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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Naphthalene: Evaluation of Mutagenicity Studies.

Barcode No.: D173073
Submission No.: S409546
EPA ID No.: 055801

Tox. Chem. No.: 587
HED Project No.: 2-0996
Case No.: 818942

FROM: Krystyna K. Locke, Toxicologist
Section I, Toxicology Branch I
Health Effects Division (H7509C)
Krystyna K. Locke 5/11/92

TO: Larry Schnaubelt/Karen Samek, PM 72
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Roger Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (H7509C)
Roger Gardner 6/16/92
KB 6/29/92

Toxicology Branch (TB)/HED has completed an evaluation of the following mutagenicity studies with naphthalene:

(1) Ames Salmonella/Microsome Plate Test; E.G. Godek; Pharmakon Research International, Inc.; Study No.: PH 301-TX-020-85; Study completed: September 27, 1985; Report issued: October 22, 1991.
MRID No.: 42071601
Guideline No.: 84-2a

(2) Ames/Salmonella Plate Incorporation Assay; L.F. Stankowski; Pharmakon Research International, Inc.; Study No.: PH 301-TX-001-87; Study completed: November 15, 1987; Report issued: October 22, 1991.
MRID No.: 42071602
Guideline No.: 84-2a

(3) Micronucleus Test (MNT) OECD; R.M. Sorg; Pharmakon Research International, Inc.; Study No.: PH 309A-TX-007-85; Study completed: October 22, 1985; Report issued: October 22, 1991.
MRID No.: 42071603
Guideline No.: 84-2b

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(4) Rat Hepatocyte Primary Culture/DNA Repair Test; T.R. Barfknecht; Pharmakon Research International, Inc.; Study No.: PH 311-TX-008-85; Study completed: September 27, 1985; Report issued: October 22, 1991.
MRID No.: 42071604
Guideline No.: 84-4

All of the studies have been classified by Tox. Branch/HED as Unacceptable. However, studies **(2)**, **(3)** and **(4)** can be upgraded to Acceptable by submitting information on the purity of the test material (naphthalene). Study **(1)** cannot be upgraded because it does not satisfy the data Guideline requirement (§84-2) for genetic effects Category I, Gene Mutations. However, study **(1)** does not have to be repeated since another study in the same category, study **(2)**, has been submitted by the sponsor/registrant (Texaco Chemical Company, Houston, TX). As has already been indicated, study **(2)** is upgradeable.

Naphthalene was not mutagenic in studies **(2)**, **(3)** and **(4)** which are well-conducted studies. No definitive conclusions regarding the mutagenicity of naphthalene can be reached in study **(1)**.

These studies were submitted in response to the 05/06/91 DCI for naphthalene to fulfill the 84-Mutagenicity guideline requirements.

DOC930057
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DATA EVALUATION REPORT

Naphthalene

Study Type: Mutagenicity: Salmonella typhimurium/Mammalian Microsome Mutagenicity Assay

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer [signature] Date 5/6/92
Lynne T. Haber, Ph.D.

Independent Reviewer [signature] for Date 5/6/92
Nancy E. McCarroll, B.S.

QA/QC Manager [signature] Date 5/6/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-83
Clement Number: 91-283
Project Officer: James Scott

GUIDELINE SERIES 84: MUTAGENICITY SALMONELLA

EPA Reviewer: Krystyna Locke, Toxicologist	Signature: Krystyna R. Locke
Section I, Tox. Branch I/HED (H7509C)	Date: 5/8/92
EPA Section Head: Roger Gardner	Signature: Roger Gardner
Section I, Tox. Branch I/HED (H7509C)	Date: 6/15/92
Secondary Reviewer: Irving Mauer, Geneticist	Signature: Irving Mauer
Section I, Tox. Branch I/HED (H7509C)	Date: 05-8-92

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Salmonella typhimurium/mammalian microsome mutagenicity assay

EPA IDENTIFICATION Numbers:

Tox. Chem. Number: 587

MRID Number: 420716-01

TEST MATERIAL: Naphthalene

SYNONYMS: None provided

SPONSOR: Texaco Chemical Company, Houston, TX

STUDY NUMBER: PH 301-TX-020-85

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Ames Salmonella/Microsome Plate Test

AUTHOR: Godek, E. G.

REPORT ISSUED: October 22, 1991; Study completed September 27, 1985

CONCLUSIONS--EXECUTIVE SUMMARY: No definitive conclusions can be reached from the Salmonella typhimurium/mammalian microsome plate incorporation assay conducted with naphthalene at concentrations ranging from 3 to 300 µg/plate. No evidence of mutagenicity was found at any tested concentration of naphthalene; however, there was also no cytotoxicity at the highest nonactivated or S9-activated dose in S. typhimurium strains TA1535, TA1537, TA1538, TA98, or TA100. Although the sponsor submitted a report from a repeat of this assay, in which naphthalene, tested over a comparable range (3-300 µg/plate +/-S9), was cytotoxic but not mutagenic (see Data Evaluation Record 91-284), the lack of a cytotoxic response and the absence of test material purity in the currently reviewed assay precludes the use of this study as an individual data source.

STUDY CLASSIFICATION: Unacceptable. The study does not satisfy the data Guideline requirement (§84-2) for genetic effects Category I, Gene Mutations.

However, the study does not need to be repeated since a technically acceptable S. typhimurium/mammalian microsome mutagenicity test of naphthalene, which can be upgraded by submission of test material purity information, was submitted by the sponsor.

A. MATERIALS:

1. Test Material: Naphthalene

Description: White flake
Identification number: 5601-56-1
Purity: Not reported
Receipt date: August 13, 1985
Stability: Not reported
Contaminants: None listed
Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: The test material was stored at room temperature. Dosing solutions were prepared within 4 hours of use.

