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LETTER FROM MOBIL OIL CORP TO US EPA REGARDING SUBMISSION OF STUDIES ON 318 FURFURAL EXTRACT AND FERNDAL SYNTOWER BOTTOMS WITH ATTACHMENTS

Chemical Category

318 FURFURAL EXTRACT

SUPPL

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Shell Oil Corporation 122 - Pages

November 30, 1990

ENVIRONMENTAL HEALTH AND SAFETY DEPARTMENT
TOXICOLOGY BRIGON
P.O. BOX 1088
PRINCETON, NEW JERSEY 08543-1020
TELEPHONE (609) 737-6800
FAX NO. (609) 737-6801

REGISTERED MAIL
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Office of Toxic Substances
U.S. Environmental Protection Agency
401 "M" Street, S.W.
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C.J. MACKERER
MANAGER TOXICOLOGY DIVISION

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We are providing final reports for two studies mentioned in our supplemental submission on the relationship between refinery stream composition and toxicity, relevant to the EPA Document Control Number cited above. With this submission, reports for four additional studies remain outstanding and will be forwarded when they are available.

Reports for the following studies are being submitted at this time:

Study #	CAS #	Study Title
61737	64742-04-7	Thirteen Week Administration of 318 Furfural Extract to Rats
63123	64174-62-4	Developmental Toxicity Study in Rats Exposed Orally to a Single Dose of Ferndale Sycowater Bottoms

Final reports are not currently available for the following:

Study #	CAS #	Study Title
61791	64741-81-7	Thirteen Week Dermal Administration of Heavy Coker Gas Oil to Rats
61996	64741-82-8	Thirteen Week Dermal Administration of Light Coker Gas Oil to Rats
62710	64741-62-4	Thirteen Week Dermal Administration of Sycowater Bottoms to Rats
63124	64742-04-7	Developmental Toxicity Screen in Rats Exposed Orally to a Single Dose of 318 Furfural Extract

Study NO. 61737 - 67 pages
Study NO. 63123 - 55

122 - 1185-0576
C. R. Mackerer

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FINAL REPORT

Thirteen-Week Administration of
318 Isthmus Furfural Extract to Rats

STUDY NO. 61737 - 67 - Pages

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Environmental Project 610

MOBIL ENVIRONMENTAL AND HEALTH SCIENCE LABORATORY
P.O. BOX 1029
PRINCETON, NEW JERSEY 08543-1029

0003

Study Final Report

Study Performed By:

M.H. Fauston 7-12-90
M.H. Fauston, Ph.D. Date
Study Director

C.E. Hamilton 7-12-90
C.E. Hamilton, B.S. Date
Toxicologist II

61737 Final Report

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* Volume 2 will not be distributed with this report, but will be stored in the NERSL Archives.

** Appendices were originally created for a Biophase Report. They have since been rearranged for the Final Report. Each section has been provided with a coversheet indicating the Appendix/Section number. Appendix number on the individual pages should be ignored.

SUMMARY

318 Isthmus Furfural Extract (Furfural Extract) was applied to the clipped backs of male and female Sprague-Dawley rats (10 animals/gender/group) five days per week for thirteen weeks at dose levels of 30, 125, 500 and 1250 mg/kg/day. In addition, two groups of 10 males were administered Furfural Extract five days per week for thirteen weeks via oral gavage at levels of 125 and 500 mg/kg/day. Rats dosed dermally were fitted with cardboard Elizabethan collars to minimize ingestion of the applied test material, which was dispensed by volume from a syringe and left uncovered on the skin. The animals which were administered the test material by gavage were also shaved and collared. A similar group of 10 males and 10 females served as controls; they were treated in the same manner as the dermally exposed animals except that no test material was administered. Parameters used to assess toxic response which are described in this Final Report include: clinical observations, skin irritation, body weights, hematology, serum chemistry, urinalysis, organ weights, histopathology, and sperm morphology.

All of the 1250 mg/kg/day animals were terminated prior to the scheduled sacrifice. At the 500 mg/kg/day level, all of the males and three of the females which were exposed dermally and four of the males administered the test material by gavage were terminated prior to schedule. All other rats survived until the scheduled necropsy. Clinical signs which could be attributed to the test material were observed at 500 and 1250 mg/kg/day. Males appeared to be more affected than females. Minimal skin irritation was apparent in animals exposed dermally to Furfural Extract. Male rats exposed to 500 mg/kg/day or greater and females exposed to 30 mg/kg/day or greater gained significantly ($p < 0.05$) less weight than the controls.

