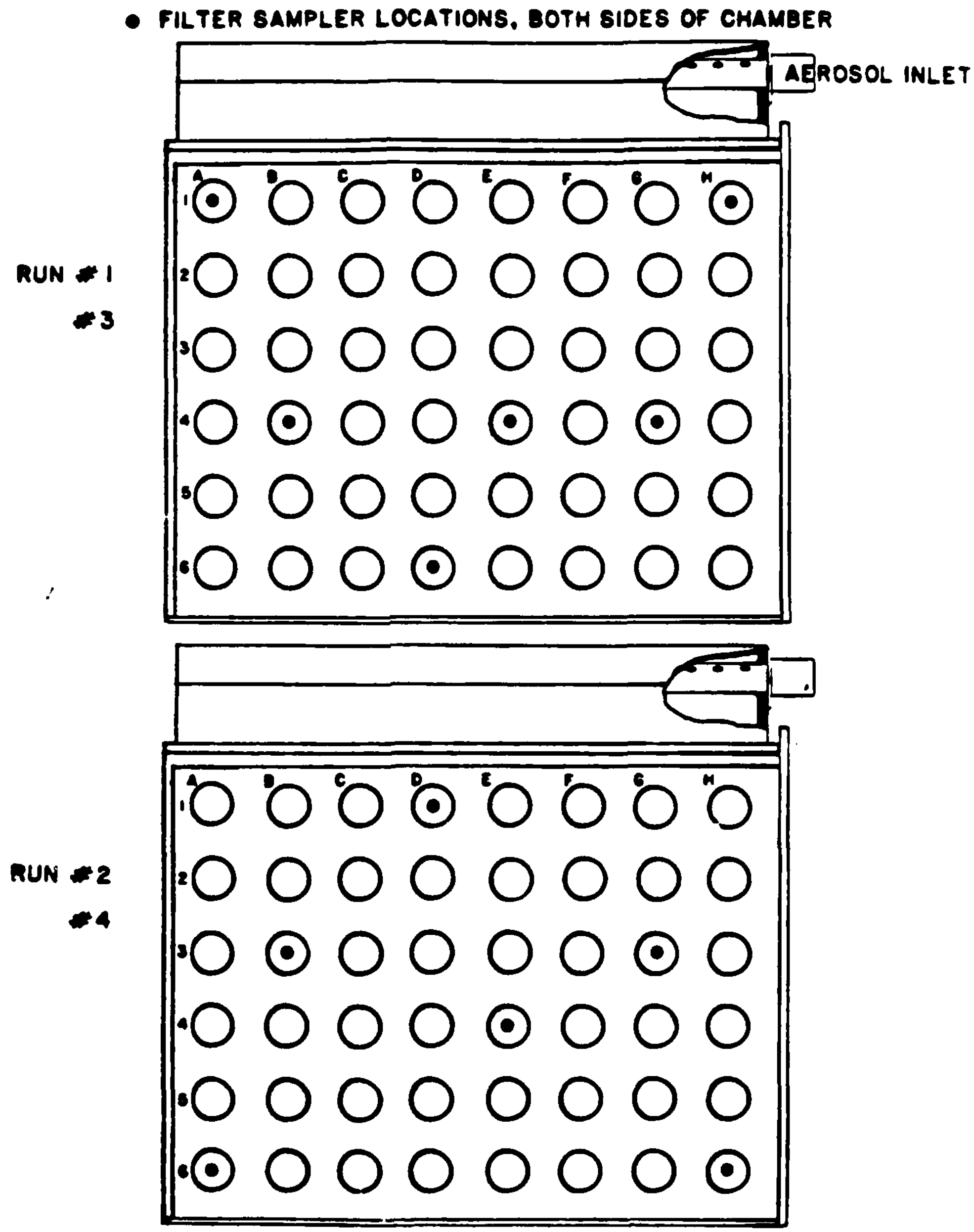
We modified the RAM-S units to improve their service life and extend the time between maintenance. Modifications involved (1) using sheathing air to help keep optical components clean and (2) diverting the aerosol to a filter external to the RAM-S units. These modifications provided metered, clean air to protect the optical components of the systems and prevented clogging of the system filters. Using the modified flow system allowed using the RAM-S monitors 6 hours/day, 5 days/week for more than one month without breakdown or the need for routine maintenance. The modifications had no effect on accuracy of the instruments.

5. Exposure Chamber Aerosol Distribution Evaluations

The following procedures were used to quantitate aerosol generator output and uniformity of aerosol concentration within the exposure chambers used for Phase II. Two nose-only exposure chambers were used and both required testing prior to animal exposures. One chamber was set at 10 mg Cu-Zn/m^3, the other chamber was set at 40 mg Cu-Zn/m^3.

Tests were conducted four hours per day, on three separate days with no animals in the exposure chambers. Previously identified exposure ports were sampled simultaneously to evaluate the aerosol concentration at each port. The amounts of test material were determined by weighing the filters before and after the aerosol collection intervals. Twelve simultaneous filter samples were collected, six from each side of each exposure chamber. The pattern for sampling is indicated in Figure 4. Both

Figure 4. Sampling Arrangement for 96-Port Nose-only Animal Exposure Chamber



sides of the chambers had the same exposure port identification scheme and were sampled at the same time. Positions "E4" served as reference points and were sampled for every day's experiment. Each experiment consisted of four tests. Tests number 1 and 3 included chamber port positions A1, H1, B4, E4, G4, and D6; tests 2 and 4 included positions D1, B3, G3, E4, A6, and H6. Aerosols were collected on these filters for 40 minutes with 1 liter/minute sampling flow rates. A total of 144 samples were collected for each nose-only exposure chamber and used in the evaluation of spatial and temporal distribution patterns. Lovelace Multijet impactor samples were also collected for aerosol size determinations.

F. Animal Exposure Procedures

Two hundred thirty female and 300 male rats were exposed in Phase II. Seventy (30 females and 40 males) were sham-exposed, the rest were exposed to the Cu-Zn in the groups indicated in Table 1. The exposures were conducted over a five week period so that the number of rats per day processed for endpoint evaluations could be properly evaluated.

We had determined the aerosols were almost uniformly distributed in the nose-only chambers. However, to minimize variability which might result from not randomly placing rats in the exposure ports for each exposure, we used a randomization procedure to assign each rat to its exposure location for each exposure. A different list of exposure locations was produced for each group of rats for every exposure. The procedure used computer software which randomized the list of rats to be exposed in each chamber and overlaid the random list of rats on the list of exposure ports available. Exposure ports were identified by a 3-digit code where each port of an exposure chamber was assigned a unique number. The procedure not only randomly assigned the rats to their exposure locations each day, the computer output file was used to generate labels which were placed on the exposure tubes at the time the rats were loaded into them. The labels facilitated accounting for each rat and reduced errors associated with handling rats for nose-only exposures and returning them to their assigned housing cages. The exposure location history for each rat in the study is in a master computer file for examination if needed.

The animals were not housed in the same room in which they were exposed. On exposure days, the rats were transported between the housing room and the exposure room. Animals to be sham-exposed were handled and transported first. They were loaded into polycarbonate nose-only exposure tubes in the housing room and transported in the tubes to the exposure room, which was across the hall from the housing room. After the nose-only exposures, the rats were transferred (sham animals first) from the exposure tubes to 1 liter plastic containers for transport back to the housing room. The plastic transport containers had lids with five approximately 8 mm diameter holes punched in the top to allow air to the rats while they were in the transport containers.

G. Aerosol Characterization During Exposures

During the animal exposures, three types of aerosol samples were collected for each exposure. These included (1) the Lovelace Multijet (LMJ) impactor samples for determining aerodynamic size distributions of the aerosols, (2) filter samples for aerosol concentration determinations, and (3) a point-to-plane electrostatic (ESP) sample for electron microscope observations. The flow rates were set at 16.4 liters/minute for impactors, 1 liter/minute for filter samplers, and 0.2 liters/minute for the ESP. One sample each of the LMJ and ESP were collected at the beginning and end of each exposure. One pair of filter samples was collected for the entire 1.5 hour exposures, two filter samples were collected for the 3.0 hour exposures.

H. Observations During and After Exposures

The rat housing area was inspected twice daily for dead or moribund rats. More thorough examinations occurred twice per week when all of the rats were weighed. Any dead or moribund rats were taken to necropsy where they were necropsied as "unscheduled deaths" as indicated in ITRI Protocol FY85-089. Personnel handling rats for exposures noted any unusual behavior, coat color, excretions, and overall general appearance.

All rats were weighed twice weekly during the exposure series and during the two-week recovery period. These body weights measurements were taken between 0630 and 0830 on days when animal weighing was scheduled.

After their last scheduled exposure, the rats were returned to their housing as usual. Three days later, excluding the rats assigned for immunology and respiratory function evaluations, half of the rats were transported to the LITRI necropsy facility, anesthetized with halothane, killed by exsanguination, and samples were collected for the variety of endpoints. The same procedures were repeated two weeks later with the other rats assigned for these endpoint evaluations. These endpoints are summarized in Table 2, along with the numbers of rats evaluated for each endpoint. Rats assigned to the pulmonary function evaluations were killed and discarded as biological waste after their final pulmonary function tests.

Lavage Fluid Biochemistry and Cytology

The lung is a primary route of entry into the body for inhaled materials. Some inhaled materials cause responses in the lung which can be measured by changes in composition of the lung tissue or by changes in the fluids and cells lining the bronchoalveolar airways. Since fibrosis of the lung was a possible response to the inhaled Cu-Zn, the lung tissue was analyzed for indications of developing fibrosis. Analysis of bronchoalveolar lavage fluid was used to detect an inflammatory response in the lung. This method has proven useful in previous studies on the toxicity of inhaled mineral dusts, coal combustion ash, and other toxicants (Beck et al., 1981, 1982; Henderson et al., 1978a, b, 1979a, b; Moores et al., 1980, 1981).

The rats were anesthetized with halothane, then exsanguinated by cardiac puncture. Halothane anesthesia caused the least changes in baseline parameters used in a screening test for lung injury (Henderson and Lowrey, 1983), which is why it was the procedure of choice for this study. Blood was collected in syringes containing 100 units of heparin and used for hematology evaluations. The trachea and lungs were removed en bloc from sacrificed rats, and lavaged with physiological saline (2 washes of 5 mL each for females and 2 washes of 7 mL each for males). The two recovered lavage fluid washes from individual rats were combined and centrifuged at 1000 x g for 15 minutes to remove cells. The supernatant was analyzed for lactate dehydrogenase (indicator of cell death), beta-glucuronidase (lysosomal enzyme indicating high phagocytic activity and/or lysis of phagocytic cells), alkaline phosphatase (measure of type II lung cell response), and protein content (indicator of damage to the alveolar/capillary barrier). The cells in the pellet were resuspended in physiological saline and evaluated using a Coulter counter (Coulter Electronics, Hialeah, FL). An aliquot of the cell suspension was processed using a cytocentrifuge and differential cell counts were made.

Total airway collagen was measured as an indicator of possible remodeling of lung structural protein (Pickrell et al., 1975). The analysis was done only for the rats exposed to 40 mg Cu-Zn/m^3, 2 days/week, 3 hr/day. If results had indicated significant changes relative to the sham-exposed rats, additional groups of rats would have been analyzed. One half of the control animals from the group sacrificed at the end of exposure was pooled with one half of the control animals sacrificed after the recovery period. This was done to provide controls for this screening analysis and also for the additional analyses if they would have been justified. We demonstrated in the final report for Phase I of this project (Snipes et al., 1986) that there was little variation between sham-exposed rats sacrificed at two different times. Most of the variation was among animals, not age, and we pooled results to improve statistics. An aliquot of the lavage fluid supernatant was hydrolyzed in 6 N HCl (sealed under N_2) for 16 to 18 hours. The acid was evaporated, the material was resuspended in 0.001 N HCl, and a colorimetric procedure was used to quantitate the amount of collagen present. Right lung lobes were hydrolyzed using the same procedure as for the lavage fluid. The acid was evaporated, the material was resuspended in 0.001 N HCl, and samples were decolorized with charcoal filtration, evaporated, and finally suspended in 0.001 N HCl and analyzed colorimetrically for hydroxyproline, and the collagen content was calculated.

Hematology

Hematology and clinical chemistry measurements were made according to standard methodology. Specifically, erythrocyte and leukocyte counts were made with an electronic counter (Coulter ZB1, or S550), which produce equivalent results on rat blood. These counters also measured hemoglobin (spectrophotometric), mean corpuscular volume (electronic) and calculated a value for packed cell volume (hematocrit) using the previously obtained results. A differential leukocyte analysis was made from a stained (Wright's) blood smear from which 100 leukocytes were examined with a light microscope. Nucleated erythrocytes and platelets were enumerated from the smear. Blood was stained with brilliant cresyl blue and a second smear made to enumerate reticulocytes.

Immunology

The lung-associated lymph nodes are the primary site for the production of immunity to particulate antigens present in the lung (Bice et al., 1979). The results of previous studies indicate that damage of the lung epithelium by inhalation of toxicants (Schnizlein et al., 1980) or damage of the lung-associated lymph nodes by toxic materials that translocate from the lung (Schnizlein et al., 1982) can alter immune responses to antigens in the lungs. Because inhaled Cu-Zn might be toxic and might accumulate in lung-associated lymph nodes, inhalation exposures could alter the lung and/or the lung-associated lymph nodes and lead to changes in the immune defenses in the lung. Therefore, the development of lung immunity was evaluated.

Antibody levels in serum are a measure of toxicity of particles that have translocated from the lung to the lung-associated lymph nodes. Specific antibodies found in serum after lung immunization are produced in the lung-associated lymph nodes and represent a measure of lymph node function. Our immunologic tests included enumerating the antigen-specific antibody-forming cells in the lung-associated lymph nodes after immunization in the lung with a particulate antigen. The levels of IgM and IgG antibodies in sera were then evaluated by an enzyme-linked immunoassay (Voller et al., 1976).

Immunization was by intratracheal instillation of antigen (Bice et al., 1979) seven days prior to sacrifice of the rats. The rats were anesthetized with halothane, and the trachea was intubated with a catheter. The placement of the catheter in the trachea was verified by ventilating the lungs after placement of the catheter. Particulate antigen (sheep red blood cells) was instilled just above the bifurcation of the trachea. A total of 10^8 sheep red blood cells (SRBC) obtained from a single donor sheep were used for each rat.

The number of lymphoid cells producing IgM anti-SRBC antibody were determined in the lung-associated lymph nodes and the spleen by the Cunningham modification of the Jerne plaque assay (Cunningham and Szenberg, 1968). The evaluation of the number of anti-SRBC in the spleen after lung immunization was necessary to determine if exposure to the Cu-Zn altered the antigen trapping capacity of the lung-associated lymph nodes. Particulate antigen (SRBC) that leaves the lung via the lymphatics is normally removed in the lung-associated lymph nodes. This antigen does not reach distant lymphoid tissues since the number of antigen-forming cells in the spleen is not significantly elevated above background level (Bice et al., 1979).

Antibody-forming cell data were expressed as the number of IgM anti-SRBC antibody-forming cells per million lymphoid cells in the lung-associated lymph nodes or in the spleen. A statistical comparison of the level of immunity in control rats and in exposed rats was made. Results of past studies indicated that the variance of the data increases linearly as the mean level of the immune response increases (Gottlieb, 1974). Therefore, a logarithmic transformation of the data was evaluated using an unpaired t-test with the BMDP computer program (Dixon and Brown, 1979).

Phagocytosis

As described above, lavage fluid was centrifuged and the supernatant was used for biochemical analyses. Pulmonary alveolar macrophages from the cell pellet were evaluated for their ability to phagocytize opsonized sheep red blood cells (SRBC), called EA, which had been sensitized by incubation with anti-SRBC antibody (Harmsen et al., 1980). One mL of a 1 percent (v/v) suspension of EA was added to 500,000 alveolar macrophages in suspension. The mixture of macrophages and EA was incubated at 37°C for 60 minutes, centrifuged, and the pellet resuspended in distilled water for 30 seconds to lyse any EA not phagocytized. Cell lysis was stopped by addition of 1 mL of 0.3 mM saline. Cytocentrifuge preparations were made, and the number of EA phagocytized by 100 alveolar macrophages was counted using light microscopy.

Pulmonary Function Measurements

The respiratory function of 10 rats in the sham-exposed (control) group and six of the eight exposed groups was measured at the end of the 4-week exposure and at 2 weeks after the end of exposure. The exposed groups included those exposed two days per week to 60, 120 or 240 mg·hr Cu-Zn/m3 per week (60-2, 120-2 and 240-2, respectively), and those exposed 4 days per week to achieve the same weekly cumulative exposures (60-4, 120-4 and 240-4, respectively).

Tests included a spectrum of measured and calculated parameters, allowing evaluation of the different facets of respiratory function: ventilation, lung mechanics, gas distribution, and alveolar-capillary gas transfer. The tests included assays that are sensitive and used most commonly in humans.

Respiratory function measurements were similar to those previously published (Harkema _et al._, 1982; Likens and Mauderly, 1982; Mauderly, 1982). Tests were conducted using a 1.4 L combination flow (volume displacement) and pressure (constant volume) plethysmograph. The plethysmograph was heated by a resistance element and maintained at approximately 37°C. Rats were intubated with tracheal catheters, 5.5 cm long x 1.78 mm I.D., fabricated from 14 gauge intravenous catheters (Cathlon IV. No. 4428, Jelco, Raritan, NJ) as previously described (Mauderly, 1977) and positioned in the plethysmograph. The breathing port in the plethysmograph wall was a luer fitting (No. 6161, Popper, New York, NY) drilled to 2.5 mm I.D. The frequency response of the plethysmograph-respirator-tracheal catheter system was tested and found adequate to record forced expirations of rats. The phasing of flow, volume, and Ptp signals was tested by oscillating volumes into and out of the plethysmograph; no significant phase lag was detected within the frequency range of spontaneous breathing, the only condition in which phasing is critical.

Flows were determined by measuring differential pressures (MP45 transducer, Validyne, Northridge, CA) across 6 layers of 400-mesh wire cloth covering a 1.3 cm hole in the plethysmograph wall. Volumes were calculated by integrating flow (Model 6 pulmonary mechanics analyzer, Buxco, Sharon, CT). In the pressure mode, used only for measurement of functional residual capacity, the hole was sealed and volume changes were measured as pressure changes, using the same transducer.

Transpulmonary pressure (Ptp) was measured using transducers (P23ID, Gould, Hato Rey, Puerto Rico) connected to the external airway and to a 2.2 mm O.D. esophageal catheter by liquid-filled tubes. The transducer outputs were conditioned by a differential amplifier (Buxco), which produced outputs for both transpulmonary and airway pressures.

A positive-negative pressure respirator system was used to induce quasistatic and forced expiratory movements. Reservoirs (4.6 L) maintained at +40 and -50 cm H_2O were connected to the airway by solenoid valves. Inspiratory and quasistatic expiratory flow rates were limited by needle valves to 5 and 3 mL/second, respectively. Inspiration was stopped automatically at a Ptp of +30 cm H_2O. Forced expiration was induced by opening a valve having a 9.5 mm diameter orifice (V52DA3012, Skinner, New Britain, CT) without intentional flow restriction between the valve and the low pressure reservoir.

The measurement sequence was as follows. The rats were anesthetized with halothane in air, intubated with the tracheal catheter, and placed prone in the plethysmograph. The esophageal catheter was inserted and adjusted to maximize the Ptp signal. Anesthetic depth was standardized by adjusting the halothane concentration to yield a respiratory frequency of 55 ± 5 breaths/minute. Respiratory frequency, tidal volume, minute volume, dynamic lung compliance, and total pulmonary resistance were measured during spontaneous breathing by the mechanics analyzer, averaged for 15-20 breaths by a data logger (DL-12, Buxco) and displayed on a teletype terminal. The measurement of dynamic lung mechanics by the mechanics analyzer was identical in principal to the method of Amdur and Mead (1958).

Prior to each subsequent test procedure, the rats were hyperventilated with a syringe to induce temporary apnea and to establish a uniform lung volume history. A quasistatic exhalation was performed by inflating the lungs to +30 cm H_2O Ptp, then slowly deflating the lungs until expiratory flow stopped. Volume and Ptp signals were recorded on a strip-chart recorder. The inspired volume was defined as inspiratory capacity, the expired volume as vital capacity, and the difference as the expiratory reserve volume. Quasistatic pressure-volume relationships were analyzed by a microprocessor contained within the data logger, and results were displayed on a teletype terminal. Quasistatic lung compliance was measured as the chord compliance between the apneic lung volume and that volume +10 cm H_2O Ptp.

Functional residual capacity was measured by the Boyle's Law principle (DuBois et al., 1956) by inducing apnea, blocking the breathing port, and measuring airway pressure and lung volume changes as breathing resumed. Residual volume was calculated by subtracting expiratory reserve volume from functional residual capacity, and total lung capacity was calculated by adding residual volume to vital capacity.

A forced expiration was induced by inflating the lungs to +30 cm H_2O Ptp and rapidly deflating the lung until expiratory flow stopped. The event was analyzed by a microprocessor contained within the data logger, and both the flow-volume curve and several calculated variables were displayed on a teletype terminal. These variables included forced vital capacity, peak expiratory flow rate, percent of forced vital capacity expired in 0.1 second, mean mid-expiratory flow rate, and the maximal expiratory flow rates at 10, 25, and 50 percent of forced vital capacity.

Diffusing capacity for CO was measured by a single breath method (Ogilvie et al., 1957). The gas volume required to increase Ptp from functional residual capacity to 20 cm H_2O was determined, and that volume of test gas containing 0.4 percent CO and 0.5 percent Ne in air was injected into the lung with a syringe. After approximately six seconds, one-half the injected volume was withdrawn from the lung and the remainder (alveolar sample) was withdrawn into a second syringe. Gas concentrations in the alveolar gas sample was determined by gas chromatography (Carle Model 111).

A single-breath N_2 washout was performed as described above for quasistatic exhalation, except that the test was started by deflating the lungs to residual volume and the subsequent inflation was with O_2 instead of air. An X-Y plot of volume exhaled versus N_2 concentration (percent) of the expirate was constructed and analyzed to calculate the slope of Phase III, the alveolar plateau.

Histopathology

Ten male and 10 female rats from each exposure group listed in Table 2 were sacrificed at the end of the exposure series, the other half after the 2-week recovery period. The rats were anesthetized with halothane and exsanguinated via cardiac puncture. Organs grossly examined, weighed, saved in fixative, and examined microscopically are listed in Table 3.

Any rats that died before their scheduled termination were examined for lesions and to determine the cause of death. In addition to the tissues noted in Table 3, any lesions were fixed and examined microscopically.

All tissues were fixed in 10 percent neutral buffered formalin (NBF). The lungs were instilled intratracheally with 10 percent NBF to approximately their normal inspiratory volume. The nasal cavity was perfused with 1-3 mL of 10 percent NBF to remove air before immersion in the fixative. The stomach was injected with 10 percent NBF and fixed for gross examination. Tissues were trimmed, embedded in paraffin, and sectioned at 5 microns with a microtome. The sections were mounted on glass slides, and stained with hematoxylin and eosin. Comparisons were made among the exposure groups for

Table 3

Organs Grossly Examined, Weighed, Saved in Fixative, and Examined Microscopically

Organs	Examine	Weigh	Save Tissues	Routine Histology
Whole-Body	X	X		
Skin	X		X	
Breast	X		X	
Thymus	X		X	X
Tracheobronchial Lymph Nodes	X		X	X
Submandibular Lymph Nodes	X		X	
Spleen	X		X	X
Femur plus marrow	X		X	X
Vertebrae	X		X	
Muscle	X			
Larynx	X		X	X
Nasal Cavity	X		X	X
Trachea	X		X	X
Lung	X	X	X	X
Heart	X		X	X
Esophagus	X			
Stomach	X		X	X
Liver	X	X	X	X
Pancreas	X		X	
Kidney	X	X	X	X
Urinary Bladder	X		X	X
Epididymus	X		X	
Testes	X		X	X
Prostate	X		X	
Uterus	X		X	
Ovary	X		X	X
Adrenal	X		X	X
Thyroid	X		X	X
Brain (section through thalamus)	X		X	X
Pituitary	X		X	
Eye	X		X	
Lesions	X		X	X

presence of lesions, types of lesions, and their severity. Results are summarized below and details are included in the Appendix.

Tissue Content of Cu and Zn

Tissue content of Cu and Zn was determined for organs most likely to accumulate Cu and Zn as a result of the inhalation exposures to powdered Cu-Zn alloy. The main purpose for determining tissue content of the Cu and Zn was to model the deposition and fate of the Cu-Zn and Cu and Zn which would have dissolved from the particles after deposition in the body. These results would provide information essential to modeling the deposition and fate of the same material in humans.

Three male and three female rats from the groups indicated in Table 2 were designated for tissue analyses for Cu and Zn. The tissues to be analyzed were (1) lung, (2) liver, (3) kidneys, (4) femurs, (5) muscle sample, (6) tracheobronchial lymph nodes, and (7) urine sample. We elected to analyze samples from the group of rats from the 240-4 exposure group first, then decide if other groups should be analyzed. The samples were analyzed using the furnace atomic absorption procedure described below.

I. Atomic Absorption Analytical Procedures

Samples of rat tissue were dried for about 15 hours at ~ 120°C, then transferred to Teflon digestion vessels containing 3 mL of ultrapure concentrated HNO_3, 1.0 mL of ultrapure concentrated HCl, and 0.1 mL of ultrapure concentrated HF. Samples were next placed in a microwave oven for 6 minutes, then cooled in ice water. Cooled digestates were added to 5 mL of 5 percent boric acid and diluted to 25 mL with 0.06 M citric acid. The diluted solutions were assayed for copper and zinc by atomic absorption spectroscopy using an Instrumentation Laboratories IL 951 graphite furnace atomic absorption instrument. The limits of detection and quantitation (American Chemical Society Committee on Environmental Improvement, 1983), and average recoveries of standard copper and zinc are shown in Table 4. Attempts to measure recovery of the metal alloy powder added to animal tissues were not successful as a result of difficulty in quantitatively transferring small weights of the Cu-Zn.

Tissues from sham-exposed rats were assayed for Cu and Zn and the results are summarized in Table 5. During later routine assays of tissues from unexposed rats, reagent blanks and quality control samples to monitor recovery were analyzed at a frequency of about 5 quality control samples per 30 unknown samples. Similar procedures were used for all types of samples analyzed in Phase II.

J. Statistical Comparisons

Statistical comparisons presented in this report included analysis of variance to detect overall differences in mean and variance. Specific differences were measured using the Student t-statistic with appropriate corrections for multiple comparisons according to the inequality of Bonferroni. The number of contrasts was limited to the immediate family of comparisons in order to prevent too many type II errors. Significant changes with a type I error probability of 0.05 or 0.01 for the entire family of comparisons are marked. We used the Levene test for equal variance to determine if we should use separate or pooled variance t values in our comparisons. If $p > 0.05$ for the Levene test, we used pooled variance values; for $p \leq 0.05$, we used the separate variance t.

In addition, effects were investigated for exposure-effect relationships, even if all or most of the differences were found not to be

Table 4

Quality Control Results from Atomic Absorption Assays
(N = 42)

Metal	Micrograms (mean ± SD)	Detection Limit µg	Detection Limit ppm	Quantitation Limit µg	Quantitation Limit ppm
Cu	0.193 ± 0.19	0.77	0.031	2.11	0.084
Zn	0.186 ± 0.086	0.44	0.018	1.04	0.042

NOTES:

Recovery of NBS SRM #393 (Cu) = 97.7 ± 7.7% SD.

Recovery of NBS SRM #728 (Zn) = 101.5 ± 9.5% SD.

Detection limit = mean + 3 SD of N reagent blank assays.

Quantitation limit = mean + 10 SD of N reagent blank assays.

All reagent blank assays were 25 mL, the same as biological samples.

Table 5

Copper and Zinc Contents of
Sham-Exposed Rat Tissues
(all sham-exposed rats combined)

Tissue	μg Cu/g Sample (mean ± SD, n = 12)	μg Zn/g Sample (mean ± SD, n = 12)
Kidneys	14.6 ± 4.7	11.0 ± 6.2
Liver	2.6 ± 1.3	5.6 ± 3.4
Lung	1.1 ± 0.1	19.8 ± 2.7
LALN[a]	2.0 ± 0.3	18.1 ± 2.9
Femurs	0.7 ± 0.3	154 ± 64
Muscle	0.8 ± 0.2	5.2 ± 3.7

[a]Lung-associated lymph nodes.

significant at the P = 0.95 level. In promising cases, i.e., for apparent exposure-effect relationships, we did a trend analysis for effects of two exposures per week and four exposures per week. Results for trend analyses are discussed in text and presented in detail in Appendix E.

VI. RESULTS

A. Exposure Aerosol Chamber Distribution Evaluations

Table 6 summarizes the temporal and spatial variation of aerosol concentrations within the two nose-only exposure chambers. We define the temporal variation as the variation with time at a given position and the spatial variation as the variation from location to location at a given time or average over a given time period. The temporal variation was calculated from data for a given position from all test runs, and the spatial variation was calculated from average concentrations of all sampling locations. Table 6 indicates that the temporal and the spatial variation for both exposure chambers was less than 10 percent and air concentrations of the Cu-Zn were close to the target concentrations of 10 and 40 mg Cu-Zn/m^3.

The average aerosol concentrations at sampling locations are shown in Figure 5 for the chamber used to deliver 10 mg Cu-Zn/m^3, and Figure 6 for the chamber used to deliver 40 mg Cu-Zn/m^3. The concentration distribution within the chamber was relatively uniform and a two-way analysis of variance for all 22 sampling locations (including side-to-side, top-to-bottom and back-to-back) did not indicate any significant differences among the sampling positions within either exposure chamber.

The aerosol size distributions as determined using the Lovelace multijet cascade impactor during the chamber aerosol distribution evaluations

Table 6

Coefficient of Variation for Aerosol Distribution
Without Animals Present in Exposure Chambers

Measurement	Aerosol Concentration of Cu-Zn: 10 mg/m^3	Aerosol Concentration of Cu-Zn: 40 mg/m^3
Temporal Variation	8.5 ± 2.9%[a] (3.2% - 13.9%)[b]	7.0 ± 3.7%[a] (2.9% - 18.0%)[b]
Spatial Variation	3.9%	6.8%
Mean Concentration	10.3 mg/m^3	39.9 mg/m^3

[a]Mean ± standard deviation for the coefficient of variation.

[b]Range for coefficient of variation.

Figure 5. Cu-Zn Alloy Powder Aerosol Concentrations (Mean ± SE) at Defined Sampling Points for 96-Port Chamber Used for 10 mg Cu-Zn Alloy/m^3

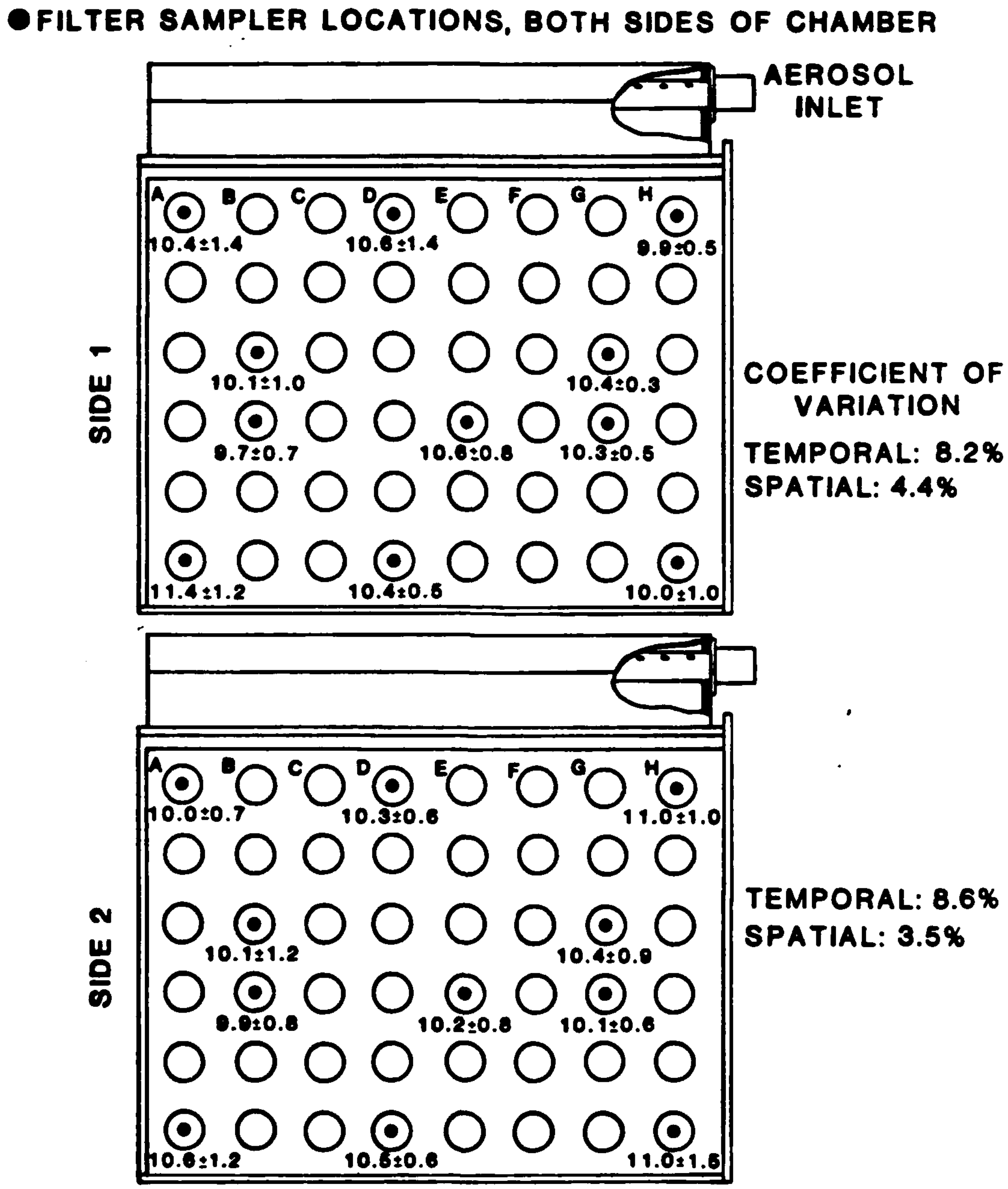
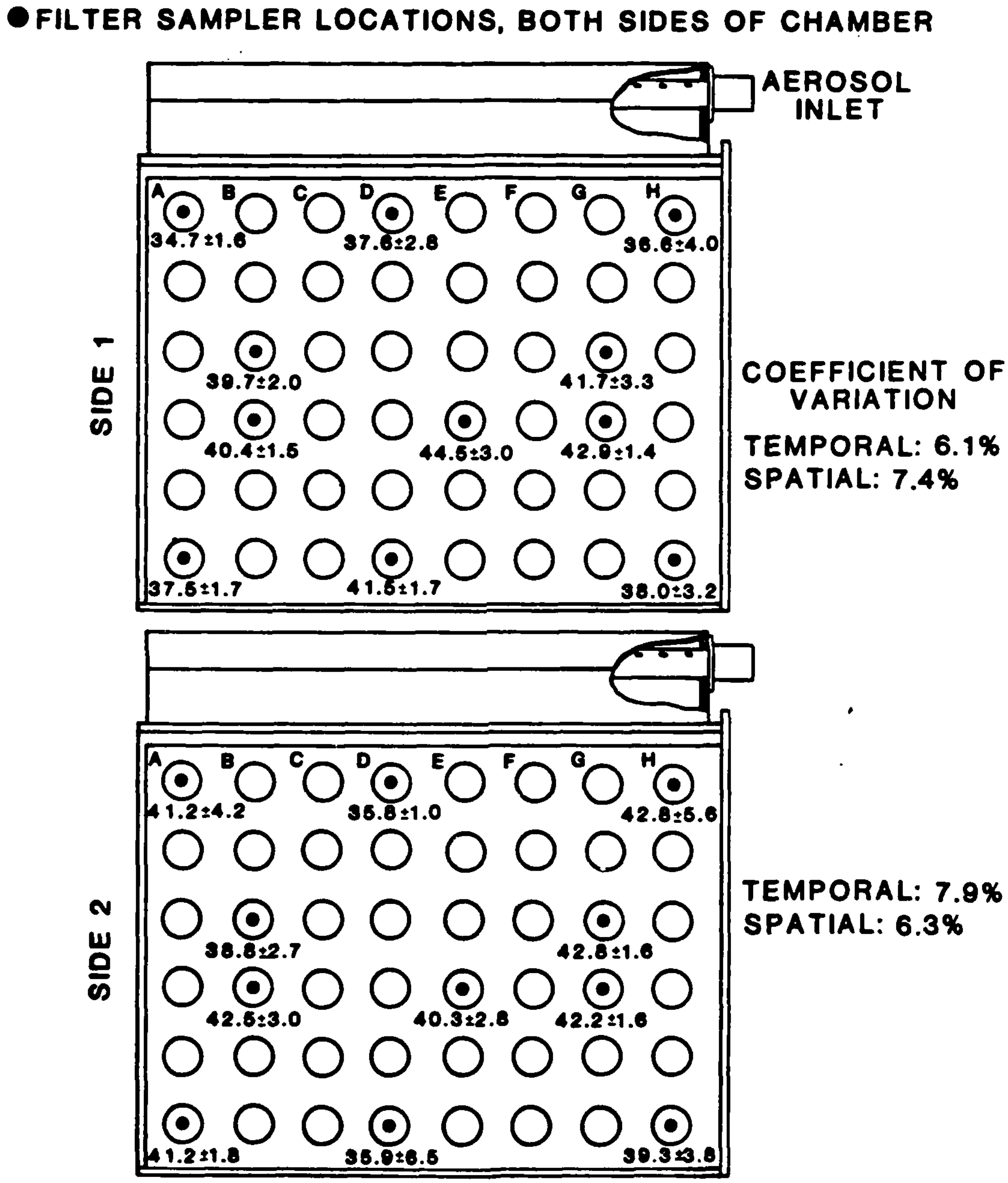


Figure 6. Cu-Zn Alloy Powder Aerosol Concentrations (Mean ± SE) at Defined Sampling Points for 96-Port Chamber Used for 40 mg Cu-Zn Alloy/m^3



are indicated in Table 7. These results were similar for both aerosol concentrations and were comparable to those from Phase I of this project, where we generated aerosols having 100 mg Cu-Zn/m^3.

B. Aerosol Characterization During Exposures

Figure 7 shows the daily aerosol concentrations for both exposure chambers over the 5 week period of rat exposures. The overall aerosol concentrations (mean ± SD) were 10.2 ± 1.2 mg Cu-Zn/m^3 and 41.5 ± 3.6 mg Cu-Zn/m^3. We maintained daily aerosol concentrations within 30 percent of the target aerosol concentrations, and the overall coefficient of variation was less than 15 percent.

Table 8 shows the accumulated weekly exposures and the mean aerosol concentration for each group of rats. Mean aerosol concentrations were within 6 percent of the target values for all 8 groups of rats, and the coefficients of variation were all less than 15 percent.

The aerosol size distributions, as determined by the LMJ cascade impactor samples during the 5 weeks of exposures are listed in Tables 9 and 10. Table 9 shows the aerosol size distributions for each exposure group; Table 10 is the summary for all groups combined. Analysis of variance indicated there were no significant size differences between the two exposure chambers ($F = 0.34$; $P > 0.05$) or among the eight exposure groups ($F = 0.74$; $P > 0.05$).

C. Observations During and After Exposures

Animal Deaths During Exposure

Five rats, all females, died during the four-week exposure. The code "FD" in the "assignment code" for Appendix C indicates which rats these were. The deaths were accidental, the result of the animals turning around

Table 7

Aerosol Size Distribution During
Chamber Aerosol Distribution Evaluation

	Aerosol Concentration of Cu-Zn	
	(10 mg/m^3)	(40 mg/m^3)
MMAD[a]	1.22 ± 0.44 (1.22 ± 0.18)	1.00 ± 0.19 (1.00 ± 0.13)
σ_g[b]	3.01 ± 0.70 (3.01 ± 0.29)	4.19 ± 0.37 (4.19 ± 0.26)

[a]Mass median aerodynamic diameter in micrometers.
Mean ± SD (mean ± SE).

[b]Geometric standard deviation.
Mean ± SD (mean ± SE).

Figure 7. Aerosol Concentrations of Cu-Zn Alloy Powder During the 35 Days of Rat Exposures

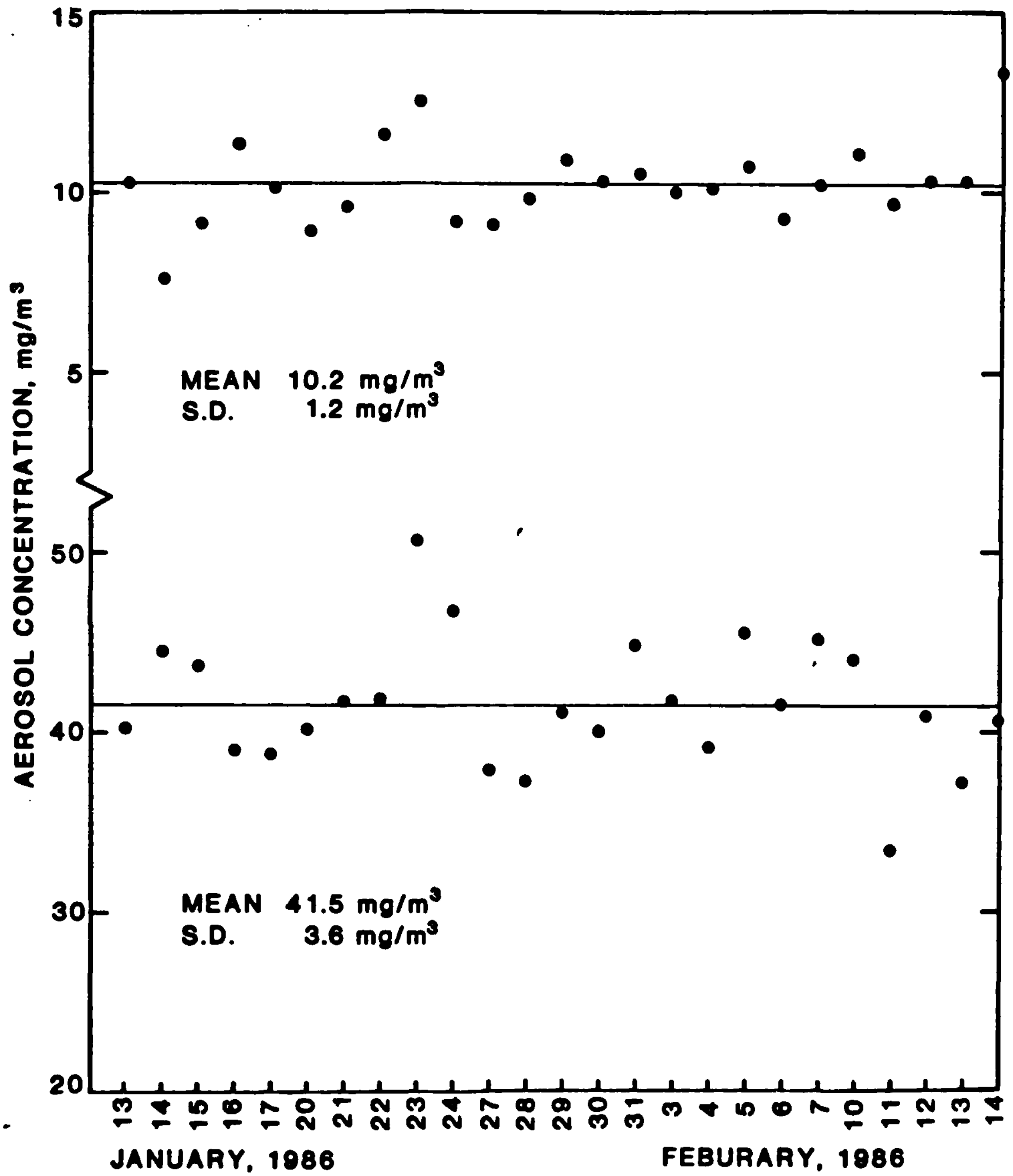


Table 8

Summary of Cu-Zn Alloy Powder Exposure Atmosphere Concentrations for Phase II

	Weekly	Aerosol Concentration (mg/m^3)		
Experiment	$mg \cdot hr/m^3$	Mean ± SD	C.V. (%)	N[a]
4269	30-2[b]	10.1 ± 1.3	13	8
4271	60-2	9.9 ± 0.9	9	11[c]
4273	60-4	10.4 ± 1.5	14	16
4270	120-2	41.4 ± 5.0	12	8
4275	120-4	9.8 ± 1.3	13	16
4272	240-2	40.1 ± 2.8	7	8
4274	240-4	41.6 ± 2.8	7	16
4276	480-4	42.7 ± 5.8	14	32[d]

[a]Number of filter samples, typically one per exposure day.

[b]The first number indicates the weekly exposure level in $mg \cdot hr$ Cu-Zn/m^3 and the -2 and -4 indicates there were 2 or 4 exposures per week.

[c]On three exposure days, two filter samples were collected. One sample during the first half of the exposure, the second sample during the last half of the exposure. One filter was collected per day for the other 5 exposure days.

[d]Two filters were collected per exposure day.

Table 9

Aerosol Size Distribution of Cu-Zn Alloy Powder for Each Exposure Group (Experiment)

Experiment	MMAD[a]	σ_g[b]
4269	0.93 ± 0.16 (0.93 ± 0.06)	3.42 ± 0.22 (3.42 ± 0.08)
4271	1.19 ± 0.28 (1.19 ± 0.10)	3.03 ± 0.29 (3.03 ± 0.10)
4273	1.20 ± 0.30 (1.20 ± 0.08)	3.15 ± 0.37 (3.15 ± 0.09)
4270	1.06 ± 0.28 (1.06 ± 0.09)	3.28 ± 0.58 (3.28 ± 0.19)
4275	1.12 ± 0.21 (1.12 ± 0.05)	3.02 ± 0.25 (3.02 ± 0.06)
4272	1.32 ± 0.37 (1.32 ± 0.13)	3.04 ± 0.67 (3.04 ± 0.24)
4274	0.97 ± 0.24 (0.97 ± 0.06)	3.39 ± 0.37 (3.39 ± 0.10)
4276	0.96 ± 0.32 (0.96 ± 0.06)	3.41 ± 0.56 (3.41 ± 0.11)

[a]Mass median aerodynamic diameter in micrometers.
Mean ± SD (mean ± SE).

[b]Geometric standard deviation.
Mean ± SD (mean ± SE).

Table 10

Aerosol Size Distribution of Cu-Zn Alloy Powder
During 5 Weeks of Exposure

	Aerosol Concentration of Cu-Zn Alloy	
	10 mg/m^3	40 mg/m^3
MMAD[a]	1.18 ± 0.28 (1.18 ± 0.04)	1.02 ± 0.31 (1.02 ± 0.04)
σ_g[b]	3.07 ± 0.36 (3.07 ± 0.05)	3.37 ± 0.56 (3.37 ± 0.07)

[a]Mass median aerodynamic diameter in micrometers.
Mean ± SD (mean ± SE).

[b]Geometric standard deviation.
Mean ± SD (mean ± SE).

in their exposure tubes and asphyxiating. No deaths occurred during the study directly as a result of inhalation of the Cu-Zn.

Body and Organ Weights

Body weight results for the nine experimental groups are presented in Figure 8a, b, and c, and Table 11. The typical pattern for body weight changes was an initial drop in body weight during the first few days of the exposure series, followed by stabilization and an increase in body weight, especially after the exposures ended. The solid symbols in Figures 8a, b, and c indicate body weight the morning following an exposure, the open symbols indicate body weight two days after an exposure. The cyclic patterns of body weight reflect the short-term influence of exposure on body weight. On exposure days, the body weight dropped or did not increase; during the days between exposures, the body weight increased.

These rats had been randomized for exposure groups on the basis of body weight. The nine experimental groups had the same average initial body weight as a result of that process. During the time between randomization and the first exposure (about one week) the groups became slightly, but significantly different, in body weight. To allow an appropriate comparison among the groups, body weight for each rat was expressed as a percentage of the body weight on the day before its first exposure. Next, an analysis of variance comparing males and females in terms of their normalized body weights over the course of the study was done. The result indicated no significant differences for males versus females and they were combined to produce Table 11. For unknown reasons, body weights were higher for rats exposed to Cu-Zn than for sham-exposed rats in many of the comparisons. Those differences were judged to be of no consequence and were ignored in evaluating toxic effects of

Figure 8a. Body Weight Summary for Rats (Mean ± SE)

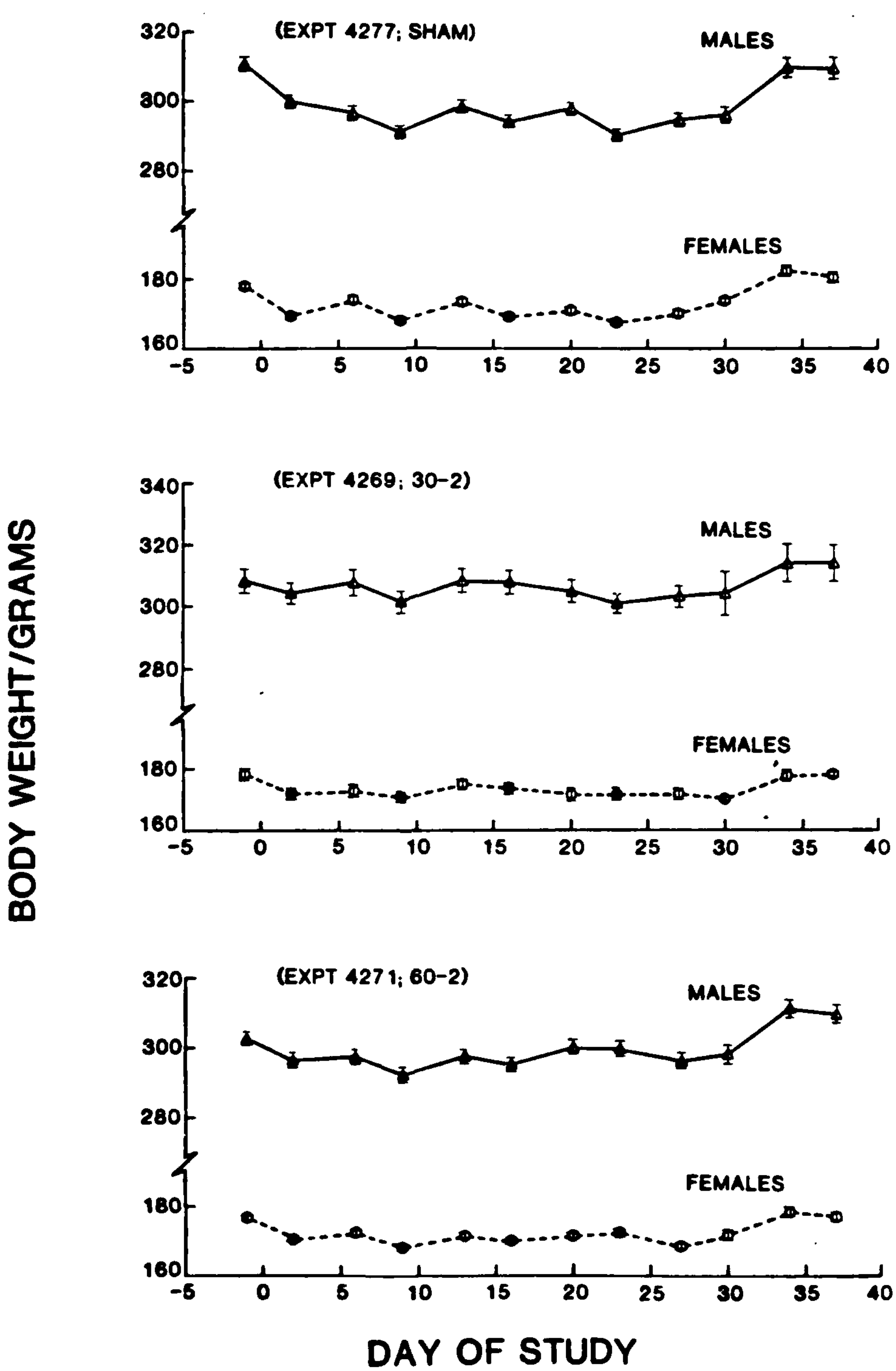


Figure 8b. Body Weight Summary for Rats (Mean ± SE)

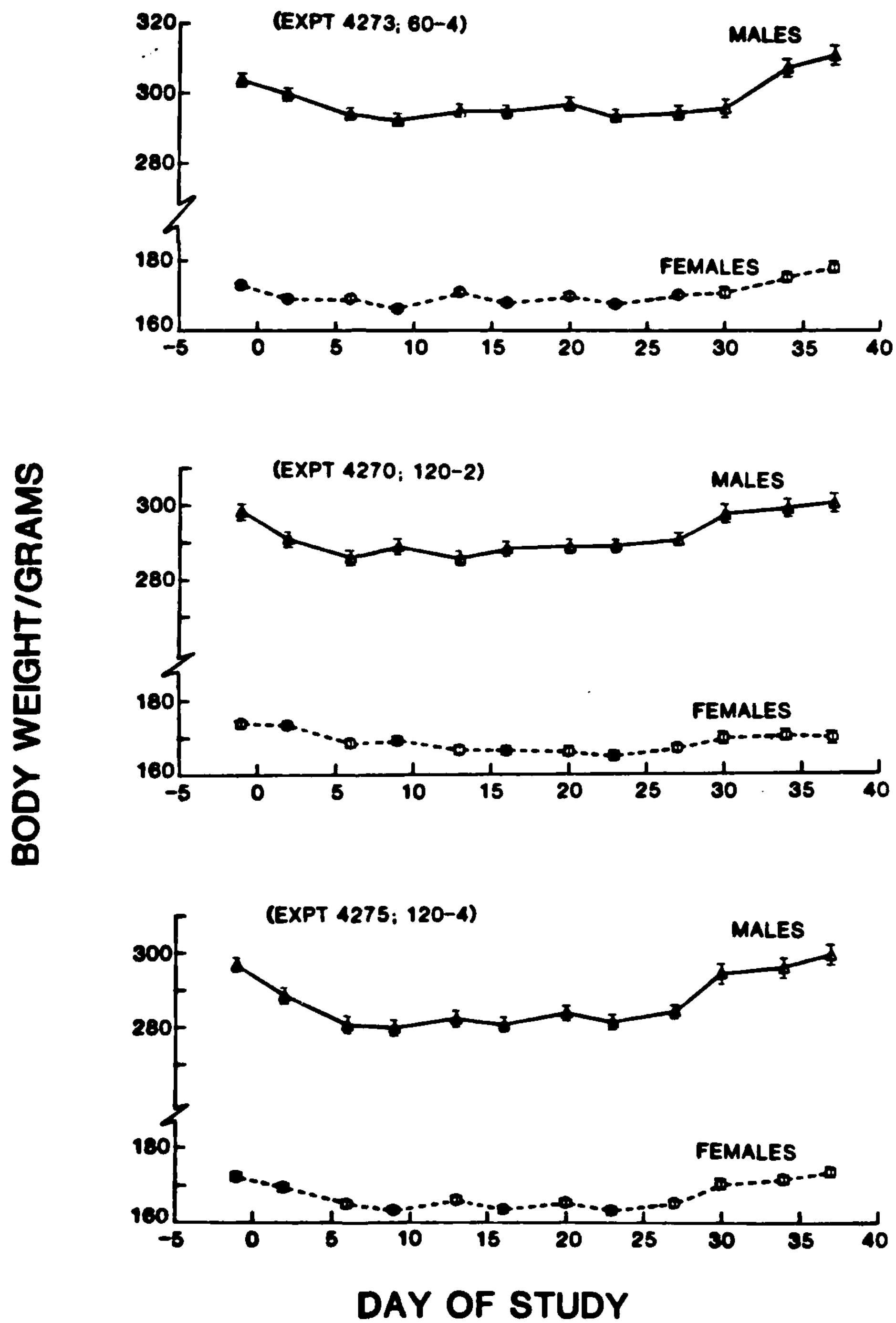


Figure 8c. Body Weight Summary for Rats (Mean ± SE)

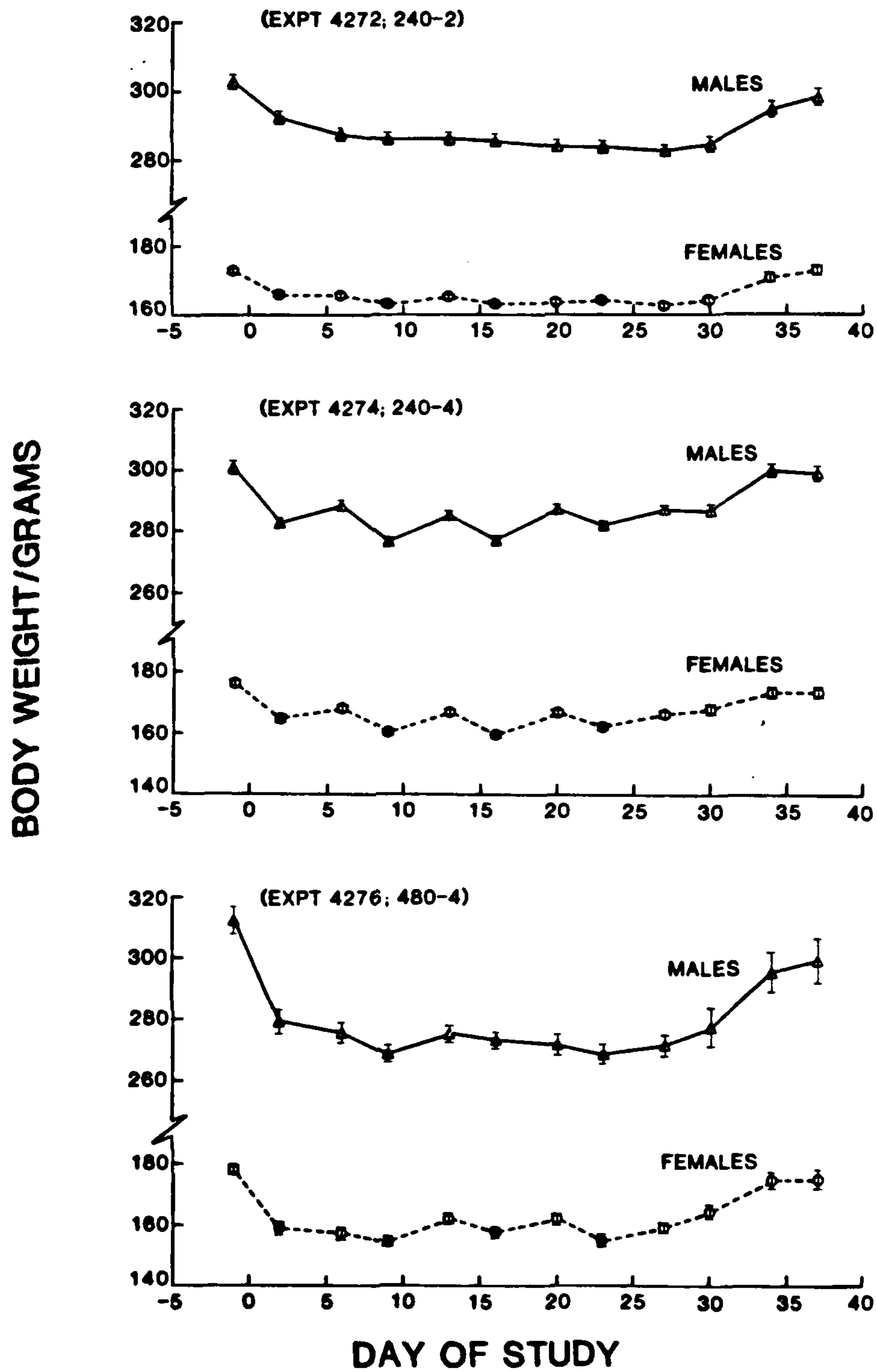


Table 11

Body Weight as Percentage of Body Weight One Day Before the First Inhalation Exposure of F344/N Rats to Cu-Zn Alloy; Males and Females Combined

	Exposures Four Days Per Week					Exposures Two Days Per Week			
Day	Sham	60-4	120-4	240-4	480-4	30-2	60-2	120-2	240-2
-1	100 (70)[a]	100 (70)	100 (70)	100 (70)	100 (20)	100 (20)	100 (70)	100 (70)	100 (70)
2	95.8 ± 0.2 (68)	98.4 ± 0.2[b] (70)	97.7 ± 0.3[b] (70)	93.8 ± 0.2[d,e] (70)	89.3 ± 0.3[e] (20)	97.6 ± 0.4[c] (20)	97.3 ± 0.2[b] (70)	98.5 ± 0.2[b] (70)	96.4 ± 0.2 (70)
6	96.4 ± 0.3 (68)	97.3 ± 0.2 (70)	95.2 ± 0.3 (70)	95.7 ± 0.2 (70)	88.3 ± 0.6[e] (20)	98.4 ± 0.4 (20)	97.9 ± 0.3 (70)	96.5 ± 0.2 (70)	95.4 ± 0.2 (70)
9	93.9 ± 0.3 (68)	96.3 ± 0.2[b] (70)	94.5 ± 0.3[d] (70)	91.5 ± 0.3[d,e] (70)	86.5 ± 0.5[e] (20)	96.8 ± 0.4[b] (20)	95.9 ± 0.2[b] (70)	97.1 ± 0.2[b] (70)	94.5 ± 0.3 (70)
13	96.6 ± 0.3 (68)	98.0 ± 0.3[c] (70)	95.7 ± 0.3 (70)	94.7 ± 0.3[e] (70)	89.6 ± 0.6[e] (20)	99.1 ± 0.5[c] (20)	97.7 ± 0.3 (70)	95.9 ± 0.2 (70)	95.0 + 0.3[e] (70)
16	94.8 ± 0.3 (68)	97.3 ± 0.3[b] (70)	94.7 ± 0.3[d] (70)	91.4 ± 0.3[d,e] (70)	88.0 ± 0.6[e] (20)	98.7 ± 0.5[b] (20)	96.9 ± 0.3[b] (70)	96.4 ± 0.2[b] (70)	94.4 ± 0.3 (70)
20	95.9 ± 0.3 (68)	98.2 ± 0.3[b] (70)	95.8 ± 0.3 (70)	95.1 ± 0.3 (70)	89.0 ± 0.8[e] (19)	97.6 ± 0.5 (20)	98.2 ± 0.3[b] (70)	96.4 ± 0.3 (70)	94.3 ± 0.3[e] (70)
23	93.7 ± 0.3 (68)	97.0 ± 0.2[b] (70)	94.9 ± 0.3 (69)	92.9 ± 0.3 (70)	86.6 ± 0.7[e] (19)	97.0 ± 0.4[b] (20)	98.3 ± 0.4[b] (69)	96.2 ± 0.3[b] (70)	94.4 ± 0.3 (69)
27	95.5 ± 0.3 (68)	97.8 ± 0.3[b] (70)	95.8 ± 0.3 (69)	94.9 ± 0.3 (70)	88.2 ± 0.7[e] (19)	97.4 ± 0.4 (20)	96.7 ± 0.4 (69)	97.0 ± 0.3[c] (70)	93.7 ± 0.3[e] (69)
30	95.9 ± 0.4 (39)	98.3 ± 0.4[c] (40)	98.6 ± 0.6[c] (40)	95.2 ± 0.4 (40)	90.9 ± 0.7[f] (9)	97.4 ± 0.7 (10)	98.6 ± 0.5[b] (40)	99.2 ± 0.4[b] (40)	94.6 ± 0.3 (40)
34	100.4 ± 0.5 (39)	101.6 ± 0.4 (40)	99.2 ± 0.5 (39)	99.1 ± 0.4 (40)	96.6 ± 0.7[f] (9)	101.2 ± 1.0 (10)	102.7 ± 0.5 (40)	99.7 ± 0.3 (40)	98.2 ± 0.4 (40)
37	100.0 ± 0.5 (39)	103.1 ± 0.4[c] (39)	100.4 ± 0.6 (39)	98.9 ± 0.4 (40)	97.4 ± 0.8 (9)	101.4 ± 0.8 (10)	102.1 ± 0.5 (39)	99.8 ± 0.4 (40)	99.3 ± 0.3 (40)

[a]Number of animals in parenthesis. In a few cases, body weights were missing or not usable for statistical comparisons, the treated group was compared with the sham-exposed group using the Student t-test for unequal variance when Levene's test indicated the variance were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

[b]Body weight greater than for sham-exposed rats ($p < 0.01$).

