

Katherine E. Reed, Ph.D.
Staff Vice President

3M Environmental, Health and
Safety Operations

900 Bush Avenue, Building 42-2E-26
PO Box 33331
St. Paul, MN 55133-3331
651 778 4331

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RE: TSCA 8(E) SUBSTANTIAL RISK NOTICE ON:
Isopropylmorpholine CASRN 1004-14-4 and 1331-24-4

Dear Sirs:

3M has received the final report for a study on the acute oral toxicity in rats conducted on a research and development chemical [*isopropylmorpholine*] that 3M purchases from a supplier. At an exposure dose level of 300mg/kg body weight, the rats showed possible signs of neurotoxicity.

The study was conducted by NOTOX Safety and Environmental Research Laboratory and carried out based on the guidelines described in: OECD No. 423 (2001) "Acute Toxicity-Oral, Acute Toxic Class Method." Three female Wistar rats were dosed by oral gavage at 300mg/kg body weight. Using the protocol's stepwise procedure, additional groups of rats were administered 300 and subsequently 2000mg/kg body weight. No rats died in the 300mg/kg dose group, but they showed clinical signs of lethargy, hunched posture and uncoordinated movements. It should be noted, however, that isopropylmorpholine is a corrosive material. All three rats in the 2000mg/kg dose group died within 15 minutes post-treatment.

The surviving animals from the 300mg/kg dose group recovered from the symptoms by day 2 post-treatment, and their macroscopic post mortem examination did not reveal and abnormalities. The 2000mg/kg group had dark red discoloration of their stomach at post mortem examination.

According to the OECD 423 test guideline, the LD50 cut-off value for the classification of chemical substances was considered to be 500mg/kg body weight for this test substance. The final report is enclosed.

Please contact Dayna Blomquist (651-736-5413) if you have any questions or if we can provide additional information.

Sincerely,

Katherine E. Reed

Katherine E. Reed

Staff Vice President, Environmental Health and Safety Operations



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REPORT

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Study Title

**ASSESSMENT OF ACUTE ORAL TOXICITY WITH
MTDID 7144
IN THE RAT (ACUTE TOXIC CLASS METHOD)**

Author

Dr. M.J.J. Hooiveld

Study completion date

June 6, 2006

Test Facility

NOTOX B.V.
Hambakenwetering 7
5231 DD 's-Hertogenbosch
The Netherlands

Laboratory Project Identification

NOTOX Project 458911
NOTOX Substance 163134/A
3M MTDID Number 7144
3M Study ID Number 06-049

TABLE 2 CLINICAL SIGNS

TEST DAY		1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HOURS AFTER TREATMENT	MAX GRADE	0	2	4													
FEMALES 2000 MG/KG																	
Ptoxis	(3)	1	*														
ANIMAL 8																	
Spasms																	
Saltatory spasms	(3)	3	*														
Tremor (General)	(3)	3	*														
Posture																	
Ventric-lateral recumbency	(1)	1	*														
Breathing																	
Slow breathing	(1)	1	*														
Skin / fur / plumage																	
Piloerection	(1)	1	*														
Secretion / excretion																	
Chromodacryorrhoea (Shout)	(3)	2	*														
Various																	
Ptoxis	(3)	2	*														
ANIMAL 9																	
Behavior																	
Lethargy	(3)	2	*														
Spasms																	
Tremor (General)	(3)	3	*														
Posture																	
Flat posture	(1)	1	*														
Hunched posture	(1)	1	*														
Gait / motility																	
Uncoordinated movements	(3)	3	*														
Breathing																	
Slow breathing	(1)	1	*														
Skin / fur / plumage																	
Piloerection	(1)	1	*														
Various																	
Ptoxis	(3)	1	*														

TABLE 3 BODY WEIGHTS (GRAM)

SEX/DOSE LEVEL	ANIMAL	DAY 1	DAY 8	DAY 15
FEMALES 300 MG/KG				
	1	189	230	241
	2	193	233	238
	3	186	222	227
	MEAN	189	228	235
	ST DEV	4	6	7
	N	3	3	3
FEMALES 300 MG/KG				
	4	183	220	246
	5	178	218	243
	6	164	210	229
	MEAN	175	216	239
	ST DEV	10	5	8
	N	3	3	3

