Ciba Specialty Chemicals
USA
Water
Treatments

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8EHQ-98-14334

Document Processing Center
Room G-99, East Tower
Attn: Section 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Re: TSCA Section 8(e) Notice

88990000053

Dear Sir or Madam:

Ciba Specialty Chemicals Water Treatments, Inc. ("Ciba") is submitting the studies discussed below pursuant to Section 8(e) of the Toxic Substances Control Act ("TSCA").

Salsorb 84: 28 Day Inhalation Toxicity in the Rat (dated 10/4/89). This study reported effects to the lungs in the high-dose (100.86 ug/l) and mid-dose (18.27 ug/l) groups from a polymer of sodium acrylate and acrylic acid, CAS No. 9033-79-8. The high-dose males and females showed increased absolute and relative lung weights that were not observed in the mid- and low-dose groups. Further, the lungs of males and females in the high- and mid-dose groups showed macrophage (histiocyte) accumulation at the alveoli which had progressed to inflammation and proliferation of tissue repair responses in the high-dose group only. The study determined the no observed effect concentration to be 3.95 ug/l and the lowest observed effect concentration to be 18.27 ug/l.

Ciba believes that this study may not be 8(e) reportable in part because the inhalation effects of polyacrylate absorbents like Salsorb 84 at these levels were likely well known to EPA by 1989. However, because reconstructing the state of the Agency's knowledge as of 1989 is an uncertain undertaking, Ciba is submitting this study under Section 8(e) as a precautionary measure.

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Allied Colloids
Ciba Specialty Chemicals Water Treatments, Inc.
2301 Wilroy Rd.
P.O. Box 820
Suffolk, Virginia 23439-0820
Tel. 757 538 3700
Fax 757 538 3989

Aquatic Toxicity Data. The attached letter dated August 2, 1994, contains data indicating that two products, epiamine (dimethylamine-ethylenediamine-epichlorohydrin copolymer, CAS No. 42751-79-1) and DIMDAC (diallyldimethylammonium chloride, CAS No. 26062-79-3), may be toxic to certain aquatic organisms at concentrations as low as 0.14 mg/l. These materials are used in products that are sold in commerce. Ciba believes that such effects were well known to the Agency by the time these data appear to have became known to Ciba's predecessor, Allied Colloids, Inc., in August, 1994. However, as with the Salsorb 84 study discussed above, Ciba is submitting these data because it has not yet been able to reconstruct the Agency's state of knowledge as of 1994.

Ciba has a worldwide policy for environmental and safety audits and due diligence that is designed to meet the standards of EPA's policy on "Incentives for Self-Policing: Discovery, Disclosure, Correction and Prevention of Violations," 60 Fed. Reg. 66706 (Dec. 22, 1995). Ciba undertook a program of TSCA management systems audits in 1997, and these audits are continuing. Earlier this year, Ciba acquired the business of Allied Colloids, Inc., and has been incorporating Allied into Ciba's audit and due diligence program. Ciba recently completed a targeted toxicology audit of the former Allied facility in Suffolk, Virginia, to ensure that all studies reportable under Section 8(e) had been submitted to EPA. During the course of this audit, Ciba identified the studies discussed above. Ciba is also participating in EPA's "Compliance Incentive Program" for the Industrial Organic Chemical sector (SIC Code 2869), and will submit to EPA by January 31, 1999, a final report identifying all potential areas of noncompliance uncovered pursuant to this program.

Please call me at (757) 538-3700 if you have any questions regarding this matter.

Sincerely yours,

Paul Whitwell, SES

Paul Whitwell
Technical Manager
Ciba Specialty Chemicals Water Treatments, Inc.

Enclosures

cc: Aquanetta Dickens, U.S. EPA, Region III

GULBRANDSEN

August 2, 1994

Attn: Jim DeVere
Allied Colloids
2301 Wilroy Rd.
Suffolk, VA 23434

Dear Mr. DeVere:

Enclosed please find toxicity data for the polymers blended into the products we discussed August 1. If I can be of further assistance please call me at (908) 454-5815.

Epiamine

Test species	LC_{50} (mg/L)	Comments
Fathead minnow	0.40 (96 hr.)	Synthetic water
Bluegill	0.14 (96 hr.)	"
Rainbow trout	0.22 (96 hr.)	"
Daphnia magna	0.14 (48 hr.)	"
Cetiodaphnia dubia	0.17 (48 hr.)	"

DIMDAC

Test species	LC_{50} (mg/L)	Comments
Fathead minnow	0.30 (96 hr.)	Synthetic water
Fathead minnow	6.51 (96 hr.)	With 10 mg/L humic acid
Daphnia magna	0.23 (48 hr.)	Synthetic water
Daphnia magna	11.8 (48 hr.)	With 10 mg/L TOC

Sincerely,

Christopher Reed

Christopher Reed
Gulbrandsen Co, Inc.

GULBRANDSEN COMPANY, INC.
P.O. Box 508 - Milford, NJ 08848 - 908-995-7759 - Fax 908-995-9482

SALSORB 84: 28 DAY INHALATION TOXICITY IN THE RAT

HAZLETON UK

HAZLETON UK
Otley Road, Harrogate
North Yorkshire HG3 1PY England

CONFIDENTIAL

SALSORB 84: 28 DAY INHALATION TOXICITY IN THE RAT

Report for: Allied Colloids Ltd.,
PO Box 38,
Low Moor,
BRADFORD,
BD12 0JZ.

Prepared by: C.J. Collins, B.Tech., M.I.Biol.,
Study Director

Hazleton UK,
Otley Road,
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ENGLAND,
HG3 1PY.

Report No: 5919-760/33

Date: September 1989

a CORNING Laboratory Services Company

AUTHENTICATION

REPORT NO. 5919-760/33

I, the undersigned, hereby declare that the work described in this report was performed under my supervision, as Study Director, in accordance with the agreed protocol, and with Hazleton Standard Operating Procedures, unless otherwise stated, and that the report provides a true and accurate record of the results obtained.

C J Collins

4 October 1989

C.J. Collins, B.Tech., M.I.Biol.,
Study Director

Date:

I, the undersigned, hereby declare that I have reviewed this report in conjunction with the Study Director and that the interpretation and presentation of the data in the report are consistent with the results obtained.

M J Goodyer

M.J. Goodyer, B.Sc.(Hons)., M.I.Biol.,
Manager, Study Directors - Toxicology

Date: 4 October 1989

QUALITY ASSURANCE RECORD

REPORT NO. 5919-760/33

The project described in this report was subject to audit/inspection by the independent HUK Quality Assurance Unit for the aspects and at the intervals specified below. The findings of each audit, unless indicated otherwise, were reported to the Study Director and to HUK management as prescribed by Standard Operating Procedures.

The study report audit was designed to confirm that so far as can reasonably be established the methods described and results incorporated in the final report accurately reflect the raw data produced during the study.

Phase of study audited	Date of audit	Date of report
Protocol review	3 February 1988	8 February 1988
Procedures inspection	3 March 1988	12 April 1988
Procedures inspection	31 March 1988	
Study report (draft)	August 1989	17 August 1989
Study report (final)	September 1989	2 October 1989

Pamela R. Cooper, B.Sc., Ph.D., M.P.S.
Quality Assurance Manager

Date: 2 October 1989

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SECTION A

1. SUMMARY
2. INTRODUCTION
3. EXPERIMENTAL PROCEDURES
4. RESULTS
5. DISCUSSION AND CONCLUSION
6. ARCHIVE

1. SUMMARY

1.1 This study was conducted to determine the inhalation toxicity of the test article in the rat following administration over a four week period. The following study design was used:

Group number	Group designation	Dose level (µg/l) Nominal	Target	Actual	Animals/group Male	Female
1	Control	0	0	0	5	5
2	Salsorb 84 - low	24.51	4	3.95	5	5
3	Salsorb 84 - intermediate	84.31	20	18.27	5	5
4	Salsorb 84 - high	523.67	100	100.86	5	5

1.2 The daily mean temperature and relative humidity for the control and treated groups ranged between 20 and 23°C and 36 and 61% respectively. The daily mean chamber ventilation rates for the treated and control groups were in the range 203 to 230 l/min.

1.3 Particle size distribution data showed considerable variability but demonstrated that a significant fraction of the aerosol was inspirable by the animal and respirable by the lung.

1.4 There were no deaths during the study and no treatment-related clinical abnormalities.

1.5 Treated and control animals had comparable body weights and food consumption throughout the study.

1.6 There were no effects of treatment on the haematology and clinical chemistry parameters measured.

1.7 At necropsy the high dose group had elevated absolute and relative lung weights compared with controls. The lung weights of the low and intermediate groups were comparable with controls.

1.8 Histopathologically a low grade lung leucocyte response was seen in the high dose group and an increased incidence of alveolar

histiocyte foci was seen in the intermediate dose group. There was no effect in the low dose group.

1.9 It was concluded that 3.95 µg/l was the no-effect level in the rat but minor pulmonary changes could be induced at levels of 18.27 µg/l or greater of Salsorb 84, possibly as a result of its hygroscopic nature. However the hazard of Salsorb 84 or similar materials may be small because of the difficulty of producing respirable aerosols.

2. INTRODUCTION

The study was performed to assess the inhalation toxicity of the test article in the rat following administration over a 4 week period.

The inhalation route was chosen by the study sponsor as a possible route of human exposure. The rat was selected as it is a readily available rodent species acceptable to the regulatory authorities and known to respond to the administration of materials similar to the test article.

The study was preceded by a 5 day range-finding study (HUK project no. 760/32), and by aerosol development work using Salsorb 84 and Salsorb DD. This work demonstrated that there were severe difficulties in producing an aerosol of the latter material.

The animals for the present study were received by HUK on 28 January 1988. Exposure started on 3 March 1988 and the necropsies were conducted on 31 March 1988.

3. EXPERIMENTAL PROCEDURES

3.1 Protocol adherence

This study was conducted in accordance with the agreed protocol, HUK Protocol number P3945d and 1 amendment, presented in Appendix 10. There were no major deviations from the protocol. Minor deviations, which did not affect the integrity or outcome of the study, are also presented in Appendix 10.

3.2 Test article

Approximately 9 kg of the test article Salsorb 84, a white solid, were supplied by the sponsor and received at HUK on 15 October 1987.

The test article was micronised prior to use using a high speed pin mill followed by the use of an air classifier, at Powder Products Ltd., Spondon, Derby.

The test article was stored in a sealed container at ambient temperature and humidity in the dark when not in use. The test article was dried overnight at 100°C before use. This procedure was used to improve the flow characteristics of the test article in the aerosol generator and commenced on day 8 of the study. The stability of the test article during this procedure was confirmed by the sponsor.

The purity was stated to be 93%. Appropriate information concerning the stability of the test article, if required, is to be retained on file by the sponsor.

3.3 Test system

3.3.1 Species, strain and supplier

A sufficient number of Sprague Dawley-derived rats of the Crl:CD(SD)BR strain to provide 29 healthy animals of each sex was obtained from Charles River (UK) Ltd., Margate. The animals were ordered in the weight ranges 150 to 200 g for males and 125 to 175 g for females and about 6 to 8 weeks old on arrival.

The animals were given an external examination on arrival at HUK and acclimatised to the holding room for 35 days. During the acclimatisation period 5 animals of each sex were killed and a microscopic examination of the lungs performed. Following the examination and at the request of the pathologist a further 4 animals of each sex were killed and their lungs also examined (Appendix 8). These examinations indicated that although occasional minor focal pneumonitis was seen, the batch of animals was suitable for use on the study.

During the acclimatisation period the animals were re-examined by a veterinary officer and their suitability for experimental purposes confirmed.

3.3.2 Environment and husbandry

The animals were housed in a single room, in groups of 5 by sex, in grid-floor cages.

The room was maintained routinely at 19 to 25°C and 40 to 70% relative humidity and was provided with fluorescent lighting, automatically controlled to give a cycle of 12 hours light and 12 hours darkness. The ventilation system maintained a minimum of 15 air changes per hour.

3.3.3 Diet and drinking water

Except during the exposure period and overnight prior to blood sampling and necropsy, the animals were allowed free access to mains water and food (SQC Rat and Mouse Maintenance Diet No. 1 Expanded, Special Diets Services Ltd., Witham).

Mains drinking water was available ad libitum except during the exposure period, from glass water bottles attached to the cages. The contents of the bottles were changed daily.

The diet and water were considered not to have contained any contaminant at a level which might have affected the integrity or outcome of the study.

3.3.4 Allocation to treatment group and identification

The animals were assigned to treatment groups using a randomisation procedure based on stratified body weight, during the acclimatisation period. Group mean body weights were calculated and inspected to ensure there were no unacceptable differences between groups.

Treatment positions on the battery were assigned using a set of random letter permutations.

After allocation to treatment group each animal was permanently numbered by ear tattoo as follows:

Group number	Colour code	Animal identification numbers Male	Female
1	buff	1-5	26-30
2	green	6-10	31-35
3	blue	11-15	36-40
4	pink	16-20	41-45

Each cage was labelled with a card, coloured according to treatment group, showing HUK project number, cage number, species, animal numbers and sex, chamber concentration, route of administration, start date of exposure and Home Office licensee.

3.3.5 Experimental design and dose levels

Group number	Group designation	Test article concentration Target µg/l	Mean measured µg/l	Animals/group Male	Female
1	air control	0	-	5	5
2	low	4	3.95	5	5
3	intermediate	20	18.27	5	5
4	high	100	100.86	5	5

The treated animals were exposed (whole body) for 6 hours a day, 5 days a week for 4 weeks.

A group of 10 rats (5 males, 5 females), exposed under similar conditions to an atmosphere of filtered air, acted as a control.

The animals were killed and necropsied on day 29 of the study.

3.3.6 Production of test atmosphere

A schematic diagram of the dynamic (continuous flow) system employed is shown in Figure 3. The compressed air supply to the generator used was from a clean dry filtered source.

A rotating flat disc generator (Figure 4) containing the test article in a groove at its periphery was used to generate the aerosol. An eductor (pick-up tube) supplied with compressed air was used to pick up the test article from a nozzle in the groove and produce the atmosphere of test article within a 1 m^3 aluminium and glass exposure chamber.

3.3.7 Distribution study

The chamber distribution study was conducted once before animal exposures started. For groups 2 (low dose) and 3 (intermediate dose) gravimetric analysis was used to measure the test article concentration at 6 points in the chamber and at a central reference point. The 6 points were at the top, bottom, front, back, left side, and right side of the chamber. Sampling from each pair of points and from the central reference point was performed simultaneously. For group 4 (high dose) the same measurements had been already conducted in HUK Project 760/32. This data was therefore used to support the present study.

Additionally in Project 760/32, chamber distribution was assessed by the introduction of smoke into each chamber under the generator conditions used and found to be satisfactory.

The exposure cages were rotated weekly around their positions in the centre of the exposure chamber. Chamber air flow rates were monitored continuously and recorded routinely at hourly intervals. The atmospheres were filtered, exhausted to the outside of the building and vented.

3.4 Experimental observations

3.4.1 Exposure chamber temperature and relative humidity

The temperature and relative humidity inside the exposure chamber were measured continuously and recorded routinely at hourly intervals throughout the 6-hour exposure period, using a glass/mercury thermometer and a hair hygrometer located in the chamber.

3.4.2 Exposure chamber oxygen concentration

The airflow through the chamber was set at a value adequate to maintain the oxygen concentration at the minimum value of 19% required by the protocol. The concentration was confirmed once for all chambers in the presence of animals using an oxygen analyser incorporating a remote sensor.

3.4.3 Exposure chamber test article concentration

3.4.3.1 Measured concentration

The concentration of the test article was determined gravimetrically. The samples were obtained over periods up to 35 minutes, routinely 3 times daily during the exposure period.

The atmosphere was sampled from the chamber by drawing a known volume through a glass fibre disc in a cassette held on a probe just above the breathing zone of the animals at the centre of the chamber at the middle level. This position was selected as being representative based on the preliminary distribution study. The filter disc was weighed before and after sampling and the measured concentration of the test atmosphere calculated as follows:

$$\text{Gravimetric concentration } (\mu g/l) = \frac{\text{total weight gain } (\mu g)}{\text{volume of sample } (l)}$$

3.4.3.2 Nominal concentration

The total weight of test article used and the volume of diluent air used to generate the test atmosphere were recorded and the nominal concentration of the test article in the exposure chamber was calculated as shown:

$$\text{Nominal concentration } (\mu g/l) = \frac{\text{weight of test article used } (\mu g)}{\text{flowrate } (l/min) \times \text{duration } (min)}$$

The nominal concentration was calculated daily for each exposure group.