2. Control Materials:

Solvent/final concentration: DMSO/100µl per plate

Positive:

Nonactivation:

Sodium azide	10	µg/plate TA100, TA1535
2-Nitrofluorene	5	µg/plate TA98, TA1538
9-aminoacridine	150	µg/plate TA1537

Activation:

2-Anthramine	2.5	µg/plate all strains

3. Activation: S9 derived from male Sprague-Dawley

x	Aroclor 1254	x	induced	x	rat	x	liver
	phenobarbital		noninduced		mouse		lung
	none				hamster		other
	other				other		

The rat liver S9 homogenate was prepared by the testing laboratory on February 4, 1985 and was reported to have a protein concentration of 35.7 mg/mL.

S9 mix composition:

Component:	Volume/mL
Water	0.355 mL
0.2 M Phosphate buffer (pH 7.4)	0.50 mL
1 M Glucose 6-phosphate	0.005 mL
0.1 M NADP	0.04 mL
1.65 M KCl/0.4 M $MgCl_2$	0.02 mL
S9	0.08 mL

4. Test Organism Used: S. typhimurium strains
   ____ TA97 __x__ TA98 __x__ TA100 ____ TA102 ____ TA104
   __x__ TA1535 __x__ TA1537 __x__ TA1538
   list any others:

   Test organisms were properly maintained: Yes.
   Checked for appropriate genetic markers (rfa mutation, R factor): Yes.

5. Test Compound Concentrations Used:

   (a) Preliminary cytotoxicity assay: Five doses (50, 166, 500, 1666, and 5000 µg/plate) were evaluated without S9 activation in S. typhimurium strains TA100 and TA1538. A single plate was used, per dose, per condition.

   (b) Mutation assay: Five doses (3, 10, 30, 100, and 300 µg/plate) were evaluated in triplicate in the presence and absence of S9 activation; all tester strains were used.

B. TEST PERFORMANCE:

1. Type of Salmonella Assay:
   __x__ Standard plate test
   ____ Pre-incubation (____) minutes
   ____ "Prival" modification
   ____ Spot test
   ____ Other (describe)

2. Methods:

   (a) Preliminary cytotoxicity/mutation assays: Similar procedures were used for the preliminary cytotoxicity and the mutation assays.

   Tester strains were grown to late log or early stationary phase in Oxoid broth; 0.1 mL of the appropriate tester strain and 0.1 mL of the appropriate test material dose, solvent, or positive control were added to tubes containing 2-mL volumes of molten top agar. For the S9-activated assay, 0.5 mL of the S9-cofactor mix was also added. The contents of the tubes were mixed, poured over minimal glucose plates, and incubated at 37°C for 48-72 hours. Means and

standard deviations for the mutation test were determined from the counts of triplicate plates per strain, per dose, per condition.

(b) Sterility controls: The sterility of the solvent, top agar, highest test dose, and the S9 mix was determined.

3. Evaluation Criteria:

(a) Assay validity: The assay was considered valid if the solvent control values fell within "the acceptable historical mean values." Historical means and 95% confidence limits for each strain, -/+S9 activation were: TA1535: 13.6±6.4/13.4±4.8; TA1537: 14.0±5.8/16.3±7.4; TA1538: 17.4±7.2/26.9±9.6; TA98: 29.1±8.8/40.5±15.6; and TA100: 169±71/157±69.

(b) Positive response: The test material was considered positive if it caused a reproducible, dose-related increase in the mean number of revertants per plate of at least one strain, with at least one dose inducing a doubling of revertant levels compared to the control value. The test material was also considered positive if the maximum number of revertants induced by the test chemical was three times the solvent control.

4. Statistical Analysis: The data were analyzed for a dose response using linear regression analysis by the method of Moore and Felton[1], with a 95% confidence limit.

5. Protocol: No protocol was provided; however, a copy of the raw data was included.

C. REPORTED RESULTS

1. Preliminary Cytotoxicity Assay: Five doses of the test material ranging from 50 to 5000 µg/plate were evaluated without S9 activation using strains TA100 and TA1538. A review of the primary data accompanying the study report indicated that compound precipitation occurred at levels ≥1666 µg/plate. No revertants of either strain survived exposure to the high dose (5000 µg/plate). With strain TA1538, pinpoint colonies, indicative of a reduction in the background lawn of growth, were observed at 500 and 1666 µg/plate, and normal growth at lower doses. With strain TA100, no growth was seen at levels ≥500 µg/plate, reduced levels of revertant colonies were seen at 166 µg/plate, and normal growth was observed at 50 µg/plate. Based on these findings, the concentration range selected for the mutation assay was 3-300 µg/plate +/-S9.

2. Mutation Assay: In contrast to the results of the preliminary cytotoxicity assay, no cytotoxicity was observed with strain TA100 at

[1]Moore, D. and J.S. Felton. 1983. A Microcomputer Program for Analyzing Ames Test Data. Mutat. Res. 119:95-102.

the high dose (300 µg/plate +/-S9). In addition, no cytotoxicity was seen in any other strain at any nonactivated or S9-activated dose. Similarly, there was no evidence of mutagenicity at any concentration with or without S9 activation in any of the tester strains (Table 1). All strains responded in the expected manner to the appropriate nonactivated and S9-activated positive controls. From the overall findings, the study authors concluded that naphthalene was not mutagenic in this test system.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study author correctly concluded that naphthalene was not mutagenic. However, the results do not fully support a negative conclusion because no cytotoxicity was demonstrated at the highest tested concentration (300 µg/mL +/-S9). Although results from the preliminary assay showed that 166 µg/plate -S9 was cytotoxic to strain TA100, no cytotoxicity was observed in this strain at 300 µg/plate +/-S9 in the mutation assay. The results from the preliminary assay showing cytotoxicity in strain TA1538 beginning at 500 µg/plate and insolubility at levels ≥1666 µg/plate should also have prompted the study author to test naphthalene at higher concentrations. In addition, there was no information on the purity of the test material.

