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601 762-0870 Fax: 601 938-2734

6084  
8EHQ - 0598 - 13977 S



April 24, 1998

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Document Control Office (7407)  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
401 M St. S.W.  
Washington, DC 20460-0001

Re: TSCA Section 8(e) Notification

Dear Sir or Madam:

ChemFirst Inc is submitting this notice on behalf of First Chemical Corporation in accordance with Section 8(e) of the Toxic Substances Control Act (TSCA) and EPA's Statement of Interpretation and Enforcement Policy, 43 Fed. Reg. 1110 (March 16, 1978).

The basis for this submission is information in a draft report of a rangefinding inhalation toxicity study in rats of N-ethyl-meta-toluidine (NEM), CAS no. 102-27-2. This study was sponsored by ChemFirst Inc. Rats were exposed by inhalation for six hours per day for a total of 3 days to concentrations of 7, 100, or 219 ppm. All animals in the high exposure group died, as did half of those in the mid exposure group. There were no deaths at the low exposure concentration. The gross necropsy found mottled lungs or scattered red foci in the lungs at all exposure concentrations. Other findings occurring in several animals at the mid and high exposure levels included enlarged or black spleens, urinary bladders that were dilated or contained red fluid, and red fluid in the stomach or intestines. Analysis of blood samples found increases in methemoglobin levels at 7 ppm, the only level tested. A copy of the draft report is attached.

ChemFirst Inc. submitted a notice under Section 8(e) previously for this chemical, based on methemoglobin formation after acute oral exposure of rats. The document control number for this submission was 8EHQ-97-13977.

NEM is manufactured in a totally enclosed process. When exposure potential exists, workers use personal protective equipment, including appropriate protective suits, neoprene gloves, boots, and full-face respirators. Protective clothing and equipment are specified on the Material Safety Data Sheet (attached). NEM is produced by First Chemical Corporation, a ChemFirst Inc. Company, for use as a cure accelerator in polymerizations.

8EHQ-97-13977

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The MSDS will be updated to include this information after a final report is received. A copy of the completed final report will be sent as a follow up to this submission.

ChemFirst Inc. would like to maintain as confidential only information that identifies the testing laboratory. Substantiation of this claim is attached.

If you have any further questions related to this submission, please contact me.

Sincerely,



Ellen R. Stephens, Ph.D. DABT  
Manager, Toxicology  
228-938-2219

enclosure

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**DRAFT REPORT**

**Testing Facility:**

**Sponsor:**

**ChemFirst, Inc.  
1001 Industrial Highway  
Pascagoula, MS 39581-3237**

**Sponsor Representative:  
Ellen R. Stephens, Ph.D.**

**April 1998**

**QA AUDITED  
DRAFT**  
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**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**FOREWORD**

This abbreviated report describes a study conducted by

for ChemFirst, Inc. during the period of September 24, 1997 (receipt of test animals) to October 3, 1997 (final in-life date). The study was performed under

.. Ellen R. Stephens, Ph.D., served as representative of ChemFirst, Inc. Sullivan, M.S., served as the Study Director. Narayanan Rajendran, Ph.D., Scott Garthwaite, also participated in the study. assisted in the preparation of this report.

All study data generated : and a copy of the final report will be archived . The contents of this report include:

- Title Page
- 
- Summary
- 
- Inhalation exposure methods and results narrative with summary table
- Summary Toxicology tables
  - Clinical observations
  - Body weights
  - Body weight gains
  - Met Hemoglobin determination
  - Necropsy observations
- Protocol, protocol amendment and protocol deviation

Respectfully submitted,

\_\_\_\_\_  
Date

Approved by:

\_\_\_\_\_  
Date

## THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF N-ETHYL-M-TOLUIDINE (NEM) IN RATS

Study Initiation Date: September 23, 1997  
Treatment Initiation Date: September 30, 1997  
Biophase Termination Date: October 3, 1997

### SUMMARY

A three-day range-finding inhalation toxicity study was initiated with N-ethyl-m-toluidine (NEM) in Sprague-Dawley rats for the determination of appropriate test atmosphere concentrations for a subsequent 14-day study.

Specifically, the range-finding study consisted of fifteen male and fifteen female CrI:CD® (SD)BR rats that were exposed by whole-body exposure to target concentrations of 10, 100 or 200 ppm of test substance NEM for three consecutive days. Toxicologic endpoints consisted of clinical observations, body weight, body weight gain and met hemoglobin measurements (low exposure group). All spontaneously dying rats were necropsied and all gross pathological changes were recorded. Similarly, all animals surviving to termination were euthanized and subjected to gross necropsy.

The average test atmosphere exposure concentrations of NEM (sum of vapor and aerosol phases, as determined by gas chromatography and chemical analysis of gravimetric filter samples) were 7.3, 99.5 and 219 ppm for the low, mid and high NEM concentration groups, respectively. All of the animals in the high concentration group (*i.e.*, five males and five females) were found dead on either Study Day 1 or 2. Half of the animals in the mid concentration group (*i.e.*, three males and two females) were found dead on either Study Day 2, 3 or 4. No mortality or moribundity was observed in any of the animals in the low concentration group.

Significant clinical observations were seen throughout the study in both the mid- and high-exposure groups at scheduled observation times, during the exposure period and at the time of necropsy. Clinical signs in both the males and females of the mid concentration group included some or all of the following: red material around the mouth, eyes and/or nose, wet inguinal fur, colored urine, prostration and decreased activity. Onset and duration of these individual clinical signs ranged from Study Day 1 through Study Day 4. Clinical observations in the high-exposure group included some or all of the following: red ocular discharge, nasal discharge, wet inguinal fur, decreased activity, prostration and red material around the mouth and/or nose. Eight animals exhibited wet inguinal fur. The two female rats in the high exposure group found dead on Study Day 1 had test material deposition on the body surface, red material around the nose, and opacity

in both eyes at the time of necropsy. The eight surviving animals in this group exhibited some or all of the clinical signs noted on Study Day 1 prior to their deaths on Study Day 2.

