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Submitting Organization

MOBIL OIL CORP

Contractor

INTL RES & DEVELOP CORP

Document Title

INITIAL SUBMISSION: PILOT TERATOLOGY STUDY IN RATS (FINAL REPORT) WITH ATTACHMENTS AND COVER LETTER CONTAINING INFORMATION FROM FOUR OTHER REPORTS DATED 022592

Chemical Category

P-ETHYLTOLUENE

CONTAINS NO CB,

Mobil Oil Corporation

THIS DOCUMENT RECEIPT OFF

92 FEB 25 PH 1:44

ENVIRONMENTAL HEALTH AND SAFETY DEPARTMENT
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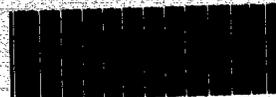
February 25, 1992

8EHO-0292-2290

CARL R. MACKERER, Ph.D.
MANAGER, ENVIRONMENTAL AND HEALTH
SCIENCES LABORATORY

Init

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Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: CAP ID #: 8ECAP-0053

Dear Sir:

As part of the Compliance Audit Program, we are providing data from a study done on para-ethyltoluene, CAS number 622-96-8. Most of the CAP-reportable information on this material was submitted to the EPA in response to a TSCA Section 4 data call-in. This information is "listed" only, and will not be re-submitted at this time. Relevant document numbers are indicated in the table below. The report for the pilot teratology test is enclosed.

The data are contained in the following report(s):

Report Number	Title
M791-78	Acute Oral LD50 (Rat) (OPTS-42034)
511-79	Acute Inhalation Toxicity of p-Ethyltoluene (PET) (OPTS-42034)
20732	<i>In Vivo</i> Hepatocyte Unscheduled DNA Synthesis Assay (EPA/OTS Document #878214711)
10701	Thirteen Week Gavage Administration of PET to Rats (EPA/OTS Document #878214712)
M3100-79	Pilot Teratology Test in Rats (MCTR-310-79)

Findings are summarized below:

Forty albino rats (5M, 5F/group) (M791-78) were given PET neat by gavage in a single dose of 3,000, 4,000, 5,000 and 6,000 mg/kg. Rats were observed at least daily for fourteen days post-dosing. Acute oral LD50 is 4,850 mg/kg. Ataxia was observed in some animals at some time in all dose groups throughout the study and intermittent tonic convulsions were observed in non-moribund rats given 5,000 mg/kg.

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In the acute inhalation test (511-79) nitrogen was bubbled through the liquid to produce vapors for two 6-hour exposures (511-79). One exposure was to a vapor concentration (determined by IR) of ~3,900 ppm (~19.4 mg/L). There were tremors, lack of coordination and other signs during exposure and a "lack of support in the limbs" of 8/9 rats for 3 subsequent days. A separate exposure to 1,960 ppm (9.8 mg/L) also resulted in tremors, lack of coordination, and lack of limb support during exposure. Only rales and some signs of irritation persisted after exposure. Tremors and other signs of effects on the nervous system were observed only transiently and only at very high concentrations.

Rats were given neat PET in a single dose (20732), orally by gavage at concentrations of 0.5, 0.75, 1.0, 1.25 and 1.7 g/kg. Two hours later, hepatocytes were isolated and allowed to repair any DNA damage in the presence of tritiated thymidine. Results of analysis indicate that PET produced reportable primary DNA damage in rat hepatocytes over a narrow range of doses.

Fischer 344 rats (20M, 20F/group) (10701) were given PET in corn oil orally by gavage daily for 13 weeks at doses of 0, 100, 300 and 900 mg/kg/day. Dose related mortality was observed in 300, 900 mg/kg/day dose groups for both sexes. Lower body weight gains and body weight depression were noted for mid and high dose males with similar alteration of female body weights during the first four weeks. Liver weights were increased for both sexes at 300 and 900 mg/kg/day. Dose related reductions in absolute and relative testes/epididymides weights were observed for mid and high dose males. Microscopically, high dose males showed testicular atrophy and hypospermatogenesis of testes, and hypospermia or aspermia of the epididymides. No microscopic indications of atrophy were reported in mid dose rats, and low dose rats appeared normal.

Pregnant rats were given PET neat in a single daily dose by gavage (M3100) from day 6 through 19 of gestation at doses of 0, 100, 300, 750, 1,500 and 3,000 mg/kg/day. Control rats received distilled water. All rats at 3,000, 4 at 1,500 and 1 at 750 mg/kg/day died prior to Cesarean section. Decreases in mean maternal body weight gain was observed in all surviving dose groups. An increase in mean number of late resorptions was observed at the 100 mg/kg/day level. Increases in early resorptions at 100, 300, 750 and 1,500 mg/kg/day with corresponding increase in mean post-implantation loss were also observed.

