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ATT: 8 (e) COORDINATOR

RE : TOXICITY OF N-CYCLOHEXYL MALEIMIDE

MARUBENI AMERICA CORPORATION SUBMITS THE FOLLOWING DOCUMENTS

N-CYCLOHEXYL MALEIMIDE:
ACUTE INHALATION TOXICITY IN RATS 4-HOUR EXPOSURE

THE DOCUMENT CONTAINS INFORMATION WHICH MAY REASONABLY SUPPORT THE CONCLUSION THAT THE REFERENCED CHEMICAL MAY PRESENT A SUBSTANTIAL RISK OF INJURY TO HUMAN HEALTH OR THE ENVIRONMENT, AS INDICATED IN THE REPORTING GUIDE PROVIDED BY EPA. THE CONCLUSION OF THE INFORMATION IS AS FOLLOWS:

THE LC50(4-HOUR) FOR N-CYCLOHEXYL MALEIMIDE, WHEN ADMINISTERED TO RATS IN THE FORM OF A PARTICULATE AEROSOL, IS LESS THAN 0.013 MG/L OF AIR.

THERE WERE NO DEATHS FOLLOWING A SINGLE 4-HOUR EXPOSURE TO A TEST ATMOSPHERE CONTAINING THE VAPOR OF N-CYCLOHEXYL MALEIMIDE AT A CONCENTRATION OF 0.015 MG/L.

MARUBENI AMERICA CORPORATION REQUESTS GUIDANCE FROM EPA WHETHER THE AGENCY BELIEVES THE INFORMATION CONTAINED IN THIS DOCUMENT SATISFIES THE SECTION 8(e) REPORTING CRITERIA.

IF YOU HAVE ANY QUESTIONS OR COMMENTS PLEASE DO NOT HESITATE TO CONTACT ME ON THE PHONE OR BY FAX TO THE NUMBERS MENTIONED ABOVE.

BEST REGARDS,

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N. KOHNO
CHEMICALS & PLASTICS DEPARTMENT
LOS ANGELES BRANCH
MARUBENI AMERICA CORPORATION

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**N-CYCLOHEXYL MALEIMIDE:
ACUTE INHALATION TOXICITY
IN RATS
4-HOUR EXPOSURE**

Study completed: 31 August 1993

Regulation: EPA TSCA: 798.1150

Addressee:

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Report issued: 31 August 1993

CONFIDENTIALITY STATEMENT

This report contains the unpublished results of research sponsored by NOF Corporation. These results may not be published, either wholly or in part, or reviewed or quoted in any other publication without the prior authorisation of the Sponsor.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

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

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.

Japanese Ministry of International Trade and Industry, Directive 31 March 1984 (Kanpogyo No. 39 Environmental Agency, Kikyoku No. 85 MITI).

Organisation for Economic Co-operation and Development, ISBN 92-64-12367-9, Paris 1982.

G. C. Jackson

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

31 August 1993

Date

G. C. Clark

Gerald C. Clark, B.Sc.,
HRC Management

28 July 1993

Date

RESPONSIBLE PERSONNEL

We the undersigned, hereby declare that the work was performed under our supervision according to the procedures herein described, and that this report provides a correct and faithful record of the results obtained.

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Study Director,
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Division of Toxicology.

QUALITY ASSURANCE STATEMENT

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.

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.

Date(s) of inspection

3 June 92

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

4 June 92

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

26 May 93

G. R. Keeble

G.R. Keeble,
Systems Compliance Auditor,
Department of Quality Assurance,
Huntingdon Research Centre Ltd.

26 August 1993

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SUMMARY

Test substance: A white powder identified as N-cyclohexyl maleimide.
Lot No.: 720328.

Test animals: Albino rats (Sprague-Dawley). One control group and 2 test groups each of 5 male and 5 female rats.

Route of administration: By inhalation of a test atmosphere containing (a) a particulate aerosol or (b) a vapour generated from the test substance.

Duration of exposure: 4 hours continuous whole-body exposure.

Observation period: 14 days post exposure.

Results

Exposure levels and mortality:	Level (mg/l)	Mortality		
		Males	Females	Total
(a) 0.013		3/5	5/5	8/10
(b) 0.015		0/5	0/5	0/10
	(a) Particulate aerosol			
	(b) Vapour			

Clinical signs: (a) During exposure to particulate: signs consistent with exposure to an irritant aerosol, including partial closing of the eyes, wet around the snout and mouth, restless behaviour and abnormalities to respiration.

During exposure to vapour: signs consistent with exposure to an irritant vapour including partial closing of the eyes and restlessness.

- (b) During observation period: signs seen in rats exposed to a particulate aerosol of N-cyclohexyl maleimide included death, abnormal respiration, wet fur around the snout and jaws and brown staining around snout and jaws. The female rats showed signs of lethargy and had yellow staining around urogenital region. Rats exposed to the vapour of N-cyclohexyl maleimide included noisy respiration and a few instances of wet fur around snout and jaws, staining around the urogenital region and one rat had red coloured discharge from the eyes.

Rats exposed to vapour of N-cyclohexyl maleimide were normal by Day 4 of the observation period.

Bodyweight:

Reduced bodyweight or reduced rate of bodyweight gain for up to 7 days following exposure to a particulate aerosol of N-cyclohexyl maleimide, and for up to 3 days in rats exposed to the vapour of N-cyclohexyl maleimide.

Food and water consumption:

Food consumption was reduced for up to 8 days following exposure to N-cyclohexyl maleimide.

Water consumption was reduced for 4 days in surviving male rats exposed to a particulate aerosol of N-cyclohexyl maleimide. Rats exposed to the vapour of N-cyclohexyl maleimide had a reduced consumption for up to 2 days. Subsequently water consumption was similar to that of the controls rats.

Lung weight to bodyweight ratio:

The lung weight to bodyweight ratios for all rats that died as a result of exposure were higher than control values. The lung weight to bodyweight ratios for rats that survived exposure to N-cyclohexyl maleimide were within normal limits.

Macroscopic pathology:

Abnormalities in rats that died as a result of exposure to a particulate aerosol of N-cyclohexyl maleimide were congestion of the lungs or raised areas on the lungs and instances of gas filled stomachs. In addition, the rats had brown staining around the snout and jaws. One male rat exposed to the vapour of N-cyclohexyl maleimide had dark subpleural foci on the lungs.

There were no treatment-related macroscopic abnormalities in rats that survived exposure to N-cyclohexyl maleimide.

Microscopic pathology:

The preserved tissues will be retained for at least 3 months following the date of issue of this report.

CONCLUSION

The LC_{50} (4-hour) for N-cyclohexyl maleimide, when administered to rats in the form of a particulate aerosol, is less than 0.013 mg/l of air.