3.4.4 Exposure chamber particle size analysis

The particle size was determined initially using a CS5 Cascade Impactor with 5 separation stages corresponding to maximum mass median aerodynamic diameters of 0.5, 1.0, 2.0, 4.0 and 8.0 µm. The samples were obtained over a period of up to 55 minutes during the exposure period. Particle size analysis was carried out pre-study, at least once during weeks 1, 2 and 3 for group 2, during weeks 1, 2 and 4 for group 3, and each week for group 4.

The cumulative percentage by weight of test article collected at each successive stage was plotted by computer as a probability value against the logarithmic value of the upper class limit of that stage. The point at which the cumulative distribution line crossed the 50 percentile was the estimate of the mass median aerodynamic diameter.

Particle size measurements were made pre-study using ungreased separation stages in the cascade impactor. Thereafter the top stage was greased to minimise particle bounce down the instrument. An Andersen (1 CFM) ambient

sampler was used instead of the Delron instrument in week 4 to provide an estimate of particle size by an instrument with multiple openings on each separation stage. This configuration is considered to be more resistant to problems of overloading and particle bounce (i.e. re-entrainment of particles after impaction).

3.4.5 Clinical observations

3.4.5.1 Morbidity and mortality

All animals were examined twice daily to detect any which were dead or moribund.

3.4.5.2 Clinical observations

All animals were examined once daily for signs of ill health or overt toxicity. In addition each animal was given a detailed clinical examination at weekly intervals. An individual record was maintained of the clinical condition of each animal.

3.4.6 Body weight

Individual body weights were recorded before exposure on the first day of the study, at weekly intervals thereafter and at necropsy.

3.4.7 Food consumption

The amount of food consumed by each cage of animals was determined weekly.

3.5 Laboratory investigations (Methods and units, Appendix 9)

Blood samples were obtained from all animals in week 4. The samples were collected by orbital sinus puncture under light halothane anaesthesia following an overnight period without food (about 13 hours). Samples were collected before any exposure that day.

3.5.1 Haematology

The following parameters were measured on blood collected into EDTA anticoagulant:

- haemoglobin
- mean cell volume
- red blood cell count and indices:
  - mean cell haemoglobin
  - packed cell volume
  - mean cell haemoglobin concentration
- total and differential white blood cell count
- platelet count

Repeat samples for eight animals at necropsy were necessary due to clotting of some of the haematology samples. The samples were taken from the abdominal aorta into EDTA anticoagulant and the above parameters measured.

3.5.2 Clinical chemistry

The following parameters were measured on blood collected into lithium heparin anticoagulant:

- glutamate oxaloacetate transaminase
- glutamate pyruvate transaminase
- alkaline phosphatase
- gamma glutamyl transferase (transpeptidase)

sodium	potassium
chloride	calcium
inorganic phosphorus	glucose
cholesterol	blood urea nitrogen
total bilirubin	creatinine
total protein	albumin
albumin/globulin ratio	

Urinalysis was not performed because there was no evidence of any renal change.

3.6 Pathology

The following procedures were applied to all animals killed at the end of the study.

3.6.1 Necropsy

The animals were killed following an overnight period without food by an intraperitoneal injection of sodium pentobarbitone and exsanguination. A full internal and external examination was made under the supervision of a pathologist and all lesions were recorded.

3.6.2 Organ weights

The following organs were dissected free from fat and other contiguous tissue and weighed before fixation:

adrenals	kidneys	testes
liver	lungs	

Paired organs were weighed separately.

3.6.3 Histology

Samples of the following tissues were fixed in neutral buffered 10% formalin, with the exception of the eyes which were fixed in Davidson's fluid:

adrenals	eyes
heart	kidneys
larynx and thyroid LS	liver
lungs	nasal turbinates (4 levels)
spleen	tongue
trachea at the bifurcation	all gross lesions

All tissues from all control and high dose animals and lungs from all other animals were embedded in paraffin wax B.P. (mp 56°C), sectioned at a nominal thickness of 5 µm, stained with haematoxylin and eosin and evaluated by the study pathologist.

3.7 Statistical evaluation

Data were processed, where appropriate, to give group mean values and standard deviations.

Some tables and appendices presented in the report are computer generated. The group mean and individual data are generated independently from the values held on a data base and rounded appropriately for inclusion in the report. As a consequence calculation of group mean data from the individual data presented in the report will, in some instances, yield a minor variation in the last decimal place.

Absolute and relative lung and adrenal weights were analysed using analysis of variance and t-test.

No other statistical evaluations were carried out.

References

Analysis of variance (ANOVA)

Snedecor, G.W. and Cochran, W.G. (1980) Statistical methods, 7th ed. Iowa: Iowa State Univ. Press.

t-test

Snedecor, G.W. and Cochran, W.G. (1980) Statistical methods, 7th ed. Iowa: Iowa State Univ. Press.

4. RESULTS

4.1 Atmosphere control

4.1.1 Exposure chamber distribution studies (Table 1)

Smoke testing of the chamber to visualise the airflows was conducted as part of the range-finding study HUK project no. 760/32. It indicated that a wide stream of air proceeded vertically downwards from the eccentric head of each chamber where the make-up air is introduced. This airflow changed direction at the level of the animal cages, moving outwards in all directions to the periphery of the chamber and then upwards close to the walls. The latter airflows were attributed to re-entrainment of chamber air by the downward incoming air stream at the top of the chamber, indicating good mixing in the chamber. The smoke test demonstrated good air mixing and distribution within the exposure chamber.

Values for gravimetric samples obtained in the middle horizontal plane of the chamber demonstrated that the values for the sample points were in the range 72 to 115% of their respective sample reference points. Some values at the top and bottom of the chamber fell outside this range. Exposure cage positions were therefore located in the middle horizontal plane of the chamber.

4.1.2 Exposure chamber temperature and relative humidity (Table 2)

The daily mean temperature for the control and treated groups ranged between 20 and 23°C and the relative humidity between 36 and 61%.

4.1.3 Exposure chamber diluent air flow rates (Table 2)

The daily mean air flow rates for the treated and control groups were in the narrow range of 203 to 230 l/min.

4.1.4 Exposure chamber oxygen concentration

The exposure chamber oxygen concentration was monitored on study day one and was 21% for all groups.

4.2 Measured exposure chamber atmosphere concentration (Table 3, Appendix 1)

Mean measured atmosphere concentrations were as follows:

Group	Target	Mean test article concentration (µg/l) Nominal (day 1 to 28)	Measured (days 1 to 28)	Range of daily mean measured values (days 1 to 28)
2	4	24.51	3.95	2.45 - 5.35
3	20	84.31	18.27	12.65 - 21.37
4	100	523.67	100.86	83.53 - 123.79

The overall mean measured atmosphere concentrations of 3.95, 18.27 and 100.86 µg/l showed good correlation with their respective target concentrations. The day-to-day variability was considered to be satisfactory. The measured concentrations were normally in the region of 20% of the corresponding nominal concentrations, but marked day-to-day variation occurred. This difference between actual and nominal concentration is not unusual for aerosols of powders.

4.3 Exposure chamber particle size analysis (Table 4)

There was considerable variability in the mass median aerodynamic particle size of the atmospheres at the various time points. This reflects the difficulties of micronising and generating an aerosol of an elastic and hygroscopic test article. These same characteristics also tend to reduce the separation efficiency of the instruments used for particle size analysis. For these reasons a variety of methodologies using two instruments was used in order to evaluate the particle size distribution of the atmospheres.

The mass median diameter estimated using the Delron (single orifice) instrument was often greater than the largest collection range of the instrument (i.e. greater than 50% of the collected mass was impacted onto the first stage). Mass median diameter was not therefore considered to be the best measure of particle size distribution. The percentage smaller than the first stage of the two instruments (8 or 9 µm), and the percentage smaller than a

stage corresponding to the upper limit of respirability (4 or 4.7 µm), were used for evaluation of particle size distribution.

A significant proportion of the aerosol was smaller than each of these class limits implying significant inspirability into the animal, and respirability to the lung, respectively. The test article was dried prior to use from day 8 onwards but this did not give any obvious improvement in particle size distribution. The considerable day-to-day variation in particle size distribution may reflect varying quality of the aerosol or variation in the performance of the instrument. The Andersen instrument is considered to be more resistant to problems of overloading and particle bounce and gave a smaller particle size distribution than the Delron instrument. This suggests that the actual particle size distribution might be less than the values indicated by the Delron instrument. Overall the results for different substrates in each instrument were similar suggesting particle bounce was not a significant problem.

4.4 Mortality

There were no deaths during the study.

4.5 Clinical observations

There were no clinical signs related to treatment.

4.6 Body weight (Table 5, Appendix 2, Figures 1 and 2)

Treated and control animals had comparable body weights during the study. All animals lost body weight in week four compared to their week three values. These reductions were attributed to the period of food deprivation associated with the blood sampling procedure.

4.7 Food consumption (Table 6)

Treated animals had similar food consumption to controls. The reduced food consumption during week four was attributed to the period of food deprivation associated with the blood sampling procedure.

4.8 Clinical pathology

4.8.1 Haematology (Table 7, Appendix 3)

There were no changes in any of the haematology parameters that were considered to be treatment-related.

4.8.2 Clinical chemistry (Table 8, Appendix 4)

There were no changes in any of the clinical chemistry parameters that were considered to be treatment-related.

4.9 Pathology

4.9.1 Organ weights (Table 9 and 10, Appendices 5 & 6)

At termination high dose animals had elevated absolute and relative lung weights when compared with controls. The mean relative lung weight was increased by 40% for males and 39% for females ($p<0.001$ for both sexes). Intermediate and low dose animals had absolute and relative lung weights that were comparable with those of controls.

Treated animals showed variation in absolute and relative adrenal weights. There was a trend in the male groups towards decreased adrenal weights compared with controls. The absolute and relative adrenal weights of the high dose female group were significantly increased ($p<0.001$ and $p<0.01$) respectively. In view of the opposite directions of the differences in the two sexes, their small numerical size, and the absence of any histopathological changes, the differences were not attributable to treatment.

There were no other changes in organ weights attributable to treatment.

4.9.2 Necropsy findings (Appendix 7)

At necropsy there was no evidence of toxicity.

4.9.3 Histopathology (Appendix 7)

Control animals showed minimal to slight pneumonitis with minimal leucocyte response and occasionally focal alveolar histiocytes.

High dose animals had a prominent increase in the population of alveolar histiocytes. Histiocyte foci were found in the alveoli surrounding the terminal airways. Associated with these foci were slight increases in the degree of perivascular leucocyte cuffing and infiltration, and minimal proliferation of alveolar type 2 epithelial cells localised to alveoli containing the histiocyte foci. In the intermediate dose group there was a slight increase in the number of animals showing alveolar histiocyte foci, but no significant associated reaction.

The lungs of the low dose and control groups were comparable.

There were no other histological changes attributable to treatment.

5. DISCUSSION AND CONCLUSION

Exposure to Salsorb 84 at an atmosphere concentration of 100.86 µg/l resulted in increases in lung weight and a low grade lung leucocyte response histologically. At 18.27 µg/l Salsorb 84 induced only a slightly increased incidence of alveolar histocyte foci. The no-effect level was 3.95 µg/l suggesting the test article did not accumulate in the lungs at that exposure level.

It had been necessary to micronise the test article supplied in order to produce an aerosol that would induce the observed changes. Even using the micronised material vigorous efforts were required in order to produce an aerosol of adequate respirability. Method development work using a less highly cross-linked polymeric form (Salsorb DD) of the test article failed to produce a satisfactory aerosol probably because of the difficulty of micronising a more elastic material of this nature.

It was concluded that although minor pulmonary changes could be induced by the test article, possibly due only to its hygroscopic nature, the hazard in use may be small because of the difficulty of producing respirable aerosols. It was concluded that the hazard of Salsorb DD may be no greater than Salsorb 84 because the chemical natures of the two materials are similar but Salsorb DD is more difficult to comminute.

6. ARCHIVE

All primary data, or copies thereof, and specimens will be retained in the HUK archives for 10 years after submission of the final report. At this time the sponsor will be contacted to decide if storage for a longer period is required.

Specimens will be taken to include test/control articles, any tissue, tissue blocks or slides derived from a test system for examination or analysis. Biofluids are specifically excluded from the above definition because of the lability of the constituents.

Primary data will be taken to include laboratory data sheets, records, memoranda, notes, photographs, microfilm and computer records that are a result of the original observations and activities of the study and which are necessary for the reconstruction and evaluation of the report of the study.

SECTION B

7. TABLES
8. FIGURES

TABLE 1

Distribution of test article in exposure chamber

Position	Measured concentration % +		
	low dose	intermediate dose	high dose
Centre top	160	93	172
Centre bottom	95	99	59
Centre left wall	104	106	85
Centre right wall	91	112	94
Centre front	97	96	72
Centre back	113	115	111

+ percentage of value at reference point at chamber centre.
Investigations conducted separately for the vertical and the two horizontal planes.
The data for the high dose was collected in connection with the range-finding study HUK project no. 760/32.

TABLE 2

Mean exposure chamber conditions

Group			Chamber condition on day: 1	2	5	6	7	8	9	12	13	14	15	16	19	20	21	22	23	26	27	28
1	Temperature °C	Mean	23	23	22	21	21	23	23	23	22	22	21	22	22	21	22	22	21	22	22	22
		S.D.	5	1	1	0	1	1	0	0	0	1	1	0	0	1	1	1	1	1	1	1
	Relative humidity %	Mean	49	42	55	57	58	53	54	53	57	53	56	55	52	53	50	49	49	53	50	49
		S.D.	2	1	1	3	1	4	1	2	2	2	1	1	2	1	1	1	2	3	1	2
	Chamber air flowrate l/min	Mean	223	220	220	224	228	230	229	229	230	219	230	230	230	230	230	230	230	230	220	220
		S.D.	5	0	0	5	10	0	4	4	0	4	0	0	0	0	0	0	0	0	0	0
2	Temperature °C	Mean	23	22	21	21	21	22	23	23	22	22	21	22	22	21	22	23	22	22	22	22
		S.D.	1	1	1	1	1	1	1	0	0	1	1	0	0	1	1	1	0	1	1	0
	Relative humidity %	Mean	42	36	56	59	60	54	56	56	61	57	61	59	50	52	50	49	49	49	47	48
		S.D.	2	1	2	3	1	3	2	3	2	3	1	2	2	1	3	1	1	3	2	2
	Chamber air flowrate l/min	Mean	209	218	210	214	225	214	227	217	217	220	223	220	221	216	210	219	224	220	210	210
		S.D.	3	4	0	5	5	5	5	10	8	0	10	0	7	5	0	4	5	0	0	0
3	Temperature °C	Mean	23	23	22	21	22	23	23	23	23	23	21	23	22	22	22	22	22	22	22	22
		S.D.	0	1	0	1	0	1	0	0	1	1	1	1	0	1	1	0	0	1	1	0
	Relative humidity %	Mean	50	44	56	58	61	56	56	51	54	52	54	51	50	51	49	48	49	50	48	47
		S.D.	2	1	2	4	2	3	1	3	2	3	2	1	2	1	2	2	1	3	1	1
	Chamber air flowrate l/min	Mean	214	213	214	217	215	222	220	220	219	220	220	220	219	219	220	220	220	219	211	217
		S.D.	4	5	5	5	5	7	0	0	4	0	0	0	2	4	0	0	0	4	4	5
4	Temperature °C	Mean	22	22	21	21	21	22	22	23	22	23	20	22	21	20	21	22	21	22	22	22
		S.D.	0	1	0	1	1	0	0	0	0	1	1	0	1	1	1	0	0	0	1	0
	Relative humidity %	Mean	50	44	55	57	61	56	56	54	59	57	59	57	53	55	54	52	51	52	50	52
		S.D.	2	1	2	2	3	3	2	3	2	1	1	2	1	1	2	2	1	4	2	1
	Chamber air flowrate l/min	Mean	203	220	216	222	218	218	219	220	222	217	217	221	220	221	222	219	212	216	214	203
		S.D.	5	4	5	8	10	10	2	0	6	3	5	3	10	11	5	2	12	5	7	9

TABLE 3

Mean exposure chamber test article concentration (µg/l)

