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October 18, 1994

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Dear Sir/Madam:

I am writing to supply your office with additional information on an "EPA Information Request" form for the above referenced TSCA 8(e) file.

- 1) The recently received (10/17/94) final contract laboratory report entitled "m-TMI - Acute Inhalation Toxicity In Rats 4-Hour Exposure"
- 2) Commercial Uses - m-TMI is a

If you have any questions or require further information, please contact me at (201) 357-3375.

Sincerely,

Patricia Ann Vernon
Associate Toxicologist
Toxicology & Product Stewardship Dept.

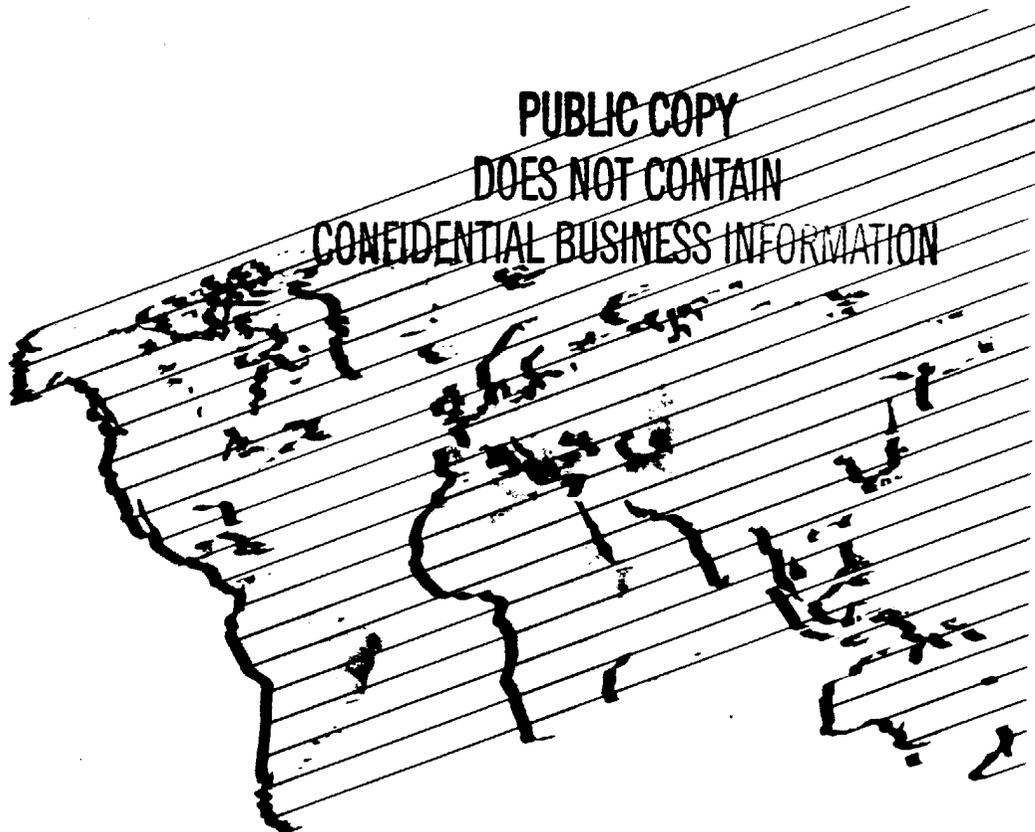
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HRC Report

m-TMI
ACUTE INHALATION TOXICITY IN RATS
4-HOUR EXPOSURE

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Research
Centre**

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m-TMI

**ACUTE INHALATION TOXICITY IN RATS
4-HOUR EXPOSURE**

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Data requirement	EPA TSCA 798.1150
HRC project identity	CTI 1
Study completed on	14 October 1994

Sponsor

Cytec Industries Inc,
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USA.

Testing facility

Huntingdon Research Centre Ltd.,
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Sponsor's representative

Patricia Ann Vernon

Study Director

Graham C. Jackson

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

This report contains the unpublished results of research sponsored by the Cytec Industries Inc. These results may not be published, either wholly or in part, or reviewed or quoted in any other publication without the prior authorisation of the Sponsor.

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

Good Laboratory Practice, The United Kingdom Compliance Programme, Department of Health & Social Security 1986 and subsequent revision, Department of Health 1989.

EC Council Directive, 87/18 EEC of 18 December 1986, (No. L 15/29).

Good Laboratory Practice in the testing of Chemicals OECD, ISBN 92-64-12367-9, Paris 1982, subsequently republished OECD Environment Monograph No. 45, 1992.

United States Environmental Protection Agency, (TSCA), Title 40 Code of Federal Regulations Part 792, Federal Register, 29 November 1983 and subsequent amendment Federal Register 17 August 1989.

G. C. Jackson

14 October 1994

Graham C. Jackson, B.A. (Hons.), L.R.S.C.,
Study Director,
Huntingdon Research Centre Ltd.

Date

QUALITY ASSURANCE STATEMENT

This report has been audited by the Huntingdon Research Centre Quality Assurance Department. The methods, practices and procedures reported herein are an accurate description of those employed at HRC during the course of the study. Observations and results presented in this final report form a true and accurate representation of the raw data generated during the conduct of the study at HRC.

Certain studies such as that described in this report, are conducted at HRC in a setting which involves frequent repetition of similar or identical procedures. At or about the time the study described in this report was in progress, 'process-based' inspections were made by the Quality Assurance Department of critical procedures relevant to this study type. The findings of these inspections were reported promptly to the Study Director and to HRC Management.

Date(s) of inspection

12 - 13 May 94

Date(s) of reporting inspection findings
to the Study Director and HRC Management

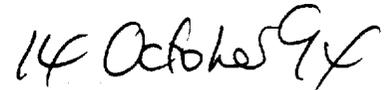
13 May 94

Date of reporting audit findings to the
Study Director and HRC Management

6 October 94



K.P. de-Salis, B.A. (Hons.), C.Biol., M.I.Biol., Dip.R.Q.A.,
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Date

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SUMMARY

Introduction

The objective of this study was to establish the acute inhalation toxicity (LC_{50}) of m-TMI to rats.

Methods

Five groups, each of 5 male and 5 female Sprague-Dawley CD rats, were exposed to a test atmosphere containing a chemically analysed concentration of m-TMI of 0.32, 0.076, 0.023, 0.050 or 0.034 mg/l. Exposure was continuous for 4 hours using a whole-body exposure system. An additional group of 5 male and 5 females acted as controls and were exposed to clean air only for 4 hours.

The rats were observed during the exposure period and for up to 14 days post exposure. The bodyweight of the surviving rats was measured daily throughout the observation period. Each rat was subjected to a *post mortem* examination.

Results

Mortality was as follows:

Group	Exposure level (mg/l)	Males	Females	Total
2	0.32	5/5	5/5	10/10
3	0.076	5/5	5/5	10/10
4	0.023	0/5	0/5	0/10
5	0.050	4/5	4/5	8/10
6	0.034	2/5	2/5	4/10

Deaths occurred between Day 1 to Day 13 of the observation period.

Clinical signs seen during exposure in all test groups were reddening of the ears and feet. In rats exposed at 0.32, 0.076 or 0.050 mg/l additional signs seen during exposure were breathing abnormalities (including irregular respiration and a reduced respiration rate or exaggerated respiratory movements) and the adoption of a hunched or prone posture. Partial closing of the eyes was seen in all rats during exposure except rats exposed at 0.023 mg/l.

Signs seen during the observation period included death, exaggerated respiratory movements, lethargy, noisy or irregular respiration, an increased respiration rate, a clear discharge from the snout, hypothermia and gasping. All female rats exposed at 0.023 mg/l were normal throughout the observation period.

The majority of decedents lost weight prior to death. Rats exposed at 0.023 mg/l had a slightly reduced bodyweight gain for 2 days after the exposure. Bodyweight gain for surviving test rats exposed at 0.050 or 0.034 mg/l was markedly reduced throughout the observation period.

Lung weight to bodyweight ratios for surviving and decedent test rats were higher than ratios for the control rats.

Macroscopic abnormalities seen in rats exposed to m-TMI included slight to severe congestion of the lungs, gas-filled stomachs (decedents only), brown staining around the snout and jaws and a swollen appearance of the lungs.

Treatment-related microscopic changes were detected at all exposure levels of m-TMI and included:

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles in rats exposed at 0.034 mg/l or higher concentrations. This lesion was clearly dose-related, being marked in all the animals receiving 0.076 mg/l or 0.324 mg/l.

Associated inflammatory exudate/cell debris in bronchiolar lumina was seen in the majority of affected animals from the above four treatment groups.

Inflammation of the bronchiolar wall occurred in animals receiving 0.034 mg/l or above. However, it was noted that the majority of animals receiving 0.32 mg/l died early in the study and these did not show an inflammatory response.

Bronchiolar epithelial hyperplasia was seen in a few decedent animals receiving 0.034 mg/l or 0.050 mg/l.

Prominent goblet cells in the bronchial epithelium were seen in a number of both decedent and terminal animals receiving 0.023 mg/l, 0.034 mg/l or 0.050 mg/l.

Aggregations of alveolar macrophages/or alveolitis were seen in rats at exposure levels of 0.023 mg/l to 0.076 mg/l. These treatment-related changes showed no obvious dose relationship.

Intra-alveolar haemorrhage, vascular congestion or perivascular oedema were observed in treated rats from all dosage groups. These changes most frequently occurred in rats which died during the study. Although these changes may in part be agonal in origin the possibility that they may have been exacerbated could not be excluded.

Conclusion

The LC₅₀ (4-hour) and the 95% confidence limits (95% CL) for m-TMI were as follows:

	LC ₅₀ (mg/l)	95% CL (mg/l)
Males:	0.039	0.027 - 0.052
Females:	0.039	0.027 - 0.052
Combined:	0.040	0.032 - 0.047

INTRODUCTION

The acute inhalation toxicity of m-TMI was assessed by exposing 5 groups of rats each, for a period of 4 hours, to a test atmosphere containing a droplet aerosol and vapour or vapour only of the test substance. An additional group was exposed to clean air only for 4 hours.