There were no deaths following a single 4-hour exposure to a test atmosphere containing the vapour of N-cyclohexyl maleimide at a concentration of 0.015 mg/l.

INTRODUCTION

The acute inhalation toxicity of N-cyclohexyl maleimide was assessed by exposing 2 groups of rats, for a period of 4 hours, to a particulate aerosol or to the vapour produced from the test substance. A control group was exposed to air only.

The study was conducted at the Huntingdon Research Centre during the period 15 July 1992 and 18 February 1993.

The protocol for the study was approved by the Study Director and HRC Management on 5 March 1992 and approved by the Sponsor on 26 March 1992.

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

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.

MATERIALS AND METHODS

Test substance

The test substance was a white powder identified as N-cyclohexyl maleimide. Lot No. 720328, purity 98.2%.

The sample was received on 9 April 1992 and was stored in the dark at room temperature and in the original container.

The data supplied by the Sponsor indicated that the test substance was stable until at least October 1992.

Animals and maintenance

Fifteen male and 15 female albino rats (Sprague-Dawley), about 6 weeks and 8 weeks old respectively, were selected from 2 consignments of rats obtained from Charles River UK Limited, Manston Road, Margate, Kent, England, on 15 July 1992 and 27 January 1993.

The 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 3 groups, each of 5 males and 5 females and were identified individually by a number tattooed on the ears. The rats were housed by sex in groups of 5 and acclimatised to laboratory conditions for at least 5 days before the day of exposure.

The holding cages (size 35 cm x 53 cm x 25 cm height) were made of stainless steel sheet and wire mesh and were suspended on a movable rack. While in their cages all rats had free access to a measured excess amount of food (SDS RM1) 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 group were kept in a ventilated cabinet to allow dispersal of any residual test substance. Room lighting was by artificial light between 8 a.m. and 8 p.m. daily.

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

The temperature of the holding area during the study remained within the limits of 18°C and 24°C and the relative humidity was between the limits of 23% and 65%.

Inhalation exposures

Two groups of rats were exposed continuously for 4 hours to test atmospheres containing a particulate aerosol or vapour only generated from N-cyclohexyl maleimide.

A further group acting as a control received clean air only for 4 hours.

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

Group 1	(Control)	:	22 July 1992.
Group 2	(Test)	:	22 July 1992.
Group 3	(Test)	:	4 February 1993.

The mean concentrations of the particulate aerosol and the vapour are given in the 'Results' section of this report.

Exposure system

Dust generator

A Wright dust generator ⁽¹⁾ was used to produce the test atmosphere containing the particulate aerosol of N-cyclohexyl maleimide.

The design of the generator is shown in Figure 1. The generator was designed to produce and maintain test atmospheres containing dust by suspending material scraped from the surface of a compressed powder in a stream of dry air. The concentration of dust in the air may be altered by changing the rate at which the scraper blade is advanced into the compressed powder.

Aerosol conditioning

The test atmosphere was passed through a glass elutriation column to reduce, by sedimentation, the amount of non-respirable particulate in the test atmosphere.

Vapour generator

The generator consisted of a flat-bottomed reaction vessel and a transfer column, packed with glass wool to act as a particulate trap, connecting the reaction vessel to the exposure chamber. Air was passed into generator by an inlet tube extending to the bottom of the vessel. All parts of the generator in contact with the test substance were made of glass.

The test substance was placed into the reaction vessel, heated to 35°C, and air was passed through the generator at 25 litres per minute. The compressed air supply to the generator was dried, filtered and oil-free.

⁽¹⁾ Wright, B.M., J. Scient. Instruments, 27, (1) 1950. p.12

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 top 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.

The exposure systems for Wright dust feed mechanism ⁽¹⁾ is shown in Figure 2.

Procedure for particulate

A sample of N-cyclohexyl maleimide was packed into the container of the Wright dust generator using a hydraulic bench press to assist packing. Even density of the powder was achieved by packing the container in stages and applying a force of 0.2 tons weight. The packed container was weighed.

The dust generator was positioned on a stand beside the exposure chamber and the output connected to an inlet port in the top centre of the chamber by the elutriation column. The speed controller of the generator mechanism was set to give a concentration of dust ⁽²⁾ that was expected to produce some deaths.

A supply of clean dried compressed air was connected to the dust generator and the supply pressure was adjusted to give a flow rate of 25 litres per minute measured at the generator outlet nozzle. The total chamber air supply was derived from the air flow through the dust generator.

The group of rats (5♂ and 5♀) to be exposed were placed into separate compartments of the exposure chamber.

The powder container of the Wright dust generator was advanced manually until a trace of suspended dust was seen in the chamber. The gearing on the generator was then engaged and the generator motor switched on to start the exposure. After an 11-minute ⁽³⁾ equilibration period, the exposure was timed for 4 hours. The generator was then switched off and the chamber 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.

⁽¹⁾ Wright, B.M., J. Scient. Instruments, 27, (1) 1950. p 12

⁽²⁾ The performance of the dust generator with this test substance was assessed in a preliminary experiment

⁽³⁾ 11 minutes is the theoretical time required for the concentration of aerosol to reach 90% of its final value under the conditions of exposure employed

Procedure for vapour

A supply of clean dried air, was passed through the vapour generator held at 35°C in a water bath and the supply pressure required to give a flow rate of 25 litres per minute measured at the generator outlet was determined.

The air supply was turned off and 20 g of the test substance was added to the glass reaction vessel (vapour generator).

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

The air supply was turned on and the exposure timed for 4 hours, following an 11-minute ⁽¹⁾ equilibration period.

After 4 hours, the air supply to the generator was discontinued and the exposure chamber was cleared using a separate air supply 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.

Chamber atmosphere analyses

Five air samples were taken from the chamber during each exposure and the collected material was analysed gravimetrically or by UV spectrophotometry to determine the concentration of N-cyclohexyl maleimide in the chamber air.

To determine the concentration of particulate each air sample was withdrawn, at 4 litres per minute, through a weighed glass fibre filter (Whatman GF/A) mounted in an open face filter holder. The filters were removed and reweighed.

To determine the concentration of vapour each air sample was withdrawn, at 2 litres per minute, through a gas absorption trap, containing approximately 25 ml of methanol. The absorbance of the sample solution was determined following the procedure described in Appendix 1.

The volume of the air samples was measured with a wet-type gas meter.

Two additional air samples were taken during the exposure to particulate using a Marple cascade impactor ⁽²⁾. The material collected on the stages of the sampler was weighed to determine the particle size distribution of N-cyclohexyl maleimide in the test atmospheres. The collection characteristics for the Marple used at a sampling rate of 2 litres per minute are shown in Table 2. Two additional air samples were taken during the vapour exposure using a Royco 218 particle counter to confirm the absence of particles.