There were no clinical observations in the low-exposure group with the exception of one male exhibiting red material around its nose on Study Day 4.

Statistically significant decreases in body weight and body weight gain of rats in the mid exposure group were seen on Study Days 3 and 4 (males) and Study Day 3 (females) compared to the low exposure group. Determination of met hemoglobin levels in the low exposure group revealed significant increases in both males and females compared to background levels.

Gross necropsy findings in the euthanized low exposure group revealed mottled red lungs or scattered red foci on the lobes of the lungs of eight of the ten low exposure animals. Gross necropsy findings in the spontaneously dying mid exposure animals included varying degrees of mottled lung appearance, dilated urinary bladder filled with red fluid, spleen enlargement, dilated uterine horns and/or bloated or empty stomachs. Gross necropsy findings in the euthanized mid exposure group included varying degrees of mottled lung appearance, scattered foci on the lobes of the lungs, spleen enlargement and/or brown livers. It is significant to note that all animals in the mid exposure group had some form of lung lesion and a majority (*i.e.*, 70%) had enlarged spleens. Gross necropsy findings in all high concentration animals subsequent to their spontaneous deaths included some of the following: varying degrees of mottled lung appearance, red fluid in stomach, urinary bladder and/or small or large intestines, dilated urinary bladder, blackened spleen, opaque eye(s), hard stomach and/or white focus on the kidney. It is significant to note that all high exposure animals, except for one female, displayed some form of lung lesion.

Based on these data, 3, 35 and 100 ppm were selected by the Sponsor as appropriate test atmosphere exposure concentrations for a subsequent 14-day study.



## I. INHALATION EXPOSURE

The study was conducted in Laboratory I of the inhalation exposure facility. Animals were exposed to test atmospheres in 1-m<sup>3</sup> whole-body inhalation exposure chambers for six-hour (4 T<sub>90</sub>) periods and housed in 2-m<sup>3</sup> whole-body inhalation exposure chambers supplied with filtered air during non-exposure periods.

The 1-m<sup>3</sup> exposure and the 2-m<sup>3</sup> housing chambers were supplied with filtered air conditioned to the required temperature and relative humidity by a facility-dedicated HVAC system. Air entering the chamber air supply system was filtered through a carbon adsorber and a HEPA filter.

Test Atmosphere: The NEM test atmospheres were generated by flash evaporation technique. The evaporator consisted of a 30 cm long and 20 mm ID Hempel distillation column packed with 3 mm diameter glass beads. The column at its lower end was fitted into a 500 ml glass flask containing two side arms. A constant flow rate of liquid was introduced into the top of the column and through one side arm a countercurrent flow of carrier air was fed into the base of the column. The test substance was completely vaporized (no residual material was evident in the evaporators) and the carrier air swept the test substance vapor into the exposure chamber through a teflon/ stainless steel transfer line. Through the second side arm a thermocouple was positioned with its active end located approximately 5 cm from the top of the glass beads in the distillation column. The temperature of the column was regulated using a thermostat-controlled heating tape. The column temperatures for individual vapor generation system were maintained in the range of 144-162°C.

Test Atmosphere Concentration: The inhalation chambers were monitored for aerosol and vapor concentration of the test substance using filter-collected samples and gas chromatography (GC), respectively. The aerosol mass concentration of NEM in the breathing zone of the rats was determined gravimetrically by filter samples collected once each hour during the exposure. The sampling train consisted of a pre-weighed filter in series with a dry-gas meter connected to a constant flow vacuum pump. The dry-gas meter measured the corresponding volume of chamber air sampled and the weight to volume ratio was determined. In addition, vapor samples were monitored by GC.

Nominal concentrations were also determined daily for each test substance exposure chamber by dividing the weight of test substance consumed during the exposure by the total airflow through the chamber.

Test Atmosphere Monitoring Results: The overall test substance concentration within each chamber was measured once an hour during the daily 6-hr exposure period. The average chamber concentrations of NEM (aerosol and vapor) were reasonably close to the target levels at 7.3, 99.5, and 219 ppm for the 10, 100, and 200 ppm target concentrations, respectively (Table 1). However, significant day-to-day variations in concentration as indicated by large RSD values were encountered, possibly due to the low vapor pressure of NEM.

TABLE 1  
**Summary of Chamber Test Substance Concentrations  
 Determined by Gas Chromatography (GC)**

| Exposure Group | Test Substance Concentration (ppm) |                   |      |                    | % Mean/<br>Target |
|----------------|------------------------------------|-------------------|------|--------------------|-------------------|
|                | Target                             | Mean <sup>a</sup> | ± SD | % RSD <sup>b</sup> |                   |
| 1              | 10                                 | 7.3               | 6.1  | 84.5               | 73.0              |
| 2              | 100                                | 99.5              | 30.4 | 30.5               | 99.5              |
| 3              | 200                                | 219               | 30.7 | 14.0               | 110               |

<sup>a</sup> Overall means for the three-day exposure period.

<sup>b</sup> % RSD: SD/Mean expressed as percent.