[c]Body weight greater than for sham-exposed rats ($p < 0.05$).

[d]Body weight decreased for 4 days exposure per week relative to 2 days per week for the same cumulative weekly exposure ($p < 0.01$).

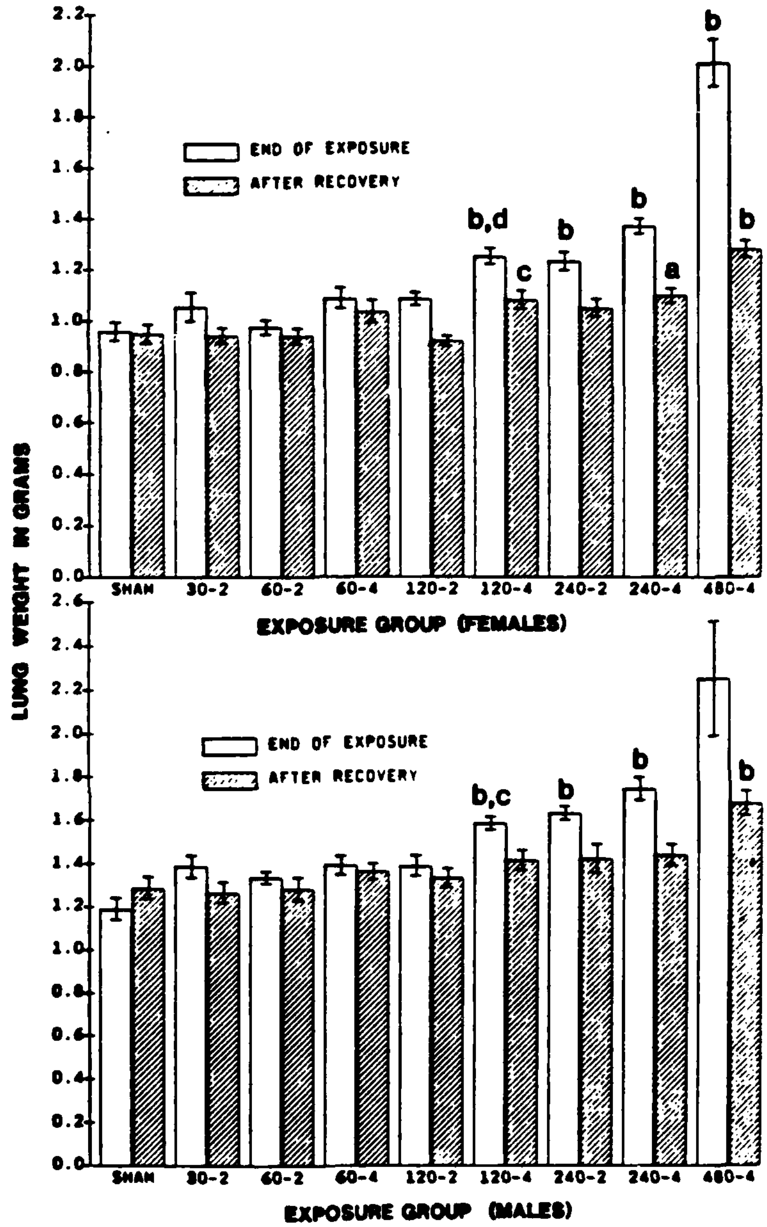
[e]Body weight less than for sham-exposed rats ($p < 0.01$).

[f]Body weight less than for sham-exposed rats ($p < 0.05$).

the inhaled Cu-Zn. Significant decreases in body weight that reflected morbidity due to inhalation of the Cu-Zn occurred only with exposure levels of 240-2, 240-4, and 480-4. In comparisons of 2 days exposure per week versus 4 days exposure per week, a greater body weight loss occurred for days 9 and 16 for the 120-4 group and for days 2, 9, and 16 for the 240-4 group. Stress during 2 versus 4 days exposure only accounts for part of the differences in body weight between 2 and 4 days exposure per week to 120 and 240 mg·hr Cu-Zn/m^3. A significant part of the more pronounced decrease in body weight with exposures 4 days per week was due to receiving the total exposures to Cu-Zn in four increments rather than two.

Lung, liver, spleen, kidney, and thymus weights were evaluated at the end of the exposures and after the recovery period. The only organ that changed significantly as a result of the exposures to Cu-Zn was the lung. Figure 9 presents the results for lung; the results for these tissues for individual rats are summarized in Appendix D. A trend analysis (Appendix E) was used to determine if differences existed in lung responses of males and females and to determine if exposure-related responses were different if exposures were two days per week versus four days per week. Lung weights for both male and female rats showed significant exposure-related increases, despite the fact that not a single difference with the weights of sham-exposed animals was significant at the end of exposure for males and females. The only statistically significant difference was seen in the 120-2 group for females, after recovery, where the lung weights were smaller than for controls ($P < 0.05$). For both males and females, the slope of a linear function fitted to the data was the same within the error (Appendix E). After the recovery

Figure 9. Lung Weight Comparisons for Rats (Mean ± SE)



a = Different from shams, $p < 0.05$.
b = Different from shams, $p < 0.01$.
c = Different from same exposure delivered 2 days/week, $p < 0.05$.
d = Different from same exposure delivered 2 days/week, $p < 0.01$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

period, the lung weights still showed a reduced effect with a slope a little more than one third of the initial value.

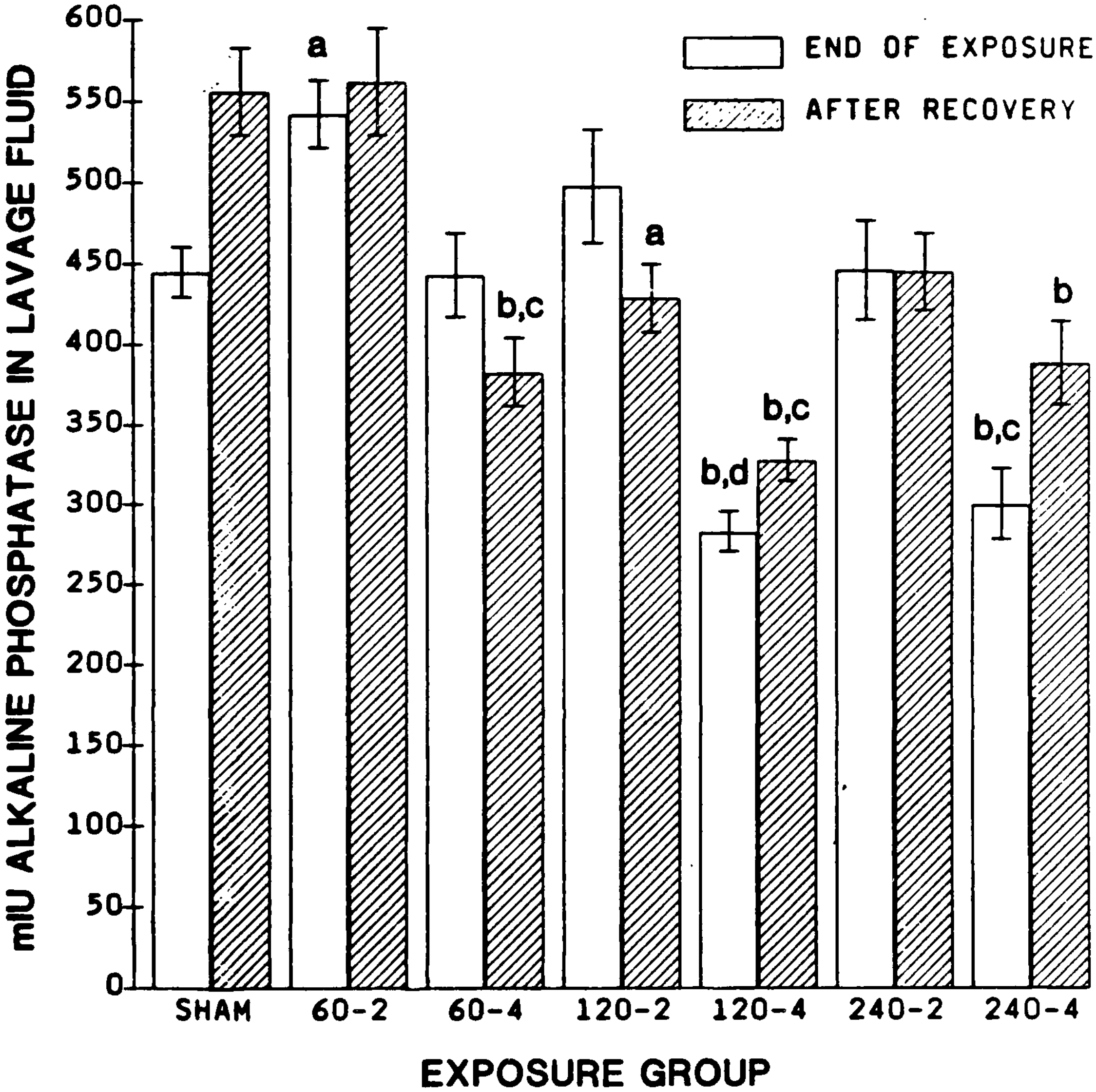
Lavage Fluid Biochemistry and Cytology

Results for alkaline phosphatase, beta-glucuronidase, lactate dehydrogenase (LDH), pulmonary alveolar macrophages, polymorphonuclear leukocytes, protein, and collagen in lung lavage fluid are summarized in Figures 10 thru 16. There was an exposure-related inflammatory response evident at the end of exposure. This was shown by exposure-dependent increases in lavage fluid beta-glucuronidase (Figure 11), LDH in lavage fluid (Figure 12), inflammatory cells in lavage fluid (Figures 13 and 14), and protein in lavage fluid (Figure 15). In all cases where significant differences occurred, values had returned to normal by the end of the recovery period.

There was no increase in alkaline phosphatase (Figure 10), suggesting that Type II cell hypersecretion did not occur. Despite significant differences in several comparisons, no exposure-related trend was evident or established by fitting a straight line to the data for all animals (Appendix E). This resulted from the fact that animals exposed only twice per week showed no significant effects, whereas animals exposed four times per week did show an apparent trend toward lower values for increasing exposures. The fits to these reduced data sets (not shown) were uncertain and slopes were not different from zero in either case.

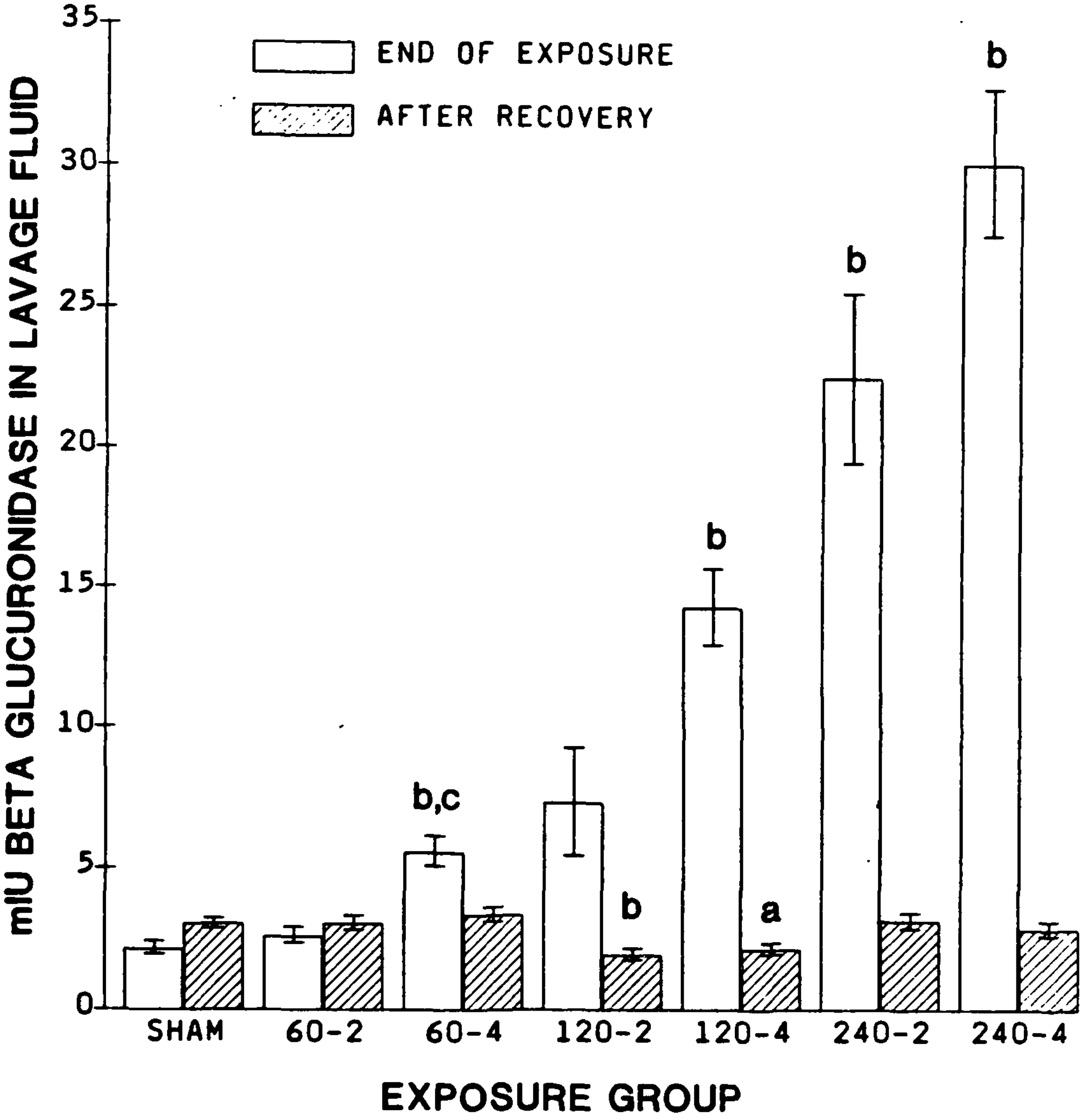
A clear exposure-effect relationship is evident for beta-glucuronidase in Figure 11, with a total recovery after two weeks. Results for a trend analysis for these data are shown in Appendix E. The slope measured in units of mIU/(mg·hr Cu-Zn/m^3) was 0.110 ± 0.018 (mean ± SD) for

Figure 10. Alkaline Phosphatase Content of Lung Lavage Fluid
(Mean ± SE)



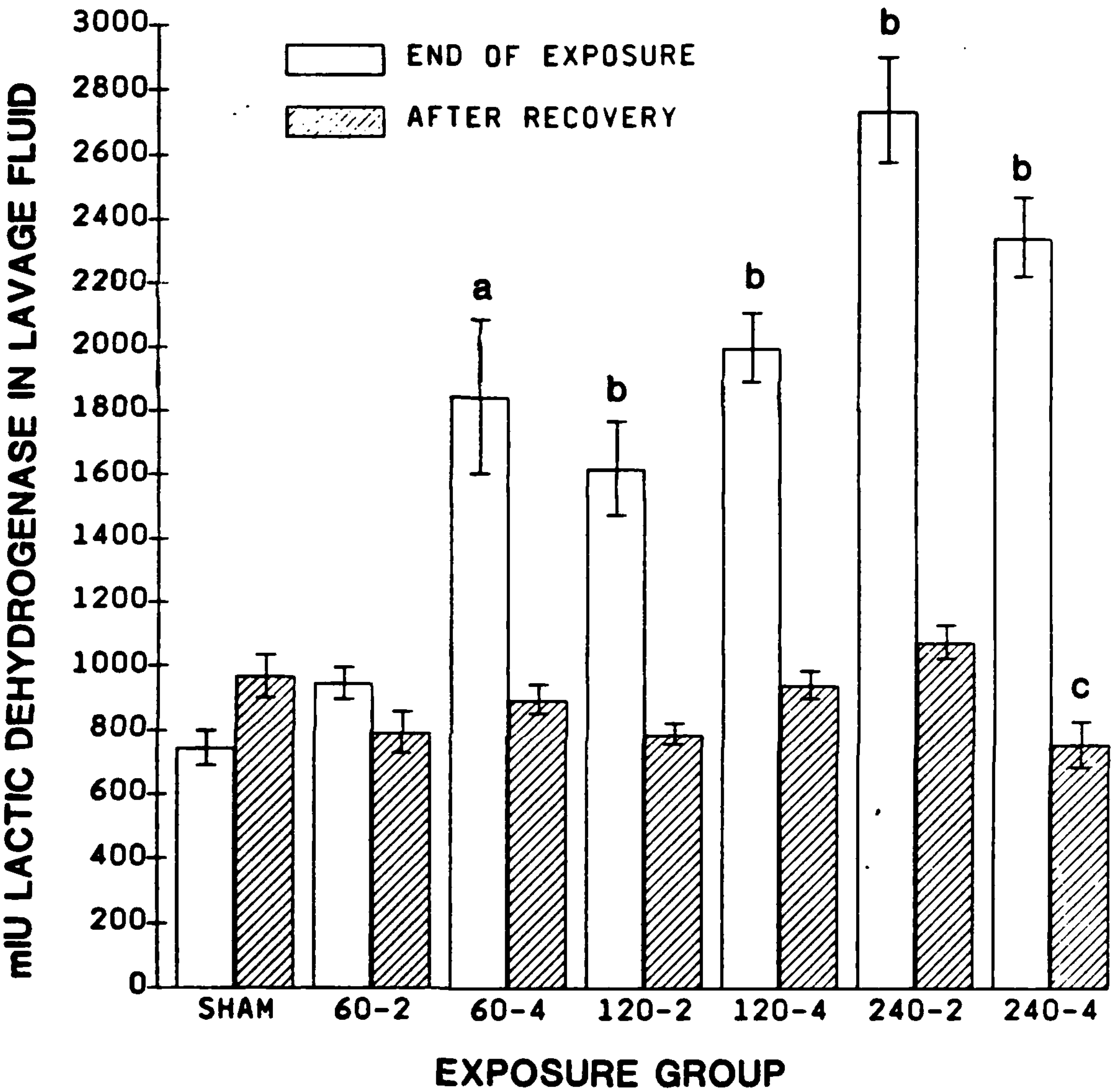
a = Different from shams, $p < 0.05$.
b = Different from shams, $p < 0.01$.
c = Different from same exposure delivered 2 days/week, $p < 0.05$.
d = Different from same exposure delivered 2 days/week, $p < 0.01$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 11. Beta Glucuronidase Content of Lung Lavage Fluid
(Mean ± SE)



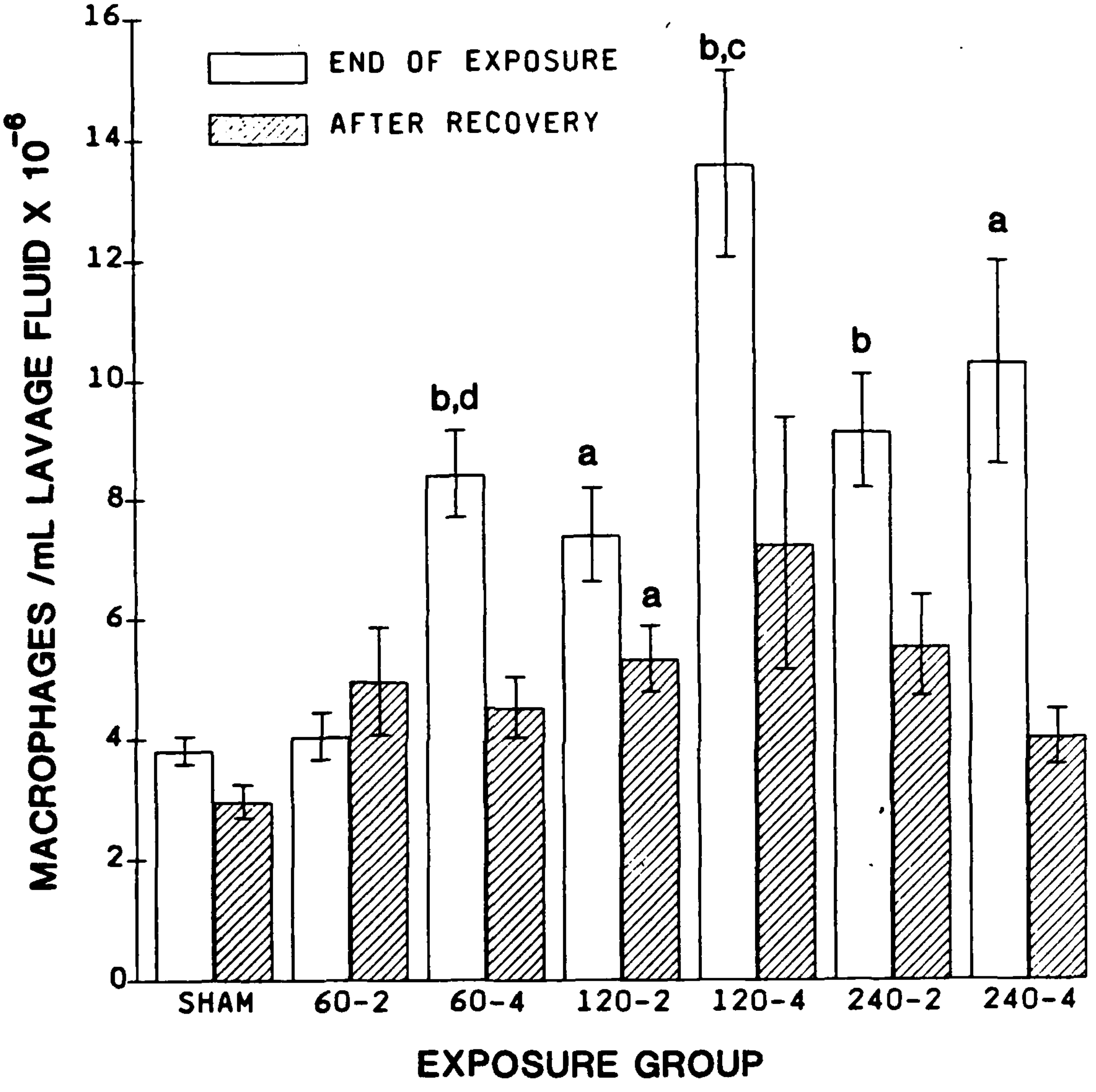
a = Different from shams, $p < 0.05$.
b = Different from shams, $p < 0.01$.
c = Different from same exposure delivered 2 days/week, $p < 0.01$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 12. Lactate Dehydrogenase Content of Lung Lavage Fluid (Mean ± SE)



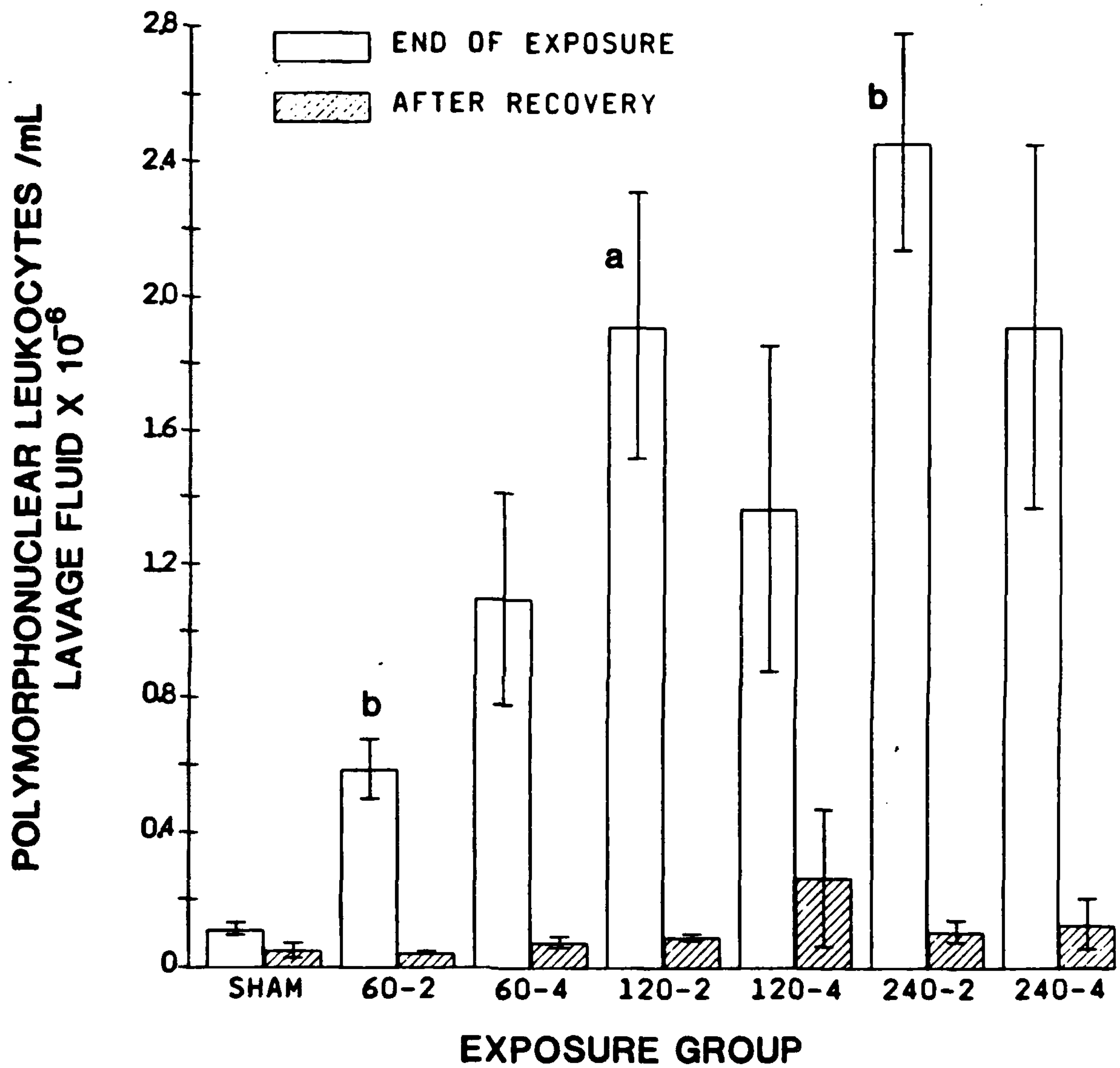
a = Different from shams, $p < 0.05$.
b = Different from shams, $p < 0.01$.
c = Different from same exposure delivered 2 days/week, $p < 0.05$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 13. Pulmonary Alveolar Macrophage Numbers in Lung Lavage Fluid (Mean ± SE)



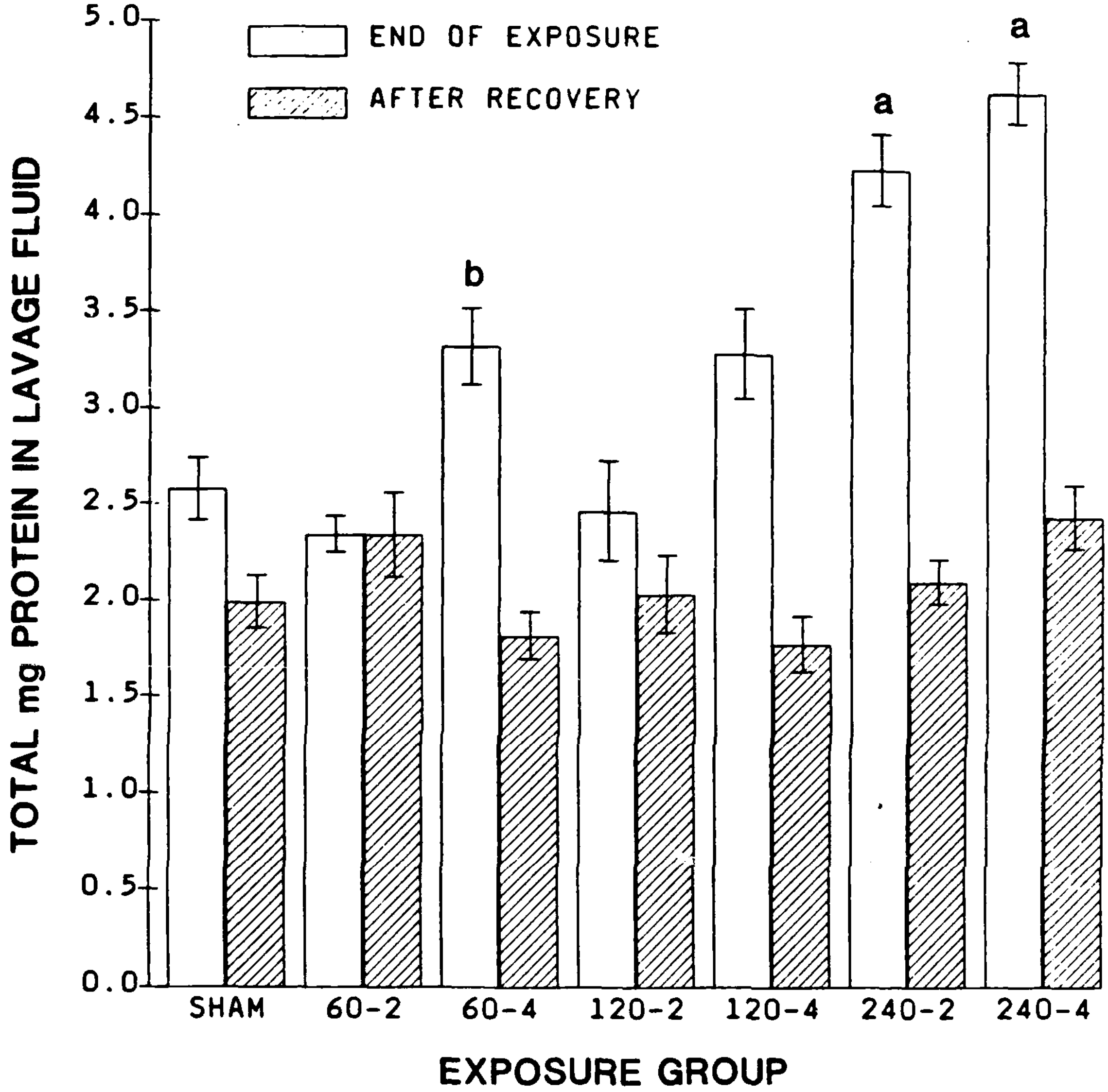
a = Different from shams, $p < 0.05$.
b = Different from shams, $p < 0.01$.
c = Different from same exposure delivered 2 days/week, $p < 0.05$.
d = Different from same exposure delivered 2 days/week, $p < 0.01$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 14. Polymorphonuclear Leukocyte Numbers in Lung Lavage Fluid (Mean ± SE)



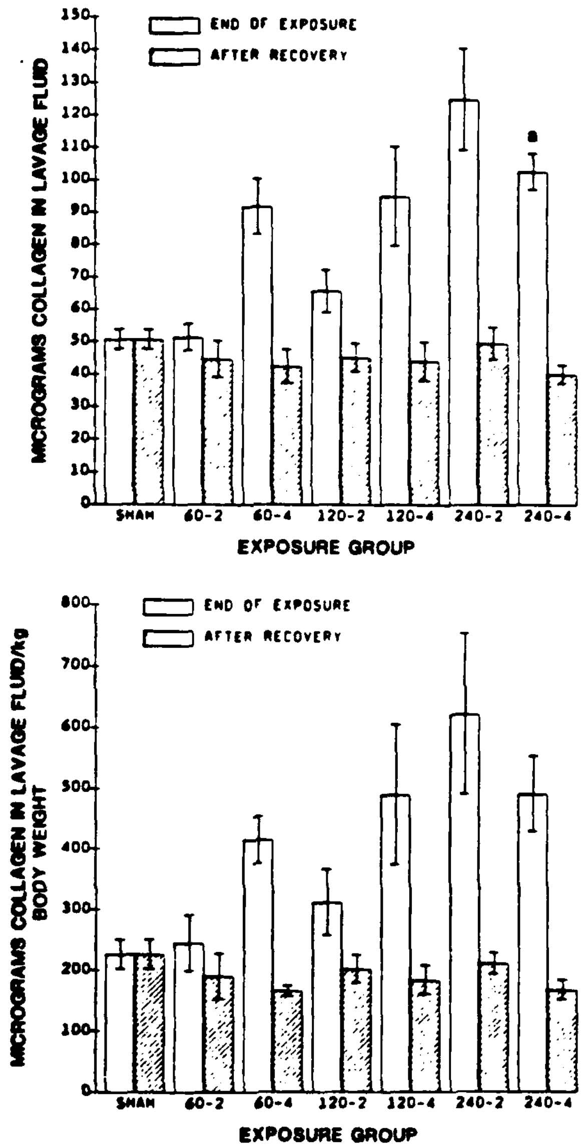
a = Different from shams, $p < 0.05$.
b = Different from shams, $p < 0.01$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 15. Protein Content of Lung Lavage Fluid
(Mean ± SE)



a = Different from shams, $p < 0.01$.
b = Different from same exposure delivered 2 days/week, $p < 0.05$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 16. Collagen Content of Lung Lavage Fluid
(Mean ± SE)



a = Different from shams, $p < 0.01$. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

all animals together; it was 0.089 ± 0.019 for animals exposed twice, and 0.121 ± 0.012 for animals exposed four times. Again, the difference between the effects of the two exposure frequencies was not significant, but the effect for two exposures weekly was less than that of four exposures per week. For LDH (Figure 12 and Appendix E, Figure E-5), a strong exposure-effect relationship was evident, but the effects disappeared by the end of the recovery period.

Significant changes were observed in numbers of pulmonary alveolar macrophages at the end of exposure (Figure 13), but only one exposure group (120-2) was different from sham-exposed rats after the recovery period. The trend analysis (Appendix E) indicated there was no exposure-response for this endpoint.

A significant trend was clearly evident for polymorphonuclear leukocytes (Figure 14), although some rather large errors made the apparent differences not significant. A trend analysis (Appendix E) indicated an exposure-response relationship at the end of the four-week exposure. After the recovery period, no effects were discernible.

Protein content of lavage fluid also showed an exposure-effect relationship (Appendix E) at the end of the exposures, but complete recovery after the two-week recovery period (Figure 15).

The effects of the same cumulative exposure were greater for many lavage fluid constituents if the exposure was delivered 4 days per week instead of 2 days per week (Appendix E). This can be stated for beta-glucuronidase, for LDH, for polymorphonuclear leukocytes, for protein, and for collagen. This cannot be stated for alkaline phosphatase or numbers of pulmonary alveolar macrophage. In 17 of 21 comparisons of responses for exposures 4 days versus 2 days per week (Appendix E, Figures E-1 thru E-13), the responses were more intense when exposures were 4 days per week.

Lavage fluid collagen (LFC) was significantly elevated only in rats exposed to the 240 level in 4 days (Figure 16). Other LFC values appeared elevated but were not significantly different from the sham-exposed rats. These changes indicate that level of exposure produced sufficient lung injury to increase the turnover of the extracellular collagenous matrix. Both the content and the specific content per unit body weight showed exposure-effect relationships at the end of exposure (Appendix E, Figure E-9) that resolved during the recovery period.

Lungs of rats exposed to 240 mg·hr Cu-Zn/m^3 for 2 days per week were analyzed for total lung collagen. Total lung collagen was not altered in that group (Figure 17), as compared with the control group.

Hematology

No significant changes were observed in the hematology results as a consequence of exposures to the Cu-Zn at the end of exposure or after the recovery period. Detailed results for the hematology measurements are included in Appendix D.

Immunology

In comparison to sham-exposed controls, total cells present in the lung-associated lymph nodes (Figure 18) were significantly elevated in the 120-4, 240-2, and 240-4 exposure groups when they were examined at the end of the 4-week exposure period. However, this change was not permanent, and after the 2-week recovery period the number of cells present in the lung-associated lymph nodes from all exposure groups was not different from the sham-exposed rats. As indicated in the trend analysis (Appendix E), an exposure-response

Figure 17. Total Lung Collagen in Rats (Mean ± SE)

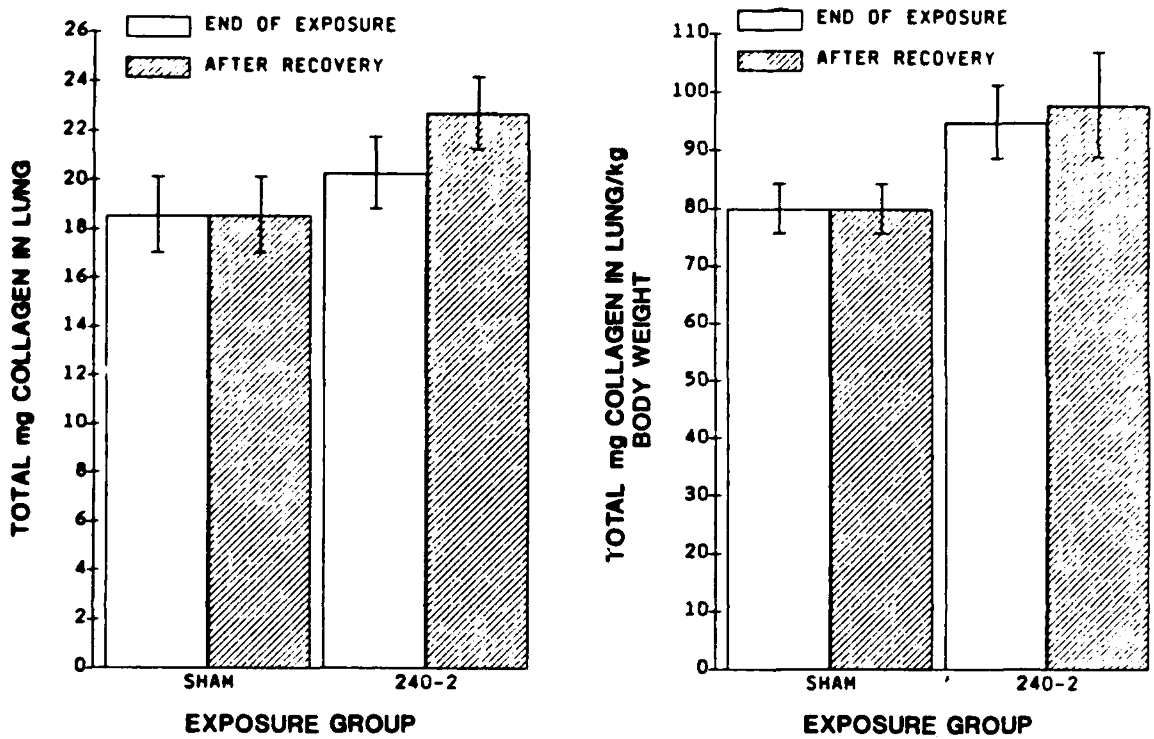
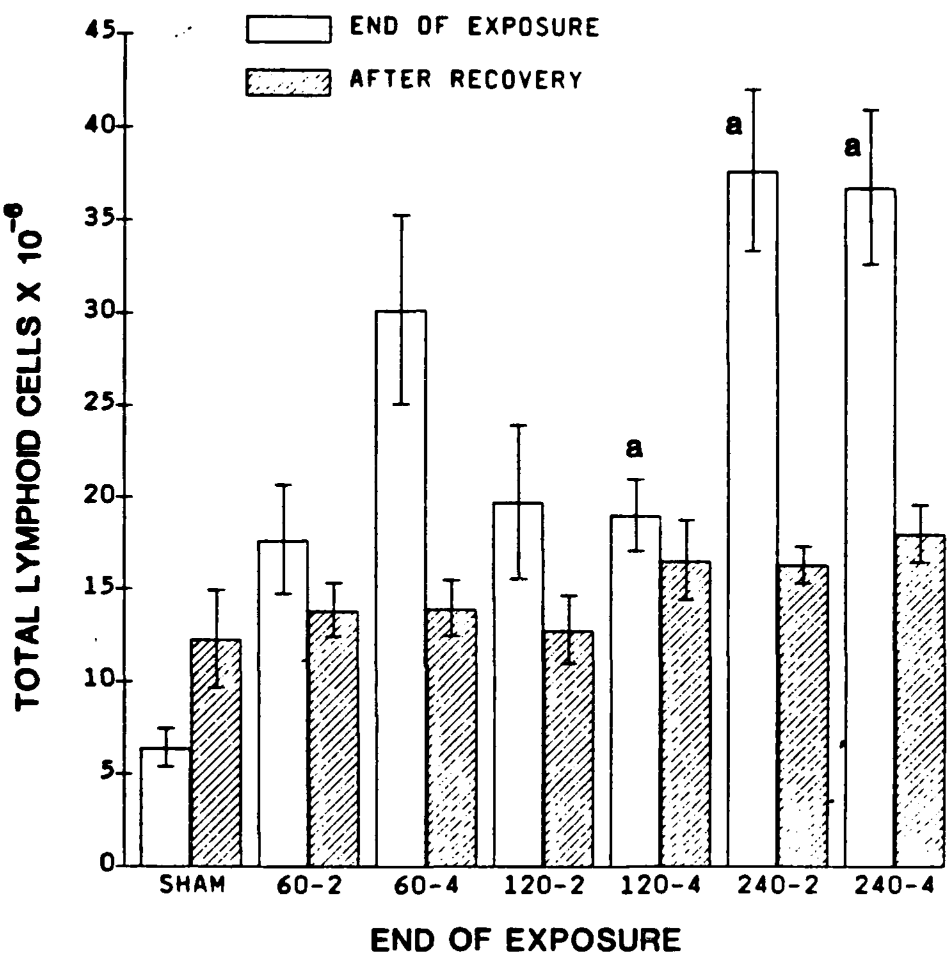


Figure 18. Total Numbers of Cells in Lung-associated Lymph Nodes (Mean ± SE)



a = Different from shams, $p < 0.01$. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

relationship was observed, but there was no clear indication that exposures 2 or 4 days per week produced different responses.

Figures 19 and 20 present results for numbers of antibody-forming cells in lung-associated lymph nodes expressed as total numbers of cells, and as numbers of antibody-forming cells per million lymphocytes. A trend analysis (Appendix E) indicated an exposure-response relationship for the total antibody-forming cells at the end of exposure. The numbers of IgM antibody-forming cells/million lymphoid cells in the lung-associated lymph nodes were not significantly different from responses in sham-exposed controls. Only the 120-4, 240-2, and 240-4 exposure groups had apparent reduced numbers of antibody-forming cells after the two week recovery period. These differences were also not significant and there were no exposure-response trends in data at the end of the recovery period.

Phagocytosis

Significant depression of phagocytosis of opsonized sheep red blood cells (EA) by pulmonary alveolar macrophages (PAM) occurred at the end of exposure only at the 240-4 exposure level (Figure 21). Although only one exposure group had a difference that was of statistical significance, a trend toward lower values with increasing exposures seemed possible. Results of trend analyses to evaluate these results are presented in Appendix E. A fit with a linear function showed negative slopes [EA/100 cells per (mg·hr Cu-Zn/m^3)] of (-1.1 ± 0.5) and (-0.7 ± 0.3) with significance levels of 0.08 and 0.06 for the null hypothesis, respectively. Together, since both slopes were negative at the 0.1 level of significance, these data constitute evidence for the presence of a small negative correlation of the effects with exposure.

Figure 19. Numbers of Antibody-forming Cells (AFC) in Lung-associated Lymph Nodes (Mean ± SE)

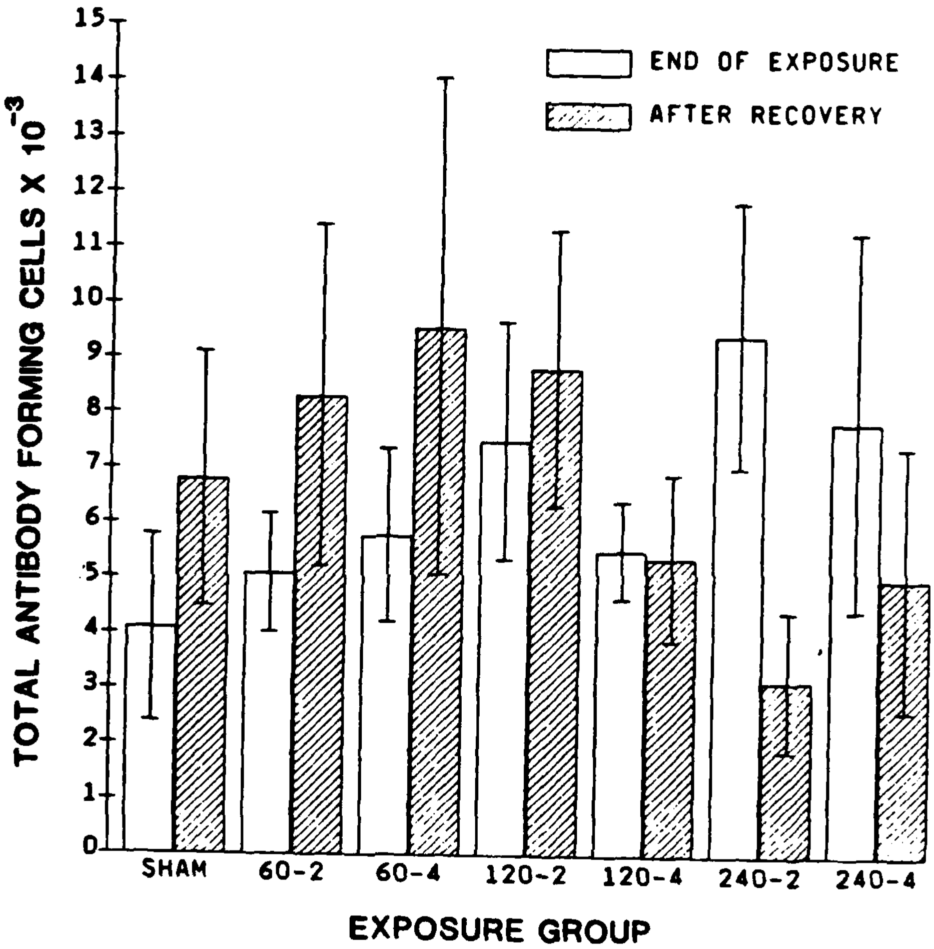


Figure 20. Numbers of Antibody-forming Cells (AFC) Per Million Lymphocytes in Lung-associated Lymph Nodes (Mean ± SE)

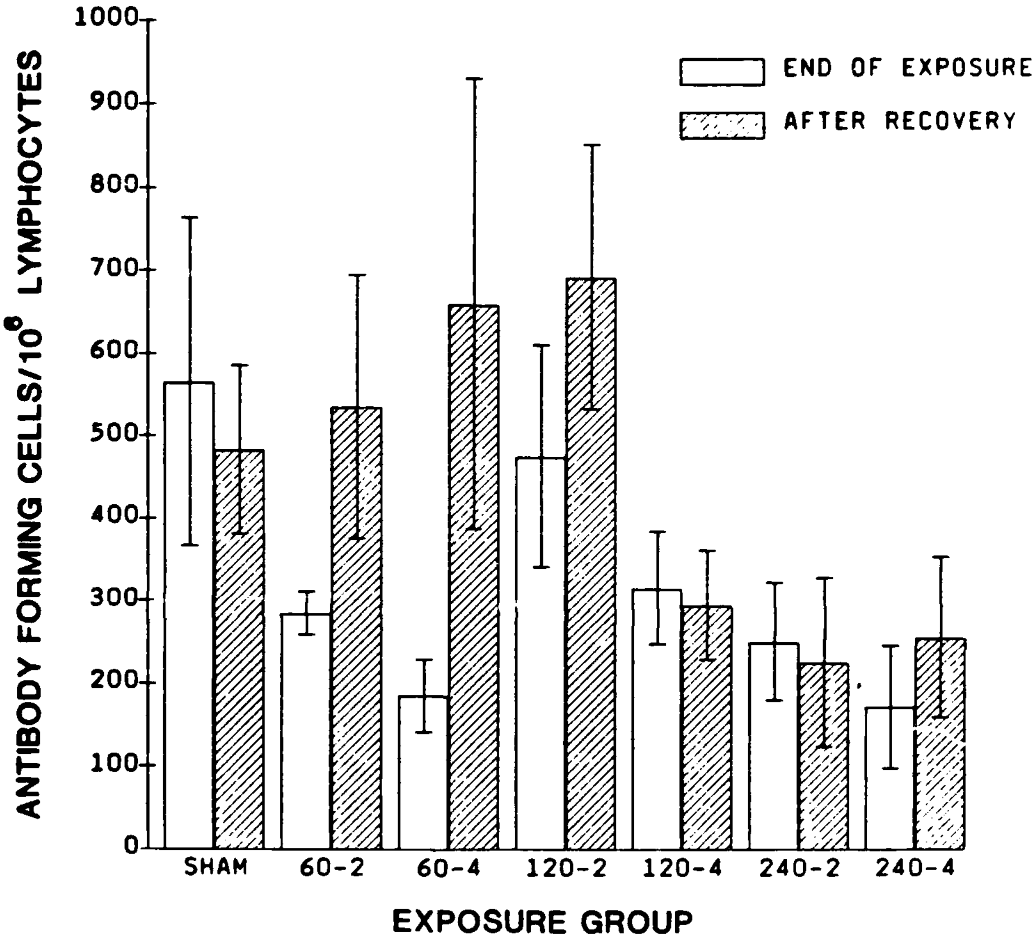
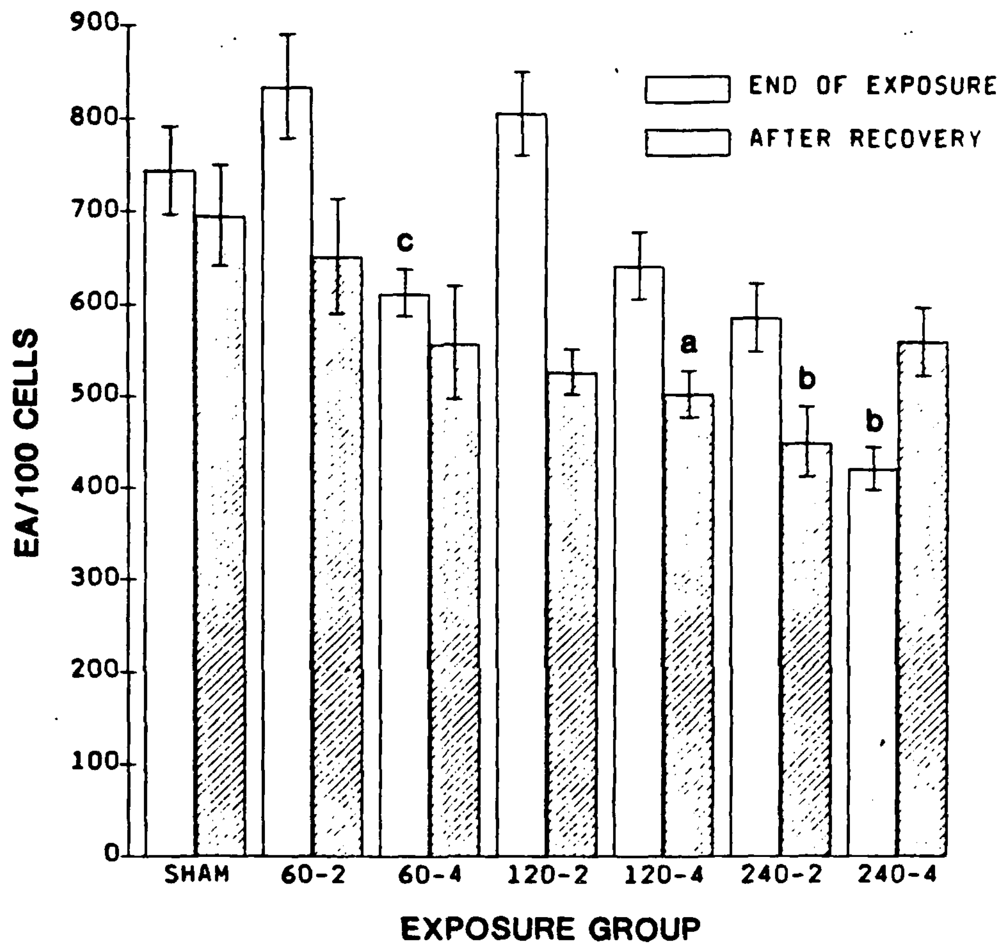


Figure 21. Number of Opsonized Sheep Red Blood Cells (EA) Phagocytized Per 100 Pulmonary Alveolar Macrophages (Mean ± SE)



a = Different from shams, $p < 0.05$.
b = Different from shams, $p < 0.01$.
c = Different from same exposure delivered 2 days/week, $p < 0.01$.
NOTE: Groups were compared using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Pulmonary Function

The 240-2 and 240-4 groups were the only exposure groups having values significantly different from those of the controls at either measurement time (Table 12; Figures 22-25). At the end of exposure, these groups had smaller, stiffer lungs and less efficient alveolar-capillary gas exchange than the controls. These three principal changes are illustrated by graphs of total lung capacity (lung volume), quasistatic chord compliance (lung stiffness) and carbon monoxide diffusing capacity (gas exchange) in Figures 22-25. Both total lung capacity and vital capacity were reduced by exposure to Cu-Zn, but the vital capacity/total lung capacity ratio was not. The functional residual capacity was increased slightly in the 240-2 group and significantly in the 240-4 group. The functional residual capacity/total lung capacity ratio was increased significantly in both groups. An increased elastic recoil (stiffening) of the lung was demonstrated by a reduced quasistatic lung compliance. The effect was not sufficiently severe to reduce lung compliance during tidal breathing. The impaired alveolar-capillary gas exchange was demonstrated by a reduced CO diffusing capacity. Diffusing capacity remained significantly reduced when normalized for the reduced lung volume.