The study design was in compliance with the following test guidelines for acute inhalation studies:

EPA TSCA:	798.1150.
OECD:	Method 403.
EEC:	Method B2.

The study was conducted at the Huntingdon Research Centre during the period 13 April to 7 July 1994.

The protocol for the study was approved by the Study Director and HRC Management on 22 March 1994 and approved by the Sponsor on 5 April 1994.

On completion of the study all data relating to the study, including preserved tissues and a copy of the final report, were lodged in the Huntingdon Research Centre Archives, Huntingdon, Cambridgeshire, England.

TEST SUBSTANCE

Identity: TMI® (Meta) unsaturated aliphatic isocyanate

Reference: CT 545-94

Chemical name: m-Isopropyl- α,α -dimethyl benzyl isocyanate

Appearance: Clear colourless liquid

CAS no.: 2094-99-7

Batch no.: UC 284

Purity: 94.7%

Date received: 15 February 1994

Storage: -20°C under dry conditions and in the original container

Expiry date: August 1994

The test substance is referred to as m-TMI in this report.

EXPERIMENTAL PROCEDURE

ANIMALS AND MAINTENANCE

Thirty male and 30 female albino rats (Sprague-Dawley), about 6 weeks and 8 weeks old respectively, were selected from 5 consignments of rats obtained from Charles River UK Limited, Manston Road, Margate, Kent, England on 13 and 20 April, 6 and 27 May and 17 June 1994. The ages of rats were selected so that males and females would be of similar bodyweight (*ca* 200 g) on the day of exposure.

On arrival the rats were allocated to 1 of 6 groups, each of 5 males and 5 females and were identified individually by a number tattooed on the ears. The rats were singly housed and acclimatised to laboratory conditions for at least 5 days before the day of exposure.

The holding cages were made of stainless steel sheet and wire mesh (size 31 cm × 19 cm × 20 cm height) and were suspended on a movable rack. While in their cages all rats had free access to a measured excess amount of food (R&M 1) and tap water. Food and water supplies were analysed routinely to determine the levels of chemical or microbiological contaminants.

The rats remained in a holding room except for the 4-hour exposure and an overnight post exposure period when the rats in the test groups were kept in a ventilated cabinet to allow dispersal of any residual test substance. Room lighting was by artificial light between 8 am and 8 pm daily.

The temperature and relative humidity of the holding room air were monitored continuously using a Kent Clearspan thermohygrograph.

The temperature of the holding area during the study remained within the limits of 19°C to 25.5°C and the relative humidity was between the limits of 38% to 65%. There were no extremes of temperature or relative humidity considered likely to have influenced the results of the study.

INHALATION EXPOSURES

Four groups of rats were exposed continuously for 4 hours to test atmospheres containing a droplet aerosol and vapour or vapour only of the test substance.

An additional group acting as a control was exposed to clean air only for 4 hours.

The group identifications and dates of exposure for the groups were:

Group 1 (Control):	20 April 1994
Group 2 (Test):	20 April 1994
Group 3 (Test):	28 April 1994
Group 4 (Test):	13 May 1994
Group 5 (Test):	2 June 1994
Group 6 (Test):	23 June 1994

The mean concentrations of the test substance in air for the test groups are given in the **RESULTS** section of this report.

EXPOSURE SYSTEM

The test atmospheres for Groups 2 and 3 were generated using a stainless steel atomiser and the atmospheres for Groups 4, 5 and 6 were produced using a small glass vaporiser.

Stainless steel atomiser (Groups 2 and 3)

The aerosol generator was designed to produce and maintain an atmosphere containing a high proportion of respirable droplets. All parts of the generator in contact with the test substance were made of stainless steel.

Vapour generator (Groups 4, 5 and 6)

The generator was designed to produce and maintain an atmosphere containing only the vapour of the test substance. All parts of the generator in contact with the test substance were made of glass.

The test substance was delivered to the generators at a constant flow rate from a syringe driven by a syringe pump. The air supplied to the generators was dried, filtered and oil free.

The exposure system for Groups 4, 5 and 6 was similar to that shown in Figure 1.

Exposure chambers

The whole-body exposure chambers used for the exposures were of square section and were fitted with pyramidal tops. The chambers were made of perspex and had an internal volume of approximately 120 litres. Each chamber was divided by wire mesh partitions to provide 10 separate animal compartments.

The test atmosphere entered through a port at the base centre of the chamber and passed out through small holes in the lower edge of the square section. Each chamber was positioned inside a large cabinet equipped with an extract fan exhausting to atmosphere through a collection filter.

PROCEDURE

For the exposure of Groups 2 and 3, a supply of clean, dried air, was connected to the generator and the supply pressure was adjusted to give a flow rate of 15 litres per minute into the exposure chamber. The total chamber air flow was made up to 25 l/minute using an additional air supply of 10 l/minute. The air flow throughout the exposure was monitored using in-line flow meters.

A 20 ml (Group 2) or 2.5 ml (Group 3) syringe filled with the test substance was fitted to the syringe pump and connected to the generator with PTFE tubing. A flow rate of 0.025 or 0.006 ml/min was selected for the exposure. For the exposures of Groups 4, 5 and 6, air was passed through the glass vaporiser and diluted by a second supply of air before entering the chamber. The air supplies were adjusted as necessary to maintain a constant concentration of m-TMI at the required air flow rate of 25 l/minute (12 air changes/hour).

The rats to be exposed were placed into separate compartments of the exposure chamber.

The syringe pump was switched on and the exposure timed for 4 hours, following an 11-minute ⁽¹⁾ equilibration period.

After 4 hours the supply of test substance was discontinued and the exposure chamber was allowed to clear before the rats were removed for examination.

Following exposure the rats were returned to the holding cages and food and water supplies were restored. The test rats were kept in a ventilated cabinet overnight and then returned to the holding room for the remainder of the observation period.

The control group was treated similarly but exposed to clean air only for 4 hours. The control rats were returned to the holding room at the end of the exposure procedure.

CHAMBER ATMOSPHERE ANALYSES

Five air samples were taken from the chamber during each exposure and analysed to determine the concentration of m-TMI in the chamber atmosphere.

The samples were drawn through a Whatman GF/A glass fibre filter and gas absorption trap in series or through a gas absorption trap alone. The trapping agent was toluene and solvent trap was chilled to approximately 0°C by immersion in iced water during sample collection.

Two additional samples were taken during the exposures of Groups 2 and 3 for the determination of particle size using a Marple Cascade impactor⁽²⁾. The samples were drawn at 2 l/min at approximately 1.5 and 3.5 hours after the start of the exposure.

The analytical method used to determine the concentration of m-TMI in air samples is described in Appendix 1.

- ⁽¹⁾ 11 minutes is the theoretical time required for the concentration of aerosol in the chamber to reach 90% of its final value under the conditions of exposure employed
- ⁽²⁾ Model 296, Anderson Samplers Inc, Atlanta, GA, USA

CHAMBER AIR TEMPERATURE AND RELATIVE HUMIDITY

The air temperature in the exposure chamber was measured with a mercury-in-glass thermometer and the water vapour concentration was measured with an Analytical Development Co Ltd water vapour analyser, Model 225. The temperature and water vapour concentrations were recorded at the start of exposure and then at 30-minute intervals during the 4-hour exposure.

OBSERVATIONS

Clinical signs

The rats were observed continuously for signs of reaction to the test substance during exposure and at least twice daily throughout the observation period. The clinical signs were recorded at the end of the chamber equilibration period, at 0.25, 0.5 and 1.0 hours and then at hourly intervals during the exposure. During the observation period, the clinical signs were recorded once in the morning and then as necessary following a later check for clinical signs.

Bodyweight

All surviving rats were weighed daily from the day of delivery to the Huntingdon Research Centre until the end of the observation period.

TERMINAL STUDIES

At the end of the 14-day observation period, the surviving rats were anaesthetised by intraperitoneal injection of pentobarbitone sodium and killed by exsanguination.

All rats that died as a result of exposure and those killed at the end of the observation period were subjected to a detailed macroscopic examination. The lungs were removed, dissected clear of surrounding tissue and weighed in order to calculate the lung weight to bodyweight ratio. The lungs were infused with 10% buffered formalin prior to preservation.

The lungs and all macroscopic abnormalities were preserved in buffered 10% formalin. All other tissues were discarded.

The left lung and all lobes of the right lung were embedded in paraffin wax and processed routinely. Four-micron sections were prepared, stained with haematoxylin and eosin and examined under the light microscope.

ESTIMATION OF THE LC₅₀ (4-HOUR) AND STANDARD ERROR

The concentration of the test substance likely to cause death in 50% of exposed rats following a single 4-hour exposure was calculated by the log probit method of Miller and Tainter⁽¹⁾. The 95% confidence limits were calculated as $LC_{50} \pm 1.96 \times \text{standard error of } LC_{50}$.

The standard error (SE) was calculated from the formula:

$$SE \text{ of } LC_{50} = \frac{2s}{\sqrt{2} N}$$

where 2s is the estimated increment in concentration of the test substance between probits 4.0 and 6.0 corresponding to 16% and 84% mortality and N is the total number of rats in groups with mortality between 6.7% and 93.3% (probits 3.5 - 6.5).

(¹) MILLER, L.C. and TAINTER, M.L., *Proc. Soc. Exp. Bio. Med.*, **57**, (2), 1944, pp 261 - 264

RESULTS

CHAMBER ATMOSPHERE CONDITIONS

Concentrations of m-TMI

The analysis results for the air samples taken during the exposures are shown in Table 1.