Group		Mean concentration (µg/l) on day: 1	2	5	6	7	8	9	12	13	14	15	16	19	20	21	22	23	26	27	28	Overall mean days 1-28
2 Nominal		21.96	28.52	30.86	26.52	72.15	26.40	27.42	24.91	17.44	18.44	19.41	19.58	19.58	28.78	24.55	17.28	16.98	12.29	21.76	15.43	24.51
Gravimetric	Mean	2.72	3.08	3.66	3.82	5.33	4.79	4.62	5.00	5.35	4.77	4.13	4.18	2.45	3.64	4.04	2.63	3.46	3.55	3.99	3.72	3.95
	S.D.	0.14	0.80	0.92	1.55	1.32	0.57	0.98	0.49	0.59	1.68	0.54	0.50	0.13	-	1.00	0.76	1.40	0.13	0.08	0.21	
3 Nominal		102.27	106.54	97.67	83.83	103.54	91.78	64.20	98.77	81.85	102.47	91.36	96.30	76.88	70.68	77.78	69.14	61.73	70.68	64.00	74.74	84.31
Gravimetric	Mean	21.37	19.24	21.06	16.78	15.69	19.30	19.73	20.06	19.60	16.13	18.96	15.35	20.51	16.62	12.65	18.84	15.32	21.02	18.53	18.60	18.27
	S.D.	5.59	3.79	3.58	2.21	2.18	4.19	2.17	2.23	3.08	0.85	0.73	2.53	2.52	-	1.95	4.44	3.66	1.30	4.68	1.04	
4 Nominal		588.78	662.49	626.88	411.79	343.92	563.00	497.53	533.43	529.97	526.91	556.60	558.00	409.29	413.61	502.94	512.35	731.40	451.70	657.83	394.74	523.67
Gravimetric	Mean	92.50	113.23	111.63	99.23	96.84	115.50	94.87	106.15	95.61	83.53	104.56	103.23	90.60	120.16	123.79	98.73	84.31	94.89	98.89	88.98	100.86
	S.D.	15.13	4.94	8.25	5.60	-	7.73	2.29	8.13	7.58	3.60	13.02	11.61	21.17	-	24.21	14.22	5.15	8.06	21.40	6.05	

TABLE 4

Exposure chamber particle size analysis - mass median diameter (µm)

Group	Day	Mass Median diameter (µm)	% less than stated size		Collection substrate
			<8 µm	<4 µm	
2	-1	=8≠	31.38	19.68	Delron - ungreased
	6	>8≠	32.10	29.63	Delron - greased top plate
	12	>8≠	30.80	19.01	Delron - greased top plate
	15	2.30	66.67	44.44	Delron - greased top plate
3	-1	=8≠	38.95	12.79	Delron - ungreased
	2	>8≠	24.27	15.90	Delron - greased top plate
	9	4.79	47.83	23.91	Delron - greased top plate
	14	4.01	51.05	25.17	Delron - greased top plate
			<9 µm	<4.7 µm	
	28	2.48	74.89	59.82	Andersen - ungreased steel plates
			<8 µm	<4 µm	
4	-28	1.57	91.30	73.91	Delron - ungreased
	-28	4.84	42.62	19.67	Delron - ungreased
	-10	6.34	32.48	9.08	Delron - ungreased
	-10	>8≠	20.98	1.79	Delron - ungreased
	-9	3.40	57.14	24.40	Delron - ungreased
	1	4.09	51.23	26.98	Delron - greased top plate
	8	>8≠	16.86	4.81	Delron - greased top plate
	13	>8≠	23.71	8.02	Delron - greased top plate
	16	6.10	34.88	16.05	Delron - ungreased
	16	>8≠	30.05	18.65	Delron - greased top plate
			<9 µm	<4.7 µm	
	26	4.13	68.96	35.12	Andersen - filter substrate
	27	3.43	72.98	48.49	Andersen - filter substrate
	27	3.19	71.48	46.78	Andersen - ungreased steel plates
	27	3.40	67.62	48.57	Andersen - ungreased steel plates

≠ values for mass median diameter above the largest collection range of the instruments are not presented because of the errors in computation by extrapolation.

TABLE 5

Group mean body weight (g)

Date of printing: 4 May 1988 Computer id. : CS760033

Week of Study		Group and Sex 1M	2M	3M	4M
Start	Mean	360.2	376.2	389.8	364.8
	S.D.	21.06	18.87	27.72	21.64
1	Mean	378.0	390.5	402.9	379.4
	S.D.	20.14	24.88	33.20	19.60
2	Mean	398.6	409.8	419.4	397.9
	S.D.	21.09	30.39	34.22	25.32
3	Mean	412.4	435.7	440.1	412.7
	S.D.	19.93	33.40	40.44	25.14
4	Mean	383.9	407.2	411.6	391.0
	S.D.	16.38	32.46	37.90	18.16

TABLE 5

Group mean body weight (g)

Date of printing: 4 May 1988 Computer id. : CS760033

Week of Study		Group and Sex 1F	2F	3F	4F
Start	Mean	220.6	213.7	211.9	224.3
	S.D.	19.49	7.82	3.84	20.59
1	Mean	232.0	220.1	222.2	235.6
	S.D.	18.31	3.84	2.98	15.43
2	Mean	238.1	231.1	231.9	242.0
	S.D.	17.07	5.17	3.63	11.81
3	Mean	241.4	236.6	239.9	248.9
	S.D.	15.79	4.24	5.43	14.33
4	Mean	222.1	217.0	220.9	230.9
	S.D.	19.03	3.11	4.01	13.24

TABLE 6

Group mean food consumption (g/animal/week)

Date of printing: 4 May 1988 Computer id. : CS760033

Week of Study	Group and Sex 1M	2M	3M	4M
1	190.5	192.0	194.2	189.2
2	192.1	188.9	187.3	190.3
3	194.1	195.1	199.0	194.2
4	166.2	173.2	167.1	173.1

TABLE 6

Group mean food consumption (g/animal/week)

Date of printing: 4 May 1988 Computer id. : CS760033

Week of Study	Group and Sex 1F	2F	3F	4F
1	144.4	130.3	140.5	152.8
2	131.2	132.6	133.9	145.3
3	128.4	132.3	133.1	146.9
4	109.3	111.9	114.8	125.2

TABLE 7

Group mean haematology
Occasion: Week 4

Gp Sex		Hb g/dl	RBC mil/cmm	PCV %	MCV fl	MCH pg	MCHC g/dl	PLAT 1000/cmm
1M	Mean	14.6	7.30	44.1	60.4	20.0	33.1	1217
	S.D.	.7	.29	2.1	1.6	.7	.5	109
2M	Mean	15.1	7.52	45.3	60.3	20.1	33.4	1122
	S.D.	.6	.37	1.9	1.1	.4	.2	285
3M	Mean	14.4	7.29	43.3	59.4	19.8	33.3	1140
	S.D.	.4	.27	1.3	.9	.4	.3	236
4M	Mean	15.3	7.70	45.6	59.3	19.9	33.5	1070
	S.D.	.9	.46	2.5	3.0	1.1	.2	108

TABLE 7

Group mean haematology
Occasion: Week 4

Gp Sex		Hb g/dl	RBC mil/cmm	PCV %	MCV fl	MCH pg	MCHC g/dl	PLAT 1000/cmm
1F	Mean	13.6	6.97	41.0	58.9	19.5	33.1	940
	S.D.	1.0	.59	3.1	.8	.5	.4	49
2F	Mean	14.8	7.43	44.4	59.7	20.0	33.4	1197
	S.D.	1.0	.39	2.7	1.2	.6	.4	97
3F	Mean	14.1	7.15	42.9	60.1	19.7	32.9	970
	S.D.	.9	.37	3.0	2.2	.7	.4	128
4F	Mean	13.5	6.80	40.7	59.9	19.9	33.2	1004
	S.D.	.6	.31	1.5	.9	.3	.3	106

TABLE 7

Group mean haematology
Occasion: Week 4

Gp Sex		TOT WBC 1000/cmm	WBC 1000 / cmm (%) N	L	M	E	B
1M	Mean	11.4	2.20(19)	8.78(77)	.38(3)	.04(0)	.00(0)
	S.D.	2.7	1.09(-)	2.19(-)	.25(-)	.05(-)	.00(-)
2M	Mean	13.2	2.66(20)	10.22(78)	.22(2)	.08(1)	.00(0)
	S.D.	5.0	1.22(-)	3.98(-)	.16(-)	.08(-)	.00(-)
3M	Mean	12.5	2.42(20)	9.72(78)	.22(2)	.08(1)	.00(0)
	S.D.	3.8	.81(-)	3.26(-)	.08(-)	.08(-)	.00(-)
4M	Mean	12.1	2.06(17)	9.68(80)	.38(3)	.00(0)	.00(0)
	S.D.	2.7	.48(-)	2.33(-)	.13(-)	.00(-)	.00(-)

TABLE 7

Group mean haematology
Occasion: Week 4

Gp Sex		TOT WBC 1000/cmm	WBC 1000 / cmm (%) N	L	M	E	B
1F	Mean	8.6	1.80(21)	6.58(77)	.14(2)	.02(0)	.00(0)
	S.D.	4.0	.98(-)	3.06(-)	.05(-)	.04(-)	.00(-)
2F	Mean	7.1	1.78(24)	5.22(73)	.14(2)	.02(0)	.00(0)
	S.D.	1.8	.70(-)	1.18(-)	.11(-)	.04(-)	.00(-)
3F	Mean	6.2	1.44(25)	4.64(74)	.08(1)	.04(0)	.00(0)
	S.D.	2.7	.67(-)	2.13(-)	.08(-)	.09(-)	.00(-)
4F	Mean	7.3	1.58(22)	5.60(76)	.12(1)	.04(0)	.00(0)
	S.D.	2.7	.38(-)	2.34(-)	.04(-)	.05(-)	.00(-)

TABLE 8

Group mean clinical chemistry
Occasion: Week 4

Gp Sex		GOT(AST) Iu/l	GPT(ALT) Iu/l	ALK PHOS Iu/l	GAMMA GT Iu/l	Na meq/l	K meq/l	Cl meq/l	Ca mg/dl	P mg/dl
1M	Mean	74	32	195	3	149	3.9	107	9.9	6.8
	S.D.	6	9	30	2	1	.4	1	.3	.9
2M	Mean	73	33	194	4	148	3.9	106	10.0	6.5
	S.D.	10	10	39	1	2	.1	1	.2	.4
3M	Mean	66	36	164	5	147	3.8	106	9.8	7.7
	S.D.	9	9	49	1	2	.2	2	.2	2.0
4M	Mean	69	39	198	5	148	4.1	106	10.1	7.0
	S.D.	9	7	38	1	2	.3	1	.1	1.0

TABLE 8

Group mean clinical chemistry
Occasion: Week 4

Gp Sex		GOT(AST) Iu/l	GPT(ALT) Iu/l	ALK PHOS Iu/l	GAMMA GT Iu/l	Na meq/l	K meq/l	Cl meq/l	Ca mg/dl	P mg/dl
1F	Mean	70	26	118	5	147	3.7	109	10.1	5.6
	S.D.	7	4	38	2	1	.3	1	.3	.7
2F	Mean	70	25	135	7	147	3.4	108	10.0	5.8
	S.D.	7	6	33	1	1	.2	1	.2	.8
3F	Mean	78	28	130	4	146	3.5	108	9.9	5.6
	S.D.	13	3	39	2	2	.3	2	.2	.3
4F	Mean	71	26	126	6	145	3.5	107	9.6	4.9
	S.D.	2	5	21	1	2	.2	1	.2	.7

TABLE 8

Group mean clinical chemistry
Occasion: Week 4

Gp Sex		GLUCOSE mg/dl	BUN mg/dl	T BILI mg/dl	CREAT mg/dl	T PROT g/dl	ALBUMIN g/dl	AG RATIO	TOT CHOL mg/dl
1M	Mean	87	13	.2	.6	6.2	3.5	1.3	59
	S.D.	12	1	.0	.1	.4	.1	.2	11
2M	Mean	101	12	.2	.6	6.2	3.6	1.3	73
	S.D.	27	1	.0	.0	.4	.3	.1	20
3M	Mean	98	15	.2	.7	6.0	3.4	1.3	69
	S.D.	8	6	.1	.1	.2	.2	.2	20
4M	Mean	105	14	.2	.6	6.0	3.4	1.3	54
	S.D.	4	2	.0	.0	.4	.1	.1	6

TABLE 8

Group mean clinical chemistry
Occasion: Week 4

Gp Sex		GLUCOSE mg/dl	BUN mg/dl	T BILI mg/dl	CREAT mg/dl	T PROT g/dl	ALBUMIN g/dl	AG RATIO	TOT CHOL mg/dl
1F	Mean	98	18	.1	.7	6.5	4.0	1.7	65
	S.D.	12	4	.1	.0	.7	.3	.2	13
2F	Mean	90	19	.2	.7	6.2	3.8	1.6	60
	S.D.	12	2	.0	.0	.5	.2	.2	21
3F	Mean	104	17	.2	.7	6.3	3.9	1.6	62
	S.D.	3	1	.1	.1	.3	.2	.1	4
4F	Mean	100	18	.1	.7	6.0	3.6	1.5	51
	S.D.	13	1	.0	.1	.3	.1	.2	7

TABLE 9

Group mean organ weights (g)

Gp. Sex		Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1M	Mean:	383.0	.031	.030	1.116	1.093	8.861	1.618	1.614	1.383
	S.D.:	17.1	.004	.004	.066	.077	.569	.070	.068	.058
2M	Mean:	405.1	.030	.027	1.172	1.185	9.598	1.723	1.695	1.474
	S.D.:	33.5	.004	.004	.153	.120	.920	.092	.128	.071
3M	Mean:	410.1	.030	.027	1.138	1.123	9.919	1.616	1.615	1.481
	S.D.:	37.7	.003	.002	.175	.216	1.075	.150	.136	.070
4M	Mean:	389.8	.026	.026	1.058	1.074	8.803	1.478	1.494	1.969***
	S.D.:	18.6	.004	.005	.063	.079	.469	.475	.483	.196

*** $p<0.001$ (t-test)

TABLE 9

Group mean organ weights (g)

Gp. Sex		Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1F	Mean:	219.7	.029	.027	.699	.691	5.748			1.096
	S.D.:	17.2	.003	.004	.075	.068	.508			.066
2F	Mean:	215.0	.034	.028	.702	.720	5.545			1.063
	S.D.:	2.2	.004	.002	.053	.062	.157			.021
3F	Mean:	219.1	.031	.029	.687	.668	5.737			1.111
	S.D.:	3.9	.003	.004	.061	.053	.422			.058
4F	Mean:	227.6	.038	.036###	.700	.753	6.330			1.576***
	S.D.:	12.7	.006	.004	.035	.033	.380			.087

*** p<0.001 (t-test)
p<0.001 (t-test for left and right organs combined)

TABLE 10

Group mean organ/body weight ratios (%)

Gp. Sex		Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1M	Mean:	383.0	.0082	.0079	.2915	.2853	2.3126	.4226	.4216	.3612
	S.D.:	17.1	.0008	.0007	.0100	.0155	.0700	.0098	.0119	.0037
2M	Mean:	405.1	.0075	.0065	.2899	.2931	2.3675	.4281	.4216	.3658
	S.D.:	33.5	.0005	.0006	.0372	.0273	.0512	.0474	.0550	.0349
3M	Mean:	410.1	.0073	.0066	.2777	.2737	2.4202	.3949	.3946	.3629
	S.D.:	37.7	.0010	.0008	.0325	.0433	.1666	.0294	.0248	.0285
4M	Mean:	389.8	.0066	.0068	.2715	.2757	2.2597	.3760	.3801	.5059***
	S.D.:	18.6	.0012	.0013	.0161	.0172	.1102	.1152	.1174	.0527