-- = SIGN NOT OBSERVED / - = OBSERVATION NOT PERFORMED / * = ANIMAL DEAD

TABLE 1 MORTALITY DATA

TEST DAY	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HOURS AFTER TREATMENT		0	2	4													
FEMALES 300 MG/KG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 300 MG/KG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 2000 MG/KG	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

TABLE 2 CLINICAL SIGNS

TEST DAY	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HOURS AFTER TREATMENT		0	2	4													
		MAX		GRADE													

FEMALES 300 MG/KG																	
ANIMAL 1																	
Posture																	
Hunched posture	(1)	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Gait / motility																	
Uncoordinated movements	(3)	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin / fur / plumage																	
Piloerection	(1)	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 2																	
Posture																	
Hunched posture	(1)	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin / fur / plumage																	
Piloerection	(1)	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 3																	
Posture																	
Hunched posture	(1)	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin / fur / plumage																	
Piloerection	(1)	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 300 MG/KG																	
ANIMAL 4																	
Posture																	
Hunched posture	(1)	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 5																	
Posture																	
Hunched posture	(1)	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 6																	
Posture																	
Hunched posture	(1)	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 2000 MG/KG																	
ANIMAL 7																	
Behavior																	
Lethargy	(3)	2	+														
Spasms																	
Saltatory spasms	(3)	1	+														
Tremor (General)	(3)	3	+														
Posture																	
Hunched posture	(1)	1	+														
Gait / motility																	
Uncoordinated movements	(3)	3	+														
Breathing																	
Slow breathing	(1)	1	+														
Skin / fur / plumage																	
Piloerection	(1)	1	+														
Various																	

- = SIGN NOT OBSERVED / . = OBSERVATION NOT PERFORMED / + = ANIMAL DEAD

MTDID 7144

NOTOX Project 458911

- according to the EC criteria for classification and labelling requirements for dangerous substances and preparations (Council Directive 67/548/EEC), MTDID 7144 should be labelled as: harmful if swallowed (R22).

7. RESULTS

	Dose level	Date of treatment
First set of females	300 mg/kg	April 13, 2006
Second set of females	300 mg/kg	April 19, 2006
Third set of females	2000 mg/kg	April 21, 2006

7.1. Mortality (Table 1)

The incidence of mortality was as follows presented in chronological order of treatment:

Dose level	Mortality	Date of treatment
300 mg/kg	0/3	April 13, 2006
300 mg/kg	0/3	April 19, 2006
2000 mg/kg	3/3	April 21, 2006

The dead animals were found within 15 minutes post-treatment

7.2. Clinical Signs (Table 2)

Clinical signs observed during the study period were as follows:

Dose level	Clinical signs
300 mg/kg	Hunched posture, uncoordinated movements, piloerection
2000 mg/kg	Lethargy, spasms, flat and/or hunched posture, uncoordinated movements, slow breathing, piloerection, ptosis, ventro-lateral recumbency, chromodacryorrhoea.

The surviving animals had recovered from the symptoms by day 2

7.3. Body Weights (Table 3)

The body weight gain shown by the surviving animals over the study period was considered to be similar to that expected of normal untreated animals of the same age and strain.

7.4. Macroscopic Findings (Table 4)

Dark red discolouration of the stomach and many dark red foci in duodenum and jejunum were found in the animals that died during the study, at macroscopic post mortem examination. Macroscopic post mortem examination of the surviving animals at termination did not reveal any abnormalities.

8. CONCLUSION

The oral LD50 value of MTDID 7144 in Wistar rats was established to be within the range of 300-2000 mg/kg body weight.

According to the OECD 423 test guideline the LD50 cut-off value was considered to be 500 mg/kg body weight.

Based on these results:

- according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations (New York and Geneva, 2003), MTDID 7144 should be classified as harmful if swallowed (Category 4).

Clinical signs	At periodic intervals on the day of dosing (day 1) and once daily thereafter, until day 15. The symptoms were graded according to fixed scales and the time of onset, degree and duration were recorded. Maximum grade 4 grading slight (1) to very severe (4) Maximum grade 3 grading slight (1) to severe (3) Maximum grade 1 presence is scored (1).
Necropsy	At the end of the observation period, animals were sacrificed by oxygen/carbon dioxide procedure and subjected to necropsy. Descriptions of all internal macroscopic abnormalities in all animals were recorded.