The mean concentrations of m-TMI and the standard deviations (SD) for each group were:

Group	m-TMI in air (mg/l)	(SD)
2	0.32	(0.012)
3	0.076	(0.0060)
4	0.023	(0.0036)
5	0.050	(0.0023)
6	0.034	(0.0058)

Particle size distribution of m-TMI

The analytical results of the particle size distribution samples taken during the exposure of Groups 2 and 3 are shown in Table 2.

The results are summarised in the following table:

Group	MMAD (μm)	σg	% respirable ($< 7 \mu\text{m}$)
2	2.6	2.23	88.7
3	3.2	2.96	76.0

The amounts of m-TMI collected for the analysis samples for Group 3 showed that only 21% of the total m-TMI was present as a droplet aerosol.

Chamber air temperature and relative humidity

The mean chamber air temperatures, relative humidity and the standard deviation (SD) of the means, during exposure of the groups were:

Group	Temperature ($^{\circ}\text{C}$)		Relative humidity (%)	
	Mean	(SD)	Mean	(SD)
1 (Control)	24	(0.0)	48	(10.8)
2 (0.32 mg/l)	23	(0.0)	73	(7.7)
3 (0.076 mg/l)	25	(0.3)	73	(6.8)
4 (0.023 mg/l)	24	(0.3)	53	(8.4)
5 (0.050 mg/l)	25	(0.3)	39	(8.3)
6 (0.034 mg/l)	24	(0.3)	50	(6.2)

There were no extremes of temperature or relative humidity considered to have influenced the results of the study.

CLINICAL OBSERVATIONS

Mortality

The data are summarised as follows:

Group	Mortalities		
	Males	Females	Total
2 (0.32 mg/l)	5/5	5/5	10/10
3 (0.076 mg/l)	5/5	5/5	10/10
4 (0.023 mg/l)	0/5	0/5	0/10
5 (0.050 mg/l)	4/5	4/5	8/10
6 (0.034 mg/l)	2/5	2/5	4/10

In Group 2 (0.32 mg/l), 2 male rats and 1 female rat were found dead on the morning of Day 1. Three male rats and 3 female rats died during Day 1 and 1 female rat was found dead on Day 2 of the observation period.

In Group 3 (0.076 mg/l), 1 female rat was found dead on Day 1. Two male and 3 female rats died on Day 1. One male and 1 female rat were found dead on Day 2 and 1 male was found dead on Days 3 and 4 of the observation period.

In Group 4 (0.023 mg/l) all rats survived the 14-day observation period.

In Group 5 (0.050 mg/l), 1 male and 2 female rats were found dead on the morning of Day 2. One male rat was found dead on Day 2. One male rat died on Day 3, 1 female died on Day 6, 1 male rat died on Day 12 and 1 female rat died on Day 13 of the observation period.

In Group 6 (0.034 mg/l), 1 male rat was found dead on the morning of Day 3. One female rat was found dead on Days 8 and 13 and 1 male rat was found dead on Day 14 of the observation period.

Clinical signs

During the exposure - The incidence of clinical signs observed during exposure is shown in Table 3.

Signs seen during exposure in rats exposed at 0.023 mg/l were limited to reddening of feet and ears. Additional signs seen during exposure at all higher concentrations included exaggerated respiratory movements, irregular respiration and a reduced respiration rate, the adoption of a hunched or prone posture and partial closing of the eyes.

During the observation period - The incidence of clinical signs observed during the observation period is shown in Table 4.

All female animals exposed at 0.023 mg/l of air were normal in appearance and behaviour during the observation period. Male rats exposed at 0.023 mg/l were normal during the first 5 days and then 2 rats developed signs of noisy respiration and exaggerated respiratory movements which persisted during the observation period. Clinical signs seen in rats exposed at all higher concentrations of m-TMI included exaggerated respiratory movements, noisy respiration, an increased respiration rate, gasping, lethargy and some incidences of hypothermia, peripheral vasodilation and a clear discharge from the snout.

Bodyweight

The group mean and individual bodyweights are shown in Table 5 and the group mean figures are shown graphically in Figure 2.

The majority of rats that died lost weight prior to death. Rats exposed at 0.023 mg/l had a slightly reduced bodyweight gain to Day 2 of the observation period. The bodyweight gain for surviving test rats exposed at 0.050 or 0.034 mg/l was markedly reduced throughout the observation period.

TERMINAL STUDIES

Lung weight to bodyweight ratio

The lung weight to bodyweight ratio for individual rats is shown in Table 6.

The lung weight to bodyweight ratios for surviving and decedent test rats were higher than those of control rats.

Estimation of the LC₅₀ for m-TMI

The LC₅₀ (4-hour) and the 95% confidence limits (95% CL) for m-TMI were as follows:

	LC ₅₀ (mg/l)	95% CL (mg/l)
Males:	0.039	0.026 - 0.052
Females:	0.039	0.026 - 0.052
Combined:	0.040	0.032 - 0.048

Macroscopic pathology

The macroscopic pathological findings for individual rats are presented in Appendix 2.

Abnormalities seen in rats exposed at any concentration of m-TMI included slight to marked congestion of the lungs. Other abnormalities seen in rats exposed at 0.034 mg/l or higher concentrations were a gas-filled gastrointestinal tract (decedents only) and brown staining of the body fur.

Microscopic pathology

Individual animal findings are included in Appendix 2 and summarised in Table 7. The following comments are made in summary:

Treatment-related microscopic changes were detected at all exposure levels of m-TMI and included:

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles in rats exposed at 0.034 mg/l or higher concentrations. This lesion was clearly dose-related, being marked in all the animals receiving 0.076 mg/l or 0.324 mg/l.

Associated inflammatory exudate/cell debris in bronchiolar lumina was seen in the majority of affected animals from the above four treatment groups.

Inflammation of the bronchiolar wall occurred in animals receiving 0.034 mg/l or above. However, it was noted that the majority of animals receiving 0.32 mg/l died early in the study and these did not show an inflammatory response.

Bronchiolar epithelial hyperplasia was seen in a few decedent animals receiving 0.034 mg/l or 0.050 mg/l.

Prominent goblet cells in the bronchial epithelium were seen in a number of both decedent and terminal animals receiving 0.023 mg/l, 0.034 mg/l or 0.050 mg/l.

Aggregations of alveolar macrophages/or alveolitis were seen in rats at exposure levels of 0.023 mg/l to 0.076 mg/l. These treatment-related changes showed no obvious dose relationship.

Intra-alveolar haemorrhage, vascular congestion or perivascular oedema were observed in treated rats from all dosage groups. These changes most frequently occurred in rats which died during the study. Although these changes may in part be agonal in origin the possibility that they may have been exacerbated could not be excluded.

Conclusion

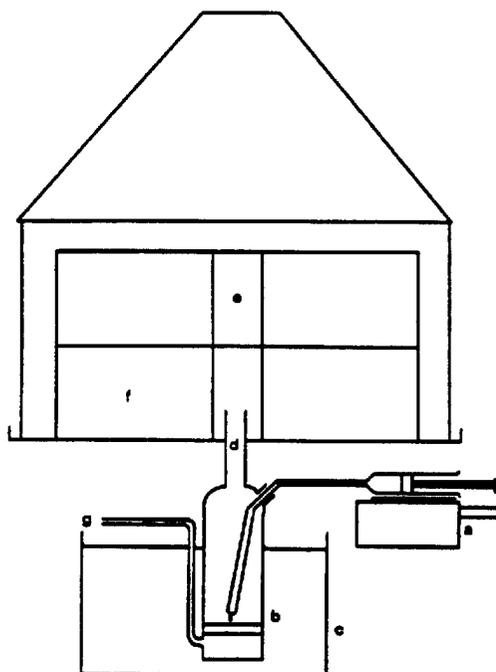
Degenerative bronchiolar epithelial changes and associated inflammatory response in rats receiving 0.034 mg/l or above.

Prominent goblet cells and bronchiolar epithelial hyperplasia, aggregations of alveolar macrophages and/or alveolitis were present at exposures of 0.023 mg/l to 0.076 mg/l.

A possible treatment-related exacerbation in the incidence of intra-alveolar haemorrhage, vascular congestion and perivascular oedema in rats from all dosage groups.

A no-effect dosage level was not detected in the study.

FIGURE 1
Exposure system



- a Syringe pump
- b Sintered glass disc
- c Water bath
- d Vapour entry port
- e Exposure chamber
- f Exposure holding cage
- g Air supply (25 litres/minute)

FIGURE 2

Group mean bodyweights

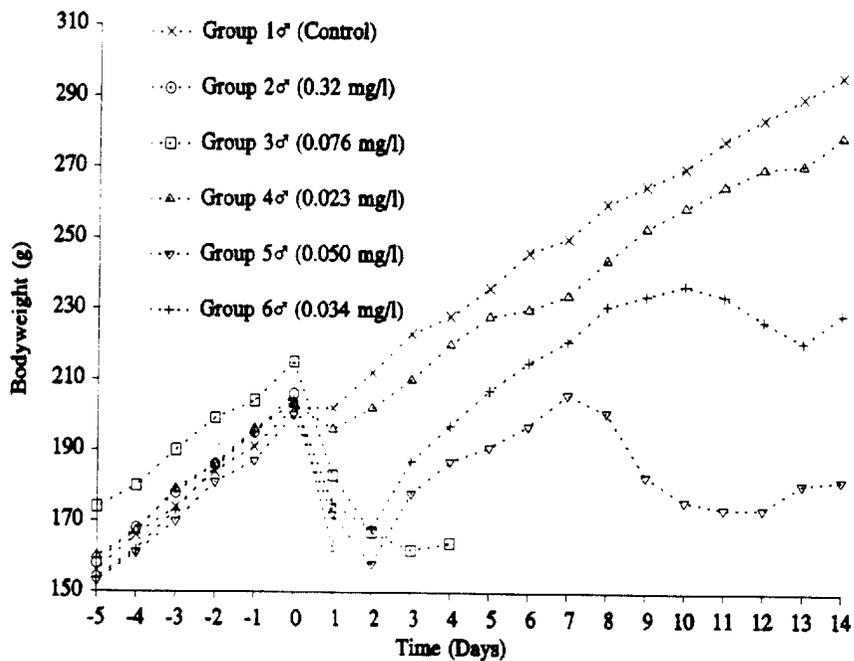


FIGURE 2

(Group mean bodyweights - continued)

