THE TOXICITY OF ORALLY AND
INTRAVENOUSLY ADMINISTERED
PARAQUAT DICHLORIDE
IN CYNOMOLGUS MONKEYS

Addressee:
Dr. M. S. Rose,
Central Toxicology Laboratory,
Imperial Chemical Industries Limited
Alderley Park,
CHESHIRE
SK10 4TJ

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Authors:
David A. Purser,
Colin J. Hardy,
Gerald C. Clark,
Leon M. Cobb,
Huntingdon Research Centre,
HUNTINGDON
Cambridgeshire
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<td>94</td>
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</table>
SUMMARY

Test compound: Paraquat dichloride.

Test species: Cynomolgus monkey (Macaca fascicularis)

Sex: Male

Route of administration:
- Intravenous: 9 animals
- Oral: 20 animals

Dose levels and deaths:

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<th>No. dosed</th>
<th>Deaths</th>
<th>Survival time (days)</th>
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<td>1</td>
<td>0</td>
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<td>1</td>
<td>2, 9</td>
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<tr>
<td>16 mg.kg⁻¹ (single dose)</td>
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<td>2</td>
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<td>24 mg.kg⁻¹ (single dose)</td>
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<td>2</td>
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<td>32 mg.kg⁻¹ (single dose)</td>
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<td>2</td>
<td>2, 2</td>
</tr>
<tr>
<td>40 mg.kg⁻¹ (single dose)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Oral:
- 45 mg.kg⁻¹ (single dose) 6 1 8
- 55 mg.kg⁻¹ (single dose) 2 0
- 65 mg.kg⁻¹ (single dose) 6 3 2, 3, 4
- 85 mg.kg⁻¹ (single dose) 6 5 2, 2, 3, 8, 15

* Dose levels in mg.kg⁻¹ of paraquat ion (M.W. 257)

Clinical findings:

1. Intravenously administered paraquat caused death within 3 days in 7 animals.
2. The main symptoms resulting from paraquat administered by both routes were acute renal failure and lung congestion/oedema.
3. The following changes occurred in blood and urine constituents, and are considered to be significant:

uremic
polyuria followed by oliguria/anuria
high serum glutamic-pyruvic transaminase levels
hypocalcemia
low blood and urine pH
haematuria
glycosuria (all indicative of renal damage)
high levels of serum leucine amino-peptidase
high levels of serum glutamic dehydrogenase
high levels of serum gamma glutamyl transpeptidase (all indicative of hepatic damage)

4. The toxicity of orally administered paraquat was dose related, but it was not possible to establish a clear LD 50.

5. Within any one dose group it was observed that the monkeys most likely to die were those excreting the greatest amounts of paraquat during the first 48 hours.

6. It is suggested that paraquat poisoning consists of an acute phase mainly due to renal failure, occurring within 48 hours of dosing, and a sub-acute phase caused by lung damage 7-15 days after dosing.
INTRODUCTION

The following report contains the results of 3 experiments on the toxicity of paraquat in cynomolgus monkeys. The general aim of the experiments was to study the effects produced by paraquat, administered by both intravenous and oral routes. The 3 experiments were:

ICI/40 The toxicity of intravenously administered paraquat

In a previous dosing test 2 male cynomolgus monkeys were given 6 mg kg\(^{-1}\) and 40 mg kg\(^{-1}\) of paraquat intravenously. The 6 mg kg\(^{-1}\) dose produced no detectable symptoms, while the 40 mg kg\(^{-1}\) dose caused severe respiratory distress and death after 48 hours. Following these results, it was decided to dose 3 groups of 2 animals with 32, 24 and 16 mg kg\(^{-1}\) of paraquat ion respectively.

ICI/50 The toxicity of orally administered paraquat

The results of the previous study (ICI/40) and previous experiments by other investigators (Murray and Gibson, 1972; Murray and Gibson, 1974) showed that there were considerable differences between the effects of paraquat administered intravenously, and the effects of the substance administered orally. In this series of experiments 4 oral dose levels of 85, 65, 55 and 45 mg kg\(^{-1}\) were used on 4 groups of 2 monkeys. In addition, one animal was dosed intravenously with 10 mg kg\(^{-1}\) as an extension of ICI/40.

ICI/52 Preliminary dose-range tests for paraquat in the male cynomolgus monkey

Two previous studies of paraquat administered orally to cynomolgus monkeys (ICI/50 and Murray and Gibson, 1972) failed to establish a clear LD50. The purpose of this study was to provide further information towards this end, using 3 dose levels of 85, 65 and 45 mg kg\(^{-1}\) on 3 groups of 4 monkeys.

All dose levels are quoted as weights of paraquat ion (M.W. 257) unless stated otherwise.
MATERIALS AND METHODS

Animals

Twenty-nine cynomolgus monkeys (Macaca fascicularis) were obtained from a commercial supplier (Shamrock Farms Ltd). Animal bodyweights ranged from 3.4 kg to 5.5 kg, and in the case of the dose-range test project (ICI/52) animals were chosen so that each group mean weight was approximately the same, and each group contained the same number of light and heavy animals. Otherwise animals were allocated to groups at random.

On arrival at the Huntingdon Research Centre, and at monthly intervals thereafter, all animals were examined by our veterinary surgeon. Examination included intrapalpebral tuberculin tests (10,000 l.u. mammalian PPD) and chest X-ray.

Accommodation

The animals were housed in rack mounted stainless steel cages in a well ventilated holding area, maintained at a temperature of 71°F.

Diet

The animals were fed with a dry diet suitable for primates. A 1:1 ratio of ‘FP1’ (Dixon and Sons Ltd., Ware), and ‘Laboratory Animal Diet No. 427/7’ (Speciality Products, Witham, Essex) was used, each animal being offered 100 g of this diet and a 50 g ‘Kennmeal’ biscuit (Spratt’s Patent Ltd., Central House, Barkingside, Essex) daily. In addition, fresh fruit or vegetable produce (approximately 75 g) and 35 g of bread were offered. The total amount of food available for each animal was therefore 260 g per day, except when haematological tests were to be performed on the following day, in which case food was withheld. Food consumption was monitored 3 times per week, and water was available at all times.

Test material

The test material was a fine white powder received from the Central Toxicology Laboratory, Imperial Chemical Industries Limited, Alderley Park, Cheshire. The substance was supplied as the herbicide paraquat (N,N’ dimethyl 4, 4’ bipyridilium) dichloride M.W. 257 (100.0 % pure).

The powder was dried in an oven at 110°C for 1 hour before use, and the required amounts were then weighed, dissolved and made up to volume in sterile, pyrogen-free, water for injections (May & Baker Ltd., Dagenham, Essex).
Dosing

Intravenous (ICI/40)

Six male Cynomolgus monkeys were allocated to 3 groups of 2 animals for ICI/40 and one animal was allocated in ICI/50. All were dosed with paraquat by intravenous injection lasting ten seconds; the substance being administered at 15.15 hours on day 0 according to the dose schedule shown below:

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Weight (g)</th>
<th>Dose Pqt. kg.⁻¹ (mg)</th>
<th>Wt. Pqt-Cl₂ kg⁻¹ (mg)</th>
<th>Total dose Pqt-Cl₂ (mg)</th>
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<tr>
<td>16</td>
<td>4500</td>
<td>10</td>
<td>13.8</td>
<td>62</td>
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Oral (ICI/50, ICI/52)

Twenty male Cynomolgus monkeys were allocated to 3 groups of 6 animals, and one group of 2 animals. They were dosed with paraquat by oral gavage in approximately 40 ml of water. In the case of animals Nos 4 and 7, 5 g of 'Complan' (Glaxo-Farley Foods, Plymouth) were added to the water immediately prior to dosing to 'buffer' the effects of paraquat on the stomach. All animals were anaesthetized with 'Saffan' (Glaxo Laboratories Ltd., Greenford)¹ during and (for at least 2 hours) after dosing (1 ml.kg⁻¹ i.v., followed by 0.5 ml.kg⁻¹ i.m. every 25 minutes), to reduce the risk of vomiting before the substance could be absorbed.

The doses were administered to 8 animals at 15.00 hours, and to 12 animals at 10.00 hours on day 0 according to the schedule shown below:

1. 'Saffan' contains - Alphaxalone (0.9 % w/v)
   Alphadolone (0.3 % w/v)
<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Time (hrs)</th>
<th>Weight (g)</th>
<th>Dose Pqt. kg(^{-1}) (mg)</th>
<th>Wt. Pqt-Cl(_2), kg(^{-1}) (mg)</th>
<th>Total dose Pqt-Cl(_2) (mg)</th>
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Clinical investigations

(1) Clinical signs

The condition of the animals was observed during the day and at intervals during the night, any symptoms being recorded. Animals were killed only when they were found to be suffering pain which was either severe or likely to endure, and when the main result of the experiment had been attained.

(2) Food consumption

The quantity of food consumed overnight was recorded 3 times per week pre-exposure, and during the test period.
Bodyweight

Bodyweights were recorded weekly.

Radiographs

Lateral and antero-posterior radiographs were taken pre-exposure and whenever possible preterminally.

Electrocardiography

Electrocardiograms (ECGs) were recorded on a Hewlett-Packard Model 1504 A electrocardiograph. The ECG was obtained from the fully conscious animal restrained in the supine position, using the standard limb leads (I, II and III), the augmented unipolar limb leads (aVR, aVL and aVF) and three chest leads (MV I, MVII, and MVIII). The chest leads corresponded to the 4th intercostal space approximately 3 cm to the right and left of the mid-sternal line and the 5th intercostal space in the mid-axillary line respectively (Atta and Vanace, 1960).

ECGs were recorded pre-exposure on all animals in ICI/40 and ICI/50, and pre-terminally whenever possible.

Lung function tests

These consisted of:

(i) Lung mechanics

This test was used to assess the mechanical behaviour of the lungs and airways.

(ii) Lung ventilation

This test was used to assess the efficiency and distribution of pulmonary ventilation.

(iii) Blood gases

Measurements of pH, PCO₂ and PO₂ were made to assess the efficiency of gaseous exchange across the alveolar wall, and the body's acid-base balance.
Measurements of lung ventilation were made with the unanaesthetized animal seated quietly in a restraining chair and fitted with a face mask. The dead space within the face mask was minimized by using rubber liners especially moulded to fit the snouts of individual animals. The airtight seal around the face was achieved by using a rubber dam stretched tightly over the back of the mask, through which the snout of the animal was fitted. For ICI/40, lung mechanics were measured with the animals set up in the same way as above, but for ICI/50 the measurements were carried out under 'Saffan' anaesthesia (1 ml kg⁻¹ i.v.).

Lung mechanics (Figure 1)

For unanaesthetized animals, air flow into and out of the lungs was measured by means of a pneumotachograph fitted to the front of the mask, and a differential gas pressure transducer (model 270; Hewlett-Packard Equipment Ltd., 224 Bath Road, Slough, Bucks) which measured the pressure differential across the pneumotachograph.

Lung volume changes were derived by electrical integration of the flow signal with respect to time.

Intrathoracic pressure was measured by means of a saline-filled nylon catheter of 0.7 mm internal diameter connected to a pressure transducer (Hewlett-Packard 2688). The catheter was inserted, under local anaesthesia, at a level of the fourth intercostal space, approximately 3 cm lateral to the mid-sternal line on the right side of the chest.

The mechanical properties of the lung were measured using an on-line digital computer system which gave almost instantaneous teletype presentation of the parameters. Data extraction was based on standard methods (Frank, Mead & Ferris, 1957; Amund and Mead 1958) from simultaneous measurement of flow, volume and pressure changes during quiet respiration. A typical print-out from the monitoring system, and a list of the parameters measured, is shown in Figure 2.

Anaesthetized animals were intubated, and air flow was measured by connecting the endotracheal tube to a pneumotachograph. Pressure measurements were made with an oesophageal balloon, which was connected to the pressure transducer. Volume measurements and data extraction were carried out in the same way as for unanaesthetized animals.