Similar trends were observed in all the other exposed groups, but to a lesser extent and observables were not statistically different from sham-exposed controls. The mean CO diffusing capacity of the 120-4 group was identical to that of the 240-2 group, but the slightly higher variance made the difference significant at only $p < 0.10$.

Significant differences from control values were observed in the forced expiratory data of the 240-4 group; however, these differences did not

Table 12

Selected Pulmonary Function Results
(Mean ± SE)

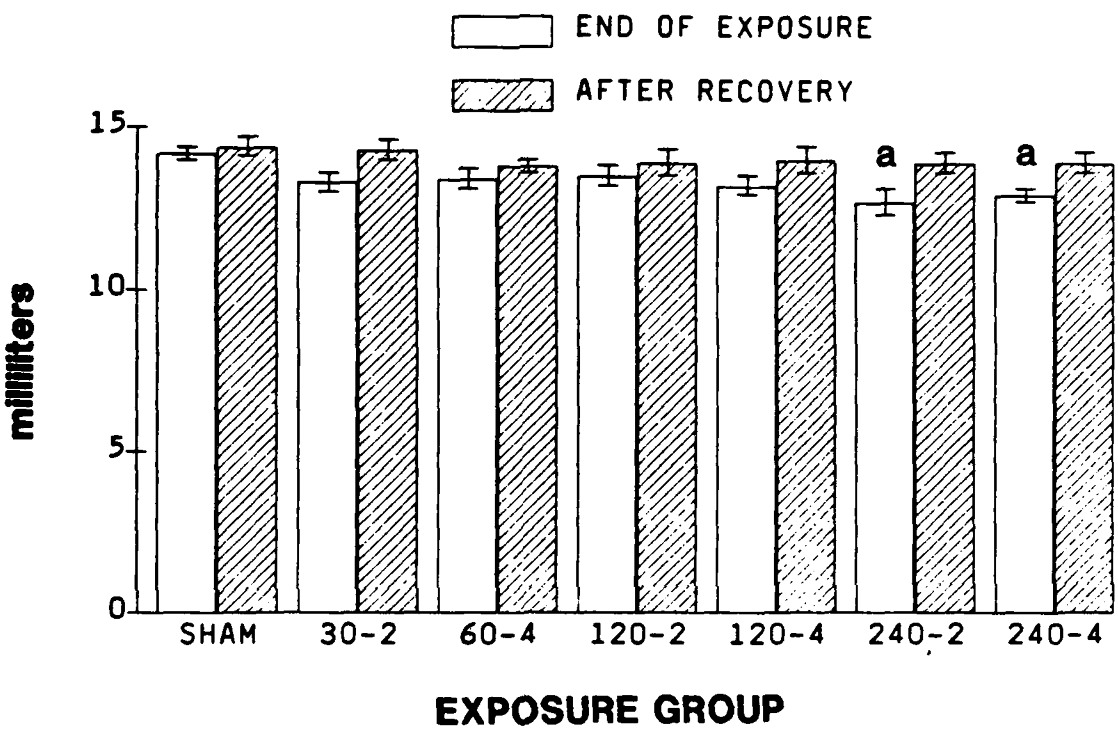
Exposure	Total Lung Capacity (mL)		Quasistatic Lung Compliance (mL/cm H_2O)		CO Diffusing Capacity (mL/min/mm Hg)		Percent Forced Vital Capacity Exhaled in 0.1 Second (%)	
Group	EOE[a]	REC[b]	EOE	REC	EOE	REC	EOE	REC
Sham	14.2 ± 0.2	14.4 ± 0.3	0.84 ± 0.02	0.93 ± 0.02	0.290 ± 0.009	0.294 ± 0.008	58 ± 3	60 ± 2
60-2	13.3 ± 0.3	14.3 ± 0.3	0.77 ± 0.03	0.88 ± 0.03	0.274 ± 0.005	0.276 ± 0.009	56 ± 3	63 ± 2
60-4	13.4 ± 0.3	13.8 ± 0.2	0.74 ± 0.03	0.83 ± 0.02	0.286 ± 0.005	0.277 ± 0.008	64 ± 3	64 ± 1
120-2	13.5 ± 0.3	13.9 ± 0.4	0.78 ± 0.03	0.88 ± 0.03	0.280 ± 0.010	0.296 ± 0.008	63 ± 3	62 ± 3
120-4	13.2 ± 0.3	14.0 ± 0.4	0.75 ± 0.03	0.88 ± 0.03	0.256 ± 0.009	0.295 ± 0.010	60 ± 3	59 ± 4
240-2	12.7 ± 0.4[c]	13.9 ± 0.3	0.70 ± 0.03[c]	0.84 ± 0.02	0.256 ± 0.007[c]	0.273 ± 0.005	64 ± 3	63 ± 1
240-4	12.9 ± 0.2[c]	13.9 ± 0.3	0.68 ± 0.02[c]	0.79 ± 0.02[c]	0.252 ± 0.005[c]	0.270 ± 0.012	68 ± 2[c]	62 ± 3

[a]EOE indicates the sampling period was at the end of the exposure period.

[b]REC indicates the sampling period was after a two week recovery following the exposure period.

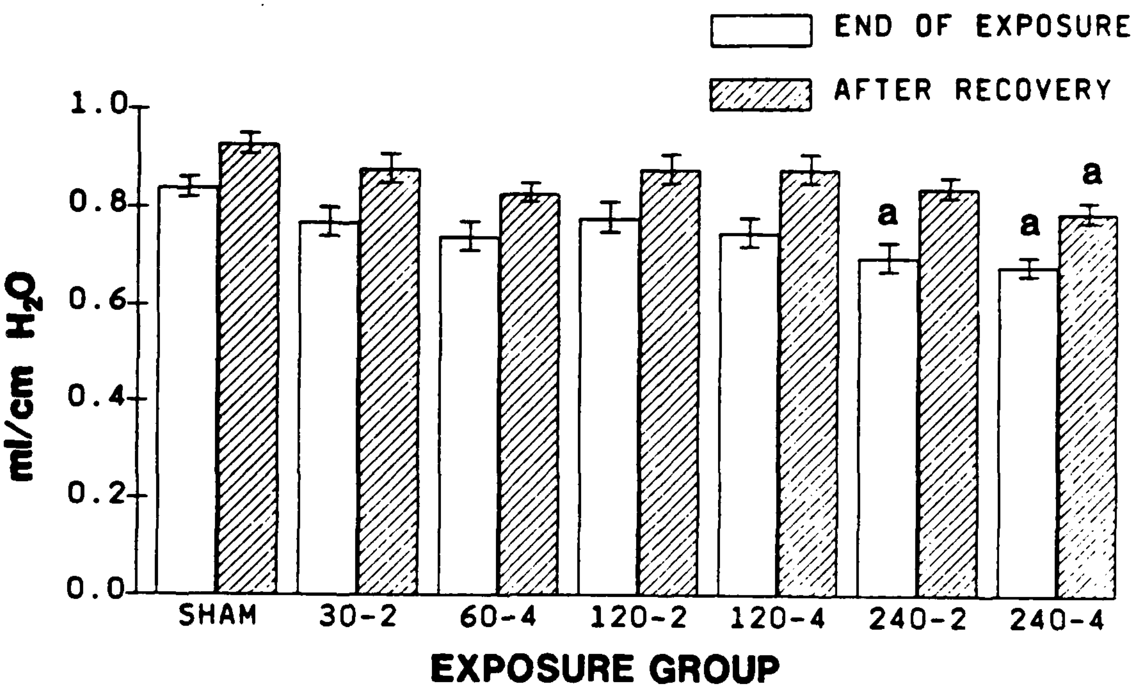
[c]Different from sham, $p < 0.05$. The pulmonary function data were analyzed as described in Section V.J. The values of the exposed groups were compared to those of the controls by multiple t tests using pooled variance. The probability values were adjusted for six comparisons using Bonferroni's inequality.

Figure 22. Total Lung Capacity
(Mean ± SE)



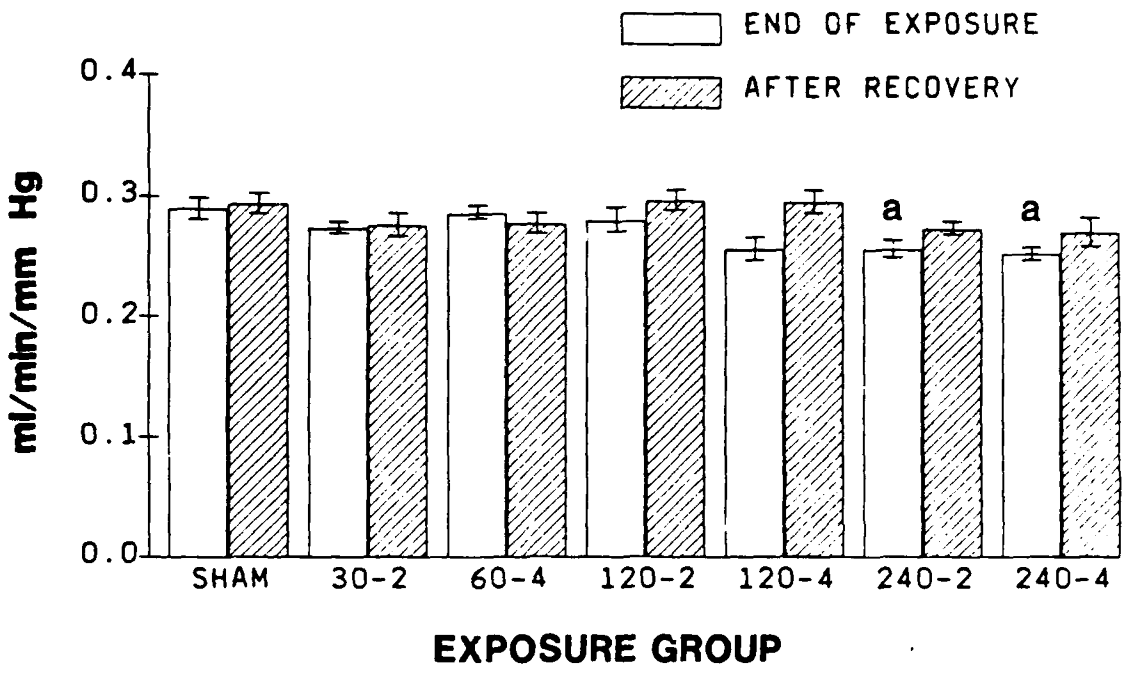
a = Different from sham-exposed rats, $p < 0.01$. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 23. Quasistatic Chord Compliance
(Mean ± SE)



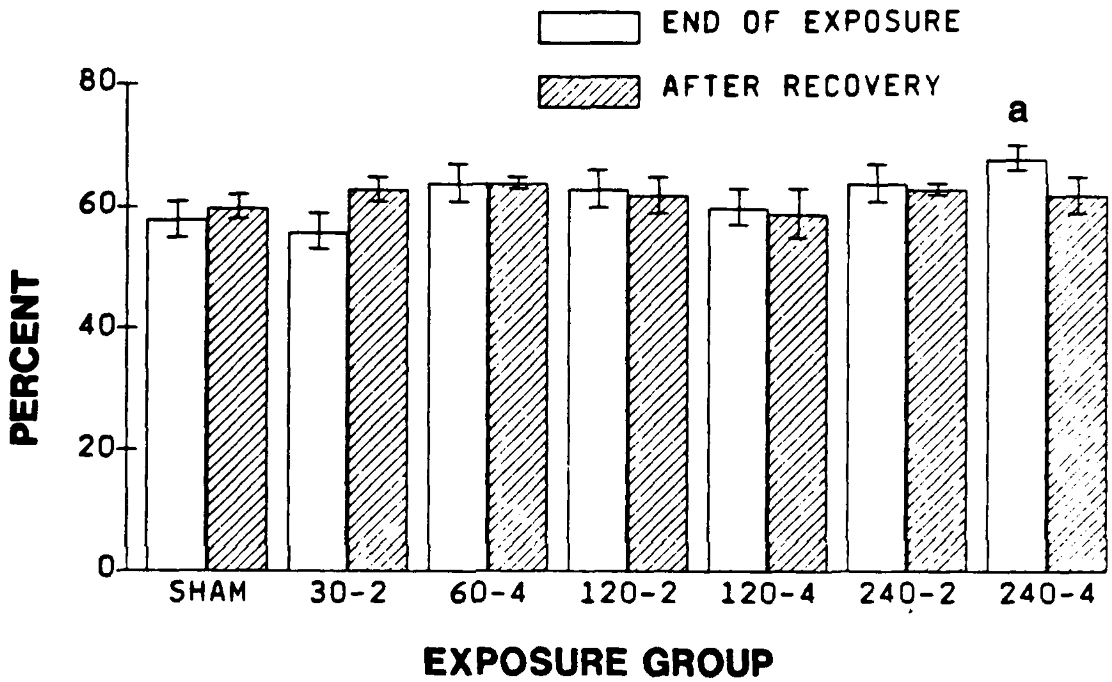
a = Different from sham-exposed rats, $p < 0.01$. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 24. Carbon Monoxide Diffusing Capacity
(Mean ± SE)



a = Different from sham-exposed rats, $p < 0.01$. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Figure 25. Percent Forced Vital Capacity Exhaled in 0.1 Seconds (Mean ± SE)



a = Different from sham-exposed rats, $p < 0.01$. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

indicate restriction of airflow. Forced vital capacity was reduced, but expiratory flow rates were not reduced by exposure. The values for expiratory events normalized by volume, therefore, were higher for the 240-4 group. These included the percent of forced vital capacity exhaled in 0.1 sec (Figure 25) and the peak flow and flow at 50 percent vital capacity normalized by volume. These significant differences did not indicate a deleterious change, other than the reduction of lung volume.

At 2 weeks after exposure, residual trends toward the changes described above were observed, but only the quasistatic lung compliance of the 240-4 group remained as a significant difference from control values (Figure 23).

Histopathology

No significant toxicant-related lesions were microscopically evident in the trachea, larynx, testes, heart, stomach, brain, adrenal glands, mandibular lymph nodes, spleen, kidney, liver, thyroids, urinary bladder, ovaries, or bone of rats in any of the exposed groups. A lesion that occurred with a high frequency in this study was lacrimal duct inflammation. This lesion occurred with similar incidence and severity in all experimental groups, including sham-exposed rats. Such inflammation is a frequently observed low grade lesion in rats, although detailed descriptions of its nature and incidence are not found in the literature. This lesion was not produced specifically by exposure to the Cu-Zn. We summarized information about this lesion in Appendix G, but not in Table 13, which identifies specific lesions produced by exposure to Cu-Zn, frequency of the lesions, and an average severity rating for those lesions.

Exposure-related lesions occurred in tracheobronchial lymph nodes and thymuses of rats exposed to 240 or 480 mg·hr Cu-Zn/m^3. Significant lesions

Table 13

Incidence[a] and Average Severity[b] of Lesions in Respiratory Tracts of Rats Exposed by Inhalation to Cu-Zn Alloy Powder (Males and Females Combined)

Tissue Designation	Sampling Time[c]	Exposure Group:								
		Sham	30-2[d]	60-2	60-4	120-2	120-4	240-2	240-4	480-4
NOSE/TURBINATES:										
Atrophy, Olfactory Epithelium	EOE	0/9	2/10 (1.0)	10/10 (1.1)	3/10 (1.0)	10/10 (1.7)	10/10 (1.6)	9/10 (2.3)	10/10 (2.2)	10/10 (2.2)
	REC	0/10	0/10	0/10	0/10	0/10	0/10	3/10 (1.0)	2/9 (1.0)	8/9 (1.4)
Goblet Cell Hyperplasia, Respiratory Epithelium	EOE	1/9 (1.0)	4/10 (1.3)	2/10 (1.0)	1/10 (1.0)	2/10 (1.5)	5/10 (1.4)	4/10 (2.3)	3/10 (1.7)	8/10 (1.8)
	REC	2/10 (1.5)	0/10	1/10 (2.0)	2/10 (1.0)	0/10	2/10 (1.0)	1/10 (1.0)	2/9 (1.0)	4/9 (1.0)
LUNGS:										
Alveolitis, Focal Necrotizing	EOE	0/9	0/10	0/10	0/10	1/10 (1.0)	4/10 (1.0)	8/10 (1.4)	8/10 (1.3)	10/10 (3.0)
	REC	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Alveolar Macrophage Hyperplasia	EOE	0/9	3/10 (1.3)	10/10 (1.3)	10/10 (1.9)	10/10 (1.4)	10/10 (2.3)	10/10 (2.3)	10/10 (2.7)	10/10 (3.2)
	REC	0/10	0/10	8/10 (1.0)	10/10 (1.2)	9/10 (1.0)	10/10 (1.5)	10/10 (1.9)	9/9 (1.9)	8/9 (2.5)
Goblet Cell Hyperplasia in Bronchi and Bronchioles	EOE	0/9	1/10 (1.0)	0/10	0/10	2/10 (1.0)	5/10 (1.4)	6/10 (1.0)	9/10 (1.3)	10/10 (3.0)
	REC	0/10	0/10	0/10	0/10	0/10	0/10	1/10 (1.0)	0/9	0/9

[a]Incidence = number of rats with lesion/number of rats evaluated.

[b]Average Severity = $\left(\frac{\text{Lesion score (1 to 4)}}{\text{Number of rats with lesion}}\right)$.

[c]Sampling time = end of exposure (EOE) or after recovery (REC).

[d]The first number of this code represents mg·hr Cu-Zn/m^3 per week; the second number indicates the exposure was delivered in 2 or 4 increments per week.

related to inhalation of Cu-Zn were limited to the nasal cavity and lung. These lesions are summarized below and details for each rat are presented in the Appendix.

(1) Lesions in Nasal Cavity.

Atrophy of the olfactory epithelium and goblet cell hyperplasia were toxicant-induced nasal lesions that were only observed in all rats exposed to the Cu-Zn. Atrophy was characterized by marked thinning of the olfactory epithelium along the mid-dorsal aspect of the nasal septum and maxilloturbinates. Many of the remaining olfactory epithelial cells had abnormal cytoplasmic vacuolation. Goblet cell hyperplasia and hypertrophy were prominent in the ciliated respiratory epithelium lining the anterior portion of the nasal septum and occasionally the epithelium lining the anterior portion of the maxilloturbinate. Severity of the lesions increased as exposure level increased (Appendix E). Olfactory epithelium atrophy completely resolved by the end of the recovery period in rats exposed to less than 240 mg·hr Cu-Zn/m^3 per week. A similar recovery was observed for the goblet cell hyperplasia.

(2) Lesions in Lung.

Three principal alterations were present in the lungs of rats after exposure to Cu-Zn:

(a) Multifocal necrotizing alveolitis

(b) Alveolar macrophage hyperplasia

(c) Goblet cell hyperplasia of bronchial and bronchiolar epithelium

All three types of pulmonary lesions were present in rats that had weekly exposures to 120 mg·hr Cu-Zn/m^3 or more; alveolar macrophage hyperplasia was produced in all exposure groups. As presented in Appendix E, exposure-responses existed for all three types of lesions.

The multifocal necrotizing alveolitis was actually found only in the lungs of rats that had weekly exposures of 120 mg·hr Cu-Zn/m^3 or higher. The alveolitis was associated with the centriacinar region of the lung lobule, the terminal bronchioles, proximal alveolar ducts, and adjacent alveoli. Peribronchiolar interstitium and alveolar septa in these regions were widened due to an infiltration of mononuclear cells and neutrophils. Numerous neutrophils and macrophages were also present in bronchiolar and alveolar airspaces. A key feature of this lesion was necrosis of neutrophils, macrophages, and, occasionally, septal cells. Incidence and severity of this lesion were related to exposure level. The frequency or duration of exposure did not influence the severity of the lesion; however, exposure group 120-2 had an incidence of 1/10 and exposure group 120-4 had an incidence of 4/10, suggesting there may be a relationship between exposure frequency and response when exposure levels are moderate. In rats examined two weeks after the exposures to Cu-Zn, no alveolitis was present, indicating this lung lesion, which was observed immediately after the higher-level exposures to Cu-Zn, did not persist.

In a high percentage of the rats in groups exposed to 60, 120, and 240 mg·hr Cu-Zn/m^3 per week, alveolar macrophage hyperplasia was a consistent finding immediately after exposure and after the allowed recovery period of two weeks. Alveolar macrophage hyperplasia was not observed in the lungs of sham-exposed rats, and was only infrequently observed in the lungs of the 30-2 exposure group.

Increased numbers (hyperplasia) of goblet cells within the bronchial and bronchiolar epithelia were only consistently observed in rats exposed to 120 mg·hr Cu-Zn/m^3 or more per week and examined immediately after the end of exposure. This change was observed in pulmonary airways of only one rat (240-2 group) after the two week recovery period, indicating the lesion essentially fully resolved during that period.

<u>Tissue Content of Cu and Zn</u>

We had preliminary indications that the Cu-Zn inhaled by these rats cleared rapidly from the lung and therefore would not be present in significant quantities in any tissues. The decision was made to complete analyses for all tissues and urine only for the sham-exposed rats and the rats exposed to achieve the exposure level designated 240-4. These were the rats exposed to 40 mg Cu-Zn/m^3, 1.5 hr/day, 4 days/week. Individual values are presented in Appendix E. Table 14 presents results for tissue samples collected three days after the last exposure, Table 15 presents results for tissue samples collected after the recovery period, and Table 16 contains the net tissue content of Cu and Zn. Analysis of urine was complicated by small sample size. Only milligram quantities of urine could be adequately collected from the urinary bladder because the rats invariably urinated during the anesthesia procedure. There was no statistically significant difference from control values for urine content of Cu and Zn. Individual values for urine content of Cu and Zn are presented in Appendix E, but not included in Tables 14-16.

Lungs and lung-associated lymph nodes were the only samples that contained amounts of Cu significantly different from the sham-exposed rats. The amounts of Cu and Zn in lung were very low at the end of the 4-week

Table 14

Atomic Absorption Results (μg metal/gram of sample) at the End of Exposure[a] for Cu and Zn Content of Tissues From Sham-exposed Rats and Rats Exposed to 40 mg Cu-Zn/m^3, 1.5 Hours/Day, 4 Days/Week, for 4 Weeks (N = 6)

		Sham-exposed Rats			Cu-Zn-exposed Rats		
Tissue	Value	Cu	Zn	Cu+Zn	Cu	Zn	Cu+Zn
Kidneys	Mean	13.4	8.8	22.2	17.4	9.5	26.9
	SE	1.7	1.7	3.0	1.8	1.4	2.7
Liver	Mean	2.7	6.7	9.4	3.1	9.0	12.1
	SE	0.6	1.9	2.3	0.8	2.1	2.9
Lung	Mean	1.2	19.7	20.9	3.5[c]	18.5	22.0
	SE	0.1	1.2	1.2	0.3	3.4	3.3
LALN[b]	Mean	2.2	19.2	21.4	3.3[c]	16.6	19.9
	SE	0.3	1.5	1.6	0.2	6.5	6.7
Femurs	Mean	0.8	146	147	0.6	149	150
	SE	0.2	32	91	0.1	42	42
Muscle	Mean	0.8	6.7	7.5	0.8	5.0	5.8
	SE	0.1	1.9	1.9	0.1	1.1	1.2

[a]Samples collected 3 days after the last exposure.

[b]Lung-associated lymph nodes plus supportive tissue.

[c]$p < 0.01$ for statistical comparison with sham-exposed rats. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Table 15

Atomic Absorption Results (μg metal/gram of tissue) After the Two-week Recovery Period for Cu and Zn Content of Tissues from Sham-exposed Rats and Rats Exposed to 40 mg Cu-Zn/m^3, 1.5 Hours/Day, 4 Days/Week, for 4 Weeks (N = 6)

		Sham-exposed Rats			Cu-Zn-exposed Rats		
Tissue	Value	Cu	Zn	Cu+Zn	Cu	Zn	Cu+Zn
Kidneys	Mean	15.8	13.2	29.0	15.6	10.4	26.0
	SE	2.1	3.0	4.3	2.4	2.3	2.4
Liver	Mean	2.4	4.6	7.0	4.1	13.8	17.9
	SE	0.4	0.5	0.9	0.5	2.5	2.9
Lung	Mean	1.1	19.8	20.9	2.2[b]	16.0	18.2
	SE	0.1	1.1	1.1	0.2	1.4	1.4
LALN[a]	Mean	1.7	17.0	18.8	2.5[b]	16.6	19.1
	SE	0.1	0.7	0.7	0.1	4.7	4.7
Femurs	Mean	0.7	163	163	0.8	99	100
	SE	0.1	22	22	0.1	24	24
Muscle	Mean	0.8	3.6	4.4	0.9	5.2	6.1
	SE	0.1	0.5	0.5	0.1	1.1	1.1

[a]Lung-associated lymph nodes plus supportive tissue.

[b]$p < 0.01$ for statistical comparison with sham-exposed rats. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

Table 16

Atomic Absorption Results (μg metal/gram of tissue) for Net Tissue Content of Cu and Zn for Tissues from Rats Exposed to 40 mg Cu-Zn/m^3, 1.5 Hours/Day, 4 Days/Week, for 4 Weeks (Results were calculated from Tables 15 and 16)

	Net Micrograms of Metal per Gram of Tissue					
	Cu		Zn		Cu+Zn	
Tissue	EOE[a]	REC[b]	EOE	REC	EOE	REC
Kidneys	4.0	-0.2	0.7	-2.8	4.7	-3.0
Liver	0.4	1.7	2.3	9.3	2.7	10.9
Lung	2.3[c]	1.1[c]	-1.2	-3.8	1.1	-2.7
LALN[d]	1.1[c]	0.8[c]	-2.6	-0.4	-1.5	0.3
Femurs	-0.2	0.1	3.0	-64	3.0	-63
Muscle	-0.02	0.1	-1.8	1.6	-1.8	1.7

[a]Samples collected for analysis 3 days after the last exposure.

[b]After the two-week recovery period following the 4-week exposure.

[c]$p < 0.01$ for statistical comparison with sham-exposed rats. The treated group was compared with the sham-exposed group using the Student t-test for unequal variances when Levene's test indicated the variances were not the same. When Levene's test did not show differences between the variances, the Student t-test for equal variances was used. Probability values were adjusted for multiple comparisons using Bonferroni's inequality.

[d]Lung-associated lymph nodes plus supportive tissue.

exposure series, suggesting a very rapid clearance of the Cu-Zn after deposition in the lung during the 4-week exposure series. There were no significant differences in tissue content of Cu and Zn after the recovery period for comparisons between sham-exposed and rats exposed at this level. Results for all other exposure levels were projected to be comparable to these.

VII. SUMMARY AND CONCLUSIONS

This study evaluated biological responses to a respirable powder of Cu-Zn alloy (Cu-Zn) inhaled by male and female F344/N rats. The exposures were designed to provide exposure-response data and evaluate the effects of aerosol concentration, exposure frequency, and exposure duration on biological effects produced by the inhaled Cu-Zn. Aerosol concentrations were 10 and 40 mg Cu-Zn/m^3. Exposures were defined in terms of cumulative weekly exposures, which were the product of:

$$(\text{mg Cu-Zn/m}^3) \times (1.5 \text{ or } 3 \text{ hours/day}) \times (2 \text{ or } 4 \text{ days/week})$$

Therefore, units of exposure were mg·hr Cu-Zn/m^3 per week. Exposures were for 4 weeks, followed by a 2-week recovery period. Cumulative weekly exposures were 0, 30, 60, 120, 240, and 480 mg·hr Cu-Zn/m^3. Within the 9 exposure groups were 3 pairs of groups that received the same cumulative weekly exposures in 2 or 4 days/week; these were 60, 120, and 240 mg·hr Cu-Zn/m^3 per week.

In presenting results of this study, comparisons between specific groups of rats exposed to Cu-Zn and the sham-exposed rats were given. However, for most of the evaluations, we also did a trend analysis to demonstrate if a linear relationship existed between exposure and response. Our presentation of the results used both kinds of analytical treatment to help understand which exposure levels produced significant responses relative to the sham-exposed rats, and also to determine if exposure-response relationships existed, with or without the presence of individual differences among experimental groups.

No rats died as a result of inhalation of Cu-Zn. Rats were weighed twice per week during the study. After the 4 weeks exposures, and again after the 2-week recovery period, specific endpoint evaluations were made with rats exposed to 0, 60, 120, and 240 mg·hr Cu-Zn/m^3 per week to determine biological effects of the inhaled Cu-Zn. Evaluations included atomic absorption analyses to determine the amounts of Cu and Zn in specific tissues, analyses of bronchoalveolar lavage fluid, hematology, immunology, and phagocytic ability of pulmonary alveolar macrophages. Histopathological evaluations were done for all groups of rats. The pulmonary function measurements were conducted on male rats before, during, and immediately after the 4-week exposures, as well as after the 2-week recovery period.

The amounts of Cu and Zn in kidneys, liver, lungs, lung-associated lymph nodes (LALN), femurs, and a sample of skeletal muscle of the group of rats exposed to 40 mg Cu-Zn/m^3, 1.5 hours/day, 4 days/week were measured by atomic absorption analysis. Lungs and LALN were the only tissues that contained amounts of either metal significantly different from those of sham-exposed rats. The amounts of Cu and Zn in these tissues were much lower than expected. Average values for mass median aerodynamic diameter and geometric standard deviation of the Cu-Zn aerosols inhaled by this group of rats were 1 um and 3.4, respectively.

The daily pulmonary deposition of the aerosol was approximated as follows, based on generally accepted assumptions about respiratory parameters and fractional pulmonary deposition in rats. Assuming an average respiratory minute volume of 0.2 L/minute, and a fractional pulmonary deposition of 0.05, lung deposition of the Cu-Zn should have been on the order of 30-40 μg/day, or a total of about 500 μg (300 μg Cu and 200 μg Zn) for the 16 days of exposure. The net lung burdens of the inhaled Cu in the exposed rats three days after the last exposure averaged 2.3 μg Cu/gram of lung (lung weight about 1 g). These Cu burdens were significantly different from those of controls, but the Zn burdens in the same lungs were not different from those of controls. The fact that lung burdens of the Cu-Zn exposure material were so small clearly indicates a very rapid clearance of the inhaled material after its deposition in lung.

The body weights were significantly less for rats exposed to 240 and 480 mg·hr Cu-Zn/m^3 per week than for sham-exposed rats. Body weights for rats exposed 4 days per week to achieve the weekly cumulative exposures of 120 mg·hr Cu-Zn/m^3 were not different from body weights of sham-exposed rats exposed 3 hr/day, 4 days per week. However, during the first two weeks of exposures to 120 mg·hr Cu-Zn/m^3 per week (also for rats exposed to 240 mg·hr Cu-Zn/m^3 per week), body weight was adversely affected more by exposures 4 days per week than by exposures 2 days per week. This suggests that the morbidity effect of reduced body weight associated with exposures to Cu-Zn was accentuated if exposures were 4 days per week for a given cumulative exposure to the Cu-Zn.

Lung weights were significantly increased in rats exposed to 120 mg·hr Cu-Zn/m^3 or more per week, delivered over 4 days per week. Also, the lung weights for female rats exposed to 240 and 480 mg·hr Cu-Zn/m^3 (4 days/week) and males exposed to 480 mg·hr Cu-Zn/m^3 per week were still significantly high after the recovery period. The increased lung weights were associated with inflammatory responses caused by the inhaled Cu-Zn. As indicated below for the bronchoalveolar lavage fluid indicators of damage and the histopathology evaluations, the inflammatory responses were substantially resolved after the 2-week recovery period. Trend analyses for lung weights of males and females indicated that there were exposure-related increases in lung weight at the end of exposure ($p = 0.0001$) and the increased lung weights persisted through the 2-week recovery period ($p \leq 0.001$). These results demonstrate that exposures of F344/N rats to 120 mg·hr Cu-Zn/m^3 or more per week produce significant increases in lung weight; exposures to less than 120 mg·hr Cu-Zn/m^3 per week produce slight exposure-related increases in lung weight not significantly different from sham-exposed rats.

Respiratory functional changes were not observed in rats exposed to 60 or 120 mg·hr Cu-Zn/m^3 per week, but were observed in rats exposed to 240 mg·hr Cu-Zn/m^3 per week. The changes included a reduced total lung capacity, reduced quasistatic lung compliance, reduced carbon monoxide diffusing capacity, and increased percent forced vital capacity exhaled in 0.1 second. These alterations were consistent with a restrictive functional disorder, with no evidence of airflow obstruction. The pattern of reduced lung volumes indicated that only the maximum lung expansion, rather than the relaxed or minimum lung volume, was affected by exposure to the Cu-Zn. The respiratory functional changes were not severe, averaging 15% different from normal values at the end of the exposure. There were no statistically significant differences from control values in any of the respiratory parameters after the 2-week recovery period.

Bronchoalveolar lavage fluid analyses at the end of exposure indicated that the inhaled Cu-Zn produced an inflammatory response in the lung, accompanied by a turnover of the extracellular collagenous matrix. Trend analyses indicated that the following lavage fluid constituents had exposure-related responses at the end of exposure: (1) beta-glucuronidase (an indicator of macrophage activation) increased ($p = 0.002$), (2) lactate dehydrogenase (an indicator of cytotoxicity) increased ($p = 0.006$), (3) polymorphonuclear leukocytes increased ($p = 0.005$), (4) total protein increased ($p = 0.02$), and (5) airway collagen increased ($p = 0.03$). Alkaline phosphatase, which is associated with secretions of type II cells of the lung, was not increased as a result of the exposures to Cu-Zn. Despite significant differences in alkaline phosphatase content of lavage fluid in several comparisons, no exposure-related trend was evident. The numbers of pulmonary alveolar macrophages were increased at the end of exposure, especially for exposures 4 days per week, but a trend analysis indicated no exposure-related response. The changes in numbers of macrophages have no clear biological significance. While there were exposure-related changes in lavage fluid indicators of damage exposures to at least 60 mg·hr Cu-Zn/m^3 per week were generally required to produce responses significantly different from sham-exposed rats, and the differences resolved during the 2-week recovery period.

Hematological, immunological, and phagocytosis parameters were not significantly affected by inhaled Cu-Zn. Hematological parameters were unaffected at all exposure levels. Immunological results for rats exposed to Cu-Zn were not significantly different from those of sham-exposed rats at the end of exposure or after the recovery period. Trend analyses, however, indicated slight exposure-related increases in total cells ($p = 0.02$) and total number of antibody-forming cells in LALN ($p = 0.004$). The total number of antibody-forming cells ($p = 0.02$) remained elevated after the 2-week recovery period, but to a lower degree. Although these trends were significant, there was no clear pattern which indicated that the lung immune system was at risk as a result of inhalation of the powdered Cu-Zn. The phagocytic ability of pulmonary alveolar macrophages was unaffected by the exposures to Cu-Zn.

Lesions of the nose caused by inhalation of Cu-Zn included atrophy of the nasal olfactory epithelium and hyperplasia of goblet cells in respiratory epithelium. Atrophy of the nasal olfactory epithelium occurred at all exposure levels, and both the incidence and severity were exposure-related. The average severity ranged from slight in rats exposed to 30 mg·hr Cu-Zn/m^3 per week (for 10 of 10 rats). This lesion completely resolved during the 2-week recovery period for rats exposed to 120 mg·hr Cu-Zn/m^3 per week, or less. Goblet cell hyperplasia and hypertrophy were prominent in the ciliated epithelium lining the anterior portion of the nasal septum and occasionally the epithelium lining the anterior portion of the maxilloturbinate. This lesion had a severity rating of slight to moderate and also resolved during the 2-week recovery period. Therefore, while inhalation of Cu-Zn produced changes in the nasal region of the respiratory tract, the changes resolved after 2 weeks recovery if exposures were less than the equivalent of 120 mg·hr Cu-Zn/m^3 per week for 4 weeks.

Histopathological effects observed in the lung for groups of rats exposed to 120 mg·hr Cu-Zn/m^3 or more per week included focal necrotizing alveolitis in at least 1 of 10 rats, and goblet cell hyperplasia of bronchial and bronchiolar epithelium in at least 2 of 10 rats. The incidence and severity were exposure-related. Severity was "mild" in rats exposed to 120 mg·hr Cu-Zn/m^3 per week. Exposures to 480 mg·hr Cu-Zn/m^3 per week produced the lesions in 10 of 10 rats, and the severity rating was "moderate." One of 10 rats exposed to 30 mg·hr Cu-Zn/m^3 per week developed goblet cell hyperplasia with a severity rating of "slight." The focal necrotizing alveolitis was associated with the terminal bronchioles, proximal alveolar ducts, and adjacent alveoli. This response included infiltration of the interstitium and alveolar septae by mononuclear cells and neutrophils and the presence of numerous neutrophils and macrophages in the bronchiolar and alveolar airspaces. Both of these lesions represented significant responses to exposures to 120 mg Cu-Zn/m^3 or more per week, but both lesions resolved during the 2-week recovery period.

Alveolar macrophage hyperplasia was observed in 3 of 10 rats exposed to 30 mg·hr Cu-Zn/m^3 per week and was present in all rats exposed to levels higher than 30 mg·hr Cu-Zn/m^3 per week. The severity ranged from slight to marked, with more severe responses produced by the higher-level exposures. This lesion only partially resolved during the recovery period and persisted in most rats exposed to 60 mg·hr Cu-Zn/m^3 per week or more. Alveolar macrophage hyperplasia was the most persistent histopathological response observed in lungs of these rats, but appeared to be completely resolvable after exposures to 30 mg·hr Cu-Zn/m^3 per week.

In conclusion, exposure-related responses occurred in rats exposed to powdered Cu-Zn for 4 weeks. Responses were most apparent for bronchopulmonary lavage fluid indicators of damage and inflammation, lung weights, and histopathology. Exposures to at least 60 mg·hr Cu-Zn/m^3 per week were needed to produce significant responses. Most of the responses resolved during the 2-week recovery period, especially if exposures were to no more than 60 mg·hr

Cu-Zn/m^3 per week. Responses to a given cumulative weekly exposure were generally more marked when exposures were delivered during 4 days per week instead of during 2 days per week. While responses were related to the weekly product of aerosol concentration multiplied by exposure time, and exposures 4 days per week generally produced larger responses than exposures 2 days per week for the same cumulative exposure, no relationship was detected for daily exposure duration (1.5 vs. 3 hr/day) or exposure concentration (10 mg Cu-Zn/m^3 vs. 40 mg Cu-Zn/m^3). This was probably a consequence of the relatively small difference between 1.5 hours and 3 hours per day, and the fact that the total amount of Cu-Zn deposited per day was more important than either the aerosol concentration or exposure duration.

With the exception of the decreased body weight, all of the observed biological responses to inhaled Cu-Zn were restricted to the respiratory tract. A weekly product of aerosol concentration multiplied by time of 60 mg·hr Cu-Zn/m was required to elicit statistically significant responses. Most differences in biological responses between sham-exposed rats and rats exposed to Cu-Zn had resolved by the end of a 2-week recovery period. The only significant unresolved changes were the nasal epithelial goblet cell hyperplasia, increased lung weight, and alveolar macrophage hyperplasia. These unresolved changes were associated with weekly cumulative exposures of at least 60 mg·hr Cu-Zn/m^3. The time required for full recovery was not determined, but the severity of the lesions and degree of recovery by 2 weeks suggest that recovery would likely be complete.

Within the spectrum of exposures used in this study, the inhaled Cu-Zn alloy caused exposure-related inflammatory and cytotoxic responses in the respiratory tract, but the inhaled Cu-Zn cleared rapidly and the responses largely resolved after cessation of exposures.

VIII. QUALITY ASSURANCE STATEMENT

This research was conducted in accordance with the Good Laboratory Practice Regulations for Nonclinical Laboratory Studies (FDA, 1978). The study phases were inspected by the LITRI Quality Assurance Unit and findings reported to study scientists and to LITRI management. The final report is in accordance to the experimental methods described in study protocols and in standard operating procedures.

LITRI Quality Assurance Officer: D. L. Harris 8-13-88
D. L. Harris

QA UNIT AUDIT SCHEDULE

Experimental Phase Date	Inspection Date	Report
Protocol FY85-089 Audit	10/27/85	10/27/85
Protocol FY85-089 Approval	12/18/85	12/18/85
Animal Quarantine/Records	12/18/85	12/18/85
Exposure Room Pre-study	12/18/85	12/18/85
Animal ID/Assignments	01/06/86	01/31/86
Path/Tox Protocol Approval	01/07/86	01/07/86
Exposure Room (Dosing)	01/15/86	01/31/86
Animal Weighing/Observations	02/08/86	02/28/86
Necropsy	02/10/86	02/28/86
	03/03/86	03/13/86
Data Audit	03/13/86	03/13/86
Data Audit	11/05-06/86	11/10/86
Draft Report Audit	04/16/87	04/16/87
Final Report Data Audit	01/25-02/01/88	02/01/88
Final Report Audit	05/06/88	05/06/88

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X. ACKNOWLEDGMENTS

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XI. APPENDICES

A. Explanation of Symbols and Abbreviations.

B. Aerosol Concentrations of Cu-Zn Metal Alloy Powder.

C. Body Weights (Grams) for Individual Animals.

D. Endpoint Evaluation Results for Individual Animals.

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F. Atomic Absorption Analysis Results.

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I. Miscellaneous.

A. APPENDIX A: EXPLANATION OF SYMBOLS AND ABBREVIATIONS

These symbols and abbreviations are defined in alphabetical order.

1. ACKG = Airway collagen expressed as micrograms present in the lavage fluid per kilogram body weight.

2. AFC = Antibody-forming cells per million lymphocytes in lung-associated lymph nodes.

3. AIRC = Airway collagen expressed as micrograms present in the lavage fluid.

4. ALKP = Alkaline phosphatase in lavage fluid; milli-international units in the total volume of lavage fluid.

5. Animal Number = Animal number. Metal eartags were used in this study for permanent animal identification.

6. Assign Code = Assignment code, indicating the fate of the animals used in this study.

   EOE = Animals sacrificed for endpoint evaluations after the exposure period.

   REC = Animals sacrificed for endpoint evaluations after the recovery period followiny aerosol exposures.

   FD = Found dead in housing facilities or died during exposure.

   PF = Assigned for pulmonary function evaluations.

7. BGLU = Beta glucuronidase in lavage fluid; milli-international units in the total volume of lavage fluid.

8. BPRO = Total protein in blood plasma, expressed as grams of protein per deciliter of plasma.

9. BWBC = Leukocyte (WBC) numbers per cubic millimeter of blood multiplied by 0.001.

10. BWT = Animal body weight in grams.

11. CCORD = Quasistatic cord compliance (mL per cm water).

12. CDYN = Dynamic lung compliance (mL per cm of water).

13. DLCO = Carbon monoxide diffusing capacity (mL per minute per millimeter of mercury).

14. E10 = Forced expiratory flow rate at 10 percent of FVC (mL per second).

15. EA/100 Cells = Number of opsonized sheep red blood cells (SRBC) phagocytized per 100 pulmonary alveolar macrophages.

16. EOSI = Eosinophils in blood, expressed as numbers of eosinophils per 100 leukocytes.

17. Exposure Code:

SHAM = Exposures of rats to humidified, filtered air using the same kind of nose-only exposure system as used for the Cu-Zn alloy powder. Exposures were 3 hr/day, 4 days/week.

30-2 = Accumulated weekly exposure to 30 mg.hr Cu-Zn alloy delivered 1.5 hr/day, 2 days/week using an aerosol containing 10 mg Cu-Zn alloy/m3.

60-2 = Accumulated weekly exposure to 60 mg.hr at 3 hr/day, 2 days/week, 10 mg Cu-Zn/m3.

60-4 = Accumulated weekly exposure to 60 mg.hr at 1.5 hr/day, 4 days/week, 10 mg Cu-Zn/m3.

120-2 = Accumulated weekly exposure to 120 mg.hr at 1.5 hr/day, 2 days/week, 40 mg Cu-Zn/m3.

120-4 = Accumulated weekly exposure to 120 mg.hr at 3 hr/day, 4 days/week, 10 mg Cu-Zn/m3.

240-2 = Accumulated weekly exposure to 240 mg.hr at 3 hr/day, 2 days/week, 40 mg Cu-Zn/m3.

240-4 = Accumulated weekly exposure to 240 mg.hr at 1.5 hr/day, 4 days/week, 40 mg Cu-Zn/m3.

480-4 = Accumulated weekly exposure to 480 mg.hr at 3 hr/day, 4 days/week, 40 mg Cu-Zn/m3.

18. Expt Number = ITRI experiment number.

19. FRC = Functional residual capacity (mL).

20. FVC = Forced vital capacity (mL).

21. FVI = Percent of FVC exhaled in 0.1 second.

22. HEMA = The percentage ratio of volume of packed red blood cells to volume of whole blood centrifuged by a hematocrit.

23. HGB = Hemoglobin levels in blood, expressed as grams per deciliter of blood.

24. Histopathology codes:

-> = No changes relative to normal.
1> = Minimum change, or very slight degree or amount.
2> = Slight degree of change, or small amount present.
3> = Moderate, median, or middle severity or amount.
4> = Marked severity or degree of change, large amount present.