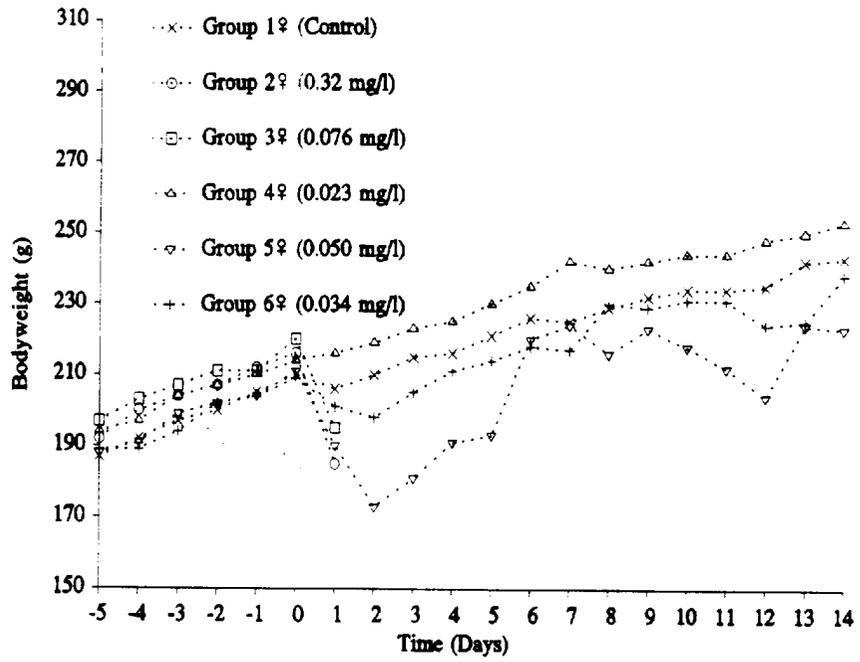


TABLE 1

Concentrations of m-TMI in chamber air

Group	Sample	Time	Concentration of m-TMI (mg/l)
2	1	0h : 40m	0.309
	2	1h : 00m	0.320
	3	2h : 00m	0.318
	4	3h : 00m	0.334
	5	3h : 50m	0.338
		Mean SD	
3	1	0h : 30m	0.067
	2	1h : 00m	0.074
	3	2h : 00m	0.077
	4	3h : 00m	0.083
	5	3h : 50m	0.079
		Mean SD	
4	1	0h : 30m	0.0180
	2	1h : 00m	0.0208
	3	2h : 00m	0.0229
	4	3h : 00m	0.0263
	5	3h : 45m	0.0264
		Mean SD	
5	1	0h : 30m	0.0467
	2	1h : 00m	0.0495
	3	2h : 00m	0.0513
	4	3h : 00m	0.0527
	5	3h : 50m	0.0516
		Mean SD	
6	1	0h : 30m	0.0285
	2	1h : 00m	0.0280
	3	2h : 00m	0.0357
	4	3h : 00m	0.0395
	5	3h : 50m	0.0401
		Mean SD	

SD Standard deviation

TABLE 2

Particle size distribution of m-TMI

(a) Analysis results (Group 2)

Sample	Time taken	Stage	Cut-off size (μm)	Amount collected (μg)
PSD 1	1h : 30m	3	9.8	83.3
		4	6.0	260.3
		5	3.5	644.3
		6	1.55	55.3
		7	0.93	412.5
		8	0.52	119.1
		Filter	0.0	62.7
PSD 2	3h : 30m	3	9.8	79.9
		4	6.0	181.8*
		5	3.5	526.3
		6	1.55	1240.3
		7	0.93	169.5
		8	0.52	79.0*
		Filter	0.0	71.2

* Estimated value

(b) Calculations

Cut-off size (μm)	% less than size (cumulative)
9.8	96.1
6.0	85.0
3.5	55.6
1.55	23.0
0.93	8.4
0.52	3.4
MMAD (μm)	2.7 μm
σg	2.25
% respirable	88.4

MMAD Mass median aerodynamic diameter

 σg Standard geometric deviation% respirable % <7 μm size

TABLE 2

(Particle size distribution of m-TMI - continued)

(a) Analysis results (Group 3)

Sample	Time taken	Stage	Cut-off size (μm)	Amount collected (μg)
PSD1	1h : 30m	3	9.8	30.6
		4	6.0	78.0
		5	3.5	99.5
		6	1.55	114.5
		7	0.93	0.0
		8	0.52	0.0
		Filter	0.0	45.6
PSD 2	3h : 30m	3	9.8	32.4
		4	6.0	126.8
		5	3.5	133.6
		6	1.55	155.5
		7	0.93	0.0
		8	0.52	0.0
		Filter	0.0	53.6

(b) Calculations

Cut-off size (μm)	% less than size (cumulative)
9.8	92.7
6.0	69.2
3.5	42.4
1.55	11.4
0.93	11.4
0.52	11.4
MMAD (μm)	3.2 μm
σ_g	2.96
% respirable	76.1

MMAD Mass median aerodynamic diameter

 σ_g Standard geometric deviation% respirable % <7 μm size

TABLE 3
Clinical signs during exposure

Group	Signs	Number in showing signs						
		Time in hours						
		0*	0.25	0.5	1.0	2.0	3.0	4.0
1♂ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5
1♀ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5
2♂ (0.32 mg/l)	Partially closed eyes	5	5	5	5	5	5	5
	Reddening of feet and ears						5	5
	Irregular respiration			5	5	5	5	5
	Hunched posture	5	5	3	5	5	5	5
	Restless behaviour			2				
2♀ (0.32 mg/l)	Partially closed eyes	5	5	5	5	5	5	5
	Reddening of feet and ears						5	5
	Irregular respiration			5	5	5	5	5
	Hunched posture	5	4	3	4	5	5	5
	Arched back		1	1	1			
3♂ (0.076 mg/l)	Partially closed eyes	5	5	5	5	5	5	5
	Reddening of feet and ears						5	5
	Irregular respiration					5	5	5
	Hunched posture		5	5	5	5	5	5
3♀ (0.076 mg/l)	Partially closed eyes	5	5	5	5	5	5	5
	Wet snout				1	1	1	1
	Wet around the mouth				1	1	1	1
	Reddening of feet and ears						5	5
	Irregular respiration					5	5	5
	Hunched posture		5	5	5	5	5	5
4♂ (0.023 mg/l)	Normal appearance and behaviour	5	5	5	5	5	5	
	Reddening of feet and ears							5
4♀ (0.023 mg/l)	Normal appearance and behaviour	5	5	5	5	5	5	
	Reddening of feet and ears							5

* Clinical signs recorded during the 11-minute equilibration period

TABLE 3

(Clinical signs during exposure - continued)

Group	Signs	Number in showing signs						
		Time in hours						
		0*	0.25	0.5	1.0	2.0	3.0	4.0
5♂ (0.050 mg/l)	Normal appearance and behaviour	5						
	Partially closed eyes		5	5	1		3	2
	Reddening of ears					5	5	5
	Reddening of feet							1
	Slow respiration					2		
	Exaggerated respiratory movements			2	5	3	5	5
	Prone posture			2				
5♀ (0.050 mg/l)	Normal appearance and behaviour	5						
	Partially closed eyes		5	5	1	1		1
	Reddening of ears					5	5	5
	Slow respiration					1		
	Exaggerated respiratory movements				5	4	5	5
	Excessive grooming			3	1			
6♂ (0.034 mg/l)	Partially closed eyes		5	5	5	5	5	5
	Reddening of ears			5	5	5	5	5
	Prone posture			2				
	Restless behaviour	5						
6♀ (0.034 mg/l)	Partially closed eyes		5	5	5	5	5	5
	Reddening of ears			5	5	5	5	5
	Restless behaviour	5						

* Clinical signs recorded during the 11-minute equilibration period

TABLE 4
Clinical signs during observation period

Group	Signs	Number showing signs															
		Day of observation period															
		0*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1♂ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
	Normal appearance and behaviour	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
	Peripheral vasodilation	5	1														
	Wet fur snout and jaws	1															
	Exaggerated respiratory movements	5															
	Brown staining around snout and/or jaws	4	2														
	Gasping	2	2														
	Lethargic	2	2														
	Matted fur	2	2														
	Noisy respiration	1	5 ¹														
Dead (Total)																	
2♀ (0.32 mg/l)	Exaggerated respiratory movements	5															
	Peripheral vasodilation	5	1														
	Wet fur snout and jaws	1															
	Clear discharge from eyes	2															
	Dark appearance of eyes	5	3														
	Brown staining around snout and/or jaws	1	1														
	Lethargic	2	2														
	Wet fur urogenital region	3	3														
	Gasping	4 ¹	5														
	Dead (Total)																

* Clinical signs recorded after exposure on the day of exposure

¹ Two rats found dead at afternoon check

TABLE 4
(Clinical signs during observation period - continued)