No confidentiality claim is being made for this submission.

Sincerely,

C.R. Mackerer
C. R. Mackerer, Ph.D.
Director, Environmental and
Health Sciences Laboratory

Enclosures

0 0 0 4

CONTAINS NO CBI.

M 3100-79



International Research and Development Corporation

MATTAWAN, MICHIGAN 49071 / U. S. A. / AREA CODE 616 / TELEPHONE 969-3338

0005



**International Research
and Development Corporation**

MATTAWAN, MICHIGAN, U.S.A. 49071 TELEPHONE (616) 668-3336

SPONSOR: Mobil Oil Corporation

TEST ARTICLE: Sample 01038003

SUBJECT: Pilot Teratology Study in Rats
(MCTR-310-79)

DATE OF SUBMISSION: December 11, 1980

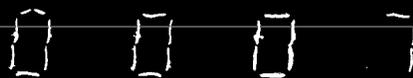
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"credence through research"

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Personnel Involved in the Study

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I. QUALITY ASSURANCE STATEMENT

Study Title: Pilot Teratology Study in Rats (NCTR-310-79)

Test Article: Sample 01038003

The conduct of this study has been subjected to periodic inspections. The dates of inspection and the dates that findings were reported to management and the Study Director are listed in Appendix I.

This report has been reviewed by the International Research and Development Corporation Quality Assurance Department in accordance with the United States Food and Drug Administration's Good Laboratory Practice Regulations of June 20, 1979.

Approved and
Submitted By:


Barry W. Benson, B.S.
Director of Quality Assurance

12/9/80
Date

II. SYNOPSIS

Pregnant Charles River COBS® CD® rats were used in this pilot study to determine dosage levels of Sample 01038003 for a teratology study. Dosage levels of 100, 300, 750, 1500 and 3000 mg/kg/day were administered orally by gavage as a single daily dose on days 6 through 19 of gestation, at volumes of 0.116, 0.349, 0.872, 1.744 and 3.488 ml/kg, respectively. The control group received distilled water only on a comparable regimen at a volume of 3.488 ml/kg. Uterine examinations were performed on all surviving dams on gestation day 20.

There were no biologically meaningful differences in appearance or behavior or mean uterine examination values in the 100 mg/kg/day treatment group when compared to the control group. All rats in the 3000 mg/kg/day group, four rats in the 1500 mg/kg/day group and one rat in the 750 mg/kg/day dosage group died prior to the scheduled sacrifice date. A cause of death for all of these rats could not be determined at necropsy examination.

Postmortem findings in the 1500 and 3000 mg/kg/day groups included inflammation and reddening of the gastrointestinal mucosa and erosions of the stomach lining. Antemortem findings included stained or matted haircoat and dried red or brown matter around the nose and mouth.

A severe decrease in mean maternal body weight gain occurred in the 300, 750 and 1500 mg/kg/day dosage groups and a moderate reduction in mean maternal body weight gain was noted in the 100 mg/kg/day treatment group over the entire treatment period.