Based on the above considerations, we conclude that the study is unacceptable. However, it is not necessary to repeat the assay, since a technically acceptable Salmonella typhimurium mutagenicity assay confirming the nonmutagenic status of naphthalene was submitted by the sponsor (see Data Evaluation Record 91-284).

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLP? Yes. (A quality assurance statement was signed and dated November 26, 1985.)

F. CBI APPENDICES: Appendix A, Materials and Methods, CBI pp. 8-12.

CORE CLASSIFICATION: Unacceptable. As an individual data source, this study does not satisfy the data Guideline requirement (§84-2) for genetic effects Category I, Gene Mutations.

TABLE 1: Representative Results of the Salmonella typhimurium/Mammalian Microsome Mutation Assay with Naphthalene

Substance	Dose/Plate	S9 Activation	Revertants per Plate of Bacterial Tester Strain[a]				
			TA1535	TA1537	TA1538	TA98	TA100
Solvent Control							
Dimethyl sulfoxide	100 µL	-	17±4	12±0	19±8	31±7	172±13
	100 µL	+	10±3	10±4	24±5	44±9	129±11
Positive Controls							
Sodium azide	10 µg	-	1152±111	--	--	--	1329±18
9-Aminoacridine	150 µg	-	--	1644±216	--	--	--
2-Nitrofluorene	5 µg	-	--	--	565±312	579±49	--
2-Anthramine	2.5 µg	+	217±13	259±61	1072±210	1682±221	1635±120
Test Material							
Naphthalene	300 µg[b]	-	15±3	8±4	18±7	27±2	156±16
	300 µg[b]	+	10±4	7±6	24±3	44±13	134±21

[a]Means and standard deviations of the counts from triplicate plates.

[b]Results for lower doses (3, 10, 30, and 100 µg/plate +/-S9) did not suggest a mutagenic effect.

Page_____ is not included in this copy.

Pages 10 through 15 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) __________.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

DOC930058

FINAL

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DATA EVALUATION REPORT

NAPHTHALENE

Study Type: Mutagenicity: Salmonella typhimurium/Mammalian Microsome Mutagenicity Assay

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer [signature] for Nancy E. McCarroll, B.S. Date 5/6/92

Independent Reviewer [signature] Lynne Haber, Ph.D. Date 5/6/92

QA/QC Manager [signature] Sharon Segal, Ph.D. Date 5/6/92

Contract Number: 68D10075
Work Assignment Number: 1-83
Clement Number: 91-284
Project Officer: James Scott

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MUTAGENICITY STUDIES

EPA Reviewer: Krystyna Locke, Ph.D. Signature: Krystyna R. Locke
Section I, Toxicology Branch I/HED (H7509C) Date: 5/8/92

EPA Section Head: Roger Gardner, Ph.D. Signature: Roger Gardner
Section I, Toxicology Branch I/HED (H7509C) Date: 6/16/92

Secondary reviewer: Irving Mauer, Geneticist Signature: [signature]
Section I, Toxicology Branch I/HED (H7509C) Date: 05-08-92

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Salmonella typhimurium mammalian microsome mutagenicity assay

EPA IDENTIFICATION Numbers:

Tox. Chem. Number: 587

MRID Number: 420716-02

TEST MATERIAL: Naphthalene

SYNONYMS: None

SPONSOR: Texaco Chemical Co., Houston, TX

STUDY NUMBER: PH 301-TX-001-87

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Ames/Salmonella Plate Incorporation Assay

AUTHOR: L.F. Stankowski, Jr.

REPORT ISSUED: October 22, 1991; Study completed November 15, 1987.

CONCLUSIONS--EXECUTIVE SUMMARY: Five doses of naphthalene ranging from 3 to 300 µg/plate +/-S9 were not mutagenic in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, or TA100. The highest dose (300 µg/plate) with and without S9 activation was cytotoxic in all strains. Based on these findings, it was concluded that naphthalene was tested over an appropriate range of concentrations with no evidence of mutagenic effect in a well-conducted study. However, the lack of purity information for the test material renders the study incomplete.

STUDY CLASSIFICATION: Unacceptable. The study does not fully satisfy Guideline requirements (§84.2) for genetic effects Category I, Gene Mutations, but can be upgraded if test material purity information is submitted.

A. MATERIALS:

1. Test Material: Naphthalene

Description: White crystalline flakes
Identification Number: Sample number 5601-56-1
Purity: Not reported
Receipt date: November 10, 1987
Stability: Not reported
Contaminants: None listed
Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: The test material was stored at room temperature. Solutions of the test material were prepared within 2 hours of use.