## II. TOXICOLOGY TABLES

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 2**

**Summary of Clinical Observations<sup>a</sup>**

| Observation               | 10 ppm (Low)   | 100 ppm (Mid) | 200 ppm (High) |
|---------------------------|----------------|---------------|----------------|
| <u>Males</u>              |                |               |                |
| Animal Found Dead         | 0 <sup>b</sup> | 3             | 5              |
| Normal                    | 5              | 1             | 0              |
| Red Material Around Eyes  | 0              | ✓2            | 0              |
| Red Ocular Discharge      | 0              | 0             | ✓3             |
| Nasal Discharge           | 0              | 0             | ✓4             |
| Red Material Around Mouth | 0              | ✓4            | 0              |
| Red Material Around Nose  | 1              | ✓4            | 0              |
| Wet Inguinal Fur          | 0              | ✓5            | ✓5             |
| Decreased Activity        | 0              | ✓3            | ✓2             |
| Prostrate                 | 0              | ✓1            | 0              |
| Total Number of Animals   | 5              | 5             | 5              |
| <u>Females</u>            |                |               |                |
| Animal Found Dead         | 0              | 2             | 5              |
| Normal                    | 5              | 0             | 0              |
| Red Material Around Eyes  | 0              | ✓2            | 0              |
| Red Ocular Discharge      | 0              | 0             | ✓1             |
| Red Material Around Mouth | 0              | ✓5            | ✓1             |
| Red Material Around Nose  | 0              | ✓5            | ✓1             |
| Colored Urine             | 0              | ✓2            | 0              |
| Wet Inguinal Fur          | 0              | ✓5            | ✓3             |
| Decreased Activity        | 0              | ✓1            | ✓3             |
| Prostrate                 | 0              | ✓1            | ✓2             |
| Total Number of Animals   | 5              | 5             | 5              |

<sup>a</sup> Total number of rats displaying the sign at least once during the observation period.

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 3**

**Summary of Body Weights (g)**

| <u>Exposure Group</u> | <u>Concentration (ppm)</u> | <b>Males</b>   |                        |                 |              |
|-----------------------|----------------------------|----------------|------------------------|-----------------|--------------|
|                       |                            |                | <u>Body Weight (g)</u> |                 |              |
|                       |                            |                | <u>Day 1</u>           | <u>Day 3</u>    | <u>Day 4</u> |
| Low                   | 10                         | Mean           | 179                    | 201             | 204          |
|                       |                            | SD             | 12.5                   | 14.9            | 17.4         |
|                       |                            | N              | 5                      | 5               | 5            |
| Mid                   | 100                        | Mean           | 180                    | 175*            | 166*         |
|                       |                            | SD             | 9.0                    | 5.8             | 14.8         |
|                       |                            | N              | 5                      | 4               | 2            |
| High                  | 200                        | Mean           | 182                    | -- <sup>a</sup> | --           |
|                       |                            | SD             | 7.5                    | --              | --           |
|                       |                            | N              | 5                      | 0               | 0            |
| <u>Exposure Group</u> | <u>Concentration (ppm)</u> | <b>Females</b> |                        |                 |              |
|                       |                            |                | <u>Body Weight (g)</u> |                 |              |
|                       |                            |                | <u>Day 1</u>           | <u>Day 3</u>    | <u>Day 4</u> |
| Low                   | 10                         | Mean           | 164                    | 173             | 174          |
|                       |                            | SD             | 6.6                    | 5.4             | 8.6          |
|                       |                            | N              | 5                      | 5               | 5            |
| Mid                   | 100                        | Mean           | 167                    | 158*            | 158          |
|                       |                            | SD             | 8.0                    | 11.5            | 15.3         |
|                       |                            | N              | 5                      | 3               | 3            |
| High                  | 200                        | Mean           | 165                    | --              | --           |
|                       |                            | SD             | 9.4                    | --              | --           |
|                       |                            | N              | 5                      | 0               | 0            |

\* Significantly different from Low Exposure Group,  $p \leq 0.05$  (Dunnett's)

<sup>a</sup>-- = No data available due to animal death

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 4**

**Summary of Body Weight Gains (g)**

| <u>Exposure Group</u> | <u>Concentration (ppm)</u> | <u>Males</u> |                             |              |
|-----------------------|----------------------------|--------------|-----------------------------|--------------|
|                       |                            |              | <u>Body Weight Gain (g)</u> |              |
|                       |                            |              | <u>Day 3</u>                | <u>Day 4</u> |
| Low                   | 10                         | Mean         | 11.0                        | 2.8          |
|                       |                            | SD           | 1.46                        | 3.49         |
|                       |                            | N            | 5                           | 5            |
| Mid                   | 100                        | Mean         | -0.8*                       | -9.5*        |
|                       |                            | SD           | 2.18                        | 7.78         |
|                       |                            | N            | 4                           | 2            |
| High                  | 200                        | Mean         | -- <sup>a</sup>             | --           |
|                       |                            | SD           | --                          | --           |
|                       |                            | N            | 0                           | 0            |

| <u>Exposure Group</u> | <u>Concentration (ppm)</u> | <u>Females</u> |                             |              |
|-----------------------|----------------------------|----------------|-----------------------------|--------------|
|                       |                            |                | <u>Body Weight Gain (g)</u> |              |
|                       |                            |                | <u>Day 3</u>                | <u>Day 4</u> |
| Low                   | 10                         | Mean           | 4.6                         | 0.8          |
|                       |                            | SD             | 1.98                        | 3.56         |
|                       |                            | N              | 5                           | 5            |
| Mid                   | 100                        | Mean           | -3.3*                       | -0.3         |
|                       |                            | SD             | 3.40                        | 4.04         |
|                       |                            | N              | 3                           | 3            |
| High                  | 200                        | Mean           | --                          | --           |
|                       |                            | SD             | --                          | --           |
|                       |                            | N              | 0                           | 0            |