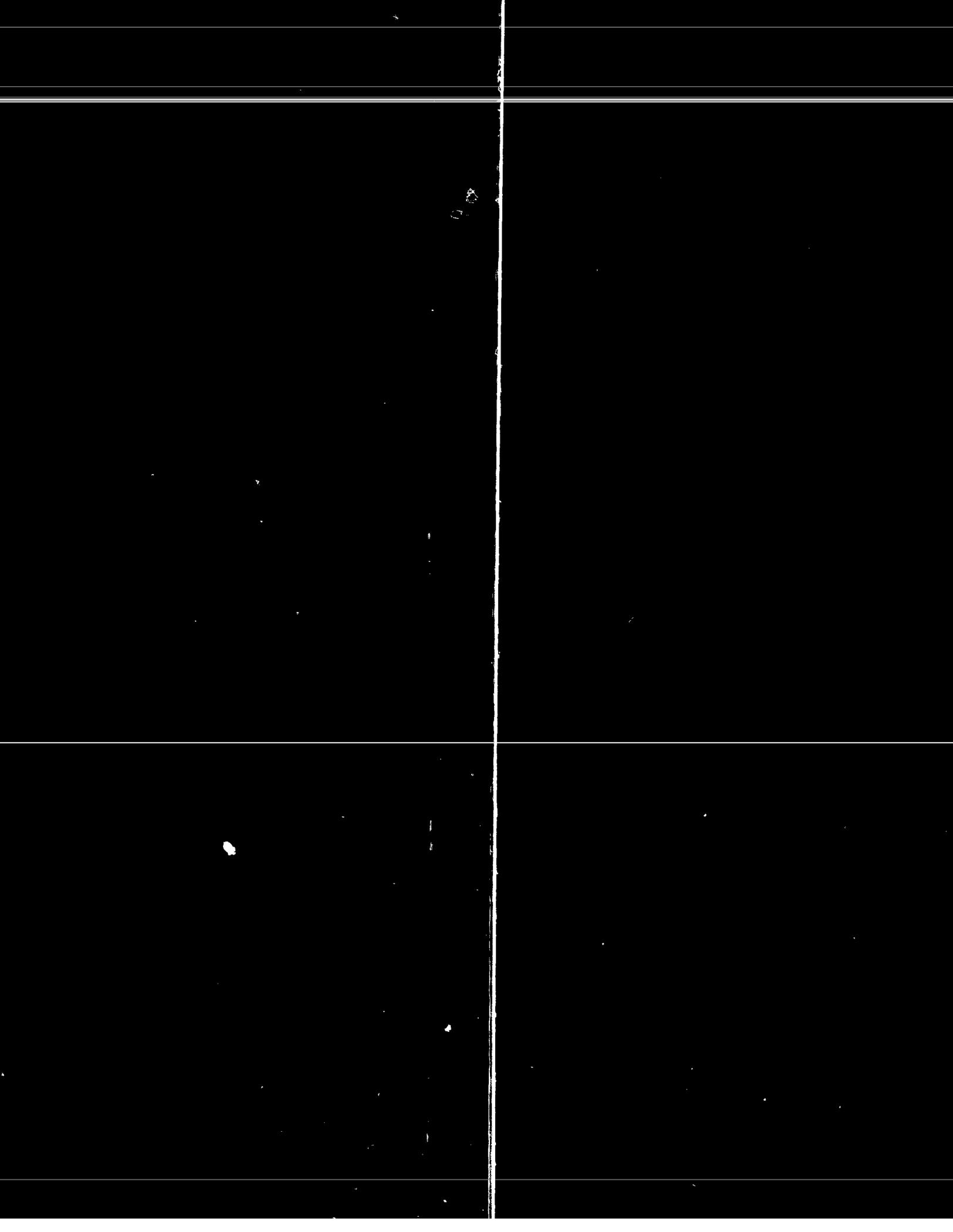
Uterine examination findings revealed an increase in the mean number of early resorptions in the 300, 750 and 1500 mg/kg/day treatment groups with a corresponding increase in mean postimplantation loss in these treatment groups when compared to the control group values.

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Based on these results, a dosage level of 300 mg/kg/day would be considered excessive for a teratology study in rats with Sample 01038003.

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III. INTRODUCTION

A. OBJECTIVE

To establish dosage levels of the test article for a teratology study.

B. TEST ARTICLE

The test article was received from the Mobil Oil Corporation, Princeton, New Jersey on January 14, 1980 as indicated below:

<u>Label</u>	<u>Description</u>
#01038003 Second Label: Caution: Combustible Keep away from heat and open flame Use with adequate ventilation Keep container closed For industrial use only PET-D579-282-13	clear liquid

IV. METHODS AND PROCEDURES

A. EXPERIMENTAL DESIGN

1. Animals

Thirty untreated, sexually mature, virgin female Charles River COBS® CD® rats (The Charles River Breeding Laboratories, Inc., Portage, Michigan) were used to establish dosage levels of Sample 01038003 for a teratology study. These rats were approximately 15 weeks of age at the time of mating and had been acclimated in this laboratory for a minimum of 10 days prior to study initiation. Each rat was assigned a unique number and ear-tagged for identification when placed on study. All rats were individually housed, except during mating, in suspended wire-mesh cages and maintained in a temperature-, humidity- and light-controlled (12-hour light/dark cycle) environment. During the treatment period all animals were moved to a specially ventilated room and maintained under identical conditions. Purina® Certified Rodent Chow® #5002 and tap water were available ad libitum.

Mating was initiated on February 18, 1980 and the last uterine examination was performed on March 13, 1980.

2. Mating

One female and one male rat of the same strain were placed together for mating. The occurrence of copulation was determined by daily inspection for a copulatory plug or by a vaginal smear for sperm. The day that evidence of mating was detected was designated day 0 of gestation and the female was returned to an individual cage.

3. Organization of Test Groups

Mated females were consecutively assigned in a block design to a vehicle control group and five treatment groups consisting of five rats each.

B. TEST ARTICLE ADMINISTRATION

Sample 01038003 (specific gravity: 0.86 g/ml) was dispensed daily

V. RESULTS

A. MATERNAL OBSERVATIONS

1. Appearance and Behavior

There were no biologically meaningful differences in appearance or behavior of the rats in the 100 mg/kg/day treatment group. Scabbing around the nose and mouth was noted for three of the rats in the 100 mg/kg/day dosage group during the latter part of the treatment period. Scabbing around the nose and mouth was not observed in the rats in the 300, 750, 1500 and 3000 mg/kg/day treatment groups and therefore, was not considered treatment-related.