25. LDH = Lactic dehydrogenase in lavage fluid; milli-international units in the total volume of lavage fluid.

26. LYMP = Lymphocytes in blood, expressed as numbers of lymphocytes per 100 leukocytes.

27. MCV = Mean corpuscular volume. The average volume of red blood cells in units of cubic micrometers.

28. MEF = Mean mid-expiratory flow rate (mL per second).

29. MONO = Monocytes in blood, expressed as numbers of monocytes per 100 leukocytes.

30. MV = Minute volume (mL per minute).

31. NRBC = Nucleated erythrocytes per 100 leukocytes in blood.

32. PAM = Pulmonary alveolar macrophages in total lavage fluid volume multiplied by 0.000001.

33. PEFR = Peak expiratory flow rate (mL per second).

34. PMN = Polymorphonuclear leukocytes in total lavage fluid volume multiplied by 0.000001.

35. RBC = Erythrocytes (RBC) per cubic millimeter of blood multiplied by 0.000001.

36. RL = Total pulmonary resistance (cm water per mL per second).

37. RV = Residual volume (mL).

38. S3 = Slope of phase III of a single-breath nitrogen washout (percent of the nitrogen per mL).

38. SBWT = Sacrifice body weight, the body weights of rats at the time they were killed for endpoint evaluations.

40. SEGM = Segmenter (neutrophil) levels in blood, expressed as numbers of neutrophils per 100 leukocytes.

41. TCOL = Total milligrams of collagen in the analyzed lungs.

42. TKG = Total milligrams of collagen per kilogram body weight.

43. TLC = Total lung capacity (mL).

44. Total AFC = Total IgM anti-SRBC antibody-forming cells in lung-associated lymph nodes.

45. Total Cells = Number of lymphoid cells in lung-associated lymph nodes multiplied by 0.000001.

46. TPRO = Total milligrams of protein in lavage fluid.

47. VC = Vital capacity (mL).

48. WBC = White blood cells in total lavage fluid volume multiplied by 0.000001.

B. APPENDIX B: AEROSOL CONCENTRATIONS OF Cu-Zn METAL ALLOY POWDER

EXPOSURE DATE	EXPERIMENT NUMBER	Cu-Zn mg/m3	NUMBER OF FILTERS	COLLECTION TIME (MIN)
21-JAN-1986	4269	9.28	2	90
24-JAN-1986	4269	9.36	2	90
28-JAN-1986	4269	9.59	2	90
31-JAN-1986	4269	9.88	2	90
04-FEB-1986	4269	9.62	2	90
07-FEB-1986	4269	9.67	2	90
11-FEB-1986	4269	9.71	2	90
14-FEB-1986	4269	13.35	2	90
13-JAN-1986	4270	40.26	2	90
16-JAN-1986	4270	39.48	1	90
20-JAN-1986	4270	37.11	2	90
23-JAN-1986	4270	53.03	1	90
27-JAN-1986	4270	37.70	1	90
30-JAN-1986	4270	40.90	2	90
03-FEB-1986	4270	41.76	1	90
06-FEB-1986	4270	41.04	2	90
14-JAN-1986	4271	8.17	2	180
17-JAN-1986	4271	10.11	2	180
21-JAN-1986	4271	10.22	2	180
24-JAN-1986	4271	9.36	2	90
24-JAN-1986	4271	8.99	1	90
28-JAN-1986	4271	10.85	2	180
31-JAN-1986	4271	9.88	2	90
31-JAN-1986	4271	11.17	2	90
04-FEB-1986	4271	9.89	2	180
07-FEB-1986	4271	9.67	2	90
07-FEB-1986	4271	10.79	2	90
20-JAN-1986	4272	43.28	2	180
23-JAN-1986	4272	39.13	1	180
27-JAN-1986	4272	38.08	2	180
30-JAN-1986	4272	36.71	2	180
03-FEB-1986	4272	41.57	2	90
06-FEB-1986	4272	40.93	2	180
10-FEB-1986	4272	43.99	2	180
13-FEB-1986	4272	37.18	2	180
20-JAN-1986	4273	8.14	2	90
21-JAN-1986	4273	9.28	2	90
22-JAN-1986	4273	11.72	2	90
23-JAN-1986	4273	14.81	2	90
27-JAN-1986	4273	9.29	2	90
28-JAN-1986	4273	9.59	2	90
29-JAN-1986	4273	11.39	2	90
30-JAN-1986	4273	9.81	2	90
03-FEB-1986	4273	10.76	2	90
04-FEB-1986	4273	9.62	2	90
05-FEB-1986	4273	10.11	2	90
06-FEB-1986	4273	10.58	2	90

B. APPENDIX B: AEROSOL CONCENTRATIONS OF Cu-Zn METAL ALLOY POWDER (continued)

EXPOSURE DATE	EXPERIMENT NUMBER	Cu-Zn mg/m3	NUMBER OF FILTERS	COLLECTION TIME (MIN)
10-FEB-1986	4273	11.09	2	90
11-FEB-1986	4273	9.71	2	90
12-FEB-1986	4273	10.34	2	90
13-FEB-1986	4273	10.31	2	90
14-JAN-1986	4274	44.52	2	90
15-JAN-1986	4274	43.69	2	90
16-JAN-1986	4274	38.49	2	90
17-JAN-1986	4274	38.74	2	90
21-JAN-1986	4274	43.62	2	90
22-JAN-1986	4274	42.26	2	90
23-JAN-1986	4274	47.31	2	90
24-JAN-1986	4274	40.90	2	90
28-JAN-1986	4274	37.04	2	90
29-JAN-1986	4274	40.89	2	90
30-JAN-1986	4274	38.83	1	90
31-JAN-1986	4274	40.92	2	90
04-FEB-1986	4274	40.99	2	90
05-FEB-1986	4274	45.93	1	90
06-FEB-1986	4274	40.88	2	90
07-FEB-1986	4274	41.36	2	90
13-JAN-1986	4275	10.24	2	180
14-JAN-1986	4275	7.00	2	180
15-JAN-1986	4275	9.12	2	180
16-JAN-1986	4275	11.32	2	180
20-JAN-1986	4275	9.66	2	180
21-JAN-1986	4275	9.22	2	180
22-JAN-1986	4275	11.45	2	180
23-JAN-1986	4275	10.19	2	180
27-JAN-1986	4275	8.92	2	180
28-JAN-1986	4275	9.01	2	180
29-JAN-1986	4275	10.43	2	180
30-JAN-1986	4275	10.82	2	180
03-FEB-1986	4275	9.31	2	180
04-FEB-1986	4275	10.82	2	180
05-FEB-1986	4275	11.35	2	180
06-FEB-1986	4275	7.98	2	180
21-JAN-1986	4276	43.62	2	90
21-JAN-1986	4276	39.75	2	90
22-JAN-1986	4276	42.26	2	90
22-JAN-1986	4276	41.28	2	90
23-JAN-1986	4276	47.31	2	90
23-JAN-1986	4276	63.38	2	90
24-JAN-1986	4276	40.90	2	90
24-JAN-1986	4276	52.62	2	90
28-JAN-1986	4276	37.04	2	90
28-JAN-1986	4276	37.52	2	90

B. APPENDIX B: AEROSOL CONCENTRATIONS OF Cu-Zn METAL ALLOY POWDER (continued)

EXPOSURE DATE	EXPERIMENT NUMBER	Cu-Zn mg/m3	NUMBER OF FILTERS	COLLECTION TIME (MIN)
29-JAN-1986	4276	40.89	2	90
29-JAN-1986	4276	41.41	2	90
30-JAN-1986	4276	38.83	1	90
30-JAN-1986	4276	43.70	2	90
31-JAN-1986	4276	40.92	2	90
31-JAN-1986	4276	48.74	2	90
04-FEB-1986	4276	40.99	2	90
04-FEB-1986	4276	37.16	2	90
05-FEB-1986	4276	45.93	1	90
05-FEB-1986	4276	44.98	2	90
06-FEB-1986	4276	40.88	2	90
06-FEB-1986	4276	43.09	2	90
07-FEB-1986	4276	41.36	2	90
07-FEB-1986	4276	49.14	2	90
11-FEB-1986	4276	33.36	2	180
12-FEB-1986	4276	40.95	2	180
13-FEB-1986	4276	37.18	2	180
14-FEB-1986	4276	41.58	2	180

C. APPENDIX C: BODY WEIGHT (GRAMS) FOR INDIVIDUAL ANIMALS

DOSE CODE	EXPT. NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
					DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
30-2	4269	001	MALE	REC	327.7	321.7	331.9	318.3	328.3	330.1	322.8	318.3	323.8	326.7	330.2	330.5
30-2	4269	002	MALE	REC	323.5	317.1	320.8	312.3	322.2	317.4	313.8	308.6	310.9	315.4	326.4	325.4
30-2	4269	003	MALE	EOE	312.0	305.7	309.9	300.6	309.2	310.2	306.1	303.0	301.0			
30-2	4269	004	MALE	EOE	315.7	313.4	314.6	312.3	303.0	316.6	316.3	310.4	312.6			
30-2	4269	005	MALE	EOE	306.2	304.3	302.2	299.3	301.4	300.2	301.5	296.3	301.9			
30-2	4269	006	MALE	REC	300.6	300.4	308.0	301.3	315.5	305.5	305.6	300.4	300.6	296.5	309.1	305.5
30-2	4269	007	MALE	REC	285.9	284.5	284.0	278.7	286.3	286.6	280.6	282.3	283.0	286.3	312.0	298.1
30-2	4269	008	MALE	EOE	302.6	303.8	304.1	301.8	309.9	306.2	308.4	303.2	308.2			
30-2	4269	009	MALE	EOE	311.4	300.2	305.8	298.2	304.6	304.2	302.2	293.2	300.1			
30-2	4269	010	MALE	REC	298.1	294.1	299.3	295.5	307.0	305.9	298.0	300.3	296.7	299.7	296.1	314.7
30-2	4269	501	FEMALE	EOE	186.6	176.1	177.2	177.4	176.1	176.0	179.3	178.3	178.6			
30-2	4269	502	FEMALE	REC	179.6	174.1	177.2	173.4	176.0	177.1	177.7	175.3	175.0	170.8	181.6	178.5
30-2	4269	503	FEMALE	EOE	182.2	173.3	178.6	173.4	176.7	178.0	170.3	176.1	172.1			
30-2	4269	504	FEMALE	EOE	174.6	168.0	172.0	169.8	172.8	173.7	164.3	168.1	169.9			
30-2	4269	505	FEMALE	REC	180.2	176.3	174.3	169.3	177.6	175.8	171.9	170.7	170.6	171.6	181.6	180.0
30-2	4269	506	FEMALE	REC	174.2	168.7	168.2	166.3	171.7	172.7	162.9	171.1	166.8	169.1	174.1	179.9
30-2	4269	507	FEMALE	EOE	183.4	179.7	179.6	177.7	183.6	179.3	180.6	178.7	179.4			
30-2	4269	508	FEMALE	REC	173.2	165.8	165.5	168.2	168.4	166.6	167.6	164.1	165.9	167.5	172.7	175.0
30-2	4269	509	FEMALE	EOE	166.8	162.2	161.0	162.2	167.3	162.1	163.7	160.5	162.7			
30-2	4269	510	FEMALE	REC	181.0	174.2	174.2	167.9	176.9	172.2	174.8	172.1	173.4	169.7	177.0	176.1
120-2	4270	011	MALE	EOE	320.6	311.5	305.3	313.5	310.1	315.5	315.7	315.6	311.1			
120-2	4270	012	MALE	REC	319.2	306.1	303.4	307.9	303.2	300.8	305.3	301.1	302.4	312.3	314.6	319.2
120-2	4270	013	MALE	PF	314.6	312.3	300.4	303.4	293.7	302.6	301.6	301.0	301.2	304.8	312.1	313.3
120-2	4270	014	MALE	PF	322.6	314.4	307.5	304.7	298.3	300.2	300.9	299.6	303.5	305.7	307.4	310.9
120-2	4270	015	MALE	PF	315.8	292.9	289.1	293.2	288.7	293.6	290.9	291.6	294.2	304.4	306.5	315.5
120-2	4270	016	MALE	EOE	297.3	288.0	280.2	284.2	279.2	280.6	281.5	283.1	286.8			
120-2	4270	017	MALE	PF	285.3	275.6	270.3	274.1	271.1	273.2	278.3	276.4	274.1	281.7	287.4	288.0
120-2	4270	018	MALE	REC	309.8	297.8	295.0	297.3	295.3	296.6	301.2	301.0	297.4	309.6	309.5	315.1
120-2	4270	019	MALE	REC	282.1	273.5	265.4	269.9	265.9	270.3	272.7	270.9	277.1	281.8	285.9	293.9
120-2	4270	020	MALE	REC	285.7	280.1	274.5	270.2	277.1	277.1	279.0	282.2	283.8	287.4	287.8	286.4
120-2	4270	021	MALE	EOE	275.6	269.2	267.1	270.3	268.1	273.6	274.1	276.7	278.2			
120-2	4270	022	MALE	REC	294.4	288.1	286.7	290.7	288.4	292.3	289.5	289.4	294.7	300.9	304.2	296.5
120-2	4270	023	MALE	REC	300.1	285.3	282.7	286.0	284.8	289.7	289.7	289.4	288.0	299.4	303.0	301.0
120-2	4270	024	MALE	EOE	290.4	284.3	282.5	286.1	287.3	287.6	286.6	288.4	291.1			
120-2	4270	025	MALE	REC	291.9	278.5	275.1	273.6	276.4	277.2	276.4	278.1	282.6	286.5	294.2	283.4
120-2	4270	026	MALE	REC	272.6	268.6	265.1	264.0	262.7	266.6	266.1	267.6	269.3	275.2	276.6	277.0
120-2	4270	027	MALE	REC	291.7	280.2	276.7	284.6	280.5	284.0	283.8	288.4	291.6	299.2	298.1	304.8
120-2	4270	028	MALE	PF	311.0	300.0	294.0	298.5	294.3	298.4	293.5	297.0	304.3	303.4	310.7	311.2
120-2	4270	029	MALE	EOE	293.5	293.7	288.1	283.9	283.9	284.9	285.8	283.5	290.3			
120-2	4270	030	MALE	EOE	311.0	298.3	294.0	296.6	295.8	298.1	303.3	299.6	300.0			
120-2	4270	031	MALE	PF	289.6	284.1	281.9	285.8	280.4	279.0	279.0	281.2	282.0	288.8	289.1	294.9
120-2	4270	032	MALE	PF	299.5	289.1	287.0	290.1	287.1	291.9	294.6	292.5	294.0	302.9	301.7	300.9
120-2	4270	033	MALE	REC	298.0	293.3	288.6	295.7	293.9	299.0	294.5	294.6	298.7	308.7	305.0	310.4
120-2	4270	034	MALE	REC	292.3	287.8	284.6	289.7	283.2	287.4	289.1	284.8	290.0	297.9	302.4	303.7
120-2	4270	035	MALE	REC	279.9	271.5	264.7	267.3	261.8	268.6	271.7	267.6	267.7	276.8	277.3	282.6
120-2	4270	036	MALE	EOE	292.8	289.9	285.9	291.5	294.0	297.0	295.9	295.9	300.3			
120-2	4270	037	MALE	EOE	305.2	295.5	287.0	295.8	288.1	292.3	293.8	296.5	297.1			

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
					DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
120-2	4270	038	MALE	PF	305.4	304.9	292.3	296.9	294.0	291.9	294.2	295.1	296.3	299.7	296.1	295.9
120-2	4270	039	MALE	EOE	281.1	282.5	278.1	283.0	281.0	285.6	283.6	282.5	283.7			
120-2	4270	040	MALE	EOE	288.1	283.0	282.4	288.0	283.7	286.2	287.3	288.7	289.1			
120-2	4270	041	MALE	REC	309.7	299.6	295.1	297.3	296.0	294.6	299.8	304.0	300.7	312.8	316.7	316.5
120-2	4270	042	MALE	REC	314.0	309.2	305.2	311.1	303.9	303.3	304.1	303.7	307.4	317.5	315.0	319.0
120-2	4270	043	MALE	PF	307.1	300.3	294.7	298.8	295.4	297.8	296.2	296.8	299.2	305.4	303.6	303.3
120-2	4270	044	MALE	EOE	291.5	290.8	286.8	288.6	284.6	288.4	288.3	289.5	292.2			
120-2	4270	045	MALE	EOE	305.6	299.2	294.9	297.0	291.7	296.1	291.4	295.6	298.7			
120-2	4270	046	MALE	EOE	293.1	286.5	281.3	285.9	283.4	285.6	290.1	286.9	289.8			
120-2	4270	047	MALE	EOE	301.2	294.2	301.5	291.1	291.0	292.2	293.3	292.3	292.0			
120-2	4270	048	MALE	REC	313.2	309.3		303.3	300.8	299.0	300.1	300.9	302.6	314.2	315.0	311.0
120-2	4270	049	MALE	PF	287.7	282.0	285.2	277.2	274.2	272.9	279.3	280.1	279.4	289.4	287.9	289.1
120-2	4270	050	MALE	EOE	289.5	286.5	280.4	281.6	281.2	281.8	284.5	285.1	286.3			
120-2	4270	511	FEMALE	EOE	176.1	180.0	171.4	169.8	170.1	167.9	168.0	168.4	166.9			
120-2	4270	512	FEMALE	EOE	176.8	177.7	166.9	169.8	168.8	166.0	165.8	163.0	166.2			
120-2	4270	513	FEMALE	EOE	184.0	183.0	177.4	175.3	171.3	175.1	173.8	171.5	175.2			
120-2	4270	514	FEMALE	REC	172.4	173.7	167.7	170.4	165.1	166.7	167.7	167.0	166.5	170.6	171.3	172.4
120-2	4270	515	FEMALE	EOE	178.7	179.6	171.0	173.7	168.1	169.1	168.4	165.0	168.8			
120-2	4270	516	FEMALE	EOE	179.1	177.8	169.8	169.4	168.1	169.5	169.5	167.2	171.0			
120-2	4270	517	FEMALE	REC	170.7	159.5	159.3	157.6	156.3	157.9	159.3	160.3	162.1	168.3	168.4	168.0
120-2	4270	518	FEMALE	REC	174.7	172.2	173.2	173.5	172.5	173.1	173.2	167.7	169.7	171.9	174.8	174.5
120-2	4270	519	FEMALE	REC	169.8	166.5	161.5	162.8	158.4	159.9	160.2	158.2	161.5	163.7	168.8	165.9
120-2	4270	520	FEMALE	REC	171.7	173.3	167.3	170.5	166.7	168.2	166.9	162.9	164.2	169.4	172.8	173.2
120-2	4270	521	FEMALE	REC	177.5	174.9	172.2	171.0	171.8	169.4	167.8	165.6	167.3	172.7	177.2	173.4
120-2	4270	522	FEMALE	REC	174.3	173.0	167.9	167.2	163.1	161.7	163.4	158.8	160.8	166.7	169.9	168.0
120-2	4270	523	FEMALE	EOE	168.2	169.6	164.8	166.5	165.2	165.2	164.5	162.3	160.8			
120-2	4270	524	FEMALE	REC	178.2	178.3	173.2	172.3	171.4	170.1	170.5	168.7	171.1	174.6	173.2	171.2
120-2	4270	525	FEMALE	REC	165.5	167.8	159.6	162.6	154.6	155.4	152.9	150.4	156.8	156.3	154.1	152.6
120-2	4270	526	FEMALE	EOE	177.2	175.5	170.1	170.4	167.9	170.2	169.0	170.5	169.5			
120-2	4270	527	FEMALE	EOE	182.1	175.9	168.7	171.5	168.2	168.1	168.9	165.4	168.0			
120-2	4270	528	FEMALE	EOE	166.3	164.6	158.2	160.4	157.6	156.9	158.0	156.2	159.5			
120-2	4270	529	FEMALE	REC	170.8	170.4	165.1	166.2	162.9	163.0	159.7	162.9	163.6	168.5	170.2	169.5
120-2	4270	530	FEMALE	REC	168.1	163.3	160.0	162.9	156.3	158.3	162.3	156.2	158.6	161.9	163.4	163.6
120-2	4270	531	FEMALE	REC	171.8	173.3	170.2	173.2	165.9	170.1	168.1	171.6	170.5	173.9	173.4	170.2
120-2	4270	532	FEMALE	REC	173.1	173.2	173.2	172.1	172.3	169.1	170.8	173.4	175.6	178.9	174.7	175.0
120-2	4270	533	FEMALE	EOE	173.3	175.2	173.5	171.7	170.9	169.9	173.3	168.8	169.7			
120-2	4270	534	FEMALE	EOE	171.6	177.2	169.7	170.3	167.2	165.9	164.8	164.3	165.1			
120-2	4270	535	FEMALE	REC	174.9	168.9	164.9	164.7	167.1	165.5	164.3	166.3	166.9	171.1	170.1	177.1
120-2	4270	536	FEMALE	EOE	186.5	183.7	180.4	182.3	180.0	174.3	179.4	177.8	179.3			
120-2	4270	537	FEMALE	EOE	174.6	180.8	175.1	177.7	175.7	173.3	176.8	173.1	173.7			
120-2	4270	538	FEMALE	REC	167.2	170.1	165.9	163.2	162.8	159.9	163.0	163.6	162.1	170.5	167.9	163.5
120-2	4270	539	FEMALE	EOE	164.1	164.7	162.9	161.8	158.9	157.4	145.9	150.1	159.2			
120-2	4270	540	FEMALE	EOE	174.2	175.3	171.1	171.0	167.3	169.6	161.5	163.9	169.0			
60-2	4271	051	MALE	EOE	333.8	323.1	318.0	320.0	320.8	314.2	323.1	321.3	320.0			
60-2	4271	052	MALE	EOE	322.7	311.9	312.4	307.3	306.9	303.4	308.2	308.2	308.1			
60-2	4271	053	MALE	EOE	320.1	307.2	305.3	298.6	304.6	294.0	308.1	304.6	304.0			
60-2	4271	054	MALE	REC	314.3	322.5	328.6	322.9	327.2	322.9	326.2	328.3	327.2	326.0	335.8	336.4
60-2	4271	055	MALE	EOE	305.8	305.3	304.3	300.7	302.1	301.8	304.3	304.7	306.6			
60-2	4271	056	MALE	EOE	292.1	284.7	272.7	274.8	284.3	285.1	291.9	293.6	280.5			
60-2	4271	057	MALE	PF	291.7	285.5	285.5	282.1	280.8	281.0	286.6	286.8	276.9	281.0	297.5	296.4
60-2	4271	058	MALE	REC	309.4	304.3	282.2	300.2	301.1	297.6	306.2	303.8	294.8	302.3	322.5	324.6

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					DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
60-2	4271	059	MALE	PF	288.9	283.2	302.8	280.4	280.0	279.3	285.5	279.0	267.2	278.8	292.3	297.3
60-2	4271	060	MALE	REC	288.5	278.0	286.2	278.4	281.7	278.7	280.6	283.1	280.6	287.2	301.9	300.1
60-2	4271	061	MALE	REC	291.4	282.4	278.2	276.7	280.6	278.1	283.8	286.4	278.6	284.8	296.5	296.0
60-2	4271	062	MALE	EOE	308.8	299.6	302.2	303.6	306.3	302.8	309.9	309.7	298.3			
60-2	4271	063	MALE	EOE	304.3	295.5	299.8	298.2	305.2	299.8	305.8	300.2	301.7			
60-2	4271	064	MALE	EOE	308.4	299.2	302.9	296.3	301.0	297.9	299.3	300.0	288.8			
60-2	4271	065	MALE	REC	292.8	282.3	285.5	282.6	285.3	286.0	287.7	286.7	279.2	281.1	296.2	291.1
60-2	4271	066	MALE	REC	278.2	272.4	281.4	273.6	281.8	277.4	281.7	284.0	284.6	284.0	299.7	301.4
60-2	4271	067	MALE	EOE	304.6	293.6	296.5	291.2	294.9	291.7	294.2	296.0	276.8			
60-2	4271	068	MALE	PF	322.5	310.7	309.3	305.9	309.0	304.8	305.0	279.0	283.8	292.9	312.9	304.0
60-2	4271	069	MALE	REC	297.3	286.2	285.6	280.6	289.3	293.0	293.9	295.8	295.3	298.9	311.5	306.2
60-2	4271	070	MALE	PF	314.1	301.2	313.3	306.8	312.7	310.6	311.7	312.6	304.9	307.0	322.4	324.9
60-2	4271	071	MALE	REC	295.0	278.0	288.7	286.1	292.0	290.9	294.3	294.7	284.8	296.6	312.5	311.9
60-2	4271	072	MALE	EOE	301.1	289.1	289.3	285.2	293.1	294.3	296.6	301.8	304.7			
60-2	4271	073	MALE	EOE	301.6	295.1	292.5	286.9	292.1	294.5	302.7	300.7	293.4			
60-2	4271	074	MALE	PF	290.8	288.9	288.8	285.7	294.9	295.8	298.6	300.1	296.7	299.2	309.9	306.1
60-2	4271	075	MALE	PF	285.9	286.0	283.2	273.8	276.6	275.2	275.1	277.1	275.6	283.7	289.8	292.0
60-2	4271	076	MALE	PF	304.9	302.3	303.3	298.1	305.0	302.5	307.8	308.4	305.7	311.0	317.0	320.1
60-2	4271	077	MALE	EOE	305.0	301.5	297.2	289.6	297.1	294.2	302.7	297.4	296.7			
60-2	4271	078	MALE	PF	309.3	295.6	300.9	294.5	303.7	300.9	306.8	305.2	305.2	307.2	315.0	314.0
60-2	4271	079	MALE	REC	281.3	274.1	276.4	267.6	273.0	270.6	277.9	276.8	276.2	274.8	291.1	293.1
60-2	4271	080	MALE	REC	289.2	280.5	282.0	278.4	285.8	284.1	289.4	291.7	291.4	296.9	307.6	305.0
60-2	4271	081	MALE	REC	314.0	326.5	322.4	314.9	314.6	313.8	317.6	318.1	318.7	312.6	324.6	328.7
60-2	4271	082	MALE	EOE	314.4	308.1	306.7	298.6	310.8	307.4	314.6	314.3	315.2			
60-2	4271	083	MALE	EOE	306.5	301.3	304.6	298.4	304.5	301.3	305.9	306.2	307.0			
60-2	4271	084	MALE	REC	301.7	299.0	302.1	290.2	292.9	293.1	298.3	298.4	305.7	302.3	314.1	314.7
60-2	4271	085	MALE	REC	302.9	300.2	301.0	292.4	299.5	297.0	306.0	307.6	304.7	308.8	325.9	324.2
60-2	4271	086	MALE	REC	300.6	293.4	292.5	289.1	289.5	287.0	293.3	296.4	292.4	298.2	308.1	304.9
60-2	4271	087	MALE	PF	305.6	298.6	300.3	293.0	296.5	294.4	301.5	297.7	299.6	305.7	317.3	315.5
60-2	4271	088	MALE	EOE	313.8	305.5	303.8	294.9	303.4	297.2	299.7	301.6	295.9			
60-2	4271	089	MALE	PF	300.4	284.8	294.6	285.1	291.1	292.2	297.1	299.7	296.3	302.6	315.6	312.6
60-2	4271	090	MALE	FD	297.9	316.6	306.5	300.5	314.9	308.0	313.3	315.0	313.3	317.1	333.1	
60-2	4271	541	FEMALE	REC	184.0	178.5	177.9	174.0	177.3	176.8	178.2	176.9	174.4	178.2	188.0	183.7
60-2	4271	542	FEMALE	REC	178.8	171.5	175.0	169.4	173.9	173.2	177.0	175.6	176.5	175.8	182.7	179.5
60-2	4271	543	FEMALE	EOE	180.4	172.6	173.4	171.7	175.2	175.9	176.4	177.7	177.6			
60-2	4271	544	FEMALE	REC	169.5	164.7	163.4	162.3	167.4	165.7	167.6	167.1	166.2	168.1	174.4	173.1
60-2	4271	545	FEMALE	EOE	172.6	169.0	172.8	170.5	174.9	167.8	170.4	174.2	175.7			
60-2	4271	546	FEMALE	REC	176.1	171.5	173.6	169.4	175.9	169.2	174.2	172.8	171.9	175.0	182.0	177.9
60-2	4271	547	FEMALE	REC	174.7	168.5	172.2	165.8	170.4	167.3	171.8	172.5	168.5	173.0	180.6	181.0
60-2	4271	548	FEMALE	REC	179.1	178.9	179.2	177.1	177.8	176.3	178.7	176.2	173.2	175.7	181.1	180.7
60-2	4271	549	FEMALE	REC	176.7	168.4	173.5	170.1	170.4	171.1	170.9	172.5	170.7	171.3	177.2	177.5
60-2	4271	550	FEMALE	EOE	177.1	169.9	172.4	170.3	170.5	169.0	170.7	172.2	164.4			
60-2	4271	551	FEMALE	REC	177.1	167.0	172.2	165.3	168.8	171.2	168.1	171.2	169.0	161.7	172.2	172.1
60-2	4271	552	FEMALE	EOE	175.3	172.8	173.7	168.6	171.3	172.0	177.3	177.6	164.3			
60-2	4271	553	FEMALE	EOE	171.5	168.6	170.4	167.8	168.3	169.6	170.6	168.3	160.4			
60-2	4271	554	FEMALE	EOE	175.5	171.4	173.2	167.3	174.4	171.1	171.9	175.1	169.8			
60-2	4271	555	FEMALE	FD	173.7	166.3	168.7	160.6	163.9	164.4	165.5					
60-2	4271	556	FEMALE	REC	183.4	176.5	177.0	172.9	174.2	172.7	175.4	176.5	167.6	175.0	182.0	177.9
60-2	4271	557	FEMALE	EOE	182.8	174.1	174.1	171.9	172.3	172.7	178.1	175.0	167.0			
60-2	4271	558	FEMALE	EOE	172.5	161.8	154.4	161.3	165.4	163.9	167.2	168.1	167.1			
60-2	4271	559	FEMALE	REC	176.5	170.5	175.0	170.8	175.8	174.1	172.8	177.2	169.8	171.5	173.4	173.4

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
					DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
60-2	4271	560	FEMALE	EOE	175.9	169.9	167.0	166.6	164.0	165.4	167.2	163.2	162.7			
60-2	4271	561	FEMALE	EOE	176.3	170.2	173.5	168.8	172.9	174.5	171.9	176.7	169.7			
60-2	4271	562	FEMALE	EOE	175.4	168.2	171.0	163.4	169.8	167.9	166.4	168.0	164.5			
60-2	4271	563	FEMALE	EOE	168.8	164.2	167.9	164.2	169.5	165.8	168.2	172.2	167.8			
60-2	4271	564	FEMALE	EOE	181.1	171.6	173.1	163.5	166.8	162.3	162.5	163.0	155.6			
60-2	4271	565	FEMALE	REC	178.3	174.3	177.9	174.7	176.9	173.5	173.7	175.4	170.7	172.4	178.6	177.2
60-2	4271	566	FEMALE	REC	181.5	177.2	177.0	175.2	180.1	175.8	177.2	177.5	174.7	174.9	181.1	179.5
60-2	4271	567	FEMALE	EOE	179.9	176.3	179.7	171.3	174.0	173.3	175.2	175.9	171.7			
60-2	4271	568	FEMALE	REC	172.4	168.0	170.0	164.5	169.7	168.3	167.5	168.5	165.2	170.3	174.2	176.5
60-2	4271	569	FEMALE	REC	171.3	164.8	166.5	162.6	162.3	160.1	161.5	157.2	157.8	159.8	170.1	165.7
60-2	4271	570	FEMALE	REC	183.8	172.3	174.3	166.9	173.0	169.8	170.7	173.2	171.5	173.4	179.2	179.4
240-2	4272	091	MALE	REC	322.9	311.1	309.6	301.5	302.4	305.2	299.8	300.2	294.5	304.5	313.5	317.9
240-2	4272	092	MALE	PF	324.7	308.4	302.3	299.5	303.1	299.7	301.5	294.7	297.8	297.2	308.5	319.1
240-2	4272	093	MALE	EOE	325.0	308.3	303.7	301.0	305.8	303.0	300.6	297.7	295.8			
240-2	4272	094	MALE	REC	319.8	302.1	299.6	298.5	298.4	299.5	296.1	294.7	295.5	300.3	308.7	313.3
240-2	4272	095	MALE	REC	311.6	296.8	292.4	290.3	296.6	293.1	288.1	286.8	286.8	287.5	297.0	303.4
240-2	4272	096	MALE	EOE	300.5	287.7	279.6	276.1	275.1	275.3	274.3	272.0	275.3			
240-2	4272	097	MALE	REC	296.3	279.3	278.4	278.6	277.3	284.1	278.1	279.3	277.4	281.7	294.2	295.8
240-2	4272	098	MALE	PF	322.4	309.0	298.4	296.8	297.9	292.9	290.6	288.5	292.5	292.4	303.8	304.5
240-2	4272	099	MALE	REC	284.9	273.9	265.1	266.4	259.6	258.2	256.5	257.4	258.5	258.5	276.0	277.8
240-2	4272	100	MALE	REC	288.5	271.7	266.6	266.2	268.5	272.2	270.8	270.8	269.0	276.8	287.1	287.7
240-2	4272	101	MALE	REC	287.3	278.5	275.5	275.0	282.4	284.2	284.4	285.0	281.4	289.0	302.0	304.4
240-2	4272	102	MALE	REC	307.3	291.7	287.1	283.0	290.5	288.7	289.0	285.9	287.8	291.5	300.3	301.8
240-2	4272	103	MALE	PF	294.3	288.4	286.3	286.0	282.1	283.5	280.4	280.0	280.4	278.0	289.4	295.4
240-2	4272	104	MALE	EOE	298.1	292.3	282.6	284.6	281.1	285.6	282.5	280.2	282.8			
240-2	4272	105	MALE	REC	289.4	278.8	276.0	277.5	278.3	278.2	281.1	275.7	278.3	279.1	292.9	293.1
240-2	4272	106	MALE	REC	276.1	273.1	269.8	263.7	272.9	267.9	266.2	267.0	266.3	269.3	282.5	281.1
240-2	4272	107	MALE	EOE	305.9	291.2	284.2	283.3	282.9	282.6	283.5	279.8	280.2			
240-2	4272	108	MALE	EOE	312.2	304.3	298.2	303.5	299.0	301.1	297.3	293.3	297.1			
240-2	4272	109	MALE	EOE	295.1	288.6	284.6	278.6	284.0	282.8	281.6	280.7	282.0			
240-2	4272	110	MALE	EOE	321.1	314.0	306.5	304.6	308.0	303.9	303.9	302.6	304.1			
240-2	4272	111	MALE	REC	293.1	294.1	285.8	285.4	284.3	281.1	280.5	278.6	277.0	279.8	290.2	293.5
240-2	4272	112	MALE	EOE	298.5	298.2	291.4	290.8	285.2	290.4	288.0	287.9	286.1			
240-2	4272	113	MALE	EOE	314.1	300.8	294.4	294.0	283.5	292.6	286.1	293.6	287.4			
240-2	4272	114	MALE	PF	299.9	292.1	288.5	288.2	286.1	285.9	284.1	282.4	283.3	283.4	284.9	297.5
240-2	4272	115	MALE	EOE	299.4	273.5	274.6	272.9	270.6	272.5	271.9	266.0	266.4			
240-2	4272	116	MALE	EOE	280.3	289.6	290.1	289.5	286.7	288.4	285.4	289.7	284.8			
240-2	4272	117	MALE	PF	307.6	295.4	289.8	288.8	289.9	290.5	286.8	291.5	284.7	287.4	291.2	300.0
240-2	4272	118	MALE	PF	309.7	297.5	291.5	289.0	288.8	286.0	284.6	282.8	283.6	280.0	293.4	294.6
240-2	4272	119	MALE	REC	283.0	271.0	270.8	269.9	270.6	266.9	265.0	266.3	264.7	271.0	278.6	282.2
240-2	4272	120	MALE	REC	289.5	277.4	270.5	273.4	272.7	268.0	274.1	276.0	272.5	276.7	293.7	296.9
240-2	4272	121	MALE	EOE	308.4	299.7	292.9	295.6	293.3	286.8	284.5	286.0	286.2			
240-2	4272	122	MALE	REC	315.0	306.1	300.7	300.9	300.1	302.1	298.2	303.7	299.0	302.3	313.4	315.6
240-2	4272	123	MALE	REC	310.0	302.2	298.0	300.0	299.2	294.7	298.9	296.6	295.0	298.5	307.9	309.6
240-2	4272	124	MALE	EOE	302.2	290.4	289.5	282.1	281.0	277.4	280.6	280.7	276.8			
240-2	4272	125	MALE	EOE	311.4	296.1	290.5	289.2	290.1	290.9	287.8	294.0	287.5			
240-2	4272	126	MALE	EOE	288.6	282.3	277.8	276.2	276.1	274.6	274.4	279.8	272.6			
240-2	4272	127	MALE	PF	309.1	302.9	294.7	294.2	297.2	290.9	289.7	291.6	289.8	290.0	302.2	305.0
240-2	4272	128	MALE	PF	313.9	296.6	297.7	296.6	296.7	295.9	293.4	292.8	292.9	293.0	299.8	310.2
240-2	4272	129	MALE	PF	295.0	284.3	277.4	274.7	273.9	273.0	274.8	275.5	270.0	275.0	283.1	284.8
240-2	4272	130	MALE	PF	297.6	294.2	286.4	284.6	281.6	280.9	280.3	283.1	280.8	285.0	286.7	288.0

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					DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
240-2	4272	571	FEMALE	REC	177.9	168.6	168.4	164.7	167.7	164.1	165.2	165.6	165.4	165.8	165.3	178.6
240-2	4272	572	FEMALE	EOE	169.4	164.1	160.7	155.9	158.7	157.0	154.8	156.7	155.6			
240-2	4272	573	FEMALE	EOE	173.6	167.9	165.9	166.1	166.9	163.4	164.5	162.9	162.7			
240-2	4272	574	FEMALE	EOE	174.0	168.0	168.7	166.9	169.2	172.4	169.6	170.4	169.0			
240-2	4272	575	FEMALE	EOE	170.4	168.9	167.4	168.4	168.6	167.9	167.4	171.3	167.0			
240-2	4272	576	FEMALE	REC	174.6	174.3	167.8	170.1	168.2	166.1	164.4	164.6	161.3	164.7	170.7	174.0
240-2	4272	577	FEMALE	EOE	167.8	167.8	167.7	167.6	165.5	160.3	162.0	162.1	158.2			
240-2	4272	578	FEMALE	FD	172.0	166.1	165.5	161.7	165.8	157.4	162.6					
240-2	4272	579	FEMALE	EOE	176.1	161.3	159.9	156.8	159.0	155.3	158.3	157.4	154.5			
240-2	4272	580	FEMALE	REC	175.4	167.5	170.5	164.8	168.1	164.9	165.8	164.1	165.4	162.3	166.8	173.6
240-2	4272	581	FEMALE	EOE	177.1	161.6	171.5	165.8	170.2	162.1	167.9	170.7	170.2			
240-2	4272	582	FEMALE	EOE	173.2	166.8	167.1	161.6	166.2	168.4	162.7	162.0	158.1			
240-2	4272	583	FEMALE	EOE	164.6	160.2	159.9	157.5	157.3	159.4	158.9	158.1	155.1			
240-2	4272	584	FEMALE	REC	176.2	169.2	168.4	162.9	161.8	162.6	161.8	163.0	160.3	162.2	171.6	171.5
240-2	4272	585	FEMALE	REC	168.1	165.7	163.6	160.4	159.2	160.6	160.6	161.1	157.7	161.1	169.0	169.2
240-2	4272	586	FEMALE	REC	172.8	164.2	165.4	166.2	166.9	165.2	164.3	163.4	163.6	167.6	175.4	175.8
240-2	4272	587	FEMALE	REC	176.8	165.5	167.9	167.4	168.8	170.0	168.5	172.7	170.4	169.9	178.4	179.8
240-2	4272	588	FEMALE	REC	165.9	156.2	157.3	156.0	160.5	158.2	156.7	155.0	157.3	160.4	165.3	164.8
240-2	4272	589	FEMALE	EOE	170.4	163.7	165.5	162.9	166.6	167.7	165.3	166.9	166.3			
240-2	4272	590	FEMALE	REC	166.8	160.1	161.3	158.3	158.4	157.2	156.2	158.4	155.8	157.6	163.2	164.7
240-2	4272	591	FEMALE	REC	172.5	165.0	166.0	162.9	164.1	159.1	160.9	159.2	161.2	161.0	173.6	175.4
240-2	4272	592	FEMALE	REC	173.7	165.4	162.7	163.6	165.0	165.7	165.7	165.9	161.1	169.3	177.2	176.5
240-2	4272	593	FEMALE	EOE	173.9	164.6	164.5	160.3	163.1	157.8	158.9	164.1	160.3			
240-2	4272	594	FEMALE	REC	173.3	166.4	165.6	164.5	168.3	165.2	165.7	166.6	163.3	167.6	173.6	176.5
240-2	4272	595	FEMALE	EOE	178.2	170.0	164.6	164.9	163.8	161.9	161.9	161.8	158.7			
240-2	4272	596	FEMALE	REC	178.4	174.8	176.0	165.1	170.5	170.0	172.8	173.1	172.8	168.9	174.7	173.4
240-2	4272	597	FEMALE	REC	175.7	171.5	168.2	163.0	170.1	166.7	166.3	162.7	164.0	165.1	171.5	172.7
240-2	4272	598	FEMALE	EOE	175.2	166.5	164.4	165.9	165.2	167.0	167.7	168.2	164.4			
240-2	4272	599	FEMALE	REC	167.6	162.6	161.9	157.8	162.0	157.4	162.8	162.4	162.4	158.5	164.2	162.7
240-2	4272	600	FEMALE	EOE	175.2	167.3	166.5	165.3	171.0	166.0	171.3	169.1	169.5			
60-4	4273	131	MALE	EOE	321.3	308.4	304.2	307.6	310.6	312.6	306.9	304.6	310.8			
60-4	4273	132	MALE	REC	319.8	308.8	302.2	306.2	304.7	304.5	301.9	302.8	303.3	311.2	322.9	329.0
60-4	4273	133	MALE	REC	323.8	312.5	303.5	305.5	311.3	307.1	311.1	304.9	284.8	282.3	296.3	312.5
60-4	4273	134	MALE	REC	316.0	304.2	299.2	297.9	301.2	300.0	302.5	300.9	300.6	303.0	316.4	319.5
60-4	4273	135	MALE	REC	310.4	308.0	306.5	304.5	308.7	310.9	313.0	305.2	304.7	307.1	316.3	320.0
60-4	4273	136	MALE	EOE	305.0	296.7	293.3	293.5	298.1	298.1	300.7	293.8	291.6			
60-4	4273	137	MALE	PF	295.0	293.4	290.5	284.9	291.3	288.1	292.1	290.4	289.4	288.6	299.0	300.6
60-4	4273	138	MALE	PF	314.6	305.6	300.2	299.1	304.6	306.4	309.7	304.0	310.1	309.9	317.1	322.4
60-4	4273	139	MALE	EOE	286.7	287.6	280.7	277.9	283.3	281.8	286.1	281.4	287.4			
60-4	4273	140	MALE	REC	285.0	277.4	281.6	272.4	278.3	273.8	281.0	274.7	283.1	284.0	302.3	299.6
60-4	4273	141	MALE	REC	292.9	287.5	285.5	279.8	282.4	281.9	280.2	278.5	278.2	281.2	292.8	298.3
60-4	4273	142	MALE	EOE	315.3	303.9	299.5	293.2	303.4	298.1	304.1	295.8	296.4			
60-4	4273	143	MALE	REC	299.9	295.5	295.3	296.7	297.8	293.6	300.4	294.9	294.2	301.6	309.7	312.5
60-4	4273	144	MALE	REC	302.3	298.5	292.4	292.8	298.7	296.5	298.6	295.4	295.1	298.9	311.6	318.2
60-4	4273	145	MALE	REC	295.3	291.8	285.6	288.7	285.6	284.6	285.0	286.0	281.3	287.2	299.0	300.0
60-4	4273	146	MALE	PF	283.8	277.3	274.8	273.1	276.2	274.4	275.7	273.5	275.3	264.9	276.5	278.7
60-4	4273	147	MALE	REC	307.0	301.5	293.2	293.4	301.5	300.5	304.2	300.8	303.7	307.1	323.0	324.9
60-4	4273	148	MALE	REC	315.8	313.2	312.7	304.9	308.6	307.5	313.3	314.5	317.0	317.1	334.4	336.9
60-4	4273	149	MALE	EOE	299.5	293.5	291.8	288.9	288.9	288.4	290.9	286.9	289.1			
60-4	4273	150	MALE	EOE	326.1	317.4	316.4	313.9	317.7	319.0	320.7	313.6	321.1			
60-4	4273	151	MALE	EOE	302.4	295.0	289.1	294.0	293.7	297.7	299.1	296.8	297.4			

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60-4	4273	152	MALE	REC	301.7	295.9	295.8	291.7	300.2	294.0	301.8	291.9	296.9	307.1	315.0	318.9
60-4	4273	153	MALE	PF	304.1	299.6	294.5	291.7	295.1	298.5	299.7	296.6	294.6	294.7	307.0	313.6
60-4	4273	154	MALE	EOE	305.3	300.5	290.4	293.5	297.2	299.7	306.2	300.5	301.2			
60-4	4273	155	MALE	PF	275.8	275.5	276.7	270.1	270.3	274.6	274.4	272.6	275.4	276.4	287.5	286.9
60-4	4273	156	MALE	REC	303.7	305.8	302.3	300.3	298.0	305.7	304.0	302.2	305.0	304.0	315.2	319.0
60-4	4273	157	MALE	REC	311.2	305.4	302.8	298.4	303.4	296.9	302.0	303.0	303.7	304.6	319.3	323.9
60-4	4273	158	MALE	PF	307.8	299.1	297.3	289.9	295.7	293.4	286.9	295.6	298.9	300.0	313.4	314.3
60-4	4273	159	MALE	EOE	279.3	276.5	270.7	272.7	272.4	274.5	269.1	271.8	269.8			
60-4	4273	160	MALE	REC	294.2	292.5	290.6	286.0	287.3	289.9	296.7	288.9	292.6	295.0	305.0	306.0
60-4	4273	161	MALE	PF	313.7	305.9	306.4	304.3	302.2	302.9	308.3	298.0	301.0	302.0	312.2	315.5
60-4	4273	162	MALE	EOE	306.9	303.6	300.3	292.6	297.9	301.1	305.3	299.0	300.5			
60-4	4273	163	MALE	EOE	309.0	306.7	301.0	299.5	304.5	305.1	309.1	305.0	304.8			
60-4	4273	164	MALE	EOE	309.4	295.2	291.6	288.1	289.5	291.7	291.3	289.1	289.1			
60-4	4273	165	MALE	PF	302.9	305.6	292.6	295.5	293.3	294.5	295.4	293.9	295.9	298.0	302.0	307.5
60-4	4273	166	MALE	EOE	296.7	292.7	284.5	283.4	286.5	288.6	295.7	296.3	297.8			
60-4	4273	167	MALE	EOE	309.3	309.0	300.1	299.3	299.3	301.3	304.5	298.0	295.4			
60-4	4273	168	MALE	PF	310.2	327.6	304.5	306.8	304.9	308.8	310.8	305.8	309.0	307.0	317.2	325.4
60-4	4273	169	MALE	PF	295.9	316.7	289.0	295.4	292.1	294.8	292.8	295.4	299.0	298.0	310.2	314.9
60-4	4273	170	MALE	EOE	297.3	303.8	283.4	289.4	290.4	289.4	293.0	287.9	287.1			
60-4	4273	601	FEMALE	REC	175.0	173.2	171.4	176.4	175.8	175.2	178.2	174.8	178.5	178.8	182.1	187.0
60-4	4273	602	FEMALE	EOE	173.5	169.1	170.0	164.7	170.0	168.5	172.6	167.1	169.5			
60-4	4273	603	FEMALE	FD	177.7	175.8	170.4	173.2	176.6	171.1	174.8	173.1	176.0	174.8	180.2	
60-4	4273	604	FEMALE	EOE	171.7	167.9	165.1	164.6	170.9	162.7	169.1	167.1	169.4			
60-4	4273	605	FEMALE	EOE	172.2	168.2	168.5	165.3	171.8	165.8	165.4	162.2	168.5			
60-4	4273	606	FEMALE	EOE	174.9	167.8	167.0	164.0	171.9	163.7	168.9	165.2	167.7			
60-4	4273	607	FEMALE	EOE	176.5	169.9	168.3	165.6	170.7	165.7	170.3	168.3	168.5			
60-4	4273	608	FEMALE	EOE	175.0	170.4	171.4	169.1	171.4	170.5	171.3	166.8	170.2			
60-4	4273	609	FEMALE	EOE	167.4	164.6	163.0	160.2	165.5	161.4	163.5	161.6	168.2			
60-4	4273	610	FEMALE	REC	174.2	167.8	168.6	163.4	168.8	164.6	170.1	165.2	163.4	167.5	169.4	173.8
60-4	4273	611	FEMALE	REC	179.6	175.8	174.5	168.9	159.0	169.6	174.4	169.5	176.4	177.8	181.6	185.0
60-4	4273	612	FEMALE	REC	172.2	168.7	168.6	165.5	173.4	165.5	171.1	165.8	169.6	170.9	177.2	175.4
60-4	4273	613	FEMALE	REC	166.9	162.8	166.5	165.7	167.6	164.0	164.0	167.3	168.3	165.1	174.3	175.2
60-4	4273	614	FEMALE	REC	172.4	170.9	170.3	166.1	171.9	173.3	169.4	167.3	170.4	167.8	174.4	179.1
60-4	4273	615	FEMALE	EOE	176.1	162.9	158.6	154.9	162.4	156.5	157.2	157.8	159.0			
60-4	4273	616	FEMALE	REC	182.0	176.9	175.6	173.0	177.8	176.0	177.0	173.4	175.2	177.4	180.4	182.1
60-4	4273	617	FEMALE	EOE	177.1	171.6	175.1	169.1	177.4	173.8	173.9	174.3	178.0			
60-4	4273	618	FEMALE	REC	166.1	163.4	161.8	161.2	167.3	166.5	166.7	164.1	168.3	170.9	172.6	175.9
60-4	4273	619	FEMALE	REC	172.7	166.3	173.2	167.2	170.7	165.3	170.3	167.2	170.7	173.0	175.5	175.9
60-4	4273	620	FEMALE	REC	165.1	163.7	169.7	155.9	164.5	163.4	163.5	162.9	163.6	161.3	165.3	167.2
60-4	4273	621	FEMALE	EOE	172.2	170.3	161.4	164.1	171.5	164.0	168.4	165.6	167.9			
60-4	4273	622	FEMALE	REC	174.6	171.7	176.4	171.3	175.7	172.2	173.9	169.0	172.1	175.3	178.9	183.2
60-4	4273	623	FEMALE	REC	171.8	168.7	171.7	168.9	173.3	172.2	167.5	169.4	170.0	165.8	169.8	176.3
60-4	4273	624	FEMALE	EOE	175.6	171.5	168.7	165.6	169.3	167.9	169.4	168.6	171.3			
60-4	4273	625	FEMALE	EOE	165.8	167.4	168.8	166.6	168.2	168.7	170.4	165.7	170.3			
60-4	4273	626	FEMALE	REC	172.7	171.4	172.8	173.3	174.9	173.0	176.7	172.8	175.4	172.7	176.8	182.1
60-4	4273	627	FEMALE	EOE	173.2	176.0	173.1	169.1	178.0	171.5	174.5	170.2	173.2			
60-4	4273	628	FEMALE	REC	169.7	165.1	167.9	164.2	162.9	162.0	163.1	162.0	165.0	160.2	167.2	170.7
60-4	4273	629	FEMALE	EOE	167.6	161.7	161.9	164.0	166.9	168.0	167.0	166.5	165.0			
60-4	4273	630	FEMALE	EOE	172.0	170.4	170.8	166.9	175.7	168.8	169.4	172.1	170.6			
240-4	4274	171	MALE	REC	327.7	302.8	309.7	293.6	304.3	298.2	308.0	295.1	303.3	306.3	321.5	320.8
240-4	4274	172	MALE	REC	318.4	291.8	287.6	279.6	292.4	283.5	298.1	286.0	299.3	300.7	312.6	314.2

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
240-4	4274	173	MALE	REC	321.6	299.0	303.3	283.2	291.4	283.8	296.0	292.7	293.8	304.5	314.3	309.4
240-4	4274	174	MALE	REC	315.6	290.7	290.7	289.7	293.8	284.6	293.5	284.9	290.1	292.1	314.1	308.2
240-4	4274	175	MALE	REC	312.1	289.1	300.9	281.1	290.4	282.1	289.7	279.0	291.7	291.1	307.3	306.9
240-4	4274	176	MALE	REC	296.2	282.7	289.0	280.0	290.5	282.2	292.1	279.9	288.7	292.3	304.3	304.6
240-4	4274	177	MALE	REC	292.4	272.9	280.5	273.4	278.5	272.5	277.2	273.5	273.9	279.6	294.8	297.1
240-4	4274	178	MALE	EOE	305.0	286.8	293.4	285.4	296.0	285.4	300.0	289.9	294.8			
240-4	4274	179	MALE	PF	287.9	267.4	274.0	263.4	275.0	263.0	281.6	271.0	274.4	276.4	287.8	292.3
240-4	4274	180	MALE	REC	282.9	270.6	276.6	267.6	276.4	263.7	272.2	267.8	272.6	278.4	290.9	290.2
240-4	4274	181	MALE	REC	294.0	271.9	271.8	266.3	276.2	270.7	278.2	268.5	268.9	281.4	295.6	290.7
240-4	4274	182	MALE	PF	307.4	289.9	290.5	280.5	293.8	284.2	290.8	285.7	291.3	289.0	298.0	301.1
240-4	4274	183	MALE	EOE	298.0	279.5	281.8	272.5	282.9	277.8	286.9	286.0	298.0			
240-4	4274	184	MALE	EOE	299.4	276.3	284.0	274.7	282.2	276.7	285.7	282.3	282.3			
240-4	4274	185	MALE	EOE	291.0	277.7	280.5	288.6	280.9	271.0	281.9	275.8	290.0			
240-4	4274	186	MALE	EOE	272.4	259.6	263.9	267.7	268.0	258.3	269.9	269.4	278.4			
240-4	4274	187	MALE	PF	299.0	287.3	286.9	278.8	284.1	275.9	288.1	284.9	296.6	282.3	300.6	303.4
240-4	4274	188	MALE	PF	315.2	297.7	298.0	255.9	291.9	285.5	297.3	290.6	293.8	292.1	303.8	311.4
240-4	4274	189	MALE	EOE	293.5	272.8	278.5	268.0	278.9	271.7	278.0	276.2	269.8			
240-4	4274	190	MALE	EOE	320.4	297.2	305.6	286.4	297.6	285.3	305.8	290.3	293.9			
240-4	4274	191	MALE	PF	294.0	275.9	283.1	272.2	281.7	274.4	282.9	278.3	286.9	279.3	296.8	290.0
240-4	4274	192	MALE	REC	300.9	282.0	295.3	278.2	291.9	273.7	287.1	286.6	287.3	290.4	307.2	307.0
240-4	4274	193	MALE	EOE	302.3	288.4	294.8	284.1	283.9	283.8	294.7	292.3	295.9			
240-4	4274	194	MALE	PF	303.4	281.3	288.9	274.4	283.0	276.2	283.2	277.5	284.6	285.3	294.1	290.1
240-4	4274	195	MALE	REC	266.6	253.5	261.6	249.5	260.0	257.2	264.6	263.1	265.5	267.6	279.3	277.2
240-4	4274	196	MALE	EOE	309.1	293.3	300.5	288.5	290.9	284.4	290.5	282.5	287.9			
240-4	4274	197	MALE	REC	305.7	281.1	293.8	278.1	284.4	278.0	284.8	279.1	286.1	287.8	299.0	295.2
240-4	4274	198	MALE	EOE	309.9	291.4	295.2	282.7	292.7	280.1	287.7	291.2	289.5			
240-4	4274	199	MALE	REC	279.1	268.8	273.0	261.0	273.2	266.7	274.5	268.1	273.0	276.2	284.0	279.6
240-4	4274	200	MALE	REC	290.5	270.8	274.8	264.3	275.5	267.0	274.9	271.5	279.1	271.9	287.0	281.5
240-4	4274	201	MALE	PF	304.1	289.4	294.9	278.8	283.0	274.3	283.0	282.5	285.6	286.1	294.7	290.1
240-4	4274	202	MALE	EOE	311.9	294.5	298.6	278.1	291.5	282.1	296.1	288.1	293.2			
240-4	4274	203	MALE	PF	310.2	288.7	297.1	285.4	289.2	281.2	293.2	289.8	292.9	294.5	302.7	305.3
240-4	4274	204	MALE	PF	294.9	277.8	285.6	266.1	271.3	263.1	274.7	273.7	279.3	275.7	285.4	284.8
240-4	4274	205	MALE	EOE	303.9	284.5	292.5	282.2	285.7	277.5	292.5	288.0	294.0			
240-4	4274	206	MALE	EOE	297.7	284.1	287.2	279.3	284.6	275.6	285.8	280.4	285.2			
240-4	4274	207	MALE	PF	305.5	287.7	295.8	281.4	289.0	283.4	290.7	289.0	293.9	293.9	301.3	301.8
240-4	4274	208	MALE	EOE	310.7	292.7	297.0	287.8	294.3	285.1	294.4	288.3	291.9			
240-4	4274	209	MALE	REC	288.4	276.8	278.6	271.1	274.4	267.6	275.3	268.7	272.5	273.2	290.6	289.8
240-4	4274	210	MALE	EOE	290.7	278.2	288.6	271.5	276.5	268.2	278.9	277.9	279.8			
240-4	4274	631	FEMALE	REC	183.5	173.3	173.8	166.1	171.7	162.4	172.1	167.8	172.5	171.6	180.9	180.1
240-4	4274	632	FEMALE	REC	178.2	170.8	167.5	160.5	168.1	158.3	165.3	159.6	164.2	168.8	170.4	170.3
240-4	4274	633	FEMALE	REC	178.7	166.1	171.5	159.9	167.0	156.7	170.4	160.0	166.7	171.0	176.4	174.2
240-4	4274	634	FEMALE	REC	171.3	158.0	162.3	154.6	161.8	150.9	162.9	159.3	165.2	163.8	170.0	169.7
240-4	4274	635	FEMALE	EOE	176.4	167.3	165.1	158.6	165.1	156.1	164.5	161.2	167.7			
240-4	4274	636	FEMALE	REC	180.5	173.3	171.8	168.7	173.4	164.3	172.8	167.8	173.4	169.5	179.7	183.0
240-4	4274	637	FEMALE	REC	171.5	160.1	163.5	155.5	163.4	152.7	159.8	153.3	159.5	159.8	164.6	166.5
240-4	4274	638	FEMALE	EOE	179.3	170.5	167.7	163.5	169.4	165.2	171.9	166.7	172.7			
240-4	4274	639	FEMALE	REC	167.8	162.0	163.5	157.1	161.9	155.5	161.2	155.5	158.7	160.5	165.7	166.5
240-4	4274	640	FEMALE	REC	178.0	156.2	164.4	158.7	165.6	157.6	164.8	162.6	163.6	165.1	169.5	169.5
240-4	4274	641	FEMALE	REC	177.7	172.2	174.6	166.1	176.7	163.8	177.4	171.0	177.6	179.6	184.2	182.5
240-4	4274	642	FEMALE	REC	162.7	152.2	150.7	151.3	164.2	154.7	163.5	159.5	165.2	167.7	174.4	170.0
240-4	4274	643	FEMALE	EOE	172.9	159.6	165.8	158.4	160.9	151.9	159.7	156.3	160.0			

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
					DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
240-4	4274	644	FEMALE	EOE	174.2	160.5	167.6	158.8	164.6	160.2	165.4	161.1	167.1			
240-4	4274	645	FEMALE	REC	172.3	163.9	168.2	160.4	164.8	158.5	163.8	160.0	160.6	161.2	162.1	168.1
240-4	4274	646	FEMALE	EOE	184.4	170.6	176.7	166.3	174.1	170.5	175.2	168.5	172.8			
240-4	4274	647	FEMALE	EOE	174.8	164.4	166.5	159.8	162.4	156.0	160.9	156.1	162.1			
240-4	4274	648	FEMALE	EOE	171.0	160.6	167.0	158.0	164.4	156.4	166.9	160.1	162.2			
240-4	4274	649	FEMALE	EOE	174.0	162.0	156.4	156.8	166.3	158.1	164.3	161.5	164.2			
240-4	4274	650	FEMALE	EOE	173.4	153.7	166.0	147.6	153.2	150.3	154.2	150.9	153.3			
240-4	4274	651	FEMALE	EOE	169.6	159.5	164.3	156.4	161.2	155.1	163.9	157.6	164.2			
240-4	4274	652	FEMALE	EOE	174.7	167.8	172.7	162.7	169.0	163.4	170.3	165.2	167.2			
240-4	4274	653	FEMALE	EOE	176.0	163.3	168.4	162.0	172.0	167.0	171.5	167.2	169.9			
240-4	4274	654	FEMALE	EOE	176.5	163.4	169.7	161.8	166.6	159.7	169.4	164.8	170.9			
240-4	4274	655	FEMALE	REC	181.8	169.9	172.0	162.8	167.7	163.0	169.3	169.6	168.6	172.7	178.9	180.4
240-4	4274	656	FEMALE	REC	192.3	183.8	185.7	174.3	181.1	175.0	178.4	175.1	176.6	173.7	179.3	181.1
240-4	4274	657	FEMALE	EOE	186.6	172.2	174.6	161.0	168.0	159.6	169.0	165.8	169.8			
240-4	4274	658	FEMALE	EOE	170.9	157.9	162.6	152.6	162.3	155.5	161.9	155.0	158.0			
240-4	4274	659	FEMALE	REC	169.6	158.3	162.3	157.0	163.0	158.1	157.5	155.4	158.6	162.3	166.3	165.9
240-4	4274	660	FEMALE	REC	178.9	164.9	168.8	165.7	168.2	164.9	170.1	163.8	172.6	172.2	179.2	174.4
120-4	4275	211	MALE	PF	321.6	313.3	305.6	304.8	311.1	304.4	308.1	304.5	307.3	311.4	314.3	313.8
120-4	4275	212	MALE	EOE	310.6	304.5	301.5	296.6	300.7	294.8	302.7	293.0	295.6			
120-4	4275	213	MALE	PF	315.1	306.5	296.3	296.9	301.5	298.0	301.5	300.3	306.6	310.2	315.4	317.9
120-4	4275	214	MALE	REC	304.1	260.9	246.9	248.2	250.6	251.1	254.6	253.5	256.0	261.9	267.8	271.0
120-4	4275	215	MALE	REC	301.2	298.6	290.3	273.7	288.1	287.9	290.0	285.7	287.1	299.2	310.5	310.4
120-4	4275	216	MALE	EOE	292.4	286.0	275.1	287.3	275.8	275.3	278.4	274.9	279.2			
120-4	4275	217	MALE	REC	287.3	281.6	276.5	275.5	279.2	276.2	275.6	276.0	283.3	290.8	291.4	300.1
120-4	4275	218	MALE	REC	302.4	293.8	288.4	285.2	288.4	287.9	291.3	291.7	289.0	301.2	312.8	312.2
120-4	4275	219	MALE	REC	280.9	271.5	267.1	266.4	271.9	274.5	274.7	275.8	278.5	285.3	282.2	287.6
120-4	4275	220	MALE	PF	273.0	271.2	265.8	264.8	269.8	270.4	279.9	276.9	276.3	284.1	286.4	294.4
120-4	4275	221	MALE	EOE	277.8	271.0	266.1	265.9	267.9	267.4	271.8	269.4	270.2			
120-4	4275	222	MALE	REC	303.6	300.3	288.6	286.9	284.3	285.2	280.8	284.5	288.1	300.7	300.6	307.8
120-4	4275	223	MALE	PF	289.2	261.6	250.1	248.4	250.8	249.1	255.0	248.8	258.1	258.9	262.2	268.2
120-4	4275	224	MALE	PF	292.7	282.2	275.6	277.0	278.0	277.4	280.6	285.5	282.5	294.3	293.9	299.5
120-4	4275	225	MALE	EOE	290.1	280.8	269.6	268.5	271.3	270.8	274.9	271.7	281.6			
120-4	4275	226	MALE	EOE	275.7	264.0	259.3	259.9	258.7	255.9	262.3	259.9	268.7			
120-4	4275	227	MALE	EOE	303.7	301.2	288.3	285.8	287.2	284.0	290.1	287.1	290.4			
120-4	4275	228	MALE	PF	307.5	298.1	289.5	291.3	296.4	288.2	293.5	290.2	294.2	303.5	304.3	309.3
120-4	4275	229	MALE	REC	292.3	283.4	275.2	277.3	284.1	277.0	285.1	283.4	288.8	297.0	298.4	299.2
120-4	4275	230	MALE	EOE	322.6	309.7	298.4	301.7	300.6	298.3	302.3	295.9	298.7			
120-4	4275	231	MALE	REC	292.6	285.7	273.1	275.7	279.1	281.7	275.3	279.8	282.9	291.3	288.5	292.2
120-4	4275	232	MALE	EOE	295.9	289.5	283.6	280.7	286.0	282.8	287.5	281.1	285.9			
120-4	4275	233	MALE	REC	305.1	289.4	281.0	281.5	279.5	276.1	281.3	275.9	281.2	293.6	296.2	296.2
120-4	4275	234	MALE	REC	298.4	293.2	286.5	283.5	284.5	282.5	280.8	278.6	281.1	293.5	299.9	300.6
120-4	4275	235	MALE	EOE	276.5	274.7	265.1	267.1	270.6	273.5	275.3	272.7	268.0			
120-4	4275	236	MALE	EOE	300.9	294.6	286.1	284.2	287.5	287.4	289.5	289.3	288.9			
120-4	4275	237	MALE	EOE	299.2	290.7	282.2	279.1	284.6	284.0	286.3	284.2	283.3			
120-4	4275	238	MALE	REC	307.3	300.1	294.6	289.0	293.1	290.7	296.7	289.0	294.8	306.0	308.5	314.7
120-4	4275	239	MALE	PF	283.0	279.6	269.3	271.6	270.4	268.9	271.0	270.5	268.3	277.9	274.8	273.7
120-4	4275	240	MALE	EOE	282.8	284.3	277.7	276.6	278.6	279.6	284.2	280.3	286.3			
120-4	4275	241	MALE	REC	308.1	297.3	291.9	286.1	290.6	289.0	293.1	291.2	297.2	306.3	305.4	309.6
120-4	4275	242	MALE	PF	309.0	300.8	294.8	291.2	291.8	286.7	291.5	287.8	285.9	300.4	297.5	303.9
120-4	4275	243	MALE	PF	299.1	290.0	286.6	285.5	287.9	283.3	286.1	285.1	286.4	298.7	294.7	293.4
120-4	4275	244	MALE	EOE	298.3	298.2	287.0	283.0	282.7	284.3	285.1	290.1	284.4			