Group	Signs	Number showing signs															
		Day of observation period															
		0*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
3♂ (0.076 mg/l)	Peripheral vasodilation	5															
	Wet fur snout	1															
	Exaggerated respiratory movements	5	1	1	1												
	Wet fur snout and jaws	2															
	Brown staining around snout and/or jaws		4	1	1	1											
	Gasping		2	2	2	1											
	Lethargic		1														
	Extremities cold		1														
	Red coloured discharge from eyes		1	1	1												
	Noisy respiration		2 ¹	3	4 ¹	5 ¹											
	Dead (Total)		5	3													
3♀ (0.076 mg/l)	Exaggerated respiratory movements	5															
	Peripheral vasodilation	5															
	Wet fur snout and jaws	2															
	Clear discharge from eyes	1															
	Brown staining around snout and/or jaws		4	1	1												
	Lethargic		1														
	Cold extremities		1														
	Gasping		2														
	Dead (Total)		4 ³	5													
	4♂ (0.023 mg/l)	Normal appearance and behaviour	5	5	5	5	5	4	2	3	3	3	3	3	3	3	3
		Noisy respiration															
Exaggerated respiratory movements																	
Lethargic																	
4♀ (0.023 mg/l)	Normal appearance and behaviour	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	

* Clinical signs recorded after exposure on the day of exposure
 1 One rat found dead at afternoon check
 3 Three rats found dead at afternoon check

TABLE 4
(Clinical signs during observation period - continued)

Group	Signs	Number showing signs														
		Day of observation period														
		0*	1	2	3	4	5	6	7	8	9	10	11	12	13	14
5♂ (0.050 mg/l)	Normal appearance and behaviour															
	Exaggerated respiratory movements							2								
	Peripheral vasodilation	3	4	2	2	2	2	2	1	2	2	2	2	1	1	
	Brown staining around snout and/or jaws	3	3	2		1					2	1				
	Increased respiration rate	2														
	Lethargic		5	4						2						
	Noisy respiration	4	2	1	1				2	2	2	2	1			
	Hair loss back of head	2	2	2	2	2	2									
	Gasping	1	1	2												
	Clear discharge from snout	1	1													
	Swollen abdomen	3	3	1												
	Dark appearance of eyes											2	1	1	1	
	Emaciated											2	2	1	1	
	Ataxia											2	2	1	1	
Dead (Total)			2	3								4				
5♀ (0.050 mg/l)	Normal appearance and behaviour															
	Brown staining around snout and/or jaws															
	Peripheral vasodilation	4	5	1	1	1	1									
	Exaggerated respiratory movements	5	2	2	2	3	3	2								
	Noisy respiration	5	2	3	1	1	1		2	2	2	2	2	1	1	
	Lethargic		5	2												
	Gasping		3	1	1											
	Swollen abdomen		2	1												
	Clear discharge from snout		1													
	Cold extremities															
	Brown staining on forepaws															
	Hair loss back of head															
	Emaciated															
	Dark appearance of eyes															
Dead (Total)			2	3							3					

* Clinical signs recorded after exposure on the day of exposure

TABLE 4
(Clinical signs during observation period - continued)

Group	Signs	Number showing signs													
		Day of observation period													
		0*	1	2	3	4	5	6	7	8	9	10	11	12	13
6♂ (0.034 mg/l)	Normal appearance and behaviour									4	2	1	1	1	
	Wet fur snout and jaws	1													
	Increased respiration rate	5	3	1	1	1	1	1	1	1					
	Brown staining around snout and/or jaws	1	3	3	3	3	4	4	4	4		2	2	2	1
	Exaggerated respiratory movements		4	4	3	3	4	4	4	4		2	3	3	2
	Noisy respiration		1	1	1	1	1	1	1	1		2	2	2	1
	Gasping														
	Whole body cold														
	Lethargic														
	Irregular respiration											1	2	2	2
	Dark appearance of eyes											2	2	3	2
	Emaciated												2	2	1
	Dead (total)														2
	6♀ (0.034 mg/l)	Normal appearance and behaviour													
Increased respiration rate		5	2	2	1	1	1	1	1	1	4	2	2	2	2
Clear discharge from eyes		2													
Gasping															
Cold to touch															
Exaggerated respiratory movements															
Brown staining around snout and/or jaws															
Noisy respiration															
Irregular respiration															
Poorly groomed															
Lethargic															
Matted fur underbody															
Dark appearance of eyes															
Brown staining on head															
Emaciated															
Unconscious (no pinch reflex)															
Dead (total)														1	

* Clinical signs recorded after exposure on the day of exposure
 † One animal found dead at afternoon check

TABLE 5
Individual and group mean bodyweight (g)

Group	Rat	Day of observation																				
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1 ♂ (Control)	21	157	162	169	178	182	191	191	200	209	215	219	230	232	241	247	249	254	259	257	260	
	22	156	167	173	184	191	201	202	211	221	226	238	247	248	254	261	271	275	281	284	292	
	23	156	169	177	189	194	210	206	216	229	238	246	253	264	268	270	282	288	297	304		
	24	155	165	177	185	195	205	208	222	232	240	249	258	269	280	283	288	297	307	316	324	
	25	156	165	175	184	191	205	205	213	222	229	237	247	250	259	264	272	281	289	298	302	
	Mean	156	166	174	184	191	202	202	212	223	228	236	246	250	260	265	270	278	285	290	296	
1 ♀ (Control)	26	190	189	196	200	207	212	210	216	222	223	221	233	233	234	236	237	238	239	245	247	
	27	184	191	191	198	204	209	194	194	204	209	211	209	214	221	221	219	223	226	232	230	
	28	193	198	205	211	216	225	223	231	240	241	244	248	251	256	258	262	266	263	269	272	
	29	184	193	196	194	196	208	206	206	206	209	217	224	215	220	224	231	222	226	234	235	
	30	184	190	196	199	201	195	199	204	205	200	211	217	214	212	222	223	222	220	230	233	
	Mean	187	192	197	200	205	210	206	210	215	216	221	226	225	229	232	234	234	235	242	243	

0 Bodyweight taken on the day of exposure, before exposure

TABLE 5
(Individual and group mean bodyweight - continued)

Group	Rat	Day of observation																			
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2♂ (0.32 mg/l)	31	154	166	177	183	193	204	161	Dead												
	32	157	168	183	194	203	217	Dead													
	33	160	173	179	188	197	205	Dead													
	34	157	163	172	178	186	199	164	Dead												
	35	160	170	177	186	198	206	Dead													
	Mean	158	168	178	186	195	206	163													
2♀ (0.32 mg/l)	36	194	198	205	209	214	216	Dead													
	37	192	202	204	209	212	212	185	Dead												
	38	191	196	201	203	211	214	185	Dead												
	39	191	199	199	199	209	215	Dead													
	40	194	204	212	215	216	225	185	Dead												
Mean	192	200	204	207	212	216	185														

0 Bodyweight taken on the day of exposure, before exposure

TABLE 5
(Individual and group mean bodyweight - continued)

Group	Rat	Day of observation																				
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
3♂ (0.076 mg/l)	41	173	184	192	203	213	222	190	Dead													
	42	177	184	195	204	208	216	184	Dead													
	43	171	178	190	199	193	213	177	165	167	164	Dead										
	44	167	171	181	189	198	207	Dead														
	45	180	183	190	198	210	215	182	168	156	Dead											
	Mean	174	180	190	199	204	215	183	167	162	164											
3♀ (0.076 mg/l)	46	195	200	211	206	205	219	Dead														
	47	210	214	216	229	230	234	209	Dead													
	48	190	195	197	197	198	205	181	Dead													
	49	199	209	213	216	209	225	198	Dead													
	50	193	198	200	206	214	219	190	Dead													
Mean	197	203	207	211	211	220	195															

0 Bodyweight taken on the day of exposure, before exposure

TABLE 5
(Individual and group mean bodyweight - continued)

Group	Rat	Day of observation																			
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4♂ (0.023 mg/l)	1	154	165	176	184	194	198	192	204	207	219	220	198	222	228	234	248	256	263	262	283
	2	159	166	179	186	194	198	200	205	215	225	232	239	253	265	269	276	284	284	286	300
	3	163	168	179	186	199	204	192	202	212	219	229	238	226	236	247	259	264	279	264	256
	4	168	174	183	193	202	210	203	205	213	226	233	239	249	260	269	268	278	291	294	298
	5	158	162	176	183	192	205	195	194	204	213	227	235	222	230	245	244	242	234	251	259
	Mean	160	167	179	186	196	203	196	202	210	220	228	230	234	244	253	259	265	270	271	279
4♀ (0.023 mg/l)	6	199	194	203	203	205	210	212	212	217	221	222	227	236	234	244	241	240	248	249	254
	7	199	202	211	215	219	216	223	231	232	232	238	245	251	246	238	239	247	249	252	253
	8	194	194	203	207	208	212	215	220	224	219	225	231	237	232	235	242	243	244	244	248
	9	190	197	204	204	211	217	218	214	223	231	234	237	247	250	252	255	253	259	261	264
	10	190	196	204	206	207	216	213	216	221	221	230	237	240	236	240	241	239	242	243	247
	Mean	194	197	205	207	210	214	216	219	223	225	230	235	242	240	242	244	244	248	250	253

0 Bodyweight taken on the day of exposure, before exposure

TABLE 5
(Individual and group mean bodyweight - continued)

Group	Rat	Day of observation																			
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
♂ (0.050 mg/l)	51	151	158	164	178	183	197	170	161	178	191	193	197	208	206	188	182	173	165	Dead	
	52	154	158	173	178	186	200	172	156	Dead											
	53	152	164	168	181	188	200	172	Dead												
	54	154	162	173	183	189	203	173	157	Dead											
	55	155	161	173	183	190	200	172	159	177	183	188	197	203	196	177	170	175	182	181	182
	Mean	153	161	170	181	187	200	172	158	178	187	191	197	206	201	183	176	174	174	181	182
♀ (0.050 mg/l)	56	180	188	197	203	200	208	188	170	189	201	206	220	222	203	215	220	226	223	224	223
	57	190	194	201	204	211	214	199	Dead												
	58	190	191	192	201	206	210	183	183	196	208	215	220	226	229	230	216	198	186	Dead	
	59	186	187	199	199	195	202	180	167	159	165	157	Dead								
	60	193	197	206	205	208	219	199	Dead												
	Mean	188	191	199	202	204	211	190	173	181	191	193	220	224	216	223	218	212	205	224	223