6.7. Electronic data capture

Observations/measurements in the study were recorded electronically using the following programme(s):

- REES version 1.5 (REES scientific, Trenton, NJ, USA): Environmental monitoring.
- TOXDATA version 8.0 (NOTOX B.V., 's-Hertogenbosch, The Netherlands): Clinical signs, Body weights.

6.8. Interpretation

The oral LD₅₀ value of the test substance was ranked within the following ranges: 0-5, 5-50, 50-300 or 300-2000 mg/kg b.w. or as exceeding 2000 mg/kg b.w. The LD₅₀ cut-off value was established based on OECD guideline 423.

No statistical analysis was performed (The method used is not intended to allow the calculation of a precise LD₅₀ value).

The results were evaluated according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations (New York and Geneva, 2003) and the EC criteria for classification and labelling of dangerous substances and preparations (Council Directive 67/548/EEC and all adaptations to technical progress and amendments of this Directive published in the Official Journal of the European Communities).

6.9. List of deviations

6.9.1. List of protocol deviations

There were no deviations from the protocol.

6.9.2. List of standard operating procedures deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

Health inspection A health inspection was performed prior to commencement of treatment to ensure that the animals were in a good state of health

6.3. Animal husbandry

Conditions

Animals were housed in a controlled environment, in which optimal conditions were considered to be approximately 15 air changes per hour, a temperature of $21.0 \pm 3.0^\circ\text{C}$ (actual range: 20.8 – 23.1°C), a relative humidity of 30-70% (actual range: 36 – 67%) and 12 hours artificial fluorescent light and 12 hours darkness per day.

Accommodation

Group housing of 3 animals per cage in labelled Macrolon cages (MIV type, height 18 cm.) containing sterilised sawdust as bedding material (Woody-Clean type 3/4, Tecnilab-BMI BV, Someren, The Netherlands) and paper as cage-enrichment (Enviro-ori, Tecnilab-BMI BV, Someren, The Netherlands).

Acclimatisation period was at least 5 days before start of treatment under laboratory conditions.

Diet

Free access to standard pelleted laboratory animal diet (from Altromin (code VRF 1), Lage, Germany).

Water

Free access to tap water.

Results of analysis for each batch of diet (nutrients) and results of quarterly analysis of diet (contaminants), sawdust, paper and water were assessed and did not reveal any findings that were considered to have affected the study integrity. All certificates and results of analysis are retained in the NOTOX archives

6.4. Study design

The toxicity of the test substance was assessed by stepwise treatment of groups of 3 females. The first group was treated at a dose level of 300 mg/kg. The absence or presence of mortality of animals dosed at one step determined the next step, based on the test procedure defined in the guidelines. The onset, duration and severity of the signs of toxicity were taken into account for determination of the time interval between the dose groups

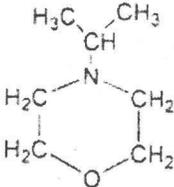
6.5. Treatment

Method	Oral gavage using a stainless steel stomach tube.
Fasting	Food was withheld overnight (for a maximum of 20 hours) prior to dosing until 3-4 hours after administration of the test substance.
Frequency	Single dosage, on day 1.
Dose level (volume)	300 mg/kg (20 ml/kg) body weight 2000 mg/kg (20 ml/kg) body weight.

6.6. Observations

Mortality/Viability	Twice daily. The time of death was recorded as precisely as possible.
Body weights	Days 1 (pre-administration), 8 and 15

6. MATERIALS AND METHODS**6.1. Test substance****6.1.1. Test substance information**

Identification	MTDID 7144
Structure	
Molecular formula	C ₇ H ₁₅ NO
Molecular weight	129.2
CAS Number	1331-24-4
Description	Colourless liquid (determined at NOTOX)
Batch	TC36B14R
Purity	≈ 99.68%
Test substance storage	At room temperature in the dark
Stability under storage conditions	Stable
Expiry date	30 December 2007