\* Significantly different from Low Exposure Group,  $p \leq 0.05$  (Dunnett's)

<sup>a</sup>-- = No data available due to animal death

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 5**

**Summary of Met Hemoglobin Determination**

| <u>Group</u> | <u>Sex<sup>a</sup></u> | <u>Exposure Group<br/>Concentration (ppm)</u> | <u>Parameter</u>              |                            |       |
|--------------|------------------------|---|-------------------------------|----------------------------|-------|
|              |                        |   | <u>THB<sup>b</sup> (g/dL)</u> | <u>MHB<sup>c</sup> (%)</u> |       |
| Low          | M                      | 10 ppm  | Mean                          | 13.80                      | 4.46  |
|              |                        |   | SD                            | 1.046                      | 0.673 |
|              |                        |   | N                             | 5                          | 5     |
| Low          | F                      | 10 ppm  | Mean                          | 14.98                      | 5.06  |
|              |                        |   | SD                            | 0.958                      | 0.658 |
|              |                        |   | N                             | 5                          | 5     |

<sup>a</sup> M = male, F= female

<sup>b</sup> THB = Total Hemoglobin

<sup>c</sup> MHB = Met Hemoglobin

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 6**

**Summary of Necropsy Observations<sup>a</sup>**

| <u>Organ - Observation</u>                     | <u>10 ppm</u> |               | <u>100 ppm</u> |               | <u>200 ppm</u> |               |
|--|---------------|---------------|----------------|---------------|----------------|---------------|
|  | <u>Male</u>   | <u>Female</u> | <u>Male</u>    | <u>Female</u> | <u>Male</u>    | <u>Female</u> |
| Number of animals                              | 5             | 5             | 5              | 5             | 5              | 5             |
| No gross lesions                               | 1             | 1             | 0              | 0             | 0              | 0             |
| Lungs - slightly mottled                       | 0             | 0             | 0              | 1             | 0              | 0             |
| Lungs - mottled                                | 0             | 0             | 0              | 0             | 1              | 0             |
| Lungs - mottled red                            | 1             | 3             | 3              | 1             | 2              | 3             |
| Lungs - mottled brown                          | 0             | 0             | 1              | 0             | 0              | 0             |
| Lungs - mottled dark red                       | 0             | 0             | 1              | 2             | 2              | 1             |
| Lungs - scattered red foci (all lobes)         | 3             | 0             | 0              | 1             | 0              | 0             |
| Lungs - scattered red foci (left lobe)         | 0             | 1             | 0              | 0             | 0              | 0             |
| Urinary bladder - dilation/contained red fluid | 0             | 0             | 1              | 1             | 1              | 0             |
| Urinary bladder - dilation                     | 0             | 0             | 0              | 0             | 0              | 1             |
| Spleen - black                                 | 0             | 0             | 0              | 0             | 1              | 0             |
| Spleen - enlarged                              | 0             | 0             | 4              | 3             | 0              | 0             |
| Liver - dark brown                             | 0             | 0             | 0              | 1             | 0              | 0             |
| Liver - brown                                  | 0             | 0             | 1              | 0             | 0              | 0             |
| Stomach - bloated                              | 0             | 0             | 1              | 0             | 0              | 0             |
| Stomach - hard; packed with food               | 0             | 0             | 0              | 0             | 0              | 1             |
| Stomach - empty                                | 0             | 0             | 0              | 1             | 0              | 0             |
| Stomach - contained red fluid                  | 0             | 0             | 0              | 0             | 1              | 0             |
| Uterine horns - dilation                       | 0             | 0             | 0              | 1             | 0              | 0             |
| Small intestine - contained red fluid          | 0             | 0             | 0              | 0             | 1              | 1             |
| Large intestine - contained red fluid          | 0             | 0             | 0              | 0             | 1              | 0             |
| Eyes (one or both) - opacity                   | 0             | 0             | 0              | 0             | 2 ✓            | 4 ✓           |
| Kidney - white focus                           | 0             | 0             | 0              | 0             | 1              | 0             |

<sup>a</sup> Total number of rats having the observation.

### CERTIFICATE OF AUTHENTICITY

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| Submitting Organization | CHEMFIRST INC  |               |                  |
| Contractor              | CONFIDENTIAL   |               |                  |
| Document Title          | SUPPORT: FINAL REPORT, THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF N-ETHYL-M-TOLUIDINE (NEM) IN RATS, WITH COVER LETTER DATED 5/21/1998 (SANITIZED) |               |                  |
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401 M St. S.W.  
Washington, DC 20460-0001

8EHQ-97-13977

89980000 2085

Re: Followup to TSCA Section 8(e) Notification

Dear Sir or Madam:

As a followup to our TSCA 8(e) submission of 4/24/98, ChemFirst Inc is submitting the final report of a rangefinding inhalation toxicity study in rats of N-ethyl-meta-toluidine (NEM), CAS no. 102-27-2. We have not received a document control number for the original submission.

ChemFirst Inc. would like to maintain as confidential only information that identifies the testing laboratory. Substantiation of this claim is attached.

If you have any further questions related to this submission, please contact me.

Sincerely,

A handwritten signature in cursive script that reads 'Ellen R. Stephens'.

Ellen R. Stephens, Ph.D. DABT  
Manager, Toxicology  
228-938-2219

enclosure

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1001 Industrial Road Pascagoula, MS 39581-3237

601.762-0870 Fax: 601.938-2734

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401 M St. S. W.  
Washington, D.C. 20460-0001

Re: Followup to TSCA Section 8(e) Notification of Results from Three-Day Range-Finding Inhalation Toxicity Study of N-Ethyl-m-toluidine (NEM) in Rats

Dear Sir or Madam::

The following information is provided to substantiate confidentiality claims in the attached followup to the 8(e) notification submitted on 4/24/98 for this chemical. We would like to maintain as confidential the name, address, personnel and other information that identify the testing laboratory. Responses to relevant questions are given below.