⁽¹⁾ 11 minutes is the theoretical time required for the concentration of vapour chamber to reach 90% of its final value under the conditions of exposure employed

⁽²⁾ Model 296, Anderson Samplers Inc., Atlanta, GA, U.S.A.

Nominal concentration

The nominal concentration of test substance in the exposure chamber was calculated from the amount of N-cyclohexyl maleimide particulate dispersed in the generator and the total air flow through the generator.

Chamber air temperature

The air temperature in the exposure chamber was measured with a mercury-in-glass thermometer and recorded at the start of exposure and then at 30-minute intervals during the 4-hour exposure.

Relative humidity

The relative humidity was measured using an infra-red vapour analyser. The humidity was recorded for the particulate exposure only, at start of the 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 rats were weighed daily from the day of delivery to the Huntingdon Research Centre until the end of the observation period.

Food and water consumption

The amount of food and water consumed by each cage of rats was measured daily from the day following arrival. The daily mean intakes of food and water for each rat were calculated from the recorded data.

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, and preserved in, buffered 10% formalin together with samples of the liver and kidneys for possible microscopic examination.

RESULTS

CHAMBER ATMOSPHERE CONDITIONS

Concentration of N-cyclohexyl maleimide

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

The mean concentrations of N-cyclohexyl maleimide in the chamber air, standard deviation (SD) and nominal concentration for each group were:

Group	N-cyclohexyl maleimide in air (mg/l)	SD	Nominal concentration (mg/l)
2	(a) 0.013	0.0008	0.18
3	(b) 0.015	0.0002	-
(a)	Particulate		
(b)	Vapour		

Particle size distribution

The results for the air samples taken for determination of the particle size distribution of N-cyclohexyl maleimide are shown in Table 2. The particle size data are summarised below:

Group	MMAD (μm)	σ_g	% < 1 μm	Size for 25% (μm)	% respirable (6 μm)
2 (0.013 mg/l)	4.3	3.23	10.7	1.9	61.3

The results are consistent with those expected for a powdered material. There were no particles, within the size range detectable by the Royco particle counter (0.5 - 10 μm), in the Group 3 test atmosphere.

Chamber air temperature and relative humidity

The mean chamber air temperature, 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)	25	0.0	57	6.7
2 (0.013 mg/l)	23	0.0	83	6.4
3 (0.015 mg/l)	24	0.5	-	-

There were no extremes of temperature or relative humidity considered likely to influence the results of the study.

CLINICAL OBSERVATIONS**Mortality**

The mortality is summarised below:

Group	Deaths		Total
	Male	Female	
1 (Control)	0/5	0/5	0/10
2 (0.013 mg/l)	3/5	5/5	8/10
3 (0.015 mg/l)	0/5	0/5	0/10

In Group 2 (0.013 mg/l) one male and 1 female rat died overnight following exposure. One male and 3 female rats were found dead (a.m.) on Day 1. One male rat and 1 female rat were found dead on Day 2 (a.m.) of the observation period.

Clinical signs**(a) During the exposure**

The incidence of clinical signs observed during exposure is shown in Table 3. The signs seen during exposure to particulate were considered to be consistent with inhalation of an irritant and toxic aerosol and included partial closing of the eyes, abnormal respiration, restless behaviour and wetness around the mouth and snout.

The signs seen during exposure to the vapour of N-cyclohexyl maleimide included partial closing of the eyes and restless behaviour.

(b) During the observation period

The incidence of clinical signs seen during the observation period is shown in Table 4. Column 0 of this table shows the observations made when the rats were removed from the exposure chamber. At this time signs evident in rats exposed to particulate N-cyclohexyl maleimide included death, abnormal respiration, wet fur around the snout and jaws, and brown staining around the snout and jaws. Some female rats were lethargic and had yellow staining around the urogenital region. The deaths occurred within 2 days of exposure and were considered to be related to the inhalation of particles of N-cyclohexyl maleimide.

Signs evident in rats exposed to vapour of N-cyclohexyl maleimide included noisy respiration, in addition, on the day of exposure, male rats showed signs of wet fur around the snout and jaws, and a few instances of staining around the urogenital region. One male rat had a red coloured secretion from the eyes.

The rats exposed to the vapour of N-cyclohexyl maleimide were normal in appearance and behaviour by Day 4 of the observation period.

Bodyweight

The group mean and individual bodyweights are shown in Table 5. The group mean bodyweights are also shown in Figure 3.

There were moderate decreases of bodyweight or reductions in the rate of bodyweight gain for up to 7 days in male rats exposed to a particulate aerosol of N-cyclohexyl maleimide. Rats exposed to the vapour of N-cyclohexyl maleimide had moderate decreases in bodyweight for up to 3 days.

Food consumption

The food consumption data are presented in Table 6.

Food consumption was reduced for up to 8 days in surviving male rats exposed to a particulate aerosol of N-cyclohexyl maleimide. Consumption was reduced in rats exposed to the vapour of N-cyclohexyl maleimide for 4 - 5 days.

Water consumption

The water consumption data are presented in Table 7.

Water consumption was reduced for 4 days in surviving male rats exposed to a particulate aerosol N-cyclohexyl maleimide. Consumption was reduced for up to 2 days in rats exposed to the vapour of N-cyclohexyl maleimide. Subsequently water consumption was similar to that of the control rats.

TERMINAL STUDIES

Lung weight to bodyweight ratio

The lung weight to bodyweight ratio for individual rats is shown in Table 8.

The lung weight to bodyweight ratios were higher than control values for all rats that died as a result of exposure to a particulate aerosol of N-cyclohexyl maleimide. The ratios were within normal limits for the control rats and for the rats that survived exposure to N-cyclohexyl maleimide in particulate or vapour form.