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
					DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
120-4	4275	245	MALE	EOE	297.8	292.9	287.6	285.5	287.7	285.3	288.1	278.7	280.7			
120-4	4275	246	MALE	REC	288.3	285.6	280.7	281.4	279.2	279.9	279.6	277.6	277.9	287.9	288.3	298.2
120-4	4275	247	MALE	EOE	301.0	296.6	285.5	282.3	284.0	282.3	284.6	278.6	283.4			
120-4	4275	248	MALE	PF	305.3	297.8	292.5	294.0	299.5	295.6	296.7	296.3	297.1	311.2	308.8	311.5
120-4	4275	249	MALE	REC	289.6	280.8	278.4	275.1	279.8	278.6	279.6	277.3	282.6	291.8	295.9	297.5
120-4	4275	250	MALE	REC	286.7	282.3	276.6	272.0	276.2	273.5	278.9	272.8	277.8	291.0	287.8	291.8
120-4	4275	661	FEMALE	REC	178.1	172.1	171.9	163.3	165.4	163.6	164.8	164.1	164.8	170.5	173.2	172.0
120-4	4275	662	FEMALE	REC	173.4	169.2	171.0	161.9	167.5	164.8	165.8	164.3	161.6	166.3	168.9	170.8
120-4	4275	663	FEMALE	EOE	176.6	181.9	178.5	171.8	173.1	173.8	176.4	175.2	172.7			
120-4	4275	664	FEMALE	REC	170.7	171.5	164.1	165.8	166.9	163.7	160.7	159.1	162.8			
120-4	4275	665	FEMALE	REC	180.4	172.6	170.9	166.1	168.3	168.5	167.9	166.2	166.4	169.5	172.0	172.4
120-4	4275	666	FEMALE	EOE	177.0	174.9	170.8	170.2	172.5	174.0	169.6	169.4	171.1	178.6		
120-4	4275	667	FEMALE	EOE	164.1	164.9	162.4	160.6	164.1	158.5	159.8	158.6	160.1			
120-4	4275	668	FEMALE	REC	174.5	172.0	167.7	163.8	170.7	165.8	168.9	165.6	167.3	169.6	171.0	178.4
120-4	4275	669	FEMALE	EOE	159.5	160.2	157.3	158.3	160.1	154.5	159.5	155.5	157.2			
120-4	4275	670	FEMALE	REC	173.1	167.6	163.7	162.3	166.8	167.0	170.1	165.7	169.3	176.8	176.9	181.4
120-4	4275	671	FEMALE	EOE	174.5	168.1	162.2	159.5	167.6	163.8	166.9	164.1	165.2			
120-4	4275	672	FEMALE	REC	174.7	170.0	162.4	160.1	165.3	160.7	164.2	160.7	164.2	170.3	173.3	175.8
120-4	4275	673	FEMALE	EOE	169.0	165.8	163.8	159.5	161.2	158.5	160.5	156.0	159.1			
120-4	4275	674	FEMALE	REC	173.8	173.4	166.6	163.9	165.0	162.1	166.1	163.8	164.1	167.3	172.8	174.5
120-4	4275	675	FEMALE	EOE	164.7	162.2	159.7	157.0	157.2	153.5	156.2	152.3	158.2			
120-4	4275	676	FEMALE	EOE	179.3	171.8	167.0	164.2	169.0	168.2	166.6	164.0	167.8			
120-4	4275	677	FEMALE	REC	172.8	166.9	164.1	163.4	166.9	163.7	166.8	166.4	167.2	162.8	172.4	171.5
120-4	4275	678	FEMALE	REC	163.4	165.8	160.2	160.3	159.3	159.9	162.0	158.2	160.6	165.8	164.6	166.1
120-4	4275	679	FEMALE	REC	167.6	165.4	166.2	166.4	172.3	170.0	168.3	174.5	177.0	178.4	173.4	174.3
120-4	4275	680	FEMALE	EOE	168.3	157.7	156.9	154.7	159.8	157.3	161.1	157.4	159.2			
120-4	4275	681	FEMALE	EOE	170.1	168.4	156.6	167.1	164.9	163.8	161.6	164.8	168.0			
120-4	4275	682	FEMALE	REC	175.9	176.4	167.1	166.2	167.7	164.8	168.2	165.8	166.9	175.3	177.3	180.2
120-4	4275	683	FEMALE	REC	174.7	173.1	162.5	160.8	164.7	163.2	167.9	166.0	163.5	171.0	173.8	176.2
120-4	4275	684	FEMALE	EOE	174.5	171.7	164.0	163.7	167.4	164.1	164.7	163.4	165.1			
120-4	4275	685	FEMALE	FD	178.8	169.9	168.2	166.8	170.1	167.5	168.1					
120-4	4275	686	FEMALE	EOE	179.4	175.3	169.1	170.9	174.2	169.8	174.4	171.9	175.1			
120-4	4275	687	FEMALE	EOE	175.5	178.8	174.3	173.9	173.7	169.9	171.6	167.8	172.3			
120-4	4275	688	FEMALE	REC	170.5	166.2	161.9	160.9	164.4	160.3	164.6	163.7	166.2	170.3	169.0	172.1
120-4	4275	689	FEMALE	EOE	162.6	158.9	154.3	152.8	165.2	150.4	156.9	151.3	154.8			
120-4	4275	690	FEMALE	REC	171.6	171.9	168.6	165.5	152.8	161.8	164.0	160.3	159.5	163.6	164.1	165.1
480-4	4276	251	MALE	REC	333.1	298.5	297.1	280.5	285.1	283.9	286.9	274.5	290.0	301.0	318.2	322.6
480-4	4276	252	MALE	EOE	332.5	297.3	272.5	269.7	277.8	275.1	275.6	269.0	269.5			
480-4	4276	253	MALE	EOE	328.1	292.1	291.8	283.1	288.4	284.1	281.9	277.5	281.8			
480-4	4276	254	MALE	REC	307.4	276.6	275.8	272.9	278.5	279.9	278.9	282.6	271.9	277.3	296.6	305.5
480-4	4276	255	MALE	EOE	313.6	277.8	273.4	266.8	276.3	278.1	276.4	273.3	275.0			
480-4	4276	256	MALE	REC	303.1	273.2	269.5	260.7	265.7	263.6	255.5	253.6	257.1	265.5	286.6	288.6
480-4	4276	257	MALE	REC	298.9	270.1	273.5	271.6	277.5	272.9	270.6	266.0	268.7	273.7	290.3	295.3
480-4	4276	258	MALE	EOE	309.8	268.9	267.8	261.2	264.5	263.5	263.4	270.2	275.1			
480-4	4276	259	MALE	EOE	299.8	270.4	268.7	262.4	270.6	265.6	265.5	259.7	262.7			
480-4	4276	260	MALE	REC	295.7	266.7	264.9	256.4	263.7	261.2	257.6	256.7	257.8	266.8	281.1	280.9
480-4	4276	691	FEMALE	EOE	181.6	161.4	163.5	158.5	169.3	161.1	163.7	160.0	162.8			
480-4	4276	692	FEMALE	REC	178.8	161.5	160.3	156.9	163.3	156.2	160.9	156.6	158.0	164.5	176.6	174.6
480-4	4276	693	FEMALE	FD	183.2	167.7	163.1	161.7	167.4	161.3						
480-4	4276	694	FEMALE	EOE	169.6	146.0	147.5	144.5	153.6	150.2	154.1	143.9	154.7			
480-4	4276	695	FEMALE	EOE	179.2	155.3	147.2	148.8	162.8	153.2	160.5	150.8	158.7			

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
					DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
480-4	4276	696	FEMALE	REC	179.7	161.1	158.0	157.2	167.3	169.1	170.8	163.5	169.2	170.6	181.3	184.2
480-4	4276	697	FEMALE	EOE	182.1	167.1	165.7	159.9	163.4	159.4	166.6	157.5	161.2			
480-4	4276	698	FEMALE	REC	180.1	159.2	158.9	155.6	158.9	155.4	156.7	154.3	154.7	160.2	170.3	171.1
480-4	4276	699	FEMALE	EOE	169.9	152.6	153.6	149.6	155.9	155.6	160.5	154.8	157.0			
480-4	4276	700	FEMALE	REC	176.4	156.0	154.5	153.4	159.1	154.3	163.4	152.6	156.9	162.4	170.7	170.3
SHAM	4277	261	MALE	PF	329.4	306.7	292.3	294.5	305.8	297.0	302.3	290.5		293.6	312.2	315.3
SHAM	4277	262	MALE	PF	326.8	311.9	310.8	297.7	310.5	305.7	310.4	302.1		301.4	316.8	320.5
SHAM	4277	263	MALE	PF	333.3	323.2	318.6	308.8	317.6	313.6	315.1	301.7		306.1	325.1	326.4
SHAM	4277	264	MALE	REC	327.1	316.2	310.9	306.0	312.7	308.5	306.4	299.8	310.3	308.4	327.9	324.6
SHAM	4277	265	MALE	PF	323.6	303.3	295.1	301.1	311.9	304.3	312.6	302.8		301.2	322.3	322.0
SHAM	4277	266	MALE	EOE	317.3	307.1	302.3	297.3	301.4	298.6	299.8	287.7	294.9			
SHAM	4277	267	MALE	EOE	300.9	288.4	285.8	273.9	285.3	280.0	285.9	278.5	285.4			
SHAM	4277	268	MALE	EOE	318.0	307.4	308.9	300.3	309.4	302.2	306.7	298.3	301.4			
SHAM	4277	269	MALE	PF	299.8	275.9	263.9	269.1	282.6	280.4	287.5	276.4		279.8	289.4	300.0
SHAM	4277	270	MALE	EOE	286.4	281.0	276.6	269.4	278.0	276.5	275.4	271.4	273.3			
SHAM	4277	271	MALE	REC	295.5	283.6	277.1	276.2	283.3	279.5	285.6	275.6	279.2	279.6	294.2	296.8
SHAM	4277	272	MALE	EOE	312.3	301.9	295.9	290.1	297.6	293.1	300.5	289.5	292.0			
SHAM	4277	273	MALE	REC	297.5	287.2	283.9	280.1	289.2	287.9	293.0	284.5	292.1	290.9	280.9	261.9
SHAM	4277	274	MALE	REC	306.9	295.6	290.3	285.0	295.4	291.3	291.3	285.2	292.8	295.4	309.2	312.5
SHAM	4277	275	MALE	REC	299.9	289.4	289.6	279.6	289.6	289.1	292.1	279.9	285.2	288.4	297.7	300.7
SHAM	4277	276	MALE	FD	287.0											
SHAM	4277	277	MALE	REC	306.9	301.5	291.5	285.8	291.7	286.6	289.5	285.3	287.0	289.9	301.3	307.1
SHAM	4277	278	MALE	PF	321.1	304.4	298.7	297.9	303.2	301.7	307.4	294.3	305.8	305.0	315.7	316.8
SHAM	4277	279	MALE	EOE	309.5	300.4	300.9	294.0	301.9	301.8	304.8	293.4	304.2			
SHAM	4277	280	MALE	REC	306.2	322.4	318.0	309.9	314.4	307.8	316.8	310.6	316.0	315.7	330.6	330.0
SHAM	4277	281	MALE	EOE	336.0	298.8	293.8	285.5	286.6	282.4	287.7	282.8	285.8			
SHAM	4277	282	MALE	REC	305.5	293.6	291.8	291.4	298.2	296.2	295.7	295.4	301.2	297.9	320.9	317.4
SHAM	4277	283	MALE	REC	311.7	305.4	301.7	297.9	304.0	297.9	303.4	292.6	299.2	302.6	318.6	312.1
SHAM	4277	284	MALE	PF	305.3	302.3	297.8	289.9	295.9	294.2	297.2	289.0	291.7	291.0	302.0	301.2
SHAM	4277	285	MALE	REC	288.3	279.9	279.6	277.3	286.5	283.3	288.5	282.2	284.1	285.8	301.0	295.3
SHAM	4277	286	MALE	REC	311.7	299.4	295.3	287.4	292.4	286.2	286.5	280.6	282.1	284.7	299.0	304.8
SHAM	4277	287	MALE	EOE	313.5	303.6	305.1	296.1	306.6	301.1	301.3	297.0	300.4			
SHAM	4277	288	MALE	PF	314.8	308.4	304.9	299.9	308.6	304.9	309.3	304.5	308.2	311.0	322.2	320.1
SHAM	4277	289	MALE	REC	292.5	281.8	277.2	272.2	279.1	266.9	273.7	268.7	269.8	270.7	292.2	291.3
SHAM	4277	290	MALE	EOE	299.5	290.7	287.1	284.8	288.1	284.4	288.1	279.8	290.5			
SHAM	4277	291	MALE	EOE	324.7	312.5	306.6	299.7	302.5	297.3	298.5	295.8	301.0			
SHAM	4277	292	MALE	EOE	322.8	313.7	312.9	304.3	311.4	306.0	309.5	302.2	305.9			
SHAM	4277	293	MALE	REC	315.9	306.1	299.4	291.9	301.9	299.9	300.9	294.1	300.8	298.1	313.5	320.1
SHAM	4277	294	MALE	EOE	311.6	302.5	305.4	297.7	303.0	298.1	299.2	290.7	293.2			
SHAM	4277	295	MALE	PF	317.5	297.7	307.9	300.3	304.7	297.7	300.7	299.9	303.8	305.0	317.7	315.3
SHAM	4277	296	MALE	REC	310.4	305.4	300.1	297.3	303.3	300.0	301.2	296.1	302.4	303.0	319.1	312.8
SHAM	4277	297	MALE	REC	320.6	304.1	299.3	295.9	305.3	300.0	304.2	299.1	302.6	305.8	322.3	323.5
SHAM	4277	298	MALE	EOE	320.8	305.7	311.3	299.4	306.2	303.3	311.5	301.8	303.6			
SHAM	4277	299	MALE	PF	299.8	289.0	288.0	279.5	287.7	284.1	291.1	284.1	287.9	287.0	289.9	289.5
SHAM	4277	300	MALE	EOE	296.5	285.8	287.0	279.5	283.3	278.5	282.8	279.7	285.9			
SHAM	4277	701	FEMALE	EOE	181.2	173.5	182.7	174.2	179.8	174.8	177.3	172.8	174.8			
SHAM	4277	702	FEMALE	EOE	176.5	170.1	169.9	167.4	173.1	170.3	170.3	166.1	170.1			
SHAM	4277	703	FEMALE	REC	181.7	174.4	180.3	170.3	179.6	176.0	177.5	173.2	176.7	171.7	185.3	182.7
SHAM	4277	704	FEMALE	REC	176.0	168.7	176.2	166.8	173.1	170.1	170.8	167.5	171.5	171.7	181.2	181.8
SHAM	4277	705	FEMALE	EOE	180.5	171.6	175.8	166.5	175.4	171.4	172.2	167.6	170.8			
SHAM	4277	706	FEMALE	REC	184.1	168.3	175.7	164.2	170.0	168.6	169.7	166.6	169.2	173.5	182.1	178.0

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	DAY OF STUDY RELATIVE TO THE FIRST DAY OF INHALATION EXPOSURES TO Cu-Zn ALLOY POWDER											
					DAY-1	DAY 2	DAY 6	DAY 9	DAY 13	DAY 16	DAY 20	DAY 23	DAY 27	DAY 30	DAY 34	DAY 37
SHAM	4277	707	FEMALE	REC	178.0	170.1	177.0	171.2	174.0	169.8	171.2	168.3	169.6	171.8	179.1	180.8
SHAM	4277	708	FEMALE	REC	176.6	168.4	176.3	167.3	173.3	168.5	173.0	167.3	161.3	175.1	'184.9	183.6
SHAM	4277	709	FEMALE	EOE	167.9	160.2	167.9	160.8	166.0	162.8	165.9	161.1	171.8			
SHAM	4277	710	FEMALE	REC	178.8	169.5	172.7	170.2	174.3	169.6	170.9	168.5	172.5	174.7	182.0	178.8
SHAM	4277	711	FEMALE	REC	187.4	179.8	184.7	176.7	183.5	177.3	181.1	175.0	180.4	181.3	192.9	193.4
SHAM	4277	712	FEMALE	EOE	175.1	165.8	168.7	162.6	168.4	164.4	163.4	163.1	164.9			
SHAM	4277	713	FEMALE	EOE	173.1	167.7	172.0	165.4	169.4	166.1	164.6	165.4	163.5			
SHAM	4277	714	FEMALE	EOE	178.4	170.6	174.3	169.3	173.7	169.7	173.5	168.4	172.2			
SHAM	4277	715	FEMALE	EOE	173.2	161.2	166.4	160.8	167.6	163.4	163.4	158.8	164.2			
SHAM	4277	716	FEMALE	FD	183.8											
SHAM	4277	717	FEMALE	EOE	180.3	174.5	178.2	168.3	178.1	173.0	173.0	167.8	171.2			
SHAM	4277	718	FEMALE	EOE	173.6	163.8	163.1	160.3	165.5	160.2	165.1	157.2	162.9			
SHAM	4277	719	FEMALE	EOE	173.8	164.8	168.2	165.4	168.1	163.7	164.1	162.3	165.4			
SHAM	4277	720	FEMALE	REC	176.5	168.7	169.7	166.2	170.0	163.2	167.2	161.7	165.4	165.7	171.3	168.9
SHAM	4277	721	FEMALE	EOE	176.9	167.1	173.1	170.3	172.5	168.7	169.2	167.6	168.1			
SHAM	4277	722	FEMALE	REC	179.9	171.4	178.0	171.4	175.1	169.9	171.0	169.0	171.8	174.4	180.4	177.3
SHAM	4277	723	FEMALE	EOE	177.5	168.6	175.3	171.3	174.5	171.5	175.0	170.9	172.4			
SHAM	4277	724	FEMALE	REC	176.0	167.8	173.2	168.0	172.3	168.6	170.1	168.4	168.0	171.6	179.0	181.5
SHAM	4277	725	FEMALE	REC	180.6	170.8	177.0	168.5	177.6	170.8	175.6	174.1	174.6	176.0	185.4	180.3
SHAM	4277	726	FEMALE	REC	183.1	178.2	182.1	179.1	182.8	179.1	178.4	177.0	175.5	177.9	188.0	184.4
SHAM	4277	727	FEMALE	EOE	186.8	178.5	180.7	177.0	183.9	180.0	182.8	178.8	184.0			
SHAM	4277	728	FEMALE	REC	173.1	164.7	170.7	168.4	172.3	166.1	167.1	165.9	168.3	174.1	179.1	176.8
SHAM	4277	729	FEMALE	EOE	172.9	159.9	163.1	161.4	166.0	162.3	166.3	161.9	166.5			
SHAM	4277	730	FEMALE	REC	178.0	173.8	176.1	162.9	171.2	166.9	167.7	167.5	168.8	174.3	181.2	178.5

D. APPENDIX D: ENDPOINT EVALUATION RESULTS FOR INDIVIDUAL ANIMALS

PART 1. BOD[illegible]HTS, ORGAN WEIGHTS, MACROPHAGE ACTIVITY, AND IMMUNE RESPONSE DATA

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	SBWT (GRAMS)	LUNG (GRAMS)	KIDNEYS (GRAMS)	LIVER (GRAMS)	SPLEEN (GRAMS)	THYMUS (GRAMS)	EA/100 CELLS	TOTAL CELLS	AFC	TOTAL AFC
30-2	4269	001	MALE	REC	335.5	1.300	2.500	11.131						
30-2	4269	002	MALE	REC	328.6	1.425	2.260	9.048						
30-2	4269	003	MALE	EOE	309.6	1.268	2.138	10.958						
30-2	4269	004	MALE	EOE	213.5	1.531	2.027	10.215						
30-2	4269	005	MALE	EOE	303.5	1.480	2.124	9.990						
30-2	4269	006	MALE	REC	297.6	1.230	2.043	8.973						
30-2	4269	007	MALE	REC	298.6	1.250	1.997	8.358						
30-2	4269	008	MALE	EOE	306.4	1.360	2.219	9.343						
30-2	4269	009	MALE	EOE	294.4	1.305	2.049	9.372						
30-2	4269	010	MALE	REC	316.3	1.134	2.038	9.535						
30-2	4269	501	FEMALE	EOE	179.0	1.130	1.377	5.414						
30-2	4269	502	FEMALE	REC	184.3	0.904	1.284	4.725						
30-2	4269	503	FEMALE	EOE	171.2	1.101	1.226	4.916						
30-2	4269	504	FEMALE	EOE		0.932	1.173	4.792						
30-2	4269	505	FEMALE	REC	179.5	0.888	1.292	4.593						
30-2	4269	506	FEMALE	REC	177.3	1.043	1.352	4.874						
30-2	4269	507	FEMALE	EOE	183.2	1.191	1.307	6.245						
30-2	4269	508	FEMALE	REC	176.9	0.895	1.290	5.213						
30-2	4269	509	FEMALE	EOE	162.3	0.914	1.210	4.877						
30-2	4269	510	FEMALE	REC	177.4	0.968	1.344	5.673						
120-2	4270	011	MALE	EOE	315.0	1.610								
120-2	4270	012	MALE	REC	332.1	1.471	2.144	10.383						
120-2	4270	016	MALE	EOE	284.1	1.220	1.967	9.160						
120-2	4270	018	MALE	REC	322.4	1.373	2.284	11.209						
120-2	4270	019	MALE	REC	306.6	1.680					589			
120-2	4270	020	MALE	REC	299.0	1.120	2.240	10.150	0.592	0.182		18.4	1277.2	23500
120-2	4270	021	MALE	EOE	276.0	1.440					762			
120-2	4270	022	MALE	REC	305.0				0.601	0.230		11.9	940.7	11194
120-2	4270	023	MALE	REC	304.3	1.321	2.063	10.087						
120-2	4270	024	MALE	EOE	290.1	1.370					737			
120-2	4270	025	MALE	REC	273.0	1.080	2.010	7.930	0.529	0.133		8.9	1373.3	12222
120-2	4270	026	MALE	REC	285.6	1.260								
120-2	4270	027	MALE	REC	307.3	1.370					488			
120-2	4270	029	MALE	EOE	285.0	1.110	1.960	9.890	0.584	0.191		9.2	221.6	2028
120-2	4270	030	MALE	EOE	296.0	1.190	2.290	10.290	0.600	0.233		17.5	139.3	2437
120-2	4270	033	MALE	REC	323.0	1.456	2.051	11.112						
120-2	4270	034	MALE	REC	317.0	1.400					518			
120-2	4270	035	MALE	REC	298.6	1.192	2.006	9.721						
120-2	4270	036	MALE	EOE	388.0				0.613	0.193		7.8	636.2	4962
120-2	4270	037	MALE	EOE	295.8	1.619	2.203	10.463						
120-2	4270	039	MALE	EOE	283.5	1.480								
120-2	4270	040	MALE	EOE	289.6	1.320	2.158	9.530						
120-2	4270	041	MALE	REC	328.0	1.410					405			
120-2	4270	042	MALE	REC	331.0	1.410								
120-2	4270	044	MALE	EOE	290.6	1.359	2.250	9.728						
120-2	4270	045	MALE	EOE	295.3	1.610					1014			
120-2	4270	046	MALE	EOE	289.0	1.190	1.990	10.060	0.611	0.166		26.5	151.2	4008

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120-2	4270	047	MALE	EOE	295.0	1.600								
120-2	4270	048	MALE	REC	326.0	1.150	2.250	10.520	0.648	0.194		6.9	338.2	2333
120-2	4270	050	MALE	EOE	282.8	1.359	1.938	9.320						
120-2	4270	511	FEMALE	EOE	166.0				0.409	0.140		11.8	900.7	10628
120-2	4270	512	FEMALE	EOE	164.2	1.089	1.343	4.772						
120-2	4270	513	FEMALE	EOE	171.9	1.090	1.258	5.058						
120-2	4270	514	FEMALE	REC	176.3	0.940					493			
120-2	4270	515	FEMALE	EOE	165.0	1.150								
120-2	4270	516	FEMALE	EOE	172.0	1.020	1.270	4.930	0.381	0.161		43.0	75.6	3250
120-2	4270	517	FEMALE	REC	168.8	0.883	1.048	4.382						
120-2	4270	518	FEMALE	REC	181.0	1.000					596			
120-2	4270	519	FEMALE	REC	170.0	0.810	1.180	4.870	0.407	0.189		20.5	218.2	4472
120-2	4270	520	FEMALE	REC	174.0	0.810	1.170	4.620	0.369	0.152		7.0	496.0	3472
120-2	4270	521	FEMALE	REC	183.0	0.980					609			
120-2	4270	522	FEMALE	REC	175.0	0.830	1.260	4.780	0.419	0.182		16.5	601.0	9917
120-2	4270	523	FEMALE	EOE	158.2	1.021	1.158	5.034						
120-2	4270	524	FEMALE	REC	181.4	0.970					511			
120-2	4270	525	FEMALE	REC	155.5		0.987	3.645						
120-2	4270	526	FEMALE	EOE	168.7	1.057	1.231	5.295						
120-2	4270	527	FEMALE	EOE	169.0	1.190					815			
120-2	4270	528	FEMALE	EOE	159.6	1.150								
120-2	4270	529	FEMALE	REC	168.2	0.910	1.105	4.305						
120-2	4270	530	FEMALE	REC	171.1	0.927	1.111	4.624						
120-2	4270	531	FEMALE	REC	176.2	0.942	1.136	4.666						
120-2	4270	532	FEMALE	REC	182.0				0.425	0.193		12.1	293.9	3555
120-2	4270	533	FEMALE	EOE	169.0	0.910	1.240	5.180	0.406	0.141		26.5	613.8	16267
120-2	4270	534	FEMALE	EOE	167.0	1.000					708			
120-2	4270	535	FEMALE	REC	182.0	0.980								
120-2	4270	536	FEMALE	EOE	178.4	1.180					796			
120-2	4270	537	FEMALE	EOE	173.9	1.100								
120-2	4270	538	FEMALE	REC	165.2	0.960								
120-2	4270	539	FEMALE	EOE	159.0	0.960	1.220	4.920	0.402	0.153		15.6	1062.3	16572
120-2	4270	540	FEMALE	EOE	164.7	1.250	1.199	4.787						
60-2	4271	051	MALE	EOE	307.0	1.200	2.130	10.090	0.616	0.240				
60-2	4271	052	MALE	EOE	307.6	1.436	2.139	9.823						
60-2	4271	053	MALE	EOE	304.0	1.400					791			
60-2	4271	054	MALE	REC	348.2	1.490								
60-2	4271	055	MALE	EOE	298.5	1.304	2.020	9.680						
60-2	4271	056	MALE	EOE	289.9	1.347	1.903	8.763						
60-2	4271	058	MALE	REC	337.0	1.600								
60-2	4271	060	MALE	REC	307.8	1.205	2.061	10.184						
60-2	4271	061	MALE	REC	300.0	1.010	2.100	8.880	0.610	0.210		12.6	425.5	5361
60-2	4271	062	MALE	EOE	309.4	1.341	2.118	10.397						
60-2	4271	063	MALE	EOE	300.0	1.150	2.170	9.420	0.624	0.185		26.5	328.6	8708
60-2	4271	064	MALE	EOE	298.1	1.480					574			
60-2	4271	065	MALE	REC	310.0	1.500					495			
60-2	4271	066	MALE	REC	301.0	0.980	2.020	9.470	0.615	0.245		11.5	256.0	2944
60-2	4271	067	MALE	EOE	292.0				0.644	0.158		18.2	187.5	3412
60-2	4271	069	MALE	REC	317.6	1.350	2.061	10.089						
60-2	4271	071	MALE	REC	321.9	1.323	2.048	11.097						
60-2	4271	072	MALE	EOE	305.8	1.410								
60-2	4271	073	MALE	EOE	294.7	1.281	2.018	9.728						
60-2	4271	077	MALE	EOE	295.9	1.430					675			

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60-2	4271	079	MALE	REC	304.3	1.050					482			
60-2	4271	080	MALE	REC	313.0	1.280					519			
60-2	4271	081	MALE	REC	337.8	1.415	2.180	12.162						
60-2	4271	082	MALE	EOE	309.0	1.430					771			
60-2	4271	083	MALE	EOE	305.0	1.160	2.230	10.010	0.665	0.212		20.1	290.3	5834
60-2	4271	084	MALE	REC	318.5	1.295	2.002	10.211						
60-2	4271	085	MALE	REC	327.6	1.390								
60-2	4271	086	MALE	REC	307.0	1.080	2.190	10.160	0.605	0.211		18.1	669.1	12111
60-2	4271	088	MALE	EOE	301.0	1.340								
60-2	4271	090	MALE	FD										
60-2	4271	541	FEMALE	REC	184.0	0.850	1.300	5.610	0.427	0.183		18.7	1143.8	21389
60-2	4271	542	FEMALE	REC	183.0									
60-2	4271	543	FEMALE	EOE	173.0	1.080					933			
60-2	4271	544	FEMALE	REC	179.0	0.890					736			
60-2	4271	545	FEMALE	EOE	170.8	0.980								
60-2	4271	546	FEMALE	REC	185.0	0.911	1.345	5.653						
60-2	4271	547	FEMALE	REC	182.4	1.150					907			
60-2	4271	548	FEMALE	REC	189.6	1.016	1.281	5.671						
60-2	4271	549	FEMALE	REC	183.8	0.911	1.293	5.515						
60-2	4271	550	FEMALE	EOE	165.2	0.980	1.215	5.209						
60-2	4271	551	FEMALE	REC	182.0	0.900								
60-2	4271	552	FEMALE	EOE	171.0	0.790	1.240	5.420	0.365	0.132		15.3	332.4	5086
60-2	4271	553	FEMALE	EOE	164.9	1.043	1.226	4.507						
60-2	4271	554	FEMALE	EOE	168.0	0.780	1.200	4.890	0.382	0.180		8.4	287.7	2417
60-2	4271	555	FEMALE	FD	158.5	1.617	1.455	7.727						
60-2	4271	556	FEMALE	REC	189.5	0.970								
60-2	4271	557	FEMALE	EOE	170.0	1.060					1031			
60-2	4271	558	FEMALE	EOE	167.0	1.070								
60-2	4271	559	FEMALE	REC	178.4	0.850					791			
60-2	4271	560	FEMALE	EOE	160.7	0.975	1.241	4.732						
60-2	4271	561	FEMALE	EOE	182.0	0.830	1.280	5.510	0.426	0.180				
60-2	4271	562	FEMALE	EOE	168.6	1.060					959			
60-2	4271	563	FEMALE	EOE	172.6	1.050					941			
60-2	4271	564	FEMALE	EOE	155.7	0.931	1.150	4.082						
60-2	4271	565	FEMALE	REC	180.0	0.840	1.260	5.400	0.401	0.227		11.3	693.2	7833
60-2	4271	566	FEMALE	REC	183.0	0.810	1.230	5.070	0.403	0.211		11.1	22.5	250
60-2	4271	567	FEMALE	EOE	170.9	0.984	1.370	5.065						
60-2	4271	568	FEMALE	REC	176.7	0.952	1.234	5.202						
60-2	4271	569	FEMALE	REC	170.0	0.910					631			
60-2	4271	570	FEMALE	REC	184.6	1.166	1.256	5.182						
240-2	4272	091	MALE	REC	319.6	1.445	2.136	9.687						
240-2	4272	093	MALE	EOE	303.0	1.670	1.870	10.480	0.600	0.184		53.9	244.0	13151
240-2	4272	094	MALE	REC	308.9		1.955	9.077						
240-2	4272	095	MALE	REC	312.0	1.690								
240-2	4272	096	MALE	EOE	276.0	1.670					483			
240-2	4272	097	MALE	REC	293.1		2.210	9.503						
240-2	4272	099	MALE	REC	280.0	1.410					478			
240-2	4272	100	MALE	REC	290.7	1.328	1.948	9.098						
240-2	4272	101	MALE	REC	304.6	1.590					570			
240-2	4272	102	MALE	REC	298.0	1.210	1.960	9.350	0.602	0.185		17.6	211.5	3722
240-2	4272	104	MALE	EOE	290.0	1.330	1.910	9.010	0.585	0.172		33.3	157.0	5228
240-2	4272	105	MALE	REC	297.0	1.160	2.160	9.770	0.601	0.102		11.2	816.0	9139
240-2	4272	106	MALE	REC	291.2	1.590								

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240-2	4272	107	MALE	EOE	286.0	1.730					662			
240-2	4272	108	MALE	EOE	294.6	1.769	1.971	8.695						
240-2	4272	109	MALE	EOE	284.0	1.780					528			
240-2	4272	110	MALE	EOE	303.1	1.581	1.956	10.293						
240-2	4272	111	MALE	REC	295.4	1.182	2.059	9.077						
240-2	4272	112	MALE	EOE	289.0	1.720								
240-2	4272	113	MALE	EOE	296.0	1.550	2.170	10.520	0.607	0.138		48.5	246.0	11931
240-2	4272	115	MALE	EOE	268.9	1.740								
240-2	4272	116	MALE	EOE	266.1	1.602	2.020	8.778						
240-2	4272	119	MALE	REC	290.0	1.090	1.930	9.170	0.564	0.185		14.1	145.8	2056
240-2	4272	120	MALE	REC	306.0	1.660					425			
240-2	4272	121	MALE	EOE	282.7	1.649	1.984	9.500						
240-2	4272	122	MALE	REC	322.0				0.620	0.206		19.1	37.8	722
240-2	4272	123	MALE	REC	319.1	1.760					501			
240-2	4272	124	MALE	EOE	279.6	1.540					527			
240-2	4272	125	MALE	EOE	293.0				0.616	0.177		45.1	134.9	6083
240-2	4272	126	MALE	EOE	266.1	1.580	1.844	8.023						
240-2	4272	571	FEMALE	REC	176.1	1.153	1.161	4.266						
240-2	4272	572	FEMALE	EOE	159.1	1.370								
240-2	4272	573	FEMALE	EOE	164.8	1.239	1.278	4.945						
240-2	4272	574	FEMALE	EOE	169.0	1.130	1.170	4.840	0.376	0.161		25.5	372.6	9500
240-2	4272	575	FEMALE	EOE	166.7	1.068	1.212	4.812						
240-2	4272	576	FEMALE	REC	186.0	1.130								
240-2	4272	577	FEMALE	EOE	161.0	1.250					561			
240-2	4272	578	FEMALE	FD	152.3	2.115	1.443	7.087						
240-2	4272	579	FEMALE	EOE	169.0	1.170	1.110	4.800	0.385	0.139		33.7	591.5	19932
240-2	4272	580	FEMALE	REC	185.5	1.190					301			
240-2	4272	581	FEMALE	EOE	173.0	1.440					800			
240-2	4272	582	FEMALE	EOE	159.0	0.970	1.010	4.420	0.365	0.137		24.2	11.5	278
240-2	4272	583	FEMALE	EOE	159.9	1.156	1.272	4.723						
240-2	4272	584	FEMALE	REC	177.0	1.100					325			
240-2	4272	585	FEMALE	REC	168.1		1.298	4.324						
240-2	4272	586	FEMALE	REC	176.9	1.112	1.208	4.843						
240-2	4272	587	FEMALE	REC	179.5	0.855	1.397	4.937						
240-2	4272	588	FEMALE	REC	174.1	1.170								
240-2	4272	589	FEMALE	EOE	167.3	1.347	1.215	5.640						
240-2	4272	590	FEMALE	REC	167.0	0.900	1.210	4.810	0.370	0.170		20.0	45.8	917
240-2	4272	591	FEMALE	REC	172.1	1.021	1.200	4.197						
240-2	4272	592	FEMALE	REC	185.0				0.428	0.189		16.0	505.2	8083
240-2	4272	593	FEMALE	EOE	163.2	1.320					513			
240-2	4272	594	FEMALE	REC	184.0	0.970					399			
240-2	4272	595	FEMALE	EOE	164.0	1.320								
240-2	4272	596	FEMALE	REC	182.0	0.950	1.200	5.050	0.416	0.182		17.5	6.4	111
240-2	4272	597	FEMALE	REC	178.1	1.190					599			
240-2	4272	598	FEMALE	EOE	168.9	1.320					604			
240-2	4272	599	FEMALE	REC	172.0	0.900	1.210	5.150	0.306	0.188		15.4	36.1	556
240-2	4272	600	FEMALE	EOE	174.1	1.145	1.399	5.465						
60-4	4273	131	MALE	EOE	315.0	1.670								
60-4	4273	132	MALE	REC	336.6	1.385	2.234	11.263						
60-4	4273	133	MALE	REC	324.3	1.510					602			
60-4	4273	134	MALE	REC	330.0				0.664	0.230		16.0	2260.4	36167
60-4	4273	135	MALE	REC	325.0	1.130	2.220	10.480	0.677	0.183		15.8	233.8	3694
60-4	4273	136	MALE	EOE	292.1	1.393	2.102	9.694						

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60-4	4273	139	MALE	EOE	284.8	1.316	1.885	9.012						
60-4	4273	140	MALE	REC	316.0	1.500					466			
60-4	4273	141	MALE	REC	304.4	1.380					572			
60-4	4273	142	MALE	EOE	299.0	1.180	2.110	9.860						
60-4	4273	143	MALE	REC	320.0	1.220	2.300	9.980	0.694	0.159		15.4	501.4	7722
60-4	4273	144	MALE	REC	329.4	1.339	2.251	10.223						
60-4	4273	145	MALE	REC	308.0	1.160	2.200	9.910	0.655	0.227		12.2	257.3	3139
60-4	4273	147	MALE	REC	336.4	1.420								
60-4	4273	148	MALE	REC	351.5	1.190	2.207	11.662						
60-4	4273	149	MALE	EOE	290.9	1.266	2.015	9.306						
60-4	4273	150	MALE	EOE	321.0	1.210	2.120	10.590	0.608	0.114		37.7	71.9	2712
60-4	4273	151	MALE	EOE	303.3	1.320								
60-4	4273	152	MALE	REC	330.2	1.470	2.154	10.251						
60-4	4273	154	MALE	EOE	302.0									
60-4	4273	156	MALE	REC	324.0	1.460					634			
60-4	4273	157	MALE	REC	331.0	1.520								
60-4	4273	159	MALE	EOE	272.9	1.460					543			
60-4	4273	160	MALE	REC	312.0	1.406	2.065	9.299						
60-4	4273	162	MALE	EOE	308.0	1.540					562			
60-4	4273	163	MALE	EOE	303.8	1.684	2.084	9.602						
60-4	4273	164	MALE	EOE	295.0	1.450					615			
60-4	4273	166	MALE	EOE	297.1	1.303	1.928	9.596						
60-4	4273	167	MALE	EOE	305.0	1.200	2.010	10.010	0.645	0.153		47.2	257.5	12153
60-4	4273	170	MALE	EOE	293.2	1.500					758			
60-4	4273	601	FEMALE	REC	194.9	1.310								
60-4	4273	602	FEMALE	EOE	169.9	1.064	1.306	4.871						
60-4	4273	603	FEMALE	FD	204.3	1.412	1.532	7.549						
60-4	4273	604	FEMALE	EOE	167.9	0.965	1.213	5.247						
60-4	4273	605	FEMALE	EOE	168.0	1.020					547			
60-4	4273	606	FEMALE	EOE	168.2	1.054	1.249	5.162						
60-4	4273	607	FEMALE	EOE	169.0	0.910	1.120	4.870	0.389	0.136		27.7	36.2	1002
60-4	4273	608	FEMALE	EOE	172.1	1.078	1.145	4.857						
60-4	4273	609	FEMALE	EOE	164.7	1.110								
60-4	4273	610	FEMALE	REC	180.0	1.080								
60-4	4273	611	FEMALE	REC	191.7	1.210					579			
60-4	4273	612	FEMALE	REC	180.0	0.930	1.280	5.720	0.404	0.205		11.9	557.9	6639
60-4	4273	613	FEMALE	REC	186.7	1.190					198			
60-4	4273	614	FEMALE	REC	184.0	1.070					807			
60-4	4273	615	FEMALE	EOE	161.0	1.210								
60-4	4273	616	FEMALE	REC	182.0		1.153	4.713						
60-4	4273	617	FEMALE	EOE	176.5	1.075	1.218	5.214						
60-4	4273	618	FEMALE	REC	179.1	0.918	1.223	5.148						
60-4	4273	619	FEMALE	REC	182.0	0.870	1.280	4.990	0.402	0.210		6.8	477.9	3250
60-4	4273	620	FEMALE	REC	178.0	1.020					599			
60-4	4273	621	FEMALE	EOE	170.0	0.910	1.200	4.940	0.400	0.153		23.3	233.0	5428
60-4	4273	622	FEMALE	REC	181.0	0.887	1.317	4.795						
60-4	4273	623	FEMALE	REC	178.0	0.880	1.410	5.890	0.456	0.179		19.5	320.5	6250
60-4	4273	624	FEMALE	EOE	171.0				0.377	0.160		34.3	199.5	6843
60-4	4273	625	FEMALE	EOE	172.0	1.300					599			
60-4	4273	626	FEMALE	REC	183.5		1.285	5.051						
60-4	4273	627	FEMALE	EOE	175.0	1.420					600			
60-4	4273	628	FEMALE	REC	175.0		1.347	4.472						
60-4	4273	629	FEMALE	EOE	168.0	0.890	1.220	5.020	0.381	0.191		11.0	311.5	6542

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60-4	4273	630	FEMALE	EOE	173.6	1.180					670			
240-4	4274	171	MALE	REC	337.1	1.430								
240-4	4274	172	MALE	REC	320.1	1.390					588			
240-4	4274	173	MALE	REC	322.9	1.573	2.151	10.375						
240-4	4274	174	MALE	REC	318.0	1.508	2.177	10.106						
240-4	4274	175	MALE	REC	312.6	1.519	2.160	9.420						
240-4	4274	176	MALE	REC	312.0	1.720								
240-4	4274	177	MALE	REC	310.0	1.770								
240-4	4274	178	MALE	EOE	290.0	2.110					437			
240-4	4274	180	MALE	REC	302.9	1.330					468			
240-4	4274	181	MALE	REC	298.1	1.460	2.098	9.163						
240-4	4274	183	MALE	EOE	286.4	1.749	2.139	9.577						
240-4	4274	184	MALE	EOE	281.6	1.622	1.929	8.900						
240-4	4274	185	MALE	EOE	279.7	1.940								
240-4	4274	186	MALE	EOE	266.0	1.870								
240-4	4274	189	MALE	EOE	279.3	1.511	1.887	9.253						
240-4	4274	190	MALE	EOE	289.0	1.760	2.190	10.050	0.611	0.165			23.0	5807
240-4	4274	192	MALE	REC	316.0	1.560					403			
240-4	4274	193	MALE	EOE	293.8	1.740					381			
240-4	4274	195	MALE	REC	297.0	1.140	2.100	9.030	0.590	0.225		12.5	455.6	5694
240-4	4274	196	MALE	EOE	284.0				0.557	0.196		49.6	544.4	27000
240-4	4274	197	MALE	REC	300.0				0.623	0.195		24.8	859.1	21306
240-4	4274	198	MALE	EOE	288.9	1.760	2.053	9.789						
240-4	4274	199	MALE	REC	289.0	1.180	1.980	9.700	0.764	0.226		22.7	63.6	1444
240-4	4274	200	MALE	REC	294.0	1.240	2.060	9.780	0.565	0.222		18.6	204.6	3806
240-4	4274	202	MALE	EOE	288.2	1.760					560			
240-4	4274	205	MALE	EOE	284.1	1.862	1.926	9.963						
240-4	4274	206	MALE	EOE	284.0	1.360	2.030	9.170	0.576	0.193		47.5	128.8	6118
240-4	4274	208	MALE	EOE	290.0	1.950					371			
240-4	4274	209	MALE	REC	292.3	1.361	1.933	9.450						
240-4	4274	210	MALE	EOE	278.0	1.480	2.120	9.500	0.621	0.165		25.0	78.5	1962
240-4	4274	631	FEMALE	REC	189.1	1.200	1.273	5.224						
240-4	4274	632	FEMALE	REC	177.0	0.900	1.220	4.990	0.375	0.195		18.4	43.8	806
240-4	4274	633	FEMALE	REC	179.6	1.129	1.184	4.431						
240-4	4274	634	FEMALE	REC	177.0	1.110					561			
240-4	4274	635	FEMALE	EOE	169.5	1.330					426			
240-4	4274	636	FEMALE	REC	187.6	1.000								
240-4	4274	637	FEMALE	REC	169.3	1.029	1.213	4.584						
240-4	4274	638	FEMALE	EOE		1.377	1.245	4.466						
240-4	4274	639	FEMALE	REC	167.6	1.132	1.225	4.849						
240-4	4274	640	FEMALE	REC	174.0	0.950	1.290	5.060	0.394	0.168		16.9	154.5	2611
240-4	4274	641	FEMALE	REC	187.0	1.040	1.320	5.200	0.432	0.226		12.1	92.2	1115
240-4	4274	642	FEMALE	REC	172.3	1.080	1.113	4.856						
240-4	4274	643	FEMALE	EOE	150.0	1.220	1.230	5.170						
240-4	4274	644	FEMALE	EOE	158.5	1.393	1.338	4.884						
240-4	4274	645	FEMALE	REC	172.0	1.200					636			
240-4	4274	646	FEMALE	EOE	171.0	1.620								
240-4	4274	647	FEMALE	EOE	160.1	1.390					395			
240-4	4274	648	FEMALE	EOE	164.0	1.190	1.240	4.740	0.377	0.148		28.2	9.9	278
240-4	4274	649	FEMALE	EOE	159.6	1.513	1.156	4.429						
240-4	4274	650	FEMALE	EOE	155.0	1.370					445			
240-4	4274	651	FEMALE	EOE	161.0	1.360	1.240	4.630	0.377	0.168		32.1	334.5	10736
240-4	4274	652	FEMALE	EOE	162.2	1.439	1.369	5.078						

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240-4	4274	653	FEMALE	EOE	166.0				0.408	0.153		38.6	84.8	3274
240-4	4274	654	FEMALE	EOE	167.0	1.410					347			
240-4	4274	655	FEMALE	REC	184.0	1.270					691			
240-4	4274	656	FEMALE	REC	183.8	1.210					568			
240-4	4274	657	FEMALE	EOE	165.9	1.260								
240-4	4274	658	FEMALE	EOE	154.6	1.317	1.192	4.479						
240-4	4274	659	FEMALE	REC	173.0	1.120								
240-4	4274	660	FEMALE	REC	184.0				0.462	0.206		18.7	181.2	3389
120-4	4275	212	MALE	EOE	296.0				0.576	0.167		26.8	188.6	5056
120-4	4275	214	MALE	REC	280.1	1.096	1.927	9.606						
120-4	4275	215	MALE	REC	324.4	1.610					472			
120-4	4275	216	MALE	EOE	281.0	1.590								
120-4	4275	217	MALE	REC	311.9	1.440					527			
120-4	4275	218	MALE	REC	326.0	1.170	2.320	10.840	0.639	0.251		13.1	144.2	1889
120-4	4275	219	MALE	REC	305.5	1.660								
120-4	4275	221	MALE	EOE	269.1	1.553	1.928	10.035						
120-4	4275	222	MALE	REC	319.0	1.550					410			
120-4	4275	225	MALE	EOE	277.6	1.630					622			
120-4	4275	226	MALE	EOE	263.6	1.740					530			
120-4	4275	227	MALE	EOE	286.6	1.598	2.020	9.464						
120-4	4275	229	MALE	REC	313.0	1.230	2.240	9.870	0.640	0.192		18.8	245.3	4611
120-4	4275	230	MALE	EOE	297.4	1.730								
120-4	4275	231	MALE	REC	299.6	1.408	2.149	9.608						
120-4	4275	232	MALE	EOE	286.7	1.464	2.020	9.210						
120-4	4275	233	MALE	REC	308.0				0.590	0.230		11.0	237.4	2611
120-4	4275	234	MALE	REC	306.0	1.620					411			
120-4	4275	235	MALE	EOE	275.2	1.430	1.959	9.330						
120-4	4275	236	MALE	EOE	288.0	1.460	2.150	9.260	0.567	0.226		19.6	186.4	3653
120-4	4275	237	MALE	EOE	279.0	1.700					746			
120-4	4275	238	MALE	REC	321.0	1.525	2.100	10.556						
120-4	4275	240	MALE	EOE	281.0	1.420	1.980	9.070	0.542	0.196		14.5	166.3	2411
120-4	4275	241	MALE	REC	325.0	1.250	2.090	10.370	0.682	0.237		25.0	263.3	6583
120-4	4275	244	MALE	EOE	285.0	1.736	2.036	9.558						
120-4	4275	245	MALE	EOE	288.0	1.550	2.010	8.720	0.594	0.198		25.1	155.5	3903
120-4	4275	246	MALE	REC	305.0	1.450								
120-4	4275	247	MALE	EOE	282.0	1.640								
120-4	4275	249	MALE	REC	306.5	1.410	1.927	9.291						
120-4	4275	250	MALE	REC	292.3	1.420	2.078	9.101						
120-4	4275	661	FEMALE	REC	182.7	1.031	1.198	5.380						
120-4	4275	662	FEMALE	REC	166.7	1.008	1.208	4.428						
120-4	4275	663	FEMALE	EOE	167.2	1.395	1.368	5.121						
120-4	4275	664	FEMALE	REC	161.7	1.240								
120-4	4275	665	FEMALE	REC	177.0	1.040								
120-4	4275	666	FEMALE	EOE							752			
120-4	4275	667	FEMALE	EOE	158.4	1.341	1.113	7.830						
120-4	4275	668	FEMALE	REC	184.5	1.100								
120-4	4275	669	FEMALE	EOE	160.0	1.200								
120-4	4275	670	FEMALE	REC	190.3	1.350					600			
120-4	4275	671	FEMALE	EOE	164.4	1.220					607			
120-4	4275	672	FEMALE	REC	184.0	0.920	1.220	5.210	0.375	0.195		19.8	498.0	9861
120-4	4275	673	FEMALE	EOE	155.8	1.260								
120-4	4275	674	FEMALE	REC	181.0	1.210					580			
120-4	4275	675	FEMALE	EOE	161.0	1.050	1.250	4.390	0.348	0.170		14.6	539.4	7875

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120-4	4275	676	FEMALE	EOE	167.0	1.090	1.370	5.200	0.379	0.133		17.6	419.8	7389
120-4	4275	677	FEMALE	REC	180.0	1.170					473			
120-4	4275	678	FEMALE	REC	168.2	0.998	1.198	4.222						
120-4	4275	679	FEMALE	REC	182.7	1.057	1.344	5.240						
120-4	4275	680	FEMALE	EOE	157.5	1.200	1.228	4.800						
120-4	4275	681	FEMALE	EOE	168.0	1.240	1.260	4.680	0.404	0.127		15.1	552.8	8347
120-4	4275	682	FEMALE	REC	179.2	1.092	1.161	6.251						
120-4	4275	683	FEMALE	REC	181.0	0.910	1.260	4.950	0.408	0.199		19.6	572.6	11222
120-4	4275	684	FEMALE	EOE	163.2	1.399		4.872						
120-4	4275	685	FEMALE	FD	160.8	2.047	1.449	7.952						
120-4	4275	686	FEMALE	EOE	171.5	1.435	1.360	5.630						
120-4	4275	687	FEMALE	EOE	173.0	1.270								
120-4	4275	688	FEMALE	REC	180.0	1.230					542			
120-4	4275	689	FEMALE	EOE	152.0	1.170					592			
120-4	4275	690	FEMALE	REC	171.0	0.840	1.210	4.150	0.352	0.181		8.8	107.3	944
480-4	4276	251	MALE	REC	326.8	1.697	2.043	9.828						
480-4	4276	252	MALE	EOE	274.6	2.773	2.000	9.518						
480-4	4276	253	MALE	EOE	280.6	1.245	2.039	10.034						
480-4	4276	254	MALE	REC	303.8	1.790	2.130	9.304						
480-4	4276	255	MALE	EOE	276.7	2.345	2.181	9.414						
480-4	4276	256	MALE	REC	279.7	1.589	1.919	8.578						
480-4	4276	257	MALE	REC	297.9	1.520	2.064	9.305						
480-4	4276	258	MALE	EOE	268.3	2.511	2.058	9.495						
480-4	4276	259	MALE	EOE	264.2	2.394	1.875	8.499						
480-4	4276	260	MALE	REC	292.1	1.814	2.020	8.173						
480-4	4276	691	FEMALE	EOE	160.9	1.861	1.235	5.414						
480-4	4276	692	FEMALE	REC	182.7	1.232	1.331	4.759						
480-4	4276	693	FEMALE	FD	151.2	2.951	1.386	7.367						
480-4	4276	694	FEMALE	EOE	148.7	2.093	1.233	5.264						
480-4	4276	695	FEMALE	EOE	148.7	1.774	1.251	5.091						
480-4	4276	696	FEMALE	REC	189.7	1.279	1.371	5.618						
480-4	4276	697	FEMALE	EOE	159.4	2.016	1.385	5.148						
480-4	4276	698	FEMALE	REC	177.0	1.375	2.811	4.927						
480-4	4276	699	FEMALE	EOE	155.2	2.299	1.123	4.902						
480-4	4276	700	FEMALE	REC	176.6	1.239	1.363	5.275						
SHAM	4277	264	MALE	REC	326.4	1.244	2.160	10.102						
SHAM	4277	266	MALE	EOE	295.0	0.940	2.090	10.710	0.622	0.175		8.5	294.2	2486
SHAM	4277	267	MALE	EOE	292.0	1.180					754			
SHAM	4277	268	MALE	EOE	308.2	1.470					563			
SHAM	4277	270	MALE	EOE	266.9	1.097	1.195	8.417						
SHAM	4277	271	MALE	REC	312.0	1.530					770			
SHAM	4277	272	MALE	EOE		1.408	2.466	9.957						
SHAM	4277	273	MALE	REC	264.8	1.640					718			
SHAM	4277	274	MALE	REC	315.4	1.320								
SHAM	4277	275	MALE	REC	300.0	1.277	2.153	9.300						
SHAM	4277	276	MALE	FD										
SHAM	4277	277	MALE	REC	310.6	1.117	2.036	8.816						
SHAM	4277	279	MALE	EOE	303.6	1.440					869			
SHAM	4277	280	MALE	REC	336.0	1.410								
SHAM	4277	281	MALE	EOE	291.0	1.160								
SHAM	4277	282	MALE	REC	325.9	1.430					541			
SHAM	4277	283	MALE	REC	318.0				0.635	0.183		14.3	551.7	7889
SHAM	4277	285	MALE	REC	293.1	1.325	2.030	8.395						