*** $p<0.001$ (t-test)

TABLE 10

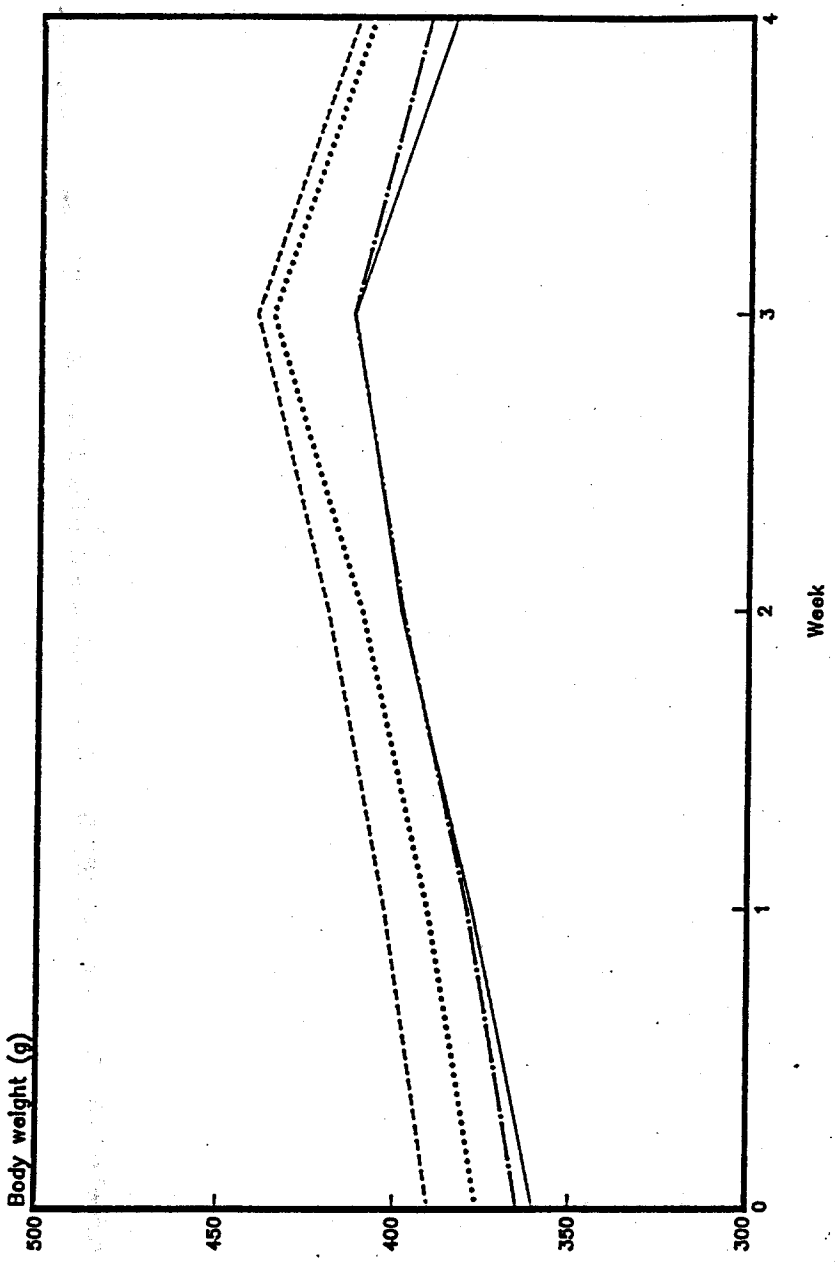
Group mean organ/body weight ratios (%)

Gp. Sex		Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1F	Mean:	219.7	.0133	.0122	.3178	.3148	2.6195			.5007
	S.D.:	17.2	.0018	.0019	.0203	.0214	.1869			.0436
2F	Mean:	215.0	.0159	.0131	.3266	.3351	2.5788			.4943
	S.D.:	2.2	.0020	.0008	.0272	.0317	.0629			.0117
3F	Mean:	219.1	.0140	.0131	.3140	.3050	2.6180			.5071
	S.D.:	3.9	.0015	.0019	.0296	.0249	.1712			.0268
4F	Mean:	227.6	.0169	.0159##	.3089	.3319	2.7910			.6939***
	S.D.:	12.7	.0034	.0027	.0311	.0295	.2659			.0480

*** $p<0.001$ (t-test)
$p<0.01$ (t-test for left and right organs combined)

FIGURE 1

Group mean body weight (g) – males



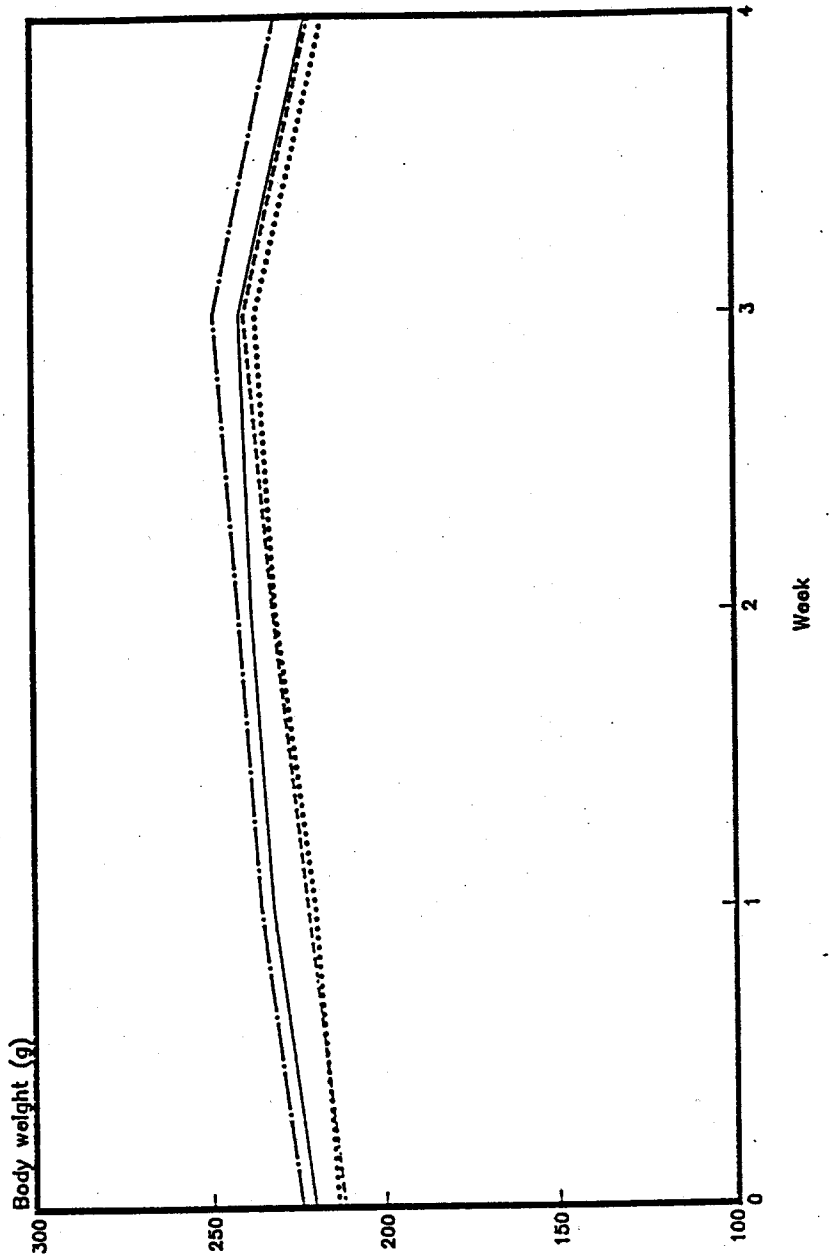


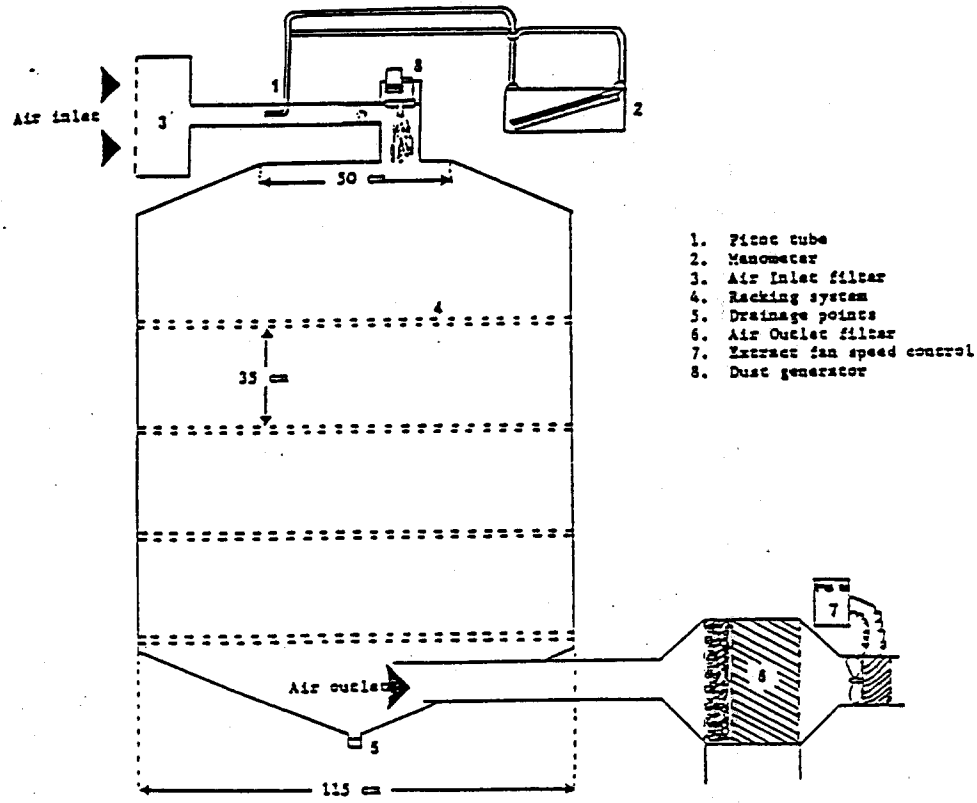
FIGURE 2

Group mean body weight (g) — females

GROUP 1 ——— GROUP 2 ····· GROUP 3 - - - - GROUP 4 —·—·—

FIGURE 3

Exposure chamber (side view)



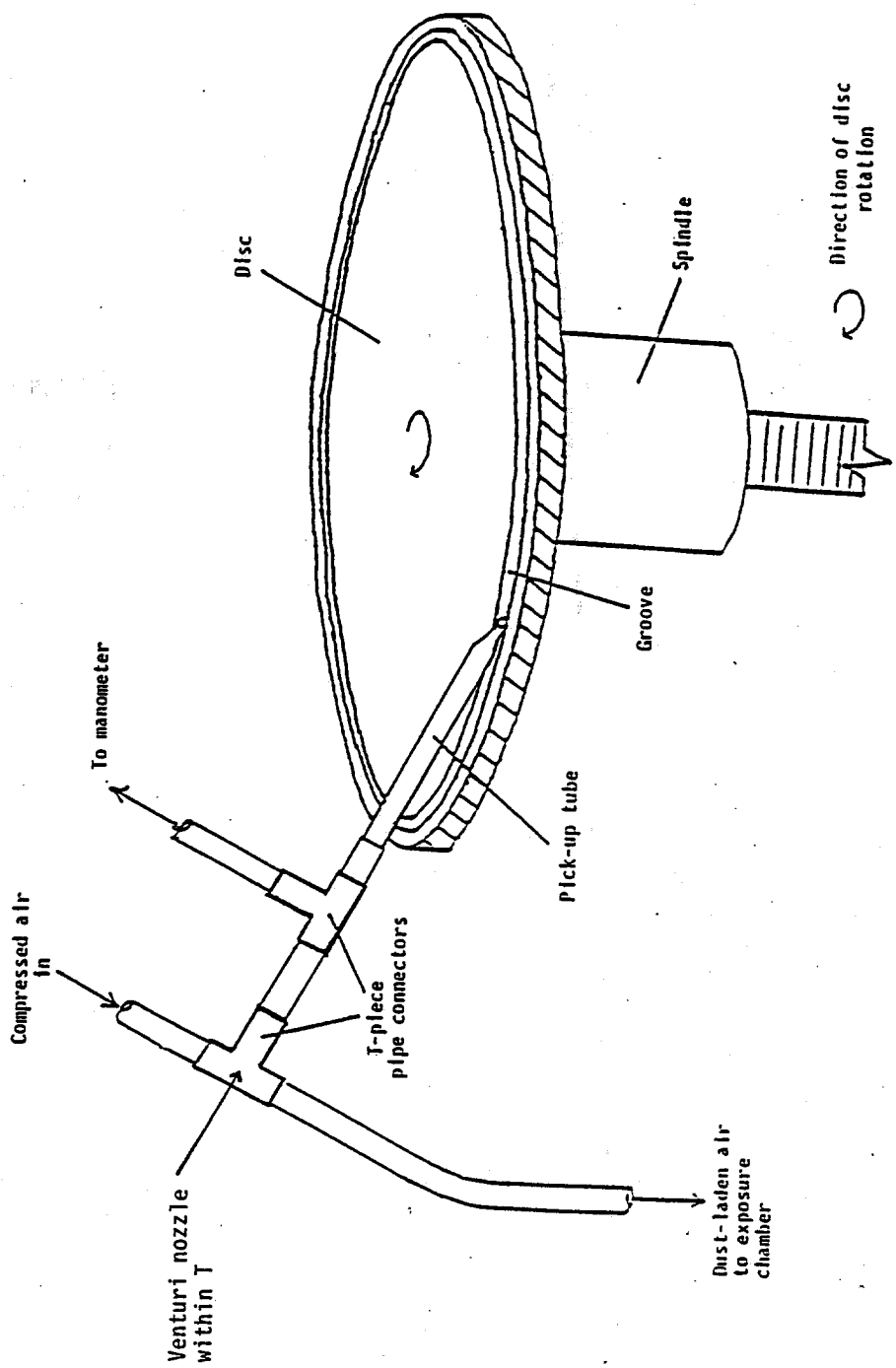


FIGURE 4
Rotating flat disc generator

SECTION C

9. APPENDICES

APPENDIX 1

Individual exposure chamber test article concentration (µg/l) - gravimetric analysis
Group 2

Day	Nominal concentration µg/l	Concentration (µg/l) in each 2 hour interval: 1	2	3	Mean measured concentration µg/l	± S.D.
1	21.96	2.62	2.88	2.65	2.72	±0.14
2	28.52	2.17	3.43	3.65	3.08	±0.80
5	30.86	2.60	4.21	4.17	3.66	±0.92
6	26.52	2.17	4.03	5.25	3.82	±1.55
7	72.15	5.75	3.85	6.38	5.33	±1.32
8	26.40	5.38	4.75	4.25	4.79	±0.57
9	27.42	5.05	3.50	5.30	4.62	±0.98
12	24.91	5.12	5.42	4.47	5.00	±0.49
13	17.44	6.02	5.12	4.92	5.35	±0.59
14	18.44	2.83	5.60	5.87	4.77	±1.68
15	19.41	4.68	4.10	3.60	4.13	±0.54
16	19.58	3.62	4.57	4.35	4.18	±0.50
19	19.58	2.47	2.32	2.57	2.45	±0.13
20	28.78	4.18	3.10	-	3.64	-
21	24.55	5.19	3.36	3.57	4.04	±1.00
22	17.28	2.95	1.77	3.18	2.63	±0.76
23	16.98	5.03	2.35	3.00	3.46	±1.40
26	12.29	3.52	3.43	3.69	3.55	±0.13
27	21.76	3.98	3.92	4.07	3.99	±0.08
28	15.43	3.85	3.48	3.83	3.72	±0.21

APPENDIX 1

Individual exposure chamber test article concentration (µg/l) - gravimetric analysis
Group 3

Day	Nominal concentration µg/l	Concentration (µg/l) in each 2 hour interval: 1	2	3	Mean measured concentration µg/l	± S.D.
1	102.27	14.95	25.15	24.00	21.37	±5.59
2	106.54	20.78	14.93	22.02	19.24	±3.79
5	97.67	25.18	18.70	19.30	21.06	±3.58
6	83.83	14.23	18.03	18.08	16.78	±2.21
7	103.54	13.20	16.63	17.25	15.69	±2.18
8	91.78	22.13	14.48	21.28	19.30	±4.19
9	64.20	18.83	22.20	18.15	19.73	±2.17
12	98.77	18.08	22.48	19.63	20.06	±2.23
13	81.85	17.14	23.05	18.60	19.60	±3.08
14	102.47	15.58	15.70	17.10	16.13	±0.85
15	91.36	18.20	19.03	19.65	18.96	±0.73
16	96.30	12.53	16.08	17.43	15.35	±2.53
19	76.88	23.25	18.28	20.00	20.51	±2.52
20	70.68	22.03	11.20	-	16.62	-
21	77.78	14.81	11.00	12.15	12.65	±1.95
22	69.14	23.95	15.85	16.73	18.84	±4.44
23	61.73	17.33	17.53	11.10	15.32	±3.66
26	70.68	22.51	20.15	20.40	21.02	±1.30
27	64.00	18.48	13.88	23.23	18.53	±4.68
28	74.74	18.07	19.80	17.93	18.60	±1.04

APPENDIX 1

Individual exposure chamber test article concentration (µg/l) - gravimetric analysis
Group 4

Day	Nominal concentration µg/l	Concentration (µg/l) in each 2 hour interval: 1	2	3	Mean measured concentration µg/l	± S.D.
1	588.78	89.50	108.91	79.10	92.50	±15.13
2	662.49	107.60	115.30	116.80	113.23	± 4.94
5	626.88	121.08	105.90	107.90	111.63	± 8.25
6	411.79	99.50	104.70	93.50	99.23	± 5.60
7	343.92	86.60	*	107.08	96.84	-
8	563.00	122.80	116.30	107.40	115.50	± 7.73
9	497.53	97.50	93.77	93.33	94.87	± 2.29
12	533.43	102.25	100.70	115.50	106.15	± 8.13
13	529.97	91.30	104.36	91.17	95.61	± 7.58
14	526.91	85.20	79.40	86.00	83.53	± 3.60
15	556.80	118.29	103.00	92.40	104.56	±13.02
16	558.00	116.50	98.30	94.90	103.23	±11.61
19	409.29	66.17	103.60	102.02	90.60	±21.17
20	413.61	137.33	102.98	-	120.16	-
21	502.94	115.25	105.00	151.11	123.79	±24.21
22	512.35	91.70	115.10	89.40	98.73	±14.22
23	731.40	89.67	83.86	79.40	84.31	± 5.15
26	451.70	90.30	104.20	90.17	94.89	± 8.06
27	657.83	121.90	95.20	79.58	98.89	±21.40
28	394.74	82.00	92.10	92.83	88.98	± 6.05

