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8DF	87110000007	4 6 11

COMMENTS: COMMUN S (DECLASS)

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86960000614

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11 APR -6 AM 11:24

334522

CODING FORMS FOR SRC INDEXING

Microfiche No.		OTS0558815	
New Doc ID	86960000614S	Old Doc ID	
Date Produced	08/06/80	Date Received	
Submitting Organization		STANDARD OIL CO	
Contractor		IIT RESEARCH INST	
Document Title		ACUTE ORAL TOXICITY STUDY OF [] IN RATS, FINAL REPORT	
Chemical Category		9016-45-9	
		CONFIDENTIAL DECLASSIFIED VIA EMAIL 1/25/2011	

SM5HE410CM

Contains No CBI



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ACUTE ORAL TOXICITY STUDY
OF IN RATS

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FINAL REPORT

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IITRI Project No. L8100
Study No. 36
Test Article No. 14

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Life Sciences Research
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Standard Oil Co. (Indiana)
200 East Randolph Drive
Chicago, IL 60601

August 6, 1980

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IITRI Project No. L8100

ACUTE ORAL TOXICITY STUDY
OF IN RATS

Study No. 36
Test Article No. 14

This study was conducted by IIT Research Institute for the Standard Oil Company (Indiana).

Bruce K. Bernard, Ph.D., Senior Toxicologist, served as study director and was responsible for the overall conduct of the study. John M. Burns, D.V.M., served as study pathologist. Marcia Reckers, B.S., Assistant Toxicologist, was responsible for the collection of test data. Calvin Reaves, Experimentalist, was responsible for animal care personnel. Josephine M. Reed, M.M., M.S., Supervisor, Quality Assurance, was responsible for the quality assurance program.

This report was prepared by Marcia Reckers, B.S., Assistant Toxicologist.

Bruce K. Bernard 8/6/80

Bruce K. Bernard, Ph.D. Date
Study Director
Program Director
Life Sciences Research

Richard Ehrlich 8/4/80

Richard Ehrlich, Ph.D. Date
Director
Life Sciences Research

Josephine M. Reed 7/31/80

Josephine M. Reed, M.M., M.S. Date
Supervisor Quality Assurance
Life Sciences Research

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ACUTE ORAL TOXICITY STUDY OF
IN RATS
Study No. 36
Test Article No. 14

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SUMMARY

Single doses of (Sample No. A-013-J9) were diluted with polyethylene glycol 400 and administered by gavage to groups of Sprague-Dawley rats. The calculated LD₅₀ for males was 1982 mg/kg (95% confidence interval 1414-2778 mg/kg); the LD₅₀ for females was 785 mg/kg (95% confidence interval 566-1038 mg/kg).

A slight loss of body weight was observed (prior to death) in animals which died on test. Gross necropsy of animals which died during the test revealed altered color of the lungs, brain, liver, bladder, intestines and/or heart, and distention of the caecum, stomach, bladder and/or small intestine. None of these appearance changes was noted in animals sacrificed at the termination of the 14-day observation period.

ACUTE ORAL TOXICITY STUDY OF
IN RATS

I. INTRODUCTION

The purpose of this study was to assess the acute oral toxicity of in rats, including the determination of an LD₅₀ for each sex and the associated 95% confidence intervals, the slope of each mortality curve and a tabulation of toxic signs.

II. MATERIALS AND METHODS

a. Test Article. (sample no. A-013-J9; gross weight 3.543 kg; approximately 3.3 l), was received December 4, 1979. The original polyethylene container and contents were stored in a ventilated cabinet at room temperature (approximately 22 ± 1°C). A 10 ml sample of the test article was removed from the original container, sealed in a clean amber glass container, and held in the laboratory under ambient conditions as a check against possible sample contamination or degradation. The sample was returned to the Sponsor on May 22, 1980.

b. Dosage Formulation. Two stock solutions were prepared by weighing the appropriate quantity of test article with a volumetric flask. The first stock solution (650 mg/ml) was prepared by weighing 65.0 g of test article directly into a 100 ml volumetric flask. The vehicle polyethylene glycol 400 (PEG 400; lot no. unknown) was added to bring to volume. Subsequent concentrations were prepared in accordance with the following.