1. The company is asserting this confidential business information (CBI) claim on its own behalf.
2. The claim of confidentiality is asserted indefinitely.
3. The information has not been previously disclosed to any other governmental agency or to the EPA.
4. The information we are claiming CBI is not provided to anyone outside the company unless we have a confidentiality agreement with them.
5. The testing laboratory is restricted by a confidentiality agreement with the company. The laboratory agrees not to disclose any proprietary technical information owned by the company.
6. The information is not referred to in any advertising, material safety data sheet, trade publication or any other publications.

7. No agency or court has made any confidentiality determination regarding this information.

8. If the name of the testing laboratory were made available to the public, competitors could focus efforts on a particular laboratory to attempt to get confidential information on other developmental products, with resulting harm to the company's competitive position.

9., 10., 11. Since the test material is not claimed confidential, these questions do not apply.

12. Disclosure of the testing laboratory would reveal information unrelated to the effects of the substance on human health or the environment. It would reveal the name of a contract laboratory where the company conducts business.

13. The CAS no. has been supplied.

14. None of the information is the subject of FIFRA regulation or reporting.

If you have any further questions related to this submission, please contact me.

Yours truly,



Ellen R. Stephens, Ph.D. DABT  
Manager, Toxicology  
228-938-2219

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

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**FINAL REPORT**

**Testing Facility:**

**Sponsor:**

**ChemFirst, Inc.  
1001 Industrial Highway  
Pascagoula, MS 39581-3237**

**Sponsor Representative:  
Ellen R. Stephens, Ph.D.**

**May 1998**

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

## THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF N-ETHYL-M-TOLUIDINE (NEM) IN RATS

Study Initiation Date: September 23, 1997  
Treatment Initiation Date: September 30, 1997  
Biophase Termination Date: October 3, 1997

### SUMMARY

A three-day range-finding inhalation toxicity study was initiated with N-ethyl-m-toluidine (NEM) in Sprague-Dawley rats for the determination of appropriate test atmosphere concentrations for a subsequent 14-day study.

Specifically, the range-finding study consisted of fifteen male and fifteen female CrI:CD<sup>®</sup>(SD)BR rats that were exposed by whole-body exposure to target concentrations of 10, 100 or 200 ppm of test substance NEM for three consecutive days. Toxicologic endpoints consisted of clinical observations, body weight, body weight gain and met hemoglobin measurements (low exposure group). All spontaneously dying rats were necropsied and all gross pathological changes were recorded. Similarly, all animals surviving to termination were euthanized and subjected to gross necropsy.

The average test atmosphere exposure concentrations of NEM (sum of vapor and aerosol phases, as determined by gas chromatography and chemical analysis of gravimetric filter samples) were 7.3, 99.5 and 219 ppm for the low, mid and high NEM concentration groups, respectively. All of the animals in the high concentration group (*i.e.*, five males and five females) were found dead on either Study Day 1 or 2. Half of the animals in the mid concentration group (*i.e.*, three males and two females) were found dead on either Study Day 2, 3 or 4. No mortality or moribundity was observed in any of the animals in the low concentration group.

Significant clinical observations were seen throughout the study in both the mid- and high-exposure groups at scheduled observation times, during the exposure period and at the time of necropsy. Clinical signs in both the males and females of the mid concentration group included some or all of the following: red material around the mouth, eyes or nose, wet inguinal fur, colored urine, prostration and decreased activity. Onset and duration of these individual clinical signs ranged from Study Day 1 through Study Day 4. Clinical observations in the high-exposure group included some or all of the following: red ocular discharge, nasal discharge, wet inguinal fur, decreased activity, prostration and red material around the mouth or nose. Eight animals exhibited wet inguinal fur. The two female rats in the high exposure group found dead on Study Day 1 had test material deposition on the body surface, red material around the nose, and opacity

in both eyes at the time of necropsy. The eight surviving animals in this group exhibited some or all of the clinical signs noted on Study Day 1 prior to their deaths on Study Day 2.

There were no clinical observations in the low-exposure group with the exception of one male exhibiting red material around its nose on Study Day 4.

Statistically significant decreases in body weight and body weight gain of rats in the mid exposure group were seen on Study Days 3 and 4 (males) and Study Day 3 (females) compared to the low exposure group. Determination of met hemoglobin levels in the low exposure group revealed significant increases in both males and females compared to background levels.

Gross necropsy findings in the euthanized low exposure group revealed mottled red lungs or scattered red foci on the lobes of the lungs of eight of the ten low exposure animals. Gross necropsy findings in the spontaneously dying mid exposure animals included varying degrees and combinations of mottled lung appearance, dilated urinary bladder filled with red fluid, spleen enlargement, dilated uterine horns or bloated or empty stomachs. Gross necropsy findings in the euthanized mid exposure group included varying degrees and combinations of mottled lung appearance, scattered foci on the lobes of the lungs, spleen enlargement or brown livers. It is significant to note that all animals in the mid exposure group had some form of lung lesion and a majority (*i.e.*, 70%) had enlarged spleens. Gross necropsy findings in high concentration animals subsequent to their spontaneous deaths included the following: varying degrees and combinations of mottled lung appearance, red fluid in stomach, urinary bladder, small or large intestines, dilated urinary bladder, blackened spleen, opaque eye(s), hard stomach or white focus on the kidney. It is significant to note that all high exposure animals, except for one female, displayed some form of lung lesion. Opacities observed in animals found dead were deemed agonal to death and not test material related.