* exposure omitted for 1½ hours and restarted using dried test article

APPENDIX 2

Individual body weights (g)

Date of printing: 4 May 1988 Computer id. : S760033

Group number	Animal number	Body weights (g) at week : 0	1	2	3	4
1M	1	324.4	343.1	362.0	378.9	354.7
	2	375.9	393.4	413.8	423.4	392.5
	3	375.5	389.6	411.8	427.1	392.4
	4	361.8	380.9	403.0	423.3	390.9
	5	363.3	383.0	402.5	409.2	388.9
2M	6	390.5	403.3	429.0	455.5	428.3
	7	395.1	424.1	450.6	481.2	453.6
	8	383.4	390.3	403.4	428.5	387.5
	9	357.1	359.8	373.4	395.4	376.7
	10	355.1	375.0	392.6	417.7	389.9
3M	11	362.5	367.6	383.1	392.4	374.8
	12	427.6	449.1	465.4	488.0	455.1
	13	387.2	392.3	405.1	431.6	402.6
	14	406.6	424.2	444.4	474.7	447.4
	15	365.1	381.4	398.9	413.6	377.9
4M	16	355.2	367.6	383.0	403.5	383.4
	17	372.5	389.6	410.7	428.3	403.8
	18	377.0	392.9	413.7	433.1	408.0
	19	332.0	350.6	360.8	372.6	363.1
	20	387.1	396.2	421.4	426.0	396.5

APPENDIX 2

Individual body weights (g)

Date of printing: 4 May 1988 Computer id. : S760033

Group number	Animal number	Body weights (g) at week : 0	1	2	3	4
1F	26	224.0	240.3	241.3	242.2	226.7
	27	208.1	218.6	221.1	228.9	209.2
	28	212.4	226.1	236.1	241.0	221.4
	29	253.0	259.9	265.2	267.0	251.3
	30	205.3	215.3	226.8	227.8	201.9
2F	31	201.1	217.1	222.8	234.2	213.6
	32	215.7	216.1	233.9	231.7	215.8
	33	222.6	219.0	230.0	235.3	220.1
	34	215.4	224.3	232.5	242.2	214.9
	35	213.8	224.0	236.3	239.6	220.4
3F	36	210.9	218.9	231.2	243.2	218.9
	37	209.4	220.4	227.7	231.4	217.3
	38	217.0	226.8	235.7	245.1	226.3
	39	207.6	222.7	235.5	241.8	224.1
	40	214.6	222.3	229.2	237.9	218.1
4F	41	242.9	249.7	245.1	259.3	242.5
	42	191.5	210.1	222.7	228.7	210.6
	43	217.8	236.2	245.8	251.8	229.3
	44	237.4	245.7	254.7	264.0	243.1
	45	232.1	236.5	241.9	240.6	229.0

APPENDIX 3

Individual haematology
Occasion: Week 4

Gp Sex	Anml. no.	Hb g/dl	RBC mil/cmm	PCV %	MCV fl	MCH pg	MCHC g/dl	PLAT 1000/cmm
1M	1	14.8	7.57	45.7	60.4	19.6	32.4	1092
1M	2+	15.4	7.32	46.0	62.8	21.0	33.5	1221
1M	3•	15.1	7.60	45.2	59.4	19.9	33.4	1373
1M	4	13.6	7.09	41.5	58.5	19.2	32.8	1259
1M	5	14.2	6.93	42.3	61.1	20.5	33.6	1141
Mean		14.6	7.30	44.1	60.4	20.0	33.1	1217
S.D.		.7	.29	2.1	1.6	.7	.5	109
2M	6	16.0	7.92	48.1	60.7	20.2	33.3	1116
2M	7	14.5	7.11	43.7	61.5	20.4	33.2	1188
2M	8	15.3	7.86	46.1	58.6	19.5	33.2	1380
2M	9	14.6	7.20	43.4	60.2	20.3	33.6	645
2M	10+	15.2	7.53	45.4	60.3	20.2	33.5	1282
Mean		15.1	7.52	45.3	60.3	20.1	33.4	1122
S.D.		.6	.37	1.9	1.1	.4	.2	285
3M	11	14.2	7.03	42.3	60.1	20.2	33.6	1102
3M	12	14.0	7.18	42.0	58.5	19.5	33.3	1104
3M	13+	14.9	7.70	44.9	58.3	19.4	33.2	1404
3M	14	14.4	7.12	42.8	60.1	20.2	33.6	788
3M	15	14.7	7.44	44.6	60.0	19.8	33.0	1303
Mean		14.4	7.29	43.3	59.4	19.8	33.3	1140
S.D.		.4	.27	1.3	.9	.4	.3	236
4M	16	15.4	8.26	46.0	55.6	18.6	33.5	1091
4M	17+	16.2	7.49	48.0	64.1	21.6	33.8	923
4M	18	14.8	7.55	44.5	59.0	19.6	33.3	1213
4M	19	16.0	8.08	47.7	59.1	19.8	33.5	1019
4M	20	14.0	7.12	41.9	58.8	19.7	33.4	1105
Mean		15.3	7.70	45.6	59.3	19.9	33.5	1070
S.D.		.9	.46	2.5	3.0	1.1	.2	108

\+ rebled at necropsy due to clotting of first sample
• additional parameters POLYC +; SPHER ++

APPENDIX 3

Individual haematology
Occasion: Week 4

Gp Sex	Anml. no.	Hb g/dl	RBC mil/cmm	PCV %	MCV fl	MCH pg	MCHC g/dl	PLAT 1000/cmm
1F	26	12.7	6.41	37.7	58.8	19.8	33.7	894
1F	27	13.7	6.81	41.0	60.1	20.1	33.4	987
1F	28	12.6	6.51	38.4	59.0	19.4	32.8	910
1F	29	13.8	7.25	42.3	58.4	19.0	32.6	911
1F	30	15.0	7.85	45.5	58.0	19.1	33.0	1000
Mean		13.6	6.97	41.0	58.9	19.5	33.1	940
S.D.		1.0	.59	3.1	.8	.5	.4	49
2F	31	15.1	7.74	45.6	58.9	19.5	33.1	1125
2F	32+	15.4	7.59	45.7	60.1	20.3	33.7	1343
2F	33	15.0	7.58	45.0	59.4	19.8	33.3	1171
2F	34	13.1	6.75	39.6	58.6	19.4	33.1	1104
2F	35+	15.6	7.48	46.0	61.5	20.9	33.9	1242
Mean		14.8	7.43	44.4	59.7	20.0	33.4	1197
S.D.		1.0	.39	2.7	1.2	.6	.4	97
3F	36	13.7	6.72	41.7	62.0	20.4	32.9	929
3F	37	13.7	7.05	41.8	59.3	19.4	32.8	869
3F	38+	14.6	7.18	43.5	60.6	20.3	33.6	1168
3F	39+	15.5	7.74	47.8	61.8	20.0	32.4	1023
3F	40	13.1	7.04	39.8	56.6	18.6	32.9	860
Mean		14.1	7.15	42.9	60.1	19.7	32.9	970
S.D.		.9	.37	3.0	2.2	.7	.4	128
4F	41	14.2	7.12	42.2	59.3	19.9	33.6	1007
4F	42	13.5	6.82	41.0	60.1	19.8	32.9	999
4F	43	13.8	7.07	41.7	59.0	19.5	33.1	1099
4F	44	13.4	6.59	40.3	61.2	20.3	33.3	832
4F	45	12.7	6.40	38.3	59.9	19.8	33.2	1084
Mean		13.5	6.80	40.7	59.9	19.9	33.2	1004
S.D.		.6	.31	1.5	.9	.3	.3	106

+ rebled at necropsy due to clotting of first sample

APPENDIX 3

Individual haematology
Occasion: Week 4

Gp Sex	Anml. no.	TOT WBC 1000/cmm	WBC 1000 / cmm (%) N	L	M	E	B
1M	1	13.3	1.50(11)	11.00(83)	.80(6)	.00(0)	.00(0)
1M	2+	8.2	2.10(26)	5.70(70)	.20(3)	.10(1)	.00(0)
1M	3	10.2	1.50(15)	8.30(81)	.30(3)	.10(1)	.00(0)
1M	4	10.3	1.80(17)	8.10(79)	.40(4)	.00(0)	.00(0)
1M	5	15.0	4.10(27)	10.80(72)	.20(1)	.00(0)	.00(0)
Mean		11.4	2.20(19)	8.78(77)	.38(3)	.04(0)	.00(0)
S.D.		2.7	1.09(-)	2.19(-)	.25(-)	.05(-)	.00(-)
2M	6	16.4	2.50(15)	13.40(82)	.30(2)	.20(1)	.00(0)
2M	7	13.5	3.60(27)	9.50(70)	.40(3)	.00(0)	.00(0)
2M	8	16.9	3.90(23)	12.70(75)	.30(2)	.00(0)	.00(0)
2M	9	14.7	2.50(17)	11.90(81)	.10(1)	.10(1)	.00(0)
2M	10+	4.5	.80(18)	3.60(80)	.00(0)	.10(2)	.00(0)
Mean		13.2	2.66(20)	10.22(78)	.22(2)	.08(1)	.00(0)
S.D.		5.0	1.22(-)	3.98(-)	.16(-)	.08(-)	.00(-)
3M	11	6.4	1.30(20)	4.90(77)	.20(3)	.00(0)	.00(0)
3M	12	11.8	2.60(22)	8.90(75)	.20(2)	.10(1)	.00(0)
3M	13+	12.9	3.20(25)	9.40(73)	.10(1)	.10(1)	.00(0)
3M	14	15.7	1.90(12)	13.30(85)	.30(2)	.20(1)	.00(0)
3M	15	15.5	3.10(20)	12.10(78)	.30(2)	.00(0)	.00(0)
Mean		12.5	2.42(20)	9.72(78)	.22(2)	.08(1)	.00(0)
S.D.		3.8	.81(-)	3.26(-)	.08(-)	.08(-)	.00(-)
4M	16	14.3	2.60(18)	11.40(80)	.30(2)	.00(0)	.00(0)
4M	17+	9.5	1.40(15)	7.90(83)	.20(2)	.00(0)	.00(0)
4M	18	15.0	2.10(14)	12.50(83)	.50(3)	.00(0)	.00(0)
4M	19	12.6	2.40(19)	9.70(77)	.50(4)	.00(0)	.00(0)
4M	20	9.1	1.80(20)	6.90(76)	.40(4)	.00(0)	.00(0)
Mean		12.1	2.06(17)	9.68(80)	.38(3)	.00(0)	.00(0)
S.D.		2.7	.48(-)	2.33(-)	.13(-)	.00(-)	.00(-)

+ rebled at necropsy due to clotting of first sample

APPENDIX 3

Individual haematology
Occasion: Week 4

Gp Sex	Anml. no.	TOT WBC 1000/cmm	WBC 1000 / cmm (%) N	L	M	E	B
1F	26	4.6	.80(17)	3.60(78)	.20(4)	.00(1)	.00(0)
1F	27	9.3	2.20(24)	6.90(74)	.20(2)	.00(0)	.00(0)
1F	28	5.0	1.20(24)	3.70(74)	.10(2)	.00(0)	.00(0)
1F	29	14.4	3.30(23)	10.90(76)	.10(1)	.00(0)	.00(0)
1F	30	9.5	1.50(16)	7.80(82)	.10(1)	.10(1)	.00(0)
Mean		8.6	1.80(21)	6.58(77)	.14(2)	.02(0)	.00(0)
S.D.		4.0	.98(-)	3.06(-)	.05(-)	.04(-)	.00(-)
2F	31	5.9	1.10(19)	4.50(76)	.30(5)	.00(0)	.00(0)
2F	32+	6.1	1.60(26)	4.50(73)	.10(1)	.00(0)	.00(0)
2F	33	10.2	2.70(26)	7.30(72)	.20(2)	.00(0)	.00(0)
2F	34	7.3	2.30(31)	5.00(68)	.00(0)	.10(1)	.00(0)
2F	35+	6.1	1.20(20)	4.80(78)	.10(2)	.00(0)	.00(0)
Mean		7.1	1.78(24)	5.22(73)	.14(2)	.02(0)	.00(0)
S.D.		1.8	.70(-)	1.18(-)	.11(-)	.04(-)	.00(-)
3F	36	5.8	1.00(17)	4.60(80)	.20(3)	.00(0)	.00(0)
3F	37	7.0	2.00(28)	4.90(70)	.10(2)	.00(0)	.00(0)
3F	38+	2.6	1.10(41)	1.50(59)	.00(0)	.00(0)	.00(0)
3F	39+	5.5	.80(15)	4.70(85)	.00(0)	.00(0)	.00(0)
3F	40	10.2	2.30(23)	7.50(74)	.10(1)	.20(2)	.00(0)
Mean		6.2	1.44(25)	4.64(74)	.08(1)	.04(0)	.00(0)
S.D.		2.7	.67(-)	2.13(-)	.08(-)	.09(-)	.00(-)
4F	41	6.4	1.70(27)	4.50(71)	.10(2)	.00(0)	.00(0)
4F	42	5.2	1.30(25)	3.80(74)	.10(1)	.00(0)	.00(0)
4F	43	6.5	1.40(21)	5.00(77)	.10(1)	.10(1)	.00(0)
4F	44	12.1	2.20(18)	9.70(80)	.20(2)	.00(0)	.00(0)
4F	45	6.4	1.30(20)	5.00(78)	.10(1)	.10(1)	.00(0)
Mean		7.3	1.58(22)	5.60(76)	.12(1)	.04(0)	.00(0)
S.D.		2.7	.38(-)	2.34(-)	.04(-)	.05(-)	.00(-)

+ rebled at necropsy due to clotting of first sample

APPENDIX 4

Individual clinical chemistry
Occasion: Week 4

Gp Sex	Anml. no.	GOT(AST) Iu/l	GPT(ALT) Iu/l	ALK PHOS Iu/l	GAMMA GT Iu/l	Na meq/l	K meq/l	Cl meq/l	Ca mg/dl	P mg/dl
1M	1	77	38	150	2	148	3.9	107	10.0	6.3
1M	2	67	35	216	6	147	3.6	106	9.5	5.9
1M	3	73	35	176	2	149	4.3	108	10.2	8.3
1M	4	70	17	217	3	149	3.4	105	9.9	6.7
1M	5	83	37	214	4	150	4.1	108	10.0	6.6
Mean		74	32	195	3	149	3.9	107	9.9	6.8
S.D.		6	9	30	2	1	.4	1	.3	.9
2M	6	74	31	210	3	149	3.9	106	10.2	6.1
2M	7	59	32	168	5	148	3.9	107	10.3	6.8
2M	8	67	28	229	5	147	4.1	105	10.0	6.5
2M	9	82	49	224	2	149	4.0	107	9.8	6.9
2M	10	83	23	139	4	145	3.7	104	9.9	6.0
Mean		73	33	194	4	148	3.9	106	10.0	6.5
S.D.		10	10	39	1	2	.1	1	.2	.4
3M	11	65	20	141	4	145	3.7	104	9.9	6.3
3M	12	72	38	237	5	145	4.0	105	9.8	9.9
3M	13	66	40	117	6	146	3.8	105	9.5	6.8
3M	14	52	41	188	4	149	3.6	108	10.0	IS
3M	15	77	39	136	5	149	3.9	107	10.0	IS
Mean		66	36	164	5	147	3.8	106	9.8	7.7
S.D.		9	9	49	1	2	.2	2	.2	2.0
4M	16	63	39	209	4	145	4.4	105	10.0	6.7
4M	17	64	37	188	6	150	4.0	107	10.2	8.7
4M	18	84	50	184	5	148	4.0	106	10.2	6.5
4M	19	61	34	153	7	149	4.5	108	10.1	6.3
4M	20	71	34	257	5	146	3.8	106	10.0	6.9
Mean		69	39	198	5	148	4.1	106	10.1	7.0
S.D.		9	7	38	1	2	.3	1	.1	1.0