The above technique was used on all the ICI/50 (orally dosed) animals, because in the previous study (ICI/40) the health of the animals was so poor that lung mechanics could be measured in only a few cases.
FIGURE 1

Apparatus used for monitoring the mechanical characteristics of the lungs of a restrained, fully conscious, monkey
FIGURE 2

A typical print-out from the lung mechanics system

3350

PRE-EXPOSURE

<table>
<thead>
<tr>
<th>VT</th>
<th>RR</th>
<th>RMV</th>
<th>DEDEC</th>
<th>VTP</th>
<th>CDYNL</th>
<th>RLI</th>
<th>RLE</th>
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<td>.042</td>
</tr>
<tr>
<td>48.0</td>
<td>25</td>
<td>1210</td>
<td>50</td>
<td>6.3</td>
<td>7.60</td>
<td>.041</td>
<td>.031</td>
<td>133</td>
<td>.049</td>
</tr>
<tr>
<td>48.0</td>
<td>28</td>
<td>1351</td>
<td>55</td>
<td>5.3</td>
<td>9.30</td>
<td>.035</td>
<td>.044</td>
<td>87</td>
<td>.042</td>
</tr>
<tr>
<td>2.8</td>
<td>1.6</td>
<td>130</td>
<td>2.3</td>
<td>1.0</td>
<td>1.84</td>
<td>.010</td>
<td>.012</td>
<td>43.8</td>
<td>.005</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>10</td>
<td>4</td>
<td>19</td>
<td>20</td>
<td>28</td>
<td>27</td>
<td>50</td>
<td>12</td>
</tr>
</tbody>
</table>

The figures which appear on the top left hand side of the print-out refer to:

- Project no.
- Date
- Species of animal
- Sex
- Animal No.
- Wt of animal (gm)
- Treatment

VT  Tidal volume - ml (Vt)
RR  Respiratory rate - per min (f)
RMV Respiratory minute volume - ml.min⁻¹
DEDEC Duration of expiratory phase as a percentage of the complete cycle
VTP Tidal volume pressure swing (cm H2O)
CDYNL Dynamic lung compliance (Cdyn (f)) ml.cm H2O⁻¹
RLI Pulmonary resistance during inspiration (Rl (f)) cm H2O.ml⁻¹.sec⁻¹
RLE Pulmonary resistance during expiration (Rl (e)) cm H2O.ml⁻¹.sec⁻¹
RI Average pulmonary resistance (Rl) cm H2O.ml⁻¹.sec

The final 3 lines of the printout indicate mean, standard deviation and coefficient of variation for each parameter.
Lung ventilation (Figure 3)

The distribution of pulmonary ventilation was assessed using a nitrogen washout technique based on the method of Darling, Jumana & Richards (1940).

After being fitted with a face mask and a suitable valve system, the animal breathed room air until a steady 'normal' respiratory pattern was obtained. To begin the test, at the end of a normal expiration, the animal began to breathe from a continuous stream of pure oxygen. Breath by breath analysis of the nitrogen content of respired air was made using a nitrogen analyser. The animal continued to breathe pure oxygen until the nitrogen content of the expired air was reduced to 2%.

From this test the following parameters were determined:

Tidal volume (VT)

Respiratory Rate (RR)

Respiratory minute volume (RMV)

Total time breathing pure oxygen to reach 2% nitrogen in expired air (T - 2%).

Total number of breaths of pure oxygen to reach 2% nitrogen in expired air (N - 2%).

Cumulative volume of expired air to reach 2% nitrogen in expired air (CVT - 2%)
FIGURE 3
Measurement of distribution of pulmonary ventilation
Blood gases

Measurements of blood gases, pH and base excess (Siggard-Andersen, 1971), were made on 200 μl samples of blood taken from the femoral artery of a restrained, fully conscious, supine animal. Analyses were carried out immediately after sampling, using a BMS3 blood microsystem (Radiometer A/S Emdrupvej 72, DK 2400, Copenhagen NV, Denmark) after the methods of Severinghaus (1968) and Siggard-Andersen (1963).

Base excess (B.E) measured in mEq.l⁻¹ indicates the accumulation of non-volatile acid or base in the blood. A positive value indicates a base excess (non-volatile acid deficit), a negative value indicates a base deficit (non-volatile acid excess).

The partial pressure of carbon dioxide in arterial blood (PCO₂), measured in mm Hg, is determined directly by means of the PCO₂ electrode. The partial pressure of oxygen (PO₂), measured in mm Hg, is determined 2 and 4 minutes after withdrawal of the blood sample by a PO₂ electrode and the PO₂ at the time of sampling calculated by extrapolation.

Example of calculation:

<table>
<thead>
<tr>
<th>PO₂ (2 min)</th>
<th>PO₂ (4 min)</th>
<th>PO₂ (0 min)</th>
<th>Corrected PO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>mm Hg</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>mm Hg</td>
</tr>
<tr>
<td>90</td>
<td>80</td>
<td>100</td>
<td>100 x K = 104</td>
</tr>
</tbody>
</table>

K = Correction Factor (1.04).

The correction factor is applied to account for the calibration of the electrodes with gas mixtures in which the rate of diffusion differs from that of liquids by a factor of 1.04.

Haematology

Ten ml of blood was obtained from the femoral vein of the restrained animal in the supine position. Food was withdrawn at 17.00 hours on the day before sampling.

Brief details of the investigations performed, methods used and appropriate units for the parameters measured are given below:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>Erythrocyte sedimentation rate (ESR) - Method of Wintrrobe</td>
</tr>
<tr>
<td>(2)</td>
<td>Packed cell volume (PCV) - Estimated by Technicon SMA4A</td>
</tr>
<tr>
<td>(3)</td>
<td>Haemoglobin (Hb) - Estimated by Technicon SMA4A</td>
</tr>
<tr>
<td>(4)</td>
<td>Red cell count (RBC) - Estimated by Technicon SMA4A</td>
</tr>
<tr>
<td>Units</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mm/hr⁻¹</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>g.100 ml blood⁻¹</td>
</tr>
<tr>
<td></td>
<td>millions. μl⁻¹</td>
</tr>
</tbody>
</table>
(5) Reticulocyte count (Retics) - brilliant cresyl blue and new methylene blue

(6) Total white blood cell count (WBC) - Estimated by Technicon SMA4A

(7) Differential count

(N) = Neutrophils
(L) = Lymphocytes
(E) = Eosinophils
(B) = Basophils
(M) = Monocytes


(9) Prothrombin time - Quick's one-stage method using Simplastin

Biochemistry


Plasma glucose - Technicon autoanalyser method (glucose oxidase)

Total serum proteins - Technicon autoanalyser method (Biuret)

Serum protein electrophoresis and AG ratio - electrophoretic breakdown of albumin, a1, a2, β and γ globulins - using millipore phorosidles, staining with ponceau S.

Serum glutamic - pyruvic transaminase (SGPT) - LKB 8600

Reaction Rate Analyser diamed test kit (J.T. Baker)

Serum leucine amino-peptidase (LAP) - (Sigma Technical Bulletin 251)


Gamma Glutamyl Transpeptidase (GCT)

Glutamic Dehydrogenase (GLDH)

Creatine Phosphokinase (CPK) LKB 8600 Reaction Rate Analyser

Boehringer test kit 15721

Sodium (Na+) - Flame photometer (E.E.L.)

Potassium (K+) - Flame photometer (E.E.L.)

Calcium (Ca++) - Technicon Autoanalyser method (Cresolphthalein complexone)

% red cells

x10^3 cells µl^-1

mg %

mg %

g %

% 

mU.ml^-1

Goldberg & Rutenberg or GR units

mg %

mU.ml^-1

mU.ml^-1

mU.ml^-1

mEq.1^-1

mEq.1^-1

mEq.1^-1

: 12 :

SYNG-PQ-02451877_R
Urinalysis.

(a) **Collection**

Normal procedure for urine samples collected for routine analysis is to take an overnight sample from animals whose drinking water has been withheld. However, in the present study all urine was required for paraquat level analysis as well as urinalysis. For this reason water was not withheld, urine volumes were measured every 24 hours, and samples retained for paraquat analysis and urinalysis.

(b) **Specific gravity of urine (SG)**

This is a standard test, but of little value in the present experiment since water was not withheld, and also because water spilled by the animal from the automatic watering system is collected with the urine and false values may be introduced. For the same reason total urine volumes, especially very high ones, are suspect.

(c) **Quantitative tests**

pH (by pH meter) and protein (by sulphosalicylic acid test).

(d) **Qualitative tests**

Reducing substances (Clinistix® * ** = orange)
Glucose (Clinistix®)
Ketones (Acetest®) - confirmed by Rothera's test when positive
Bile pigments (Ictolet® ** = strongly positive)
Urobilinogen (Bogomolow's test)
Haemoglobin (Haemistix®)
* Diagnostic reagents of Ames Company, Stoke Poges, England

(e) **Microscopy**

The specimen of urine was centrifuged at 3,000 r.p.m. for 10 minutes and then the deposit was microscopically examined for:

- Epithelial cells
- Polymorphonuclear leucocytes
- Mononuclear leucocytes
- Erythrocytes
- Organisms
- Casts
- Abnormal constituents
The grading of cell frequency in the spun deposit was as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nil</td>
</tr>
<tr>
<td>1</td>
<td>Few in some fields examined</td>
</tr>
<tr>
<td>2</td>
<td>Few in all fields examined</td>
</tr>
<tr>
<td>3</td>
<td>Many in all fields examined</td>
</tr>
</tbody>
</table>

(f) Estimation of urinary paraquat levels

Standard solutions were made up by adding known amounts of paraquat to 5 ml samples of cynomolgus urine. These were then treated with 2 ml of a fresh solution containing 0.05 g ml⁻¹ sodium dithionite, and 0.05 g ml⁻¹ sodium bicarbonate. The optical density of the free radical of paraquat formed by this procedure was then measured at 604 nm against a blank containing the same proportions of urine and reducing solution as the test samples, and a standard curve (of optical density against concentration) was constructed.

Urinary paraquat levels were estimated by measuring the optical density of the samples treated in the same way as above, and obtaining the paraquat concentrations from the standard curve.

(10) Bacteriology

Samples of the cardiac lobe of the lung were taken aseptically during autopsy, and were incubated in aerobic media (tryptcase soy broth), and anaerobic media (fluid thioglycollate), for 24 hours at 37°C. Bacterial growth in the tubes was examined microscopically after Gram staining and motility was observed by phase contrast microscopy. Samples were then subcultured onto the surface of blood agar plates (IC/50). Antibiotic sensitivity discs were placed on the plates which were then incubated at 37°C overnight and examined for the presence of zones of inhibited growth around the sensitivity discs.

(11) Autopsies

All animals were subjected to detailed macroscopic examination, and all abnormalities were noted. Selected tissues/organs were fixed in formalin (10%) and are available for examination (Kidneys, liver, heart, lungs and adrenals).
Clinical investigations were performed as far as possible at the following times for ICI/40 and ICI/50:

<table>
<thead>
<tr>
<th></th>
<th>Pre-exposure</th>
<th>Pre-terminally</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG and Radiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lung Mechanics</strong></td>
<td>Pre-exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-terminally</td>
<td></td>
</tr>
<tr>
<td><strong>Lung Ventilation and Blood gases</strong></td>
<td>Pre-exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48 hours after dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 days after dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 days after dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-terminally</td>
<td></td>
</tr>
<tr>
<td><strong>Haematology, Blood Biochemistry and Urinalysis</strong></td>
<td>Pre-exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 hours after dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48 hours after dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 days after dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-terminally</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS

RESULTS OF INTRAVENOUS DOSING STUDY (ICI/40)

The symptoms shown by the six animals, together with the results of all the clinical investigations carried out, are summarized in the following Clinical signs sheets (Appendix 1). The detailed results of all tests are given in Appendices 2-7.

The condition of all animals declined rapidly after dosing, 5 being dead by the third day, and one surviving 8 days (Figure 4). The results of the clinical investigations were as follows:

**Clinical signs**

Animals No. 2 and 6 began to show adverse symptoms within 2 hours of dosing, becoming lethargic and eating very little. Within the next 24 hours all the animals except No. 9 developed similar symptoms, consisting of vomiting, anorexia, dyspnoea and hypothermia. A copious oily secretion was also produced, which saturated the animals' body fur. An initial polyuria during the first 24 hours was followed by a marked reduction in urine volumes by 48 hours after dosing.

**Food consumption**

The animals were fed 2 hours after dosing; 2 failed to eat and 4 others vomited during the night. All animals showed a marked decrease in food consumption throughout the test period.

**Bodyweight**

A fall in bodyweights was recorded during the test period.

**Radiography**

No changes were detected.

**Electrocardiography**

Four of the 5 animals tested after dosing showed tall, narrow-peaked T-waves on leads V1 and V2. In addition 1 and 8 had prominent notched P-waves on V1 and V2, while No. 6 had inverted T-waves and broad flattened P-waves.
FIGURE 4

A comparison of dose level with survival time for monkeys dosed intravenously with paraquat.
Lung function tests

The condition of the animals was so poor that only one (No. 9) could be used successfully for lung mechanics testing, and 3 for lung ventilation (Nos 6, 9 and 10). All three had high respiratory rates, low tidal volumes and large respiratory minute volumes.