All rats in the 3000 mg/kg/day treatment group died between gestation days 6 and 9. Four rats in the 1500 mg/kg/day treatment group and one rat in the 750 mg/kg/day treatment group died between gestation days 9 and 16. A cause of death could not be determined for any of these animals at necropsy. Slight hair loss, primarily of the anogenital region, was observed in a few rats in the 100, 300, 750 and 1500 mg/kg/day treatment groups and did not occur in a dose-related pattern.

Excessive salivation was noted at various times during the treatment period for three rats in the 750 mg/kg/day treatment group. Labored or rattled breathing was observed infrequently in three rats in the 750 mg/kg/day treatment group; dam #50943 on gestation day 13, dam #50947 on gestation day 20 and dam #50945, one day prior to death on gestation day 12. Staining and/or matting of the haircoat, occurring primarily in the anogenital region, and dry red or brown matter around the nose and mouth were noted in the majority of rats in the 1500 and 3000 mg/kg/day dosage groups throughout the treatment period.

One rat in the 1500 mg/kg/day treatment group (Dam #50951) had a brown ocular discharge three days prior to death on gestation day 12. Two rats in the 3000 mg/kg/day dosage group (Dam #50953 and #50954) had swollen conjunctiva one day prior to death on gestation

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day 9. Additional antemortem findings in this group included one female (Dam #50957) with a brown ocular discharge one day prior to death on gestation day 8.

Postmortem findings for three rats in the 3000 mg/kg/day treatment group and four of the rats in the 1500 mg/kg/day group which died prior to the scheduled sacrifice included erosions of the stomach mucosal membrane. In two animals from each of these groups, areas of inflammation of the stomach and/or intestinal mucosa were noted. Intestinal contents of the majority of the rats in the 1500 and 3000 mg/kg/day treatment groups were described as containing a yellowish red to tan or black creamy material. A dark red liquid contained within the urinary bladder, with severe reddening of the bladder mucosa was noted at necropsy for one rat in the 3000 mg/kg/day group (Dam #50957). Tan colored areas on the median lobe of the liver were found in two rats (Dams #50946 and #50947) in the 750 mg/kg/day treatment group. Results of the histopathological examination of the livers of these two animals revealed these tan areas to be multifocal sites of necrosis.

2. Body Weights

Individual and group mean maternal body weights are presented in Table 2. A summary of group mean body weight and body weight change is presented in Table 1.

A reduction in mean maternal body weight gain over the entire treatment period was noted in the 100 mg/kg/day dosage group, due in part to one dam from this group having an increase in the numbers of late resorptions. Body weight gains for the remaining rats in the 100 mg/kg/day treatment group were moderately reduced over the entire treatment period when compared with the control group. Severe reductions in mean maternal body weight gain were noted in the 300, 750 and 1500 mg/kg/day Sample 01038003 treatment groups when compared to

the control group over the entire treatment period. There was a severe mean maternal body weight loss noted in the 750 and 1500 mg/kg/day dosage groups during the first three days of treatment and no mean gain in the 300 mg/kg/day dosage group for this same period.

3. Uterine Examination Observations

Individual and group mean uterine examination data are presented in Table 3.

There were no biologically meaningful differences in the mean number of viable fetuses, late and early resorptions, postimplantation loss, total implantations or corpora lutea in the 100 mg/kg/day dosage group when compared to the control group. However, for one rat in this group (Dam #50933), of 17 total implantations, 13 were late resorptions. The resulting increase in mean postimplantation loss was not considered to be treatment-related as no dose-related trend was observed. In the 300 mg/kg/day treatment group a slight increase in the mean number of early resorptions was observed with a corresponding increase in mean postimplantation loss. However, mean numbers of viable fetuses, late resorptions, total implantations and corpora lutea for this group were comparable to the control group. In the 750 mg/kg/day treatment group one animal (Dam #50947) had all early resorptions, resulting in an increase in mean postimplantation loss and a corresponding decrease in the mean number of viable fetuses for this group. The mean number of total implantations and corpora lutea for the 750 mg/kg/day dosage group was comparable with the respective control group values. Only one dam in the 1500 mg/kg/day treatment group survived to the scheduled sacrifice date and of 13 total implantations, six were resorptions. The four rats in the 1500



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mg/kg/day dosage group and all five of the rats in the 3000 mg/kg/day treatment group that died prior to scheduled date of uterine examination were gravid. Nonviable fetuses were not observed in the control or in any of the Sample 01038003 treated groups.