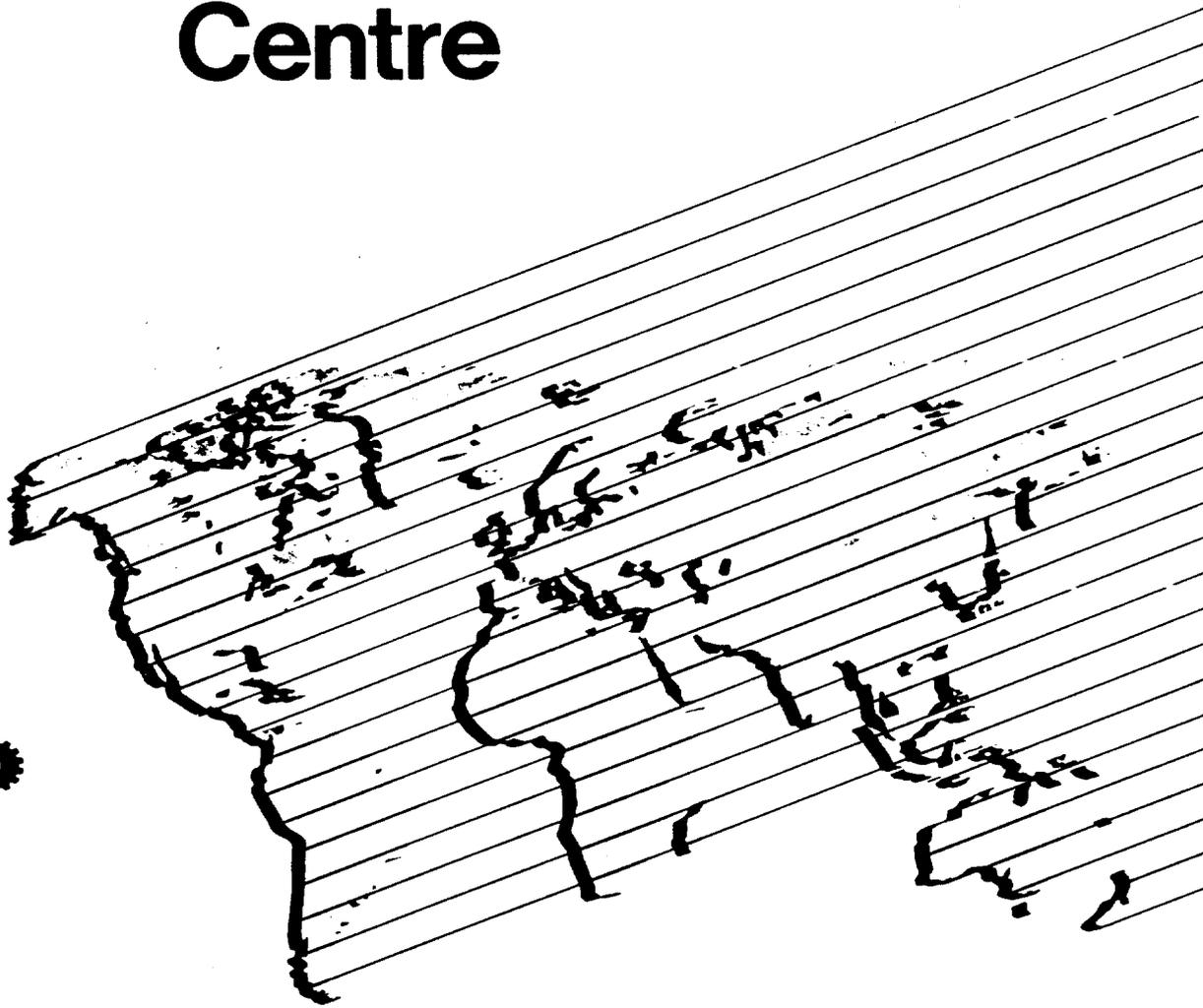
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HRC Report

N-CYCLOHEXYL MALEIMIDE:

ACUTE INHALATION TOXICITY
IN RATS
4-HOUR EXPOSURE

Huntingdon Research Centre



Estimation of the LC₅₀ (4-hour) for N-cyclohexyl maleimide

The LC₅₀ (4-hour) for N-cyclohexyl maleimide, administered to rats in the form of a particulate aerosol, is less than 0.013 mg/l of air.

Macroscopic pathology

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

The findings for rats that died as a result of exposure to N-cyclohexyl maleimide were typified by congestion of the lungs or raised areas on the lungs and instances of gas-filled stomachs. In addition, the decedent rats had brown staining around the snout and jaws.

Macroscopic abnormalities in rats that survived exposure to N-cyclohexyl maleimide were limited to one finding of dark subpleural foci on the lungs of 1 male rat exposed to the vapour of N-cyclohexyl maleimide.

Microscopic pathology

The lungs, liver and kidneys were preserved in buffered 10% formalin for possible microscopic pathology.

The tissues will be retained for at least 3 months following issue of this report.