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SHAM	4277	286	MALE	REC	312.0	1.000	2.190	10.620	0.666	0.194		8.6	274.5	2361
SHAM	4277	287	MALE	EOE	304.0	1.020	2.070	9.790						
SHAM	4277	289	MALE	REC	291.0	1.050	2.140	9.430	0.603	0.186		9.1	560.1	5111
SHAM	4277	290	MALE	EOE	281.3	1.305	2.014	8.724						
SHAM	4277	291	MALE	EOE	302.8	1.040								
SHAM	4277	292	MALE	EOE	312.0				0.634	0.171		8.1	1586.1	12847
SHAM	4277	293	MALE	REC	328.0	1.360					666			
SHAM	4277	294	MALE	EOE	294.0	0.970	1.980	9.820	0.597	0.170		2.5	90.7	227
SHAM	4277	296	MALE	REC	321.0	1.060	2.120	9.690	0.605	0.190		10.5	862.4	9056
SHAM	4277	297	MALE	REC	318.2	1.232	2.198	9.239						
SHAM	4277	298	MALE	EOE	299.2	1.302	2.071	10.201						
SHAM	4277	300	MALE	EOE	288.0	1.150								
SHAM	4277	701	FEMALE	EOE	177.0				0.387	0.157		3.6	775.5	2792
SHAM	4277	702	FEMALE	EOE	165.1	1.064	1.309	5.164						
SHAM	4277	703	FEMALE	REC	189.0	1.190					604			
SHAM	4277	704	FEMALE	REC	187.3	1.120					970			
SHAM	4277	705	FEMALE	EOE	170.0	0.740	1.130	4.350	0.388	0.166		5.7	81.1	462
SHAM	4277	706	FEMALE	REC	180.0	0.770	1.370	5.710	0.423	0.156		6.1	50.1	306
SHAM	4277	707	FEMALE	REC	185.0	0.970								
SHAM	4277	708	FEMALE	REC	183.0	0.864	1.306	5.125						
SHAM	4277	709	FEMALE	EOE	160.0	1.129	1.223	4.741						
SHAM	4277	710	FEMALE	REC	186.4	1.080					598			
SHAM	4277	711	FEMALE	REC	191.2	0.943	1.365	5.145						
SHAM	4277	712	FEMALE	EOE	165.0	0.750	1.180	5.070	0.401	0.160		6.4	422.1	2702
SHAM	4277	713	FEMALE	EOE	169.1	1.080					790			
SHAM	4277	714	FEMALE	EOE	167.4	1.120	1.301	4.543						
SHAM	4277	715	FEMALE	EOE	167.0	0.800	1.170	5.230	0.405	0.128		10.1	711.0	7181
SHAM	4277	716	FEMALE	FD										
SHAM	4277	717	FEMALE	EOE	167.7	0.952	1.226	5.045						
SHAM	4277	718	FEMALE	EOE	166.0	0.950								
SHAM	4277	719	FEMALE	EOE	167.0	0.980					[illegible]37			
SHAM	4277	720	FEMALE	REC	167.0	0.884	1.261	3.884						
SHAM	4277	721	FEMALE	EOE	165.5	0.893	1.225	4.800						
SHAM	4277	722	FEMALE	REC	188.0	0.810	1.300	5.120	0.396	0.147		10.4	392.6	4083
SHAM	4277	723	FEMALE	EOE	176.1	1.000								
SHAM	4277	724	FEMALE	REC	180.2	0.905	1.241	5.068						
SHAM	4277	725	FEMALE	REC	186.0	0.830	1.230	6.190	0.410	0.187				
SHAM	4277	726	FEMALE	REC	190.9	1.080					637			
SHAM	4277	727	FEMALE	[illegible]E	181.6	1.100					651			
SHAM	4277	728	FEMALE	REC	177.7	0.882	1.329	4.949						
SHAM	4277	729	FEMALE	EOE	168.0	0.870								
SHAM	4277	730	FEMALE	REC	178.0				0.419	0.185		27.2	691.4	18806

PART 2. PULMONARY BIOCHEMISTRY DATA

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	WBC	PAM	PMN	BGLU	ALKP	LDH	TPRO	AIRC	ACKG	TCOL
120-2	4270	011	MALE	EOE	8.96	7.08	1.344	6.10	570	1963	2.84			
120-2	4270	019	MALE	REC	5.18	4.72	0.108	1.84	455	626	2.10	66.24	216.04	
120-2	4270	021	MALE	EOE	5.05	4.00	0.252	2.44	553	1158	2.44			
120-2	4270	024	MALE	EOE	7.88	6.23	1.020	3.35	612	1228	2.81	85.25	293.86	
120-2	4270	026	MALE	REC	9.17	7.79	0.096	2.14	367	710	2.59	40.71	142.55	
120-2	4270	027	MALE	REC	4.54	4.31		1.38	557	758	2.83	38.28	124.58	
120-2	4270	034	MALE	REC	4.87	3.80		2.75	436	845	3.19			
120-2	4270	039	MALE	EOE	6.16	5.23	0.372	2.14	361	904	0.73	43.62	153.86	
120-2	4270	041	MALE	REC	6.42	5.00		2.90	526	836	2.74			
120-2	4270	042	MALE	REC	7.79	7.48	0.072	2.75	463	864	2.28			
120-2	4270	045	MALE	EOE	9.31	7.82	1.488	3.20	547	1350	1.91	59.63	201.93	
120-2	4270	047	MALE	EOE	14.34	10.32	2.868	5.03	737	2425	3.12			
120-2	4270	514	FEMALE	REC	3.48	2.68		1.78	425	957	1.96	47.09	267.13	
120-2	4270	515	FEMALE	EOE	8.09	5.99	1.620	7.74	440	1625	1.87			
120-2	4270	518	FEMALE	REC	3.70	3.18		1.40	295	603	1.23			
120-2	4270	521	FEMALE	REC	6.02	5.18		1.02	405	764	1.31			
120-2	4270	524	FEMALE	REC	7.02	5.90		2.42	483	968	1.57	40.00	220.53	
120-2	4270	527	FEMALE	EOE	19.98	13.19	5.000	25.63	305	2469	4.22			
120-2	4270	528	FEMALE	EOE	11.55	8.89	2.190	10.91	398	1987	2.92	84.38	528.71	
120-2	4270	534	FEMALE	EOE	7.32	4.83	1.460	4.95	397	1255	1.95			
120-2	4270	535	FEMALE	REC	6.18	4.94		1.40	360	746	1.33			
120-2	4270	536	FEMALE	EOE	14.39	9.93	3.740	12.69	550	1829	3.04	61.70	345.85	
120-2	4270	537	FEMALE	EOE	7.74	5.50	1.630	4.06	503	1298	1.78	60.37	347.13	
120-2	4270	538	FEMALE	REC	9.90	9.01		1.78	373	811	1.30	40.00	242.16	
60-2	4271	053	MALE	EOE	4.52	3.84	0.228	0.76	643	1223	2.36			
60-2	4271	054	MALE	REC	4.30	3.73	0.048	4.57	546	967	2.46	38.28	109.94	
60-2	4271	058	MALE	REC	10.18	7.63		2.59	696	983	3.54			
60-2	4271	064	MALE	EOE	6.20	4.46	0.564	3.05	560	785	2.88	46.82	157.07	
60-2	4271	065	MALE	REC	4.36	3.88		4.42	629	881	2.53			
60-2	4271	072	MALE	EOE	4.33	3.47	0.384	1.82	472	584	2.47	40.42	132.17	
60-2	4271	077	MALE	EOE	5.51	3.42	0.444	3.50	536	928	2.75	46.82	158.24	
60-2	4271	079	MALE	REC	14.77	12.26		2.89	758	1020	3.61	51.65	169.74	
60-2	4271	080	MALE	REC	9.05	8.95		3.05	624	1108	2.40			
60-2	4271	082	MALE	EOE	5.57	5.02	0.228	3.05	426	824	2.26			
60-2	4271	085	MALE	REC	4.69	3.61		1.98	632	742	2.87	41.93	127.99	
60-2	4271	088	MALE	EOE	10.01	7.91	0.996	4.26	660	1104	2.51			
60-2	4271	543	FEMALE	EOE	4.16	3.29	0.370	2.54	556	966	2.62			
60-2	4271	544	FEMALE	REC	3.61	2.60	0.040	3.05	440	927	1.87			
60-2	4271	545	FEMALE	EOE	4.02	2.65	0.520	2.28	473	924	2.12	52.36	306.61	
60-2	4271	547	FEMALE	REC	2.89	2.37		2.41	486	441	2.06	33.93	186.01	
60-2	4271	551	FEMALE	REC	5.41	3.84		2.16	395	391	1.60			
60-2	4271	556	FEMALE	REC	3.88	2.99		4.06	556	747	2.48	69.38	366.11	
60-2	4271	557	FEMALE	EOE	5.02	3.31	0.700	2.16	557	921	2.13			
60-2	4271	558	FEMALE	EOE	5.20	3.90	0.520	3.05	610	1096	2.06			
60-2	4271	559	FEMALE	REC	2.14	2.01		2.92	404	591	1.25	32.91	184.50	
60-2	4271	562	FEMALE	EOE	6.52	3.91	1.240	1.65	517	1115	2.30	69.71	413.44	
60-2	4271	563	FEMALE	EOE	6.55	3.47	0.850	3.55	497	913	1.71	52.36	303.36	
60-2	4271	569	FEMALE	REC	6.48	5.83		2.54	576	733	1.43			
240-2	4272	095	MALE	REC	6.70	6.49	0.072	1.98	391	798	1.98			
240-2	4272	096	MALE	EOE	12.62	9.97	1.644	18.58	558	2705	4.25			

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	WBC	PAM	PMN	BGLU	ALKP	LDH	TPRO	AIRC	ACKG	TCOL
240-2	4272	099	MALE	REC	9.89	8.70	0.096	2.58	480	1025	2.30			
240-2	4272	101	MALE	REC	8.39	7.97		3.04	514	928	1.80	73.53	241.40	25.82
240-2	4272	106	MALE	REC	10.06	8.54	0.300	4.87	536	1196	2.64	48.01	164.85	23.41
240-2	4272	107	MALE	EOE	11.27	7.55	2.484	12.79	432	1855	3.06			
240-2	4272	109	MALE	EOE	10.82	6.49	3.468	17.98	432	2740	4.60	117.27	412.92	24.01
240-2	4272	112	MALE	EOE	12.30	9.11	2.460	18.58	598	2771	4.52			
240-2	4272	115	MALE	EOE	10.80	8.32	0.864	16.91	488	2734	4.30	104.46	388.47	20.80
240-2	4272	120	MALE	REC	2.92	2.59		3.19	533	1052	2.84			
240-2	4272	123	MALE	REC	3.01	2.77		4.26	587	916	2.52	48.01	150.44	26.32
240-2	4272	124	MALE	EOE	8.90	7.21	0.888	13.70	520	2455	4.56	117.27	419.42	24.54
240-2	4272	572	FEMALE	EOE	17.08	14.69	1.540	22.59	470	2857	4.11	103.06	647.78	16.00
240-2	4272	576	FEMALE	REC	5.88	5.17		2.66	351	1251	1.75			
240-2	4272	577	FEMALE	EOE	8.80	5.72	2.460	20.18	361	2298	3.81			
240-2	4272	578	FEMALE	FD	2.12									
240-2	4272	580	FEMALE	REC	8.36	7.77	0.170	3.04	397	1096	1.68	44.06	237.50	17.82
240-2	4272	581	FEMALE	EOE	18.35	13.58	2.200	35.41	482	3830	4.61			
240-2	4272	584	FEMALE	REC	5.70	4.39	0.060	1.77	345	1074	1.85			
240-2	4272	588	FEMALE	REC	1.88	1.56	0.060	3.93	349	1127	2.01	42.03	241.41	24.01
240-2	4272	593	FEMALE	EOE	12.72	7.63	3.940	47.71	230	3288	5.14	201.79	1236.48	19.75
240-2	4272	594	FEMALE	REC	9.42	9.23	0.090	4.18	436	1479	2.19			
240-2	4272	595	FEMALE	EOE	18.27	14.07	4.020	31.85	488	3341	4.76			
240-2	4272	597	FEMALE	REC	1.72	1.48	0.020	2.28	424	991	1.66	42.03	235.99	18.81
240-2	4272	598	FEMALE	EOE	9.45	5.29	3.590	13.71	295	1984	3.11	105.73	625.99	16.54
60-4	4273	131	MALE	EOE	10.55	8.76	0.420	6.55	458	1451	3.11			
60-4	4273	133	MALE	REC	3.85	2.86		4.10	415	1074	2.11	48.01	148.03	
60-4	4273	140	MALE	REC	7.20	5.26		3.96	560	883	2.30			
60-4	4273	141	MALE	REC	6.11	5.32		3.96	422	960	2.06	45.57	149.72	
60-4	4273	147	MALE	REC	3.86	2.94		3.65	342	754	1.85	63.81	189.67	
60-4	4273	151	MALE	EOE	9.67	7.45	0.480	5.18	613	1855	3.38	99.66	328.58	
60-4	4273	156	MALE	REC	10.85	8.46	0.108	3.80	378	1081	2.41			
60-4	4273	157	MALE	REC	6.78	5.29		3.19	455	1087	2.05			
60-4	4273	159	MALE	EOE	9.30	8.65	0.468	6.55	488	1740	4.03	130.08	476.65	
60-4	4273	162	MALE	EOE	11.03	9.05	0.660	4.87	553	1832	3.84			
60-4	4273	164	MALE	EOE	5.74	4.82	0.228	4.12	482	1428	3.07			
60-4	4273	170	MALE	EOE	14.69	8.96	2.052	5.48	456	1378	3.78	78.84	268.91	
60-4	4273	601	FEMALE	REC	3.46	2.94	0.070	1.14	306	626	1.06	30.89	158.49	
60-4	4273	605	FEMALE	EOE	11.27	9.58	0.790	1.78	320	1179	2.21			
60-4	4273	609	FEMALE	EOE	7.51	6.91	0.300	4.44	383	1378	2.47	73.71	447.53	
60-4	4273	[illegible]	FEMALE	REC	4.17	3.88		2.53	297	676	1.13			
60-4	4273	611	FEMALE	REC	3.33	2.00		3.30	340	844	1.78	29.88	155.85	
60-4	4273	613	FEMALE	REC	7.41	6.00		4.69	381	857	1.68	36.97	198.00	
60-4	4273	614	FEMALE	REC	5.24	4.72	0.050	3.04	339	930	1.45			
60-4	4273	615	FEMALE	EOE	23.77	14.26	3.800	8.38	445	4211	4.60			
60-4	4273	620	FEMALE	REC	5.28	4.65		3.04	356	1020	1.97			
60-4	4273	625	FEMALE	EOE	6.04	4.95	0.240	5.21	387	1305	2.70			
60-4	4273	627	FEMALE	EOE	12.97	10.25	2.080	8.63	308	2619	3.66	80.38	459.31	
60-4	4273	630	FEMALE	EOE	9.22	7.56	1.660	6.09	420	1800	2.99	88.38	509.13	
240-4	4274	171	MALE	REC	7.38	4.73		3.35	427	822	2.47	44.36	131.59	
240-4	4274	172	MALE	REC	6.17	5.48		3.19	433	982	2.30	51.65	161.36	
240-4	4274	176	MALE	REC	6.11	5.14		4.57	532	972	3.70			
240-4	4274	177	MALE	REC	6.07	4.25		2.44	468	1118	2.87			
240-4	4274	178	MALE	EOE	6.58	4.99	0.852	24.06	341	1906	4.62			
240-4	4274	180	MALE	REC	7.76	5.82		3.96	440	539	2.64	34.64	114.35	

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	WBC	PAM	PMN	BGLU	ALKP	LDH	TPRO	AIRC	ACKG	TCOL
240-4	4274	185	MALE	EOE	5.75	4.25	1.032	26.80	262	1954	4.76	123.67	442.16	
240-4	4274	186	MALE	EOE	11.48	8.39	1.608	42.34	409	2534	5.32			
240-4	4274	192	MALE	REC	5.81	4.48	0.060	2.89	451	440	2.84			
240-4	4274	193	MALE	EOE	10.75	8.50	1.296	21.78	424	2038	4.74	104.46	355.55	
240-4	4274	202	MALE	EOE	7.74	5.42	1.008	20.56	349	2089	4.70	82.05	284.68	
240-4	4274	208	MALE	EOE	10.74	9.35	0.756	31.21	364	2921	5.32			
240-4	4274	634	FEMALE	REC	2.51	2.11		2.79	340	1086	2.20	37.98	214.57	
240-4	4274	635	FEMALE	EOE	12.42	10.18	0.620	25.89	285	2020	3.85	97.72	576.54	
240-4	4274	636	FEMALE	REC	3.51	2.28	0.280	2.79	379	867	2.52	38.99	207.84	
240-4	4274	645	FEMALE	REC	2.51	1.91	0.050	1.90	215	663	1.77			
240-4	4274	646	FEMALE	EOE	13.18	11.73	1.050	47.58	183	2940	5.24			
240-4	4274	647	FEMALE	EOE	14.04	9.97	2.530	29.95	227	2080	3.93	99.06	618.73	
240-4	4274	650	FEMALE	EOE	25.49	16.06	6.630	30.45	272	2690	4.72			
240-4	4274	654	FEMALE	EOE	34.14	25.95	4.780	40.60	214	2934	4.72			
240-4	4274	655	FEMALE	REC	4.29	3.30		2.66	389	527	2.61			
240-4	4274	656	FEMALE	REC	2.67	2.35		2.28	309	647	1.72	32.91	179.08	
240-4	4274	657	FEMALE	EOE	11.86	8.66	0.830	21.06	281	2042	3.71	109.73	661.44	
240-4	4274	659	FEMALE	REC	9.00	6.48		1.40	274	442	1.63			
120-4	4275	215	MALE	REC	5.78	4.98		2.90	334	858	1.36	38.28	118.01	
120-4	4275	216	MALE	EOE	14.45	11.41	1.008	14.32	364	1894	3.31			
120-4	4275	217	MALE	REC	35.84	28.68	1.080	1.68	319	901	2.23	38.28	122.74	
120-4	4275	219	MALE	REC	5.34	4.38		2.44	391	785	2.53	72.31	236.71	
120-4	4275	222	MALE	REC	4.04	3.16	0.036	1.84	296	815	1.73			
120-4	4275	225	MALE	EOE	16.98	15.96	0.336	8.99	320	1712	2.96	34.01	122.53	
120-4	4275	226	MALE	EOE	14.05	11.66	0.564	11.57	271	1650	3.07	98.06	371.99	
120-4	4275	230	MALE	EOE	11.58	9.73	0.924	10.06	232	1766	3.22	104.46	351.25	
120-4	4275	234	MALE	REC	4.64	3.20		2.14	310	750	2.63			
120-4	4275	237	MALE	EOE	24.83	20.11	1.488	11.88	335	2489	3.97			
120-4	4275	246	MALE	REC	4.69	3.94		2.59	336	1030	2.12			
120-4	4275	247	MALE	EOE	11.52	9.91	0.804	11.27	310	1874	2.76			
120-4	4275	665	FEMALE	REC	5.42	4.34		0.89	255	1039	1.24			
120-4	4275	666	FEMALE	EOE	13.83	11.06	0.410	14.85	240	1849	2.33	73.71	455.83	
120-4	4275	668	FEMALE	REC	5.24	3.98	0.050	1.65	323	1022	1.59	36.97	200.36	
120-4	4275	669	FEMALE	EOE	13.82	11.06	0.830	18.27	300	1829	2.94			
120-4	4275	670	FEMALE	REC	3.07	2.86	0.030	1.91	340	812	1.42	32.91	172.96	
120-4	4275	671	FEMALE	EOE	12.89	9.80	0.770	12.44	273	1693	2.89	120.41	732.40	
120-4	4275	673	FEMALE	EOE	32.19	24.14	6.440	26.14	239	2887	5.46	140.42	901.28	
120-4	4275	674	FEMALE	REC	9.83	8.26		2.03	311	1029	1.18			
120-4	4275	677	FEMALE	REC	6.51	6.44		2.29	300	1071	1.39			
120-4	4275	687	FEMALE	EOE	23.02	20.72	2.300	14.47	277	2047	2.89			
120-4	4275	688	FEMALE	REC	15.03	12.93	0.150	3.56	423	1254	1.92	46.08	256.01	
120-4	4275	689	FEMALE	EOE	9.30	7.35	0.560	17.38	240	2339	3.62			
SHAM	4277	267	MALE	EOE	4.68	3.42	0.096	1.52	552	852	3.13			
SHAM	4277	268	MALE	EOE	4.60	3.91	0.132	1.68	390	442	2.70	26.01	84.39	
SHAM	4277	271	MALE	REC	3.41	2.89		3.20	628	943	2.09			
SHAM	4277	273	MALE	REC	5.26	3.68		2.89	517	907	2.21	52.87	199.65	22.29
SHAM	4277	274	MALE	REC	4.19	2.93		2.75	516	797	2.56	44.36	140.64	20.83
SHAM	4277	279	MALE	EOE	4.90	3.43		1.84	384	852	3.78	61.23	201.68	
SHAM	4277	280	MALE	REC	6.35	5.40		3.20	426	1456	2.77			
SHAM	4277	281	MALE	EOE	4.37	2.52		2.75	437	794	2.41			
SHAM	4277	282	MALE	REC	3.60	3.06		2.89	642	756	1.66	46.79	143.57	22.54
SHAM	4277	291	MALE	EOE	4.97	3.42		2.29	450	778	2.98	59.63	196.93	
SHAM	4277	293	MALE	REC	3.49	2.58	0.072	3.36	743	922	2.42			

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	WBC	PAM	PMN	BGLU	ALKP	LDH	TPRO	AIRC	ACKG	TCOL
SHAM	4277	300	MALE	EOE	4.25	3.48		2.59	385	556	2.94			
SHAM	4277	703	FEMALE	REC	2.76	1.93		2.67	519	684	1.43			
SHAM	4277	704	FEMALE	REC	2.79	2.23		2.29	522	881	1.88			
SHAM	4277	707	FEMALE	REC	2.68	2.09		2.41	477	1062	1.47	46.08	246.03	
SHAM	4277	710	FEMALE	REC	3.44	2.99		3.68	518	1004	1.57			
SHAM	4277	713	FEMALE	EOE	4.95	2.87		1.02	435	612	2.47	56.21	301.56	
SHAM	4277	718	FEMALE	EOE	5.95	4.80		3.68	457	695	1.87	53.69	317.53	14.56
SHAM	4277	719	FEMALE	EOE	4.54	4.26		1.15	445	604	2.00			
SHAM	4277	723	FEMALE	EOE	5.75	3.97		2.67	422	766	1.87			
SHAM	4277	726	FEMALE	REC	3.35	2.88	0.030	4.32	609	1249	1.90	52.36	297.33	14.28
SHAM	4277	727	FEMALE	EOE	5.88	4.59		3.43	535	1154	2.57	44.06	230.78	
SHAM	4277	729	FEMALE	EOE	5.40	5.14		1.65	443	844	2.24	65.70	361.80	16.88

PART 3. HEMATOLOGY DATA

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	TKG	RBC	HEMA	HGB	MCV	BWBC	SEGM	EOSI	LYMP	MONO	NRBC	BPRO
120-2	4270	011	MALE	EOE		8.32	43.8	15.7	52	2.5	37	1	50	2	7	6.7
120-2	4270	021	MALE	EOE		8.23	43.2	15.8	52	1.3	24	0	76	0	5	6.6
120-2	4270	034	MALE	REC		7.57	39.3	14.6	51	3.8	19	2	78	1	6	6.0
120-2	4270	041	MALE	REC		7.81	40.0	14.7	51	2.9	25	0	74	1	9	5.9
120-2	4270	042	MALE	REC		7.95	40.5	15.0	50	1.7	26	0	73	1	4	6.1
120-2	4270	047	MALE	EOE		7.89	40.2	14.9	51	2.3	32	0	64	4	9	6.3
120-2	4270	515	FEMALE	EOE		7.58	41.0	15.2	53	1.2	28	4	66	2	4	5.7
120-2	4270	518	FEMALE	REC		7.14	38.6	14.3	53	1.1	19	0	81	0	6	5.6
120-2	4270	521	FEMALE	REC		6.43	34.1	12.8	52	1.3	24	3	73	0	2	5.0
120-2	4270	527	FEMALE	EOE		7.41	39.6	15.0	53	2.3	24	0	74	2	10	5.6
120-2	4270	534	FEMALE	EOE		7.49	40.6	15.0	54	1.6	28	8	64	0	8	5.6
120-2	4270	535	FEMALE	REC		7.04	38.3	14.4	54	1.3	22	0	78	0	5	5.3
60-2	4271	053	MALE	EOE		7.74	40.4	14.5	51	2.3	20	1	78	1	2	6.0
60-2	4271	058	MALE	REC		7.69	40.9	14.5	53	3.0	25	2	71	2	2	6.1
60-2	4271	065	MALE	REC		7.95	42.5	15.4	53	1.9	26	0	74	0	3	6.5
60-2	4271	080	MALE	REC		7.81	41.2	14.9	52	1.6	28	1	70	1	9	6.2
60-2	4271	082	MALE	EOE		7.94	40.4	14.7	50	1.6	24	1	75	0	4	5.9
60-2	4271	088	MALE	EOE		7.93	40.5	15.0	50	2.2	17	2	80	1	9	5.9
60-2	4271	543	FEMALE	EOE		6.97	38.7	14.0	55	2.6	27	2	70	1	1	5.4
60-2	4271	544	FEMALE	REC		7.61	41.7	15.2	54	1.2	13	1	84	2	9	5.9
60-2	4271	551	FEMALE	REC		7.54	41.4	15.3	54	1.3	11	2	87	0	8	5.6
60-2	4271	557	FEMALE	EOE		7.49	41.0	15.3	54	3.7	23	2	74	1	3	6.3
60-2	4271	558	FEMALE	EOE		7.22	38.8	15.2	53	1.5	37	5	58	0	4	6.6
60-2	4271	569	FEMALE	REC		7.16	39.4	14.5	54	1.4	16	2	82	0	5	5.4
240-2	4272	095	MALE	REC		8.35	45.2	15.5	54	2.0	19	0	76	5	6	6.3
240-2	4272	096	MALE	EOE		8.12	42.7	15.2	52	2.4	21	0	78	1	2	6.0
240-2	4272	099	MALE	REC		8.05	41.9	15.1	51	2.3	30	0	69	1	4	5.8
240-2	4272	101	MALE	REC	84.76											
240-2	4272	106	MALE	REC	80.38											
240-2	4272	107	MALE	EOE		7.61	39.7	14.5	51	1.5	24	2	74	0	6	5.9
240-2	4272	109	MALE	EOE	84.54											
240-2	4272	112	MALE	EOE		7.64	39.9	14.3	52	2.0	34	1	65	0	4	6.3
240-2	4272	115	MALE	EOE	77.34											
240-2	4272	120	MALE	REC		7.73	40.6	14.5	52	2.9	52	2	44	2	4	6.1
240-2	4272	123	MALE	REC	82.48											
240-2	4272	124	MALE	EOE	87.77											
240-2	4272	572	FEMALE	EOE	100.56											
240-2	4272	576	FEMALE	REC		7.56	42.3	15.3	55	3.2	18	4	78	0	1	5.6
240-2	4272	577	FEMALE	EOE		7.35	40.5	14.3	55	1.0	27	3	69	1	1	5.1
240-2	4272	580	FEMALE	REC	96.08											
240-2	4272	581	FEMALE	EOE		7.40	41.4	14.9	55	1.9	27	0	73	0	5	6.0
240-2	4272	584	FEMALE	REC		7.60	42.0	15.3	55	1.4	26	6	67	1	3	5.9
240-2	4272	588	FEMALE	REC	137.92											
240-2	4272	593	FEMALE	EOE	121.02											
240-2	4272	594	FEMALE	REC		7.30	40.1	14.9	54	3.6	26	1	73	0	4	6.0
240-2	4272	595	FEMALE	EOE		7.02	38.9	14.2	55	2.1	21	0	79	0	2	5.5
240-2	4272	597	FEMALE	REC	105.60											
240-2	4272	598	FEMALE	EOE	97.92											
60-4	4273	131	MALE	EOE		7.52	39.6	14.3	52	1.6	35	2	61	2	1	6.0
60-4	4273	140	MALE	REC		7.93	41.3	15.2	52	4.8	21	1	77	1	7	6.5

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	SEX	ASSIGN CODE	TKG	RBC	HEMA	HGB	MCV	BWBC	SEGM	EOSI	LYMP	MONO	NRBC	BPRO
60-4	4273	156	MALE	REC		7.97	41.4	15.3	51	2.2	12	2	86	0	2	6.3
60-4	4273	157	MALE	REC		8.13	42.1	15.3	51	3.1	26	0	74	0	0	5.7
60-4	4273	162	MALE	EOE		8.12	42.0	15.5	51	5.0	18	1	79	2	4	6.5
60-4	4273	164	MALE	EOE		7.71	39.9	14.5	51	2.3	18	0	82	0	0	5.9
60-4	4273	605	FEMALE	EOE		7.41	40.5	14.9	54	1.6	26	0	73	1	2	5.8
60-4	4273	610	FEMALE	REC		7.87	43.7	15.9	55	2.3	16	1	82	1	2	6.7
60-4	4273	614	FEMALE	REC		7.02	37.9	14.2	53	4.1	13	2	84	1	8	5.4
60-4	4273	615	FEMALE	EOE		7.31	40.6	15.0	55	2.7	0	0	72	2	3	5.9
60-4	4273	620	FEMALE	REC		7.57	41.2	15.3	54	4.1	10	2	87	1	1	6.0
60-4	4273	625	FEMALE	EOE		7.52	42.4	15.0	56	3.6	18	0	82	0	3	6.2
240-4	4274	176	MALE	REC		8.43	43.9	15.8	52	3.9	36	0	63	1	4	6.8
240-4	4274	177	MALE	REC		7.48	38.9	14.3	51	3.5	21	1	78	0	0	5.6
240-4	4274	178	MALE	EOE		7.98	40.9	15.4	51	2.4	26	2	70	2	3	6.0
240-4	4274	186	MALE	EOE		7.80	39.4	15.1	50	2.0	34	0	66	0	3	5.6
240-4	4274	192	MALE	REC		8.25	43.7	16.0	52	3.1	48	2	49	1	9	6.6
240-4	4274	208	MALE	EOE		8.18	41.8	15.9	51	2.4	20	0	79	1	5	6.5
240-4	4274	645	FEMALE	REC		7.37	39.9	15.1	54	2.0	32	0	67	1	8	5.6
240-4	4274	646	FEMALE	EOE		7.43	40.8	15.6	54	1.9	26	2	72	0	4	5.7
240-4	4274	650	FEMALE	EOE		7.14	38.5	14.6	53	2.3	30	3	66	1	9	6.1
240-4	4274	654	FEMALE	EOE		7.52	42.8	16.0	56	2.2	28	1	71	0	5	6.7
240-4	4274	655	FEMALE	REC		7.32	40.6	15.1	55	1.4	10	0	90	0	1	5.6
240-4	4274	659	FEMALE	REC		6.92	37.6	13.9	54	1.5	12	0	88	0	2	5.4
120-4	4275	216	MALE	EOE		8.19	43.6	15.8	53	1.6	34	6	60	0	6	6.3
120-4	4275	222	MALE	REC		7.88	40.4	15.0	51	4.4	27	1	72	0	10	6.1
120-4	4275	234	MALE	REC		7.55	41.2	15.7	54	1.3	9	1	90	0	7	5.7
120-4	4275	237	MALE	EOE		8.52	43.7	16.1	51	2.8	28	0	70	2	4	6.2
120-4	4275	246	MALE	REC		7.85	40.9	15.2	52	2.8	31	1	67	1	2	6.2
120-4	4275	247	MALE	EOE		8.04	41.2	15.4	51	3.2	38	0	58	4	7	6.2
120-4	4275	665	FEMALE	REC		7.64	42.6	15.4	55	1.5	16	4	79	1	5	5.6
120-4	4275	669	FEMALE	EOE		7.90	42.7	16.0	53	2.0	20	0	79	1	3	5.8
120-4	4275	674	FEMALE	REC		7.38	41.3	15.1	55	1.5	25	3	72	0	0	5.3
120-4	4275	677	FEMALE	REC		7.53	42.4	15.4	56	1.5	29	1	70	0	1	5.6
120-4	4275	687	FEMALE	EOE		8.05	43.9	16.2	54	1.9	28	0	70	2	7	5.9
120-4	4275	689	FEMALE	EOE		7.48	40.4	15.3	53	2.0	14	0	84	2	8	5.3
SHAM	4277	267	MALE	EOE		7.95	41.3	14.9	51	2.2	26	0	73	1	8	6.9
SHAM	4277	271	MALE	REC		7.55	41.2	15.2	54	4.1	29	2	69	0	3	6.4
SHAM	4277	273	MALE	REC	84.18											
SHAM	4277	274	MALE	REC	66.04											
SHAM	4277	280	MALE	REC		7.64	40.7	15.0	53	3.8	40	1	58	1	3	6.5
SHAM	4277	281	MALE	EOE		7.72	41.5	15.0	53	1.9	26	2	72	0	4	6.3
SHAM	4277	282	MALE	REC	69.17											
SHAM	4277	293	MALE	REC		7.66	40.7	14.7	53	3.0	29	1	69	1	5	6.0
SHAM	4277	300	MALE	EOE		8.11	42.9	15.3	52	1.9	33	0	65	2	2	6.5
SHAM	4277	703	FEMALE	REC		7.06	40.2	14.8	56	2.1	27	1	72	0	8	5.8
SHAM	4277	707	FEMALE	REC		7.03	39.4	14.6	55	1.7	31	1	68	0	1	6.1
SHAM	4277	713	FEMALE	EOE	86.09											
SHAM	4277	718	FEMALE	EOE		7.54	42.5	15.1	56	1.0	31	1	68	0	2	5.7
SHAM	4277	719	FEMALE	EOE		7.19	40.9	14.6	56	1.2	44	0	56	0	0	6.5
SHAM	4277	723	FEMALE	EOE	81.09											
SHAM	4277	726	FEMALE	REC		7.10	39.7	14.7	55	3.6	13	2	82	3	3	6.2
SHAM	4277	727	FEMALE	EOE	92.96											
SHAM	4277	729	FEMALE	EOE		7.57	42.5	15.3	56	2.7	20	2	76	2	2	7.1

APPENDIX E. TREND ANALYSES

1. Overview

In addition to the usual statistical tests performed on the data, trend analyses were performed whenever a visual inspection indicated the possibility of a trend as a function of exposure. It should be noted that a trend with a clearly nonzero slope can be obtained even in situations where not a single exposure group is significantly different from control. This is due to the fact that a multi-comparison t-test and a linear trend analysis test different properties of the data.

In view of the paucity and variability of the data, only linear trend functions were used. The criterion for a slope significantly different from zero was a normal standard deviate resulting in $p < 0.05$. In the figures, the 95% confidence limits are indicated by dashed lines. These trend analysis results are summarized in Table E-1 and visually presented in Figures E-1 through E-18. Data for 2 and 4 days/week exposures were combined for these linear curve fits.

2. Summary of Trend Analyses

a) <u>Lung Weight</u>: Linear curve fits for males and females, at the end of exposure and after the recovery period, have nonnegative slopes that have a probability ≤ 0.001 of including zero. Also, where comparisons are possible for 2 days or 4 days exposure per week (60, 120, and 240 mg·hr Cu-Zn/m^3), responses were greater when exposures were 4 days per week.

b) <u>Bronchoalveolar Lavage Fluid Constituents</u>: Observables with no exposure-response ($p > 0.05$) were

(1) Alkaline phosphatase

(2) Pulmonary alveolar macrophage numbers.

Observables with exposure-responses ($p \leq 0.05$) were

(1) Beta-glucuronidase

(2) Lactate dehydrogenase

(3) Polymorphonuclear leukocytes

(4) Total protein

(5) Airway collagen.

In 17 of 21 comparisons of responses for exposure 4 days versus 2 days per week, the responses were more intense with exposures 4 days per week. This clearly denotes a pattern very suggestive that for the same cumulative weekly exposure to Cu-Zn alloy, exposures 4 days per week produce a greater response than exposures 2 days per week.

c) Immunology: Total cells and total antibody-forming cells in lung-associated lymph nodes had exposure responses at the end of exposure. Antibody-forming cells per million lymphocytes had too much variation to indicate a nonzero slope to the linear regression of response versus exposure level. Total cells remained elevated after the 2-week recovery period; total antibody-forming cells had returned to normal. There was no apparent relationship between number of exposures per week and response for the immunology evaluations.

d) Phagocytosis: While there was no clear exposure response relationship at the end of exposure, phagocytosis was lower for cumulative weekly exposures of 60, 120, and 240 mg·hr Cu-Zn/m^3 when exposures were 4 times per week as compared with 2 days per week.

e) Histopathology: These trend analyses clearly demonstrate exposure-response relationships for all 5 categories of observables. While there was still an exposure-response after the recovery period for atrophy of olfactory epithelium and alveolar macrophage hyperplasia, slopes of the linear curve fits were decreased by factors of 3 and 0.7, respectively. Goblet cell hyperplasia of lung tissue had no significant slope, indicating the exposure-related response had fully resolved during the allowed 2-week recovery period.

Table E-1

Summary of Trend Analysis Results for Phase II

Endpoint Category	Observable	Sex[a]	Time[b]	Slope[c]	Significance[d]
Organ Weight	Lung Weight	F	EOE	0.0021 ± 0.0002	0.0001
		M	EOE	0.0020 ± 0.0002	0.0001
		F	REC	0.0007 ± 0.0001	0.001
		M	REC	0.0008 ± 0.0001	0.0001
Bronchoalveolar Lavage Fluid Constituents	Alkaline Phosphatase	MF	EOE	-0.5 ± 0.4	0.3
	Beta-Glucuronidase	MF	EOE	0.11 ± 0.02	0.002
	Lactate Dehydrogenase	MF	EOE	7.0 ± 1.5	0.006
	Alveolar Macrophages	MF	EOE	0.02 ± 0.01	0.16
	Polymorphonuclear Leukocytes	MF	EOE	0.008 ± 0.002	0.005
	Total Protein	MF	EOE	0.008 ± 0.002	0.02
	Airway Collagen	MF	EOE	0.25 ± 0.08	0.03
	Airway Collagen/kg	MF	EOE	1.3 ± 0.4	0.02
Immunology	Total Cells	MF	EOE	0.11 ± 0.03	0.02
		MF	REC	0.020 ± 0.006	0.02
	Total Antibody-forming Cells	MF	EOE	0.019 ± 0.004	0.004
		MF	REC	-0.018 ± 0.008	0.07
	Antibody-forming Cells Per Million Lymphocytes	MF	EOE	-0.9 ± 0.6	0.2
		MF	REC	-1.4 ± 0.7	0.1
Phagocytosis	EA/100 Cells	MF	EOE	-1.1 ± 0.5	0.08
		MF	REC	-0.7 ± 0.3	0.06
Histopathology	Atrophy, Olfactory Epithelium	MF	EOE	0.006 ± 0.001	0.001
		MF	REC	0.0023 ± 0.0003	0.0002
	Goblet Cell Hyperplasia, Nose	MF	EOE	0.0025 ± 0.0005	0.001
	Alveolitis, Focal Necrotizing	MF	EOE	0.0065 ± 0.0005	0.0001
	Alveolar Macrophage Hyperplasia	MF	EOE	0.006 ± 0.001	0.005
		MF	REC	0.004 ± 0.001	0.008
	Goblet Cell Hyperplasia, Lung	MF	EOE	0.0062 ± 0.0008	0.0001
		MF	REC	0.004 ± 0.0003	0.2

[a] M = males, F = females, MF = males and females combined.

[b] EOE = end of 4-week exposure, REC = after 2-week recovery period.

[c] Slope = mean ± SD of units of the observable per unit of exposure.

[d] Significance of the null hypothesis (zero slope).

Figure E-1. Fits of Straight Lines to the Lung Weight Data for Rats at the End of Exposure; ● = Exposures 4 Days/Week; ○ = Exposure 2 Days/Week. Dashed Lines Represent 95% Confidence Limits.

Figure E-2. Fits of Straight Lines to the Lung Weight Data for Rats After the Recovery Period. Dashed Lines Represent 95% Confidence Limits; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week.

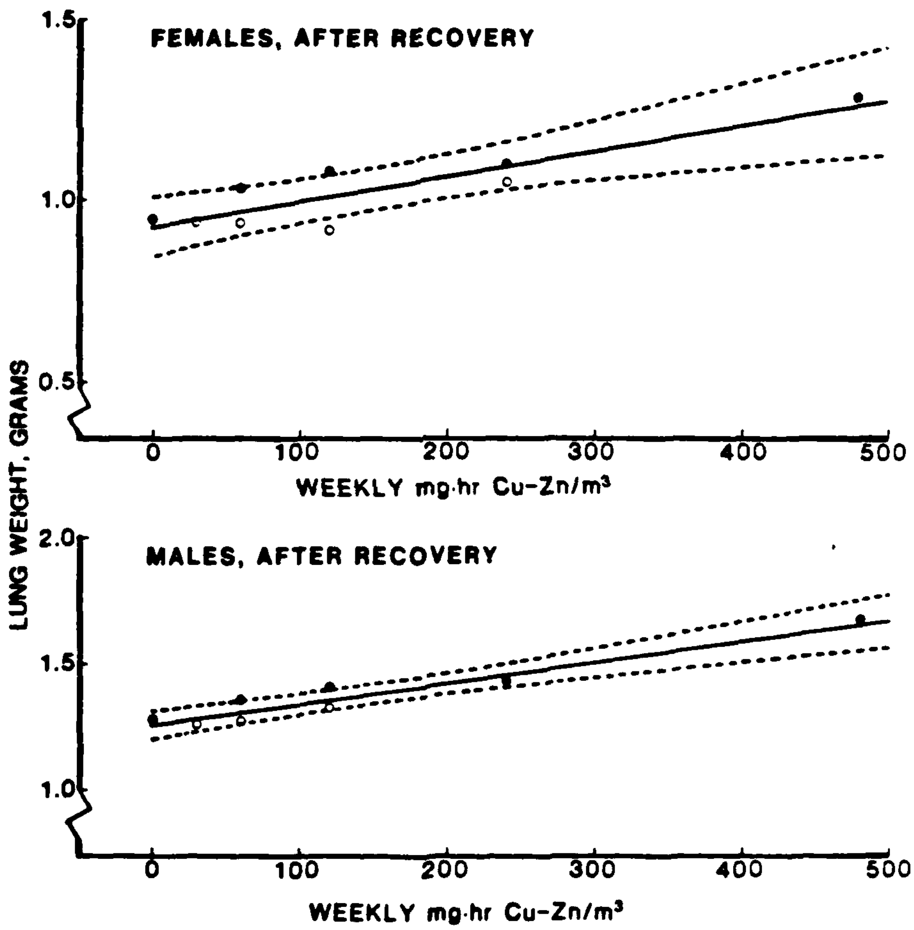


Figure E-3. Fit of a Straight Line to the Alkaline Phosphatase Content of Lung Lavage Fluid Data at the End of Exposure for Exposures Twice Per Week (○) and Four Times Per Week (●). Dashed Lines Represent 95% Confidence Limits.

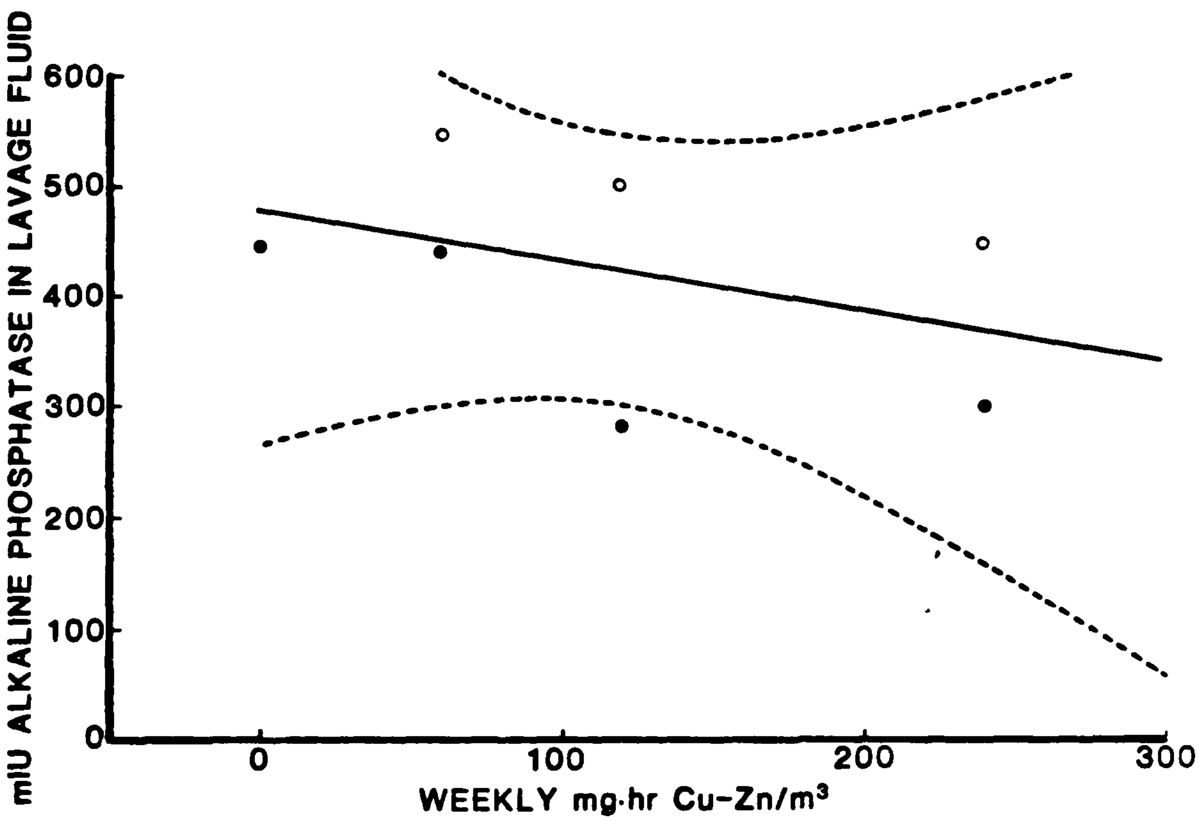


Figure E-4. Fit of a Straight Line to the Beta Glucuronidase Content of Lung Lavage Fluid at the End of Exposure for Exposures Twice Per Week (o) and Four Times Per Week (●). Dashed Lines Represent 95% Confidence Limits.

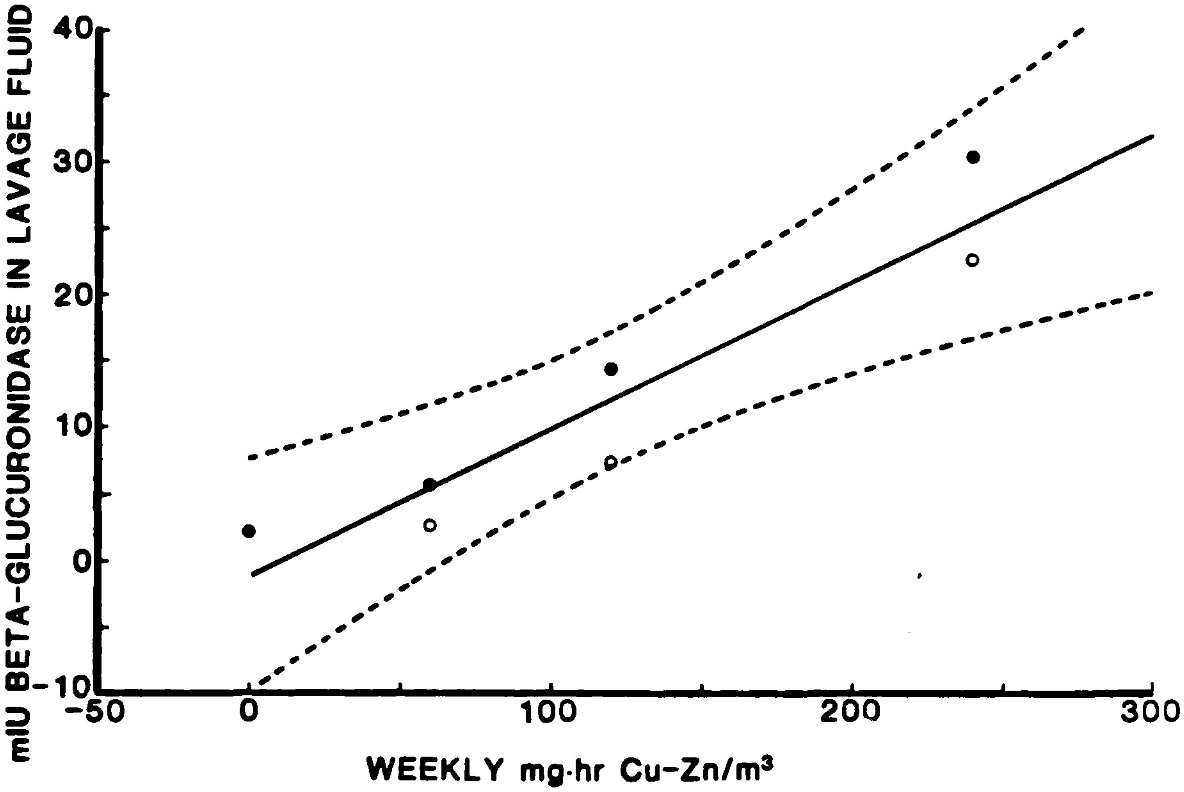


Figure E-5. Fit of a Straight Line to the Lactate Dehydrogenase Content of Lung Lavage Fluid at the End of Exposure for Exposures Twice Per Week (o) and Four Times Per Week (●). Dashed Lines Represent 95% Confidence Limits.

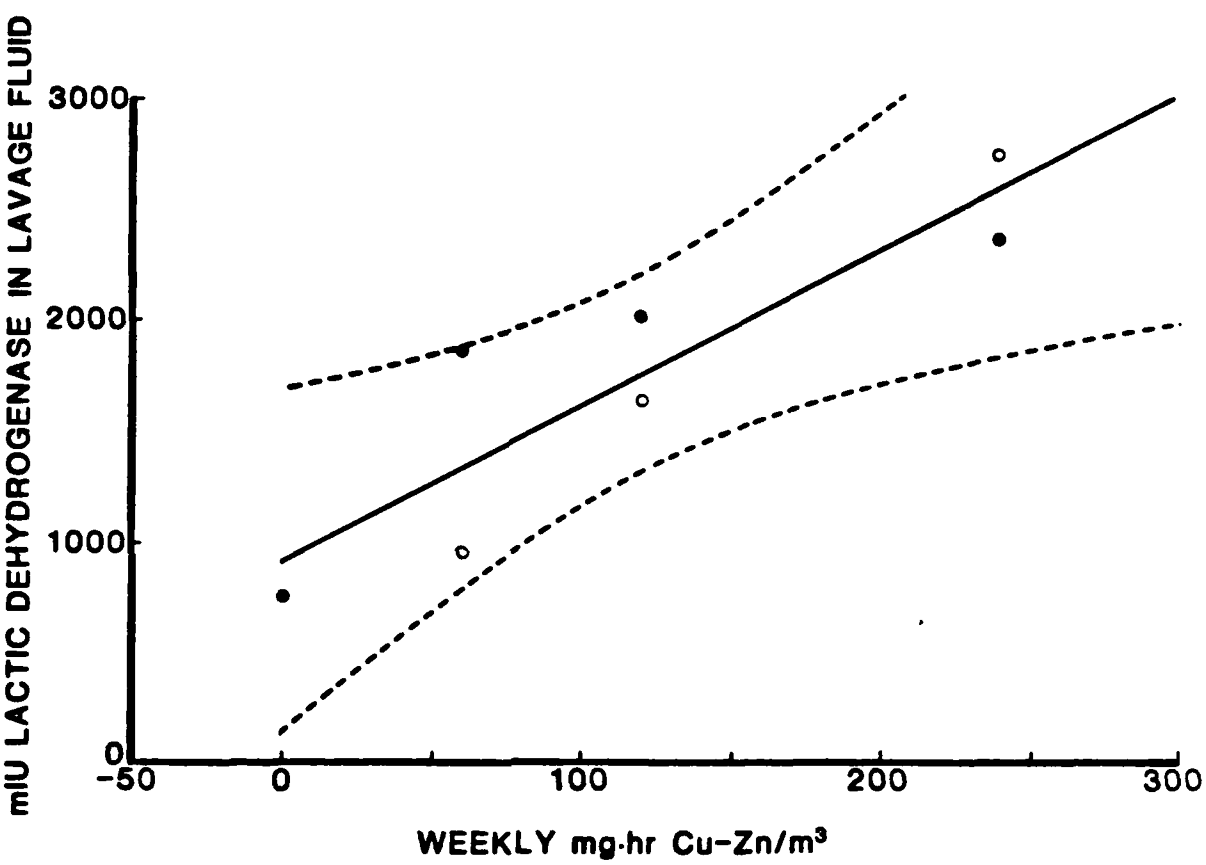


Figure E-6. Fit of a Straight Line to the Pulmonary Alveolar Macrophage Numbers in Lung Lavage Fluid at the End of Exposure for Exposures Twice Per Week (o) and Four Times Per Week (•). Dashed Lines Represent 95% Confidence Limits.

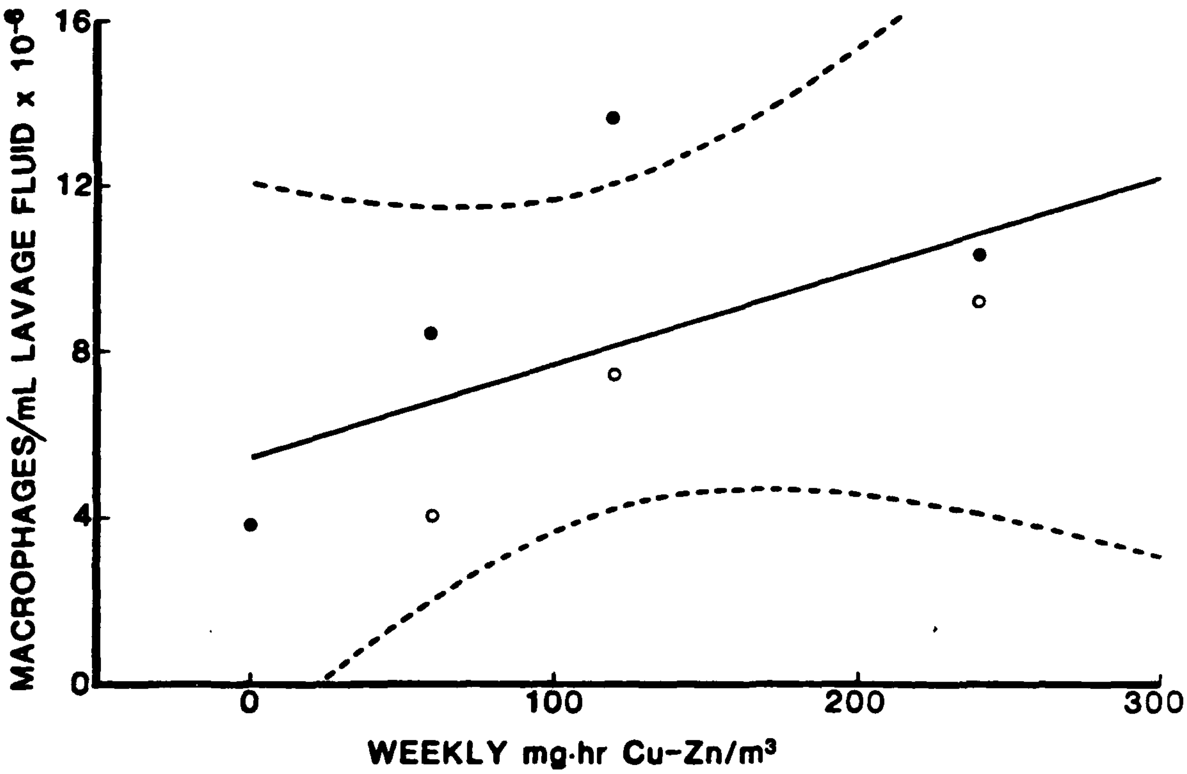


Figure E-7. Fit of a Straight Line to the Polymorphonuclear Leukocyte Numbers in Lung Lavage Fluid at the End of Exposure for Exposures Twice Per Week (○) and Four Times Per Week (●). Dashed Lines Represent 95% Confidence Limits.