Lung mechanics (Appendix 2)

No. 9 showed a marked fall in lung compliance on the two occasions after dosing when it was tested.

Lung ventilation (Appendix 3)

All 3 showed increases in the cumulative tidal volumes to 2% nitrogen, after dosing. No. 9 was tested on 3 occasions and exhibited a progressive increase in respiratory minute volume, although the CVT - 2% reached a maximum on day 2 and some improvement was apparent on days 4 and 8 (see Figure 5).

Blood gases (Appendix 4)

The 6 animals tested all had low pH, low PCO₂ and high PO₂ when tested pre-exposure. After dosing all except No. 9 showed a further fall in pH, accompanied by a further drop in PCO₂ in Nos. 1, 8 and 16. A marked increase in PO₂ occurred in Nos 6, 8 and 16. In the case of Nos 9 and 10, which were tested several times, the pH rose progressively.

Haematology, Biochemistry and Uralysis (see Appendix 5-7)

The results of the pre-exposure blood analyses of 3/6/74 on the 6 animals then intended for dosing tests showed some slight abnormalities. The experiment was postponed for one week and 10 animals were then bled on 11/6/74. All 10 animals were slightly abnormal, but since the results of the experiment were urgently required, the study was started on 17/6/74 and 4 animals were used as controls for the blood parameters throughout the study. These 4 animals subsequently showed very few readings outside the range considered to be normal.
FIGURE 5
Changes in lung ventilation and blood gas data obtained from i.v. dosed animal No. 9 during the test period

The 4 columns shown for each test represent the following:
- Column 1: Pre-exposure levels
- Column 2: 44 hours after dosing
- Column 3: 3 days after dosing
- Column 4: 8 days after dosing
The test animals developed abnormal values in several parameters, particularly in plasma urea, SGPT, Ca++, urinary pH and urinary volume, as shown in Figure 6. Glucose, reducing substances and blood pigments appeared in the urine, and there was an increase in urinary protein.

Paraquat was detected in the urine after dosing, and urinary paraquat levels and volumes are shown in Table 1.

**Bacteriology**

The cultures from animals Nos 1, 6 & 9, contained Gram positive Cocci in chains and Gram positive motile rods. The cultures from No. 10 contained Gram positive motile rods.

**Autopsies**

**Group I** Monkey No. 1m

<table>
<thead>
<tr>
<th>Organ</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>left lung - occasional areas of moderate congestion.</td>
</tr>
<tr>
<td>Liver</td>
<td>marked generalized pallor</td>
</tr>
<tr>
<td>Kidneys</td>
<td>moderate bilaterally uniform pallor</td>
</tr>
<tr>
<td>Spleen</td>
<td>large and darkly discoloured.</td>
</tr>
<tr>
<td>Pancreas</td>
<td>multiple areas of marked congestion.</td>
</tr>
<tr>
<td>Stomach</td>
<td>gross gaseous distension</td>
</tr>
<tr>
<td>Duodenum</td>
<td>moderate gaseous distension</td>
</tr>
<tr>
<td>Colon</td>
<td>moderate gaseous distension</td>
</tr>
<tr>
<td>Descending Colon</td>
<td>scattered areas of moderate mucosal congestion, probably due to the presence of a parasitic infestation by an <em>Oesophagostomum sp.</em></td>
</tr>
<tr>
<td>Ileo-caecal valve</td>
<td>congested. Probably due to the presence of a parasitic infestation by an <em>Oesophagostomum sp.</em></td>
</tr>
</tbody>
</table>

**Monkey No. 2m**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>congestion/consolidation</td>
</tr>
<tr>
<td>Liver</td>
<td>generalised pallor</td>
</tr>
<tr>
<td>Kidneys</td>
<td>generalised pallor</td>
</tr>
</tbody>
</table>

**Group II** Monkey No. 6m

<table>
<thead>
<tr>
<th>Organ</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>left anterior lobe, hilar region: an area of congestion/consolidation (15 x 8 mm).</td>
</tr>
<tr>
<td></td>
<td>Posterior margin of left posterior lobe - a similar area (15 x 12 mm).</td>
</tr>
<tr>
<td></td>
<td>Right mid-lobe, anterior border - an area of congestion/consolidation (20 x 10 mm).</td>
</tr>
<tr>
<td></td>
<td>Right anterior lobe - and adhesion to the fourth and fifth intercostal spaces, probably due to lung function procedures.</td>
</tr>
<tr>
<td>Liver</td>
<td>marked generalized pallor</td>
</tr>
<tr>
<td>Kidneys</td>
<td>moderately severe bilaterally uniform pallor.</td>
</tr>
<tr>
<td>Stomach</td>
<td>moderate gaseous distension</td>
</tr>
<tr>
<td>Ileum</td>
<td>moderate gaseous distension. Some serosanguineous fluid present.</td>
</tr>
<tr>
<td>Tongue</td>
<td>lateral aspects of the root - two areas of localized congestion.</td>
</tr>
</tbody>
</table>
FIGURE 6

Mean changes in blood and urine parameters from all i.v. dosed animals

The 4 columns shown for each test represent the following:

Column 1  (hatched at base) mean values of 19 untreated cynomolgus monkeys, tested on one occasion
Column 2  Pre-exposure levels of test animals
Column 3  24 hours after dosing
Column 4  48 hours after dosing

Standard Error bars are shown
### TABLE 1

Urine volumes and paraquat levels - i.v. dosed animals - ICI/40

<table>
<thead>
<tr>
<th>Days after dosing</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Animal No. 1</td>
<td>2</td>
<td>6, 8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Vol</td>
<td>PQT</td>
<td>Vol</td>
<td>PQT</td>
</tr>
<tr>
<td>1</td>
<td>355</td>
<td>103</td>
<td>105</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td></td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td></td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>

Urine volumes are in ml, and paraquat levels in mg (= total amount in urine)
Monkey No. 8

Trachea: frothy exudate
Lung: consolidation
Liver: pale, slight yellow discolouration
Kidneys: palid
Stomach: moderate gaseous distension
Colon: moderate gaseous distension

Group III  Monkey No. 9

Lung: all lobes, gross consolidation and congestion
Heart: enlarged, bubbles of gas in pericardium
Liver: yellow tinge and pale spots
Kidneys: pale and speckled
Fat: fat deposits in mesenteries and pericardium bright yellow
Stomach: moderate gaseous distension
Ileum: oesophagostomum infestation
Gall bladder: light green

Monkey No. 10

Lung: congestion/consolidation
Liver: pale, all lobes spotted, particularly on underside
Kidneys: pale
Gall bladder: blue, filled with copious green viscous fluid
Spleen: pale and bluish colouration
Gut: oesophagostomum infestation

Group IV  Monkey No. 16

Lung: left and right lobes marked intralobar adhesions. Dependent borders of left lobes and costal aspect of right lobes, multiple fine costal to parietal pleural adhesions. Left and right posterior lobes, posterior margins, firmly adherent to the diaphragm. Right anterior lobe costal aspect, an area of consolidation 1.5 x 1.0 cm. The dorsal margin of the right anterior lobe was markedly congested. Dorsal aspect of left and right lung, scattered yellow subpleural nodules of up to 5 mm diameter, probably due to a lung mite infestation.

Liver: marked generalized pallor
Kidneys: marked bilaterally uniform pallor. Left kidney mid-central aspect, a subcapsular cyst 6 mm diameter.
Thyroid: small
Stomach: scattered areas of mucosal ulceration, punctate up to 5 mm diameter, mainly in the fundic region.

23
RESULTS OF ORAL DOSING STUDY (ICI/50 & ICI/52)

The symptoms shown by each animal, together with the results of all clinical investigations are summarised in the clinical signs sheets (Appendix 8). For the results of the ICI/50 study, where detailed investigations were made, a separate sheet is provided for each animal, while for the ICI/52 survival study, the results for each group are summarised. The results of the clinical investigations were as follows:

Clinical signs (Appendix 8)

All animals developed some symptoms, including an unpleasant ammoniacal odour and some degree of increased apocrine and sebaceous secretions. All of the Group I animals, 4 from Group II and 2 from Group IV had diarrhoea. Vomiting occurred overnight after dosing in Nos 22, 21, 28, 29, 17, 25 and 27 and only one of these No. 22 (Group I) subsequently died. Three animals from Group I and 3 from Group II rapidly became ill and died within 3 days (see Figure 7). Two further Group I animals died later, together with one animal from Group IV (No. 12); a second Group IV animal (No. 17) became very ill, with marked dyspnoea, at 10 days, but subsequently recovered. The usual terminal symptoms were that the animal became lethargic, with some dyspnoea, especially when any stress was involved, such as removing the animal from its cage for bleeding. Obtaining arterial and venous blood samples was also very difficult at this stage. Within any one dose group the animals which died tended to be those with the highest urinary paraquat levels (see Figure 8 and Table II). Of the 3 animals surviving in Group II, 2 were dosed with a small amount of 'Complan' in the paraquat solution; these had the lowest urinary paraquat levels of the 6 animals in this group.

Radiography

No changes were detected.

Electrocardiography

Some abnormalities occurred in the T-waves which were not present pre-exposure. Just prior to death No. 12 had very high narrow T-waves, and No. 14 had inverted T-waves. Slight T-wave abnormalities were also observed in Nos 4, 7 and 26.
FIGURE 7
A comparison of dose level with survival time for monkeys dosed orally with paraquat
FIGURE 8

A comparison of total urinary paraquat and survival time for orally dosed animals.

---

Group I. Dose 85 mg, kg⁻¹

- Death
- Survival

Group II. Dose 65 mg, kg⁻¹
 TABLE II

Urine volumes and paraquat levels - orally dosed animals

<table>
<thead>
<tr>
<th>Day</th>
<th>GROUP I</th>
<th>Animal No.</th>
<th>GROUP II</th>
<th>Animal No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 VOL</td>
<td>26 VOL</td>
<td>22 VOL</td>
<td>11 VOL</td>
</tr>
<tr>
<td></td>
<td>VOL</td>
<td>PQT</td>
<td>VOL</td>
<td>PQT</td>
</tr>
<tr>
<td>Pre-experiment</td>
<td>156</td>
<td>0</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>(dosed)</td>
<td>420</td>
<td>403</td>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>1</td>
<td>290</td>
<td>4</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Dead</td>
<td>.</td>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>0</td>
<td>140</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>.</td>
<td>48</td>
<td>0</td>
</tr>
</tbody>
</table>

volumes in ml
paraquat levels in mg
? indicates sample lost
* indicates sample included in next day's volume

: 27 :
## TABLE II
(continued)

### GROUP III

<table>
<thead>
<tr>
<th>Day</th>
<th>Animal No.</th>
<th>26</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VOL</td>
<td>VOL</td>
</tr>
<tr>
<td>Pre-experiment</td>
<td>159</td>
<td>0</td>
<td>-198</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>70</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>144</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>78</td>
<td>tr.</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>42</td>
<td>0</td>
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</table>

### GROUP IV

<table>
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<tr>
<th>Day</th>
<th>Animal No.</th>
<th>3</th>
<th>12</th>
<th>17</th>
<th>24</th>
<th>25</th>
<th>27</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VOL</td>
<td>VOL</td>
<td>VOL</td>
<td>VOL</td>
<td>VOL</td>
<td>VOL</td>
</tr>
<tr>
<td>Pre-experiment</td>
<td>50</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>64</td>
<td>0</td>
<td>200</td>
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<td>1</td>
<td></td>
<td>72</td>
<td>6.3</td>
<td>70</td>
<td>47</td>
<td>270</td>
<td>169</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>38</td>
<td>4.5</td>
<td>1</td>
<td>0.4</td>
<td>64</td>
<td>0.6</td>
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<tr>
<td>3</td>
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<td></td>
<td>84</td>
<td>0</td>
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<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>110</td>
<td>314</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>538</td>
<td>0</td>
<td>306</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Dead day 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bacteriology

Bacteriological investigations showed that the lungs of all animals contained bacteria. The results of the tests are shown in Table III.

Lung function tests

Lung Mechanics

No significant changes were observed, but after dosing animals required much longer to recovery from anaesthesia. Considerable difficulty was experienced in getting consistent results using the oesophageal balloon technique on anaesthetized animals.

