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12/3/85



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

004838

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: NALED - Data Submitted Under Accession Numbers
257455 through 257464.
EPA I.D. # 239-1633 Caswell # 586

FROM: Irving Mauer, Ph.D.
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769)

J. Mauer
12-03-85

TO: William Miller/G. Otakie
Product Manager #16
Registration Division (TS-767)

THRU: Jane E. Harris, Ph.D. *JCH 12/03/85*
Section Head, Section VI
Toxicology Branch/HED (TS-769)

Action Requested:

Review and evaluate studies submitted in response to DATA
CALL-IN based on data gaps identified in the Naled Registration
Standard.

Registrant: Chevron Chemical Company

Background:

The following toxicological studies were submitted by the
registrant:

References

1. The Acute Dermal Toxicity of Chevron Naled Technical (SX-1397) in Adult Male and Female Rabbits. SOCAL 2293. February 11, 1985, S-2501. Acc. No. 257458.
2. The Acute Inhalation Toxicity of Naled Technical (SX-1554) in Rats. SOCAL 2266. February 19, 1985, S-2458. Acc. No. 257458.
3. Pilot Teratology Study in Rabbits with Chevron Naled Technical (SX-1397). SOCAL 2194. January 24, 1985, S-2192. Acc. No. 257458.
4. Teratology Study in Rabbits with Chevron Naled Technical (SX-1397). SOCAL 2206. February 28, 1985, S-2193. Acc. No. 257458.

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5. Mouse Bone Marrow Micronucleus Assay with Chevron Naled Technical (92.0% Purity, SX-1397) SOCAL 2213. November 21, 1984, S-2213. Acc. No. 257458.
6. A Pilot Rat Reproduction Study with DIBROM. Final Report. Bio/dynamics, Inc. Project NO. 82-2611. March 7, 1983, S-2018. Acc. No. 257464.
7. Addendum to Pilot Reproduction Study in Rats with Chevron Naled Technical (SX-1380). Bio/dynamics Project No. 82-2611. Chevron No. S-2018. Dosage Formulation Analyses. September 10, 1982. Acc. No. 257456.
8. Two-Generation Reproduction Study in Rats with DIBROM. Project No. 82-2612. Volumes I thru V. March 22, 1985 S-2019. Acc. No. 257459 to 247463.
9. Addendum to Two-Generation Reproduction Study in Rats with Naled Technical (SX-1397). Chevron No. S-2019. Dosage Formulation Analyses. June 1, 1984. Acc. No. 257455.

TB Conclusions:

Reviews have been completed on the acute dermal and acute inhalation studies (Ref's 1 and 2), and are being transmitted to RD at this time because of labelling requirements. In addition, a review has been completed on the micronucleus test (Ref 5) and is also being transmitted with this memo.

TB's conclusions on these three studies are as follows (see DATA REVIEWS attached to this memo):

Ref #	Study	Reported Results	TOX CAT	CORE Grade
1	Acute Dermal - Rabbit	LD50 - Male = 390 mg/kg LD50 - Female = 360 mg/kg	II	Guideline
2	Acute Inhalation - Rat	LC50 - Male = 0.20 mg/L LC50 - Female = 0.19 mg/L	I	Minimum
5	Micronucleus Assay - Mouse	Negative for induction of micronuclei at doses approaching the LD50 (HDT for males = 220 mg/kg, for females = 290 mg/kg)	-	Acceptable

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The teratology (Ref's 3 and 4) and reproduction studies (Ref's 6 thru 9) are currently under review, and will be transmitted as soon as our evaluations are completed.