IS = insufficient sample for analysis

APPENDIX 4

Individual clinical chemistry
Occasion: Week 4

Gp Sex	Anml. no.	GOT(AST) Iu/l	GPT(ALT) Iu/l	ALK PHOS Iu/l	GAMMA GT Iu/l	Na meq/l	K meq/l	Cl meq/l	Ca mg/dl	P mg/dl
1F	26	81	32	184	7	148	4.1	109	9.9	6.3
1F	27	64	22	116	4	149	3.2	109	9.7	4.8
1F	28	67	26	94	6	146	3.9	109	10.2	6.0
1F	29	74	24	99	3	146	3.8	107	10.4	6.0
1F	30	66	26	99	7	148	3.6	109	10.5	5.0
Mean		70	26	118	5	147	3.7	109	10.1	5.6
S.D.		7	4	38	2	1	.3	1	.3	.7
2F	31	63	35	139	5	146	3.3	107	9.7	5.1
2F	32	77	28	147	7	146	3.4	107	10.0	5.7
2F	33	73	22	99	6	148	3.5	108	10.3	5.1
2F	34	74	24	181	7	148	3.7	110	9.8	6.2
2F	35	61	18	108	8	146	3.3	109	10.0	6.9
Mean		70	25	135	7	147	3.4	108	10.0	5.8
S.D.		7	6	33	1	1	.2	1	.2	.8
3F	36	74	28	96	3	147	3.0	107	10.1	6.0
3F	37	64	23	102	7	146	3.5	109	9.9	5.7
3F	38	92	27	193	3	147	3.4	108	9.8	5.8
3F	39	68	28	121	5	144	3.7	106	10.0	5.5
3F	40	90	32	139	3	148	3.7	110	9.6	5.2
Mean		78	28	130	4	146	3.5	108	9.9	5.6
S.D.		13	3	39	2	2	.3	2	.2	.3
4F	41	71	24	136	6	144	3.2	107	9.5	3.7
4F	42	72	33	128	5	145	3.8	107	9.7	5.3
4F	43	73	23	106	4	142	3.4	106	9.6	4.7
4F	44	69	30	155	7	145	3.6	108	9.9	5.2
4F	45	70	22	107	6	147	3.6	108	9.5	5.4
Mean		71	26	126	6	145	3.5	107	9.6	4.9
S.D.		2	5	21	1	2	.2	1	.2	.7

APPENDIX 4

Individual clinical chemistry
Occasion: Week 4

Gp Sex	Anml. no.	GLUCOSE mg/dl	BUN mg/dl	T BILI mg/dl	CREAT mg/dl	T PROT g/dl	ALBUMIN g/dl	AG RATIO	TOT CHOL mg/dl
1M	1	83	15	.2	.6	6.2	3.5	1.3	54
1M	2	108	13	.3	.6	5.7	3.5	1.6	57
1M	3	84	12	.2	.7	6.7	3.6	1.2	75
1M	4	80	14	.2	.6	5.9	3.4	1.4	63
1M	5	79	12	.2	.7	6.4	3.4	1.1	45
Mean		87	13	.2	.6	6.2	3.5	1.3	59
S.D.		12	1	.0	.1	.4	.1	.2	11
2M	6	93	13	.2	.6	6.8	3.9	1.3	56
2M	7	94	11	.2	.6	6.3	3.4	1.2	70
2M	8	87	11	.2	.6	6.1	3.7	1.5	60
2M	9	83	13	.2	.6	6.3	3.6	1.3	71
2M	10	148	14	.2	.6	5.6	3.2	1.3	106
Mean		101	12	.2	.6	6.2	3.6	1.3	73
S.D.		27	1	.0	.0	.4	.3	.1	20
3M	11	92	13	.2	.6	5.7	3.2	1.3	105
3M	12	112	25	.3	.8	6.2	3.4	1.2	58
3M	13	92	12	.2	.7	5.9	3.3	1.3	58
3M	14	99	12	.2	.7	5.8	3.6	1.6	58
3M	15	95	14	.3	.6	6.2	3.5	1.3	68
Mean		98	15	.2	.7	6.0	3.4	1.3	69
S.D.		8	6	.1	.1	.2	.2	.2	20
4M	16	107	15	.2	.6	6.0	3.4	1.3	59
4M	17	108	14	.2	.6	6.2	3.5	1.3	52
4M	18	99	14	.2	.6	6.6	3.6	1.2	57
4M	19	105	11	.2	.6	5.8	3.4	1.4	44
4M	20	104	16	.1	.6	5.6	3.3	1.4	57
Mean		105	14	.2	.6	6.0	3.4	1.3	54
S.D.		4	2	.0	.0	.4	.1	.1	6

APPENDIX 4

Individual clinical chemistry
Occasion: Week 4

Gp Sex	Anml. no.	GLUCOSE mg/dl	BUN mg/dl	T BILI mg/dl	CREAT mg/dl	T PROT g/dl	ALBUMIN g/dl	AG RATIO	TOT CHOL mg/dl
1F	26	83	24	.1	.7	6.1	3.8	1.7	81
1F	27	114	18	.1	.7	5.5	3.6	1.9	45
1F	28	106	17	.2	.7	6.9	4.3	1.7	65
1F	29	92	16	.2	.7	6.7	4.0	1.5	71
1F	30	93	15	.1	.7	7.1	4.3	1.5	63
Mean		98	18	.1	.7	6.5	4.0	1.7	65
S.D.		12	4	.1	.0	.7	.3	.2	13
2F	31	77	21	.2	.7	5.5	3.6	1.9	44
2F	32	86	19	.2	.7	6.6	3.9	1.4	68
2F	33	99	16	.2	.7	6.7	4.0	1.5	49
2F	34	82	22	.2	.8	6.2	3.8	1.6	46
2F	35	105	18	.1	.7	6.2	3.6	1.4	94
Mean		90	19	.2	.7	6.2	3.8	1.6	60
S.D.		12	2	.0	.0	.5	.2	.2	21
3F	36	105	17	.2	.7	6.7	4.0	1.5	56
3F	37	106	18	.1	.7	6.4	3.9	1.6	61
3F	38	105	16	.2	.6	6.2	4.0	1.8	62
3F	39	99	18	.2	.6	6.4	4.0	1.7	62
3F	40	103	16	.1	.7	5.9	3.5	1.5	68
Mean		104	17	.2	.7	6.3	3.9	1.6	62
S.D.		3	1	.1	.1	.3	.2	.1	4
4F	41	119	16	.1	.7	5.9	3.6	1.6	56
4F	42	90	17	.1	.6	6.0	3.7	1.6	42
4F	43	86	18	.1	.7	5.5	3.5	1.8	50
4F	44	103	18	.1	.6	6.1	3.5	1.3	59
4F	45	102	20	.1	.7	6.3	3.6	1.3	48
Mean		100	18	.1	.7	6.0	3.6	1.5	51
S.D.		13	1	.0	.1	.3	.1	.2	7

APPENDIX 5

Individual organ weights (g)

Date of Printing: 4 May 1988

Computer id. : 76033

Gp. Sex	Animal number	Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1M	1	352.6	.029	.026	1.020	1.015	7.956	1.516	1.524	1.280
1M	2	392.0	.033	.031	1.202	1.221	8.825	1.696	1.711	1.415
1M	3	392.6	.037	.036	1.104	1.082	9.521	1.671	1.634	1.395
1M	4	390.0	.030	.030	1.111	1.071	9.026	1.599	1.603	1.411
1M	5	387.5	.028	.029	1.145	1.074	8.975	1.607	1.597	1.415
	Mean:	383.0	.031	.030	1.116	1.093	8.861	1.618	1.614	1.383
	S.D.:	17.1	.004	.004	.066	.077	.569	.070	.068	.058
2M	6	424.8	.031	.031	1.170	1.233	10.091	1.635	1.637	1.501
2M	7	454.3	.036	.030	1.314	1.297	10.971	1.690	1.590	1.443
2M	8	386.6	.027	.026	1.204	1.183	9.223	1.809	1.826	1.400
2M	9	374.1	.030	.024	1.256	1.230	8.910	1.648	1.583	1.441
2M	10	385.8	.028	.022	.916	.983	8.796	1.833	1.841	1.584
	Mean:	405.1	.030	.027	1.172	1.185	9.598	1.723	1.695	1.474
	S.D.:	33.5	.004	.004	.153	.120	.920	.092	.128	.071
3M	11	374.1	.029	.026	1.027	.943	8.755	1.593	1.602	1.416
3M	12	455.8	.030	.026	1.442	1.473	11.629	1.879	1.839	1.571
3M	13	400.3	.034	.030	1.058	1.060	9.332	1.526	1.565	1.409
3M	14	443.4	.026	.026	1.032	.965	9.934	1.556	1.595	1.483
3M	15	377.1	.029	.027	1.133	1.172	9.946	1.524	1.472	1.526
	Mean:	410.1	.030	.027	1.138	1.123	9.919	1.616	1.615	1.481
	S.D.:	37.7	.003	.002	.175	.216	1.075	.150	.136	.070
4M	16	382.6	.022	.026	1.123	1.128	9.147	1.765	1.783	1.800
4M	17	402.9	.032	.032	1.063	1.081	8.570	1.650	1.669	2.236
4M	18	407.4	.023	.020	1.024	1.048	9.435	1.549	1.527	1.762
4M	19	361.0	.029	.029	.970	.956	8.305	.644	.655	1.976
4M	20	395.2	.023	.024	1.108	1.159	8.556	1.781	1.834	2.072
	Mean:	389.8	.026	.026	1.058	1.074	8.803	1.478	1.494	1.969
	S.D.:	18.6	.004	.005	.063	.079	.469	.475	.483	.196

APPENDIX 5

Individual organ weights (g)

Date of Printing: 4 May 1988

Computer id. : 76033

Gp. Sex	Animal number	Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1F	26	223.5	.024	.027	.767	.786	6.172			1.144
1F	27	207.9	.028	.021	.643	.629	4.922			.993
1F	28	216.6	.029	.029	.626	.670	5.911			1.159
1F	29	247.1	.032	.026	.791	.736	6.108			1.080
1F	30	203.3	.032	.030	.666	.635	5.626			1.102
	Mean:	219.7	.029	.027	.699	.691	5.748			1.096
	S.D.:	17.2	.003	.004	.075	.068	.508			.066
2F	31	212.3	.029	.026	.793	.818	5.505			1.048
2F	32	214.7	.039	.030	.695	.686	5.330			1.049
2F	33	217.9	.034	.028	.664	.654	5.767			1.049
2F	34	213.8	.038	.030	.667	.725	5.587			1.097
2F	35	216.5	.031	.027	.690	.717	5.537			1.071
	Mean:	215.0	.034	.028	.702	.720	5.545			1.063
	S.D.:	2.2	.004	.002	.053	.062	.157			.021
3F	36	216.9	.034	.035	.783	.709	5.832			1.172
3F	37	215.5	.029	.024	.689	.711	5.824			1.102
3F	38	223.9	.034	.028	.695	.688	5.977			1.076
3F	39	222.7	.030	.030	.633	.646	6.050			1.167
3F	40	216.3	.026	.026	.637	.586	5.003			1.037
	Mean:	219.1	.031	.029	.687	.668	5.737			1.111
	S.D.:	3.9	.003	.004	.061	.053	.422			.058
4F	41	239.9	.031	.033	.657	.730	5.770			1.662
4F	42	208.6	.043	.042	.749	.793	6.385			1.514
4F	43	226.0	.044	.037	.681	.763	6.822			1.656
4F	44	238.7	.033	.032	.717	.768	6.436			1.463
4F	45	224.8	.040	.036	.696	.710	6.235			1.585
	Mean:	227.6	.038	.036	.700	.753	6.330			1.576
	S.D.:	12.7	.006	.004	.035	.033	.380			.087

APPENDIX 6

Individual organ/body weight ratios (%)

Date of Printing: 4 May 1988

Computer id. : 76033

Gp. Sex	Animal number	Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1M	1	352.6	.0082	.0074	.2893	.2878	2.2562	.4299	.4322	.3630
1M	2	392.0	.0084	.0079	.3066	.3115	2.2512	.4326	.4365	.3610
1M	3	392.6	.0094	.0092	.2812	.2756	2.4250	.4256	.4162	.3553
1M	4	390.0	.0077	.0077	.2848	.2746	2.3141	.4100	.4110	.3618
1M	5	387.5	.0072	.0075	.2955	.2772	2.3162	.4147	.4122	.3652
	Mean:	383.0	.0082	.0079	.2915	.2853	2.3126	.4226	.4216	.3612
	S.D.:	17.1	.0008	.0007	.0100	.0155	.0700	.0098	.0119	.0037
2M	6	424.8	.0073	.0073	.2754	.2902	2.3752	.3849	.3853	.3533
2M	7	454.3	.0079	.0066	.2892	.2855	2.4148	.3720	.3500	.3176
2M	8	386.6	.0070	.0067	.3114	.3060	2.3857	.4679	.4723	.3621
2M	9	374.1	.0080	.0064	.3358	.3288	2.3819	.4406	.4232	.3852
2M	10	385.8	.0073	.0057	.2374	.2548	2.2799	.4751	.4772	.4106
	Mean:	405.1	.0075	.0065	.2899	.2931	2.3675	.4281	.4216	.3658
	S.D.:	33.5	.0005	.0006	.0372	.0273	.0512	.0474	.0550	.0349
3M	11	374.1	.0078	.0070	.2746	.2521	2.3405	.4259	.4283	.3785
3M	12	455.8	.0066	.0057	.3164	.3232	2.5512	.4122	.4034	.3447
3M	13	400.3	.0085	.0075	.2643	.2648	2.3311	.3812	.3909	.3520
3M	14	443.4	.0059	.0059	.2328	.2176	2.2405	.3509	.3597	.3345
3M	15	377.1	.0077	.0072	.3005	.3108	2.6378	.4042	.3904	.4047
	Mean:	410.1	.0073	.0066	.2777	.2737	2.4202	.3949	.3946	.3629
	S.D.:	37.7	.0010	.0008	.0325	.0433	.1666	.0294	.0248	.0285
4M	16	382.6	.0057	.0068	.2935	.2948	2.3906	.4613	.4660	.4704
4M	17	402.9	.0079	.0079	.2638	.2683	2.1269	.4095	.4142	.5549
4M	18	407.4	.0056	.0049	.2514	.2572	2.3160	.3802	.3748	.4325
4M	19	361.0	.0080	.0080	.2687	.2648	2.3003	.1784	.1814	.5473
4M	20	395.2	.0058	.0061	.2804	.2933	2.1649	.4506	.4640	.5243
	Mean:	389.8	.0066	.0068	.2715	.2757	2.2597	.3760	.3801	.5059
	S.D.:	18.6	.0012	.0013	.0161	.0172	.1102	.1152	.1174	.0527

APPENDIX 6

Individual organ/body weight ratios (%)

Date of Printing: 4 May 1988

Computer id. : 76033

Gp. Sex	Animal number	Bodyweight g	AL	AR	KL	KR	LI	GL	GR	LU
1F	26	223.5	.0107	.0121	.3432	.3517	2.7618			.5119
1F	27	207.9	.0135	.0101	.3093	.3025	2.3674			.4776
1F	28	216.6	.0134	.0134	.2890	.3093	2.7289			.5351
1F	29	247.1	.0129	.0105	.3201	.2978	2.4715			.4370
1F	30	203.3	.0157	.0148	.3277	.3124	2.7679			.5422
	Mean:	219.7	.0133	.0122	.3178	.3148	2.6195			.5007
	S.D.:	17.2	.0018	.0019	.0203	.0214	.1869			.0436
2F	31	212.3	.0137	.0122	.3736	.3854	2.5936			.4938
2F	32	214.7	.0182	.0140	.3237	.3195	2.4822			.4885
2F	33	217.9	.0156	.0129	.3048	.3002	2.6472			.4815
2F	34	213.8	.0178	.0140	.3119	.3391	2.6129			.5130
2F	35	216.5	.0143	.0125	.3188	.3313	2.5581			.4948
	Mean:	215.0	.0159	.0131	.3266	.3351	2.5788			.4943
	S.D.:	2.2	.0020	.0008	.0272	.0317	.0629			.0117
3F	36	216.9	.0157	.0161	.3609	.3268	2.6883			.5402
3F	37	215.5	.0135	.0111	.3197	.3299	2.7021			.5113
3F	38	223.9	.0152	.0125	.3104	.3073	2.6696			.4806
3F	39	222.7	.0135	.0135	.2843	.2901	2.7168			.5240
3F	40	216.3	.0120	.0120	.2946	.2710	2.3134			.4795
	Mean:	219.1	.0140	.0131	.3140	.3050	2.6180			.5071
	S.D.:	3.9	.0015	.0019	.0296	.0249	.1712			.0268
4F	41	239.9	.0129	.0138	.2739	.3044	2.4057			.6929
4F	42	208.6	.0206	.0201	.3591	.3802	3.0610			.7258
4F	43	226.0	.0195	.0164	.3014	.3377	3.0193			.7329
4F	44	238.7	.0138	.0134	.3004	.3217	2.6960			.6129
4F	45	224.8	.0178	.0160	.3096	.3158	2.7732			.7050
	Mean:	227.6	.0169	.0159	.3089	.3319	2.7910			.6939
	S.D.:	12.7	.0034	.0027	.0311	.0295	.2659			.0480

APPENDIX 7

PATHOLOGY REPORT

I, the undersigned, hereby declare that the findings described in this appendix were compiled by me or under my supervision and accurately reflect the primary data records.