Lung ventilation (Appendix 9)

The hyperventilation recorded from the i.v. dosed animals was absent from the orally dosed groups, with the exception of No. 26; and respiratory minute volumes were generally lower than the pre-exposure values. However all animals had increased cumulative tidal volumes to 2% nitrogen at some stage of the test period. This was most marked in the high dose group animals Nos. 14, and 26, which died at 2 and 8 days respectively, and a low dose animal (No. 12) which died at 7 days. For the 3 animals the CVT - 2% N2 was increased progressively when tested at 48 hrs., and 4 days. For the other animals, all of which survived the test period, the highest values tended to occur after 7 days. Following a similar pattern, the nitrogen washout times were increased initially, followed by an improvement at 7 days, after which they were again increased in surviving animals. It must be stressed that the results of this test can be very variable under normal conditions, so that with such small groups of animals any interpretation of these figures must be tentative.

Blood gases (Appendix 10)

All animals had low pH, low PCO2 and high PO2 when tested pre-exposure, and the 2 animals that died after one week (Nos 12 and 26) exhibited further increases in these parameters at 48 hours. Both animals then developed low PO2 when tested pre-terminally. No changes considered to be significant were observed in the other animals.

Haematology (Appendix 11)

All animals except those in Group IV developed increased platelet concentrations, and Nos. 28, 29 and 30 had increased erythrocyte sedimentation rates. There was also a slight increase in clotting times.
### TABLE III

Bacteriology results

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Gram stain and morphology</th>
<th>Sensitivity to Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Penicillin 10 µg</td>
</tr>
<tr>
<td>12m TSB</td>
<td>Gram +ve rods plus Gram +ve cocci in chains</td>
<td>S</td>
</tr>
<tr>
<td>Thio</td>
<td>Gram +ve rods</td>
<td>S</td>
</tr>
<tr>
<td>3m TSB</td>
<td>Gram +ve cocci in bunches</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Gram +ve cocci</td>
<td>N.B.G.</td>
</tr>
<tr>
<td>4m TSB</td>
<td>Gram +ve cocci</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Gram +ve rods</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Gram +ve rods</td>
<td>R</td>
</tr>
<tr>
<td>Thio</td>
<td>Gram +ve cocci</td>
<td>N.B.G.</td>
</tr>
<tr>
<td>7m TSB</td>
<td>Gram +ve cocci chains</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Gram +ve cocci in bunches</td>
<td>R</td>
</tr>
<tr>
<td>Thio</td>
<td>Gram +ve cocci in chains</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Gram +ve cocci</td>
<td>S</td>
</tr>
<tr>
<td>26 m TSB</td>
<td>Gram +ve cocci</td>
<td>S</td>
</tr>
<tr>
<td>Thio</td>
<td>Gram +ve cocci</td>
<td>S</td>
</tr>
<tr>
<td>28 m TSB</td>
<td>Gram +ve cocci in bunches</td>
<td>S</td>
</tr>
<tr>
<td>Thio</td>
<td>Gram +ve cocci</td>
<td>S</td>
</tr>
<tr>
<td>29 m TSB</td>
<td>Gram +ve cocci in bunches</td>
<td>S</td>
</tr>
<tr>
<td>Thio</td>
<td>Gram +ve cocci in chains</td>
<td>S</td>
</tr>
</tbody>
</table>

S = Sensitive  R = Resistant  N.B.G. = No Bacterial Growth
Biochemistry  (Appendix 12 and Figure 9)

There was a marked increase in plasma urea, SGPT and bilirubin initially in all animals, and a decrease in Ca++ and K+. These were followed later in the study by increases in γGT, GLDH and CPK, also LAP in Nos. 12 and 26.

Urinalysis  (Appendix 13 and Figure 9)

Forty-eight hours after dosing there was a drop in pH in most animals, and most animals had polyuria at 24 hours followed by oliguria at 48 hours (Urinary volumes and paraquat levels are shown in Table II). The majority of animals also had glycosuria and haematuria, with increased urinary protein levels.
FIGURE 9

Mean changes in blood and urine parameters from all orally dosed animals

The 6 columns shown for each test represent the following:
Column 1: (hatched at base) mean values from 19 untreated cynomolgus monkeys, tested on one occasion.
Column 2: Pre-exposure levels of test animals
Column 3: 24 hours after dosing
Column 4: 48 hours after dosing
Column 5: 7 days after dosing
Column 6: Pre-terminal levels
Standard Error bars are shown
<table>
<thead>
<tr>
<th>Group</th>
<th>Monkey No.</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIm</td>
<td>14</td>
<td>Died/killed 31.7.74 Stored overnight 4°C. Good bodily condition. Liver: Moderate lobar swelling. Marked generalized pallor. Lung: Generalized congestion. Dorsal aspect of lobes most severely affected (possibly post-mortem effect) Right posterior lobe, posterior border adherent to diaphragm. Stomach: Fundic region, a single area of mucosal haemorrhage (6 x 3 mm).</td>
</tr>
<tr>
<td>IIIm</td>
<td>26</td>
<td>P.M. 1 hour after death. Lung: Scattered punctate areas of congestion. Stomach: Glandular region, mucosal surface, a pale raised area (6 mm diam). Tongue: Occasional dark areas (up to 7 mm diam).</td>
</tr>
<tr>
<td>IIIIm</td>
<td>28</td>
<td>Intestinal mesentery: Containing 7 parasites (7 m x 2 mm) Portions of small intestine adherent to right abdominal wall. Lung: Right posterior lobe, minimally adherent to parietal pleura. Left posterior lobe, minimally adherent to diaphragm. Right lobes, minimally adherent to each other. Lung: Left lobes, minimally adherent to parietal pleura. All lobes, multiple dark punctate foci. Portions of small intestine adherent to right abdominal wall. Intestinal mesentery: Containing parasites (7 x 2 mm). Stomach: Gastric/oesophageal junction, a raised pale mass (10 mm diam). Small intestine: A band of haemorrhage over the 30 mm section.</td>
</tr>
<tr>
<td>Group</td>
<td>Monkey No.</td>
<td>Observations</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>IVm</td>
<td>3</td>
<td>Lung: azygos lobe, an area of consolidation (10 x 15 mm), right anterior lobe, a subpleural fissure (20 x 2 mm). Intestinal mesentery: a haemorrhagic nodule (12 mm diam). Cut surface: white caseous material. Kidneys: minimal bilateral uniform pallor. Left kidney periphery of pelvis, a white band (2 mm diam).</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Lung: generalized congestion. Right posterior lobe, adherent to parietal pleura and diaphragm.</td>
</tr>
</tbody>
</table>
DISCUSSION

Intravenously dosed animals

Paraquat is found to be highly toxic when administered intravenously at the dose levels used in this study. There was some relationship between dose levels and death rate in that the high dose animals tended to become ill the most rapidly, while one low dose animal (No. 9) survived for 9 days, and an animal dosed with 6 mg.kg\(^{-1}\) showed no adverse symptoms. However an animal later given 10 mg.kg\(^{-1}\) was extremely susceptible, and died within 2 days.

From the results of the tests performed it is clear that in the initial stages the kidney is the most seriously affected target organ, and that the lung and possibly the liver are affected later. Analysis of blood and urine samples indicates that all the animals were suffering from acute renal failure by 48 hours after dosing, and exhibited the following symptoms:

- high plasma urea in all animals,
- high serum potassium in 6, 8 and 16,
- high SGPT levels in all animals,
- increased clotting times in 1, 6, 8 and 10,
- low serum calcium in 1, 6, 8, 9 and 10.
- Glucose and reducing substances in the urine of all animals.
- Oliguria in all animals except No. 1.
- Low blood and urine pH in all animals except No. 8.
- Blood pigments in the urines of 2, 6, 8 and 16.

These were accompanied by the presence of the following secondary symptoms:

- ammoniacoal odour due to bacterial breakdown of salivary urea.
- Hyperventilation due to acid-base disturbance,
- Tall sharply peaked T-waves in the ECG (possibly due to hyperkalemia).
- Lethargy, vomiting and muscular twitch.
- Pale kidneys.

For the first night after dosing, urine production was increased but the blood sample taken 15 hours after dosing showed already elevated plasma urea levels. It seems likely that this may have been due to excessive production of urea rather than a failure of the kidney to eliminate it. At 48 hours most animals had excreted small amounts of urine (virtual anuria in the case of 3 animals) and this was accompanied by a further considerable increase in plasma urea levels (Figure 6 and Appendix 13).

Pulmonary function tests.

The lung function tests and blood gas analyses were difficult to perform because of the poor health of the animals after dosing, and could only be carried out in a few cases. Blood gas data were influenced by 3 factors; stress, renally induced acidosis and direct lung damage.

The stress factor affects the results because when animals are restrained and an arterial blood sample is removed they tend to struggle and hyperventilate causing low PCO\(_2\) and high PO\(_2\) values, accompanied by transitory metabolic acidosis.
The second cause of metabolic acidosis is the failure of the kidney to maintain a normal acid-base balance. This leads to an excessive production of CO₂, as the acid is buffered by the blood bicarbonate, giving a high blood PCO₂ which in turn causes hyperventilation resulting in a high PO₂. This occurred in all animals at 48 hours, the symptoms produced depending upon the severity of the acidosis, and there was some relationship between the dose levels of paraquat and the degree of response. For the high dose animal (No. 1), this led to a very low pH and bicarbonate concentration, but a low PCO₂ and little evidence of hyperventilation. Both of the Group II animals showed the classical response in that the PCO₂ was raised due to the buffering action of bicarbonate, and the PO₂ was very high, indicating a considerable degree of hyperventilation. The Group III animals showed signs of mild acidosis, in that the PO₂ was elevated slightly, and the pH slightly acidic, but normal PO₂ values gave little evidence of hyperventilation. The Group IV animal (No. 16) appeared to be highly susceptible to paraquat, and although it received a low dose of 10 mg.kg⁻¹ it behaved like a high dose animal, with a very low pH and a very high PO₂. (Appendix 10).

The nitrogen washout and lung mechanics tests results indicate that apart from the metabolic/renal effects on respiration there was also some direct lung damage. The increased CVT - 2% N₂ from the nitrogen washout tests of 6,9 and 10 at 44 hours shows that ventilation was impaired at this stage. No. 9 which was tested on 3 occasions (Figure 5) shows some improvement in ventilation after 44 hours, but the further impairment of lung function can be deduced by comparing the PO₂ of the pre-exposure and pre-terminal blood samples with RMVs' from the washout tests done on the same days. When the pre-exposure RMV was 2000 ml, the PO₂ was 108.7 mm Hg, while pre-terminally when the RMV was 2800 ml, the PO₂ was only 90.4 mm Hg.

This lung damage may be partly due to oedema caused by the renal failure, and partly due to the direct effect on the lung of paraquat. It seems likely that the poor condition of No. 9 after 8 days, when it had apparently overcome the renal symptoms, and the congestion and consolidation of the lung in most animals when examined after death, must be due to paraquat. In No. 9, where the paraquat had longer to work, the lungs were more severely damaged than in the other animals, and the fall in dynamic lung compliance suggests that they had become mechanically 'stiffened'.

T-wave abnormalities were detected in several cases, and notched P waves were recorded from No. 1. The very high creatine phosphokinase level in No. 16 may be indicative of myocardial or general muscular damage.

Orally dosed animals

In general the symptoms shown by the orally dosed animals were similar to those of the intravenously dosed groups, but less severe. The majority of animals had increased urine production and evidence of kidney damage within 24 hours, followed by oliguria or anuria at 48 hours. By this time they had the same symptoms of renal failure as the intravenously dosed animals, namely: high blood urea, high SGPT, low urine pH, glycosuria, low Ca²⁺ and increased clotting times. However the urea was not as high as in the i.v. animals and severe metabolic acidosis was detected in only one animal (No. 26), which had the low pH and high PO₂ characteristic of the i.v. groups at 48 hours.
Of the 8 animals on which lung function tests were performed, early changes were detected in 3 animals, the high dose group Nos 14 and 26 and a low dose animal No. 12. These then died at 2, 8, and 7 days respectively, 12 and 26 having low P\textsubscript{2}O\textsubscript{2} pre-terminally. For the other animals, all of which survived the test period, the most severe lung symptoms tended to occur after 7 days. It seems likely that all the animals went through a renal crisis at 48 hours, when No. 14 died, while paraquat-induced lung damage increased progressively, leading to the deaths of 12 and 26 and lung function impairment in the other animals at 7 - 15 days.

There was evidence of liver damage from the raised levels of Gamma GT and GLDH in all animals, especially in Nos. 12 and 26, where LAP values were also increased. The very high CPK levels and T-wave abnormalities may indicate heart damage (Figure 9).