Attachments

OPP:HED:TOX:I.MAUER:sb 12/3/85 X77395 #M

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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EPA: 68-02-4225
DYNAMAC NO.: 39-A1
November 26, 1985

DATA EVALUATION RECORD

NALED (SX-1397)

Acute Dermal Toxicity Study in Rabbits

STUDY IDENTIFICATION: Brorby, G., Cushman, J., Wong, Z. The acute dermal toxicity of Chevron naled technical (SX-1397) in adult male and female rabbits. (Unpublished study No. SOCAL 2293 by Chevron Environmental Health Center, Richmond, CA, for Chevron Chemical Company, Richmond, CA; dated February 11, 1985.) Accession No. 257458.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-26-85

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1. CHEMICAL: Naled (SX-1397).
2. TEST MATERIAL: The Chevron naled technical (code: SX-1397) used in this study, from Lot No. 20052, was a clear viscous liquid that contained 92 percent active ingredient. It was tested as supplied.
3. STUDY/ACTION TYPE: Acute dermal toxicity study in rabbits.
4. STUDY IDENTIFICATION: Brorby, G., Cushman, J., Wong, Z. The acute dermal toxicity of Chevron naled technical (SX-1397) in adult male and female rabbits. (Unpublished study No. SOCAL 2293 by Chevron Environmental Health Center, Richmond, CA, for Chevron Chemical Company, Richmond, CA; dated February 11, 1985.) Accession No. 257458.

5. REVIEWED BY:

Robin B. Phipps, B.S.
Principal Reviewer
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Signature: Robin B. Phipps
Date: 11-26-85

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Date: November 26, 1985

6. APPROVED BY:

Finis L. Cavender, Ph.D.
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Technical Quality Control
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Date: 11/26/85

Irving Mauer, Ph.D.
EPA Reviewer

Signature: Irving Mauer
Date: 11-27-85

Jane Harris, Ph.D.
EPA Section Head

Signature: Jane S. Harris
Date: 12-2-85

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7. SUMMARY:

Groups of five male and five female New Zealand White rabbits, supplied by L.I.T. Rabbitry (Whitehall, MT), were given single dermal applications of technical naled applied neat at doses of 125, 210, 360, or 615 mg/kg of body weight. (Through an error in sexing, 6 males and 4 females were actually dosed at 360 mg/kg; a fifth female was treated 3 weeks later at this dose.) A fifth group of untreated rabbits served as controls. At the time of dosing, the males were 12-14 weeks old and weighed 2.66-3.75 kg; females were 12-17 weeks old and weighed 2.74-3.12 kg. Following a 24-hour exposure to the test material, animals were observed daily for 14 days and dermal irritation was scored at 1, 7, and 14 days. Body weights were recorded prior to dosing and at 2, 7, and 14 days after dosing. All animals that died and all survivors at 14 days post-treatment were necropsied and examined for gross and microscopic pathological changes.

All rabbits dosed at 615 mg/kg died: 3 out of 5 males died within 2 days, the remaining 2 died 1 day later; 2 females died within 1 day and 3 within 2 days. Two of six males and two of five females dosed at 360 mg/kg died on days 3, 4, 2, and 11, respectively. All other animals survived to 14 days. Signs of toxicity noted only in animals that died included tremors, salivation, abnormal respiration, and miosis. Other signs, noted for survivors and/or non-survivors, included collapse, decreased motor activity, ataxia, and reduced food intake. Well-defined to severe erythema with severe edema were observed 24 hours post-dosing; eschar formation and/or severe erythema with no to moderate edema were present 7 days post-dosing; and eschar formation was still present on day 14. Mean body weights were significantly lower than controls on day 7 for males dosed at 360 mg/kg and on days 7 and 14 for females dosed at 360 mg/kg. At necropsy, necrotic, thickened, hard, dark red or brown, and scabbed skin and/or sloughed areas at the application site were noted for all naled-dosed animals but not for controls. These skin lesions were identified histopathologically as dermal necrosis, subdermal or dermal fibrosis, hyperkeratosis, acanthosis, crusting, inflammation, and ulceration, and were most severe in rabbits that survived to day 14. The study pathologist stated that lesions observed in other tissues were considered incidental findings or secondary effects associated with illness and debilitation. Based on these data, the dermal LD₅₀ and slope for naled in rabbits, as determined with respect to time of death by the method of Berkson¹, are as follows:

LD ₅₀ (95% Confidence Limits)	Slope (95% Confidence Limits)
Males 0.39 (0.13-1.12) g/kg	1.91 (0.61-5.95)
Females 0.36 (0.13-0.99) g/kg	1.86 (0.65-5.35)

¹ Berkson, J. Tables for use in estimating the normal distribution function by Normit analysis, *Biometrika* 44:411-435, 1957.