Based on these data, 3, 35 and 100 ppm were selected by the Sponsor as appropriate test atmosphere exposure concentrations for a subsequent 14-day study.



## I. INHALATION EXPOSURE

The study was conducted in Laboratory I of the inhalation exposure facility. Animals were exposed to test atmospheres in 1-m<sup>3</sup> whole-body inhalation exposure chambers for six-hour + T<sub>90</sub> (the time required to reach 90% of the target concentration) periods and housed in 2-m<sup>3</sup> whole-body inhalation exposure chambers supplied with filtered air during non-exposure periods.

The 1-m<sup>3</sup> exposure and the 2-m<sup>3</sup> housing chambers were supplied with filtered air conditioned to the required temperature and relative humidity by a facility-dedicated HVAC system. Air entering the chamber air supply system was filtered through a carbon adsorber and a HEPA filter.

Test Atmosphere: The NEM test atmospheres were generated by flash evaporation technique. The evaporator consisted of a 30 cm long and 20 mm ID Hempel distillation column packed with 3 mm diameter glass beads. The column at its lower end was fitted into a 500 ml glass flask containing two side arms. A constant flow rate of liquid was introduced into the top of the column and through one side arm a countercurrent flow of carrier air was fed into the base of the column. The test substance was completely vaporized (no residual material was evident in the evaporators) and the carrier air swept the test substance vapor into the exposure chamber through a teflon/ stainless steel transfer line. Through the second side arm a thermocouple was positioned with its active end located approximately 5 cm from the top of the glass beads in the distillation column. The temperature of the column was regulated using a thermostat-controlled heating tape. The column temperatures for individual vapor generation system were maintained in the range of 144-162°C.

Test Atmosphere Concentration: The inhalation chambers were monitored for aerosol and vapor concentration of the test substance using filter-collected samples and gas chromatography (GC), respectively. The aerosol mass concentration of NEM in the breathing zone of the rats was determined gravimetrically by filter samples collected once each hour during the exposure. The sampling train consisted of a pre-weighed filter in series with a dry-gas meter connected to a constant flow vacuum pump. The dry-gas meter measured the corresponding volume of chamber air sampled and the weight to volume ratio was determined. In addition, vapor samples were monitored by GC.

Test Atmosphere Monitoring Results: The overall test substance concentration within each chamber was measured once an hour during the daily 6-hr exposure period. The average chamber concentrations of NEM (aerosol and vapor) were reasonably close to the target levels at 7.3, 99.5, and 219 ppm for the 10, 100, and 200 ppm target concentrations, respectively (Table 1). However, significant day-to-day variations in concentration as indicated by large RSD values were encountered, possibly due to the low vapor pressure of NEM.

TABLE 1  
**Summary of Chamber Test Substance Concentrations  
 Determined by Gas Chromatography (GC)**

| Exposure Group | Test Substance Concentration (ppm) |                   |      |                    | % Mean/<br>Target |
|----------------|------------------------------------|-------------------|------|--------------------|-------------------|
|                | Target                             | Mean <sup>a</sup> | ± SD | % RSD <sup>b</sup> |                   |
| 1              | 10                                 | 7.3               | 6.1  | 84.5               | 73.0              |
| 2              | 100                                | 99.5              | 30.4 | 30.5               | 99.5              |
| 3              | 200                                | 219               | 30.7 | 14.0               | 110               |

<sup>a</sup> Overall means for the three-day exposure period.

<sup>b</sup> % RSD: SD/Mean expressed as percent.

## II. TOXICOLOGY TABLES

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 2**

**Summary of Clinical Observations<sup>a</sup>**

| Observation               | 10 ppm (Low)   | 100 ppm (Mid) | 200 ppm (High) |
|---------------------------|----------------|---------------|----------------|
| <u>Males</u>              |                |               |                |
| Animal Found Dead         | 0 <sup>b</sup> | 3             | 5              |
| Normal                    | 5              | 1             | 0              |
| Red Material Around Eyes  | 0              | 2             | 0              |
| Red Ocular Discharge      | 0              | 0             | 3              |
| Nasal Discharge           | 0              | 0             | 4              |
| Red Material Around Mouth | 0              | 4             | 0              |
| Red Material Around Nose  | 1              | 4             | 0              |
| Wet Inguinal Fur          | 0              | 5             | 5              |
| Decreased Activity        | 0              | 3             | 2              |
| Prostrate                 | 0              | 1             | 0              |
| Total Number of Animals   | 5              | 5             | 5              |
| <u>Females</u>            |                |               |                |
| Animal Found Dead         | 0              | 2             | 5              |
| Normal                    | 5              | 0             | 0              |
| Red Material Around Eyes  | 0              | 2             | 0              |
| Red Ocular Discharge      | 0              | 0             | 1              |
| Red Material Around Mouth | 0              | 5             | 1              |
| Red Material Around Nose  | 0              | 5             | 1              |
| Colored Urine             | 0              | 2             | 0              |
| Wet Inguinal Fur          | 0              | 5             | 3              |
| Decreased Activity        | 0              | 1             | 3              |
| Prostrate                 | 0              | 1             | 2              |
| Total Number of Animals   | 5              | 5             | 5              |

<sup>a</sup> Total number of rats displaying the sign at least once during the observation period.