C. Thomson, C.Biol., M.I.Biol.,
Study Pathologist

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7.1 SUMMARY

Significant lesions were restricted to the lungs.

Group 4 animals showed a prominent increase in the alveolar histiocyte population, with associated low grade epithelial and leucocyte reactions.

Group 3 animals showed a slight increase in the alveolar histiocyte population, without significant reaction.

Group 2 animals were comparable with controls.

7.2 METHODS

Necropsy and histopathology methods were as stated in the main body of the report. In summary, all animals were subjected to a full post-mortem examination. In the case of animals from groups 1 and 4, histopathological examination was carried out on adrenal, heart, larynx, thyroid, lung, spleen, trachea, eye, kidney, liver, nasal cavity and tongue. In the case of animals from groups 2 and 3 histopathological examination was restricted to lung.

7.3 RESULTS

No significant abnormalities were found at post-mortem examination, the majority of animals were unremarkable.

Histopathological examination showed low grade lung lesions in a number of controls. Typical lesions in the control population were minimal to slight interstitial pneumonitis with minimal perivascular leucocyte cuffing and infiltration. In addition, occasional controls also showed focal accumulation of alveolar histiocytes in small areas of alveoli.

Group 4 animals showed a prominent increase in the population of alveolar histiocytes. Histiocyte foci were found in alveoli surrounding terminal airways. Changes associated with these histiocyte foci were slight increases in the degree of perivascular leucocyte cuffing and infiltration, and minimal proliferation of alveolar type 2 epithelial cells localised to alveoli containing the histiocyte foci.

In group 3 there was a slight increase in the number of animals showing alveolar histiocyte foci, without any significant associated reaction. Lungs from group 2 animals were comparable with the controls.

No other significant lesions were seen.

7.4 DISCUSSION

The absence of lung lesions in group 2 was considered to indicate that clearance of test article dust from the lungs was keeping pace with deposition at this exposure level. The increases in alveolar histiocyte population in groups 3 and 4 probably indicate accumulation of test article dust in the lung. The low-grade epithelial and leucocyte reactions associated with the histiocyte foci in group 4 animals were considered to represent slight irritation of the pulmonary tissue by the test material dust.

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TABLE 7.1
GROUP INCIDENCE: NECROPSY DATA
*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

PRINTED: 02-OCT-89
PAGE: 1

STUDY NUMBER: 76033

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4;WEEKS=ALL
DEATH=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	5	5	5	5	5	5	5	5
** TOP OF LIST **									
ADRENAL	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
EYE	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
HEART	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
KIDNEY	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
HYDRONEPHROSIS		0	0	0	0	0	0	1	0
LARYNX	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
LIVER	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
LUNG	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
RED FOCUS		0	0	1	0	0	0	0	0
NASAL CAVITY	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
SPLEEN	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
TONGUE	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
TRACHEA	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
THYROID	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
ANIMAL	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
NOT REMARKABLE		5	5	4	4	5	5	4	5
TESTIS	NUMBER EXAMINED:	5	5	5	5	0	0	0	0
DIMINISHED		0	0	0	1	0	0	0	0
** END OF LIST **									

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TABLE 7.2
GROUP INCIDENCE: HISTOPATHOLOGY DATA
*** PATH/TOX SYSTEM OUTPUT ***
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PAGE: 1

STUDY NUMBER: 76033

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIMALS-AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	5	5	5	5	5	5	5	5
** TOP OF LIST **									
LIVER	NUMBER EXAMINED:	5	0	0	5	5	0	0	5
--LEUCOCYTE FOCI		3	0	0	3	1	0	0	1
KIDNEY	NUMBER EXAMINED:	5	0	0	5	5	0	1	5
--FOCAL NEPHROPATHY		3	0	0	1	0	0	0	0
--HYDRONEPHROSIS		0	0	0	0	0	0	1	0
LUNG	NUMBER EXAMINED:	5	5	5	5	5	5	5	5
--PNEUMONITIS (INTERSTITIAL)		3	3	3	3	3	3	3	4
--LEUCOCYTE CUFFING/INFILTRATION		3	5	4	5	5	3	3	5
--ALVEOLAR HISTIOCYTE FOCI		1	1	3	5	1	1	3	5
--ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI		0	0	0	5	0	0	0	5
--HAEMORRHAGE (AGONAL)		0	0	1	0	0	0	0	0
HEART	NUMBER EXAMINED:	5	0	0	5	5	0	0	5
--NECROSIS		0	0	0	1	0	0	0	0
TESTIS	NUMBER EXAMINED:	0	0	0	1	0	0	0	0
--ATROPHY		0	0	0	1	0	0	0	0
** END OF LIST **									

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TABLE 7.3
SUMMARY TABLE - LUNG FINDINGS AND GRADES
*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT

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PAGE: 1

STUDY NUMBER: 76033

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=T

ORGAN/TISSUE EXAMINED			--- NUMBER-OF-ANIMALS-AFFECTED ---							
		SEX:	----------MALE----------				---------FEMALE---------			
		GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
		NUMBER:	5	5	5	5	5	5	5	5
** TOP OF LIST **										
LUNG (LU)	NUMBER EXAMINED:		5	5	5	5	5	5	5	5
--PNEUMONITIS (INTERSTITIAL)	GRADE	1>	2	2	2	2	3	3	3	3
		2>	1	1	1	1	0	0	0	1
--LEUCOCYTE CUFFING/INFILTRATION	GRADE	1>	3	5	4	2	5	3	3	1
		2>	0	0	0	3	0	0	0	4
--ALVEOLAR HISTIOCYTE FOCI	GRADE	1>	1	1	3	0	1	1	3	0
		3>	0	0	0	5	0	0	0	5
--ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI	GRADE	1>	0	0	0	5	0	0	0	5
--HAEMORRHAGE (AGONAL)	PRESENT		0	0	1	0	0	0	0	0
** END OF LIST **										

APPENDIX 7.1

HUK PROJECT NO : 760/33

INDIVIDUAL ANIMAL PATHOLOGY DATA

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*** PATH/TOX SYSTEM OUTPUT ***
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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00001 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 352.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-SLIGHT

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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PAGE: 2

INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00002 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 392.0 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

KIDNEY :
-FOCAL NEPHROPATHY,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, LUNG, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00003 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 392.6 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-MINIMAL

KIDNEY :
-FOCAL NEPHROPATHY,-MINIMAL

LUNG :
-PNEUMONITIS (INTERSTITIAL),-SLIGHT, MULTI-FOCAL
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00004 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 390.0 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00005 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 387.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-MINIMAL

KIDNEY :
-FOCAL NEPHROPATHY,-MINIMAL

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00006 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 424.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-SLIGHT -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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*** PATH/TOX SYSTEM OUTPUT *** .
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

PRINTED: 29-SEP-89
PAGE: 7

INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00007 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 454.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00008 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 386.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

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28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00009 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 374.1 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00010 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 385.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00011 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 374.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00012 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 455.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-SLIGHT -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00013 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 400.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

PRINTED: 29-SEP-89
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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00014 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 443.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LUNG

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

PRINTED: 29-SEP-89
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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00015 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 377.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
LUNG : -RED FOCUS; FEW ALL LOBES.	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL -HAEMORRHAGE (AGONAL),-PRESENT

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*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00016 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 382.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-PNEUMONITIS (INTERSTITIAL),-SLIGHT
-LEUCOCYTE CUFFING/INFILTRATION,-SLIGHT
-ALVEOLAR HISTIOCYTE FOCI,-MODERATE
-ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

HEART :
-NECROSIS,-MINIMAL, FOCAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00017 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 402.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-MINIMAL

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-SLIGHT
-ALVEOLAR HISTIOCYTE FOCI,-MODERATE
-ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00018 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 407.4 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-MINIMAL

LUNG :
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL
-ALVEOLAR HISTIOCYTE FOCI,-MODERATE
-ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00019 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 361.0 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

TESTIS :
-DIMINISHED, MODERATE; BILATERAL.

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-MINIMAL

KIDNEY :
-FOCAL NEPHROPATHY,-MINIMAL

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-SLIGHT
-ALVEOLAR HISTIOCYTE FOCI,-MODERATE
-ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

TESTIS :
-ATROPHY,-PRESENT

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00020 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 395.2 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MODERATE -ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00026 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 223.5 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00027 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 207.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-MINIMAL

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

LARYNX :
>SECTION EXAMINED; TISSUE NOT PRESENT

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00028 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 216.6 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00029 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 247.1 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00030 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 203.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00031 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 212.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LUNG

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00032 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 214.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00033 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 217.9 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00034 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 213.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00035 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 216.5 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00036 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 216.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
KIDNEY : -HYDRONEPHROSIS, SLIGHT; BILATERAL.	KIDNEY : -HYDRONEPHROSIS,-PRESENT LUNG : -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00037 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 215.5 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LUNG

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00038 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 223.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00039 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 222.7 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00040 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 216.3 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-MINIMAL -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MINIMAL

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00041 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 239.9 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-SLIGHT
-ALVEOLAR HISTIOCYTE FOCI,-MODERATE
-ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00042 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 208.6 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LIVER :
-LEUCOCYTE FOCI,-MINIMAL

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-SLIGHT
-ALVEOLAR HISTIOCYTE FOCI,-MODERATE
-ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00043 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 226.0 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -PNEUMONITIS (INTERSTITIAL),-SLIGHT -LEUCOCYTE CUFFING/INFILTRATION,-SLIGHT -ALVEOLAR HISTIOCYTE FOCI,-MODERATE -ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

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INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00044 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 238.7 GRAMS

PATHOLOGY OBSERVATIONS

NECROPSY	HISTOPATHOLOGY
ANIMAL : -NOT REMARKABLE	LUNG : -LEUCOCYTE CUFFING/INFILTRATION,-MINIMAL -ALVEOLAR HISTIOCYTE FOCI,-MODERATE -ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

HAZLETON LABORATORIES EUROPE LTD
OTLEY ROAD, HARROGATE
NORTH YORKSHIRE HG3 1PY ENGLAND

*** PATH/TOX SYSTEM OUTPUT ***
28 DAY INHALATION TOXICITY STUDY IN THE RAT.

PRINTED: 29-SEP-89
PAGE: 45

INDIVIDUAL ANIMAL PATHOLOGY DATA

STUDY NUMBER: 76033

ANIMAL NUMBER: A00045 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/31/88 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 224.8 GRAMS

P A T H O L O G Y O B S E R V A T I O N S

NECROPSY

ANIMAL :
-NOT REMARKABLE

HISTOPATHOLOGY

LUNG :
-PNEUMONITIS (INTERSTITIAL),-MINIMAL
-LEUCOCYTE CUFFING/INFILTRATION,-SLIGHT
-ALVEOLAR HISTIOCYTE FOCI,-MODERATE
-ALVEOLAR TYPE 2 CELL PROLIFERATION ASSOCIATED WITH HISTIOCYTE FOCI,-MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
EYE, LIVER, SPLEEN, ADRENAL CORTEX, ADRENAL MEDULLA, KIDNEY, HEART, TRACHEA, TONGUE, THYROID, LARYNX, NASAL CAVITY

APPENDIX 8

PATHOLOGY HEALTH SCREEN

The major tissues and organs from 5 male and 5 females were examined at necropsy and samples of lung from all the rats histopathologically, (Table 1). Minor lesions of focal pneumonitis were seen in four animals.

A further screen was carried out on 8 spare animals, 3 males and 5 females. Minor lesions of pneumonitis were again observed, in 2 animals, (Table 2). From these findings it was concluded that the low incidence of pneumonitis was unlikely to affect the integrity of the study.

A.J.H. Basford.

A.J.H. Basford, BVSc. MSc. MRCVS.
23 February 1988

TABLE 1

Individual animal pathology data

HEALTH SCREEN: MALES

Animal number and sex:	101M	102M	103M	104M	105M
NECROPSY					
Animal not remarkable (NR)	NR	NR	NR	NR	NR
HISTOPATHOLOGY					
Lung: haemorrhage - focal			1		
: peribronchial lymphoid hyperplasia	2	2	1	2	2
: leucocyte foci	2	2	2		2
: pneumonitis - focal				1	1

HEALTH SCREEN: FEMALES

Animal number and sex:	106F	107F	108F	109F	110F
NECROPSY					
Animal not remarkable (NR)	NR	NR	NR	NR	NR
HISTOPATHOLOGY					
Lung: peribronchial lymphoid hyperplasia	1	1	2	2	1
: leucocyte foci	1	1	1	2	2
: pneumonitis - focal	2	2			

Key: 1 - 5 = Finding present and graded minimal - severe.

TABLE 2

Individual animal pathology data

HEALTH SCREEN: MALES AND FEMALES

Animal number and sex:	111M	112M	113M	114F	115F	116F	117F	118F
NECROPSY								
Animal not remarkable (NR)	NR	NR	NR	NR	NR	NR	NR	NR
HISTOPATHOLOGY								
Lung: leucocyte foci	2	1	2	1	1	1	2	1
: peribronchial lymphoid hyperplasia	2	1	1	2	1	2	2	1
: pneumonitis - sub-acute	1						1	

Key: 1 - 5 = Finding present and graded minimal - severe.

APPENDIX 9
LABORATORY METHODS

Units

9.1 Haematology

9.1.1 Parameters measured on EDTA-treated blood

Haemoglobin (Hb) - determined by measurement of cyanmethaemoglobin using the Coulter S880 system. g/dl

Red blood cells (RBC) - determined by the Coulter S880 system. mil/cmm

Mean cell volume (MCV) - determined by the Coulter S880 system. fl

Derived indices - the packed cell volume (PCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) were calculated as follows:

PCV = MCV x RBC ÷ 10 %
MCH = Hb x 10 ÷ RBC pg
MCHC = Hb x 100 ÷ PCV g/dl

Platelets (PLAT) - determined by the Coulter S880 system. 1000/cmm

Total white blood cells (TOT WBC) - determined by the Coulter S880 system. 1000/cmm

Units

Differential white blood cell count - determined by visual appraisal of a blood smear after staining with a Romanowski-type stain (Dacie and Lewis 1984):

N = Neutrophils
L = Lymphocytes
M = Monocytes
E = Eosinophils
B = Basophils 1000/cmm (%)

Polychromatic cells (POLYC) - determined by visual appraisal of a blood smear after staining with a Romanowski-type stain (Dacie and Lewis 1984):

0 = none detected
+ = small number
++ = moderate
+++ = large
++++ = very large

Spherocytic cells (SPHER) - determined by visual appraisal of a blood smear after staining with a Romanowski-type stain (Dacie and Lewis 1984):

0 = none detected
+ = small number
++ = moderate
+++ = large
++++ = very large

9.2 Clinical chemistry

9.2.1 Parameters measured on heparinised plasma

Glutamate oxaloacetate transaminase (GOT(AST)) - determined by a UV method using L-aspartate and α-oxoglutarate as primary substrates (Henry et al. 1960. I.L. test kit•). Iu/l

	Units
Glutamate pyruvate transaminase (GPT(ALT)) - determined by a UV method using α-oxoglutarate and L-alanine as primary substrates (Henry et al. 1960. I.L. test kit•).	Iu/l
Alkaline phosphatase (ALK PHOS) - determined by a colorimetric method using p-nitrophenyl phosphate as substrate (Bowers and McComb 1966, McComb and Bowers 1972 and Bessey et al. 1946. I.L. test kit•).	Iu/l
Gamma glutamyl transferase (transpeptidase) (GAMMA GT) - determined by a colorimetric method using γ-glutamyl-p-nitroanilide as substrate (modified Szasz 1976. I.L. test kit•).	Iu/l
Sodium (Na) - determined by I.L. Monarch Model 761 ion-selective electrodes (Eisenman et al. 1957). Potassium (K) Chloride (Cl)	meq/l
Calcium (Ca) - determined by a colorimetric method based on the reaction with o-cresolphthalein complexone in alkaline solution (Moorehead and Biggs 1974. I.L. test kit•).	mg/dl
Inorganic phosphorous (P) - determined by colorimetric method based on the reaction with ammonium molybdate in acid conditions (Daley and Ertingshausen 1972. I.L. test kit•)	mg/dl
Glucose (GLUCOSE) - determined by a colorimetric method using a coupled hexokinase procedure (Kornberg and Horecker 1955 and Bathelmai and Czok 1962. I.L. test kit•).	mg/dl
Blood urea nitrogen (B.U.N.) - determined by a UV method using a coupled urease procedure (Talke and Schubert 1965. I.L. test kit•)	mg/dl

	Units
Total bilirubin (T BILI) - determined by a colorimetric method based on the reaction with diazotized sulfanilic acid (Pearlman and Lee 1974. I.L. test kit•).	mg/dl
Creatinine (CREAT) - determined by a colorimetric method based on the Jaffé reaction (Jaffé 1886. I.L. test kit•).	mg/dl
Total proteins and albumin (T PROT, ALBUMIN) - total proteins determined by a colorimetric method based on the biuret reaction (Kingsley 1939 and Doumas 1975. I.L. test kit•); albumin determined by a colorimetric method based on the BCG reaction (Spencer and Price 1977. I.L. test kit•).	g/dl
Albumin/globulin ratio (AG RATIO) $= \frac{\text{albumin}}{\text{total protein - albumin}}$	-
Total cholesterol (TOT CHOL) - determined by an enzymatic method using cholesterol oxidase/esterase as primary enzymes (Allain et al. 1974. I.L. test kit•).	mg/dl

• supplied by Instrumentation Laboratory (UK) Ltd., Warrington.