In general, a majority of the hematology and serum chemistry parameters evaluated were adversely affected by exposure to Furfural Extract. Hematology parameters affected included RBC count, hemoglobin, hematocrit and platelet count. Serum chemistry parameters affected included uric acid, glucose, urea nitrogen, aspartate amino transferase, alanine amino transferase, alkaline phosphatase, creatinine, cholesterol, triglycerides, total protein, total bilirubin, albumin, inorganic phosphorus, sodium, potassium, chloride, and sorbitol dehydrogenase. Many of these effects were observed as early as Week 5 of the study. Animals which were dermally exposed to Furfural Extract appeared to be more affected than those animals administered the test material by gavage. Also, a greater number of serum chemistry parameters were affected in male rats than in female rats at comparable dose levels.

Urinalysis showed no treatment-related effects. Sperm evaluations showed a slight increase in the frequency of sperm with abnormal heads in the rats dosed orally at 500 mg/kg/day; sperm from rats dosed dermally at 125 mg/kg/day were not affected.

A decrease in mean final body weight (fasted weight) was observed for all treated groups of females and for males exposed orally at 500 mg/kg/day. A significant ($p < 0.05$) increase in absolute and relative liver weights and a significant decrease in absolute and relative thymus weights was seen in males and females dosed at 125 or 500 mg/kg/day. A significant ($p < 0.05$) decrease in the absolute and/or relative weights of the epididymides, prostate and seminal vesicles was observed only in male rats administered Furfural Extract by gavage.

Treatment-related (and generally dose-related) histopathologic changes were most prominent in the adrenals, bone marrow, kidneys, liver, lymph nodes, treated skin, stomach and thymus. In treated animals, small focal hemorrhages were seen by gross and microscopic examinations, in several organs including the brain, spinal cord, heart, lung, testes and bone marrow.

Based on the results of the above parameters, the No-Observed-Adverse-Effect-Level for 318 Isthmus Furfural Extract could not be established and is less than 30 mg/kg/day.

1.0 INTRODUCTION

This study was conducted as part of an on-going program to evaluate the potential toxicity of refinery streams. 318 Isthmus Furfural Extract (Furfural Extract) is a byproduct of the solvent extraction of Stock 318 (a solvent refined paraffinic neutral that is used as a base stock) from isthmus crude. The production of solvent refined (furfural extracted) petroleum products could result in prolonged and repeated human skin contact with the resulting solvent extract. The primary objective of this study was to assess the potential toxicity from such contact.

Systemic toxicity (i.e. death, aberrant hematology and serum chemistry, organ weight changes and histopathologic changes) has been observed in rats from repeat dermal application of a number of refinery streams, including Clarified Slurry Oil (CSO), Heavy Coker Gas Oil, and Heavy Vacuum Gas Oil. To date, CSO has been the most toxic material tested.

Refinery streams consist largely of hydrocarbons and hetero-substituted hydrocarbons, in different proportions, within relatively few homologous series; refinery processing generally alters the ratios of component classes within the series. Components are classified as either aromatic or non-aromatic: the aromatics are described as those of fewer than 3 rings, polynuclear aromatic hydrocarbons (PAH) of 3-5 rings, and nitrogen (N) or sulfur (S) containing polycyclic aromatic compounds (PAC). The N-PACs may be further divided into non-basic (carbazole) and basic (quinoline-type). The distribution of a select number of chemical components found in CSO and Furfural Extract is presented in Table 1.

TABLE 1

Comparative Chemical Composition (Wt. %) of Furfural Extract and CSO*

Component:	Furfural Extract	CSO
Total Non-Aromatics	22.3	12.6
Total Aromatics	77.7	87.4
< 3 ring PAH	37.2	11.1
3-5 ring PAH	23.0	46.8
N-PAC (total)	2.3	12.7
non-basic	1.6	12.0
basic	0.7	0.7
S-PAC	12.8	8.0

* Data were provided by Dr. L.K. Low (Pharmacokinetics Group).

Furfural Extract has about the same amount of polynuclear aromatic hydrocarbons (PAHs) as CSO but has more non-aromatics, and fewer N-PACs. Also, in contrast to CSO, relatively few carbazole derivatives are present in this furfural extract [MEHSL Study No. 61737DA (1)].

Since results from a dermal study (Study No. 60713) in which CSO was separated into three fractions [paraffinic, aromatic, residue (primarily carbazole derivatives and asphaltenes)] indicated that the aromatic and carbazole-containing fractions contained the most toxic components, the present study was conducted to further explore this association.

Another objective of this study was to evaluate the effects of Furfural Extract when administered via gavage. Since the collars that are used in subchronic studies do not completely prevent oral ingestion of material applied to the back, it has been implied that systemic toxicity may be due to materials being absorbed from the gastrointestinal tract rather than from the skin. In the present study, two groups of male rats were dosed orally via gavage and the results were subsequently compared to results obtained from dermal exposure at the same dose levels.