2. Control Materials:

Negative: None

Solvent/concentration: DMSO/100 µL/plate

Positive:

Nonactivation:

Sodium azide	10	µg/plate TA1535, TA100
2-Nitrofluorene	5	µg/plate TA1538, TA98
9-Aminoacridine	150	µg/plate TA1537

Activation:

2-Aminoanthracene	2.5	µg/plate all strains

3. Activation: S9 derived from male Sprague-Dawley

x	Aroclor 1254	x	induced	x	rat	x	liver
____	phenobarbital	____	noninduced	____	mouse	____	lung
____	none			____	hamster	____	other
____	other			____	other		

The rat S9 liver homogenate (lot number 4-8-87) was prepared by the performing laboratory. The S9 mix contained the following components:

Component	Volume/mL of S9 mix
0.2 M Sodium phosphate buffer (pH 7.4)	0.500 mL
1.0 M Glucose 6-phosphate	0.005 mL
0.1 M NADP	0.040 mL
0.4 M $MgCl_2$; 1.65 M KCl	0.020 mL
Water	0.375 mL
S9	0.060 mL

4. Test Organism Used: *S. typhimurium* strains

____	TA97	x	TA98	x	TA100	____	TA102	____	TA104
x	TA1535	x	TA1537	x	TA1538				

list any others:

Test organisms were properly maintained: Yes.
Checked for appropriate genetic markers (rfa mutation, R factor): Yes.

5. Test Compound Concentrations Used:

(a) Preliminary cytotoxicity assay: Five doses (50, 167, 500, 1670, and 5000 µg/plate) were evaluated without S9 activation in tester strains TA1538 and TA100. Duplicate plates were used per dose, per strain.

(b) Mutation assay: Five doses (3, 10, 30, 100, and 300 µg/plate) were evaluated in the presence and absence of S9 activation; all tester strains were used. Triplicate plates were used per dose, per strain, per condition.

B. TEST PERFORMANCE:

1. Type of Salmonella Assay:
   - __x__ Standard plate test
   - _____ Pre-incubation (_____) minutes
   - _____ "Prival" modification
   - _____ Spot test
   - _____ Other (describe)

(a) Preliminary cytotoxicity: The preliminary cytotoxicity was conducted with strains TA1538 and TA100 exposed to five nonactivated doses of the test material or the solvent (DMSO) control; duplicate plates were used per strain, per dose. With these exceptions, similar procedures were used for both the preliminary cytotoxicity and mutation assays.

(b) Mutation assay: To tubes containing 2-mL volumes of top agar and 0.1 mL of 10-hour broth cultures of the appropriate tester strain, 0.1 mL of the selected test material doses, or the solvent, or the positive controls were added. For the S9-activated phase of testing, 0.5 mL of the S9-cofactor mix were added. The contents of each tube were mixed and overlaid onto plates of minimal glucose medium. Plate were incubated for 48 hours at 37°C. Following incubation, the number of revertant colonies was counted, means and standard deviations were determined for the mutation assay, and the condition of the background lawn growth was determined.

The sterility of the top agar, S9 mix, solvent control, and highest test compound dose was verified.

(c) Evaluation criteria:

(1) Assay validity: The assay was considered valid if mutant colony counts for the solvent control fell within the provided range of acceptable historical control values.

(2) Positive response: The test material was considered positive if a dose-related increase in revertant colonies for at least one S. typhimurium strain was seen, and if at least one dose caused a 2-fold increase in the mutants over the solvent control.

2. Protocol: A protocol was not furnished; however, a copy of the primary data and historical background data was presented.

C. REPORTED RESULTS:

1. Preliminary Cytotoxicity Test: A review of the primary data indicated that the two highest doses (1670 and 5000 µg/plate) were insoluble and completely cytotoxic for both strains TA1538 and TA100. Similarly, no colonies were found on plates containing the highest soluble dose (500 µg/plate). Slight cytotoxicity, as indicated by a reduction in mutant colonies and the background lawn of growth of both tester strains, was also seen at 167 µg/plate. The lowest assayed level (50 µg/plate) was not cytotoxic. Based on this information, the nonactivated and S9-activated mutation assays were performed with a dose range of 3 to 300 µg/plate naphthalene.

2. Mutation Assays: The study author stated that all tester strains were inhibited at 300 µg/plate +/-S9. This statement was supported by comments in the primary data indicating that the background lawn of growth for all strains was reduced at this level and that the reduction was more severe without S9 activation. Mutant colony counts for all strains were also slightly lower than control at 300 µg/plate +/-S9 (Table 1). There was, however, no evidence of a mutagenic response at any nonactivated or S9-activated dose. By contrast to the negative results for naphthalene, all strains responded to the mutagenic action of the corresponding nonactivated and S9-activated positive control.

Based on the overall results, the study author concluded that naphthalene was not mutagenic in this microbial test system.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study author's interpretation of the data was correct. Both in the presence and the absence of S9 activation, naphthalene was tested over an appropriate range of concentrations but failed to induce a mutagenic effect. In addition, the response of all tester strains to the appropriate nonactivated and S9-activated positive control demonstrated that the assay had an adequate level of sensitivity to detect a mutagenic response. It was concluded, therefore, that naphthalene was not mutagenic in this microbial test system. However, the lack of information on test material purity renders the study incomplete.

TABLE 1. Representative Results of the Salmonella typhimurium Mutagenicity Assay with Naphthalene

Substance	S9 Activation	Dose/plate	Revertants per Plate of Bacterial Tester Strains[a]				
			TA1535	TA1537	TA1538	TA98	TA100
Solvent Control							
Dimethyl sulfoxide	-	100 µL	13±4	9±4	12±4	39±17	106±15
	+	100 µL	17±1	11±3	32±9	43±10	114±5
Positive Controls							
Sodium azide	-	10 µg	1192±55	--	--	--	1631±118
2-Nitrofluorene		5 µg	--	--	897±127	561±111	--
9-Aminoacridine	-	150 µg	--	820±163	--	--	--
2-Aminoanthracene	+	2.5 µg	221±23	596±135	2405±234	2468±164	2756±103
Test Material							
Naphthalene	-	100 µg[b]	16±3	11±5	15±2	48±4	101±18
	-	300 µg[c]	8±0	5±1	8±0	22±7	70±14
	+	100 µg[b]	10±3	10±3	33±7	44±5	113±10
	+	300 µg[c]	13±5	8±6	25±1	38±5	74±8

[a]Means and standard deviations of triplicate plates
[b]Results for lower concentrations (3, 10, and 30 µg/plate +/-S9) did not suggest a mutagenic response.
[c]Highest assayed dose; slight reduction in the background lawn of growth for all strains at this level.