6.1.2. Study specific test substance information

Specific Gravity	0.9146
pH	10.7 at concentration of 10%
Stability at higher temperatures	Yes
Stability in vehicle:	
• Water	At least 96 hours
Solubility in vehicle:	
• Water	Yes, >10 %

6.1.3. Test substance preparation

Vehicle	Water (Milli-U) (Millipore Corporation, Bedford, USA)
Rationale	The vehicle was selected based on trial formulations performed at NOTOX and on test substance data supplied by the sponsor.
Preparation	The formulations (w/w) were prepared within 4 hours prior to dosing. Adjustment was made for specific gravity of the test substance. Homogeneity was accomplished to a visually acceptable level.

6.2. Test System

Species	Rat, Wistar strain Cri WI (outbred, SPF-Quality). Recognised by international guidelines as the recommended test system (e.g. OECD, EC). Source: Charles River Deutschland, Sulzfeld, Germany.
Number of animals	9 Females (nulliparous and non-pregnant). Each dose group consisted of 3 animals.
Age and body weight	Young adult animals (approx. 8 weeks old) were selected. Body weight variation did not exceed +/- 20% of the sex mean.
Identification	Earmark.

Japanese Ministry of Agriculture, Forestry and Fisheries (JMAFF), 12 Nousan, Notification No 8147, November 2000, including the most recent partial revisions.

5.4. Storage and retention of records and materials

Records and materials pertaining to the study including protocol, raw data, specimens (except specimens requiring refrigeration or freezing) and the final report are retained in the NOTOX archives for a period of at least 10 years after finalization of the report. After this period, the sponsor will be contacted to determine whether raw data and specimens should be returned to them, retained or destroyed on their behalf.

Those specimens requiring refrigeration or freezing will be retained by NOTOX for as long as the quality of the specimens permits evaluation but no longer than three months after finalization of the report.

NOTOX will retain a test substance sample until the expiry date, but no longer than 10 years after finalization of the report. After this period the sample will be destroyed.

5. INTRODUCTION

5.1. Preface

Sponsor	3M Medical Department 3M Corporate Toxicology – Regulatory Services 3M Center, 220-06-E-03 ST. PAUL, MINNESOTA 55144-1000 USA
Study Monitor	Dr. P. H. Lieder 3M Corporate Toxicology – Regulatory Services 3M Center Building 0220-06-E-03 ST. PAUL, MINNESOTA 55144-1000 USA
Test Facility	NOTOX B.V. Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands
Study Director	Dr. M. J. J. Hooiveld
Study Plan (in-life phase)	Start : 13 April 2006 Completion : 21 April 2006

5.2. Aims of the study

The objective of this study was to assess the toxicity of the test substance when administered in a single dose to female rats at one or more defined dosages. Furthermore, the results of the study allowed the test substance to be ranked according to most classification systems currently in use.

This study should provide a rational basis for risk assessment in man.

The oral route was selected, as it is a possible route of human exposure during manufacture, handling or use of the test substance.

5.3. Guidelines

As required by the Dutch Act on Animal Experimentation (February 1997), the study protocol was reviewed and agreed by the Laboratory Animal Welfare Officer and the Ethical Committee of NOTOX (DEC NOTOX 03-42). The study procedures described in this report were based on the following guidelines:

Organisation for Economic Co-operation and Development (OECD). OECD Guidelines for Testing of Chemicals, Section 4, Health Effects. No. 423. "Acute Oral Toxicity - Acute Toxic Class Method", 2001

European Community (EC). Council Directive 67/548/EEC, Annex V, Part B, Methods for the Determination of Toxicity, as last amended by Commission Directive 2004/73/EC, B 1 tris: "Acute Toxicity (Oral) - Acute Toxic Class Method", 2004.

United States Environmental Protection Agency (EPA). Health Effects Test Guidelines, OPPTS 870.1100, Acute Oral Toxicity. Office of Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-98-190, 2002.

4. SUMMARY

Assessment of acute oral toxicity with MTDID 7144 in the rat (Acute Toxic Class Method).