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 3**

**Summary of Body Weights (g)**

|                       |                            | <b>Males</b>   |                        |                 |              |
|-----------------------|----------------------------|----------------|------------------------|-----------------|--------------|
| <u>Exposure Group</u> | <u>Concentration (ppm)</u> |                | <u>Body Weight (g)</u> |                 |              |
|                       |                            |                | <u>Day 1</u>           | <u>Day 3</u>    | <u>Day 4</u> |
| Low                   | 10                         | Mean           | 179                    | 201             | 204          |
|                       |                            | SD             | 12.5                   | 14.9            | 17.4         |
|                       |                            | N              | 5                      | 5               | 5            |
| Mid                   | 100                        | Mean           | 180                    | 175*            | 166*         |
|                       |                            | SD             | 9.0                    | 5.8             | 14.8         |
|                       |                            | N              | 5                      | 4               | 2            |
| High                  | 200                        | Mean           | 182                    | -- <sup>a</sup> | --           |
|                       |                            | SD             | 7.5                    | --              | --           |
|                       |                            | N              | 5                      | 0               | 0            |
|                       |                            | <b>Females</b> |                        |                 |              |
| <u>Exposure Group</u> | <u>Concentration (ppm)</u> |                | <u>Body Weight (g)</u> |                 |              |
|                       |                            |                | <u>Day 1</u>           | <u>Day 3</u>    | <u>Day 4</u> |
| Low                   | 10                         | Mean           | 164                    | 173             | 174          |
|                       |                            | SD             | 6.6                    | 5.4             | 8.6          |
|                       |                            | N              | 5                      | 5               | 5            |
| Mid                   | 100                        | Mean           | 167                    | 158*            | 158          |
|                       |                            | SD             | 8.0                    | 11.5            | 15.3         |
|                       |                            | N              | 5                      | 3               | 3            |
| High                  | 200                        | Mean           | 165                    | --              | --           |
|                       |                            | SD             | 9.4                    | --              | --           |
|                       |                            | N              | 5                      | 0               | 0            |

\* Significantly different from Low Exposure Group,  $p \leq 0.05$  (Dunnett's)

<sup>a</sup>-- = No data available due to animal death

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 4**

**Summary of Body Weight Gains (g)**

| <u>Exposure Group</u> | <u>Concentration (ppm)</u> | <b>Males</b> |                             |              |
|-----------------------|----------------------------|--------------|-----------------------------|--------------|
|                       |                            |              | <u>Body Weight Gain (g)</u> |              |
|                       |                            |              | <u>Day 3</u>                | <u>Day 4</u> |
| Low                   | 10                         | Mean         | 11.0                        | 2.8          |
|                       |                            | SD           | 1.46                        | 3.49         |
|                       |                            | N            | 5                           | 5            |
| Mid                   | 100                        | Mean         | -0.8*                       | -9.5*        |
|                       |                            | SD           | 2.18                        | 7.78         |
|                       |                            | N            | 4                           | 2            |
| High                  | 200                        | Mean         | -- <sup>a</sup>             | --           |
|                       |                            | SD           | --                          | --           |
|                       |                            | N            | 0                           | 0            |

| <u>Exposure Group</u> | <u>Concentration (ppm)</u> | <b>Females</b> |                             |              |
|-----------------------|----------------------------|----------------|-----------------------------|--------------|
|                       |                            |                | <u>Body Weight Gain (g)</u> |              |
|                       |                            |                | <u>Day 3</u>                | <u>Day 4</u> |
| Low                   | 10                         | Mean           | 4.6                         | 0.8          |
|                       |                            | SD             | 1.98                        | 3.56         |
|                       |                            | N              | 5                           | 5            |
| Mid                   | 100                        | Mean           | -3.3*                       | -0.3         |
|                       |                            | SD             | 3.40                        | 4.04         |
|                       |                            | N              | 3                           | 3            |
| High                  | 200                        | Mean           | --                          | --           |
|                       |                            | SD             | --                          | --           |
|                       |                            | N              | 0                           | 0            |

\* Significantly different from Low Exposure Group,  $p \leq 0.05$  (Dunnett's)

<sup>a</sup>-- = No data available due to animal death

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 5**

**Summary of Met Hemoglobin Determination**

| <u>Group</u> | <u>Sex<sup>a</sup></u> | <u>Exposure Group<br/>Concentration (ppm)</u> |      | <u>Parameter</u>              |                            |
|--------------|------------------------|---|------|-------------------------------|----------------------------|
|              |                        |   |      | <u>THB<sup>b</sup> (g/dL)</u> | <u>MHB<sup>c</sup> (%)</u> |
| Control      | M                      | None  | Mean | 13.77                         | 0.33                       |
|              |                        |   | SD   | 0.404                         | 0.351                      |
|              |                        |   | N    | 3                             | 3                          |
| Control      | F                      | None  | Mean | 13.80                         | 0.20                       |
|              |                        |   | SD   | 0.566                         | 0.283                      |
|              |                        |   | N    | 2                             | 2                          |
| Low          | M                      | 10 ppm  | Mean | 13.80                         | 4.46*                      |
|              |                        |   | SD   | 1.046                         | 0.673                      |
|              |                        |   | N    | 5                             | 5                          |
| Low          | F                      | 10 ppm  | Mean | 14.98                         | 5.06*                      |
|              |                        |   | SD   | 0.958                         | 0.658                      |
|              |                        |   | N    | 5                             | 5                          |

<sup>a</sup> M = male, F= female

<sup>b</sup> THB = Total Hemoglobin

<sup>c</sup> MHB = Met Hemoglobin

\* Significantly different from Control Group,  $p \leq 0.05$  (Dunnett's)