FIGURE 1
Wright dust generator

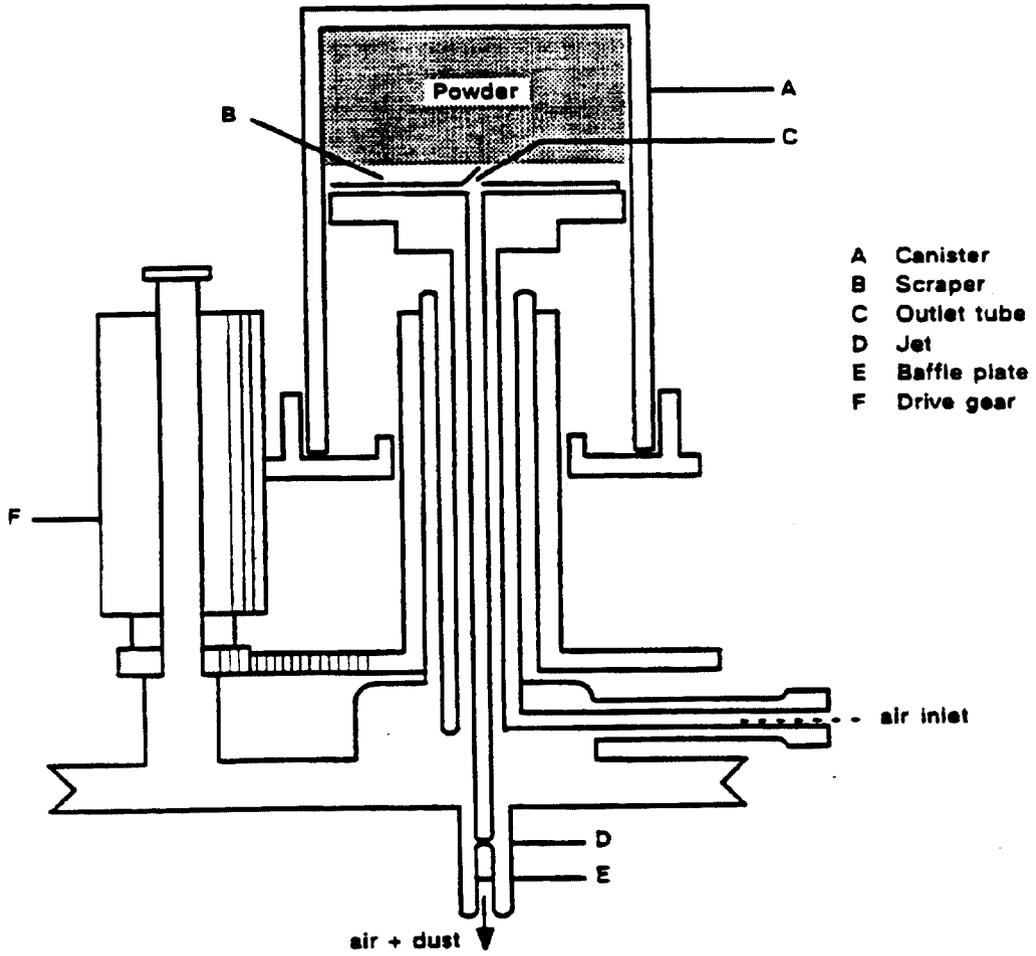
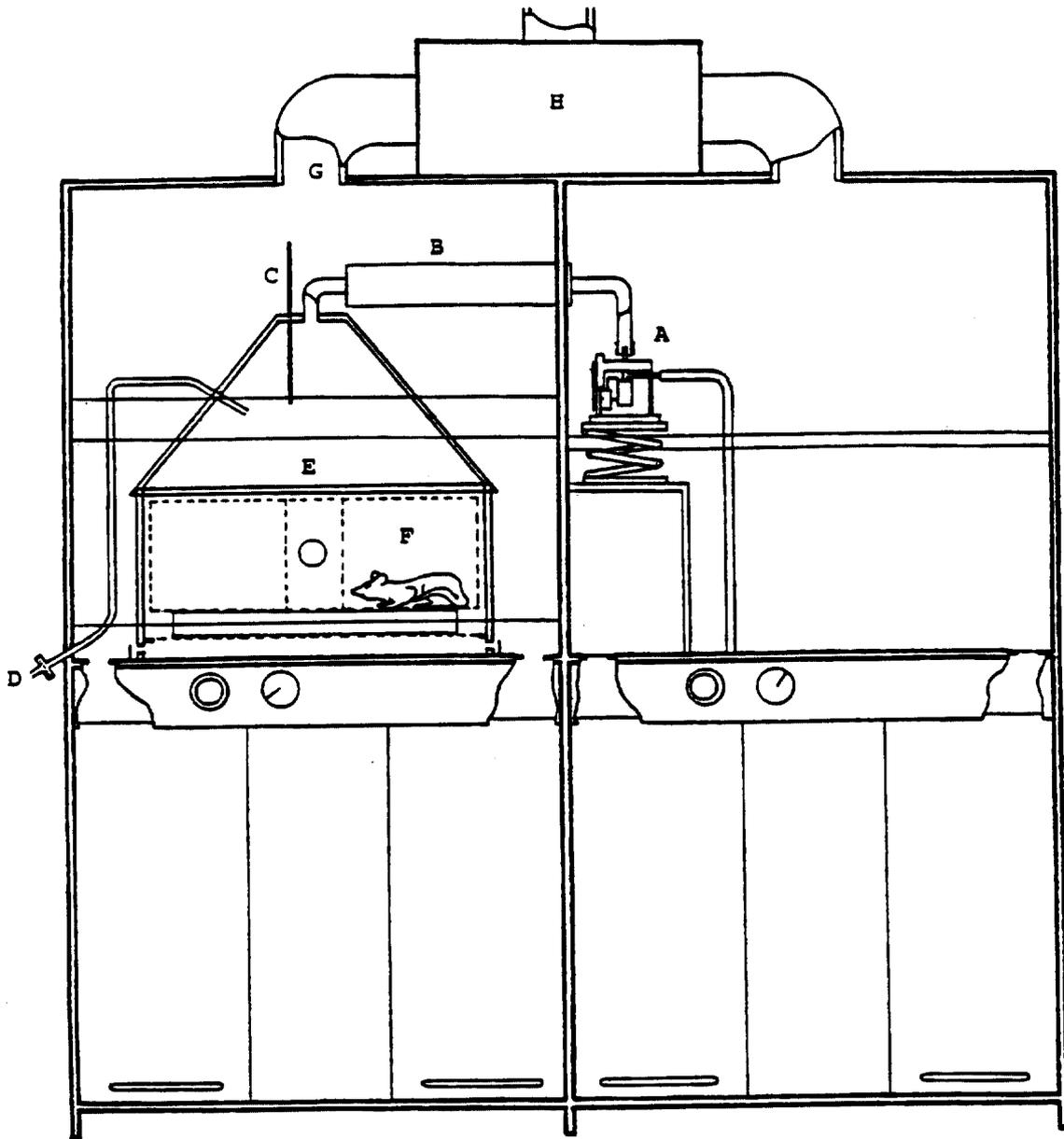


FIGURE 2

Exposure system



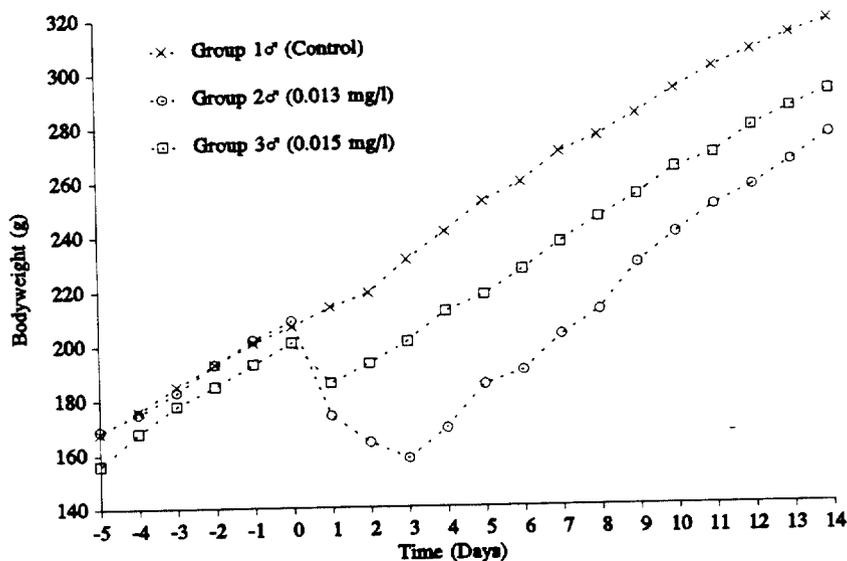
- A Wright Dust Feed Mechanism
- B Aerosol neutraliser
- C Thermometer
- D Sample line to water vapour analyser

- E Exposure chamber
- F Holding cage
- G Extract from outer chamber
- H Filter/Extract unit