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These data correspond to Toxicity Category II.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

This study appears to be valid and an LD₅₀ was determined for both sexes. A signed and dated quality assurance statement was presented in the report. Although skin irritation was reportedly scored using a modified Draize scale on days 1, 7, and 14 posttreatment, individual scores were not presented in the study report; therefore, primary irritation scores could not be determined.

9. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 3-5.

10. CLASSIFICATION:

Core Classification: Core Guideline.

Toxicity Category: II.

Dermal LD₅₀: Males - 0.39 (0.13 - 1.12) g/kg;
Females - 0.35 (0.13 - 0.99) g/kg.

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APPENDIX A
Materials and Methods
(CBI pp. 3-5)

Naled toxicology review

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EPA: 68-02-4225
TASK: 039-A2
November 7, 1985

DATA EVALUATION RECORD

NALED

Acute Inhalation Toxicity Study in Rats

STUDY IDENTIFICATION: Rittenhouse, J., Griffis, L., Wong, Z. The acute inhalation toxicity of naled technical (SX-1554) in rats. (Unpublished study No. SOCAL 2266 by Chevron Environmental Health Center, Richmond, CA, for Chevron Chemical Company, Richmond, CA; dated February 19, 1985.) Accession No. 257458.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-7-85

1. CHEMICAL: Naled (SX-1554).

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2. TEST MATERIAL: Naled technical (code: SX-1554) used in this study was a clear straw-colored liquid that contained 89.8 percent active ingredient.

3. STUDY/ACTION TYPE: Acute inhalation toxicity study in rats.

4. STUDY IDENTIFICATION: Rittenhouse, J., Griffis, L., Wong, Z. The acute inhalation toxicity of naled technical (SX-1554) in rats. (Unpublished study No. SOCA- 2266 by Chevron Environmental Health Center, Richmond, CA, for Chevron Chemical Company, Richmond, CA; dated February 19, 1985.) Accession No. 257458.

5. REVIEWED BY:

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Date: November 7, 1985

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Date: November 7, 1985

6. APPROVED BY:

Finis L. Cavender, Ph.D.
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Date: 11/7/85

Irving Mauer, Ph.D.
EPA Reviewer

Signature: Irving Mauer
Date: 11-17-85

Jane Harris, Ph.D.
EPA Section Head

Signature: Jane Harris
Date: 11-17-85

7. SUMMARY:

Groups of five male and five female Sprague-Dawley rats, supplied by Bantin and Kingman, Inc. (Fremont, CA), were given whole-body exposures for 240 minutes to aerosols of undiluted naled technical at target concentrations of 0.1, 0.15, 0.2, or 0.4 mg/L. A fifth group of rats were exposed to filtered air and served as controls. At the time of exposure, the males were 14-16 weeks old and weighed 378-482 g; females were 12-14 weeks old and weighed 242-311 g. All animals were observed during exposure and at least once daily thereafter for 14 days. Body weights were recorded prior to exposure and on days 2, 7, and 14 after exposure. All animals that died and all survivors at day 14 post-exposure were necropsied and examined for gross pathologic changes. The lungs were examined for histopathologic alterations. See Appendix A for details of materials and methods.