0 Bodyweight taken on the day of exposure, before exposure

TABLE 5
(Individual and group mean bodyweight - continued)

Group	Rat	Day of observation																			
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
6♂ (0.034 mg/l)	61	155	164	171	185	193	203	175	175	191	201	209	218	223	234	236	236	220	198	188	190
	62	157	169	181	193	201	214	184	182	195	206	216	221	219	238	246	258	262	269	269	265
	63	152	163	176	183	196	203	172	159	181	195	203	212	224	219	215	211	205	194	190	Dead
	64	158	160	174	186	198	204	174	159	Dead											
	65	150	156	163	176	188	197	171	163	182	187	198	209	218	232	237	243	249	246	238	232
	Mean	154	162	173	185	195	204	175	168	187	197	207	215	221	231	234	237	234	227	221	229
6♀ (0.034 mg/l)	66	187	187	190	199	208	211	197	176	192	205	209	220	229	232	236	238	228	203	193	Dead
	67	185	183	187	204	202	209	199	205	211	215	219	227	227	233	229	231	226	215	223	221
	68	194	195	195	204	207	211	207	210	214	216	212	199	184	Dead						
	69	190	189	195	198	196	203	196	196	197	204	210	216	218	218	217	220	230	230	232	237
	70	190	192	201	206	209	212	208	205	211	216	221	227	229	236	233	235	241	247	253	257
	Mean	189	189	194	202	204	209	201	198	205	211	214	218	217	230	229	231	231	224	225	238

0 Bodyweight taken on the day of exposure, before exposure

TABLE 6

Lung weight to bodyweight ratios

Group	Animal	Lung weight (g)	Bodyweight (g)	Lung to bodyweight ratio (LW × 100/BW)	
				Survivors	Decedents
1♂ (Control)	21	1.31	260	0.50	
	22	1.35	292	0.46	
	23	1.28	304	0.42	
	24	1.41	324	0.44	
	25	1.39	302	0.46	
			Mean SD	0.46 0.030	
1♀ (Control)	26	1.34	247	0.54	
	27	1.23	230	0.53	
	28	1.51	272	0.56	
	29	1.24	235	0.53	
	30	1.26	233	0.54	
			Mean SD	0.54 0.012	
2♂ (0.32 mg/l)	31	1.83	161		1.14
	32	1.56	217		0.72
	33	2.36	205		1.15
	34	1.80	164		1.10
	35	2.05	206		1.00
			Mean SD		1.02 0.179
2♀ (0.32 mg/l)	36	1.80	216		0.83
	37	1.50	185		0.81
	38	1.66	185		0.90
	39	2.58	215		1.20
	40	2.56	185		1.38
			Mean SD		1.02 0.253

SD Standard deviation

TABLE 6

(Lung weight to bodyweight ratios - continued)

Group	Animal	Lung weight (g)	Bodyweight (g)	Lung to bodyweight ratio (LW × 100/BW)	
				Survivors	Decedents
3♂ (0.076 mg/l)	41	1.23	190		0.65
	42	2.37	184		1.29
	43	1.82	164		1.11
	44	1.50	207		0.72
	45	1.47	156		0.94
			Mean		0.94
			SD		0.266
3♀ (0.076 mg/l)	46	1.70	219		0.78
	47	2.45	209		1.17
	48	1.25	181		0.69
	49	1.99	198		1.01
	50	1.24	190		0.65
			Mean		0.86
			SD		0.222
4♂ (0.023 mg/l)	1	1.69	283	0.60	
	2	1.59	300	0.53	
	3	1.85	256	0.72	
	4	1.43	298	0.48	
	5	2.12	259	0.82	
			Mean	0.63	
			SD	0.139	
4♀ (0.023 mg/l)	6	1.48	254	0.58	
	7	1.53	253	0.60	
	8	1.37	248	0.55	
	9	1.40	264	0.53	
	10	1.45	247	0.59	
			Mean	0.57	
			SD	0.029	

SD Standard deviation

TABLE 6

(Lung weight to bodyweight ratios - continued)

Group	Animal	Lung weight (g)	Bodyweight (g)	Lung to bodyweight ratio (LW × 100/BW)	
				Survivors	Decedents
5♂ (0.050 mg/l)	51	3.46	165		2.10
	52	2.13	156		1.37
	53	2.25	172		1.31
	54	1.50	157		0.96
	55	1.85	182	1.02	
			Mean	1.02	1.44
			SD	-	0.479
5♀ (0.050 mg/l)	56	2.09	223	0.94	
	57	1.76	199		0.88
	58	3.84	186		2.06
	59	1.72	157		1.10
	60	2.52	199		1.27
			Mean	0.94	1.33
			SD	-	0.514
6♂ (0.034 mg/l)	61	2.73	190	1.44	
	62	2.98	265	1.12	
	63	3.01	190		1.58
	64	1.12	159		0.70
	65	2.11	232	0.91	
			Mean	1.16	1.14
			SD	0.267	0.622
6♀ (0.034 mg/l)	66	2.96	193		1.53
	67	2.34	221	1.06	
	68	4.03	184		2.19
	69	2.08	237	0.88	
	70	1.39	257	0.54	
			Mean	0.83	1.86
			SD	0.264	0.467

SD Standard deviation

TABLE 7

Microscopic pathology incidence summary

Removal reason: Intercurrent	Group	Group	Group	Group	Group	Group
	1	2	3	4	5	6
	----- Males -----					
Animals on study	5	5	5	5	5	5
Animals completed	0	5	5	0	4	2
Lungs						
Examined	0	5	5	0	4	2
Necrosis/loss of bronchial epithelium in bronchi and large bronchioles (Total)	0	5	5	0	4	2
Minimal	0	0	0	0	0	1
Moderate	0	0	0	0	1	0
Marked	0	5	5	0	3	1
Inflammatory exudate/cell debris in bronchiolar lumen (Total)	0	2	5	0	4	2
Trace	0	1	3	0	1	1
Minimal	0	0	1	0	2	1
Moderate	0	1	1	0	1	0
Inflammation in bronchiolar wall (Total)	0	1	5	0	4	2
Trace	0	0	2	0	0	2
Minimal	0	1	2	0	4	0
Moderate	0	0	1	0	0	0
Prominent goblet cells in bronchial epithelium (Total)	0	0	0	0	0	1
Minimal	0	0	0	0	0	1
Aggregation of alveolar macrophages (Total)	0	0	2	0	0	0
Trace	0	0	1	0	0	0
Minimal	0	0	1	0	0	0
Alveolitis (Total)	0	0	1	0	2	2
Trace	0	0	1	0	0	1
Minimal	0	0	0	0	2	1
Perivascular oedema (Total)	0	0	3	0	1	1
Minimal	0	0	3	0	1	1
Intra alveolar haemorrhage (Total)	0	3	3	0	2	2
Trace	0	2	1	0	1	1
Minimal	0	1	2	0	0	1
Moderate	0	0	0	0	1	0

TABLE 7
(Microscopic pathology incidence summary - continued)

Removal reason: Intercurrent	Group	Group	Group	Group	Group	Group
	1	2	3	4	5	6
	----- Males -----					
Animals on study	5	5	5	5	5	5
Animals completed	0	5	5	0	4	2
Lungs	(Continued)					
Vascular congestion (Total)	0	3	4	0	4	1
Trace	0	0	2	0	2	1
Minimal	0	1	1	0	1	0
Moderate	0	2	1	0	1	0

TABLE 7
(Microscopic pathology incidence summary - continued)

Removal reason: Intercurrent	Group	Group	Group	Group	Group	Group
	1	2	3	4	5	6
	----- Females -----					
Animals on study	5	5	5	5	5	5
Animals completed	0	5	5	0	4	2
Lungs						
Examined	0	5	5	0	4	2
Necrosis/loss of bronchial epithelium in bronchi and large bronchioles (Total)	0	5	5	0	4	0
Moderate	0	0	0	0	1	0
Marked	0	5	5	0	3	0
Inflammatory exudate/cell debris in bronchiolar lumen (Total)	0	1	5	0	3	2
Trace	0	1	2	0	0	1
Minimal	0	0	3	0	1	1
Moderate	0	0	0	0	2	0
Inflammation in bronchiolar wall (Total)	0	0	5	0	4	2
Trace	0	0	3	0	2	2
Minimal	0	0	1	0	2	0
Moderate	0	0	1	0	0	0
Bronchiolar epithelial hyperplasia (Total)	0	0	0	0	1	1
Minimal	0	0	0	0	1	1
Prominent goblet cells in bronchial epithelium (Total)	0	0	0	0	1	1
Minimal	0	0	0	0	1	1
Aggregation of alveolar macrophages (Total)	0	0	0	0	1	1
Minimal	0	0	0	0	1	1
Alveolitis (Total)	0	0	1	0	2	2
Trace	0	0	0	0	1	0
Minimal	0	0	1	0	1	2
Perivascular oedema (Total)	0	0	2	0	2	2
Trace	0	0	1	0	1	1
Minimal	0	0	1	0	0	1
Moderate	0	0	0	0	1	0

TABLE 7
(Microscopic pathology incidence summary - continued)

Removal reason: Intercurrent	Group	Group	Group	Group	Group	Group
	1	2	3	4	5	6
	----- Females -----					
Animals on study	5	5	5	5	5	5
Animals completed	0	5	5	0	4	2
Lungs	(Continued)					
Intra alveolar haemorrhage (Total)	0	0	5	0	1	1
Trace	0	0	2	0	1	0
Minimal	0	0	3	0	0	1
Vascular congestion (Total)	0	2	4	0	3	1
Trace	0	0	1	0	1	1
Minimal	0	1	1	0	0	0
Moderate	0	1	2	0	2	0