This study was conducted in Sprague-Dawley rats because of the large amount of relevant background literature on this strain, and because rats have been a good model for predicting toxicological effects in humans.

This study was performed at Mobil Environmental and Health Science Laboratory; administration of the test material occurred between December 2, 1986 and March 5, 1987. Necropsies were completed on March 6, 1987.

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2.0 MATERIAL AND METHODS

2.1 Experimental Design

A summary of the experimental design is presented below. All treatments were performed daily, five days per week, for thirteen weeks.

Summary of Experimental Design

Group	Treatment	Dose (mg/kg/day)	Route	Number of Animals
1	Untreated Control	0	-----	10M, 10F
2	Furfural Extract	30	Dermal	10M, 10F
3	Furfural Extract	125	Dermal	10M, 10F
4	Furfural Extract	500	Dermal	10M, 10F
5	Furfural Extract	1250	Dermal	10M, 10F
6	Furfural Extract	125	Oral	10M, -
7	Furfural Extract	500	Oral	10M, -

2.2 Animal and Animal Husbandry Data

Ninety male and sixty female virus-free Sprague-Dawley rats (Rat/Tac: N(SD)fBR/Taconic, Germantown, New York) were received when they were approximately twenty-eight days of age. They were acclimated to the testing facility for thirteen days prior to allocation into experimental groups at the initiation of the one-week pretreatment phase.

Animals were individually housed in suspended, stainless steel cages, 7" wide x 10" long, with wire mesh bottoms and fronts. Absorbent material in the dropping pans was changed at least three times a week. Clean cages were supplied approximately every two weeks. Animals were housed in air-conditioned rooms set to maintain 68-72 F, 40-60% relative humidity, and 12-hour light-dark cycles.

Purina Certified Lab Chow, #5002 in pelleted form, was fed ad libitum, except for periods of deprivation required for serum chemistry/ hematology studies and necropsy. Tap water, also available ad libitum, was delivered by an Eds Automatic Watering System. The system was set to flush the room distribution lines daily at high pressure to minimize water stagnation and bacterial growth. No contaminant was considered to be present in animal feed or water at a level sufficient to interfere with this study.

Each animal was uniquely identified by a numbered metal ear tag after assignment to an experimental group.

2.3 Material to be Administered

Test material: 318 Isthmus Furfural Extract

Identification: CRU No. 86187

Stability: 5 years (Expiration Date: April 30, 1991)

2.4 Assignment to Experimental Groups

During the week prior to the initiation of treatment, animals were randomly assigned to groups using a computer program that provides statistically identical ($p < 0.05$) body weight distributions. Animals considered to be "unhealthy" were not assigned to groups. Any animal which became abnormal prior to the initiation of dosing was replaced with one of the healthy animals that was not assigned to an experimental group. After dosing began, no animals were replaced.

2.5 Test Material Administration/Control

Using Oster electric clippers with #40 blades, the hair was clipped (shaved) from the dorsal trunk of each animal approximately 24 hours before the start of dosing. Hair was reclipped as necessary, but at least once per week. Care was taken to avoid abrasion of the skin during removal of the hair. The animals were approximately 49 days of age at the initiation of dosing. The test material was administered weekdays, but not on weekends or Christmas. The test material was applied to the clipped back of each rat in the dermally treated groups. Rats in the oral groups were administered the test material by gavage. Each animal in Groups 2 thru 7 received an amount of Furfural Extract calculated from its most recent body weight, the density of the test material, and the dose for that treatment group. The test material was measured by volume in a syringe that allowed accuracy within 10% of the calculated volume. The dermal exposure sites were not covered, but the animals wore cardboard "Elizabethan" collars to minimize ingestion of the test material. Animals in the groups receiving the test material by the oral route were shaved and collared so that any stress from these procedures would be equivalent among the test groups. Collars were fitted at least three days prior to the start of dosing so that the rats were used to them when the first dose was administered. During the week, if an animal was found to be without a collar, a new collar was applied prior to the next dosing. Each Saturday morning, collars were removed and the backs of the dermally dosed rats were wiped off with gauze pads to remove as much residual test material as possible. This was done to minimize oral ingestion of the test material by the dermal animals while allowing any areas affected by the collars a two day period to recover.

The oral animals were uncollared and sham wiped on Saturdays. All collars were re-applied before dosing on the following Monday. The animals in the control group were handled in the same manner as the treated animals except that no test material was administered. Treated animals were dosed until the day before their scheduled sacrifice.