The measured analytical concentrations of naled for this study were 0.098, 0.14, 0.19, and 0.42 mg/L. The authors reported an average mass median aerodynamic diameter of 3.02 μ m with a geometric standard deviation of 1.87 for the aerosols (CBI, p. 6). Approximately 97 percent of the particles of each aerosol were smaller than 10 μ . All rats exposed to 0.4 mg/L naled died during exposure or within 24 hours post-exposure; three males and three females exposed to 0.2 mg/L died within 2 days; and one female exposed to 0.1 mg/L died 22 hours post-exposure. All other rats survived to day 14. During the exposures, squinted eyes, salivation, labored breathing, tremors, and/or fasciculations were observed in naled-exposed animals. Following exposures, abnormal respiration, decreased motor activity, weakness, and unkempt appearance were noted. Survivors appeared normal within 6 days of exposure. At necropsy, opaque corneas and dark red lungs and livers were noted for most animals that died. No treatment-related gross pathologic changes were apparent in surviving animals. Pulmonary congestion was observed histopathologically for rats exposed to 0.2 or 0.4 mg/L naled. Based on these data, the LC₅₀ and slope for naled in rats, determined by the method of Berkson, are as follows:

	<u>LC₅₀ (95% Confidence Limits)</u>	<u>Slope (95% Confidence Limits)</u>
Males	0.20 (0.10-0.43) mg/L	1.63 (0.75-3.55)
Females	0.19 (0.08-0.46) mg/L	1.80 (0.63-5.17)

These data correspond to Toxicity Category I.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

This study appears to be valid, and a signed and dated quality assurance statement was presented in the report.

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9. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. 2-5.

10. CLASSIFICATION:

Core Classification: Core Minimum.

Toxicity Category: I.

LC₅₀: Males - 0.20 (0.10 - 0.43) mg/L.
Females - 0.19 (0.08 - 0.46) mg/L.

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APPENDIX A
Materials and Methods
(CBI pp. 2-5)

Naled toxicology review

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EPA: 68-01-6561
TASK: 039-A4
November 11, 1985

DATA EVALUATION RECORD

Naled

Mutagenicity--Micronucleus Assay in Mice

STUDY IDENTIFICATION: Machado, M. L., Carver, J. H., and Kodama, J. K.
Mouse bone marrow micronucleus assay with Chevron Naled Technical (Un-
published study No. SOCAL 2213 performed and submitted by Chevron Chemical
Company, Richmond, CA; dated November 21, 1984.) Accession No. 257^a58.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 11-11-85

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1. CHEMICAL: Naled; Dibrom.
2. TEST MATERIAL: Naled Technical, code No. SX1397, a clear viscous liquid, stored at 4°C (nitrogen blanketed) and protected from light, had a stated purity of 92 percent.
3. STUDY/ACTION TYPE: Mutagenicity--Micronucleus Assay in Mice.
4. STUDY IDENTIFICATION: Machado, M. L., Carver, J. H., and Kodama, J. K. Mouse bone marrow micronucleus assay with Chevron Naled Technical (Unpublished study No. SOCAL 2213 performed and submitted by Chevron Chemical Company, Richmond, CA; dated November 21, 1984.) Accession No. 257458.

5. REVIEWED BY:

Brenda Worthy, M.T.
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Dynamac Corporation

Signature: Brenda Worthy
Date: 11-11-85

Nancy McCarroll, B.S.
Independent Reviewer
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6. APPROVED BY:

I. Cecil Felkner, Ph.D.
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Date: 11-11-85

Irving Mauer, Ph.D.
EPA Reviewer

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Date: 11-22-85

Jane Harris, Ph.D.
EPA Section Head

Signature: Jane E. Harris
Date: 12/2/85

7. CONCLUSIONS:

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- A. Under the conditions of the assay, Naled Technical (SX-1397) at doses of 55, 110, and 220 mg/kg for males and 55, 110, and 290 mg/kg for females did not induce increased micronucleated polychromatic erythrocytes (MPE) in mouse bone marrow cells sampled (24, 48, and 72 hours) over the entire erythropoietic cycle. The positive control, triethylenemelamine at 0.25 mg/kg ip, caused a significant increase in the number of MPE, demonstrating the sensitivity of the assay to detect a clastogenic response.
- B. The study is acceptable.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Naled Technical, code No. SX-397, described as a clear viscous liquid, was stored at 4°C, nitrogen blanketed and protected from light, and had a purity of 92 percent. The test material was diluted in 0.5% carboxymethyl cellulose (CMC), the vehicle control.
2. Test Animals: Four-week-old male and female Swiss Albino mice (Crl:CD-1,ICR,BR) were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan. Weight ranges at the initiation of the study were 23-32 g for males and 17-26 g for females.
 - (a) Animal Maintenance: The animals were acclimated to laboratory conditions for 12 days prior to dosing. The mice were grouped housed (5/cage) in ventilated, solid bottom cages in environmentally controlled room (temperature, 21°C; relative humidity, 58-70%) on a 12-hour light/dark cycle. Animals were fasted overnight prior to dosing, at all other times food and water were available ad libitum.

¹Only item appropriate to this DER have been included.

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- (b) Group Assignment: Five animals/sex were randomly assigned to control and each dose group for each sampling time using a table of random permutations. Animal cages were identified and each animal was identified by a tail mark.
- (c) Clinical Observations: Animals were observed for physiological or behavioral abnormalities frequently on the day of dosing and twice daily until sacrifice. Body weights were recorded prior to compound administration and on the day of sacrifice.
3. Preparation and Analysis of Test Material: The test material was suspended in 0.5 percent CMC and mixed until a uniform suspension was obtained. Dosing preparations were analyzed for homogeneity and stability.
4. Preliminary Toxicity Study: Five animals/sex were administered six single doses of the test material (178, 215, 261, 316, 383, or 464 mg/kg) by oral gavage. Animals were observed for toxic signs, frequently on the day of administration and twice daily thereafter.
5. Micronucleus Assay:
- (a) Dose Selection and Compound Administration: From the findings of the toxicity study, the oral LD₅₀ was 257 mg/kg for males and 336 mg/kg for female mice. The highest dose (80% of the LD₅₀) was selected to produce clinical toxicity and/or cytotoxicity. The dose chosen were 55, 110, and 220 mg/kg for males and 55, 110, and 290 mg/kg for females.

Five males and 5 females were administered the selected doses of the test material and the vehicle control via gavage. The positive control, triethylenemelamine (TEM) at 0.25 mg/kg, was administered ip to five animals per sex. Extra animals were treated at each dose level to ensure survival of five mice/sex/sampling interval.

- (b) Animal Sacrifice/Bone Marrow Harvest: Five animals of each sex/group were randomly selected for sacrifice at 24, 48, or 72 hours; the positive control mice were all sacrificed at 24 hours. Animals were sacrificed by cervical dislocation, then femoral bone marrow was aspirated into fetal calf serum and centrifuged. The supernatant

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was decanted and the marrow pellet was resuspended. Two bone marrow slides were prepared according to the method of Schmid.² The slides were fixed, stained with Giemsa, and coded.

(c) Slide Analysis: Two thousand polychromatic erythrocytes (PCE) per animal were scored for the presence of micronucleated polychromatic erythrocytes (MPE); the ratio of normochromatic erythrocyte (NCE) to PCEs was determined by counting 1000 erythrocytes.

6. Statistical Analysis: Mean body weight data were analyzed using the two-sample t-test. The PCE/PCE+NCE ratios were compared using the one-way analysis of variance and Dunnett's procedure.

7. Evaluation Criteria: A test material was considered positive according to the methods of Hart and Engberg-Pederson and of Selby and Olson (see Appendix B). A test material was considered negative if the test material did not induce a significant increase ($p < 0.05$) in the number of MPE compared to either the concurrent or historical vehicle control groups.