FIGURE 3

Group mean bodyweights

(a) Male rats



(b) Female rats

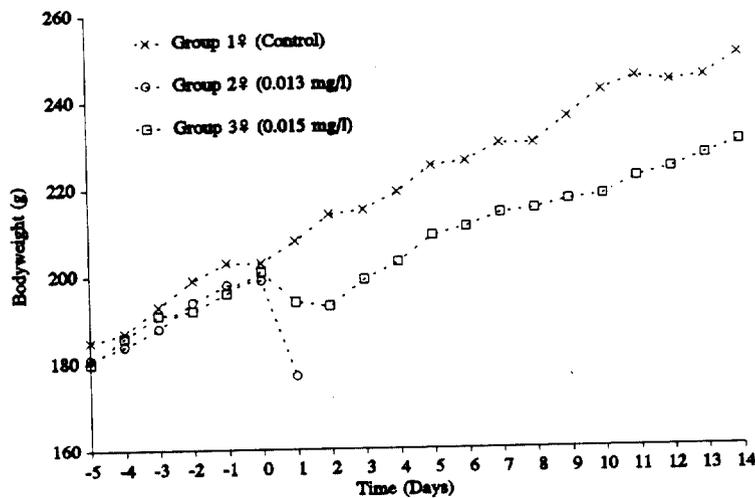


TABLE 1

Concentrations of N-cyclohexyl maleimide

Group	Sample	Time	Amount in air (mg/l)	Nominal (mg/l) (a)
2	2.1	0h : 30m	0.012	0.18
	2.2	1h : 00m	0.013	
	2.3	2h : 00m	0.014	
	2.4	3h : 00m	0.013	
	2.5	3h : 50m	0.014	
	Mean		0.013	
	SD		0.0008	
3	3.1	0h : 30m	0.012	-
	3.2	1h : 00m	0.012	
	3.3	2h : 00m	0.017	
	3.4	3h : 00m	0.016	
	3.5	3h : 50m	0.016	
	Mean		0.015	
	SD		0.002	

- (a) Calculated from the weight of test substance dispersed and the total volume of air supplied to the exposure system
SD Standard deviation

TABLE 2

Particle size distribution of N-cyclohexyl maleimide

(a) Gravimetric results

Group	Sample	Time taken	Stage	Cut-off size (μm)	Amount collected (mg)	
					PSD 1	PSD 2
2	PSD 1	1h : 30m	3	9.8	0.15	0.13
	PSD 2	3h : 30m	4	6.0	0.22	0.21
			5	3.5	0.26	0.22
			6	1.55	0.23	0.21
			7	0.93	0.01	0.02
			8	0.52	0.01	0.01
			Filter	0.0	0.08	0.06
			Totals		0.96	0.86

(b) Calculations

Cut-off size (μm)	% less than size (cumulative)
9.8	84.6
6.0	61.0
3.5	34.6
1.55	10.4
0.93	8.8
0.52	7.7
MMAD	4.3 μm
σ_g	3.23
% < 1 μm	10.7
25% size	1.938 μm
% respirable	61.3

MMAD Mass median aerodynamic diameter
 σ_g Standard geometric deviation

TABLE 3
Clinical signs during exposure

Group	Signs	Number 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♂ (0.013 mg/l)	Partial closing of eyes	5	5	5	5	5	5	5
	Wet snout			5	5	5	5	5
	Wet around the mouth			5	5	5	5	5
	Irregular respiration		5	5	5	5	5	5
	Gasping					5	5	5
	Exaggerated respiratory movements					5	5	5
2♀ (0.013 mg/l)	Restless		5	5	5	5	5	5
	Partial closing of eyes	5	5	5	5	5	5	5
	Wet snout			5	5	5	5	5
	Wet around the mouth			5	5	5	5	5
	Irregular respiration		5	5	5	5	5	5
	Gasping					5	5	5
3♂ (0.015 mg/l)	Exaggerated respiratory movements		5	5	5	5	5	5
	Restless		5	5	5	5	5	5
	Normal appearance and behaviour	5	5	5	5	5	5	5
3♀ (0.015 mg/l)	Eyes partially closed			5	5	5	5	5
	Restless behaviour			5	5	5	5	5
	Normal appearance and behaviour	5	5	5	5	5	5	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
	Brown staining around snout and/or jaws	4	2	2	1	1	1	1	1							
	Wet fur around snout and jaws	4														
	Gasping	5	4						1	1	1	1	1	1	1	1
	Râles															
	Exaggerated respiratory movements			2	2	2	2	2	2	2	1	1	1	1	1	1
	Noisy respiration			2	2	1	1	1	1	1	1	1	1	1	1	1
	Dead (total)		2**	3	3	3	3	3	3	3	3	3	3	3	3	3
	2♀ (0.013 mg/l)	Brown staining around snout and/or jaws														
Wet fur around snout and jaws																
Yellow staining in urogenital region		4														
Gasping		2														
Lethargic		5	3													
Dead (total)		1	3													
		4+	5	5	5	5	5	5	5	5	5	5	5	5	5	5

* Clinical signs recorded after exposure on the day of exposure

** One animal found dead at pm clinical signs check

+ Two animals found dead at pm clinical signs 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♂ (0.015 mg/l)	Normal appearance and behaviour				3	5	5	5	5	5	5	5	5	5	5	5
	Wet fur snout and jaws	5														
	Stained urogenital region	2														
	Red coloured secretion from eyes	1														
	Noisy respiration	5	5	5	2											
3♀ (0.015 mg/l)	Normal appearance and behaviour				3	5	5	5	5	5	5	5	5	5	5	5
	Noisy respiration	5	5	5	2											

* Clinical signs recorded after exposure on the day of exposure

TABLE 5
Individual and group mean bodyweights (g)