Considering the results from all the orally dosed animals, the relationship between the dose of paraquat and survival time does not appear to be a simple one, and it is not possible to make definitive statements on the basis of the small number of animals used in this study. However, two kinds of positive correlation do seem to be emerging. Firstly, there is a relationship between the dose administered and the death rate (Figure 7), in that from groups of 6 animals 5 died at 85 mg.kg\textsuperscript{-1}, 3 at 65 mg.kg\textsuperscript{-1}, and 1 at 45 mg.kg\textsuperscript{-1}. Secondly, there appears to be some correlation between the amount of paraquat excreted and the death rate for any particular dose level. It is therefore possible that animals which fail to excrete large amounts of paraquat have not absorbed all of the administered dose, and that this may account for the survival of some of the animals in the high and medium dose groups. This is supported by the fact that only one of the animals which vomited overnight after dosing (No. 22) subsequently died, and this was after 15 days. However, some paraquat must be absorbed fairly quickly, since No. 28, although it was sick 10 minutes after dosing, and other animals which were sick and had diarrhoea 3 - 4 hours after dosing all showed some symptoms of poisoning, in terms of abnormal values in their blood biochemistry.

A further complication is that the substance appears to cause both an acute and a sub-acute phase of toxicity. The acute phase reaches a peak at between 2 and 4 days when 6 of the 16 animals died, and when all the animals on ICI/50 showed blood and lung function changes. This is also the period when most of the i.v. dosed animals died, and is probably due to acute renal failure and general toxicosis. Animals surviving this period usually exhibit less severe symptoms for the next few days and then either go on to recover following a bout of increased lung dysfunction or die between 7 and 15 days, as did 3 orally dosed animals and 1 i. v. dosed animal. Unfortunately, this later phase is the one where we expect to see the development of pulmonary fibrosis, and the one we are trying to induce. It is possible that it will be difficult to find a dose which will reliably induce the second phase in a large proportion of animals without killing most of them during the primary phase.

Whether or not animals die from acute renal failure, or survive long enough to succumb to the later lung damage, may well depend upon the dosing regime employed. The animals in this study were dosed 23 hours after being fed in the case of ICI/50, and 18 hours after being fed for ICI/52; they have been observed to eat as soon as they are fed, and during observations at night and during the early part of the day, they have rarely been seen to feed at other times. Their stomachs were therefore probably empty when they were dosed, and since the dose was contained in 40 ml of water a large amount of paraquat is probably absorbed quickly. This would have provided a high blood level of paraquat for a relatively short time, sufficient to cause the severe renal damage.

Since it is now known that paraquat is taken up actively by the lung from low blood concentrations, it is likely that if food was included with the dose to slow down absorption, it would be possible to induce lung lesions without first causing fatal renal damage. This is supported by the fact that of the 3 monkeys surviving 65 mg.kg\textsuperscript{-1} of paraquat, 2 received a small amount of ‘Complan’ with the dose.
REFERENCES


APPENDIX 1

Clinical signs - i.v. dosed animal (ICI/40)

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal No.</th>
<th>Dose 32 mg.kg⁻¹</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/6/74</td>
<td>34</td>
<td>ml</td>
<td>Good, wt. 41.50</td>
<td></td>
<td>* Slightly high total protein, K⁺, Na⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average food consumption 250 g.day⁻¹</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test period – Dosed 17/6/74</th>
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</tr>
</thead>
<tbody>
<tr>
<td>17/6</td>
<td>0</td>
</tr>
<tr>
<td>18/6</td>
<td>1</td>
</tr>
<tr>
<td>19/6</td>
<td>2</td>
</tr>
</tbody>
</table>

Autopsy: moderate lung congestion, pallid liver, pallid kidneys, large discoloured spleen, gaseous distension of gut.
(N.B. Food consumption figures refer to previous night's intake). * all animals showed these symptoms pre-exposure.
## Appendix 1
(continued)

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td>Good, wt. 4600 g.</td>
<td>Slightly raised urea, total protein, Na⁺, K⁺</td>
<td>Normal</td>
</tr>
<tr>
<td>11/6/74</td>
<td>25 ml</td>
<td></td>
<td>Average food consumption 223 g. day⁻¹</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test period - Dosed 17/6/74**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/6</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/6</td>
<td>1</td>
<td>105 ml, 95 mg.pqt. Glucose, blood pigments</td>
<td>Lethargic, ammoniacal odour, oily secretions on body fur. Food consumed 35 g.</td>
<td>High urea, SGPT, bilirubin. (No gas data)</td>
<td>(No data)</td>
</tr>
<tr>
<td>19/6</td>
<td>2</td>
<td>2 ml Glucose, reducing subs. Blood pigments, low pH</td>
<td>Died during previous night. Food consumed 40 g.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Autopsy:**
Moderate lung congestion, pallid liver and kidneys.
APPENDIX 1
(continued)

Group II  Animal No. 6  Dose 24 mg/kg

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General conditions</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/6/74</td>
<td>0</td>
<td>19 ml</td>
<td>Good, wt 3400g, Average daily food consumption 228 g.</td>
<td>Slightly raised total protein, SGPT,</td>
<td>Normal</td>
</tr>
<tr>
<td>Test period - Dosed 17/6/74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17/6</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/6</td>
<td>1</td>
<td>165 ml, 74 mg, pqt. Blood pigments</td>
<td>Food consumed, 80 g; lethargic,</td>
<td>High urea, SGPT.</td>
<td></td>
</tr>
<tr>
<td>19/6</td>
<td>2</td>
<td>1 ml</td>
<td>reducing subs, glucose, blood pigments low pH and α cells</td>
<td>Food consumed 35 g., in extremis hyperventilation, hypothermia, sporadic pulse, killed 11.30 hrs. ECG - T-waves abnormal and inverted abnormal-shaped P-waves.</td>
<td>High prothrombin index, urea, SGPT, LAP, K⁺, PO₂ low pH, and Ca²⁺</td>
</tr>
</tbody>
</table>

Autopsy: Lung congestion/consolidation, pallid liver and kidneys, moderate gaseous distension of gut.
### APPENDIX 1

(continued)

**Group II Animal No. 8 Dose 24 mg.kg⁻¹**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/6/74</td>
<td>60 ml</td>
<td>Good, wt 3850 g, Average daily food consumption 223 g.</td>
<td>Slightly raised urea, total protein, Na⁺ K⁺</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

**Test period – Dosed 17/6/74**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/6</td>
<td>0</td>
<td></td>
<td>Food consumed 220 g. 2 hours after dosing, lethargic, lying on bottom of cage, not eating.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/6</td>
<td>1</td>
<td>55 ml. 41 mg, ppt. Reducing subs., glucose blood pigments</td>
<td>Food consumed, 210 g, vomited overnight, lethargic. 26 hrs after dosing, in extremis, hyperventilation, hypothermia, prolapsed anus, pupil constriction, reflex intact but random eye movements, no blink reflex, cornea drying out and becoming opaque, killed 18.00 hrs. ECG - T-wave abnormalities.</td>
<td>Slightly raised prothrombin time, high urea, SGPT, LAP, bilirubin K⁺, PO₂ low pH, Ca²⁺</td>
<td>(No data)</td>
</tr>
</tbody>
</table>

**Autopsy:** Lungs slightly oedematous, frothy exudate in trachea, pallid liver and kidneys, gaseous distension of gut.
### APPENDIX 1

(continued)

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/6/74</td>
<td>17 ml</td>
<td>Good, wt 3400 g, Average daily food consumption 210 g.</td>
<td>Slightly raised total protein, K⁺, Na⁺, pH.</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

**Test period - Dosed 17/6/74**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/6/74</td>
<td>0</td>
<td></td>
<td>Food consumed 245 g. 2 hours after dosing, no symptoms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/9</td>
<td>1</td>
<td>605 ml, 17 mg pqt. trace of reducing subs.</td>
<td>Active, food eaten 170 g, but vomited overnight.</td>
<td>Slightly raised urea, Na⁺.</td>
<td></td>
</tr>
<tr>
<td>19/9</td>
<td>2</td>
<td>33 ml, tr. pqt. trace of reducing subs., glucose, low pH</td>
<td>Food consumed, 105 g, active,</td>
<td>High WBC, urea PCO₂ low Ca²⁺, pH.</td>
<td>Long N₂ washout time high RR, low VT. Low compliance.</td>
</tr>
<tr>
<td>20/9</td>
<td>3</td>
<td>46 ml trace pqt.</td>
<td>Less active, hyperventilation, food consumed 85 g. 300 g wt. loss.</td>
<td>pH, normal: PCO₂ lower.</td>
<td></td>
</tr>
<tr>
<td>21/9</td>
<td>4</td>
<td>98 ml no pqt.</td>
<td>Slight recovery. Food consumed, fruit only but double measure - 140 g.</td>
<td></td>
<td>Long N₂ washout time, high RR, low VT, but symptoms less severe than previously.</td>
</tr>
<tr>
<td>22/9</td>
<td>5</td>
<td>50 ml approx.</td>
<td>Active, but occasional coughing, hypothermic and shivering, hyperventilation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 1
(continued)

Group III  Animal No. 9 (cont) Dose 16 mg kg⁻¹

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>23/9</td>
<td>6</td>
<td>50 ml approx.</td>
<td>From this day onward lethargic, but condition appears slightly improved, however exhausted by stress of lung tests on day 8, and died after being bled on day 9.</td>
<td>Low PO₂.</td>
<td>Long N₂ washout time, high RR, low VT. compliance further reduced.</td>
</tr>
<tr>
<td>24/6</td>
<td>7</td>
<td>50 ml approx.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25/6</td>
<td>8</td>
<td>150 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26/6</td>
<td>9</td>
<td>113 ml glucose, reducing substances</td>
<td>wt. loss 550 g.</td>
<td>Raised ESR, retics, platelets, high urea, glucose, SGPT, K⁺ CPK, low Ca²⁺, PCV Hb, RBC, WBC.</td>
<td></td>
</tr>
</tbody>
</table>

Autopsy: Lungs; gross consolidation and congestion, kidneys and liver pallid, heart enlarged with bubbles of gas in pericardium stomach distended with gas.
### APPENDIX 1
(continued)

**Group III  Animal No. 10  Dose 16 mg.kg⁻¹**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 11/6/74 |     | 136 ml | Good, wt. 3650 g.  
Average daily food consumption 215 g. | Slightly raised total protein, K⁺ | Normal |

**Test period - Dosed 17/6/74**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung ventilation</th>
</tr>
</thead>
</table>
| 17/6 | 0   |       | Food consumed 190 g.  
No symptoms, eating |       |                 |
| 18/6 | 1   | 85 ml 44 mg ppt.  
Reducing subs.  
glucose lowered pH | Food consumed 190 g.  
Lethargic, vomited overnight. | Raised urea. |                 |
| 19/6 | 2   | 57 ml trace ppt.  
Reducing subs.  
glucose low pH | Lethargic, ammoniacal odour, food consumed 30 g. | Slightly raised PTI, high urea,  
SGPT, LAP, PCO₂, low Ca⁺  
pH. | Long N₂ washout time,  
low VT, raised RR, CVT. |
| 20/6 | 3   | 43 ml no ppt. | Lethargic, eyes 'glazed'; sporadic nystagmus,  
hyperventilation, hypothermia, died during  
lung function test at 18:00 hours. Food  
consumed 30 g. Wt. loss 350 g. | No data. |                 |

**Autopsy:** Lungs, consolidation/congestion, kidneys and liver pallid, stomach distended with gas.
## APPENDIX 1

(continued)

**Clinical signs – i.v. dosed animals (ICl/50)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td>229 ml Glucose, Reducing subs</td>
<td>Good, wt 4500 g.</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Test period – Dosed 22/7/74**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood/Other</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/7</td>
<td>0</td>
<td></td>
<td>No symptoms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23/7</td>
<td>1</td>
<td>68 ml, 15 mg, ppt. glucose, blood pigments</td>
<td>Slightly lethargic.</td>
<td>High urea, SGPT, K⁺</td>
<td></td>
</tr>
<tr>
<td>24/7</td>
<td>2</td>
<td>61 ml trace ppt. glucose, low pH. glucose, trace of reducing subs</td>
<td>09.00 hrs., Slightly lethargic. 14.00 hrs., Very III, dyspnoea, hypothermia, low blood pressure – killed in extremis.</td>
<td>High urea, SGPT, K⁺ CPK, PO₂, low glucose, pH, PCO₂</td>
<td></td>
</tr>
</tbody>
</table>

**Autopsy:**
- Lung: consolidation and congestion
- Liver: pallid
- Kidney: pallid
## APPENDIX 2

Lung mechanics - i.v. dosed animals (ICI/40)