E. QUALITY ASSURANCE MEASURES: Was test performed under GLPs? Yes. (A quality assurance statement was signed and dated November 21, 1987).

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 8-11.

CORE CLASSIFICATION: Unacceptable. The study does not fully satisfy Guideline requirements (§84.2) for genetic effects Category I, Gene Mutations, but can be upgraded pending the submission of test material purity.

Page ______ is not included in this copy.

Pages 23 through 27 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

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_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

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_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

DOC930059

FINAL

009563

DATA EVALUATION REPORT

NAPHTHALENE

Study Type: Mutagenicity: In Vivo Micronucleus Assay in Mice

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sharon A. Segal for Date 5/6/92
Nancy E. McCarroll, B.S.

Independent Reviewer Lynne Haber Date 5/6/92
Lynne Haber, Ph.D.

QA/QC Manager Sharon A. Segal Date 5/6/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-83
Clement Number: 91-285
Project Officer: James Scott

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GUIDELINE § 84: MUTAGENICITY
MICRONUCLEUS

MUTAGENICITY STUDIES

EPA Reviewer: Krystyna Locke, Ph.D. Section I, Toxicology Branch I/HED (H7509C)	Signature: Krystyna R. Locke Date: 5/8/92
EPA Section Head: Roger Gardner, Ph.D. Section I, Toxicology Branch I/HED (H7509C)	Signature: Roger Gardner Date: 6/16/92
Secondary reviewer: Irving Mauer, Geneticist Section I, Toxicology Branch I/HED (H7509C)	Signature: Irving Mauer Date: 05-08-92

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: In vivo micronucleus assay in mice

EPA IDENTIFICATION Numbers:

Tox Chem. Number: 587

MRID Number: 420716-03

TEST MATERIAL: Naphthalene

SYNONYMS: None

SPONSOR: Texaco Chemical Co., Houston, TX

STUDY NUMBER: PH 309A-TX-007-85

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Micronucleus Test (MNT) OECD

AUTHOR: R. M. Sorg

REPORT ISSUED: October 22, 1991; study completed October 22, 1985.

CONCLUSIONS--EXECUTIVE SUMMARY: There was no increase in the frequency of micronucleus induction in polychromatic erythrocytes harvested from the bone marrow of male and female mice 30, 48, or 72 hours postexposure to a single intraperitoneal injection of 250 mg/kg naphthalene. The evidence of overt toxicity in the treated animals (i.e., reduced body tone, abnormal gait, and lacrimation) in conjunction with cytotoxic effects on bone marrow cells (i.e., reduced polychromatic to normochromatic erythrocytes ratios at all sacrifice times) clearly indicated that the maximum tolerated dose (MTD) was achieved. We conclude, therefore, that naphthalene was assayed to an adequate dose but failed to induce a clastogenic response in a well-conducted study. However, the study is incomplete because purity information on the test material was missing.

STUDY CLASSIFICATION: Unacceptable. The study does not fully satisfy Guideline requirements (§84.2) for genetic effects Category II, Structural Aberrations. The study can, however, be upgraded if purity information on the test material is submitted.

A. MATERIALS:

1. Test Material: Naphthalene

   Description: White flake
   Identification Number: Sample number 5601-56-1
   Purity: Not reported
   Receipt date: August 13, 1985
   Stability: Not reported
   Contaminants: None listed
   Solvent used: Corn oil
   Other provided information: The test material was stored at room temperature. Solutions of the test material were prepared within 2 hours of use.

2. Control Materials:

   Negative/route of administration: None

   Vehicle/final concentration/route of administration: Corn oil at a dosing volume of 10 mL/kg was administered intraperitoneally (i.p.).

   Positive/final concentration/route of administration: Triethylenemelamine (TEM) was dissolved in 0.9% saline and administered i.p. at 0.5 mg/kg.

3. Test Compound:

   Route of administration: I.p.

   Dose levels used:

   - Preliminary toxicity test: 250, 500, 1666, 3000, and 5000 mg/kg
   - Micronucleus assay: 250 mg/kg

4. Test Animals:

   (a) Species: mouse Strain: CD-1 Age: 7 1/2-8 1/2 weeks
   Weight range:

   - Preliminary toxicity test: 27-33 g (males); 26-32 g (females)
   - Micronucleus assay: 28-35 g (males); 26-29 g (females)

   Source: Charles River Breeding Laboratories, Wilmington, MA

(b) Number animals used per dose:

- Preliminary toxicity test: 2 males; 2 females/group
- Micronucleus assay: 5 males; 5 females/sacrifice time.

Note: Dosing was based on individual body weights determined immediately before compound administration.

(c) Properly maintained? Yes.