The study was carried out based on the guidelines described in:
 OECD No 423 (2001) "Acute Toxicity-Oral, Acute Toxic Class Method"
 EC, Council Directive 67/548/EEC, Annex V, B.1 tris (2004) "Acute Oral Toxicity"
 EPA, OPPTS 870.1100 (2002). "Acute Oral Toxicity - Acute Toxic Class Method"
 JMAFF guidelines (2000) including the most recent partial revisions

Initially, MTDID 7144 was administered by oral gavage to three female Wistar rats at 300 mg/kg body weight. In a stepwise procedure additional groups of females were dosed at 300 and subsequently 2000 mg/kg body weight. All animals were subjected to daily observations and weekly determination of body weight. Macroscopic examination was performed on the day of death or after terminal sacrifice (day 15).

The incidence of mortality was as follows, presented in chronological order of treatment:

Dose level	Mortality
300 mg/kg	0/3
300 mg/kg	0/3
2000 mg/kg	3/3

The dead animals were found within 15 minutes post-treatment.

Clinical signs observed during the study period were as follows:

Dose level	Clinical signs
300 mg/kg	Hunched posture, uncoordinated movements, piloerection
2000 mg/kg	Lethargy, spasms, flat and/or hunched posture, uncoordinated movements, slow breathing, piloerection, ptosis, ventro-lateral recumbency, chromodacryorrhoea.

The surviving animals had recovered from the symptoms by day 2.

The body weight gain shown by the animals over the study period was considered to be normal.

Dark red discolouration of the stomach and many dark red foci in duodenum and jejunum were found in the animals that died during the study, at macroscopic post mortem examination. Macroscopic post mortem examination of the surviving animals at termination did not reveal any abnormalities.

The oral LD50 value of MTDID 7144 in Wistar rats was established to be within the range of 300-2000 mg/kg body weight.

According to the OECD 423 test guideline the LD50 cut-off value was considered to be 500 mg/kg body weight.

Based on these results:

- according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations (New York and Geneva, 2003) MTDID 7144 should be classified as: harmful if swallowed (Category 4);
- according to the EC criteria for classification and labelling requirements for dangerous substances and preparations (Council Directive 67/548/EEC) MTDID 7144 should be labelled as: harmful if swallowed (R22)

3. QUALITY ASSURANCE STATEMENT

NOTOX B.V., 's-Hertogenbosch, The Netherlands

This report was inspected by the NOTOX Quality Assurance Unit to confirm that the methods and results accurately and completely reflect the raw data.

The dates of Quality Assurance inspections are given below.
During the on-site process inspections procedures applicable to this type of study were inspected.

The reporting date is the date of reporting to the Study Director. The QAU report was then forwarded to the Test Facility Management.

Type of inspections	Phase/Process	Start Inspection date	End Inspection date	Reporting date
Study	Protocol	05-Apr-06	05-Apr-06	05-Apr-06
	Report	24-May-06	24-May-06	24-May-06
	Amendment 1 of protocol	06-Jun-06	06-Jun-06	06-Jun-06
Process	Test substance unit Test substance handling	16-Feb-06	23-Feb-06	23-Feb-06
	SPF unit Test substance handling Exposure Observation/Measurement Specimen handling	18-Apr-06	24-Apr-06	24-Apr-06
	Pathology unit Observation/Measurement	16-Feb-06	23-Feb-06	23-Feb-06

Head of Quality Assurance
C.J. Mitchell B.Sc.



Date: 12 Jun 06

2. STATEMENT OF GLP COMPLIANCE

NOTOX B.V., 's-Hertogenbosch, The Netherlands

The study described in this report has been correctly reported and was conducted in compliance with:

The Organization for Economic Cooperation and Development (OECD) Good Laboratory Practice Guidelines (1997),

which essentially conform to:

The United States Food and Drug Administration Good Laboratory Practice Regulations.

The United States Environmental Protection Agency Good Laboratory Practice Regulations.

The sponsor is responsible for Good Laboratory Practice (GLP) compliance for all test substance information unless determined by NOTOX.

Analysis of stability, homogeneity and concentration of the test substance under test conditions was not performed as part of this study. Information concerning stability of the test substance in vehicle was available.

NOTOX B.V.

Dr. M.J.J. Hooiveld
Study Director

Drs M.S. Teunissen
Section Head Toxicology



Date: June 6, 2006

Date: 06 June 2006

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