**THREE-DAY RANGE-FINDING INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**Table 6**

**Summary of Necropsy Observations<sup>a</sup>**

| <u>Organ - Observation</u>                     | <u>10 ppm</u> |               | <u>100 ppm</u> |               | <u>200 ppm</u> |               |
|--|---------------|---------------|----------------|---------------|----------------|---------------|
|  | <u>Male</u>   | <u>Female</u> | <u>Male</u>    | <u>Female</u> | <u>Male</u>    | <u>Female</u> |
| Number of animals                              | 5             | 5             | 5              | 5             | 5              | 5             |
| No gross lesions                               | 1             | 1             | 0              | 0             | 0              | 0             |
| Lungs - slightly mottled                       | 0             | 0             | 0              | 1             | 0              | 0             |
| Lungs - mottled                                | 0             | 0             | 0              | 0             | 1              | 0             |
| Lungs - mottled red                            | 1             | 3             | 3              | 1             | 2              | 3             |
| Lungs - mottled brown                          | 0             | 0             | 1              | 0             | 0              | 0             |
| Lungs - mottled dark red                       | 0             | 0             | 1              | 2             | 2              | 1             |
| Lungs - scattered red foci (all lobes)         | 3             | 0             | 0              | 1             | 0              | 0             |
| Lungs - scattered red foci (left lobe)         | 0             | 1             | 0              | 0             | 0              | 0             |
| Urinary bladder - dilation/contained red fluid | 0             | 0             | 1              | 1             | 1              | 0             |
| Urinary bladder - dilation                     | 0             | 0             | 0              | 0             | 0              | 1             |
| Spleen - black                                 | 0             | 0             | 0              | 0             | 1              | 0             |
| Spleen - enlarged                              | 0             | 0             | 4              | 3             | 0              | 0             |
| Liver - dark brown                             | 0             | 0             | 0              | 1             | 0              | 0             |
| Liver - brown                                  | 0             | 0             | 1              | 0             | 0              | 0             |
| Stomach - bloated                              | 0             | 0             | 1              | 0             | 0              | 0             |
| Stomach - hard; packed with food               | 0             | 0             | 0              | 0             | 0              | 1             |
| Stomach - empty                                | 0             | 0             | 0              | 1             | 0              | 0             |
| Stomach - contained red fluid                  | 0             | 0             | 0              | 0             | 1              | 0             |
| Uterine horns - dilation                       | 0             | 0             | 0              | 1             | 0              | 0             |
| Small intestine - contained red fluid          | 0             | 0             | 0              | 0             | 1              | 1             |
| Large intestine - contained red fluid          | 0             | 0             | 0              | 0             | 1              | 0             |
| Eyes (one or both) - opacity                   | 0             | 0             | 0              | 0             | 2              | 4             |
| Kidney - white focus                           | 0             | 0             | 0              | 0             | 1              | 0             |

<sup>a</sup> Total number of rats having the observation.

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June 22, 1998

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401 M St. S.W.  
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Re: TSCA Section 8(e) Notification

Dear Sir or Madam:

ChemFirst Inc is submitting this notice on behalf of First Chemical Corporation in accordance with Section 8(e) of the Toxic Substances Control Act (TSCA) and EPA's Statement of Interpretation and Enforcement Policy, 43 Fed. Reg. 1110 (March 16, 1978).

The basis for this submission is the occurrence of methemoglobinemia and hemolytic anemia in rats at exposure concentrations of 5.6, 32.8, and 67.6 ppm in a fourteen day inhalation toxicity study of N-ethyl-meta-toluidine (NEM), CAS no. 102-27-2. A copy of the draft report of this study is attached. The study was sponsored by ChemFirst Inc.

ChemFirst Inc. submitted two notices under Section 8(e) previously for this chemical, based on cyanosis and methemoglobin formation after acute oral exposure and three days of inhalation exposure. The document control number for the oral study submission was 8EHQ-97-13977.

NEM is manufactured in a totally enclosed process. When exposure potential exists, workers use personal protective equipment, including appropriate protective suits, neoprene gloves, boots, and full-face respirators. Protective clothing and equipment are specified on the Material Safety Data Sheet (attached). NEM is produced by First Chemical Corporation, a ChemFirst Inc. Company, for use as a cure accelerator in polymerizations. The MSDS will be updated to include this information after a final report is received. A copy of the completed final report will be sent as a follow-up to this submission.

ChemFirst Inc. would like to maintain as confidential only information that identifies the testing laboratory. Substantiation of this claim is attached.

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If you have any further questions related to this submission, please contact me.

Sincerely,

A handwritten signature in black ink that reads "Ellen R. Stephens". The signature is written in a cursive style with a large, stylized "E" and "S".

Ellen R. Stephens, Ph.D. DABT  
Manager, Toxicology  
228-938-2219

enclosure

**FOURTEEN-DAY INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**

**DRAFT REPORT**

**Testing Facility:**

**Sponsor:**

**ChemFirst Inc.  
1001 Industrial Highway  
Pascagoula, MS 39581-3237**

**Sponsor Representative:  
Ellen R. Stephens, Ph.D.**

**June 1998**

**FOURTEEN-DAY INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS**



FOURTEEN-DAY INHALATION TOXICITY STUDY OF  
N-ETHYL-M-TOLUIDINE (NEM) IN RATS

FOREWORD

This report describes a study conducted by the Inhalation Toxicology Division, for ChemFirst Inc. during the period of October 16, 1997 (receipt of test animals) to November 26, 1997 (final in-life date of recovery animals). The study was performed under .. The study was designed to meet the requirements of OECD testing guidelines 412 entitled "Repeated Dose Inhalation Toxicity: 28-Day or 14-Day Study", 1981 and as modified by the Sponsor. Ellen R. Stephens, Ph.D., served as representative of ChemFirst Inc.

M.S.. served as the Study Director.

also participated in the study. M.S., Technical Editor, assisted in the preparation of this report. All study data generated and a copy of the final report will be archived

Respectfully submitted,

---

Date

Approved by:

---

Date