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal No.</th>
<th>Time</th>
<th>VT</th>
<th>RR</th>
<th>RMV</th>
<th>DEDC</th>
<th>VTP</th>
<th>CDYNL</th>
<th>RLI</th>
<th>RLE</th>
<th>RLI/RLE</th>
<th>RL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>Pre-exposure</td>
<td>55.6</td>
<td>33</td>
<td>1805</td>
<td>54</td>
<td>4.3</td>
<td>14.06</td>
<td>.011</td>
<td>.012</td>
<td></td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Too ill to test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Pre-exposure</td>
<td>49.2</td>
<td>26</td>
<td>1242</td>
<td>53</td>
<td>4.1</td>
<td>12.39</td>
<td>.023</td>
<td>.040</td>
<td>62</td>
<td>.029</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>Pre-exposure</td>
<td>48.0</td>
<td>28</td>
<td>1351</td>
<td>55</td>
<td>5.3</td>
<td>9.3</td>
<td>.035</td>
<td>.044</td>
<td>87</td>
<td>.042</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 hours</td>
<td>34.6</td>
<td>44</td>
<td>1529</td>
<td>59</td>
<td>3.5</td>
<td>10.7</td>
<td>.005</td>
<td>.005</td>
<td>132</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Anaes. Intubated)</td>
<td>20.5</td>
<td>38</td>
<td>781</td>
<td>56</td>
<td>1.4</td>
<td>15.17</td>
<td>.011</td>
<td>.012</td>
<td>100</td>
<td>.012</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Pre-exposure</td>
<td>52.9</td>
<td>19</td>
<td>977</td>
<td>53</td>
<td>3.7</td>
<td>14.60</td>
<td>.014</td>
<td>.021</td>
<td>68</td>
<td>.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Too ill to test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>Pre-exposure</td>
<td>38.3</td>
<td>33</td>
<td>1249</td>
<td>52</td>
<td>3.5</td>
<td>11.15</td>
<td>.013</td>
<td>.025</td>
<td>69</td>
<td>.016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 hours</td>
<td>25.1</td>
<td>95</td>
<td>2397</td>
<td>52</td>
<td>5.1</td>
<td>4.93</td>
<td>.010</td>
<td>.027</td>
<td>35</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 days</td>
<td>32.4</td>
<td>92</td>
<td>2976</td>
<td>55</td>
<td>10.3</td>
<td>3.20</td>
<td>.012</td>
<td>.019</td>
<td>68</td>
<td>.016</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Pre-exposure</td>
<td>45.0</td>
<td>25</td>
<td>1122</td>
<td>56</td>
<td>4.0</td>
<td>11.06</td>
<td>.010</td>
<td>.010</td>
<td>120</td>
<td>.009</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>Pre-exposure</td>
<td>39.6</td>
<td>18</td>
<td>725</td>
<td>57</td>
<td>1.1</td>
<td>36.52</td>
<td>.017</td>
<td>.025</td>
<td>70</td>
<td>.023</td>
</tr>
</tbody>
</table>
# APPENDIX 3

**Lung ventilation - i.v. dosed animals (ICI/40)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal No.</th>
<th>Time</th>
<th>VT (ml)</th>
<th>RR (min⁻¹)</th>
<th>RMV (ml.min⁻¹)</th>
<th>T-2 % (min)</th>
<th>N-2 %</th>
<th>CVT-2 % (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>Pre-exposure</td>
<td>88.9</td>
<td>33</td>
<td>2932</td>
<td>1.07</td>
<td>35</td>
<td>3108</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Died day 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-exposure</td>
<td>91.6</td>
<td>29</td>
<td>2632</td>
<td>1.84</td>
<td>53</td>
<td>4820</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>Pre-exposure</td>
<td>53.2</td>
<td>35</td>
<td>1855</td>
<td>1.75</td>
<td>61</td>
<td>3238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 hours after dosing</td>
<td>48.6</td>
<td>41</td>
<td>1995</td>
<td>2.41</td>
<td>99</td>
<td>4815</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Pre-exposure</td>
<td>59.1</td>
<td>19</td>
<td>1134</td>
<td>2.43</td>
<td>47</td>
<td>2760</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>Pre-exposure</td>
<td>68.8</td>
<td>30</td>
<td>2021</td>
<td>1.73</td>
<td>51</td>
<td>3505</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 hours after dosing</td>
<td>27.2</td>
<td>82</td>
<td>2222</td>
<td>2.63</td>
<td>216</td>
<td>5963</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 days after dosing</td>
<td>29.7</td>
<td>77</td>
<td>2287</td>
<td>1.90</td>
<td>146</td>
<td>4350</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 days after dosing</td>
<td>28.4</td>
<td>99</td>
<td>2808</td>
<td>1.68</td>
<td>167</td>
<td>4715</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Pre-exposure</td>
<td>78.8</td>
<td>22</td>
<td>1749</td>
<td>2.25</td>
<td>50</td>
<td>3940</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49 hours after dosing</td>
<td>35.8</td>
<td>38</td>
<td>1371</td>
<td>3.57</td>
<td>137</td>
<td>4875</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>Pre-exposure</td>
<td>126</td>
<td>38</td>
<td>4766</td>
<td>0.48</td>
<td>18</td>
<td>2304</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died day 2 - too ill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SYNG-PQ-02451913_R
## APPENDIX 4

**Blood gas analysis - i.v. dosed animals (ICI/40)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal No.</th>
<th>Time</th>
<th>pH</th>
<th>PCO₂ (mm Hg)</th>
<th>PO₂ (mm Hg)</th>
<th>Base excess (mEq. 1⁻¹)</th>
<th>Bicarb. conc. (mEq. 1⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>Pre-exposure</td>
<td>7.281</td>
<td>26.6</td>
<td>108.2</td>
<td>-12.9</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 hours</td>
<td>7.137</td>
<td>23.4</td>
<td>107.3</td>
<td>-20</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Pre-exposure</td>
<td>7.335</td>
<td>28.7</td>
<td>110.8</td>
<td>-9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>Pre-exposure</td>
<td>7.353</td>
<td>28.3</td>
<td>112.8</td>
<td>-8.7</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 hours</td>
<td>7.235</td>
<td>31.6</td>
<td>125.4</td>
<td>-13.0</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Pre-exposure</td>
<td>7.324</td>
<td>31.1</td>
<td>109.0</td>
<td>-9</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 hours</td>
<td>7.293</td>
<td>30.9</td>
<td>125.1</td>
<td>-10</td>
<td>12.8</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>Pre-exposure</td>
<td>7.270</td>
<td>25.9</td>
<td>108.7</td>
<td>-13.7</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 hours</td>
<td>7.297</td>
<td>39.3</td>
<td>100.0</td>
<td>-6.3</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 days</td>
<td>7.398</td>
<td>34.6</td>
<td>101.8</td>
<td>-2.3</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 days</td>
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APPENDIX 5

Haematology - i.v. dosed animals (ICI/40)

Pre-exposure

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<th>RBC 10^6 /cmm</th>
<th>Retics %</th>
<th>WBC 10^3 /cmm</th>
<th>%</th>
<th>Platelets 10^3 /cmm</th>
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24 hours after dosing

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<th>RBC 10^6 /cmm</th>
<th>Retics %</th>
<th>WBC 10^3 /cmm</th>
<th>%</th>
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### APPENDIX 5

(continued)

48 hours after dosing

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<th>Retics %</th>
<th>WBC 10^9/cmM</th>
<th>%</th>
<th>Platelets 10^9/cmM</th>
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#### Terminal

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<th>Retics %</th>
<th>WBC 10^9/cmM</th>
<th>%</th>
<th>Platelets 10^9/cmM</th>
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APPENDIX 6

Clinical chemistry – i.v. dosed animals (ICI/40)

Pre-exposure

| Animal No. | Urea mg % | Glucose mg % | Total protein g % | Serum Proteins % | SGPT mU.mL⁻¹ | LAP GR units | Bilirubin mg % | γ-GT mU.mL⁻¹ | GLDH mU.mL⁻¹ | Na⁺ mEq⁻¹ | K⁺ mEq⁻¹ | Ca²⁺ mEq⁻¹ | CPK mU.mL⁻¹ |
|------------|-----------|--------------|-------------------|------------------|--------------|--------------|---------------|---------------|--------------|-------------|-------------|-------------|-------------|----------------|
| GPI        | 41        | 80           | 10.6              | 36               | 6            | 8            | 26            | 24            | 30           | 202         | 0.2         | 159         | 6.1         | 5.6         | 30            |
| 2          | 52        | 92           | 10.2              | 43               | 6            | 10           | 34            | 7             | 48           | 100         | 0.3         | 164         | 5.7         | 5.4         | 31            |
| GP II      | 44        | 86           | 9.6               | 37               | 5            | 10           | 36            | 12            | 66           | 224         | 0.3         | 154         | 4.4         | 5.3         | 88            |
| 8          | 53        | 80           | 10.0              | 43               | 2            | 7            | 32            | 10            | 34           | 281         | 0.2         | 157         | 5.7         | 5.4         | 28            |
| GP III     | 38        | 96           | 10.0              | 40               | 6            | 10           | 34            | 10            | 23           | 279         | 0.3         | 160         | 5.7         | 5.8         | 30            |
| 10         | 30        | 90           | 10.6              | 34               | 8            | 14           | 33            | 11            | 46           | 256         | 0.2         | 150         | 5.8         | 5.4         | 25            |
| GP IV      | 44        | 84           | 8.6               | 45               | 4            | 14           | 20            | 17            | 47           | 226         | 0.3         | 22.2        | 4.5         | 147         | 5.1          | 5.7          | 346          |
| Controls   | 63        | 86           | 10.0              | 43               | 7            | 8            | 27            | 5             | 78           | 551         | 0.3         | 161         | 6.0         | 5.5         | 53            |
| 4          | 40        | 94           | 11.0              | 34               | 7            | 14           | 33            | 12            | 50           | 289         | 0.3         | 138         | 5.7         | 5.5         | 15            |
| 5          | 50        | 84           | 10.0              | 36               | 10           | 12           | 30            | 12            | 83           | 295         | 0.3         | 155         | 5.9         | 5.2         | 26            |
| 7          | 48        | 84           | 10.8              | 37               | 6            | 10           | 30            | 17            | 49           | 218         | 0.2         | 138         | 5.8         | 5.8         | 41            |
## APPENDIX 6

(continued)

### 24 hours after dosing

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<th>Serum Proteins %</th>
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<th>LAP GR units</th>
<th>Bilirubin mg %</th>
<th>γGT mU·mL⁻¹</th>
<th>GLDH mU·mL⁻¹</th>
<th>Na⁺ mEq L⁻¹</th>
<th>K⁺ mEq L⁻¹</th>
<th>Ca²⁺ mEq L⁻¹</th>
<th>CPK mEq L⁻¹</th>
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### APPENDIX 6

(continued)

48 hours after dosing

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<th>Urea mg %</th>
<th>Glucose mg %</th>
<th>Total protein g %</th>
<th>Serum Proteins %</th>
<th>SGPT mU, ml⁻¹</th>
<th>LAP GR units</th>
<th>Bilirubin mg %</th>
<th>γGT mU, ml⁻¹</th>
<th>GLDH mU, ml⁻¹</th>
<th>Na⁺ mEq l⁻¹</th>
<th>K⁺ mEq l⁻¹</th>
<th>Ca²⁺ mEq l⁻¹</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>GPIII 9</td>
<td>102</td>
<td>78</td>
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<td>48 4 10 30 8 36 260</td>
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<tr>
<td>GPIV 16</td>
<td>196</td>
<td>32</td>
<td>8.5</td>
<td>x</td>
<td>x</td>
<td>217</td>
<td>148</td>
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<td>2.9</td>
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</tr>
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<td>Control</td>
<td>44</td>
<td>180</td>
<td>7.3</td>
<td>56 2 4 25 13 55 398</td>
<td>0.1</td>
<td>155</td>
<td>4.9</td>
<td>5.3</td>
<td>41</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>86</td>
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<td>42 4 10 34 10 37 287</td>
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<td>154</td>
<td>5.5</td>
<td>5.8</td>
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<td>42</td>
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<td>51 3 10 25 11 41 298</td>
<td>0.1</td>
<td>154</td>
<td>5.9</td>
<td>5.0</td>
<td>19</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>76</td>
<td>7.5</td>
<td>52 4 8 22 14 41 290</td>
<td>0.1</td>
<td>154</td>
<td>6.1</td>
<td>5.6</td>
<td>27</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = Terminal
## APPENDIX 6

(continued)