TABLE 7
(Microscopic pathology incidence summary - continued)

Removal reason: Terminal	Group	Group	Group	Group	Group	Group
	1	2	3	4	5	6
	----- Males -----					
Animals on study	5	5	5	5	5	5
Animals completed	5	0	0	5	1	3
Lungs						
Examined	5	0	0	5	1	3
No abnormalities detected	5	0	0	1	0	0
Necrosis/loss of bronchial epithelium in bronchi and large bronchioles (Total)	0	0	0	0	1	0
Moderate	0	0	0	0	1	0
Inflammatory exudate/cell debris in bronchiolar lumen (Total)	0	0	0	0	1	2
Trace	0	0	0	0	0	1
Minimal	0	0	0	0	0	1
Moderate	0	0	0	0	1	0
Inflammation in bronchiolar wall (Total)	0	0	0	2	1	2
Trace	0	0	0	1	0	2
Minimal	0	0	0	1	1	0
Bronchiolar epithelial hyperplasia (Total)	0	0	0	0	1	0
Minimal	0	0	0	0	1	0
Prominent goblet cells in bronchial epithelium (Total)	0	0	0	2	0	2
Minimal	0	0	0	0	0	2
Moderate	0	0	0	2	0	0
Aggregation of alveolar macrophages (Total)	0	0	0	3	0	1
Trace	0	0	0	2	0	0
Minimal	0	0	0	1	0	1
Alveolitis (Total)	0	0	0	1	0	2
Trace	0	0	0	1	0	1
Minimal	0	0	0	0	0	1
Perivascular oedema (Total)	0	0	0	1	0	0
Minimal	0	0	0	1	0	0

TABLE 7
(Microscopic pathology incidence summary - continued)

Removal reason: Terminal	Group	Group	Group	Group	Group	Group
	1	2	3	4	5	6
	----- Males -----					
Animals on study	5	5	5	5	5	5
Animals completed	5	0	0	5	1	3
Lungs	(Continued)					
Intra alveolar haemorrhage (Total)	0	0	0	0	1	1
Trace	0	0	0	0	1	0
Minimal	0	0	0	0	0	1
Vascular congestion (Total)	0	0	0	1	1	1
Minimal	0	0	0	1	1	1
Focal squamous metaplasia in bronchial epithelium	0	0	0	0	1	0
Mucoid exudate in bronchus	0	0	0	1	0	0

TABLE 7
(Microscopic pathology incidence summary - continued)

Removal reason: Terminal	Group	Group	Group	Group	Group	Group
	1	2	3	4	5	6
	----- Females -----					
Animals on study	5	5	5	5	5	5
Animals completed	5	0	0	5	1	3
Lungs						
Examined	5	0	0	5	1	3
No abnormalities detected	5	0	0	1	0	0
Necrosis/loss of bronchial epithelium in bronchi and large bronchioles (Total)	0	0	0	0	1	0
Trace	0	0	0	0	1	0
Inflammatory exudate/cell debris in bronchiolar lumen (Total)	0	0	0	1	1	2
Trace	0	0	0	1	0	2
Minimal	0	0	0	0	1	0
Inflammation in bronchiolar wall (Total)	0	0	0	3	1	3
Trace	0	0	0	1	0	2
Minimal	0	0	0	2	1	1
Prominent goblet cells in bronchial epithelium (Total)	0	0	0	2	1	2
Minimal	0	0	0	2	1	1
Moderate	0	0	0	0	0	1
Aggregation of alveolar macrophages (Total)	0	0	0	0	0	1
Minimal	0	0	0	0	0	1
Alveolitis (Total)	0	0	0	1	0	1
Trace	0	0	0	1	0	0
Minimal	0	0	0	0	0	1
Perivascular oedema (Total)	0	0	0	0	0	1
Trace	0	0	0	0	0	1
Intra alveolar haemorrhage (Total)	0	0	0	0	0	1
Trace	0	0	0	0	0	1
Vascular congestion (Total)	0	0	0	2	1	2
Trace	0	0	0	0	1	0
Minimal	0	0	0	1	0	2
Moderate	0	0	0	1	0	0

APPENDICES

APPENDIX 1**Method of analysis for m-isopropenyl- α,α -dimethyl benzyl isocyanate (m-TMI)****INSTRUMENTATION AND APPARATUS**

Gas chromatograph:	Pye Unicam PU 4550 gas chromatograph. Pye Unicam PU 4700 autosampler. Spectra-Physics 4400 integrator.
Apparatus:	
Balance:	Sartorius R200D balance, fitted with a YDP-01 data printer.
Ultrasonic bath:	Decon FS200B ultrasonic bath.
Dispensers:	Bibby Pressmatic 2000 and Gilson Pipetteman dispensers.
General laboratory glassware:	Volumetric flasks and pipettes. Sample vials.

REAGENTS

m-TMI:	Batch no. UC 284, received from the Sponsor 15 February 1994.
Toluene:	Pesticide residue grade, BDH or glass-distilled grade, Rathburn Chemicals Ltd.

PREPARATION OF SAMPLE FOR ANALYSIS

The filter samples (Whatman GF/A) from the open face sampler were placed in appropriately labelled vials and sonicated for 5 minutes with 25 ml of toluene. An aliquot of the extract was filtered (PTFE 0.45 μm filter) prior to injection onto the GC column.

The stainless steel substrates and filters (Whatman GF/A) from the Marple cascade impactor were placed in appropriately labelled vials and sonicated for 5 minutes with 5 ml of toluene. An aliquot of the extract was filtered (PTFE 0.45 μm filter) prior to injection onto the GC column.

The solution from the liquid impinger (gas bubbler) containing toluene was transferred quantitatively into a volumetric flask (20 or 25 ml). An aliquot of the sample was filtered (PTFE 0.45 μm filter) prior to injection onto the GC column.

APPENDIX 1**(Method of analysis - continued)****GAS CHROMATOGRAPHY****Operating conditions**

Column:	DB-1, 1.5 μ m film, 15 m \times 0.53 mm id.
Temperature:	Column: 150°C Injector: 200°C Detector: 275°C
Detector:	Flame ionisation detector.
Gas flow rates:	Helium: 12 ml/min Hydrogen: 30 ml/min Air: 300 ml/min
Retention time:	Approximately 2.2 minutes.

Analysis of samples

A 1 μ l aliquot of each sample solution was injected onto the GC column using the autosampler. The concentration of m-TMI in the sample solution was evaluated from the expression:

$$C_x = \frac{(A_x - I)}{S}$$

where C_x = concentration of m-TMI in aliquot (μ g/ml)
 A_x = peak area due to m-TMI
 S = gradient of standard curve
 I = area intercept of standard curve

Standardisation

Approximately 25 mg of m-TMI was accurately weighed into a 50 ml volumetric flask, dissolved in toluene and diluted to volume with further toluene. The solution was diluted with toluene to obtain standard solutions containing m-TMI at nominal concentrations within the range 500 μ g/ml and 0.5 μ g/ml. Aliquots of the standard solutions were injected and the mean peak areas for m-TMI were calculated for each standard concentration. A standard curve was derived from the mean peak areas by regression analysis.

APPENDIX 2**Pathological findings for individual rats**

Exposure levels:

Group:	1	2	3	4	5	6
Compound:	-			m-TMI		
Level (mg/l):	Control	0.32	0.076	0.023	0.050	0.034

In this appendix the macroscopic and microscopic findings relating to each animal are listed.

The microscopic pathology was carried out by two pathologists. The initial examination was undertaken by the study pathologist, the results of which were then subjected to a routine peer review by a second pathologist. The diagnoses reported here represent the consensus opinions of both pathologists.

Study pathologist: Jeroen de Boorder, D.V.M., M.R.C.V.S.,
Pathologist
Department of Pathology

Peer review: John M. Offer, Ph.D., C.Biol., M.I. Biol.,
Consult Pathologist
Department of Pathology

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 21♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 22♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 23♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 24♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 25♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 26♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 27♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 28♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 29♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: -
Dosage Level: Control
Rat No/Sex: 30♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 31♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.
Eyes opaque.

Stomach

Gas-filled.

Lungs

All lobes, moderate congestion.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Intra alveolar haemorrhage: (Minimal , Areas)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 32♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.

Stomach

Distended with gas.

Lungs

All lobes, minimal congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 33♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout, jaws and forepaws.

Stomach

Distended with gas.

Lungs

All lobes, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:

(Marked)

Intra alveolar haemorrhage: (Trace)

Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 34♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.

Lungs

Left, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Moderate)
Inflammation in bronchiolar wall: (Minimal)
Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 35♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Wet brown staining around snout and jaws.

Stomach

Distended with gas.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)

Intra alveolar haemorrhage: (Trace)

Vascular congestion: (Minimal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 36 ♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.

Stomach

Distended with gas.

Lungs

All lobes, minimal congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 37♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout, jaws and forepaws.

Stomach

Gas-filled.

Lungs

All lobes, slight congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 38 ♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.
Right eye opaque.

Stomach

Gas-filled.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Vascular congestion: (Minimal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 39♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.
White crusty staining around mouth.

Lungs

All lobes, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.32 mg/l
Rat No/Sex: 40♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout, jaws and forepaws.

Stomach

Distended with gas.

Lungs

All lobes, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:

(Marked)

Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 41♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout, jaws and forepaws.

Stomach

Gas-filled.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)

Inflammation in bronchiolar wall: (Minimal)

Aggregation of alveolar macrophages: (Minimal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 42♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining snout and jaws.