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VI. DISCUSSION AND CONCLUSION

All dams in the 3000 mg/kg/day group, four dams in the 1500 mg/kg/day group and one dam in the 750 mg/kg/day group died during the treatment period. A moderate reduction in mean maternal body weight gain over the entire treatment period was noted for the 100 mg/kg/day treatment group. Severe reductions in mean maternal body gain for this same period were noted in the 300, 750 and 1500 mg/kg/day treatment groups and uterine examination observations revealed an increase in mean postimplantation loss for these groups also.

Based on these results, a dosage level of 300 mg/kg/day would be considered excessive for a teratology study.

TABLE 1. Summary of Group Mean Maternal Body Weights and Body Weight Changes

Day of Gestation	Group Mean Maternal Body Weights (grams)					
	0 (Control)	100	300	750	1500	3000
0	295	277	278	298	307	294
6	311	293	288	311	317	312
9	322	300	287	289	293	-
12	334	307	302	294	335	-
16	366	317	294	300	283	-
20	428	350	363	316	326	-

Days of Gestation	Group Mean Maternal Body Weight Change (grams)					
	0 (Control)	100	300	750	1500	3000
0-6	16	16	10	13	10	18
6-9	11	7	-1	-22	-24	-
9-12	12	7	15	5	42	-
12-16	32	10	-8	6	-52	-
16-20	62	33	69	16	43	-
6-20	117	57	75	5	9	-
0-20	133	73	85	18	19	-

- Not applicable

TABLE 2. Individual and Group Mean Maternal Body Weights (grams)

Test Article, Dosage Level, Dam Number	Day of Gestation					
	0	6	9	12	16	20
<u>0 mg/kg/day (Control):</u>						
50928	270	291	301	307	334	409
50929	275	283	294	308	344	406
50930	320	338	345	354	377	412
50931	316	334	357	371	411	502
50932	292	309	315	331	364	409
Mean	295	311	322	334	366	428
<u>Sample 01038003, 100 mg/kg/day:</u>						
50933	302	324	324	334	345	305
50934	259	275	280	290	303	344
50935	277	289	297	301	323	360
50936	292	307	321	330	298	388
50937	256	271	278	282	318	355
Mean	277	293	300	307	317	350
<u>Sample 01038003, 300 mg/kg/day:</u>						
50938	254	271	270	282	299	355
50939	269	281	285	293	306	340
50940	272	280	267	291	285	357
50941	295	300	303	322	273	332
50942	298	308	311	324	309	429
Mean	278	288	287	302	294	363
<u>Sample 01038003, 750 mg/kg/day:</u>						
50943	286	305	295	283	327	344
50944	299	309	301	312	282	330
50945	310	319	280	Died gestation day 12		
50946	290	303	291	301	313	360
50947	304	319	280	280	279	230
Mean	298	311	289	294	300	316

- Not applicable

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TABLE 2. Cont. Individual and Group Mean Maternal Body Weights (grams)

Test Article, Dosage Level, Dam Number	Day of Gestation					
	0	6	9	12	16	20
Sample 01038003, 1500 mg/kg/day:						
50948	292	310	261		Died gestation day 10	
50949	325	340	346	355	Died gestation day 16	
50950	320	312	299	315	283	326
50951	280	300	265	Died gestation day 12		
50952	318	321	Died gestation day 9			
Mean	307	317	293	335	283	326
Sample 01038003, 3000 mg/kg/day:						
50953	298	330	Died gestation day 9			
50954	296	316	Died gestation day 9			
50955	294	308	Died gestation day 6			
50956	275	280	Died gestation day 9			
50957	307	324	Died gestation day 8			
Mean	294	312				

- Not applicable

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TABLE 3. Individual and Group Mean Maternal Observations at Uterine Examination

Test Article, Dosage Level, Dam Number	Viable Fetuses	Nonviable Fetuses	Late Resorptions	Early Resorptions	Post- implantation Loss	Total Implantations	Corpora Lutea
<u>0 mg/kg/day (Control):</u>							
50928	14	0	0	1	1	15	17
50929	15	0	0	0	0	15	15
50930	7	0	0	0	0	7	18
50931	19	0	1	0	1	20	23
50932	18	0	0	0	0	18	19
Total	73	0	1	1	2	75	92
Mean	14.6	0.0	0.2	0.2	0.4	15.0	18.4
<u>Sample 01038003, 100 mg/kg/day:</u>							
50933	4	0	13	0	13	17	17
50934	15	0	0	0	0	15	15
50935	10	0	0	4	4	14	15
50936	17	0	0	0	0	17	19
50937	14	0	0	0	0	14	17
Total	60	0	13	4	17	77	83
Mean	12.0	0.0	2.6	0.8	3.4	15.4	16.6
<u>Sample 01038003, 300 mg/kg/day:</u>							
50938	12	0	0	2	2	14	14
50939	11	0	0	3	3	14	16
50940	11	0	1	1	2	13	15
50941	15	0	0	0	0	15	17
50942	18	0	0	0	0	18	21
Total	67	0	1	6	7	74	83
Mean	13.4	0.0	0.2	1.2	1.4	14.8	16.6