B. TEST PERFORMANCE:

1. Treatment and Sampling Times:

(a) Test compound:
Dosing: __x__ once _____ twice (24 hr apart)
_______ other (describe): ________
Sampling (after last dose): ________ 6 hr _______ 12 hr
___x___ 30 hr ___x___ 48 hr ___x___ 72 hr

(b) Vehicle control:
Dosing: __x__ once _____ twice (24 hr apart)
_______ other (describe): ________
Sampling (after last dose): ________ 24 hr ___x___ 48 hr
_______ 72 hr

(c) Positive control:
Dosing: __x__ once _____ twice (24 hr apart)
_______ other (describe): ________
Sampling (after last dose): ___x___ 30 hr _______ 48 hr
_______ 72 hr

2. Tissues and Cells Examined:

___x___ bone marrow __N/A__ others (list):
Number of polychromatic erythrocytes (PCEs) examined per animal: 1000
Number of normochromatic erythrocytes (NCEs, more mature RBCs) examined per animal: 1000 (PCEs+NCEs)

3. Details of Slide Preparation: At 30, 48, and 72 hours after administration of the test material, animals were sacrificed by cervical dislocation. Sacrifice times for the vehicle and positive groups were 48 and 30 hours, respectively. Bone marrow cells were flushed from both femurs, mixed with fetal bovine serum and centrifuged. Supernatants were discarded; cells were resuspended and spread onto slides. Slides were dried, fixed in absolute methanol, stained with 5% Giemsa, coverslipped, coded and scored.

4. Statistical Methods: Pairwise comparisons of the number of micronucleated PCEs (MPE) in treatment and vehicle control groups were ana-

lyzed using a one-tailed t-test. The ratio of PCE:NCE for each animal was transformed using an arcsin transformation and analyzed for statistical significance by a pairwise t-test. Significance was evaluated at p values of ≤ 0.05 and ≤ 0.01.

5. Evaluation Criteria:

   (a) Assay validity: The assay was considered valid if the percentage of MPEs in the vehicle control group was $<0.05\%$, the positive control induced a significant effect, and at least 7 animals in the test group survived treatment.

   (b) Positive response: The test material was considered positive if it produced a significant increase in the frequency of MPEs compared to the vehicle control group.

6. Protocol: A protocol was not provided; however, a copy of the primary data was included with the study report.

C. REPORTED RESULTS:

1. Preliminary Toxicity Test: Groups of 4 mice (2 males and 2 females) received single i.p. injections of 250, 500, 1666, 3000, and 5000 mg/kg naphthalene in the preliminary toxicity test. Animals were observed for mortality and other toxic signs immediately after dosing and at 4, 24, 48, and 72 hours posttreatment. Surviving animals were sacrificed at 72 hours. Abnormal gait was observed in all animals immediately following administration of 3000 and 5000 mg/kg of the test material. By 4 hours, all animals in these groups showed signs of prostration, decreased body tone and activity, "body drop," lacrimation, and preconvulsion; 100% mortality was reported at 24 hours. Similar signs of compound toxicity preceded the death (at 24 hours) of all mice in the 500- and 1666-mg/kg groups. No deaths occurred in the low-dose group (250 mg/kg); however, clinical signs (i.e., decreased body tone, abnormal gait, and lacrimation) were also seen in this group at various times over the observation period. Based on these findings, 250 mg/kg, which the study author estimated to be the maximum tolerated dose (MTD), was selected for evaluation in the micronucleus assay.

2. Micronucleus Assay:

   (a) Animal observations: Animals were observed for death and clinical signs as described for the preliminary toxicity test. No immediate evidence of adverse effects were seen; however, 4 hours postadministration of 250 mg/kg naphthalene, 6 males and 3 females exhibited decreased body tone, and 3 males showed signs of abnormal gait. These signs were also present at 24 hours in addition to lacrimation, which was seen in ~50% of the males and ~65% of the females at this observation time. Clinical signs were essentially unchanged at 48 hours. Prior to the scheduled 72-hour sacrifice, decreased body tone and abnormal gait was

reported for 4 of the remaining 10 animals (2 males and 2 females) and lacrimation for 4 animals (1 male and 3 females). These findings were consistent with the clinical signs reported for the preliminary toxicity test.

(b) Micronucleus assay: Presented in Table 1 are the results from the micronucleus assay. As shown, PCE:NCE ratios were lower than control for males and females sacrificed at 30, 48, and 72 hours postadministration of 250 mg/kg of the test material. The effect appeared to be time related and data combined for both sexes showed a significant ($p \leq 0.05$) reduction at 72 hours. The frequency of MPEs, however, was lower in the treated males and females at all harvest times compared to the vehicle control. By contrast, significant ($p \leq 0.01$) cytotoxic and clastogenic effects were induced in males and females receiving the positive control (0.5 mg/kg TEM).

From the overall results, the study author concluded that naphthalene was negative in this in vivo test system.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We agree with the study author's conclusion that naphthalene was negative in the mouse micronucleus assay. We further agree that the evidence of overt toxicity in the test animals and cytotoxic effects on bone marrow cells indicates that the MTD was achieved in both sexes at 250 mg/kg. In addition, the sensitivity of the test system to detect a clastogenic response was adequately demonstrated by the positive results obtained in males and females treated with 0.5 mg/kg TEM.

We concluded, however, that while naphthalene was tested to the MTD with no evidence of a positive response in the well-conducted mouse micronucleus assay, the lack of information on test material purity renders the study incomplete and, therefore, unacceptable.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A quality assurance statement was signed and dated October 31, 1985).

F. CBI APPENDICES: Appendix A, Materials and Methods, CBI pp. 8-12.

CORE CLASSIFICATION: Unacceptable. The study does not fully satisfy Guideline requirements (§84.2) for genetic effects Category II, Structural Chromosome Aberrations. The study can, however, be upgraded by submission of information on test material purity.