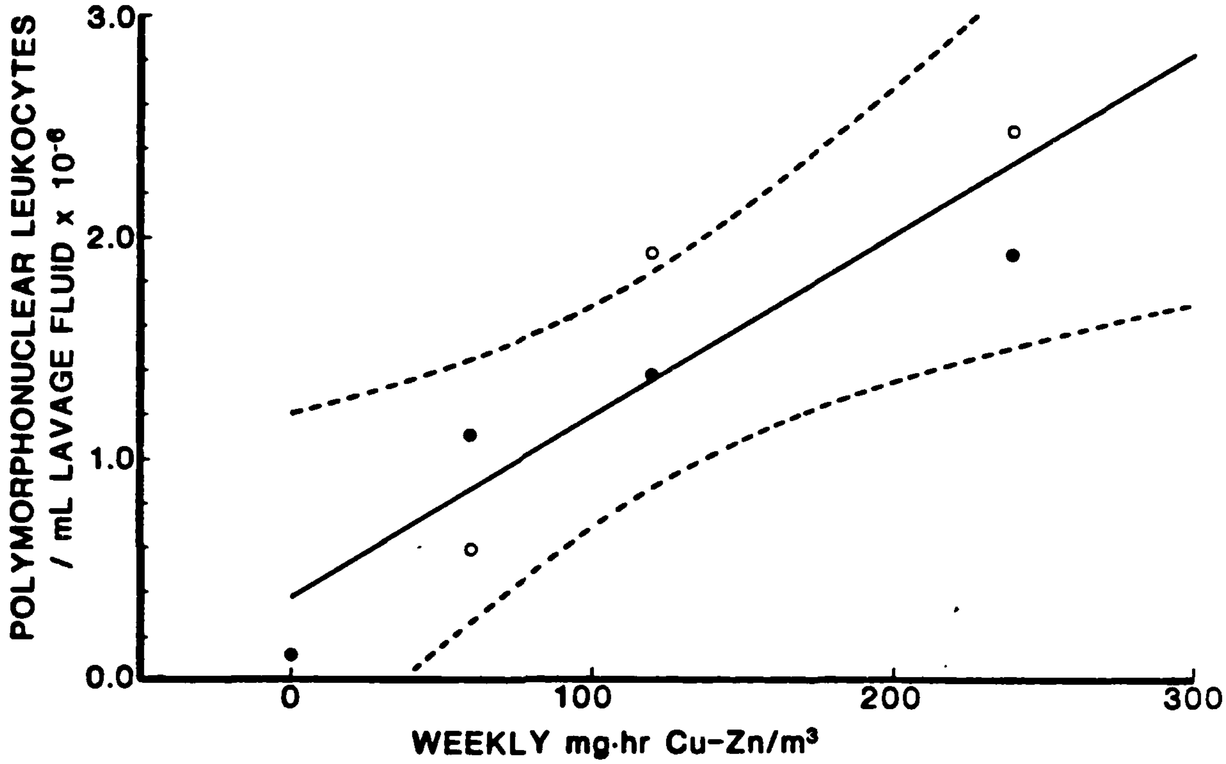


Figure E-8. Fit of a Straight Line to the Protein Content of Lung Lavage Fluid at the End of Exposure for Exposures Twice Per Week (o) and Four Times Per Week (•). Dashed Lines Represent 95% Confidence Limits.

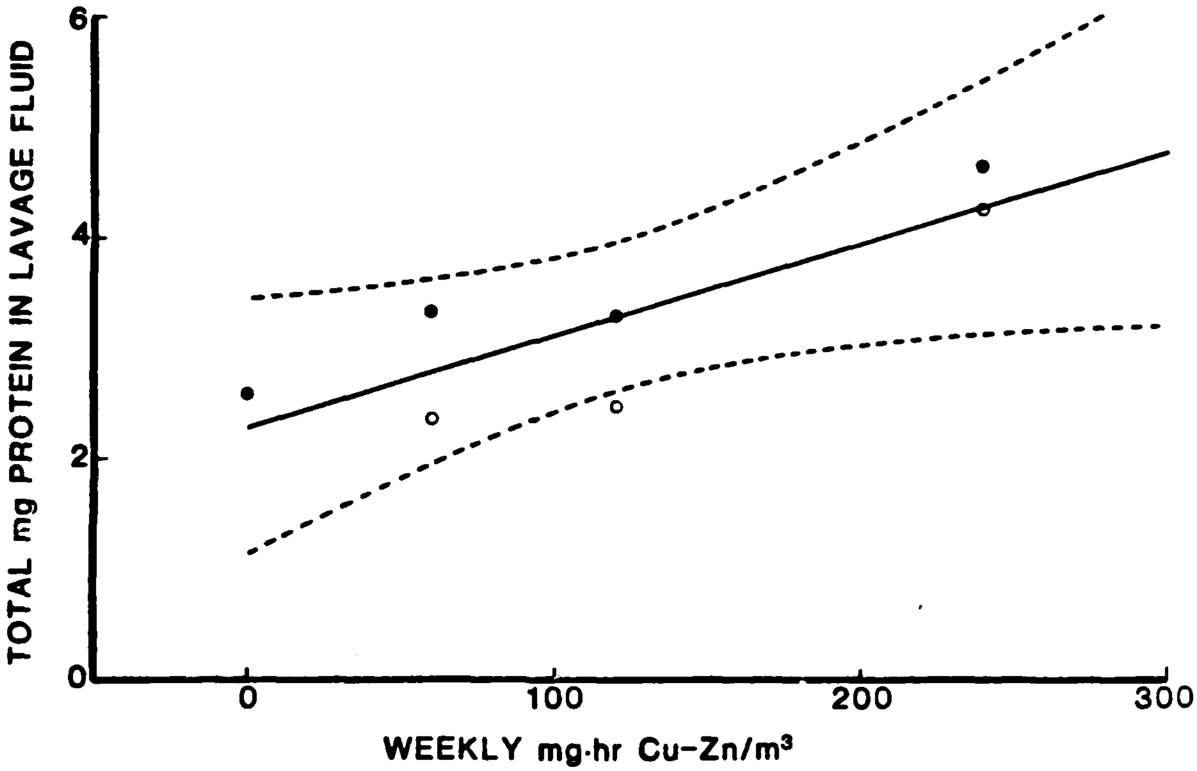


Figure E-9. Fits of Straight Lines to the Collagen Content of lung Lavage Fluid at the End of Exposure for Exposures Twice Per Week (o) and Four Times Per Week (●). Dashed Lines Represent 95% Confidence Limits.

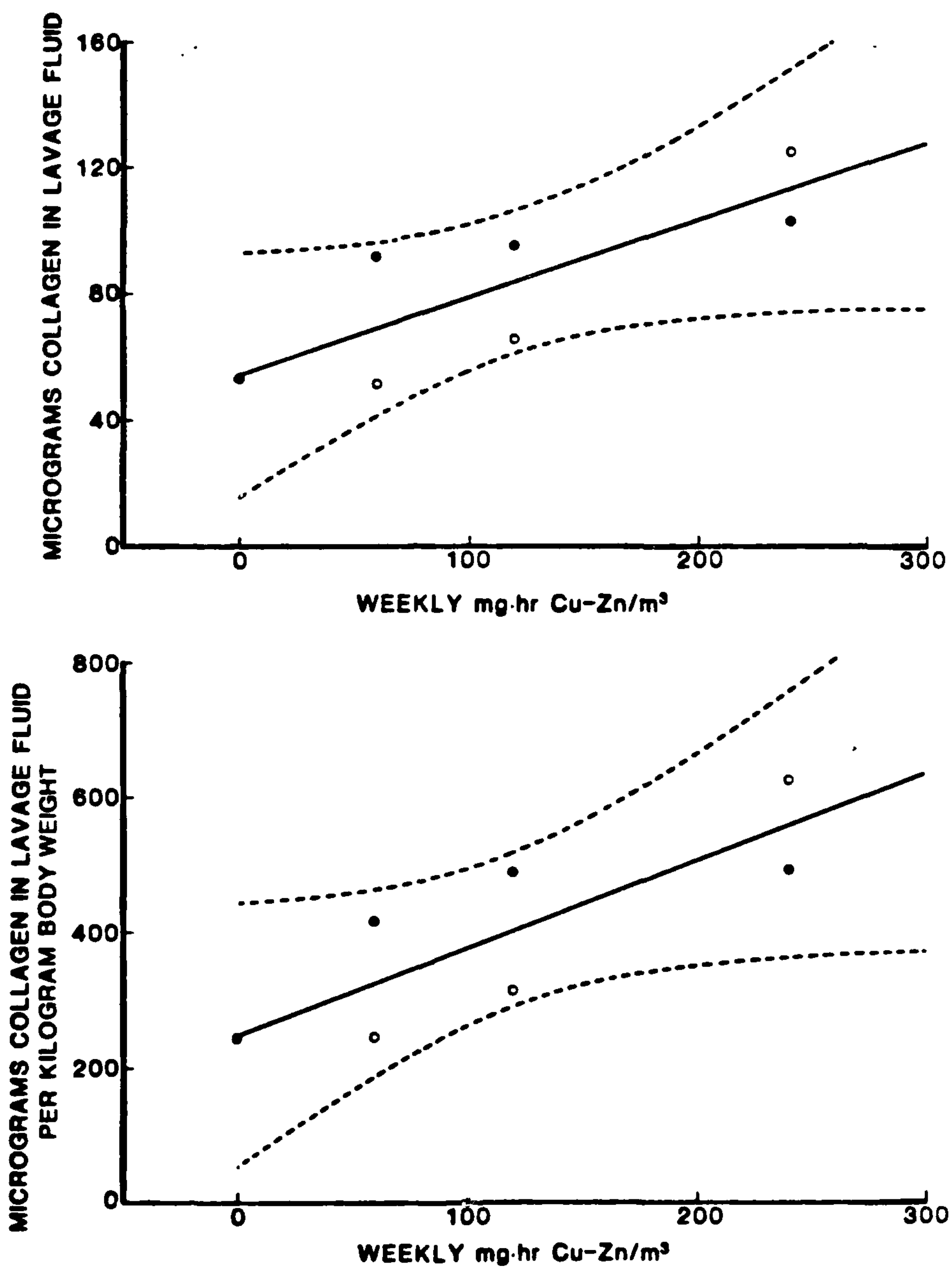


Figure E-10. Fits of Straight Lines to Date for Total Lymphoid Cells in Lung-Associated Lymph Nodes at the End of Exposure and After Recovery. Dashed Lines Represent 95% Confidence Limits; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week.

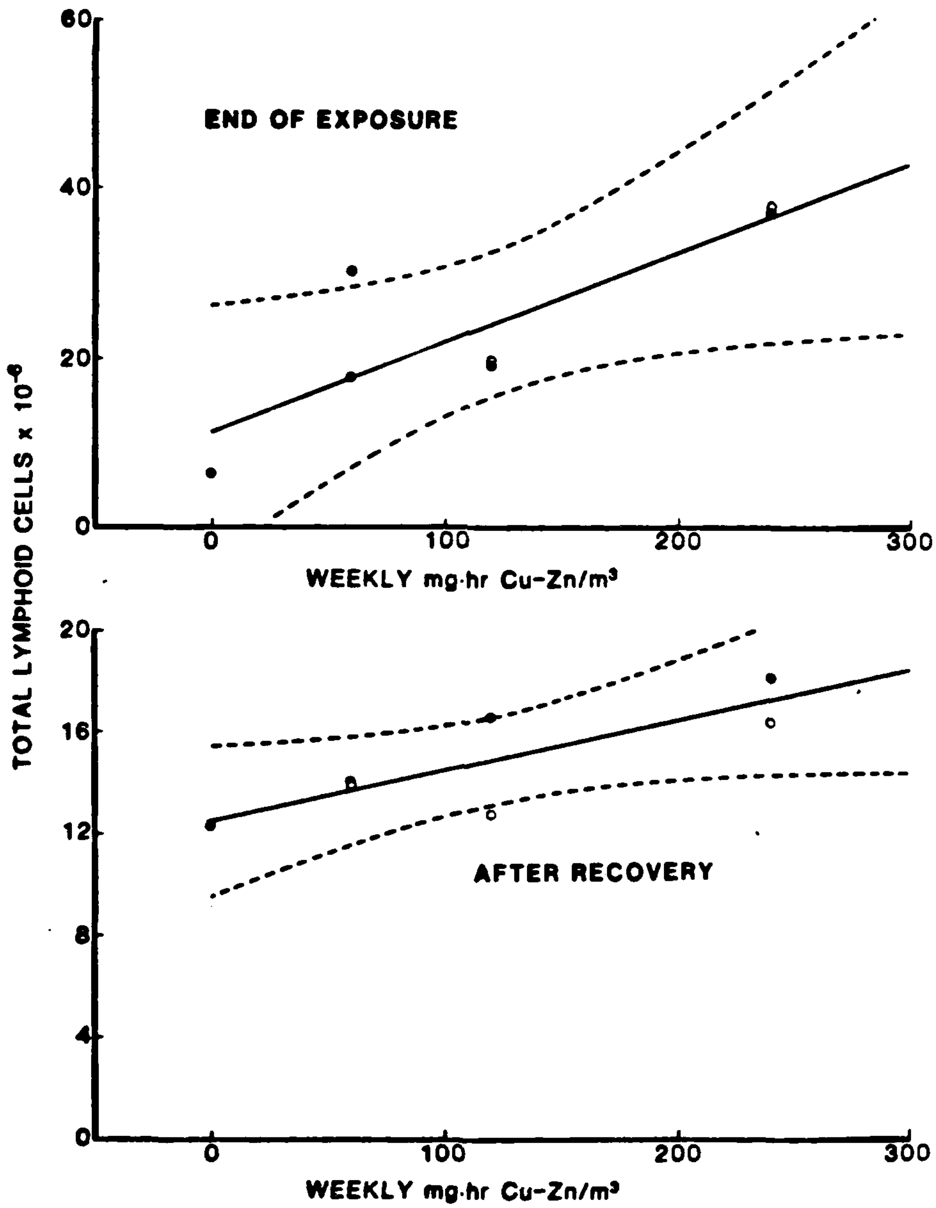


Figure E-11. Fits of Straight Lines to Data for Total Antibody-forming Cells in Lung-Associated Lymph Nodes at the End of Exposure and After Recovery. Dashed Lines Represent 95% Confidence Limits; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week.

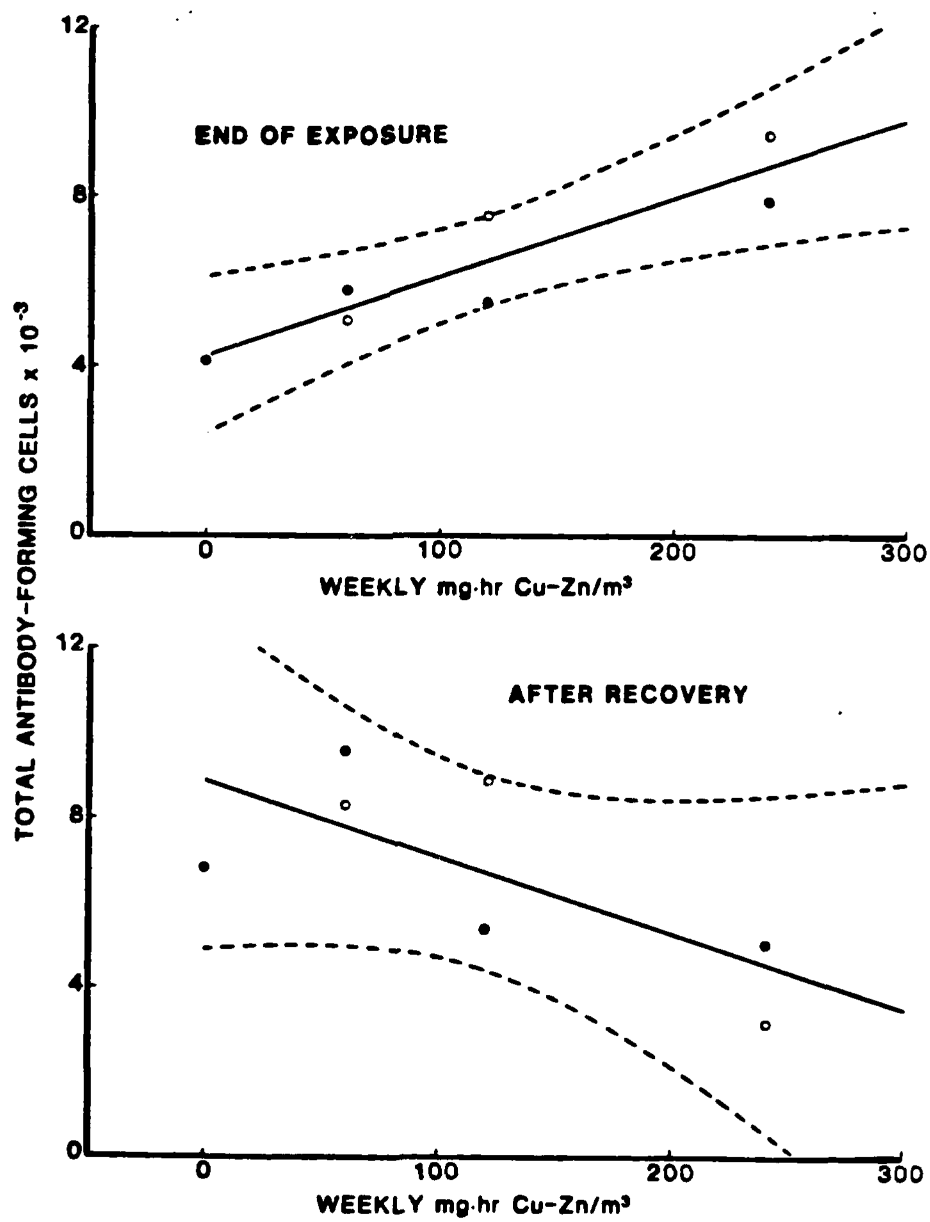


Figure E-12. Fits of Straight Lines to Data for Antibody-forming Cells per Million Lymphocytes in Lung-associated Lymph Nodes at the End of Exposure and After Recovery. Dashed Lines Represent 95% Confidence Limits; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week.

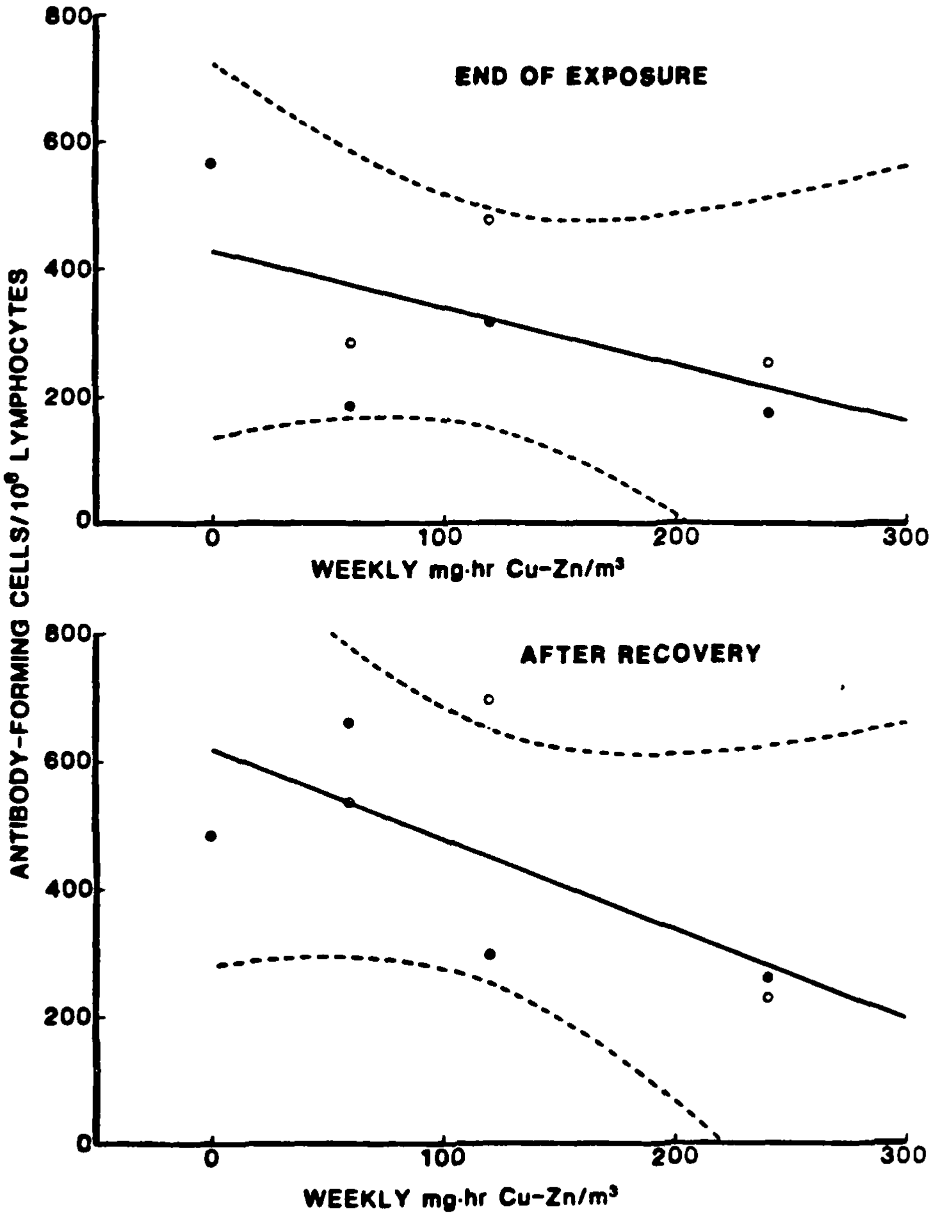


Figure E-13. Fits of Straight Lines to Phagocytosis Data for Evaluations Made at the End of Exposure and After Recovery. Dashed Lines Represent 95% Confidence Limits; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week.

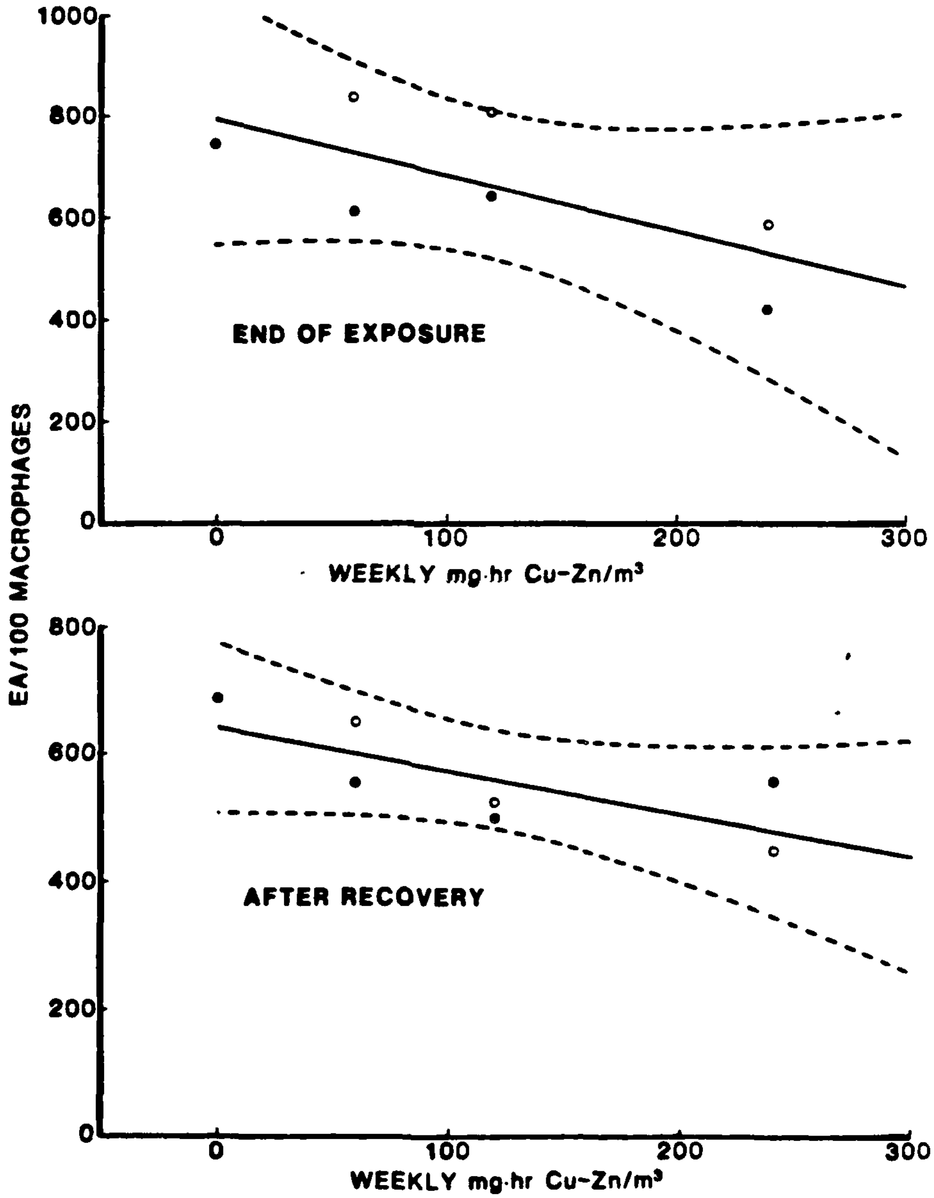


Figure E-14. Fits of Straight Lines to Histopathology Results for Atrophy of Olfactory Epithelium; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week. Dashed Lines Represent 95% Confidence Limits.

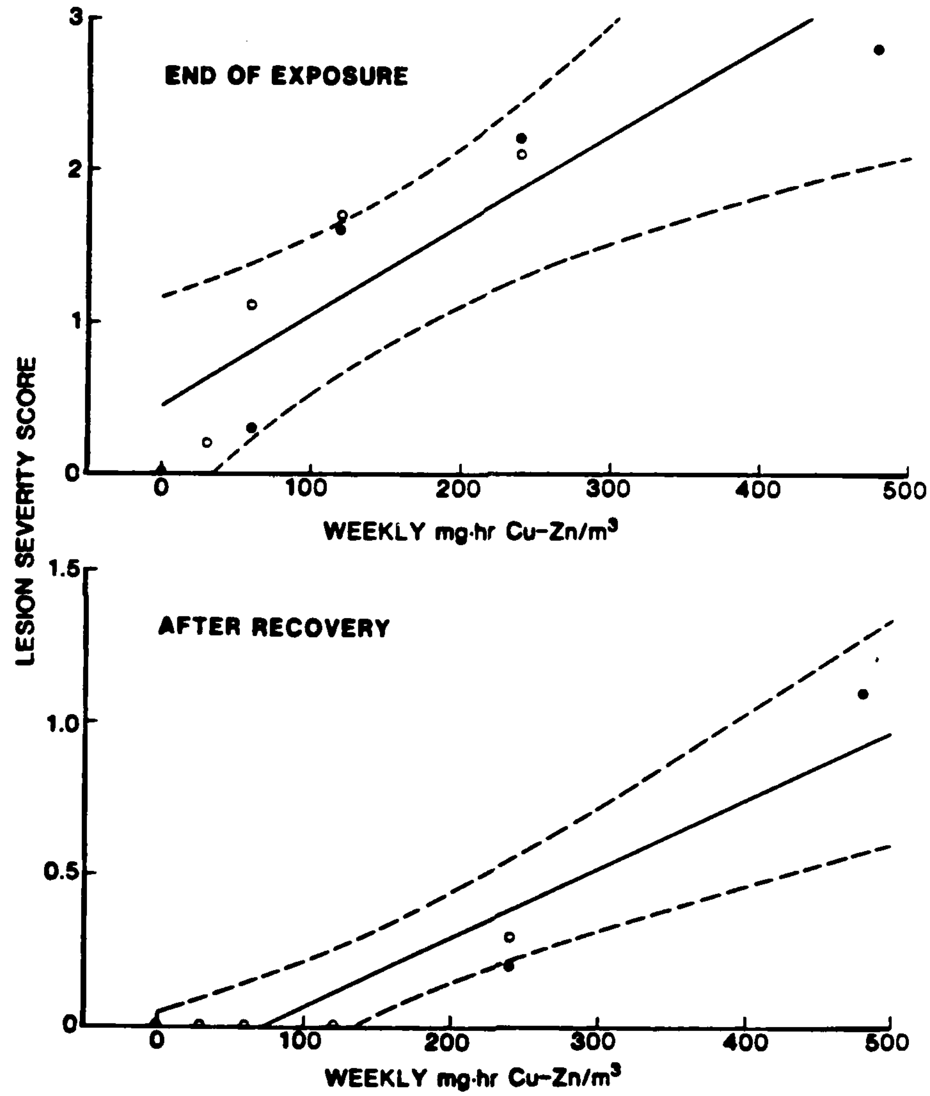


Figure E-15. Fits of Straight Lines to Histopathology Results for Goblet Cell Hyperplasia, Nasal Respiratory Epithelium; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Weeks. Dashed Lines Represent 95% Confidence Limits.

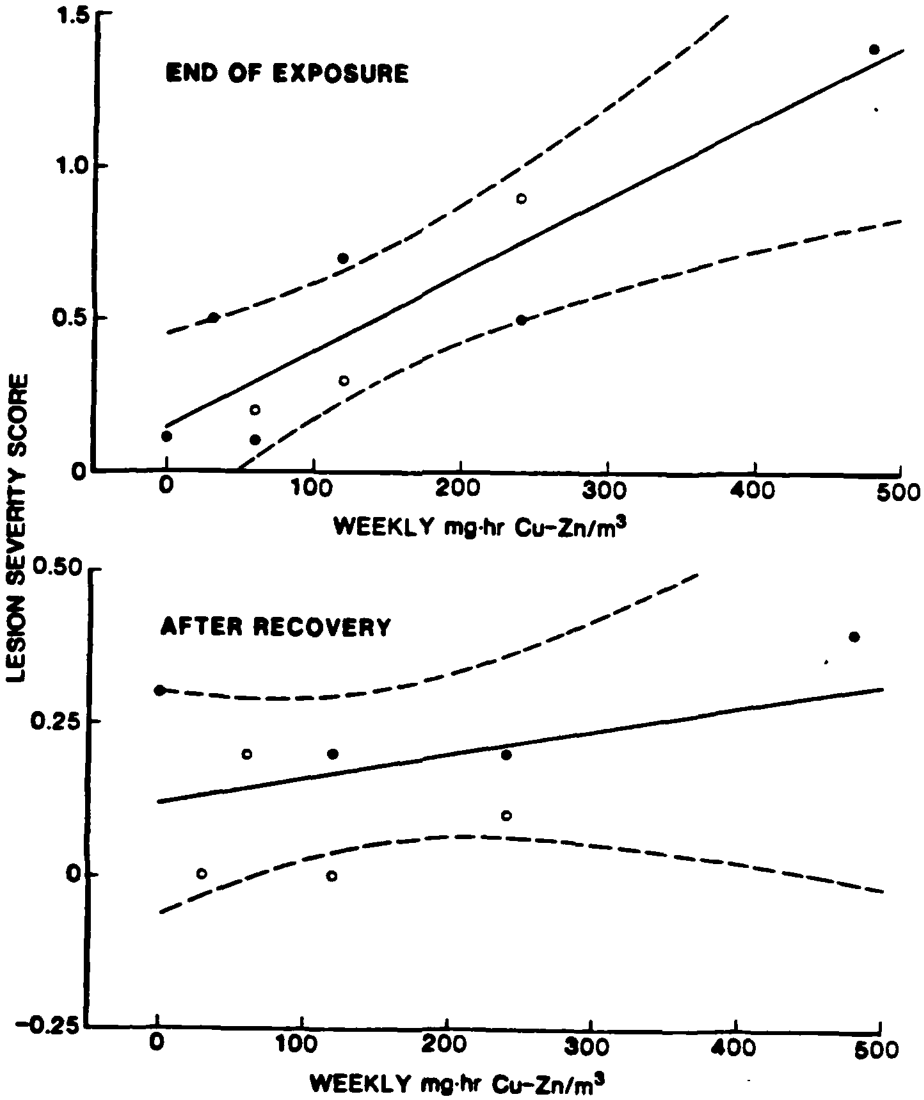


Figure E-16. Fit of a Straight Line to Histopathology Results for Focal Necrotizing Alveolitis of the Lungs at the End of Exposure; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week. Dashed Lines Represent 95% Confidence Limits.

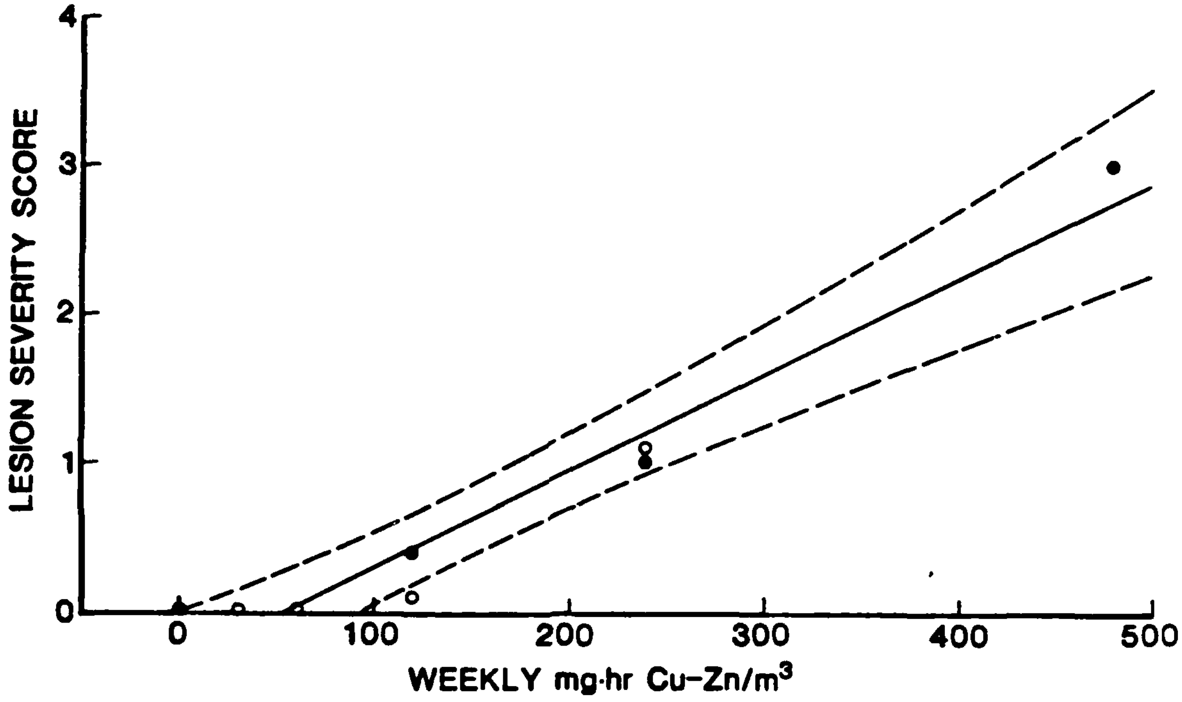


Figure E-17. Fits of Straight Lines to Histopathology Results for Alveolar Macrophage Hyperplasia ○ = Exposures 2 Days/Week; ● = Exposures 4 Days/Week. Dashed Lines Represent 95% Confidence Limits.

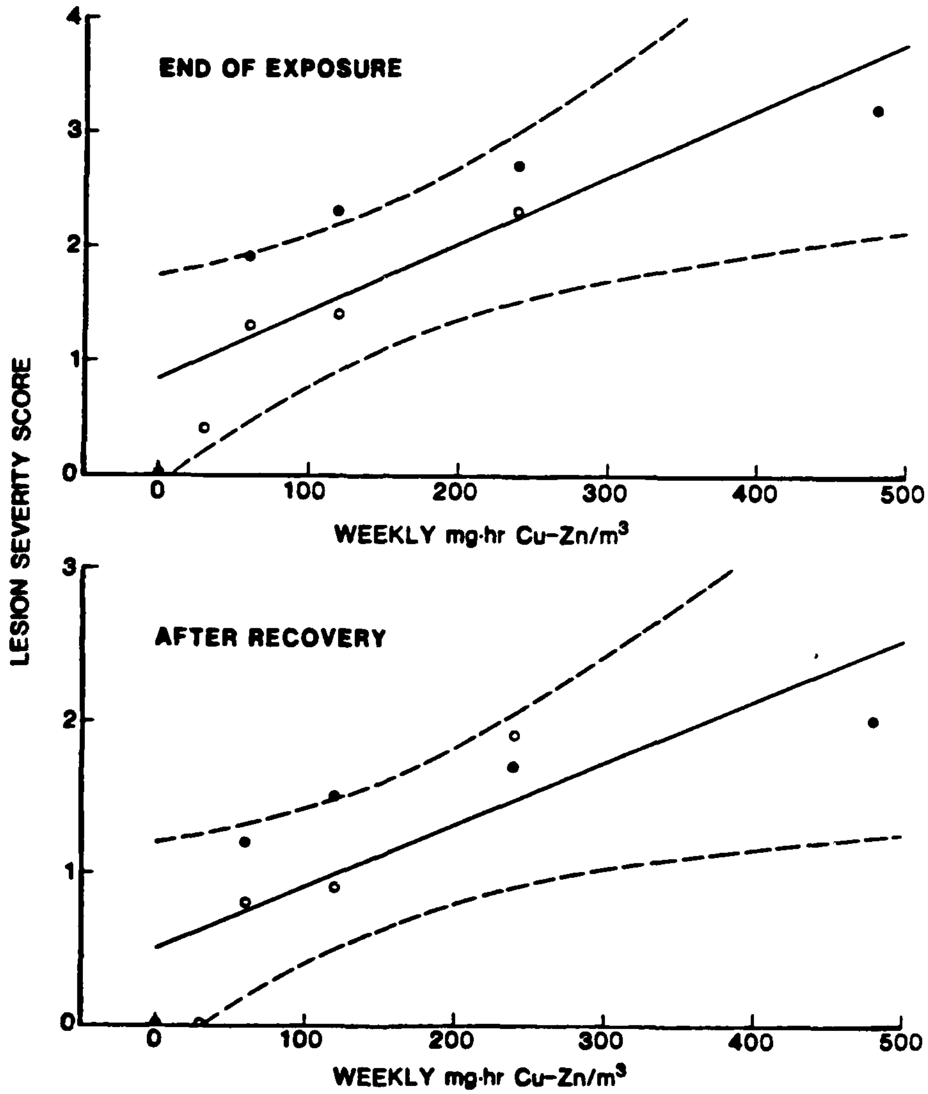
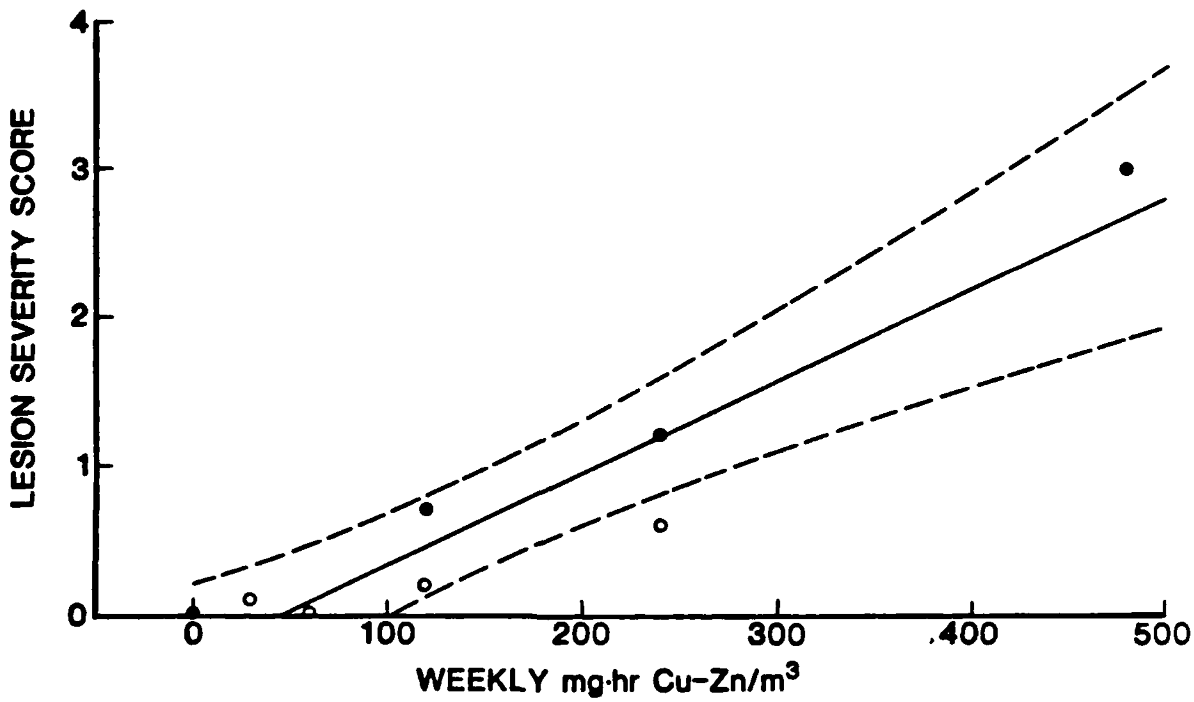


Figure E-18. Fit of a Straight Line to Histopathology Results for Goblet Cell Hyperplasia in Bronchi and Bronchioles at the End of Exposure; ● = Exposures 4 Days/Week; ○ = Exposures 2 Days/Week. Dashed Lines Represent 95% Confidence Limits.



F. APPENDIX F: ATOMIC ABSORPTION ANALYSIS RESULTS

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	ASSIGN CODE	TISSUE	GRAMS	µg Cu	µg Zn	µg Cu/g	µg Zn/g	µg(Cu+Zn)	µg(Cu+Zn)/g
240-4	4274	190	EOE	FEMUR	2.80	1.80	466.00	0.64	166.43	467.80	167.07
240-4	4274	195	REC	FEMUR	2.91	1.80	492.30	0.62	169.18	494.10	169.79
240-4	4274	199	REC	FEMUR	2.73	3.70	345.10	1.36	126.41	348.80	127.77
240-4	4274	200	REC	FEMUR	3.05	2.30	121.20	0.75	39.74	123.50	40.49
240-4	4274	206	EOE	FEMUR	2.77	1.80	108.20	0.65	39.06	110.00	39.71
240-4	4274	210	EOE	FEMUR	3.05	0.47	65.10	0.15	21.34	65.57	21.50
240-4	4274	632	REC	FEMUR	1.95	1.30	106.10	0.67	54.41	107.40	55.08
240-4	4274	640	REC	FEMUR	2.11	1.00	331.60	0.47	157.16	332.60	157.63
240-4	4274	641	REC	FEMUR	2.13	1.70	102.40	0.80	48.08	104.10	48.87
240-4	4274	643	EOE	FEMUR	1.97	1.90	304.80	0.96	154.72	306.70	155.69
240-4	4274	648	EOE	FEMUR	1.99	1.20	494.80	0.60	248.64	496.00	249.25
240-4	4274	651	EOE	FEMUR	1.97	1.00	524.10	0.51	266.04	525.10	266.55
240-4	4274	190	EOE	KIDNEYS	2.19	41.20	12.90	18.81	5.89	54.10	24.70
240-4	4274	195	REC	KIDNEYS	2.10	25.60	12.90	12.19	6.14	38.50	18.33
240-4	4274	199	REC	KIDNEYS	1.98	21.30	41.70	10.76	21.06	63.00	31.82
240-4	4274	200	REC	KIDNEYS	2.06	23.80	24.20	11.55	11.75	48.00	23.30
240-4	4274	206	EOE	KIDNEYS	2.03	24.40	12.40	12.02	6.11	36.80	18.13
240-4	4274	210	EOE	KIDNEYS	2.12	24.80	21.70	11.70	10.24	46.50	21.93
240-4	4274	632	REC	KIDNEYS	1.22	18.00	10.90	14.75	8.93	28.90	23.69
240-4	4274	640	REC	KIDNEYS	1.29	33.80	9.90	26.20	7.67	43.70	33.88
240-4	4274	641	REC	KIDNEYS	1.32	24.10	8.90	18.26	6.74	33.00	25.00
240-4	4274	643	EOE	KIDNEYS	1.23	25.10	18.70	20.41	15.20	43.80	35.61
240-4	4274	648	EOE	KIDNEYS	1.24	26.20	12.90	21.13	10.40	39.10	31.53
240-4	4274	651	EOE	KIDNEYS	1.24	25.40	11.20	20.48	9.03	36.60	29.52
240-4	4274	176	REC	LALN	0.60	1.30	8.20	2.17	13.67	9.59	15.83
240-4	4274	177	REC	LALN	0.66	1.80	7.20	2.73	10.91	9.00	13.64
240-4	4274	178	EOE	LALN	0.42	1.50	3.60	3.57	8.57	5.10	12.14
240-4	4274	185	EOE	LALN	0.51	1.40	4.40	2.75	8.63	5.80	11.37
240-4	4274	186	EOE	LALN	0.44	1.40	5.20	3.18	11.82	6.60	15.00
240-4	4274	192	REC	LALN	0.66	1.50	5.70	2.27	8.64	7.20	10.91
240-4	4274	645	REC	LALN	0.41	1.10	5.20	2.68	12.68	6.30	15.37
240-4	4274	646	EOE	LALN	0.39	1.50	19.20	3.85	49.23	20.70	53.08
240-4	4274	647	EOE	LALN	0.27	0.83	2.96	3.07	10.96	3.79	14.04
240-4	4274	654	EOE	LALN	0.30	0.98	3.20	3.27	10.67	4.18	13.93
240-4	4274	655	REC	LALN	0.42	1.10	5.80	2.62	13.81	6.90	16.43
240-4	4274	659	REC	LALN	0.46	1.10	18.30	2.39	39.78	19.40	42.17
240-4	4274	190	EOE	LIVER	10.05	14.00	36.30	1.39	3.61	50.30	5.00
240-4	4274	195	REC	LIVER	9.03	16.70	35.90	1.85	3.98	52.60	5.83
240-4	4274	199	REC	LIVER	9.70	42.40	159.10	4.37	16.40	201.50	20.77
240-4	4274	200	REC	LIVER	9.78	48.40	120.40	4.95	12.31	168.80	17.26
240-4	4274	206	EOE	LIVER	9.17	36.90	118.70	4.02	12.94	155.60	16.97
240-4	4274	210	EOE	LIVER	9.50	11.10	34.20	1.17	3.60	45.30	4.77
240-4	4274	632	REC	LIVER	4.99	23.60	107.90	4.73	21.62	131.50	26.35
240-4	4274	640	REC	LIVER	5.06	23.73	84.72	4.69	16.74	108.45	21.43
240-4	4274	641	REC	LIVER	5.20	21.20	59.60	4.08	11.46	80.80	15.54
240-4	4274	643	EOE	LIVER	5.17	17.40	55.64	3.37	10.76	73.04	14.13
240-4	4274	648	EOE	LIVER	4.74	9.40	31.60	1.98	6.67	41.00	8.65
240-4	4274	651	EOE	LIVER	4.63	29.89	76.14	6.46	16.44	106.03	22.90
240-4	4274	190	EOE	LUNG	1.76	6.40	24.20	3.64	13.75	30.60	17.39
240-4	4274	195	REC	LUNG	1.14	2.00	18.90	1.75	16.58	20.90	18.33

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	ASSIGN CODE	TISSUE	GRAMS	µg Cu	µg Zn	µg Cu/g	µg Zn/g	µg(Cu+Zn)	µg(Cu+Zn)/g
240-4	4274	199	REC	LUNG	1.18	3.00	20.60	2.54	17.46	23.60	20.00
240-4	4274	200	REC	LUNG	1.24	2.30	26.10	1.85	21.05	28.40	22.90
240-4	4274	206	EOE	LUNG	1.36	3.60	45.70	2.65	33.60	49.30	36.25
240-4	4274	210	EOE	LUNG	1.48	4.10	26.10	2.77	17.64	30.20	20.41
240-4	4274	632	REC	LUNG	0.90	2.00	14.00	2.22	15.56	16.00	17.78
240-4	4274	640	REC	LUNG	0.95	2.50	14.10	2.63	14.84	16.60	17.47
240-4	4274	641	REC	LUNG	1.04	2.00	11.00	1.92	10.58	13.00	12.50
240-4	4274	643	EOE	LUNG	1.22	4.90	18.60	4.02	15.25	23.59	19.26
240-4	4274	648	EOE	LUNG	1.19	4.60	11.30	3.87	9.50	15.99	13.36
240-4	4274	651	EOE	LUNG	1.36	5.50	28.60	4.04	21.03	34.19	25.07
240-4	4274	190	EOE	MUSCLE	4.70	1.80	27.90	0.38	5.94	29.70	6.32
240-4	4274	195	REC	MUSCLE	5.62	5.50	30.10	0.98	5.36	35.60	6.33
240-4	4274	199	REC	MUSCLE	5.42	3.00	15.40	0.55	2.84	18.40	3.39
240-4	4274	200	REC	MUSCLE	6.17	4.40	31.40	0.71	5.09	35.80	5.80
240-4	4274	206	EOE	MUSCLE	4.56	2.80	17.50	0.61	3.84	20.30	4.45
240-4	4274	210	EOE	MUSCLE	4.99	3.10	26.70	0.62	5.35	29.80	5.97
240-4	4274	632	REC	MUSCLE	3.64	3.30	9.30	0.91	2.55	12.60	3.46
240-4	4274	640	REC	MUSCLE	3.50	3.90	19.10	1.11	5.46	23.00	6.57
240-4	4274	641	REC	MUSCLE	3.97	4.80	38.60	1.21	9.72	43.40	10.93
240-4	4274	643	EOE	MUSCLE	3.36	3.50	10.90	1.04	3.24	14.40	4.29
240-4	4274	648	EOE	MUSCLE	3.04	2.70	5.40	0.89	1.78	8.10	2.66
240-4	4274	651	EOE	MUSCLE	3.41	4.20	33.20	1.23	9.74	37.40	10.97
240-4	4274	195	REC	URINE	0.02	0.73	1.60	36.50	80.00	2.33	116.50
240-4	4274	199	REC	URINE	0.22	0.02	1.10	0.10	5.00	1.12	5.10
240-4	4274	200	REC	URINE	0.01	0.02	0.61	1.80	61.00	0.63	62.80
240-4	4274	206	EOE	URINE	0.53	0.25	1.10	0.47	2.08	1.35	2.55
240-4	4274	210	EOE	URINE	0.23	0.10	1.29	0.43	5.61	1.39	6.04
SHAM	4277	266	EOE	FEMUR	3.08	3.50	391.40	1.14	127.08	394.90	128.21
SHAM	4277	286	REC	FEMUR	2.83	1.30	183.90	0.46	64.98	185.20	65.44
SHAM	4277	287	EOE	FEMUR	2.56	3.40	476.70	1.33	186.21	480.10	187.54
SHAM	4277	289	REC	FEMUR	2.80	3.10	465.20	1.11	166.14	468.30	167.25
SHAM	4277	294	EOE	FEMUR	2.69	1.10	130.40	0.41	48.48	131.50	48.88
SHAM	4277	296	REC	FEMUR	2.74	2.10	559.20	0.77	204.09	561.30	204.85
SHAM	4277	705	EOE	FEMUR	2.03	2.00	459.20	0.99	226.21	461.20	227.19
SHAM	4277	706	REC	FEMUR	2.16	1.50	465.10	0.69	215.32	466.60	216.02
SHAM	4277	712	EOE	FEMUR	1.92	0.98	429.40	0.51	223.65	430.38	224.16
SHAM	4277	715	EOE	FEMUR	2.02	0.87	128.10	0.43	63.42	128.97	63.85
SHAM	4277	722	REC	FEMUR	2.49	1.30	415.10	0.52	166.71	416.40	167.23
SHAM	4277	725	REC	FEMUR	2.09	0.87	331.90	0.42	158.80	332.77	159.22
SHAM	4277	266	EOE	KIDNEYS	2.09	16.00	10.50	7.66	5.02	26.50	12.68
SHAM	4277	286	REC	KIDNEYS	2.19	28.40	11.00	12.97	5.02	39.40	17.99
SHAM	4277	287	EOE	KIDNEYS	2.07	22.80	14.90	11.01	7.20	37.70	18.21
SHAM	4277	289	REC	KIDNEYS	2.14	35.30	11.10	16.50	5.19	46.40	21.68
SHAM	4277	294	EOE	KIDNEYS	1.98	22.90	9.20	11.57	4.65	32.10	16.21
SHAM	4277	296	REC	KIDNEYS	2.12	21.80	25.40	10.28	11.98	47.20	22.26
SHAM	4277	705	EOE	KIDNEYS	1.13	17.00	14.90	15.04	13.19	31.90	28.23
SHAM	4277	706	REC	KIDNEYS	1.37	21.40	19.70	15.62	14.38	41.10	30.00
SHAM	4277	712	EOE	KIDNEYS	1.18	18.70	17.40	15.85	14.75	36.10	30.59
SHAM	4277	715	EOE	KIDNEYS	1.17	22.50	9.20	19.23	7.86	31.70	27.09
SHAM	4277	722	REC	KIDNEYS	1.30	18.00	28.90	13.85	22.23	46.90	36.08
SHAM	4277	725	REC	KIDNEYS	1.23	31.40	25.40	25.53	20.65	56.80	46.18
SHAM	4277	267	EOE	LALN	0.56	1.09	9.50	1.95	16.96	10.59	18.91
SHAM	4277	268	EOE	LALN	0.56	1.08	8.80	1.93	15.71	9.88	17.64