TABLE 3. Cont. Individual and Group Mean Maternal Observations at Uterine Examination

Test Article, Dosage Level, Dam Number	Viable Fetuses	Nonviable Fetuses	Late Resorptions	Early Resorptions	Post- implantation Loss	Total Implantations	Corpora Lutea
Sample 01038003, 750 mg/kg/day:							
50943	13	0	0	1	1	14	16
50944	13	0	0	2	2	15	19
50945	Died, gravid			0	0	15	18
50946	15	0	0	17	17	17	18
50947	0	0	0	20	20	61	71
Total	41	0	0	5.0	5.0	15.3	17.8
Mean	10.3	0.0	0.0				
Sample 01038003, 1500 mg/kg/day:							
50948	Died, gravid						
50949	Died, gravid						
50950	7	0	2	4	6	13	24
50951	Died, gravid						
50952	Died, gravid						
Total	7	0	2	4	6	13	24
Mean	7.0	0.0	2.0	4.0	6.0	13.0	24.0
Sample 01038003, 3000 mg/kg/day:							
50953	Died, gravid						
50954	Died, gravid						
50955	Died, gravid						
50956	Died, gravid						
50957	Died, gravid						

APPENDIX I
Quality Assurance Inspections

450-026

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Sample 01038003:

Pilot Teratology Study in Rats (MCTR-310-79)

Quality Assurance Inspections

Dates of Inspections

2/18/80
2/25/80
2/29/80
3/10/80
3/12/80
11/24/80

Dates of Reports to Management

2/26/80
11/24/80

APPENDIX II
Protocol and Protocol Addenda

450-026

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INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION
PROTOCOL DISTRIBUTION SHEET

Protocol Sheet No. 1

Study No. 450-026

TITLE: PILOT TOXICOLOGY STUDY IN RATS

Dr. Wazeter	<u>X</u>	Dr. Spicer	<u> </u>
Dr. Goldenthal	<u>X</u>	Dr. Jessup	<u> </u>
Quality Assurance	<u>X</u>	Dr. Blair	<u> </u>
Accounting	<u>X</u>	Dr. Lavaglia	<u> </u>
Report Processing	<u>X</u>	Mr. Rodwell	<u> X </u>
Statistics and Computer	<u>X</u>	Dr. Lang	<u> </u>
Report Status	<u>X</u>	Pathology	<u> </u>
Sponsor	<u>X</u>	Inhalation	<u> </u>
		Chronic Toxicity ✓	<u> X </u>
		Teratology	<u> X </u>
		Acute Toxicology and Special Studies	<u> </u>
		Clinical Pathology	<u> </u>
		Laboratory Animal Medicine	<u> </u>
		Test Material Control	<u> X </u>
		Analytical Chemistry	<u> </u>

Dr. Mike Norvell
Sponsor Representative (name)

12/14/79
Date of Approval

Study Director Mr. Rodwell

Dean E. Rodwell 12/21/79
Signature Date

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION
PROTOCOL REVISION OR CLARIFICATION

Protocol Sheet No. 1

Study No. 450-026

Title: PILOT TERATOLOGY STUDY IN RATS

Justification:

Conduct study in accordance with the attached protocol.

Study Director Mr. Rodwell

Dem E. Rodwell 12/31/79
Signature Date

IR90-49-4

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1. STUDY TITLE

Pilot Teratology Study in Rats

2. PURPOSE OF THE STUDY

To establish dosage levels of the test article for a teratology study.

3. STUDY NUMBER

Mobil Oil No.: MCTR-310-79
IRDC No.: 450-026

4. TESTING FACILITY

International Research and Development Corporation
Mattawan, Michigan 49071

5. SPONSOR

Mobil Oil Corporation
Toxicology Division
P. O. Box 1026
Environmental Affairs and
Toxicology Department
Princeton, New Jersey 08540

6. SPONSOR'S REPRESENTATIVE

Michael Norvell, Ph.D.
Senior Toxicologist

7. IRDC PERSONNEL RESPONSIBILITIES

Study Director:

Dean E. Rodwell, M.S.
Director of Teratology

Director of General Toxicology
Division (Acting):

Edwin I. Goldenthal, Ph.D.

Assistant Director of General
Toxicology Division:

Malcolm Blair, Ph.D.

Director of Special Toxicology
Division:

D. Clifford Jessup, Ph.D.
Norman D. Jefferson, B.A.
Jacqueline M. Wrenn, Ph.D.
Barry W. Benson, B.S.
Patrick E. Traster, B.S.