Group	Rat	Pre-exposure											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	163	171	179	189	193	200	197	203	214	227	241	243	258	260	270	277	284	290	294	302					
	22	176	183	195	200	211	215	229	240	248	261	274	277	290	296	307	318	320	325	333	336					
	23	165	175	184	193	201	205	215	220	232	241	251	260	269	277	280	290	298	306	311	318					
	24	167	172	182	191	199	208	213	218	230	236	248	260	268	274	283	292	301	306	313	316					
	25	171	177	185	192	199	205	214	216	230	240	246	255	265	275	281	290	303	310	315	318					
	Mean	168	176	185	193	201	207	214	219	231	241	252	259	270	276	284	293	301	307	313	318					
1♀ (Control)	26	180	183	188	195	199	196	209	207	215	217	223	226	226	224	233	243	245	240	245	250					
	27	189	191	195	201	208	211	212	217	219	225	224	230	235	237	237	245	248	250	243	254					
	28	189	185	198	203	202	200	207	216	210	210	222	222	225	221	229	237	235	232	238	245					
	29	182	189	193	197	202	206	205	217	221	225	228	225	236	242	247	241	253	254	251	248					
	30	183	185	193	199	202	202	208	211	211	214	226	226	227	228	234	243	245	242	250	251					
	Mean	185	187	193	199	203	203	208	214	215	218	225	226	230	230	236	242	245	244	245	250					
2♂ (0.013 mg/l)	31	165	170	178	186	197	201	166	159	153	164	185	190	199	208	229	241	247	253	262	273					
	32	171	175	188	200	209	217	183	Dead																	
	33	157	162	171	178	191	197	165	168	163	174	184	190	206	216	229	239	253	261	270	278					
	34	183	189	192	205	207	219	180	Dead																	
	35	168	178	188	198	204	210	Dead																		
	Mean	169	175	183	193	202	209	174	164	158	169	185	190	203	212	229	240	250	257	266	276					
2♀ (0.013 mg/ml)	36	176	180	182	185	189	194	167	Dead																	
	37	184	187	195	201	208	209	186	Dead																	
	38	188	191	196	200	204	204	178	Dead																	
	39	176	177	188	192	194	194	Dead																		
	40	182	180	180	193	193	195	Dead																		
	Mean	181	183	188	194	198	199	177																		

0 Before exposure on day of exposure

D Dead

TABLE 5
(Individual and group mean bodyweights - continued)

Group	Rat	Pre-exposure						Day of observation													
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3♂ (0.015 mg/l)	81	154	166	177	184	196	205	190	195	203	213	220	230	240	248	257	271	278	290	302	299
	82	149	161	171	180	184	192	178	181	191	200	205	217	230	237	246	255	260	269	275	282
	83	150	172	181	183	192	200	188	194	199	213	216	224	231	239	244	254	258	269	277	282
	84	159	171	177	188	193	201	181	194	204	212	218	226	234	241	248	258	262	266	268	276
	85	158	171	183	191	200	208	195	203	207	220	231	240	249	263	273	282	289	301	308	319
	Mean	156	168	178	185	193	201	186	193	201	212	218	227	237	246	254	264	269	279	286	292
3♀ (0.015 mg/l)	86	176	181	181	179	193	196	188	184	192	198	204	198	207	209	204	208	214	217	217	219
	87	183	183	193	197	201	199	190	197	202	208	213	221	220	220	225	229	231	229	235	240
	88	186	195	199	203	198	207	202	198	205	203	215	219	220	213	222	223	226	222	232	234
	526R	177	186	191	193	192	198	191	186	190	199	200	202	202	209	210	212	212	220	224	224
	90	179	185	192	187	198	204	198	198	206	209	215	213	222	223	222	219	225	234	229	228
	Mean	180	186	191	192	196	201	194	193	199	203	209	211	214	215	217	218	222	224	227	229

0 Before exposure on day of exposure
R Replacement rat. Original rat (89♀) replaced because of low weight gain

TABLE 6

Group mean daily food consumption (g/rat)

Group	Days																		
	Pre-exposure					Post exposure													
	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1♂ (Control)	22	28	26	26	23	22	25	27	31	32	31	33	32	31	34	32	33	32	30
2♂ (0.013 mg/l)	22	23	25	26	24	0	5	9	16	22	22	25	26	33	35	33	34	35	34
3♂ (0.015 mg/l)	27	27	27	26	27	11	19	20	22	24	26	28	30	30	32	31	31	30	32
1♀ (Control)	20	23	23	20	20	22	23	21	23	24	23	25	23	26	26	26	24	24	24
2♀ (0.013 mg/l)	20	21	22	20	21	2	0												
3♀ (0.015 mg/l)	20	22	20	19	20	13	15	17	18	22	20	23	21	23	22	23	24	23	21

TABLE 7

Group mean daily water consumption (g/rat)

Group	Days																		
	Pre-exposure					Post exposure													
	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1♂ (Control)	25	27	26	27	24	27	28	29	30	31	32	32	30	32	34	31	32	33	35
2♂ (0.013 mg/l)	25	25	25	25	25	1	6	3	8	27	23	27	28	35	34	31	32	31	34
3♂ (0.015 mg/l)	28	28	28	27	27	14	24	23	25	25	26	29	29	30	32	33	33	32	31
1♀ (Control)	23	26	26	22	22	26	26	23	26	24	25	29	24	28	29	26	24	26	26
2♀ (0.013 mg/l)	24	24	25	23	23	4	4	0											
3♀ (0.015 mg/l)	25	27	23	25	26	21	19	23	25	31	26	29	27	29	27	31	29	29	27

TABLE 8

Lung weight to bodyweight ratios

Group	Rat	Lung weight (g)	Bodyweight (g)	Lung to bodyweight ratio (LW x 100/BW)		
				Survivors	Decedents	
1♂ (Control)	21	1.83	302	0.61		
	22	1.72	336	0.51		
	23	1.82	318	0.57		
	24	1.61	316	0.51		
	25	2.04	318	0.64		
				Mean	0.57	
				SD	0.058	
1♀ (Control)	26	1.39	250	0.56		
	27	1.27	254	0.50		
	28	1.58	245	0.64		
	29	1.39	248	0.56		
	30	1.26	251	0.50		
				Mean	0.55	
				SD	0.058	
2♂ (0.013 mg/l)	31	1.45	273	0.53		
	32	1.50	183		0.82	
	33	1.47	278	0.53		
	34	2.62	180		1.46	
	35	2.47	210		1.18	
				Mean	0.53	1.15
				SD	-	0.321
2♀ (0.013 mg/l)	36	1.43	167		0.86	
	37	2.42	186		1.30	
	38	1.35	178		0.76	
	39	1.82	194		0.94	
	40	2.62	195		1.34	
				Mean		1.04
				SD		0.264

SD Standard deviation

TABLE 8

(Lung weight to bodyweight ratios - continued)

Group	Rat	Lung weight (g)	Bodyweight (g)	Lung to bodyweight ratio (LW x 100/BW)	
				Survivors	Decedents
3♂ (0.015 mg/l)	81	1.21	299	0.40	
	82	1.25	282	0.44	
	83	1.28	282	0.45	
	84	1.29	276	0.47	
	85	1.63	319	0.51	
				Mean	0.45
			SD	0.040	
3♀ (0.015 mg/l)	86	1.33	219	0.61	
	87	1.40	240	0.58	
	88	1.17	234	0.50	
	526R	1.38	224	0.62	
	90	1.40	228	0.61	
				Mean	0.58
			SD	0.049	

SD Standard deviation

R Replacement rat

APPENDICES

APPENDIX 1**Method of analysis for N-cyclohexyl maleimide****1. Instrumentation and apparatus**

Instruments: Cecil CE-599 Scanning UV spectrophotometer.
Apparatus: Quartz 1 cm cuvettes
General laboratory glassware.