B. Protocol: See Appendix A.

12. REPORTED RESULTS:

Preliminary Toxicity Study: In the acute oral toxicity study the mortality in the highest dose (464 mg/kg) group was 5/5 animals for both male and female mice. Mortality in the lower doses for male mice was 4/5 (383 mg/kg), 4/5 (316 mg/kg), 3/5 (261 mg/kg), 1/5 (215 mg/kg), and 1/5 (178 mg/kg). Mortality of the female mice at the same dose levels was 1/5, 3/5, 2/5, 1/5, and 0/5, respectively. Additional toxic signs included decreased motor activity, salivation, convulsions, irregular and labored respiration, tremors, and ataxia.

Micronucleus Assay: Mortality was observed at the highest doses (220 mg/kg for males and 290 mg/kg for females) with 4/25 for males and 6/25 for females before scheduled sacrifice. In addition other toxic signs noted were convulsions, decreased motor activity, salivation, lacrimation, tremors, weakness, oral and ocular discharge.

No significant difference ($p < 0.05$) were reported in mean body weights or PCE/PCE+NCE ratios between dosed and control mice.

² W. Schmid, (1976) "The micronucleus test for cytogenetic analysis," in, Chemical Mutagens, Vol. 4, Plenum, New York, pp. 31-53.

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There were no significant ($p < 0.05$) increase in the number of MPE in the dosed groups compared to the vehicle controls (concurrent or historical). TEM, the positive control, induced MPE as expected. Representative results are presented in Table 1.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that "under the conditions tested, Chevron Maled Technical (SX-1397) meets all the criteria for a negative response in this mouse bone marrow micronucleus assay."

B. A quality assurance statement was signed and dated November 29, 1984.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. It is our assessment that the study was well conducted and the authors' interpretation of the data was correct. Maled Technical did not induce a clastogenic response of micronucleated polychromatic erythrocytes in the bone marrow of mice. The highest dose tested for both male and female animals elicited toxic signs; therefore, the dose range selected was adequate. The PCE: NCE ratios for test groups were comparable to the appropriate control group indicating that Maled Technical did not alter the progression of erythrocytes through the mitotic cycle.

The positive control (TEM) at the dose tested (0.25 mg/kg) induced an increase in MPE over the vehicle control; therefore, the sensitivity of the assay to detect a clastogenic/mutagenic effect was demonstrated.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A--Materials, Methods, and Protocol, CBI pp. 2-6, and CBI Appendix 1, pp. 1-8; Appendix B--CBI Appendix D, Method Evaluation.

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TABLE 1. Representative Results of the Micronucleus Assay in Mice with Maled Technical

Substance	Dose (mg/kg)	Sampling Interval (hr)	# of Animals per Group	# of PCEs per Group	Total # of ^a MPE per Group	% MPE ^a per Group	Average Group NCE/PCE
Males							
Vehicle Control							
0.5% CMC	5 ml/kg	24	5	10081	17	0.17	0.9:1
		48	5	10064	7	0.07	0.7:1
		72	5	10019	13	0.13	1.2:1
Positive Control							
TEM	0.25	24	5	10166	185	1.8	1:1
Test Material							
Maled	220 ^{b,c}	24	5	10088	21	0.21	1:1
		48	5	10113	9	0.09	1.2:1
		72	5	10130	15	0.15	1:1
Females							
Vehicle Control							
0.5% CMC	5 ml/kg	24	5	10137	17	0.17	0.1:1
		48	5	10122	6	0.06	0.1:1
		72	5	10158	18	0.18	0.9:1
Positive Control							
TEM	0.25	24	5	10065	229	2.3	0.8:1
Test Material							
Maled	290 ^{b,c}	24	5	10122	20	0.20	1.1:1
		48	5	10042	7	0.07	1.2:1
		72	5	10102	13	0.13	0.7:1

^aCalculated by the reviewers.^bHighest dose tested; lower doses (110 and 55 mg/kg, males and females) were comparable to the vehicle controls.^cToxic signs and mortality observed at this dose.

PCE = Polychromatic erythrocytes.

MPE = Micronucleated polychromatic erythrocytes.

NCE = Normochromatic erythrocytes.

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APPENDIX A

Materials, Methods, and Protocol

Naled toxicology review

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