DOSE CODE	EXPT NUMBER	ANIMAL NUMBER	ASSIGN CODE	TISSUE	GRAMS	µg Cu	µg Zn	µg Cu/g	µg Zn/g	µg(Cu+Zn)	µg(Cu+Zn)/g
SHAM	4277	271	REC	LALN	0.63	1.20	10.60	1.90	16.83	11.80	18.73
SHAM	4277	280	REC	LALN	0.63	0.98	10.50	1.56	16.67	11.48	18.22
SHAM	4277	281	EOE	LALN	0.33	0.82	5.90	2.48	17.88	6.72	20.36
SHAM	4277	293	REC	LALN	0.60	1.04	8.70	1.73	14.50	9.74	16.23
SHAM	4277	703	REC	LALN	0.45	0.82	8.90	1.82	19.78	9.72	21.60
SHAM	4277	707	REC	LALN	0.45	0.72	7.70	1.60	17.11	8.42	18.71
SHAM	4277	718	EOE	LALN	0.28	0.67	6.40	2.39	22.86	7.07	25.25
SHAM	4277	719	EOE	LALN	0.41	0.81	7.00	1.98	17.07	7.81	19.05
SHAM	4277	726	REC	LALN	0.46	0.75	8.00	1.63	17.39	8.75	19.02
SHAM	4277	729	EOE	LALN	0.33	0.81	8.10	2.45	24.55	8.91	27.00
SHAM	4277	266	EOE	LIVER	10.71	16.40	36.10	1.53	3.37	52.50	4.90
SHAM	4277	286	REC	LIVER	10.62	11.80	31.30	1.11	2.95	43.10	4.06
SHAM	4277	287	EOE	LIVER	9.79	12.80	25.40	1.31	2.59	38.20	3.90
SHAM	4277	289	REC	LIVER	9.43	14.10	33.10	1.50	3.51	47.20	5.01
SHAM	4277	294	EOE	LIVER	9.82	11.90	43.20	1.21	4.40	55.10	5.61
SHAM	4277	296	REC	LIVER	9.69	19.70	47.80	2.03	4.93	67.50	6.97
SHAM	4277	705	EOE	LIVER	4.35	18.62	41.60	4.28	9.56	60.22	13.84
SHAM	4277	706	REC	LIVER	5.71	17.00	27.40	2.98	4.80	44.40	7.78
SHAM	4277	712	EOE	LIVER	5.07	23.80	30.20	4.69	5.96	54.00	10.65
SHAM	4277	715	EOE	LIVER	5.23	16.91	75.83	3.23	14.50	92.74	17.73
SHAM	4277	722	REC	LIVER	5.12	20.20	31.80	3.95	6.21	52.00	10.16
SHAM	4277	725	REC	LIVER	6.19	18.90	30.40	3.05	4.91	49.30	7.96
SHAM	4277	266	EOE	LUNG	0.94	1.03	13.30	1.10	14.15	14.33	15.24
SHAM	4277	286	REC	LUNG	1.00	0.99	18.00	0.99	18.00	18.99	18.99
SHAM	4277	287	EOE	LUNG	1.02	1.11	20.40	1.09	20.00	21.51	21.09
SHAM	4277	289	REC	LUNG	1.05	1.01	17.60	0.96	16.76	18.61	17.72
SHAM	4277	294	EOE	LUNG	0.97	1.26	20.40	1.30	21.03	21.66	22.33
SHAM	4277	296	REC	LUNG	1.06	1.11	19.90	1.05	18.77	21.01	19.82
SHAM	4277	705	EOE	LUNG	0.74	0.84	16.60	1.14	22.43	17.44	23.57
SHAM	4277	706	REC	LUNG	0.77	0.87	15.80	1.13	20.52	16.67	21.65
SHAM	4277	712	EOE	LUNG	0.75	0.86	16.30	1.15	21.73	17.16	22.88
SHAM	4277	715	EOE	LUNG	0.80	0.99	15.30	1.24	19.13	16.29	20.36
SHAM	4277	722	REC	LUNG	0.81	0.92	19.50	1.14	24.07	20.42	25.21
SHAM	4277	725	REC	LUNG	0.83	0.89	17.40	1.07	20.96	18.29	22.04
SHAM	4277	266	EOE	MUSCLE	5.54	3.70	23.10	0.67	4.17	26.80	4.84
SHAM	4277	286	REC	MUSCLE	6.32	4.00	14.70	0.63	2.33	18.70	2.96
SHAM	4277	287	EOE	MUSCLE	4.26	2.50	61.20	0.59	14.37	63.70	14.95
SHAM	4277	289	REC	MUSCLE	5.63	3.00	20.50	0.53	3.64	23.50	4.18
SHAM	4277	294	EOE	MUSCLE	6.07	5.90	65.80	0.97	10.84	71.70	11.81
SHAM	4277	296	REC	MUSCLE	6.66	4.50	21.50	0.68	3.23	26.00	3.90
SHAM	4277	705	EOE	MUSCLE	3.57	3.10	10.00	0.87	2.80	13.10	3.67
SHAM	4277	706	REC	MUSCLE	3.77	4.50	10.70	1.19	2.84	15.20	4.03
SHAM	4277	712	EOE	MUSCLE	3.21	2.90	12.60	0.90	3.93	15.50	4.83
SHAM	4277	715	EOE	MUSCLE	3.64	3.30	15.50	0.91	4.26	18.80	5.16
SHAM	4277	722	REC	MUSCLE	3.35	3.10	19.40	0.93	5.79	22.50	6.72
SHAM	4277	725	REC	MUSCLE	3.61	3.00	13.60	0.83	3.77	16.60	4.60
SHAM	4277	266	EOE	URINE	0.04	0	0.51	0	12.75	0.51	12.75
SHAM	4277	283	REC	URINE	0.28	0.12	0.67	0.43	2.39	0.79	2.82
SHAM	4277	286	REC	URINE	0.07	0.21	0.41	3.00	5.86	0.62	8.86
SHAM	4277	287	EOE	URINE	0.08	0.96	0.91	12.00	11.38	1.87	23.38
SHAM	4277	289	REC	URINE	0.20	0.24	0.77	1.20	3.85	1.01	5.05
SHAM	4277	294	EOE	URINE	0.05	0.24	0.33	4.80	6.60	0.57	11.40

G. APPENDIX G: RESULTS FOR INDIVIDUAL ANIMAL FUNCTION EVALUATIONS

PART 1. EVALUATIONS AT THE END OF THE EXPOSURE SERIES

DOSE CODE	EXPT NO.	ANIMAL NUMBER	BWT (GRAMS)	MV	CDYN	PL	CCORD	TLC	VC	FRC	RV	DLCO	FVC	FVI	PEFR	MEF'	E10	S3
120-2	4270	013	298	78.0	0.62	0.12	0.82	14.6	12.6	3.3	1.9	0.29	13.5	62	116.9	77.0	25	0.57
120-2	4270	014	292	92.6	0.54	0.21	0.78	12.9	11.6	2.6	1.2	0.27	10.9	56	97.1	43.4	20	0.80
120-2	4270	015	291	88.8	0.42	0.13	0.75	13.2	12.0	2.3	1.2	0.27	11.2	55	93.5	44.9	18	0.61
120-2	4270	017	269	70.4	0.51	0.09	0.65	11.6	10.7	2.3	0.9	0.25	11.8	70	115.1	79.9	27	0.58
120-2	4270	028	292	93.7	0.41	0.13	0.77	13.6	11.9	2.9	1.8	0.28	12.6	52	91.7	48.8	22	0.62
120-2	4270	031	280	87.2	0.49	0.15	0.85	13.0	11.7	2.7	1.3	0.29	12.0	51	93.9	33.7	9	0.68
120-2	4270	032	294	99.8	0.38	0.16	0.82	14.1	12.7	2.9	1.4	0.31	13.7	72	134.7	98.8	19	0.59
120-2	4270	038	288	99.0	0.46	0.13	0.78	14.4	12.7	3.8	1.7	0.33	12.6	71	123.8	88.0	23	0.61
120-2	4270	043	295	95.9	0.51	0.12	0.87	13.9	12.9	2.6	1.0	0.22	13.5	73	126.0	102.8	25	0.52
120-2	4270	049	279	86.9	0.53	0.12	0.67	13.4	11.9	3.1	1.5	0.29	12.6	71	123.8	88.0	23	0.70
60-2	4271	057	277	85.5	0.44	0.15	0.71	13.9	11.9	3.4	2.0	0.27	13.1	45	87.9	36.4	11	0.68
60-2	4271	059	274	81.8	0.49	0.14	0.78	13.1	11.6	3.0	1.4	0.28	12.0	47	76.2	36.6	12	0.70
60-2	4271	068	286	99.1	0.50	0.11	0.84	14.2	12.9	3.1	1.3	0.30	14.2	65	114.4	89.0	26	0.62
60-2	4271	070	303	85.0	0.48	0.12	0.73	13.2	11.7	3.1	1.5	0.30	12.9	74	126.3	98.2	27	0.76
60-2	4271	074	297	90.5	0.46	0.13	0.70	12.4	11.2	2.6	1.2	0.28	11.7	60	107.4	56.0	16	0.76
60-2	4271	075	280	91.6	0.46	0.19	0.65	11.5	10.9	2.2	0.7	0.26	11.7	70	115.9	77.2	25	0.78
60-2	4271	076	306	91.0	0.54	0.14	0.96	15.0	14.2	3.0	0.8	0.28	15.1	47	94.0	55.7	23	0.57
60-2	4271	078	304	82.5	0.50	0.14	0.80	13.7	12.4	2.6	1.3	0.25	12.1	48	84.7	41.1	16	0.62
60-2	4271	087	300	80.7	0.58	0.15	0.75	13.3	11.8	3.1	1.5	0.26	11.9	54	104.1	39.3	8	0.70
60-2	4271	089	296	89.2	0.45	0.18	0.78	13.1	12.4	2.2	0.7	0.26	11.9	47	94.6	28.1	4	0.70
240-2	4272	092	292	67.8	0.43	0.18	0.69	13.3	11.8	3.2	1.5	0.27	13.0	46	85.7	41.9	16	0.62
240-2	4272	098	284	85.9	0.40	0.16	0.71	12.9	11.8	2.8	1.2	0.27	12.4	55	100.3	49.8	15	0.64
240-2	4272	103	276	86.4	0.36	0.17	0.57	10.8	9.7	2.7	1.1	0.26	11.4	72	111.6	81.8	21	0.77
240-2	4272	114	283	93.7	0.49	0.14	0.74	13.4	12.0	3.2	1.4	0.27	12.8	69	122.6	80.1	19	0.62
240-2	4272	117	288	78.3	0.36	0.17	0.57	11.5	10.1	2.9	1.4	0.25	11.5	72	105.5	85.3	18	0.77
240-2	4272	118	280	89.9	0.38	0.18	0.66	12.3	11.1	3.0	1.2	0.25	12.3	65	95.0	78.8	20	0.75
240-2	4272	127	290	91.8	0.56	0.14	0.79	13.8	12.4	2.8	1.4	0.25	13.5	64	107.6	82.7	18	0.56
240-2	4272	128	293	68.0	0.44	0.15	0.86	14.3	12.8	3.0	1.4	0.27	13.7	67	128.0	85.8	24	0.55
240-2	4272	129	275	78.2	0.33	0.19	0.62	11.5	10.6	2.4	0.9	0.20	10.9	69	113.4	66.4	16	0.62
240-2	4272	130	285	97.3	0.38	0.15	0.74	13.6	12.3	2.9	1.3	0.27	13.3	61	102.8	70.7	12	0.60
60-4	4273	137	288	96.3	0.64	0.11	0.85	13.9	12.8	2.8	1.1	0.28	13.6	60	95.0	83.0	24	0.64
60-4	4273	138	304	95.0	0.34	0.20	0.67	14.0	12.3	3.2	1.7	0.28	13.8	69	124.8	96.5	24	0.67
60-4	4273	146	274	96.9	0.55	0.12	0.68	12.5	11.3	2.6	1.2	0.26	12.3	61	95.2	71.6	27	0.67
60-4	4273	153	295	83.6	0.41	0.19	0.73	13.8	12.1	3.1	1.6	0.31	13.5	67	124.1	84.7	17	0.66
60-4	4273	155	273	66.8	0.45	0.18	0.64	12.1	10.8	3.1	1.4	0.26	10.7	49	64.2	44.3	18	0.80
60-4	4273	158	300	91.8	0.31	0.17	0.80	14.4	12.5	3.3	1.9	0.30	13.2	73	131.0	97.5	23	0.65
60-4	4273	161	302	102.1	0.48	0.18	0.80	13.8	12.4	3.0	1.4	0.29	13.5	50	78.6	55.9	14	0.67
60-4	4273	165	298	83.0	0.39	0.17	0.86	14.3	13.1	2.6	1.2	0.28	13.8	68	129.0	88.5	20	0.65
60-4	4273	168	307	98.4	0.47	0.18	0.80	13.8	12.3	3.0	1.5	0.30	13.4	68	115.6	93.8	22	0.62
60-4	4273	169	298	95.1	0.38	0.18	0.59	11.5	10.4	2.7	1.1	0.30	11.7	71	114.6	79.2	16	0.85
240-4	4274	179	274	91.7	0.31	0.14	0.66	12.3	10.5	3.1	1.8	0.24	11.8	68	120.9	72.3	24	0.63
240-4	4274	182	283	74.9	0.46	0.14	0.64	12.2	10.8	3.3	1.4	0.24	12.1	67	102.1	77.5	21	0.66
240-4	4274	187	283	79.2	0.44	0.14	0.62	12.8	11.5	3.6	1.4	0.25	12.5	63	100.3	74.7	18	0.67
240-4	4274	188	289	86.8	0.46	0.13	0.71	13.8	11.7	3.6	2.1	0.28	12.9	75	134.9	101.9	29	0.64
240-4	4274	191	282	88.5	0.49	0.12	0.67	12.3	11.2	3.0	1.1	0.26	12.0	74	122.0	92.0	17	0.70
240-4	4274	194	284	81.6	0.56	0.13	0.78	14.1	12.4	3.3	1.7	0.23	11.7	56	110.6	43.2	12	0.58
240-4	4274	201	283	93.6	0.41	0.19	0.65	12.4	11.1	3.1	1.2	0.25	12.5	71	125.5	84.6	20	0.63

DOSE CODE	EXPT NO.	ANIMAL NUMBER	BWT (GRAMS)	MV	CDYN	PL	CCORD	TLC	VC	FRC	RV	DLCO	FVC	FVI	PEFR	MEF	E10	S3
240-4	4274	203	289	90.1	0.33	0.22	0.67	12.9	11.5	3.1	1.4	0.28	12.4	66	114.8	77.6	23	0.74
240-4	4274	204	276	77.2	0.44	0.18	0.64	12.9	11.8	3.2	1.1	0.25	12.7	73	128.3	93.9	24	0.68
240-4	4274	207	292	92.6	0.55	0.13	0.79	13.4	12.3	2.5	1.1	0.24	12.9	71	125.9	93.1	20	0.56
120-4	4275	211	296	91.6	0.38	0.20	0.83	13.9	12.1	2.8	1.8	0.27	10.8	55	88.8	44.6	19	0.60
120-4	4275	213	299	87.2	0.48	0.12	0.81	14.0	13.0	2.8	1.0	0.24	14.0	46	84.6	48.3	14	0.46
120-4	4275	220	274	91.0	0.46	0.13	0.71	12.7	11.1	3.1	1.5	0.27	10.6	59	85.2	50.7	22	0.66
120-4	4275	223	247	86.1	0.39	0.17	0.63	11.2	10.4	2.5	0.8	0.23	10.7	48	68.3	35.8	13	0.89
120-4	4275	224	273	68.9	0.54	0.13	0.75	12.4	11.4	2.7	1.1	0.20	11.2	62	102.2	58.5	20	0.50
120-4	4275	228	292	89.1	0.47	0.14	0.85	13.6	12.0	2.8	1.6	0.25	12.4	59	124.0	50.3	6	0.52
120-4	4275	239	267	86.2	0.57	0.12	0.67	12.8	11.7	2.5	1.1	0.25	12.4	69	107.2	83.9	23	0.68
120-4	4275	242	291	93.6	0.40	0.17	0.63	12.6	10.8	3.2	1.8	0.28	11.8	71	115.8	82.5	18	0.72
120-4	4275	243	290	98.3	0.47	0.16	0.80	13.7	12.4	2.9	1.3	0.27	13.1	64	126.4	71.0	23	0.56
120-4	4275	248	300	96.1	0.42	0.18	0.85	14.8	13.6	3.1	1.2	0.30	14.4	65	129.9	87.8	25	0.51
SHAM	4277	261	284	78.8	0.46	0.13	0.79	14.1	12.8	3.0	1.3	0.26	13.3	65	118.2	80.9	20	0.57
SHAM	4277	262	289	79.5	0.42	0.16	0.87	14.9	13.3	2.9	1.6	0.32	13.4	54	98.3	60.7	11	0.55
SHAM	4277	263	291	95.6	0.49	0.15	0.88	14.8	12.8	3.3	2.0	0.30	11.8	59	110.6	46.4	9	0.66
SHAM	4277	265	288	89.5	0.55	0.12	0.93	14.8	13.6	2.8	1.3	0.33	14.6	68	128.2	98.9	25	0.58
SHAM	4277	269	268	82.7	0.55	0.12	0.78	13.7	12.4	2.9	1.4	0.25	13.2	50	87.0	46.8	17	0.45
SHAM	4277	278	305	94.6	0.51	0.12	0.92	15.0	13.5	2.8	1.5	0.32	14.1	48	84.3	52.9	21	0.63
SHAM	4277	284	291	91.8	0.40	0.15	0.84	13.9	13.1	2.2	0.8	0.30	13.7	66	124.4	86.1	25	0.62
SHAM	4277	288	311	105.0	0.41	0.16	0.84	14.0	13.1	2.4	0.9	0.28	13.9	47	95.7	35.0	11	0.65
SHAM	4277	295	305	81.0	0.32	0.22	0.71	12.7	11.3	2.8	1.4	0.28	12.4	67	110.1	79.8	24	0.74
SHAM	4277	299	287	86.2	0.51	0.11	0.82	14.0	12.4	2.7	1.6	0.26	13.8	51	97.4	51.7	7	0.68

PART 2. EVALUATIONS AFTER THE RECOVERY PERIOD

DOSE CODE	EXPT NO.	ANIMAL NUMBER	BWT (GRAMS)	MV	CDYN	PL	CCORD	TLC	VC	FRC	RV	DLCO	FVC	FVI	PEFR	MEF	E10	S3
120-2	4270	013	321	94.2	0.43	0.17	0.85	14.2	13.1	2.9	1.1	0.32	14.3	65	126.3	89.8	24	0.62
120-2	4270	014	316	99.5	0.51	0.12	0.82	13.7	13.0	3.5	0.8	0.30	14.1	64	117.4	81.9	24	0.65
120-2	4270	015	312	94.9	0.51	0.16	0.73	12.0	11.7	1.6	0.3	0.31	13.0	65	120.5	79.6	28	0.70
120-2	4270	017	301	81.0	0.57	0.12	0.76	12.9	11.8	2.7	1.1	0.27	11.9	70	120.2	78.9	23	0.68
120-2	4270	028	322	104.6	0.48	0.15	0.91	14.9	13.2	2.8	1.7	0.32	14.1	66	129.6	86.0	26	0.70
120-2	4270	031	299	84.8	0.35	0.22	0.72	12.8	11.7	2.7	1.1	0.27	12.7	66	110.5	81.5	21	0.66
120-2	4270	032	310	84.1	0.82	0.10	0.89	15.6	13.7	3.8	1.9	0.29	14.5	61	124.0	78.8	21	0.52
120-2	4270	038	308	103.3	0.50	0.14	0.98	15.3	14.1	3.1	1.3	0.33	14.8	51	110.8	54.9	18	0.54
120-2	4270	043	315	99.1	0.37	0.21	0.82	13.9	12.6	2.6	1.3	0.30	13.2	70	126.2	91.9	24	0.64
120-2	4270	049	293	100.3	0.49	0.14	0.83	13.8	12.5	3.0	1.3	0.25	12.7	42	77.0	27.5	8	0.60
60-2	4271	057	299	63.1	0.38	0.16	0.74	13.6	12.2	2.9	1.4	0.23	13.1	44	84.7	31.0	7	0.53
60-2	4271	059	295	93.2	0.40	0.15	0.73	13.3	11.7	2.7	1.6	0.25	12.5	66	115.4	72.6	10	0.67
60-2	4271	068	323	83.8	0.53	0.13	0.88	15.5	13.7	3.3	1.8	0.30	14.4	60	100.2	87.6	21	0.56
60-2	4271	070	327	82.2	0.42	0.19	0.78	14.2	12.3	3.2	1.9	0.26	13.0	69	117.0	90.6	23	0.68
60-2	4271	074	313	79.2	0.32	0.20	0.78	13.6	12.1	2.7	1.5	0.27	12.7	69	125.3	81.4	21	0.59
60-2	4271	075	301	99.5	0.50	0.16	0.78	13.3	11.9	2.9	1.4	0.29	12.6	66	102.8	83.6	22	0.62
60-2	4271	076	326	103.0	0.47	0.14	0.96	15.5	14.6	2.9	0.9	0.30	15.1	55	98.7	76.7	20	0.54
60-2	4271	078	324	96.3	0.41	0.16	0.80	13.5	12.5	2.5	1.0	0.25	12.9	65	98.9	83.1	26	0.50
60-2	4271	087	323	99.4	0.39	0.16	0.85	15.0	12.7	3.5	2.3	0.30	13.6	64	124.8	79.2	17	0.64
60-2	4271	089	324	87.7	0.45	0.12	0.88	15.1	13.4	3.2	1.6	0.31	13.9	67	124.7	89.6	27	0.50
240-2	4272	092	321	92.4	0.36	0.23	0.70	14.0	12.1	3.8	1.9	0.28	12.7	61	115.6	64.5	25	0.64
240-2	4272	098	313	82.1	0.70	0.13	0.87	14.5	13.2	3.1	1.3	0.29	13.5	64	115.4	76.7	14	0.45
240-2	4272	103	295	95.2	0.46	0.17	0.76	13.9	11.9	3.8	2.0	0.25	12.6	61	110.5	64.0	6	0.70
240-2	4272	114	298	99.5	0.48	0.16	0.78	14.0	12.8	2.9	1.2	0.25	13.5	67	114.4	89.4	14	0.56
240-2	4272	117	308	86.2	0.30	0.22	0.75	13.2	11.8	3.1	1.4	0.27	12.2	58	82.8	70.8	22	0.68
240-2	4272	118	298	94.4	0.37	0.17	0.81	14.0	12.2	3.2	1.8	0.29	12.8	67	106.3	82.0	23	0.63
240-2	4272	127	307	95.9	0.38	0.18	0.77	14.0	13.0	2.9	1.0	0.26	13.4	63	106.8	72.8	19	0.66
240-2	4272	128	311	105.5	0.40	0.19	0.85	14.6	12.9	3.2	1.6	0.29	13.5	66	121.6	84.9	26	0.56
240-2	4272	129	290	96.6	0.41	0.18	0.66	11.7	11.1	2.4	0.6	0.26	11.2	69	113.6	72.0	17	0.65
240-2	4272	130	296	86.2	0.50	0.12	0.84	15.1	13.8	3.1	1.3	0.29	14.3	58	101.5	71.1	19	0.56
60-4	4273	137	302	85.8	0.41	0.18	0.79	14.3	12.6	3.3	1.7	0.23	12.9	57	84.4	71.6	20	0.56
60-4	4273	138	323	96.0	0.34	0.21	0.78	13.9	12.7	2.8	1.2	0.31	13.7	67	116.4	92.8	25	0.60
60-4	4273	153	321	98.6	0.47	0.12	0.85	13.9	12.8	2.6	1.1	0.29	13.9	61	119.2	73.6	23	0.66
60-4	4273	155	291	89.7	0.41	0.18	0.70	12.6	11.4	2.9	1.2	0.26	12.3	66	99.2	76.9	19	0.68
60-4	4273	158	320	96.4	0.38	0.17	0.89	14.4	13.1	2.6	1.2	0.26	13.6	66	115.1	92.4	19	0.58
60-4	4273	161	324	104.5	0.34	0.21	0.75	14.4	12.5	3.5	1.9	0.30	12.8	59	90.6	71.0	22	0.69
60-4	4273	165	316	98.3	0.45	0.17	0.77	13.8	12.4	2.9	1.4	0.29	13.3	66	118.0	83.1	22	0.64
60-4	4273	168	329	84.6	0.50	0.12	0.81	13.9	13.0	2.5	0.9	0.28	13.3	66	125.9	81.5	22	0.64
60-4	4273	169	321	99.6	0.38	0.20	0.79	13.4	12.0	2.6	1.4	0.27	12.2	68	116.7	80.9	16	0.72
240-4	4274	179	302	94.2	0.35	0.17	0.69	12.2	11.1	2.7	1.1	0.26	12.4	70	121.3	86.1	21	0.63
240-4	4274	182	309	83.1	0.38	0.20	0.51	11.7	10.7	3.0	1.0	0.28	11.3	63	99.5	61.4	24	0.73
240-4	4274	187	308	90.1	0.40	0.16	0.83	15.0	13.1	3.8	1.9	0.29	13.4	62	100.1	73.0	23	0.48
240-4	4274	188	316	93.5	0.52	0.05	0.69	13.9	12.5	2.8	1.3	0.17	13.1	70	122.9	94.5	26	0.64
240-4	4274	191	301	80.8	0.42	0.16	0.83	14.5	12.3	3.5	2.2	0.25	11.4	54	77.9	44.8	16	0.57
240-4	4274	194	300	86.8	0.51	0.17	0.75	14.6	12.4	3.5	2.1	0.30	13.4	64	119.9	80.2	20	0.59
240-4	4274	201	308	109.7	0.41	0.15	0.79	14.5	12.8	3.2	1.7	0.28	13.3	44	91.9	34.6	13	0.56
240-4	4274	203	311	101.0	0.48	0.18	0.77	14.2	12.2	3.2	1.9	0.30	12.7	72	118.6	97.3	22	0.66
240-4	4274	204	296	88.4	0.42	0.17	0.77	14.0	12.6	3.3	1.4	0.28	12.6	51	96.8	45.0	9	0.62
240-4	4274	207	312	100.0	0.34	0.17	0.80	13.9	12.2	3.1	1.7	0.29	13.3	68	126.7	85.5	22	0.67

DOSE CODE	EXPT NO.	ANIMAL NUMBER	BWT (GRAMS)	MV	CDYN	PL	CCORD	TLC	VC	FRC	RV	DLCO	FVC	FVI	PEFR	MEF	E10	S3
120-4	4275	211	325	103.9	0.60	0.12	0.85	15.8	14.2	3.4	1.6	0.32	14.1	42	115.4	16.2	3	0.49
120-4	4275	213	330	90.2	0.41	0.19	0.79	14.4	12.6	3.2	1.7	0.31	14.2	51	114.9	38.1	8	0.60
120-4	4275	220	295	93.9	0.42	0.14	0.81	14.6	12.9	3.4	1.7	0.31	13.5	68	123.7	91.7	26	0.62
120-4	4275	223	281	99.1	0.39	0.16	0.70	11.9	11.4	2.2	0.6	0.23	11.8	43	77.1	30.7	9	0.64
120-4	4275	224	310	95.3	0.61	0.07	0.80	13.2	12.3	2.2	1.0	0.26	12.6	71	124.4	88.1	18	0.66
120-4	4275	228	316	102.2	0.42	0.15	0.79	13.7	11.9	3.0	1.7	0.30	13.4	69	124.1	88.3	20	0.60
120-4	4275	239	283	94.2	0.56	0.09	0.77	12.9	11.8	2.7	1.1	0.27	12.5	67	109.1	80.5	21	0.62
120-4	4275	242	314	86.0	0.39	0.21	0.83	13.9	12.8	2.6	1.2	0.32	13.3	51	96.0	51.5	24	0.54
120-4	4275	243	311	95.0	0.61	0.09	0.82	14.5	13.0	3.1	1.6	0.30	13.6	64	122.5	78.8	18	0.59
120-4	4275	248	328	91.8	0.49	0.16	0.93	15.2	13.8	3.1	1.5	0.33	14.7	64	124.9	87.7	22	0.54
SHAM	4277	261	321	91.1	0.39	0.17	0.86	14.3	12.8	3.0	1.5	0.28	13.3	64	118.4	77.5	22	0.64
SHAM	4277	262	326	79.3	0.43	0.23	0.77	14.4	12.7	3.2	1.7	0.28	13.1	62	111.0	74.3	22	0.62
SHAM	4277	263	332	85.8	0.39	0.18	0.85	14.9	12.4	3.6	2.5	0.28	11.9	60	102.8	56.8	17	0.63
SHAM	4277	265	336	82.4	0.56	0.09	0.97	15.2	14.1	2.6	1.1	0.34	14.4	54	123.2	42.9	10	0.62
SHAM	4277	269	304	84.2	0.47	0.15	0.87	13.8	13.1	2.3	0.7	0.25	13.4	61	102.0	78.2	25	0.39
SHAM	4277	278	327	89.7	0.42	0.20	0.81	13.9	13.0	2.5	1.0	0.28	13.4	65	109.4	86.3	26	0.72
SHAM	4277	284	302	95.7	0.37	0.16	0.86	14.3	13.0	2.6	1.3	0.30	12.3	47	82.3	37.7	17	0.61
SHAM	4277	288	330	103.1	0.43	0.27	0.98	16.5	14.3	3.9	2.1	0.33	14.7	57	99.4	85.7	18	0.60
SHAM	4277	295	325	97.9	0.34	0.20	0.82	13.4	12.8	2.3	0.6	0.31	13.4	62	112.3	74.4	18	0.71
SHAM	4277	299	292	102.1	0.46	0.18	0.77	13.6	12.6	2.8	1.0	0.29	12.7	65	108.9	75.9	26	0.67

H. APPENDIX H: GROUP SUMMARIES OF HISTOPATHOLOGY OBSERVATIONS

PART 1. INCIDENCE OF MICROSCOPIC OBSERVATIONS AT "END OF EXPOSURE"

T I S S U E S E X A M I N E D * * * MALE RATS * * *		EXPOSURE CODE:								
		SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
LIVER	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
KIDNEYS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-CORPORA AMYLACIA, CORTICAL TUBULES		2	1	0	3	4	3	1	1	1
ADRENAL GLANDS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
HEART	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-MYOCARDIAL FIBROSIS		0	1	0	2	1	0	0	0	0
STOMACH	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
THYROID GLANDS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
TESTES	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-ATROPHY, GERMINAL EPITHELIUM		0	0	0	0	0	0	0	1	0
-TUBULAR MULTINUCLEATE GIANT CELL		0	0	0	0	0	1	0	0	0
URINARY BLADDER	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
BRAIN	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
TRACHEA	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
BONE, FEMUR	NUMBER EXAMINED:	4	5	5	5	5	5	3	5	5
NOSE/TURBINATES	NUMBER EXAMINED:	4	5	5	5	5	5	5	5	5
-ATROPHY, OLFACTORY EPITHELIUM		0	1	5	1	5	5	5	5	5
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM		1	2	2	1	1	4	4	3	5
-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT		1	3	1	3	1	2	2	2	0
-INFLAMMATION, FOCAL SUPPURATIVE		1	0	0	0	0	1	0	0	0
-CYST, RESPIRATORY EPITHELIUM		1	0	0	0	0	0	0	0	0
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL		0	3	0	0	0	0	0	0	0
LUNGS	NUMBER EXAMINED:	4	5	5	5	5	5	5	5	5
-ALVEOLITIS, FOCAL NECROTIZING		0	0	0	0	0	2	5	3	5
-HYPERPLASIA, ALVEOLAR MACROPHAGES, FOCAL		0	1	5	5	5	5	5	5	5
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI		0	1	0	0	1	3	5	4	5
-INFILTRATES, LEUKEMIC		0	0	0	0	0	0	0	0	0
-GRANULOMA, FOCAL, MICROSCOPIC		0	1	0	0	0	0	0	0	0
LARYNX	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-LARYNGITIS, NEUTROPHILIC, SUBACUTE, FOCAL		1	0	0	0	1	0	0	0	0
SPLEEN	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
TRACHEOBRONCHAL LYMPH NODES	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-LYMPHOID HYPERLASIA, PARACORTICAL		4	3	5	5	5	5	4	5	5
-GERMINAL FOLLICLE PROLIFERATION		0	0	0	0	0	0	0	0	0
-LYMPHOID DEPLETION		0	0	0	0	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-ATROPHY, CORTICAL		4	5	2	5	5	5	4	5	5

T I S S U E S E X A M I N E D * * * FEMALE RATS * * *		SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
LIVER	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
KIDNEYS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-CORPORA AMYLACIA, CORTICAL TUBULES		2	2	3	3	2	1	0	3	2
ADRENAL GLANDS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
HEART	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-MYOCARDIAL FIBROSIS		0	0	0	0	0	0	0	0	0
STOMACH	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
THYROID GLANDS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
OVARIES	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
URINARY BLADDER	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
BRAIN	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
TRACHEA	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
BONE, FEMUR	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
NOSE/TURBINATES	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ATROPHY, OLFACTORY EPITHELIUM		0	1	5	2	5	5	4	5	5
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM		0	2	0	0	1	1	0	0	3
-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT		3	0	3	4	4	2	4	2	2
-INFLAMMATION, FOCAL SUPPURATIVE		0	0	0	0	0	0	0	0	0
-CYST, RESPIRATORY EPITHELIUM		0	0	0	0	1	0	0	0	0
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL		0	2	0	0	0	0	0	0	0
LUNGS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ALVEOLITIS, FOCAL NECROTIZING		0	0	0	0	1	2	3	5	5
-HYPERPLASIA, ALVEOLAR MACROPHAGES, FOCAL		0	2	5	5	5	5	5	5	5
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI		0	0	0	0	1	2	1	5	5
-INFILTRATES, LEUKEMIC		0	0	0	0	0	1	0	0	0
-GRANULOMA, FOCAL, MICROSCOPIC		0	0	0	0	0	0	1	0	0
LARYNX	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-LARYNGITIS, NEUTROPHILIC, SUBACUTE, FOCAL		0	0	0	0	0	0	0	0	0
SPLEEN	NUMBER EXAMINED:	5	5	5	5	5	4	5	5	5
TRACHEOBRONCHIAL LYMPH NODES	NUMBER EXAMINED:	3	5	5	5	5	5	5	5	5
-LYMPHOID HYPERPLASIA, PARACORTICAL		1	4	5	4	5	4	4	5	5
-GERMINAL FOLLICLE PROLIFERATION		0	0	0	0	0	0	1	0	0
-LYMPHOID DEPLETION		0	0	0	0	0	0	1	0	0
THYMUS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ATROPHY, CORTICAL		1	2	0	4	0	5	5	4	5

PART 2. INCIDENCE OF MICROSCOPIC OBSERVATIONS "AFTER RECOVERY"

T I S S U E S E X A M I N E D * * * MALE RATS * * *		SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
		EXPOSURE CODE:								
TRACHEA	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
NOSE/TURBINATES	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ATROPHY, OLFACTORY EPITHELIUM		0	0	0	0	0	0	2	1	4
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM		0	0	0	0	0	0	0	0	0
-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT		3	5	4	2	2	3	3	5	3
-INFLAMMATION, FOCAL SUPPURATIVE		0	1	0	0	0	0	0	0	0
-CYST, RESPIRATORY EPITHELIUM		0	0	0	0	0	0	0	0	0
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL		0	0	0	0	0	0	0	0	0
LUNGS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ALVEOLITIS, FOCAL NECROTIZING		0	0	0	0	0	0	0	0	0
-HYPERPLASIA, ALVEOLAR MACROPHAGES,FOCAL		0	0	5	5	5	5	5	5	5
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI		0	0	0	0	0	0	0	0	0
-INFILTRATES, LEUKEMIC		0	0	0	0	0	0	0	0	0
-GRANULOMA, FOCAL, MICROSCOPIC		0	0	0	0	0	0	0	0	0
LARYNX	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
TRACHEOBRONCHIAL LYMPH NODES	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-LYMPHOID HYPERLASIA, PARACORTICAL		0	0	0	0	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-ATROPHY, CORTICAL		0	0	0	0	0	0	0	0	0

T I S S U E S E X A M I N E D * * * FEMALE RATS * * *		SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
TRACHEA	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
NOSE/TURBINATES	NUMBER EXAMINED:	5	5	5	5	5	5	5	4	4
-ATROPHY, OLFACTORY EPITHELIUM		0	0	0	0	0	0	1	1	4
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM		2	0	1	2	0	2	1	2	4
-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT		1	4	3	1	5	1	3	1	2
-INFLAMMATION, FOCAL SUPPURATIVE		0	0	0	0	0	0	0	0	0
-CYST, RESPIRATORY EPITHELIUM		1	0	0	0	0	0	0	0	1
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL		1	0	0	0	0	0	0	0	0
LUNGS	NUMBER EXAMINED:	5	5	5	5	5	5	5	4	4
-ALVEOLITIS, FOCAL NECROTIZING		0	0	0	0	0	0	0	0	0
-HYPERPLASIA, ALVEOLAR MACROPHAGES,FOCAL		0	0	3	5	4	5	5	4	3
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI		0	0	0	0	0	0	1	0	0
-INFILTRATES, LEUKEMIC		0	0	0	0	0	0	0	0	0
-GRANULOMA, FOCAL, MICROSCOPIC		0	0	0	0	0	0	0	0	0
LARYNX	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
TRACHEOBRONCHIAL LYMPH NODES	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-LYMPHOID HYPERLASIA, PARACORTICAL		0	0	0	0	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-ATROPHY, CORTICAL		0	0	0	0	0	0	0	0	0

PART 3. SEVERITY RATINGS OF MICROSCOPIC OBSERVATIONS AT "END OF EXPOSURE"

TISSUES EXAMINED *** MALE RATS ***		EXPOSURE CODE: SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
LIVER	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
KIDNEYS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-CORPORA AMYLACIA, CORTICAL TUBULES										
	->	2	4	5	2	1	2	3	4	4
	2>	0	0	0	0	0	1	0	0	0
	3>	0	0	0	3	2	1	1	0	1
	4>	2	1	0	0	2	1	0	1	0
ADRENAL GLANDS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
HEART	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-MYOCARDIAL FIBROSIS	->	4	4	5	3	4	5	4	5	5
	1>	0	1	0	1	0	0	0	0	0
	2>	0	0	0	1	1	0	0	0	0
STOMACH	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
THYROID GLANDS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
TESTES	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-ATROPHY, GERMINAL EPITHELIUM										
	->	4	5	5	5	5	5	4	4	5
	4>	0	0	0	0	0	0	0	1	0
-TUBULAR MULTINUCLEATE GIANT CELL										
	->	4	5	5	5	5	5	4	5	5
	1>	0	0	0	0	0	1	0	0	0
URINARY BLADDER	NUMBER EXAMINED:	4	5	5	5	5	4	4	5	5
BRAIN	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
TRACHEA	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
BONE, FEMUR	NUMBER EXAMINED:	4	5	5	5	5	5	3	5	5
NOSE/TURBINATES	NUMBER EXAMINED:	4	5	5	5	5	5	5	5	5
-ATROPHY, OLFACTORY EPITHELIUM										
	->	4	4	0	4	0	0	0	0	0
	1>	0	1	5	1	1	1	0	1	0
	2>	0	0	0	0	4	4	3	3	1
	3>	0	0	0	0	0	0	2	1	4
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM										
	->	3	3	3	4	4	1	1	2	0
	1>	1	2	2	1	1	2	0	1	0
	2>	0	0	0	0	0	2	3	2	5
	3>	0	0	0	0	0	0	1	0	0

-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT										
	->	3	2	4	2	4	3	3	3	5
	1>	0	1	1	1	1	0	2	1	0
	2>	1	2	0	2	0	2	0	1	0
-INFLAMMATION, FOCAL SUPPURATIVE										
	->	3	5	5	5	5	4	5	5	5
	1>	1	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	1	0	0	0
-CYST, RESPIRATORY EPITHELIUM										
	->	3	5	5	5	5	5	5	5	5
	1>	1	0	0	0	0	0	0	0	0
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL										
	->	4	2	5	5	5	5	5	5	5
	1>	0	2	0	0	0	0	0	0	0
	2>	0	1	0	0	0	0	0	0	0
LUNGS .... NUMBER EXAMINED:		4	5	5	5	5	5	5	5	5
-ALVEOLITIS, FOCAL NECROTIZING										
	->	4	5	5	5	5	3	0	2	0
	1>	0	0	0	0	0	2	2	3	0
	2>	0	0	0	0	0	0	3	0	0
	3>	0	0	0	0	0	0	0	0	4
	4>	0	0	0	0	0	0	0	0	1
-HYPERPLASIA, ALVEOLAR MACROPHAGES, FOCAL										
	->	4	4	0	0	0	0	0	0	0
	1>	0	0	4	1	2	0	0	0	0
	2>	0	1	1	4	3	4	5	3	0
	3>	0	0	0	0	0	1	0	2	3
	4>	0	0	0	0	0	0	0	0	2
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI										
	->	4	4	5	5	4	2	0	1	0
	1>	0	1	0	0	1	1	5	2	0
	2>	0	0	0	0	0	2	0	2	0
	3>	0	0	0	0	0	0	0	0	4
	4>	0	0	0	0	0	0	0	0	1
-INFILTRATES, LEUKEMIC										
	->	4	5	5	5	5	5	5	5	5
-GRANULOMA, FOCAL, MICROSCOPIC										
	->	4	4	5	5	5	5	5	5	5
	1>	0	1	0	0	0	0	0	0	0
LARYNX .... NUMBER EXAMINED:		4	5	5	5	5	5	4	5	5
-LARYNGITIS, NEUTROPHILIC, SUBACUTE, FOCAL										
	->	3	5	5	5	4	5	4	5	5
	3>	1	0	0	0	1	0	0	0	0
SPLEEN .... NUMBER EXAMINED:		4	5	5	5	5	5	4	5	5

TRACHEOBRONCHIAL LYMPH NODES	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-LYMPHOID HYPERLASIA, PARACORTICAL										
	->	0	2	0	1	0	0	0	1	0
	1>	1	2	2	1	0	0	2	0	1
	2>	3	1	3	3	5	2	1	4	2
	3>	0	0	0	0	0	3	1	0	2
-GERMINAL FOLLICLE PROLIFERATION										
	->	1	5	5	5	5	5	4	5	5
-LYMPHOID DEPLETION										
	->	1	5	5	5	5	5	4	5	5
THYMUS	NUMBER EXAMINED:	4	5	5	5	5	5	4	5	5
-ATROPHY, CORTICAL										
	->	0	0	3	0	0	0	0	0	0
	1>	1	5	0	1	2	0	2	0	0
	2>	2	0	2	3	3	4	2	4	0
	3>	1	0	0	1	0	1	0	1	5

T I S S U E S E X A M I N E D * * * FEMALE RATS * * *		SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
LIVER	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
KIDNEYS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-CORPORA AMYLACIA, CORTICAL TUBULES										
	->	3	3	2	2	3	4	5	2	3
	1>	1	0	0	1	0	0	0	0	0
	2>	0	0	1	1	0	1	0	2	1
	3>	1	2	2	1	2	0	0	0	1
	4>	0	0	0	0	0	0	0	1	0
ADRENAL GLANDS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
HEART	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-MYOCARDIAL FIBROSIS										
	->	5	5	5	5	5	5	5	5	5
STOMACH	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
THYROID GLANDS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
OVARIES	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
URINARY BLADDER	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
BRAIN	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
TRACHEA	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
BONE, FEMUR	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5

NOSE/TURBINATES	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ATROPHY, OLFACTORY EPITHELIUM	->	5	4	0	3	0	0	1	0	0
	1>	0	1	4	2	2	3	0	0	0
	2>	0	0	1	0	3	2	3	3	1
	3>	0	0	0	0	0	0	1	2	4
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM	->	5	3	5	5	4	4	5	5	2
	1>	0	1	0	0	0	1	0	0	2
	2>	0	1	0	0	1	0	0	0	1
-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT	->	2	5	2	1	1	3	1	3	3
	1>	2	0	0	2	1	0	3	0	1
	2>	0	0	2	2	3	2	1	2	1
	3>	1	0	1	0	0	0	0	0	0
-INFLAMMATION, FOCAL SUPPURATIVE	->	5	5	5	5	5	5	5	5	5
-CYST, RESPIRATORY EPITHELIUM	->	5	5	5	5	4	5	5	5	5
	1>	0	0	0	0	1	0	0	0	0
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL	->	5	3	5	5	5	5	5	5	5
	1>	0	2	0	0	0	0	0	0	0
LUNGS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ALVEOLITIS, FOCAL NECROTIZING	->	5	5	5	5	4	3	2	0	0
	1>	0	0	0	0	1	2	3	3	0
	2>	0	0	0	0	0	0	0	2	2
	3>	0	0	0	0	0	0	0	0	2
	4>	0	0	0	0	0	0	0	0	1
-HYPERPLASIA, ALVEOLAR MACROPHAGES, FOCAL	->	5	3	0	0	0	0	0	0	0
	1>	0	2	3	0	4	0	0	0	0
	2>	0	0	2	5	1	3	2	0	0
	3>	0	0	0	0	0	2	3	5	5
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI	->	5	5	5	5	4	3	4	0	0
	1>	0	0	0	0	1	2	1	4	0
	2>	0	0	0	0	0	0	0	1	2
	3>	0	0	0	0	0	0	0	0	2
	4>	0	0	0	0	0	0	0	0	1
-INFILTRATES, LEUKEMIC	->	5	5	5	5	5	4	5	5	5
	2>	0	0	0	0	0	1	0	0	0
-GRANULOMA, FOCAL, MICROSCOPIC	->	5	5	5	5	5	5	4	5	5
	2>	0	0	0	0	0	0	1	0	0

LARYNX	NUMBER EXAMINED:	5	5	5	5	5	5	5	3	3
-LARYNGITIS, NEUTROPHILIC, SUBACUTE, FOCAL										
	->	5	5	5	5	5	5	5	3	3
SPLEEN	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
TRACHEOBRONCHIAL LYMPH NODES	NUMBER EXAMINED:	3	5	5	5	5	5	5	5	5
-LYMPHOID HYPERLASIA, PARACORTICAL										
	->	2	1	0	1	0	1	1	0	0
	1>	0	2	2	3	1	0	1	0	0
	2>	1	2	2	1	4	2	3	1	2
	3>	0	0	1	0	0	2	0	4	3
-GERMINAL FOLLICLE PROLIFERATION										
	->	3	5	5	5	5	4	4	5	5
	2>	0	0	0	0	0	0	1	0	0
-LYMPHOID DEPLETION										
	->	3	5	5	5	5	4	4	5	5
	1>	0	0	0	0	0	0	1	0	0
THYMUS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ATROPHY, CORTICAL										
	->	4	3	5	1	5	0	0	1	0
	1>	0	2	0	4	0	2	4	1	2
	2>	1	0	0	0	0	2	1	2	1
	3>	0	0	0	0	0	1	0	1	2

PART 4. SEVERITY RATINGS OF MICROSCOPIC OBSERVATIONS "AFTER RECOVERY"

T I S S U E S E X A M I N E D *** MALE RATS ***		EXPOSURE CODE: SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
TRACHEA	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
NOSE/TURBINATES	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ATROPHY, OLFACTORY EPITHELIUM										
	->	5	5	5	5	5	5	3	4	1
	1>	0	0	0	0	0	0	2	1	4
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM										
	->	5	5	5	5	5	5	5	5	5
-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT										
	->	2	0	1	3	3	2	2	0	2
	1>	2	2	1	1	0	2	3	3	2
	2>	1	3	3	1	2	1	0	2	1
-INFLAMMATION, FOCAL SUPPURATIVE										
	->	5	4	5	5	5	5	5	5	5
	2>	0	1	0	0	0	0	0	0	0
-CYST, RESPIRATORY EPITHELIUM										
	->	5	5	5	5	5	5	5	5	5
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL										
	->	5	5	5	5	5	5	5	5	5
LUNGS	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5
-ALVEOLITIS, FOCAL NECROTIZING										
	->	5	5	5	5	5	5	5	5	5
-HYPERPLASIA, ALVEOLAR MACROPHAGES, FOCAL										
	->	5	5	0	0	0	0	0	0	0
	1>	0	0	5	3	5	0	0	1	0
	2>	0	0	0	2	0	5	4	4	1
	3>	0	0	0	0	0	0	1	0	4
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI										
	->	5	5	5	5	5	5	5	5	5
-INFILTRATES, LEUKEMIC										
	->	5	5	5	5	5	5	5	5	5
-GRANULOMA, FOCAL, MICROSCOPIC										
	->	5	5	5	5	5	5	5	5	5
LARYNX	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
TRACHEOBRONCHIAL LYMPH NODES	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-LYMPHOID HYPERLASIA, PARACORTICAL										
THYMUS	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-ATROPHY, CORTICAL										

TISSUES EXAMINED *** FEMALE RATS ***		SHAM	30-2	60-2	60-4	120-2	120-4	240-2	240-4	480-4
TRACHEA	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
NOSE/TURBINATES	NUMBER EXAMINED:	5	5	5	5	5	5	5	4	4
-ATROPHY, OLFACTORY EPITHELIUM										
	->	5	5	5	5	5	5	4	3	0
	1>	0	0	0	0	0	0	1	1	1
	2>	0	0	0	0	0	0	0	0	3
-GOBLET CELL HYPERPLASIA, RESPIRATORY EPITHELIUM										
	->	3	5	4	3	5	3	4	2	0
	1>	1	0	0	2	0	2	1	2	4
	2>	1	0	1	0	0	0	0	0	0
-CHRONIC NONSUPPURATIVE INFLAMMATION, LACRIMAL DUCT										
	->	4	1	2	4	0	4	2	3	2
	1>	1	2	3	1	3	1	3	1	2
	2>	0	2	0	0	2	0	0	0	0
-INFLAMMATION, FOCAL SUPPURATIVE										
	->	5	5	5	5	5	5	5	4	4
-CYST, RESPIRATORY EPITHELIUM										
	->	4	5	5	5	5	5	5	4	3
	1>	1	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	1
-ATROPHY, OLFACTORY EPITHELIUM, UNILATERAL										
	->	4	5	5	5	5	5	5	4	4
	1>	1	0	0	0	0	0	0	0	0
LUNGS	NUMBER EXAMINED:	5	5	5	5	5	5	5	4	4
-ALVEOLITIS, FOCAL NECROTIZING										
	->	5	5	5	5	5	5	5	4	4
-HYPERPLASIA, ALVEOLAR MACROPHAGES, FOCAL										
	->	5	5	2	0	1	0	0	0	1
	1>	0	0	3	5	4	5	2	0	0
	2>	0	0	0	0	0	0	3	4	3
-HYPERPLASIA, GOBLET CELL OF BRONCHIOLES AND BRONCHI										
	->	5	5	5	5	5	5	4	4	4
	1>	0	0	0	0	0	0	1	0	0
-INFILTRATES, LEUKEMIC										
	->	5	5	5	5	5	5	5	4	4
-GRANULOMA, FOCAL, MICROSCOPIC										
	->	5	5	5	5	5	5	5	4	4
LARYNX	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
TRACHEOBRONCHIAL LYMPH NODES	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-LYMPHOID HYPERLASIA, PARACORTICAL										
THYMUS	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0
-ATROPHY, CORTICAL										

APPENDIX I. MISCELLANEOUS

This appendix contains example data sheets for analyses of Wayne Certified Rodent Blox Pellets done by Continental Grain Company, Libertyville, Illinois. Results for this lot of feed (P06185-1) are typical for this kind of feed, which was used in Phase II of this project.

CONTINENTAL GRAIN COMPANY
P.O. BOX 459
LIBERTYVILLE, ILLINOIS 60048
312-362-1334

RESEARCH AND DEVELOPMENT CENTER
WORLD MILLING INDUSTRIES GROUP

September 4, 1985

Dr. Charles Hobbs
Assistant Director
ITRI
P.O. Box 5980
Albuquerque, New Mexico 87185

Dear Dr. Hobbs,

Please find enclosed our raw data on the following lots of Wayne Certified Rodent Blox Pellets.

P061851
P061852
P072651
P072652

9-28-

Please contact me if you have any questions.

Sincerely,

Robert E. Beverly

Robert E. Beverly
Quality Assurance Manager
Animal Health/Pet Products

REB/jw

Enclosure

Continental Grain Co.

CERTIFICATE OF FEED ANALYSIS

PLANT NO. 010 / 938

FEED NO. 2728-00 CATEGORY NO. Cat. Rodent Bloq

☐ ROUTINE ☑ SPECIAL STUDY ☐ NON-ROUTINE

DATE MFG. 6-18-85 RUN OR BATCH NO. P06185-1

ANALYSIS: LAB NO. 4934

	GUAR.	CALC.	ASSAY
PROT.			25.1
MOIST.			9.21
ASH			7.11
FAT			4.30
FIBER			4.02
Ca			1.41
P			0.99
SALT			0.74
N.P.N.			
VIT A			
THIAMINE			

Please grind
1-5 lb
1-1 lb

REMARKS:

D.L. Burt
9-23-85

DATE RECEIVED 6/24/85

ANALYST Beverly DATE COMPLETED 6/24/85

RES-19C

RECEIPT

SPECIMEN	SPECIMEN I.D. NUMBER	ACCESSION NO
R 4934 CONTINENTAL GRAIN	159371 JUL 10 1985	159371

REFERRING CLIENT	DATE COLLECTED	TIME COLLECTED	RECEIVED
CONTINENTAL GRAIN CO.	07/01/85	00:00	07/01/8
	CLIENT LAB NO. 00000		REPORTED 00/00/0

TEST	RESULT	REFERENCE LIMITS	UNITS
BETA BHC	<0.01		PPM
DELTA BHC	<0.01		PPM
4,4'DDE	<0.10		PPM
4,4'DDD	<0.10		PPM
HCB	<0.10	DL <0.01	PPM
MIREX	<0.10	DL <0.01	PPM
METHOXYCHLOR	<0.10	DL <0.01	PPM
TELODRIN	<0.10	DL <0.01	PPM
RONNEL	<0.10	DL <0.01	PPM
ETHYL PARATHION	<0.10	DL <0.10	PPM
ALPHA ENDOSULFAN	<0.10		PPM
BETA ENDOSULFAN	<0.10		PPM
ENDOSULFAN SULFATE	<0.10		PPM

LEG Smit
9-28-85

ASSAY DONE
APPROVED BY PSD LAB MGR: JEB 25-AUG-8
DISTRIBUTE TO ROB BEVERLY

------------------------ ASSAY = R4934 ------------------------

DATE AS FED

PLANT	PROD	TYPE	MFG	BATCH	COMMENT	COMMENT
010		872800	SPECIAL	850613	P06135-1 RODENT BLOX	

TEST	UNITS	RESULT	C-VALUE	GUAR-VALUE

SPECIMEN	SPECIMEN I.D. NUMBER	ACCESSION
R 4934 CONTINENTAL GRAIN	159371	15937

REFERRING CLIENT	DATE COLLECTED	TIME COLLECTED	RECEIVED
CONTINENTAL GRAIN CO.	07/01/85	00:00	07/01/
	CLIENT LAB NO. 00000		REPORTED 00/00/

TEST	RESULT	REFERENCE LIMITS	UNITS
FEED SCREEN			
ARSENIC	0.24		PPM
CADMIUM	0.32		PPM
LEAD	0.31		PPM
MERCURY	<0.07		PPM
SELENIUM	0.53		PPM
AFLATOXIN B1	<0.01	DL <0.01	PPM
AFLATOXIN B2	<0.01	DL <0.01	PPM
AFLATOXIN G1	<0.01	DL <0.01	PPM
AFLATOXIN G2	<0.01	DL <0.01	PPM
ALDRIN	<0.01	DL <0.01	PPM
DIELDRIN	<0.01	DL <0.01	PPM
ENDRIN	<0.01	DL <0.01	PPM
HEPTACHLOR	<0.01	DL <0.01	PPM
HEPTACHLOREPOXIDE	<0.01	DL <0.01	PPM
LINDANE	<0.01	DL <0.01	PPM
CHLORDANE	<0.01	DL <0.01	PPM
DDT RELATED SUBS.	<0.10		
TOXAPHENE	<0.10	DL <0.10	PPM
PCBS	<0.10	DL <0.10	PPM
DIAZINON	<0.10		PPM
DISULFATON	<0.10	DL <0.10	PPM
ETHION	<0.10	DL <0.10	PPM
MALATHION	0.12	DL <0.10	PPM
METHYL PARATHION	<0.10	DL <0.10	PPM
PARATHION	<0.10	DL <0.10	PPM
THIMET	<0.10	DL <0.10	PPM
THIODAN	<0.10	DL <0.10	PPM
TRITHION	<0.10	DL <0.10	PPM
CAROTENE	1.85		PPM
NITROGEN, NITRATE	0.60		PPM
NITROGEN, NITRITE	<0.01		PPM
STANDARD PLATE COUNT	10500		
COLIFORMS, FECAL	0		COL/ML
E. COLI	0		MPN
BHA	<0.10	DL <0.01	PPM
BHT	<0.10	DL <0.01	PPM
NITROSAMINES	<0.10		MCG/L
ALPHA BHC	<0.01		PPM

9-25-8

XII. LIST OF PUBLICATIONS

Snipes, M. B., A. G. Harmsen, J.A. Pickrell, F. F. Hahn, H. C. Yeh and F. A. Seiler. Inhalation of Cu-Zn Alloy and TiO_2 by Rats: Exposure Stress Evaluation. Proceedings of the Smoke/Obscurants Symposium X, Harry Diamond Laboratories, Adelphi, MD, 22-24 April 1986.

XIII. PERSONNEL SUPPORTED BY PROJECT

Name	Duty
Professional	
Snipes, M. B.; Ph.D.	Principal investigator responsible for coordination of activities in the project.
Bice, D. E.; Ph.D.	Immunology evaluations.
Burt, D. G.; D.V.M.	Small animal care operations.
Damon, E. G.; Ph.D.	Data management in Path/Tox Data Base System.
Eidson, A. F.; Ph.D.	Coordinate activities associated with analytical techniques used in this project.
Hahn, F. F.; D.V.M., Ph.D.	Pathology evaluations.
Harkema, J. R.,; D.V.M., Ph.D.	Pathology evaluations.
Harmsen, A. G.; Ph.D.	Immunologist responsible for activities related to animal stress evaluation.
Harris, D. L.; M.S.	Quality Assurance.
Hobbs, C. H.; D.V.M.	Veterinarian for project and member of the ITRI directorate in charge of this research.
Lopez, J. A.; B.S., Ch.E.	Responsible for maintaining facilities.
Mauderly, J. L.; D.V.M., Ph.D.	Respiratory function evaluations.
Pickrell, J. A.; D.V.M., Ph.D.	Blood chemistry evaluations.
Seiler, F. A.; Ph.D.	Statistician for project.
Thompson, J. J.; Ph.D.	Health protection and safety.
Yeh, H. C.; Ph.D.	Responsible for aerosol science activities.

XIV. DISTRIBUTION LIST

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1	Commander/Director Chemical Research, Development and Engineering Center ATTN: SMCCR-RST-E Aberdeen Proving Ground, MD 21010-5423
1	Officer-in-Charge Naval Medical Research Institute Toxicology Detachment Building 433 Wright-Patterson AFB, OH 45433
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1	U. S. Army Medical Research and Development Command ATTN: SGRD-RMI-S Fort Detrick, Frederick, MD 21701-5012
1	Dean, School of Medicine Uniformed Services University of the Health Sciences 4301 Jones Bridge Road Bethesda, MD 20014
2	Defense Technical Information Center ATTN: DTIC-DDAC Cameron Station Alexandria, VA 22304-6145