2. Reagents

Methanol: 'HiPerSolv' grade BDH.
Cyclohexyl maleimide: Supplied by Sponsor.

3. Preparation of sample solutions for analysis

The sample solutions from the liquid impinger were rinsed into a 25 ml volumetric flask with methanol.

The solutions were diluted to volume using methanol.

4. UV analysis**4.1. Operating conditions**

Analysis wavelength: 215 nm.
Resolution: 4 nm.
Range: 1 AUFS.

APPENDIX 1**(Method of analysis - continued)****4.2. Analysis of samples**

An aliquot of the sample was placed in a matched cuvette and placed in the sample beam of the instrument. A second matched cuvette containing methanol was placed in the reference beam of the instrument. The absorbance was measured at 215 nm. The concentration of the sample solution was given from the expression below:

$$C = \frac{A - I}{S}$$

where C = concentration of cyclohexyl maleimide ($\mu\text{g/ml}$)
A = absorbance at 215 nm against methanol
I = intercept of standard curve
S = gradient of standard curve

4.3. Standardisation

Approximately 30 mg of cyclohexyl maleimide was accurately weighed into a 100 ml volumetric flask and dissolved in methanol. This solution was diluted to obtain three standards spanning the range of sample concentrations expected.

Five replicates of each standard were measured and the mean value for each standard calculated. A standard curve was obtained by regression analysis of mean absorbance against concentration.

APPENDIX 2

Macroscopic pathology

Group	Rat	Region/organ affected	Observation
1♂ (Control)	21	Lungs	Small depressed areas on all lobes of lungs
	22		No abnormalities detected
	23		No abnormalities detected
	24		No abnormalities detected
	25		No abnormalities detected
1♀ (Control)	26		No abnormalities detected
	27		No abnormalities detected
	28		No abnormalities detected
	29		No abnormalities detected
	30		No abnormalities detected
2♂ (0.013 mg/l)	31		No abnormalities detected
	32*	External appearance Stomach Lungs	Brown staining around snout and jaws Gas-filled Appeared swollen, raised areas on all lobes
	33		No abnormalities detected
	34*	External appearance Stomach and gastrointestinal tract Lungs	Brown staining around snout and jaws. Yellow staining around urogenital region Gas-filled Congested
	35*	External appearance Stomach Lungs	Brown staining around snout Gas-filled Congested
	36*	External appearance	Clear fluid around nostrils
	37*	External appearance	Brown staining around snout and jaws Yellow staining around urogenital region
	38*	Lungs External appearance	Congested Brown staining around snout and jaws Clear fluid around nose
	39*	Lungs External appearance	Raised areas on all lobes Brown staining around snout and jaws
	40*	Lungs External appearance Stomach Lungs	Swollen and congested Brown staining around snout Gas-filled Congested

* Decedents

APPENDIX 2

(Macroscopic pathology - continued)

Group	Rat	Region/organ affected	Observation
3♂ (0.015 mg/l)	81	Lungs	No abnormalities detected
	82		No abnormalities detected
	83		Dark subpleural foci, azygous lobe
	84		No abnormalities detected
	85		No abnormalities detected
3♀ (0.015 mg/l)	86		No abnormalities detected
	87		No abnormalities detected
	88		No abnormalities detected
	526R		No abnormalities detected
	90		No abnormalities detected

R Replacement rat



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

N. Kohno
Chemicals & Plastics Department
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

NOV 17 1994

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite this number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests" .

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EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12729 A

Triage of 8(e) Submissions

Date sent to triage: NOV 17 1994

NON-CAP

CAP

Submission number: 12729A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document: <u>0</u> 1 2 pages <u>1</u>	pages <u>1, TABS</u>
Notes:	
Contractor reviewer: <u>POP</u>	Date: <u>9/23/94</u>

CHEMICAL TRIAGE TRACKING DBASE ENTRY FORM

CLIENTS DATA: Submission # 8EIQ. 1093-12729 SEQ. A

TYPE: INT SUPP FLWP

SUBMITTER NAME: Macubeni America Corporation

SUB. DATE: 10/14/93 OTS DATE: 10/19/93 CSRAD DATE: 11/01/93

CHEMICAL NAME: ~~911-695~~
1631-25-0

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)
DISPOSITION:
0678 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

0401 VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP. USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EPI/CLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL. TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCC/REL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0299 OTHER	01 02 04
0211 CHIR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0212 ACUTE TOX. (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0239 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

TRIAJE DATA: YES (CONTINUE) NO (DROP) DETERMINE

NON-CBI INVENTORY: YES (DROP/REFER) NO (CONTINUE) REFER:

SPECIES: RAT

TOXICOLOGICAL CONCERN: LOW MED HIGH

USE: _____ PRODUCTION: _____

COMMENTS: Non-Cap

> <ID NUMBER>

8(e)-12729A

> <TOX CONCERN>

H

> <COMMENT>

ACUTE INHALATION TOXICITY IN THE RAT IS OF HIGH CONCERN. THE 4-HOUR LC50 IS BETWEEN 0.013 AND 0.015 MG/L. DOSAGES AND MORTALITY DATA ARE AS FOLLOWS: 0.013 MG/L (3/5 M, 5/5 F) AND 0.015 MG/L (0/5 M, 0/5 F). 0.013 MG/L WAS DOSED AS A PARTICULATE AEROSOL AND 0.015 MG/L WAS DOSED AS A VAPOR. CLINICAL OBSERVATIONS FOR THE PARTICULATE INCLUDED: PARTIAL CLOSING OF THE EYES, WET AROUND THE SNOUT AND MOUTH, RESTLESS BEHAVIOR, ABNORMALITIES TO RESPIRATION, BROWN STAINING AROUND SNOUT AND JAWS, LETHARGY, YELLOW STAINING AROUND THE UROGENITAL REGIONS. ONE RAT HAD RED COLORED DISCHARGE FROM THE EYES. CLINICAL SIGNS FOR VAPOR EXPOSURE INCLUDED: PARTIAL CLOSING OF THE EYES AND RESTLESSNESS. RATS EXPOSED TO THE VAPOR WERE NORMAL BY DAY 4. NECROPSY RESULTS OF THE ANIMALS THAT DIED AFTER EXPOSURE TO THE PARTICULATE SHOWED CONGESTION OF THE LUNGS OR RAISED AREAS ON THE LUNGS AND INSTANCES OF GAS FILLED STOMACHS. ON MALE RAT EXPOSED TO THE VAPOR HAD DARK SUBPLEURAL FOCI ON THE LUNGS.