Pre-terminal

| Animal No. | Urea mg % | Glucose mg % | Total protein mg % | Serum Proteins % | SGPT units | LAP units | Bilirubin mg % | GT mU.m⁻¹.l⁻¹ | GLDH mU.m⁻¹ | Na⁺ mEq.l⁻¹ | K⁺ mEq.l⁻¹ | Ca²⁺ mEq.l⁻¹ | CPK mEq.l⁻¹ |
|------------|-----------|--------------|--------------------|------------------|-------------|-----------|----------------|----------------|-------------|-------------|-------------|-------------|-------------|-------------|
| GPIII 9    | 89        | 111          | 6.8                | 40               | 4           | 8         | 35             | 13             | 60          | 170         | 0.3         | 144         | 6.4         | 3.1         | 1651         |
| GPIV 16    | 224       |              | 8.5                | 40               | 6           | 11        | 30             | 13             | 687         | 242         | 0.4         | 178         | 9.8         | 5.7         | 1434         |
APPENDIX 7

Urinalysis - i. v. animals (ICI/40)

Pre-exposure

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal No.</th>
<th>pH</th>
<th>Volume mls</th>
<th>SG</th>
<th>Protein mg%</th>
<th>Total red subs</th>
<th>Glucose</th>
<th>Ketones</th>
<th>Bile pigments</th>
<th>Urobilinogen</th>
<th>Blood pigments</th>
<th>Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPI</td>
<td>1</td>
<td>7.6</td>
<td>34</td>
<td>1030</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td></td>
<td>2</td>
<td>6.6</td>
<td>25</td>
<td>1035</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>GP II</td>
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<td>19</td>
<td>1042</td>
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<td>0</td>
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<td>0</td>
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<td>GPIII</td>
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<td>6.0</td>
<td>17</td>
<td>1036</td>
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<td>0</td>
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<td></td>
<td>10</td>
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<td>136</td>
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<td>+</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>GP IV</td>
<td>16</td>
<td>7.5</td>
<td>229</td>
<td>1020</td>
<td>+++</td>
<td>+</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0 0 1 0 0</td>
</tr>
</tbody>
</table>

Microscopy:
- E: Erythrocytes
- P: Pigments
- M: Melanin
- R: Red Blood Cells
- O: Other
- C: Casts
- A: Amorphous
APPENDIX 7
(continued)

24 hours after dosing

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal No.</th>
<th>pH</th>
<th>Volume mls</th>
<th>SG</th>
<th>Protein mg %</th>
<th>Total red subs</th>
<th>Glucose</th>
<th>Ketones</th>
<th>Bile pigments</th>
<th>Urobilinogen</th>
<th>Blood pigments</th>
<th>Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP I</td>
<td>1</td>
<td>6.1</td>
<td>340</td>
<td>1020</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7.9</td>
<td>100</td>
<td>1020</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP II</td>
<td>6</td>
<td>8.0</td>
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<td>0</td>
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<td>8</td>
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<td>520</td>
<td>1031</td>
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<td>+++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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<td>GP III</td>
<td>9</td>
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<td>580</td>
<td>1005</td>
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</tr>
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<td>+</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP IV</td>
<td>16</td>
<td>8.3</td>
<td>47</td>
<td>1025</td>
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<td>+</td>
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tr = trace
# APPENDIX 7

(continued)

48 hours after dosing

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<th>pH</th>
<th>Volume mls</th>
<th>SG</th>
<th>Protein mg %</th>
<th>Total red subs</th>
<th>Glucose</th>
<th>Ketones</th>
<th>Bile pigments</th>
<th>Urobilinogen</th>
<th>Blood pigments</th>
<th>Microscopy</th>
</tr>
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<tbody>
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<td>GP I</td>
<td>1</td>
<td>5.4</td>
<td>7.4</td>
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<td>10</td>
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<td>0</td>
<td>0 1 0 0 0 3 0 0</td>
</tr>
<tr>
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<td>2</td>
<td>5.7</td>
<td>3.6</td>
<td>1020</td>
<td>20</td>
<td>tr</td>
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<td>0</td>
<td>0</td>
<td>+</td>
<td>0 0 0 0 2 0 0</td>
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<tr>
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<td>10</td>
<td>+++</td>
<td>+</td>
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<td>0</td>
<td>+</td>
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<td>8</td>
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<td>0.2</td>
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<td>0</td>
<td>+</td>
<td>0 0 0 0 2 0 0</td>
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<td>4.9</td>
<td>1040</td>
<td>20</td>
<td>+++</td>
<td>+</td>
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<td>0</td>
<td>0</td>
<td>0 2 0 0 2 0 0</td>
</tr>
<tr>
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<td>6.7</td>
<td>4.8</td>
<td>1025</td>
<td>10</td>
<td>tr</td>
<td>+</td>
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*tr = trace*
APPENDIX 7

(continued)

Pre-terminal (8 days)

<table>
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<th>Group</th>
<th>Animal No.</th>
<th>pH</th>
<th>Volumes mls</th>
<th>SG</th>
<th>Protein mg %</th>
<th>Total red subs</th>
<th>Glucose</th>
<th>Ketones</th>
<th>Bile pigments</th>
<th>Urobilinogen</th>
<th>Blood pigments</th>
<th>Microscopy</th>
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<tr>
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<td>110</td>
<td>1025</td>
<td>0</td>
<td>++</td>
<td>++</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>E 0 P 0 M 0 R 0 O 0 C 2 A 0</td>
</tr>
</tbody>
</table>
**APPENDIX B**

Clinical signs - orally dosed animal (ICI/50)

Group 1  Animal No. 14  Dose 85 mg.kg⁻¹

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine (ml)</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td>156</td>
<td>Good, wt. 5300 g. Average food consumption 230 day g</td>
<td>Low pH, high gamma GT.</td>
<td>Good.</td>
</tr>
<tr>
<td>18/7/74</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test Period. Dosed 29/7/74 15.00 hrs.**

<table>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30/7</td>
<td>1</td>
<td>420. 403 mg.ppt. glucose, blood pigments.</td>
<td>Healthy.</td>
<td>High urea, SGPT, gamma GT at pre-exposure value.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31/7</td>
<td>2</td>
<td>290. 4.mg ppt.</td>
<td>Weak, diarrhoea. Collapsed and was killed at 17.00 hrs.</td>
<td>High urea, SGPT, CPK, K⁺, low gammaGT, pH.</td>
<td>Hyperventilation, long washout time.</td>
<td></td>
</tr>
</tbody>
</table>

**Autopsy: Lung: Generalized congestion, Liver: Swollen, generalized pallor, Kidney: Normal**
APPENDIX 8

(continued)

Group 1. Animal No. 26  Dose 85 mg. kg⁻¹

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td>Good, wt. 5000 g. Average daily food consumption 213 g</td>
<td>Slightly high SGPT, K⁺,</td>
<td>Normal</td>
</tr>
<tr>
<td>30/7/74</td>
<td>44</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Test Period. Dosed 31/7/74

<table>
<thead>
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<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/8</td>
<td>1</td>
<td>70 25 mg.pqt. glucose</td>
<td>Diarrhoea.</td>
<td>High glucose, SGPT, CPK.</td>
<td></td>
</tr>
<tr>
<td>3/8</td>
<td>3</td>
<td>65</td>
<td>Ibid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/8</td>
<td>4</td>
<td>65</td>
<td>Ibid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/8</td>
<td>5</td>
<td>0</td>
<td>Diarrhoea, lethargic.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/8</td>
<td>6</td>
<td>48</td>
<td>Lethargic, mucus secretion from nose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/8</td>
<td>7</td>
<td>Low pH blood pigments</td>
<td>Oily secretions on body fur. Dyspnoea, lethargic.</td>
<td>High urea, glucose, SGPT, LAP, low Ca²⁺.</td>
<td>Improved washout time.</td>
</tr>
<tr>
<td>8/8</td>
<td>8.</td>
<td>65</td>
<td>Died 14.00 hrs. wt 4800 g</td>
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<td></td>
</tr>
</tbody>
</table>

Autopsy: Lung: Scattered areas of congestion.
APPENDIX 8
(continued)

Group II  Animal No. 4  Dose  65 mg.kg⁻¹

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/7/74</td>
<td>40 ml</td>
<td>Good, wt. 3750 g. Average daily food consumption 173 g.</td>
<td>High platelet count, low pH, low PO₂⁻</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Test period. Dosed 15.00 hours 15/7/74</td>
<td></td>
<td>Dose mixed with approximately 5 g 'Complan' during administration. Regurgitated approximately 1 ml of fluid during dosing.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/7/74</td>
<td>1</td>
<td>70 18 mg. ppt. glucose, blood pigments.</td>
<td>Healthy, active, diarrhoea and some vomiting during night.</td>
<td>High SGPT, low K⁺</td>
<td></td>
</tr>
<tr>
<td>17/7</td>
<td>2</td>
<td>100 2.4 mg. ppt.</td>
<td>Ammoniacal odour of breath.</td>
<td>High urea, high SGPT, low K⁺</td>
<td>Long N2 washout time</td>
</tr>
<tr>
<td>18/7</td>
<td>3</td>
<td>226 3.6 mg ppt.</td>
<td>Ammoniacal odour, oily secretions on body fur.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19/7</td>
<td>4</td>
<td>55 1.3 mg ppt.</td>
<td>Ammoniacal odour.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/7</td>
<td>5</td>
<td>61 0 mg ppt.</td>
<td>Ibid. Diarrhoea, wt loss 250 g.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21/7</td>
<td>6</td>
<td>61</td>
<td>Ibid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22/7</td>
<td>7</td>
<td>61</td>
<td>Ibid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/7</td>
<td></td>
<td>Wt. loss 50 g - 2/8/74 wt. gain 100 g.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The animal had diarrhoea until 2/8/74, and increased apocrine and sebaceous secretions, after which it recovered. Slight drop in food consumption during first week. Terminal wt. 3650 g.

7/8

Terminal test:
Autopsy: Lung, liver and kidney normal.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>High urea</th>
<th>Long washout time, high CVt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Day</td>
<td>Urine</td>
<td>General condition</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>-------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>12/7/74</td>
<td>Pre-exposure</td>
<td>134</td>
<td>Good, wt, 3950g, Average daily food consumption 248 g</td>
</tr>
<tr>
<td>Test period</td>
<td>Dosed</td>
<td>15:00 hrs</td>
<td>15/7/74</td>
</tr>
<tr>
<td>16/7</td>
<td>1</td>
<td>104 35 mg.pqt.</td>
<td>Healthy, active, slight shivering, diarrhoea.</td>
</tr>
<tr>
<td>17/7</td>
<td>2</td>
<td>176 6.9 mg.pqt. Blood pigments in urine, day 1 and 2</td>
<td>Ammoniacal odour.</td>
</tr>
<tr>
<td>18/7</td>
<td>3</td>
<td>224 trace ppt.</td>
<td>Diarrhoea, low food consumption.</td>
</tr>
<tr>
<td>19/7</td>
<td>4</td>
<td>108 no ppt.</td>
<td>Diarrhoea, normal food consumption, ammoniacal odour.</td>
</tr>
<tr>
<td>20/7</td>
<td>5</td>
<td>71</td>
<td>Oily secretions on body fur. Diarrhoea no wt.loss.</td>
</tr>
<tr>
<td>21/7</td>
<td>6</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>22/7</td>
<td>7</td>
<td>71</td>
<td>Ibid.</td>
</tr>
<tr>
<td>30/7</td>
<td>15</td>
<td>56</td>
<td>Diarrhoea still, wt. loss 200 g</td>
</tr>
<tr>
<td>5/8</td>
<td>24</td>
<td></td>
<td>Solid stools.</td>
</tr>
<tr>
<td>Sacrificed on 8/8/74 terminal wt, 3850 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy: Tongue: Occasional dark areas.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 8

(continued)