2.6 Observations During the Study

2.6.1 Clinical Observations and Skin Irritation

Each animal was observed once daily during the pretreatment and dosing phases for normal or abnormal clinical signs. The parameters observed included appearance, behavior, excretory function, and discharges.

Skin irritation was scored weekly in animals from Groups 1-5. Erythema and edema were evaluated using the Draize scales. The skin was also examined and graded for chronic deterioration: flaking, thickening, stiffening, cracking, and sloughing. The scale used for scoring skin irritation is presented in Table 2. On days when scoring was not done and an abnormal skin condition was present, the condition was noted but a numerical score was not given.

On weekdays, animals were checked for moribundity and mortality twice daily, at least six hours apart. On weekends and holidays, they were checked once, as soon as practical each day.

Table 2. Scale for Scoring Skin Irritation

ERYTHEMA*

- 0 = Normal
- 1 = Barely perceptible
- 2 = Well defined
- 3 = Moderate
- 4 = Severe (beet red) to slight eschar

EDEMA*

- 0 = Normal
- 1 = Barely perceptible
- 2 = Edges of area well defined
- 3 = Area raised by approximately 1 mm
- 4 = Area raised by more than 1 mm or edema extends beyond area of exposure

CHRONIC DETERIORATION OF THE SKIN

- 0 = Normal
 - 1 = Desquamation (flaking of skin)
 - 2 = Feels thickened and/or stiff; feels leathery
 - 3 = Visibly thickened and/or stiffened; visibly leathery
 - 4 = Cracks and fissures; almost no pliability
 - 5 = Dermis is exposed (sloughing of crust; ulceration; open sores) or scar tissue is present
-

* From Draize, J.H., Woodward, G. and Calvery, H.O. (1944). Methods for the study of irritation and toxicity of materials applied topically to the skin and mucous membranes. J. Pharmacol Exp. Therap., 82: 377-390.

2.6.2 Body Weights

All animals were weighed the day after receipt and approximately one week before the first dosing (the latter for allocation into experimental groups). Animals allocated into experimental groups were weighed immediately before the first dosing and approximately weekly thereafter. The body weight of each animal was recorded to the nearest tenth of a gram.

2.6.3 Hematology

During Weeks 5 and 13, blood samples were collected from all surviving animals in a two-day period, males the first day and females the second day. The afternoon before blood collections, food was removed from the cage of each rat scheduled. Toxicology technicians anesthetized the rats with diethyl ether and collected blood samples from the orbital sinus.

One Microtainer tube containing EDTA as an anticoagulant was filled with approximately 250 ul of whole blood from each animal. Hematology analysis was performed by a Pathology technician using an ELT 8. Unclassified samples were analyzed on the same calendar day that they were collected for:

hematocrit	red blood cell count
hemoglobin	white blood cell count
platelet count	

Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were calculated. During blood collection, a thin smear of fresh blood was also made by a member of the Pathology Section for determination of red blood cell (RBC) morphology and white blood cell (WBC) differentials.

2.6.4 Serum Chemistry

During Weeks 5 and 13, blood samples were collected as described in Section 2.6.3. At least 1 ml of whole blood from each rat was collected in two Microtainer tubes, allowed to clot for approximately thirty minutes, and centrifuged to obtain the serum. Samples were analyzed for the following biochemical parameters by a member of the Biochemical Toxicology Section using a Centrifichem or flame photometer:

sorbitol dehydrogenase	cholesterol	glucose
alanine aminotransferase	urea nitrogen	uric acid
aspartate aminotransferase	total protein	sodium
alkaline phosphatase	albumin (A)	potassium
bilirubin, total	triglycerides	chloride
inorganic phosphorus	creatinine	calcium

Globulin (G) and A/G ratio were calculated. A detailed description of the procedures employed is available in the MEHSL Document Archives [Study No. 61737CA (2)].

2.6.5 Urinalysis

During Weeks 5 and 13, freshly voided urine samples were collected and analyzed. Samples were obtained from all rats, unless otherwise noted. The samples were examined visually by member(s) of the Toxicology Section for appearance (i.e., color and clarity), and by protometer for specific gravity. An Ames Clinitek 10 urine chemistry analyzer was used to read Multistix-SG urinalysis strips for the following:

bilirubin	blood	glucose	specific gravity
ketone	pH	protein	urobilinogen

2.5.6 Pathology

From all animals sacrificed as scheduled, the following organs were weighed to the nearest milligram:

adrenals	heart	ovaries	testes
brain	kidneys	prostate	thymus
epididymides	liver	spleen	uterus