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

Substance	Dose/kg	Exposure Time[a] (hours)	Sex	Number of Animals Analyzed per Group	Number of PCEs[b] Analyzed per Group	Number of MPEs[b] per Group	Per 1000 PCEs	Mean PCE/NCE[b] Ratio ±S.D.
<u>Vehicle Control</u>								
Corn oil	10 mL	48	M	5	5000	7	1.4	1.256
			F	5	5000	6	1.2 (1.30±1.06)[c]	1.170 (1.21±0.43)[c]
<u>Positive Control</u>								
Triethylenemelamine	0.5 mg	30	M	5	5000	315	63.0	0.809
			F	5	5000	297	59.4 (61.20±11.09)**	0.488 (0.65±0.22)***
<u>Test Material</u>								
Naphthalene	250 mg[d]	30	M	5	5000	3	0.6	1.059
			F	5	5000	3	0.6 (0.60±0.52)*	0.944 (1.00±0.17)
		48	M	5	5000	3	0.6	0.872
			F	5	5000	4	0.8 (0.70±0.82)	0.994 (0.93±0.28)
		72	M	5	5000	6	1.2	0.856
			F	5	5000	2	0.4 (0.80±63)	0.720 (0.79±0.29)*

[a]Time after compound administration by intraperitoneal injection.

[b]Abbreviations used:

PCE = Polychromatic erythrocytes
NCE = Normochromatic erythrocytes
MPE = Micronucleated polychromatic erythrocytes

[c]Values in () are combined results for both sexes.

[d]Signs of reduced body tone, abnormal gait and lacrimation were seen.

*Significantly ($p \leq 0.05$) lower than the vehicle control by pairwise t-test.
**Significantly ($p \leq 0.01$) higher than the vehicle control by pairwise t-test.
***Significantly ($p \leq 0.01$) lower than the vehicle control by pairwise t-test.

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FINAL

DATA EVALUATION REPORT

NAPHTHALENE

Study Type: Mutagenicity: Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sharon A. Segal for Nancy E. McCarroll, B.S. Date 5/6/92

Independent Reviewer Lynne Haber Lynne Haber, Ph.D. Date 5/6/92

QA/QC Manager Sharon A. Segal Sharon Segal, Ph.D. Date 5/6/92

Contract Number: 68D10075
Work Assignment Number: 1-83
Clement Number: 91-286
Project Officer: James Scott

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GUIDELINE § 84: MUTAGENICITY
UDS

MUTAGENICITY STUDIES

EPA Reviewer: Krystyna Locke, Ph.D. Signature: Krystyna R. Locke
Section I, Toxicology Branch I/HED (H7509C) Date: 5/8/92

EPA Section Head: Roger Gardner, Ph.D. Signature: Roger Gardner
Section I, Toxicology Branch I/HED (H7509C) Date: 6/16/92

Secondary reviewer: Irving Mauer, Geneticist Signature: I. Mauer
Section I, Toxicology Branch I/HED (H7509C) Date: 05-08-92

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: In vitro unscheduled DNA synthesis assay in primary rat hepatocytes

EPA IDENTIFICATION Numbers:

Tox Chem. Number: 587

MRID Number: 420716-04

TEST MATERIAL: Naphthalene

SYNONYMS: None

SPONSOR: Texaco Chemical Co., Houston, TX

STUDY NUMBER: PH 311-TX-008-85

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Rat Hepatocyte Primary Culture/DNA Repair Test

AUTHOR: T.R. Barfknecht

REPORT ISSUED: October 22, 1991; study completed September 27, 1985.

CONCLUSIONS--EXECUTIVE SUMMARY: Naphthalene, over a concentration range of 0.16 to 5000 µg/mL, was evaluated for the potential to induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes. Doses ≥166 µg/mL were insoluble and levels ≥50 µg/mL were cytotoxic. There was, however, no evidence of a UDS response in cells treated with 0.16, 0.5, 1.6, 5, or 16 µg/mL. We conclude, therefore, that naphthalene was adequately tested and did not induce a genotoxic response in a well-conducted assay. Nevertheless, the lack of information on test material purity renders the study incomplete.

STUDY CLASSIFICATION: Unacceptable. The study does not fully satisfy Guideline requirements (§84.4) for genetic effects Category III, Other Mutagenic Mechanisms. The study can, however, be upgraded if test material purity information is submitted.

A. MATERIALS:

1. Test Material: Naphthalene

Description: White crystalline flake
Identification Number: Sample number 5601-56-1
Purity: Not reported
Receipt date: August 13, 1985
Stability: Not reported
Contaminants: None listed
Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: Storage conditions were not reported, it was assumed, however, that the test material was stored at room temperature. Solutions of the test material were prepared within 4 hours of use.

2. Indicator Cells: Primary rat hepatocytes were obtained by the *in situ* perfusion of the liver of a male Fischer-344 rat weighing 192 g and purchased from Charles River Breeding Laboratories, Inc.

3. Control Substances: The negative control was culture medium and the solvent control was DMSO at a final concentration of 1%. 2-Acetylaminofluorene (2-AAF) at a final concentration of 1×10^{-7} M was used as the positive control.

4. Culture Medium: WME: Williams' Medium E; WME+: WME with 10% fetal bovine serum.

5. Test Compound Concentrations Used:

   (a) Preliminary cytotoxicity assay: Not performed; cytotoxicity was assessed concurrent with the UDS assay.

   (b) UDS assay: Ten doses (0.16, 0.5, 1.6, 5.0, 16, 50, 166, 500, 1666, and 5000 µg/mL) were evaluated.

B. TEST PERFORMANCE:

1. Cell Preparation:

   (a) Perfusion technique: The liver was perfused with Hank's balanced salts containing 0.5 mM EGTA and Hepes buffer, pH 7.35, for 4 minutes and with 100 U/mL collagenase in WME for 10 minutes. The liver was excised, removed to a culture dish containing WME, trimmed of fat and excess connective tissue, and transferred to a fresh culture dish. Hepatocytes were detached in WME containing 100 U/mL collagenase by gently combing the liver with a camel hair brush.