9.3 References

Allain, C.C., Poon, L.S., Chan, C.S.G., Richmond, W. and Fu, P.C. (1974). Clin. Chem., 20, 470.

Bathelmai, W. and Czok, R. (1962). Klin. Wochenschr., 40, 585.

Bessey, O.A., Lowry, O.H. and Brock, M.J. (1946). J. Biol. Chem., 164, 321.

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Jaffé, M. (1886). Hoppe Seylers Z. Physiol. Chem., 10, 391.

Kingsley, G.R. (1939). J. Biol. Chem., 131, 197.

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McComb, R.B. and Bowers, G.N. (1972). Clin. Chem., 18, 97.

Moorehead, R.W. and Biggs, H.G. (1974). Clin. Chem., 20, 386.

Pearlman, F.C. and Lee, R.T.Y. (1974). Clin. Chem., 20, 4.

Spencer, K. and Price, C.P. (1977). Ann. Clin. Biochem., 14, 105.

Szasz, G. (1976). Clin. Chem., 22, 2051.

Talke, H. and Schubert, G.E. (1965). Klin. Wochenschr., 43, 174.

APPENDIX 10

STUDY PROTOCOL

HAZLETON UK

Otley Road, Harrogate
North Yorkshire HG3 1PY England

PROJECT TITLE SALSORB 84 AND SALSORB DD: 28 DAY INHALATION TOXICITY STUDY IN THE RAT

PROTOCOL NUMBER P3945d

HUK PROJECT NUMBER 760/33

SPONSOR

	signature	date
Issued by Study Director (or Deputy)	C J Collins	26 Jan 88
Authorised for HUK Management by	G Waite	26 January 1988
	G. WAITE, CONTRACTS ADMINISTRATOR	
*Authorised for Sponsor by	[illegible]	29 March '89
	R. FLETCHER, MANAGING DIRECTOR.	
Acknowledged and implemented by Study Director	C J Collins	30 Mar '89

*Instruction to Sponsor. Please type your name and company status underneath your signature, and return one signed copy to HUK as soon as possible.

1. Objective

To determine the inhalation toxicity of the test article in the rat following administration over a 4 week period.

2. Experimental design

Group number	Group designation	Dose level (µg/l)	Animals/group Male	Female
1	Control	0	5	5
2	Salsorb 84 Low	4	5	5
3	Salsorb 84 Intermediate	20	5	5
4	Salsorb 84 High	100	5	5
5	Salsorb 00 High	100	5	5

3. Test system

Species and strain :rat of the Crl:CD(SD)BR strain

Supplier :Charles River (UK) Ltd.

Age at initiation :6 to 8 weeks old on arrival (approximately 150 to 200 g for males and 125 to 175 g for females)

Number :30 males, 30 females

Justification :rodent species known to respond to the administration of similar materials and acceptable to regulatory authorities

4. Environment and husbandry

Housing :exclusive room

Air conditioning :minimum 15 changes/hour

Temperature :19-25°C

DEFINITIVE

Humidity	:40-70%
Lighting	:12 hours light/12 hours dark
Caging	:groups of 5 in suspended stainless steel mesh or polypropylene walled cages

5. Diet and water

Diet	:SQC Rat and Mouse Maintenance Diet No. 1, Expanded, Special Diets Services Ltd. Each batch of diet is analysed for specific contaminants. Food removed during exposure
Water	:filtered mains water ad libitum, except during exposure. The water is periodically analysed
Contaminants	:no contaminants are known to be present in diet or water at levels which might interfere with achieving the objective of the study

6. Pre-experimental procedures

Animal health procedures	:clinical inspection for ill-health on arrival. Microscopic examination of lungs from 5 males and 5 females. Veterinary inspection before start of dosing
Acclimatisation period	:about 2 weeks
Allocation to treatment group	:stratified body weight procedure
Identification	:individual number by ear tattoo as follows:

DEFINITIVE

P3945d

Group number	Colour code	Identification numbers Male	Female
1	Buff	1-5	26-30
2	Green	6-10	31-35
3	Blue	11-15	36-40
4	Pink	16-20	41-45
5	Pink 5	21-25	46-50

:cages by colour coded card with project number, animal number, Dispensary number and dose level. A card attached to the outside of the door/wall of the room will show the project number, the route of administration, the start date and the Home Office licensee

7. Test and control articles

Test articles :Salsorb 84 and Salsorb DD

Specification :to be provided by sponsor. The test articles are to be micronised

Hazardous properties :standard safety precautions

Storage of test article :room temperature in the dark

Control article :filtered air

Administration :inhalation (whole-body)

Justification :possible route of human exposure

Frequency/duration :6 hours/day 5 days/week for 4 weeks

DEFINITIVE

Generation	:respirable particles by standard methods
Stability	:to be provided by sponsor
Proof of absorption	:not required by sponsor
Exposure system	:1 m³ stainless steel and glass whole-body chambers

8. Atmosphere control

Distribution	:once at all concentrations if possible, before the start of animal exposure. Data from the range-finding study may be used if appropriate
Temperature	:monitored continually and recorded hourly target 20-24°C
Humidity	:monitored continually and recorded hourly target 40-60% but may be lower for hygroscopic test articles
Air flow rate	:monitored continually and recorded hourly target ventilation rate 12-15 changes/hour
Oxygen concentration	:target ≥ 19%, verified before start of study and checked once for all chambers in the presence of animals
Nominal concentration	:calculated daily
Actual concentration	:normally 3 times daily

DEFINITIVE

Particle size	:for each concentration, prior to start of exposures and then weekly

9. Experimental observations

Morbidity/mortality	:twice daily. Any animal which shows marked signs of ill-health will be isolated and may be killed to prevent autolysis
Clinical signs	:daily
Body weight	:once weekly
Food consumption	:weekly

10. Clinical pathology :all animals in week 4. Blood samples withdrawn by orbital sinus puncture under Halothane anaesthesia after overnight withdrawal of food

Haematology

haemoglobin concentration (Hb)
mean cell volume (MCV)
red blood cell count (RBC) and indices:
mean cell haemoglobin (MCH)
mean cell haemoglobin concentration (MCHC)
packed cell volume
total and differential white cell count (WBC)
platelet count

Anticoagulant - EDTA

Clinical chemistry

alkaline phosphatase (Alk.P)
gamma glutamyl transpeptidase (GGT)
glutamate oxaloacetate transaminase (GOT/AST)
glutamate pyruvate transaminase (GPT/ALT)

DEFINITIVE

blood urea nitrogen (BUN)	total protein (TP)	calcium
glucose	albumin	chloride
cholesterol	albumin/globulin ratio	inorganic phosphorus
creatinine		potassium
total bilirubin		sodium

Anticoagulant - lithium heparin

Urine analysis

Only performed if there is an observed or expected renal effect

11. Pathology

Applicable to all animals

Necropsy :animals killed by exsanguination following intraperitoneal pentobarbitone sodium anaesthesia, full macroscopic examination

Organ weights :adrenals* kidneys*
liver lungs
testes*

* paired organs weighed separately. Organs weighed after dissection of fat and other contiguous tissue

DEFINITIVE

Tissue preservation:

adrenals (x 2)	eyes
heart	kidneys (x 2)
larynx and thyroid LS	liver
lungs*	nasal cavity (4 levels)
spleen	tongue
trachea at the bifurcation	gross lesions

* with mainstem bronchi

Fixative: 10% neutral buffered formalin with the exception of eyes which are fixed in Davidson's fluid.

Appropriate tissues (see next section) embedded in paraffin wax, sectioned at 5 µm, stained with haematoxylin and eosin.

Histopathology :tissues of all animals in the control and both high dose groups, and lungs from all other animals. Extended to other animals (at additional cost) if necessary

10. Data evaluation :statistical analysis where appropriate using currently accepted methods (See Appendix 1)

11. Regulatory requirements and quality assurance :this study will be conducted to OECD Guideline 412 and in accordance with OECD and UK Principles of Good Laboratory Practice (DHSS 1986)

:protocol and final report audits

:internal audits may be performed during the in-life phase

DEFINITIVE

:wherever appropriate any change to this protocol will be made by an amendment agreed by Hazleton and the study sponsor

12. Reports

:the sponsor will be informed promptly of any toxicologically significant findings and issued progress reports at appropriate intervals

:the final report will contain all procedures and results. A draft will be issued for discussion with the sponsor (see Appendix 2)

13. Archive

:all raw data, slides and wet tissue will be kept in accordance with Company Standard Procedures

DEFINITIVE

January 1988

APPENDIX 1

Statistical evaluation

Toxicity studies

Where the data allow the following methods will be used for statistical assessment:

1. Continuous or semi-continuous responses
   - Body weights
   - Body weight gains
   - Clinical chemistry
   - Food consumption
   - Haematology
   - Organ weights
   - Organ/body weight ratios

Statistical evaluation will be made using an analysis of variance technique for normally distributed errors or by non-parametric techniques for non-normally distributed errors.

Analysis of variance will establish the significance of the variability between all groups to determine a treatment-related response. If a between groups difference significant at the 5% level occurs, the standard deviation obtained from this analysis will be used for t-tests between control group and the treatment groups. Where necessary, the data will be suitably transformed before analysis.

Non-parametric testing will be carried out using a Kruskal-Wallis test for between group differences. If this indicates a between groups difference significant at the 5% level, significant differences between the control group and the treatment groups will be determined using the Wilcoxon rank sum test.

All tests will be carried out at 1% and 5% significance levels for a 2 sided risk.

DEFINITIVE

Comparisons will ordinarily be limited to a within-sex analysis unless scientific rationale supports a combination of data from both sexes.

DEFINITIVE

REFERENCES

ANOVA

Snedecor, G. W. and Cochran, W. G. (1980) Statistical methods, 7th ed., Iowa : Iowa State Univ.

t-TEST

Snedecor, G. W. and Cochran, W. G. (1980) Statistical methods, 7th ed., Iowa : Iowa State Univ.

WILCOXON rank sum test

Lehmann, E. L. (1975) Non parametrics : Statistical methods based on ranks, Ch. 1. New York : McGraw-Hill.

KRUSKAL - WALLIS test

Lehmann, E. L. (1975) Non-parametrics : Statistical methods based on ranks, Ch. 5. New York : McGraw-Hill.

DEFINITIVE

APPENDIX 2

1. Draft final report

A complete draft report will be issued for the study sponsor's comments. The report will be prepared to contain the following information:

1.1 The objectives and procedures stated in the approved protocol including any changes made to the original protocol.

1.2 The identity of the test/control substances (by name or code number) and their strength (quality/purity).

1.3 The test system - species, strain and sex of the animals used.

1.4 Procedure for identification of the test system.

1.5 The dose levels used, the dosage regimen, route of administration and duration of treatment.

1.6 Any unforeseen circumstances which may have affected the quality or integrity of the study.

1.7 The reports of the individual scientists involved in the study, e.g. pathologist/statistician.

1.8 The location of all raw data and final report.

1.9 The name and address of the testing facility, start and completion dates of the study.

1.10 The following items of data will be presented:
- experimental design
- exposure chamber conditions
- morbidity and mortality

DEFINITIVE

clinical observations
effects on body weight and food consumption
laboratory findings
organ weights and organ/body weight ratios
macroscopic and microscopic pathological findings
if possible the no-effect-level will be stated

2. Final report

The final report will be issued following QAU evaluation of the complete draft report. This report will include all the details described in Section 1 above with the following additions:

2.1 The signature of the Study Director and other scientists involved in the study as authentication of the report.

2.2 A statement that the report has been subject to quality assurance evaluation.

DEFINITIVE

PROJECT NO. 760/33

PROTOCOL NO. P3945d

APPENDIX 3

RESPONSIBLE PERSONNEL

STUDY MANAGEMENT[1]	NAME
Study Director	C.J. Collins
Deputy Study Director	P.E. Owen
Head of Pathology	J.R. Glaister
Biostatistician	J. Alexander
OPERATIONAL SUPERVISION[2]	
Animal House Supervisor	D. Breckon
Animal House Technician	A. Little
Animal Health	A. Basford
Clinical Pathology	R. Moszynski
Necropsy	V. Nelson
Histology	S. Brogden
Inhalation Chemistry	T. Halliday
QUALITY ASSURANCE[1]	
Quality Assurance Manager	P.R. Cooper
PROPOSED DATES	
Animals on site	January 88
First treatment	February 88
Study termination	March 88
Draft report	June 88

DEFINITIVE

N/A = Not applicable

1 = Any change documented by protocol amendment
2 = Any change documented in study records

DISTRIBUTION : Personnel above, Production Planning

HAZLETON UK
Otley Road, Harrogate
North Yorkshire HG3 1PY England

AMENDMENT TO PROTOCOL

PROTOCOL TITLE: SALSORB 84 AND SALSORB DD: 28 DAY INHALATION TOXICITY STUDY IN THE RAT

PROTOCOL NUMBER: P3945d — AMENDMENT NUMBER 1

PROJECT NUMBER: 760/33 — SHEET 1 OF 1

SPONSOR: Allied Colloids Ltd.,
PO Box 38,
Low Moor,
BRADFORD,
BD12 0JZ.

AMENDMENT

Experimental design

Group 5 (Salsorb DD) is deleted from the study. The various references to Salsorb DD do not apply.

The animal numbers for groups 1 to 4 are unchanged.

	signature	date
Prepared for HUK by	C J Collins	4 Mar 88
Authorised for HUK by	G. Waite	4 March 1988
	G. WAITE, CONTRACTS ADMINISTRATOR	
*Authorised for Sponsor by	[illegible]	31/1/89
Acknowledged and implemented by Study Director	C J Collins	2 Feb 89

*Instruction to Sponsor. Please type your name and company status underneath your signature, and return one signed amendment to HUK as soon as possible.

APPENDIX 10
DEVIATIONS FROM PROTOCOL

Section 4 Environment and husbandry

On four occasions the temperature was 26°C which is above the protocol limit. The actual range was 19 to 26°C. On three occasions the relative humidity was below the protocol range. The actual range was 33 to 66%.

Section 6 Pre-experimental procedures

An additional microscopic examination of the lungs was performed on a further 3 males and 5 females.

The main study animals were acclimatised in the holding room for 35 days.

Section 7 Test article

The test article was dried overnight at 100°C prior to use. This procedure was initiated for test article used from day eight of the study.

Section 8 Atmosphere control

As distribution studies relevant to the high dose group had already been conducted in connection with the previous project HUK 760/32 on the same test article this data was used for the present study.

Chamber air flow, temperature and relative humidity were measured twice hourly on the first 2 days of the study, not hourly as specified in the protocol.

On one occasion during exposure the temperature was 19°C which is below the specified minimum of 20°C. The actual range was 19 to 24°C.

On a small number of occasions during exposure the relative humidity was outside the protocol range. The actual range was 35 to 66%.

Section 8 Atmosphere control

On 3 occasions the air flow rate was below that required to maintain a ventilation rate of 12 changes/hour as specified in the protocol. The lowest rate recorded corresponded to a ventilation rate of 11.4 changes/hour.

Oxygen concentrations were not verified before the start of exposure but on the first day of exposure when animals were in the chamber.

Particle size analysis was not carried out during week four for group 2 or during week three for group 3 as stated in the protocol.

Section 10 Clinical pathology

Repeat blood samples were taken from eight animals at necropsy at the beginning of week 5 as their samples were clotted at the bleed at week 4.