Director of Chronic Toxicity:
Assistant Director of Teratology:
Director of Quality Assurance:
Director of Laboratory Services:

8. SCHEDULE

Proposed starting date of study: March, 1980
Proposed completion date of study: April, 1980
Proposed date of final report: June, 1980

9. TEST ARTICLE DATA

- a) Identification: Sample 12177903 of a volatile Mobil test substance.
- b) Lot Number: NA
- c) Batch Number: NA
- d) Physico-Chemical Properties: Colorless liquid. Insoluble in water, soluble in most organic solvents.
B.P. = 320°F, V.P. 28 mm Hg at 150°F,
S.G. = 0.86, F.P. = 140°F.
- e) Purity: 96%
- f) Shelf Life: Indefinite
- g) Storage Conditions: Room temperature in sealed container.
- h) Safety Precautions: Avoid ingestion, dermal contact or inhaling vapors.

10. TEST DIET DATA

- a) Test Diet: Purina® Certified Rodent Chow® #5002 (Identification of each lot used will be recorded in the raw data).
- b) Contaminant Levels: The diet used will be a certified diet with guarantee of appropriate analyses performed by the manufacturer.

11. TEST ANIMALS

- a) Species: Rat
- b) Strain: Charles River CD® COBS®
- c) Source: Charles River Breeding Laboratories
Portage, Michigan
- d) Age at Start of Study: 80 - 120 days old
- e) Method of Identification: Monel metal ear tags
- f) Housing: Individual suspended wire mesh cages
- g) Quarantine: 10 days (minimum)
- h) Number on Study: 30 females
- i) Reason for Selection: The rat is an acceptable model for teratology studies. This laboratory has historical control data on the incidence of fetal malformations and variations in this strain from this source.

12. STUDY DURATION

The breeding and gestation phases of the study will require approximately four (4) weeks. A study schedule will be issued that will include the following information: Dates for animal arrival, mating initiation and termination, administration of test and control articles (initiation and termination), sacrifice and uterine examination.

13. METHOD OF ADMINISTRATION OF THE TEST ARTICLE

The test and control articles shall be administered orally by gavage.

14. EXPERIMENTAL DESIGN

Untreated sexually mature virgin female rats will be acclimated for a minimum period of ten (10) days prior to mating.

A female rat, following a detailed observation, will be housed together with a male rat of the same strain and source for mating. The occurrence of copulation will be established by daily inspection for a copulatory plug or vaginal smear for sperm. This finding will be considered day "0" of gestation, and each female will then be returned to an individual cage and properly identified by ear tag. These mated female rats are consecutively assigned in a block design to five treatment groups and one control group of five (5) rats each. All females will be maintained in a temperature-, humidity- and light-controlled room (12 hour light/dark cycle). Purina® Certified Rodent Chow® #5002 and tap water will be available ad libitum. Nesting material will not be provided, since the females will be sacrificed prior to delivery.

The test article will be administered orally by gavage as a single daily dose. Test article administration will begin on day 6 and continue up to and including day 19 of gestation. The dosage levels will be 0, 100, 300, 750, 1500, and 3000 mg/kg/day of undiluted test article. The control group will receive distilled water on a comparable regimen at a rate equal to that of the highest dosage group. Individual dosages will be based on gestation day 6 body weights.

Prior to test article administration, the rats will be observed daily for mortality and overt changes in appearance and behavior. The females will then be observed daily for mortality and clinical signs of toxicity from gestation days 6 through 20. The dams will be weighed on gestation days 0, 6, 9, 12, 16 and 20. On the 20th day of gestation, each female will be sacrificed by carbon dioxide inhalation and the uterus and ovaries exposed by an abdominal incision. The location of viable and nonviable fetuses, early and late resorptions, and the number of total implantations, and corpora lutea will be recorded. The thoracic and abdominal cavities and organs of the dams will be examined for grossly evident morphological changes and the carcasses discarded.

14. EXPERIMENTAL DESIGN (continued)

Uteri from females that appear nongravid will be opened and placed in a 10% ammonium sulfide solution for confirmation of pregnancy status.

Any female showing signs of abortion or premature delivery will remain on study until the scheduled sacrifice date to determine any effect of the test article. The aborted tissue will be discarded.

A gross necropsy will be performed on all rats not surviving to the scheduled sacrifice in an attempt to determine the cause of death. Maternal tissues will be preserved for microscopic examination in 10% neutral buffered formalin only as deemed necessary by the gross findings.

15. REPORT

A comprehensive report will be prepared upon completion of the study. The report will include mean maternal body weights of pregnant animals, mean numbers of viable and nonviable fetuses, early and late resorptions, postimplantation losses, total implantations, and corpora lutea per dam.

a) Tables

Maternal body weights (individual)
Uterine examination data (individual)

b) Appendices

Protocol and protocol addenda
Test article data
Dates of Quality Assurance inspections and reports of significant deviations from protocol.