   (b) Hepatocyte Harvest/Culture Preparation. Recovered cells were added to centrifuge tubes, brought to 35-40 mL with WME, and allowed to remain quiescent for 10 minutes. Viability was

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determined by trypan blue exclusion, and $1x10^5$ hepatocytes were inoculated into 12-well replicate cluster dishes containing plastic coverslips and WME+. The cultures were placed in a 37°C, 5% CO_2 incubator for a 2-hour attachment period.

2. UDS Assay:

   (a) Treatment: Prior to use, cells were rinsed and refed WME containing the selected doses of the test material, the negative (culture medium), the solvent (DMSO), or the positive control (2-AAF), and 10 µC/mL [^{3}H] thymidine. Following exposure (18-20 hours), the cultures were washed and slides were prepared.

   (b) UDS slide preparation: Cells on coverslips were treated with 1% sodium citrate for 10-15 minutes, fixed three times with glacial acetic acid:ethanol (1:3), dried and mounted.

   (c) Preparation of autoradiographs/grain development: Slides were coated with Kodak NTB-2 emulsion, dried overnight and stored at 4°C in light-proof boxes containing a desiccant for 1 week, developed in Kodak D-19, fixed, stained with Harris Alum hematoxylin, counterstained with eosin, rinsed, dried, coded and counted.

   (d) Grain counting: The nuclear grains of 60 cells (20 cells/slide) for each dose of the test material and the negative, the solvent, and the positive controls were counted microscopically. An area/grain ratio was obtained by scoring five areas on each slide containing 3-5 nuclear grains and determining an object area count with the automatic colony counter. The mean of the differences (0.5) served as the correction factor. Net nuclear grain counts were determined by subtracting the highest cytoplasmic grain count of three nuclear-sized areas adjacent to each nucleus from the nuclear grain count of each cell.

3. Evaluation Criteria:

   (a) Assay validity: For the assay to be considered valid, the following criteria must be satisfied: (1) the solvent and untreated controls should have net nuclear grain counts of ≤ 1 and fall within the 95% confidence limits of mean historical data provided by the reporting laboratory, and (2) the positive control should yield a mean net nuclear grain count that is within one standard deviation of the historical positive control mean value for $1x10^{-5}$ M 2-AAF (final concentration $1x10^{-7}$ M 2-AAF) reported by the performing laboratory as 27.3 ± 11.5.

   (b) Positive response: The test compound was considered positive if a minimum net nuclear grain count of five grains per nuclei was consistently observed in triplicate wells; also, where possible a dose response should be observed.

4. Protocol: A protocol was not provided; however, a copy of the primary data was included with the final report.

C. REPORTED RESULTS: Ten doses (0.16, 0.5, 1.6, 5.0, 16, 50, 166, 500, 1666, and 5000 µg/mL) were examined in a parallel cytotoxicity and UDS assay. A review of the raw data indicated that levels ≥166 µg/mL formed a white precipitate in the culture medium. Cytotoxicity was reported for test material concentrations ≥50 µg/mL. Based on this information, hepatocytes treated with 0.16 to 16 µg/mL were scored for UDS. As the representative data presented in Table 1 indicate, none of the evaluated doses caused an increase in net nuclear grain count compared to the negative or solvent control. By contrast, a marked increase in UDS was observed in cultures treated with the positive control ($1x10^{-7}$M 2-AAF).

The study author concluded from the overall findings that naphthalene was negative in the primary rat hepatocyte UDS assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that naphthalene was assayed over a concentration range that included soluble (0.16-50 µg/mL) and insoluble doses (166-5000 µg/mL), and that levels ≥50 µg/mL were cytotoxic. The lack of a genotoxic effect was, therefore, not associated with an inability of naphthalene to penetrate cellular membranes. Similarly, the sensitivity of the test system to detect a genotoxic response was adequately demonstrated by the findings with the positive control ($1x10^{-7}$M 2-AAF).

We conclude that naphthalene was assayed over an appropriate range of concentrations and failed to induce UDS in a well-conducted assay. However, the study is incomplete because information on test material purity was not provided. The study is, therefore, classified as unacceptable but can be upgraded if the missing test material information is submitted.

E. QUALITY ASSURANCE MEASURES: Was test performed under GLPs? Yes. (A quality assurance statement was signed and dated October 2, 1985).

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 7-10.

CORE CLASSIFICATION: Unacceptable. The study does not fully satisfy Guideline requirements (§84.4) for genetic effects Category III, Other Mutagenic Mechanisms. The study can, however, be upgraded if test material purity information is submitted.

TABLE 1. Representative Results of the Unscheduled DNA Synthesis (UDS) Rat Hepatocyte Assay with Naphthalene

Treatment	Dose	Number of Cells Scored	Mean Nuclear Grains ±SD[a]
Negative Control			
Untreated Culture	--	60	0.2±0.6
Solvent Control			
Dimethyl sulfoxide	1%	60	0.4±1.0
Positive Control			
2-Acetamidofluorene	$1x10^{-7}$ M	60	23.9±6.9[b]
Test Material			
Naphthalene	16 μg/mL[c]	60	0.0±0.1

[a]Means and standard deviations from the counts of three slides (20 cells/slide).

[b]Fulfills reporting laboratory's criteria for positive effect (mean net nuclear grain count of ≥5 over the solvent control).

[c]Highest dose scored; higher levels (50, 166, 500, 1666, and 5000 μg/mL) were cytotoxic. Results for lower concentrations (0.16, 0.5, 1.6, and 5.0 μg/mL) were either comparable to or lower than the negative or solvent control values.

NOTE: Test material insolubility in culture medium was recorded for levels ≥166 μg/mL.

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