Gastrointestinal Tract

Gas-filled.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)
Inflammation in bronchiolar wall: (Minimal)
Aggregation of alveolar macrophages: (Trace)
Perivascular oedema: (Minimal)
Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 43♂ (Intercurrent)

MACROSCOPIC FINDINGS

Lungs

All lobes, congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Moderate)
Inflammation in bronchiolar wall: (Moderate)
Alveolitis: (Trace)
Perivascular oedema: (Minimal)
Intra alveolar haemorrhage: (Minimal)
Vascular congestion: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 44♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout, jaws and forepaws.

Lungs

Left, severe congestion.
Right, anterior lobe, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Trace)
Intra alveolar haemorrhage: (Minimal , Areas)
Vascular congestion: (Minimal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 45♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

No abnormalities detected.

Gastrointestinal Tract

Gas-filled.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)
Inflammation in bronchiolar wall: (Trace)
Perivascular oedema: (Minimal)
Intra alveolar haemorrhage: (Trace)
Vascular congestion: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 46♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.

Lungs

Right, anterior lobe, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Moderate)
Alveolitis: (Minimal , Focal)
Perivascular oedema: (Trace)
Intra alveolar haemorrhage: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 47♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining snout and jaws.

Gastrointestinal Tract

Gas-filled.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles: (Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Trace)
Perivascular oedema: (Minimal)
Intra alveolar haemorrhage: (Minimal)
Vascular congestion: (Minimal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 48♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout, jaws and forepaws.

Gastrointestinal Tract

Gas-filled.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)

Inflammation in bronchiolar wall: (Minimal)

Intra alveolar haemorrhage: (Trace)

Vascular congestion: (Moderate , Areas)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 49♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout, jaws and forepaws.

Stomach

Gas-filled.

Lungs

All lobes, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)
Inflammation in bronchiolar wall: (Trace)
Intra alveolar haemorrhage: (Minimal)
Vascular congestion: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.076 mg/l
Rat No/Sex: 50♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining snout and jaws.

Gastrointestinal Tract

Gas-filled.

Lungs

Left, slight congestion.

Right, posterior lobe, slight congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)

Inflammation in bronchiolar wall: (Trace)

Intra alveolar haemorrhage: (Minimal)

Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 1♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Aggregation of alveolar macrophages: (Minimal , Focal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 2♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammation in bronchiolar wall: (Trace)
Aggregation of alveolar macrophages: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 3♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Left, dark areas.
Right, anterior lobe, dark areas.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammation in bronchiolar wall: (Minimal)
Prominent goblet cells in bronchial epithelium: (Moderate)
Vascular congestion: (Minimal , Areas)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 4♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 5♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Left, slight congestion,
Right, azygous lobe, severe congestion.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Prominent goblet cells in bronchial epithelium: (Moderate)
Aggregation of alveolar macrophages: (Trace)
Alveolitis: (Trace)
Perivascular oedema: (Minimal)
Mucoïd exudate in bronchus

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 6♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammation in bronchiolar wall: (Minimal)
Prominent goblet cells in bronchial epithelium: (Minimal)
Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 7♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Right, anterior lobe, moderate congestion.
Right, posterior lobe, moderate congestion.
Right, middle lobe, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammation in bronchiolar wall: (Trace)
Alveolitis: (Trace , Focal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 8♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Right, anterior lobe, moderate congestion.
Right, middle lobe, moderate congestion.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)
Inflammation in bronchiolar wall: (Minimal)
Vascular congestion: (Minimal , Area)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 9♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Prominent goblet cells in bronchial epithelium: (Minimal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.023 mg/l
Rat No/Sex: 10♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 51♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining snout and forepaws.

Gastrointestinal Tract

Distended with gas.

Lungs

Swollen in appearance.

Right, azygous lobe, severe congestion.

All other lobes, slight to moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Moderate)

Inflammatory exudate/cell debris in bronchiolar lumen: (Moderate)

Inflammation in bronchiolar wall: (Minimal)

Vascular congestion: (Trace , Areas)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 52♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout.

Gastrointestinal Tract

Distended with gas.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)

Inflammation in bronchiolar wall: (Minimal)

Alveolitis: (Minimal)

Perivascular oedema: (Minimal)

Intra alveolar haemorrhage: (Trace)

Vascular congestion: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 53♂ (Intercurrent)

MACROSCOPIC FINDINGS

Lungs

All lobes, minimal congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Minimal)
Alveolitis: (Minimal)
Intra alveolar haemorrhage: (Moderate)
Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 54♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown crusty staining around snout and jaws.

Lungs

Appear swollen.

Right, middle lobe, areas of congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)

Inflammation in bronchiolar wall: (Minimal)

Vascular congestion: (Minimal)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 55♂ (Terminal)

MACROSCOPIC FINDINGS

External Appearance

Eyes appear dark in colour.

Lungs

Appear swollen.
Right, anterior lobe, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Moderate)
Inflammatory exudate/cell debris in bronchiolar lumen: (Moderate)
Inflammation in bronchiolar wall: (Minimal)
Bronchiolar epithelial hyperplasia: (Minimal , Areas)
Intra alveolar haemorrhage: (Trace)
Vascular congestion: (Minimal , Areas)
Focal squamous metaplasia in bronchial epithelium

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 56 ♀ (Terminal)

MACROSCOPIC FINDINGS

External Appearance

Eyes appear dark in colour.

Lungs

Appear swollen.
Right, posterior lobe, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Trace)
Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Minimal)
Prominent goblet cells in bronchial epithelium: (Minimal)
Vascular congestion: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 57♀ (Intercurrent)

MACROSCOPIC FINDINGS

Lungs

All lobes, minimal congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammation in bronchiolar wall: (Trace)
Prominent goblet cells in bronchial epithelium: (Minimal)
Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 58♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining on head and forepaws.

Lungs

Swollen.
All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Moderate)
Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Minimal)
Bronchiolar epithelial hyperplasia: (Minimal , Focal)
Aggregation of alveolar macrophages: (Minimal)
Alveolitis: (Minimal , Areas)
Perivascular oedema: (Trace)
Intra alveolar haemorrhage: (Trace , Areas)
Vascular congestion: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 59♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining snout, jaws and all paws.
Back of head, hair loss.

Lungs

Left, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)
Inflammatory exudate/cell debris in bronchiolar lumen: (Moderate)
Inflammation in bronchiolar wall: (Trace)
Alveolitis: (Trace)
Perivascular oedema: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.050 mg/l
Rat No/Sex: 60♀ (Intercurrent)

MACROSCOPIC FINDINGS

Lungs

All lobes, minimal congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Moderate)

Inflammation in bronchiolar wall: (Minimal)

Vascular congestion: (Moderate)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 61♂ (Terminal)

MACROSCOPIC FINDINGS

External Appearance

Brown staining around snout and jaws.

Lungs

Swollen in appearance.
Left, moderate congestion.
All other lobes, slight congestion.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Prominent goblet cells in bronchial epithelium: (Minimal)
Aggregation of alveolar macrophages: (Minimal , Areas)
Alveolitis: (Minimal , Areas)
Intra alveolar haemorrhage: (Minimal , Area)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 62♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Right, middle lobe, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)

Inflammation in bronchiolar wall: (Trace)

Vascular congestion: (Minimal , Area)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 63♂ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining on head.

Lungs

All lobes, moderate congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Minimal)
Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Trace)
Alveolitis: (Minimal , Area)
Intra alveolar haemorrhage: (Minimal , Area)
Vascular congestion: (Trace , Area)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 64♂ (Intercurrent)

MACROSCOPIC FINDINGS

Intestines

Partially gas-filled.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Necrosis/loss of bronchial epithelium in bronchi and large bronchioles:
(Marked)

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)

Inflammation in bronchiolar wall: (Trace)

Prominent goblet cells in bronchial epithelium: (Minimal)

Alveolitis: (Trace , Area)

Perivascular oedema: (Minimal)

Intra alveolar haemorrhage: (Trace , Area)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 65♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Swollen in appearance.
Right, posterior lobe, dark area.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Trace)
Prominent goblet cells in bronchial epithelium: (Minimal)
Alveolitis: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 66 ♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining head and forepaws.

Lungs

Swollen in appearance.
All lobes, moderate to severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)
Inflammation in bronchiolar wall: (Trace)
Aggregation of alveolar macrophages: (Minimal , Area)
Alveolitis: (Minimal , Area)
Perivascular oedema: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 67♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Swollen in appearance.
All lobes, areas of severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)
Inflammation in bronchiolar wall: (Trace)
Prominent goblet cells in bronchial epithelium: (Minimal)
Aggregation of alveolar macrophages: (Minimal , Area)
Alveolitis: (Minimal , Area)
Vascular congestion: (Minimal , Area)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 68♀ (Intercurrent)

MACROSCOPIC FINDINGS

External Appearance

Brown staining snout, jaws and forepaws.
Underbody and lower back, matted fur.

Lungs

Swollen in appearance.
All lobes, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammatory exudate/cell debris in bronchiolar lumen: (Minimal)
Inflammation in bronchiolar wall: (Trace)
Bronchiolar epithelial hyperplasia: (Minimal)
Prominent goblet cells in bronchial epithelium: (Minimal)
Alveolitis: (Minimal , Area)
Perivascular oedema: (Minimal)
Intra alveolar haemorrhage: (Minimal , Area)
Vascular congestion: (Trace)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 69♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs

Right, middle lobe, severe congestion.
Right, azygous lobe, severe congestion.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammatory exudate/cell debris in bronchiolar lumen: (Trace)
Inflammation in bronchiolar wall: (Minimal)
Prominent goblet cells in bronchial epithelium: (Moderate)
Perivascular oedema: (Trace)
Vascular congestion: (Minimal , Area)

Pathologist: J.de Boorder

APPENDIX 2

(Pathology - continued)

Compound: m-TMI
Dosage Level: 0.034 mg/l
Rat No/Sex: 70♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs

All lobes, moderate congestion.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Inflammation in bronchiolar wall: (Trace)
Intra alveolar haemorrhage: (Trace)

Pathologist: J.de Boorder