The following tissues, when available, were processed for microscopic examination according to MERSL Standard Operating Procedures:

adrenals (both) ^b	nerve - peripheral (sciatic) ^o
bone and marrow (sternum) ^a	ovaries (both) ^o
brain (3 sections) ^c	pancreas (head) ^c
epididymides ^a	prostate ^c
eye (left) and optic nerve ^o	salivary gland (submaxillary) ^o
gross lesions ^a	seminal vesicles ^c
heart ^c	skin - treated (2 sections) ^a
intestine, small (jejunum) ^c	spinal cord (3 sections) ^d
intestine, large (colon) ^o	spleen ^c
kidneys (both) ^b	stomach (squamous and glandular) ^c
liver (2 lobes) ^a	testes ^a
lung (left lobe) ^c	thymus (both lobes) ^a
lymph nodes ^d	thyroid (both lobes) ^c
muscle - skeletal (thigh) ^o	urinary bladder ^o

^a - processed and examined for Groups 1, 2, 3, 4, 5, 6 and 7

^b - processed and examined for Groups 1, 2, 3, 4, 5 and 7

^c - processed and examined for Groups 1, 2, 3, 4 and 7

^d - processed and examined for Groups 1, 2, 3 and 4

^o - processed and examined for Groups 1, 4 and 7

Sections for examination were stained with hematoxylin and eosin, or any special stain deemed necessary. Microscopic examination was performed by a pathologist. A summary of the tissues which were examined from each animal and a detailed description of the procedures employed is available in the MEHSL Document Archives [Study No. 61737P (3)].

2.6.7 Sperm Morphology

The left epididymides from rats exposed to Furfural Extract at 0 mg/kg/day (Untreated Control), 125 mg/kg/day (dermal exposure) and 500 mg/kg/day (oral exposure) were provided to a member of the Developmental Toxicology Group at the time of scheduled necropsy. Five animals were examined from each group. The epididymides were prepared for evaluation of spermatozoa morphology according to MEHSL Standard Operating Procedures. A detailed description of the procedures employed is available in the MEHSL Document Archives [Study No. 61737M (4)].

2.7 Data Handling and Storage

Body weights, clinical signs, skin irritation evaluations, dose calculations and evidence of dosing were recorded and maintained using the Beckman TOXSYS computer system. Urinalysis results, sperm morphology, mortality and animal husbandry data were recorded by hand. All raw data and original study documents (i.e., test request, protocol, protocol amendments, compound receipt and dispensing records, etc.) will be stored in the MEHSL Document Archives prior to or soon after the Final Report is released. Body weight, hematology and organ weight data were analyzed by parametric methods: analysis of variance (ANOVA) and associated F-test,

followed by Student-Newman-Keuls Test, provided that there was statistical significance in ANOVA. Differences between control and treated animals were considered statistically significant only if the probability of the differences being due to chance was less than 5% ($p < 0.05$). Raw data storage and a description of the statistical analyses performed on serum chemistry and sperm morphology data can be found in their respective reports [2,4] which are available in the MEHSL Document Archives.

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3.0 RESULTS

3.1 Clinical Observations and Skin Irritation

Clinical signs indicative of systemic toxicity were observed in the 500 and 1250 mg/kg/day animals and included pallor and decreased body temperature (animals were cool to the touch). All of the 1250 mg/kg/day animals were terminated prior to the scheduled sacrifice. At the 500 mg/kg/day dose level, all of the males and three of the females which were dermally dosed (Group 4), and four of the males administered the test material by gavage (Group 7) were also terminated prior to schedule. All other animals survived until the scheduled necropsy (Table 3).

Table 3. Summary of Mortality

Group Number Dose (mg/kg/day) Route Sex	1		2		3		4		5		6		7	
	0		30		125		500		1250		125		500	
	-----		-----		Dermal		-----		-----		Oral		-----	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
On Study	10	10	10	10	10	10	10	10	10	10	10	0	10	0
Sac'd in Extremis	0	0	0	0	0	0	9	2	6	9	0	-	2	-
Found Dead	0	0	0	0	0	0	1	1	4	0	0	-	2	-
Lab. Accident	0	0	0	0	0	0	0	0	0	1	0	-	0	-

Individual clinical observations may be found in the raw data. Minimal skin irritation was observed in the dermally treated groups. Individual skin scores are presented in Appendix 6.1.

3.2 Body Weights

Mean body weights are presented in Table 4 and individual body weights are presented in Appendix 6.2. Male rats exposed to 500 mg/kg/day or greater and females exposed to 30 mg/kg/day or greater gained significantly ($p < 0.05$) less weight than the controls. Inadvertently, no body weights were obtained for the male rats during Week 5.