16. PERSONNEL HEALTH AND SAFETY

Normal safety precautions will be employed in the handling of the test article.

17. DATA RETENTION

All data, including reports from this study, will be retained for at least ten (10) years after completion of the study in the IRDC Archives and will be made available for inspection upon request by authorized personnel of the Sponsor. An appropriate sample of the test article will be retained for ten (10) years following completion of the study.

18. QUALITY ASSURANCE

The final report will be reviewed by IRDC's Quality Assurance Department in accordance with IRDC's Standard Operating Procedures.

19. GOOD LABORATORY PRACTICES

This non-clinical laboratory study will be conducted in accordance with the Good Laboratory Practice regulations.

20. ALTERATION OF DESIGN

Alterations of this protocol may be made as the study progresses. No changes in the protocol will be made without the specific written request or consent of the Sponsor. In the event that the Sponsor authorizes a protocol change verbally, such change will be honored by IRDC. However, it then becomes the responsibility of the Sponsor to follow such verbal change with a written verification. All protocol modifications will be signed by the Study Director.

Approved by Sponsor

MOBIL OIL CORPORATION

By: Michael J. Norvell
Michael Norvell, Ph.D.

Title: Senior Toxicologist

Date: December 14, 1979

Issued by

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

By: Dean E. Rodwell
Dean E. Rodwell, M.S.

Title: Director of Teratology

Date: November 29, 1979

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL DISTRIBUTION SHEET

Protocol Sheet No. 2

Study No. 450-026

TITLE: PILOT TERATOLOGY STUDY IN RATS

Dr. Wazeter	<u>X</u>	Dr. Spicer	<u> </u>
Dr. Goldenthal	<u>X</u>	Dr. Jessup	<u> </u>
Quality Assurance	<u>X</u>	Dr. Blair	<u> </u>
Accounting	<u>X</u>	Dr. Laveglia	<u> </u>
Report Processing	<u>X</u>	Mr. Rodwell	<u> X </u>
Statistics and Computer	<u>X</u>	Dr. Lang	<u> </u>
Report Status	<u>X</u>	Pathology	<u> </u>
Sponsor	<u>X</u>	Inhalation	<u> </u>
		Chronic Toxicity ✓	<u> X </u>
		Teratology	<u> X </u>
		Acute Toxicology and Special Studies	<u> </u>
		Clinical Pathology	<u> </u>
		Laboratory Animal Medicine	<u> </u>
		Test Material Control	<u> X </u>
		Analytical Chemistry	<u> </u>

Dr. Michael Norvell
Sponsor Representative (name)
revised Norvell 1/20/60
Date of Approval

Study Director Dean Rodwell
Dean Rodwell 2/1/60
Signature Date

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION
PROTOCOL REVISION OR CLARIFICATION

Protocol Sheet No. 2

Study No. 450-026

Title: PILOT TERATOLOGY STUDY IN RATS

Justification:

Compound Identification: Sample 12177903
IRDC No.: 6945 & 6945B

At the Sponsor's request, the Sample 12177903 as stated on page 2 of 5 under section 9, Test Article Data, a) Identification, should read: Sample 01038003.

e) Purity: 97% (do not adjust for purity).

Study Director Dean Rodwell

Dean S. Rodwell / 2/1/80
Signature / Date

IR90-49-4

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APPENDIX III
Personnel Involved in the Study

450-026

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Pilot Teratology Study in Rats

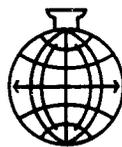
The following list of people were responsible for various phases of this study:

Stephen W. Allen, B.S.	Unit Supervisor, Test Material Control
Carol Bajo	Group Supervisor, Reproduction and Teratology
Daniel Black, B.S.	Group Supervisor, Teratology
Karen J. Bowman, B.S.	Unit Supervisor, Teratology
Joan Honeysett, B.S.	Unit Supervisor, Reproduction and Teratology
John L. Kjeldgaard, B.S.	Manager, Test Material Control
Steven Magness, B.S.	Report Writer, Teratology
Mark D. Nemecek, B.S.	Assistant to the Director, Teratology
Dean E. Rodwell, M.S.	Study Director and Director of Teratology
Colleen A. Schwartz	Manager, Reproduction and Teratology
Elaine J. Tashar, B.S.	Unit Supervisor, Report Preparation, Reproduction and Teratology
Patrick E. Traster, B.S.	Director, Laboratory Services
Debra Vogler, B.S.	Unit Supervisor, Reproduction and Teratology

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CERTIFICATE OF AUTHENTICITY

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(Month) (Day) (Year) Camera Operator

Place Syracuse New York
(City) (State)



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