Group III Animal No. 28 Dose 55 mg. kg⁻¹

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/7/74</td>
<td>159</td>
<td></td>
<td>Good, wt. 4700 g, Average daily food</td>
<td>Slightly high SGPT, low pH,</td>
<td>Normal, hyperventilating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>consumption 246 g</td>
<td>PCO₂.</td>
<td></td>
</tr>
<tr>
<td>Test period. Dosed 15.00 hrs 22/7/74</td>
<td></td>
<td></td>
<td>Vomited after 10 minutes, while still</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>anaesthetised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23/7</td>
<td>1</td>
<td>704 mg</td>
<td>No symptoms</td>
<td>High urea, SGPT, bilirubin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ppt,  glucose, blood pigments</td>
<td></td>
<td>gamma GT.</td>
<td></td>
</tr>
<tr>
<td>.. 24/7</td>
<td>2</td>
<td>144 1</td>
<td>No symptoms</td>
<td>High urea, SGPT, platelets,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg ppt.</td>
<td></td>
<td>low pH, PCO₂</td>
<td></td>
</tr>
<tr>
<td>25/7</td>
<td>3</td>
<td>78</td>
<td>No symptoms</td>
<td>Normal pH, PCO₂</td>
<td></td>
</tr>
<tr>
<td>26/7</td>
<td>4</td>
<td>42</td>
<td>No symptoms</td>
<td>Slightly improved N₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no ppt.</td>
<td></td>
<td>washout</td>
<td></td>
</tr>
<tr>
<td>27/7</td>
<td>5</td>
<td>145</td>
<td>(30/7/74) wt. loss 350 g Food consumption</td>
<td>High urea, SGPT, gamma GT,</td>
<td>Washout further improved</td>
</tr>
<tr>
<td>28/7</td>
<td>6</td>
<td>145</td>
<td>halved.</td>
<td>platelets.</td>
<td></td>
</tr>
<tr>
<td>29/7</td>
<td>7</td>
<td>145</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30/7</td>
<td>8</td>
<td>88</td>
<td></td>
<td>High CPK, low pH, PCO₂</td>
<td>Washout further improved.</td>
</tr>
<tr>
<td>31/7</td>
<td>9</td>
<td>200</td>
<td></td>
<td>(2/8/74) Low pH, PCO₂</td>
<td></td>
</tr>
<tr>
<td>2/8</td>
<td>11</td>
<td>96</td>
<td>Wt. loss further 250 g</td>
<td></td>
<td>Longer washout time</td>
</tr>
<tr>
<td>7/8</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacrificed 8/8/74 terminal wt. 4150 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy:</td>
<td></td>
<td></td>
<td>Slight lung adhesions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX 8

(continued)

### Group III Animal No. 29 Dose 55 mg.kg⁻¹

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td>Poor, old animal, wt. 4000 g. Average daily food consumption 242 g</td>
<td>High glucose, SGPT, low pH.</td>
<td>Long washout time</td>
</tr>
<tr>
<td>18/7/74</td>
<td>198</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test period, Dosed 15.00 hrs 22/7/74</td>
<td></td>
<td></td>
<td>Lethargic, possibly slightly sick overnight.</td>
<td>High urea, SGPT, bilirubin, gamma GT.</td>
<td>Very long washout time</td>
</tr>
<tr>
<td>23/7 1</td>
<td>240</td>
<td>187 mg ppt. glucose, blood pigments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/7 2</td>
<td>356</td>
<td>trace ppt. low pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25/7 3</td>
<td>280</td>
<td>no ppt.</td>
<td>Lethargic.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26/7 4</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27/7 5</td>
<td>170</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/7 6</td>
<td>170</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/7 7</td>
<td>170</td>
<td>blood pigments</td>
<td>Low food consumption, wt. loss 300 g</td>
<td>High SGPT, CPK, platelets, ESR.</td>
<td>Long washout time</td>
</tr>
<tr>
<td>30/7 8</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31/7 9</td>
<td>136</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/8 10</td>
<td>240</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/8 11</td>
<td>304</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/8 16</td>
<td>Blood pigments</td>
<td>Wt. loss further 100 g, low food consumption.</td>
<td></td>
<td>High urea, gamma GT, low pH.</td>
<td>Long washout time</td>
</tr>
<tr>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Autopsy:** Multiple dark punctate foci, slight adhesions. Small intestine, a band of Haemorrhage (30 mm).

Sacrificed 8/8/74 terminal wt. 3500 g at which time animal still losing wt. very poor food consumption.
APPENDIX 8

(continued)

Group IV Animal No. 3  Dose 45 mg.kg⁻¹

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/7/74</td>
<td>50</td>
<td></td>
<td>Good, wt. 4750 g Average daily food consumption 195 g.</td>
<td>Slightly high SGPT, low pH, PCO₂</td>
<td>Good</td>
</tr>
</tbody>
</table>

Test period. Dosed 24/7/74 17.00 hours

<table>
<thead>
<tr>
<th>Date</th>
<th>Days</th>
<th>Urine</th>
<th>Test results</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>38.4 mg pqt. low pH, glucose.</td>
<td>Slight diarrhoea.</td>
<td>High urea, SGPT, CPK, low K⁺</td>
<td>Normal</td>
</tr>
<tr>
<td>27/7</td>
<td>3</td>
<td>179</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/7</td>
<td>4</td>
<td>179</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/7</td>
<td>5</td>
<td>179</td>
<td>Wt. loss 400 g. Food consumption slightly reduced.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30/7</td>
<td>6</td>
<td>112</td>
<td>Ammoniacal odour.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31/7</td>
<td>7</td>
<td>132</td>
<td>Glucose</td>
<td>High urea, glucose, CPK.</td>
<td>Increased N2 washout time</td>
</tr>
<tr>
<td>1/8</td>
<td>8</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/8</td>
<td>12</td>
<td>86</td>
<td></td>
<td></td>
<td>Washout time greatly increased</td>
</tr>
<tr>
<td>8/8</td>
<td>15</td>
<td></td>
<td>Wt. loss further 300 g</td>
<td>High urea, glucose, gamma GT, slightly raised ESR.</td>
<td>Washout time normal</td>
</tr>
<tr>
<td>9/8</td>
<td>16</td>
<td></td>
<td>Sacrificed wt. 4050 g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APPENDIX 8
(continued)

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Urine</th>
<th>General condition</th>
<th>Blood</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td>Good, wt. 4950g, Average food consumption 247 g</td>
<td>High SGPT, LAP.</td>
<td>Good</td>
</tr>
<tr>
<td>18/7/74</td>
<td>84</td>
<td>70 147 mg/pqt.</td>
<td>Green faeces</td>
<td>High urea, SGPT.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>glucose, blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pigments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25/7</td>
<td>1</td>
<td>1 trace pqt.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26/7</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27/7</td>
<td>3</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/7</td>
<td>4</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/7</td>
<td>5</td>
<td>102</td>
<td>Cough, wt. loss 350 g, food consumption halved.</td>
<td>Blood gas normal.</td>
<td>Improved washout time</td>
</tr>
<tr>
<td>30/7</td>
<td>6</td>
<td>86</td>
<td>Cough.</td>
<td>High urea, SGPT, LAP, Na⁺, K⁺ CPK, low glucose.</td>
<td></td>
</tr>
<tr>
<td>31/7</td>
<td>7</td>
<td>86 Ketones,</td>
<td>Killed in extremis wt. 4600 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Autopsy: Lung: congestion, adhesions.
### APPENDIX 8

Clinical signs - orally dosed animals (ICI/52)

**Group 1**  Dose 85 mg/kg

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Condition</th>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test period. Dosed 5/8/74 at 10.00 hrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/8/74</td>
<td>1</td>
<td>Vomited overnight.</td>
<td>Slight regurgitation of fruit, diarrhoea, Polyuria.</td>
<td>Blood in faeces, lethargic, diarrhoea at 20.00 hours</td>
</tr>
<tr>
<td>7/8</td>
<td>2</td>
<td>Diarrhoea, oliguria.</td>
<td>Diarrhoea, lethargic, dyspnoea, slight oliguria.</td>
<td>Polyuria, In extremis, killed 10.00 hours</td>
</tr>
<tr>
<td>8/8</td>
<td>3</td>
<td>Slight vomiting overnight.</td>
<td>In extremis, dyspnoea, oliguria, killed 10.00 hours.</td>
<td>Diarrhoea.</td>
</tr>
<tr>
<td>9/8 - 13/7</td>
<td></td>
<td>No further symptoms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/8</td>
<td>15</td>
<td>In extremis, dyspnoea, died.</td>
<td></td>
<td>Recovered.</td>
</tr>
</tbody>
</table>

**Autopsy.** Lungs: consolidation.

Lung: no abnormalities.
Kidney: normal.
Liver: pallid.

**Synopsis:**
- 1 death after 2 days (No. 18)
- 1 death after 3 days (No. 11)
- 1 death after 15 days (No. 22)
# APPENDIX 8

**Clinical signs - orally dosed animals (ICI/52)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>No. 21 Condition</th>
<th>No. 13 Condition</th>
<th>No. 20 Condition</th>
<th>No. 5 Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test period. Dosed 2/8/74 at 10.00 hrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/8</td>
<td>0</td>
<td>Good.</td>
<td>Diarrhoea, 17.00 hours.</td>
<td>Good.</td>
<td>Good.</td>
</tr>
<tr>
<td>5/8</td>
<td>3</td>
<td>Diarrhoea.</td>
<td>Died overnight:</td>
<td>Good.</td>
<td></td>
</tr>
<tr>
<td>6/8</td>
<td>4</td>
<td>Diarrhoea, polyuria.</td>
<td></td>
<td>Moribund killed.</td>
<td></td>
</tr>
<tr>
<td>7/8 - 13/8</td>
<td>No further symptoms.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Autopsy:**

- Lung: congestion/consolidation.  
- Gut: mesenteries swollen and fatty grey-black colouration  
- Multiple pleural adhesions to chest wall and diaphragm.  
- Kidneys: pale and enlarged.  
- Liver: pale and dark patches.

**Synopsis:**

- 1 death after 2 days (No. 5)  
- 1 death after 3 days (No. 13)  
- 1 death after 4 days (No. 20)
## APPENDIX 8
(continued)
Clinical signs - orally dosed animals (ICI/52)

**Group IV Dose 45 mg.kg\(^{-1}\)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>No. 17 Condition</th>
<th>No. 24 Condition</th>
<th>No. 25 Condition</th>
<th>No. 27 Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test period.</td>
<td>Dosed 2/8/74 at 10.00 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/8</td>
<td>1</td>
<td>Vomited overnight, poluria.</td>
<td>Good.</td>
<td>Good, poluria.</td>
<td>Slight vomiting overnight</td>
</tr>
<tr>
<td>9/8 - 12/8</td>
<td>Condition of No. 17, worsening, reached a crisis on 12/8/74 with rapid shallow breathing, requiring great effort.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/8</td>
<td>11</td>
<td>Slight recovery, sitting on perch.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Synopsis:** No deaths, one animal very ill at 11 days, then recovered.
### APPENDIX 9

Lung ventilation - orally dosed animals (ICI/50)

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal No.</th>
<th>Time</th>
<th>VT (ml)</th>
<th>RR (min⁻¹)</th>
<th>RMV (ml.min⁻¹)</th>
<th>T-2 % (min)</th>
<th>N-2 %</th>
<th>CVT-2 % (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td></td>
<td>141</td>
<td>46</td>
<td>6560</td>
<td>.44</td>
<td>20</td>
<td>2875</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td></td>
<td>88.2</td>
<td>43</td>
<td>3796</td>
<td>.77</td>
<td>33</td>
<td>2910</td>
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<tr>
<td>II</td>
<td>4</td>
<td></td>
<td>53.5</td>
<td>54</td>
<td>2875</td>
<td>.81</td>
<td>44</td>
<td>2335</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td>64.6</td>
<td>52</td>
<td>3374</td>
<td>1.01</td>
<td>53</td>
<td>3397</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
<td></td>
<td>107</td>
<td>43</td>
<td>4657</td>
<td>.84</td>
<td>36</td>
<td>3840</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td></td>
<td>60.9</td>
<td>28</td>
<td>1690</td>
<td>1.67</td>
<td>46</td>
<td>2777</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td></td>
<td>99.8</td>
<td>50</td>
<td>5033</td>
<td>.69</td>
<td>35</td>
<td>3495</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>93.0</td>
<td>59</td>
<td>5531</td>
<td>.49</td>
<td>29</td>
<td>2732</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48 hours</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>after dosing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td></td>
<td>31.1</td>
<td>81</td>
<td>2515</td>
<td>2.05</td>
<td>166</td>
<td>5165</td>
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(continued)

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## APPENDIX 10

Blood gas analyses - orally dosed animals (ICI/50)

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### APPENDIX 10

(continued)

Treatment - 48 hours after dosing

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## APPENDIX 10

(continued)

**Treatment - 4 days after dosing**

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### APPENDIX 10

(continued)

**Treatment-7 days after dosing**

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APPENDIX 10

(continued)

Treatment -12 days after dosing

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**Treatment - Pre-terminal**

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### APPENDIX 11

Haematology – orally dosed animals (ICI/50)

Pre-exposure

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(continued)

48 hours after dosing

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APPENDIX 11

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APPENDIX 12

Clinical chemistry - orally dosed animals (IC/50)

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<th>BILIRUBIN mg %</th>
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APPENDIX 12

(continued)

24 hours after dosing

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<th>Serum Proteins %</th>
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<th>GLODH mU/mL</th>
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APPENDIX 12

48 hours after dosing

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(continued)

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SYNG-PQ-02451953_R
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(continued)

**24 hours after dosing**

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**APPENDIX 13**

(continued)

1 week after dosing

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APPENDIX 13

(continued)

Terminal

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