<u>Treatment Group</u>	<u>Dose Level (mg/kg)</u>	<u>Dosage Formulation (mg/ml)</u>	<u>Stock (ml)</u>	<u>Final Volume (ml)</u>
I	875	87.5	4.7	35
II	1307	130.7	7.0	35
III	1952	195.2	10.5	35
IV	2915	291.5	15.7	35
V	4353	435.3	23.4	35
VI	6500	650.0	35	35

The second stock solution (58.6 mg/ml) was prepared by weighing 3.223 g of test article directly into a 50 ml volumetric flask. The vehicle polyethylene glycol 400 (PEG 400; lot no. unknown) was added to bring to volume. An additional 5 ml of vehicle was added to the mixture using a volumetric pipette. Subsequent concentrations were prepared in accordance with the following.

Treatment Group	Dose Level (mg/kg)	Dosage Formulation (mg/ml)	Stock (ml)	Final Volume (ml)
VII	263	26.3	11.2	25
VIII	392	39.2	16.7	25
IX	586	58.6	25	25

c. Animals, Housing and Diet. Sprague-Dawley rats (King Animal Labs, Oregon, WI) were used for this study. Upon arrival (1/2/80, 4 weeks of age, 60-95g body weight), the rats were housed 3/cage in suspended stainless steel cages prior to treatment initiation and singly housed thereafter. A card on the front of each cage bore the study number, test article number, temporary and permanent animal numbers, species, sex, dose, purchase order number, source, date of arrival and principal investigator.

Purina Rodent Chow 5001 meal (Ralston Purina Co., St. Louis, MO) was provided *ad libitum* except for 18 hrs. prior to dosing. Tap water (supplied by an automatic watering system) was available *ad libitum*. Deotized animal cage board (DACB, Upjohn Co., Kalamazoo, MI) was provided beneath the cages.

The cage size (25 x 17.8 x 17.8 cm) conformed to the upper limit weight range recommended in the *Guide for the Care and Use of Laboratory Animals*, DHEW, (NIH) No. 78.23. Air conditioned animal rooms were maintained at $22 \pm 1^{\circ}\text{C}$ and approximately 40% relative humidity. Fluorescent lighting was provided on the basis of 12 hours of light followed by 12 hours of dark.

d. Experimental Design. One hundred twenty rats (60 male, 60 female) were assigned at random to six groups of 10 males and 10 females each. Due to a sex difference, only 3 out of the 6 dosages were common to both sexes. Each group received a different dose of the test article, and the number of deaths in each group was taken as the index of the toxicity of that dose of the test article. There was no separate control group.

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e. Method

1. Fasting. All food was removed from the cages 18 hours prior to the scheduled dosing of the test animals. Water was available throughout the interval from the automatic watering system.

2. Dosing. Ten ml/kg of the appropriate dosage formulation was administered to each animal by gavage using a plastic syringe and an 18-gauge stainless steel bail-tipped needle. Intubation was begun at 1000 hrs. on January 8, 1980 and 1030 hrs. on January 10, 1980.

3. Daily Observations. All test animals were observed approximately 2 1/2 hours and 4 hours after dosing on Test Day 1 (1/8/80) and approximately 2 hours after dosing on Test Day 1 (1/10/80). Observations for the balance of the 14-day period were made at least once per day.

4. Body Weights. Animals dosed on January 8, 1980 were weighed on Test Day 1, 2, 8 and 11. Animals dosed on January 10, 1980 were weighed on Test Day 1, 6, 8 and 11. Results for all weighings were recorded.

5. Necropsies. Gross necropsies were performed on all animals which died during the study. All animals which survived to the end of the observation period were sacrificed by carbon dioxide anesthesia and subjected to a gross necropsy. The animals were killed on January 22, 1980.

III. RESULTS

a. Mortality. The number of deaths in each of the six experimental groups was tabulated and from these data the median lethal dose (LD_{50}) was estimated separately for males and females using the method of Miller and Tainter.¹ The LD_{50} for males was estimated to be 1982 mg/kg of with a 95% confidence interval of 1414 - 2778 mg/kg. The slope of the dose mortality - curve for males was 3.50.

¹Miller, L.C. and Tainter, M.L. (1944). Estimation of the LD_{50} and its error by means of logarithmic - probit graphpaper. Proc. Soc. Exp. Biol. Med. 57, 261-264.

The LD₅₀ for females was estimated to be 785 mg/kg, with a 95% confidence interval of 566 to 1088 mg/kg. The slope of the dose - mortality curve for females was 4.67.

The number of deaths in each group are presented in Table I.

b. Daily Observations. Behavioral depression (as indicated by decreased motor activity, ataxia and/or coma) was observed in all groups in a dose dependent manner. These generally were noted to precede the death of the animal and occur with increasing frequency at the higher doses.

The clinical signs observed and the frequency with which they were noted are presented in Table II.

c. Body Weight. The body weight data for each animal at each weighing interval are presented in Appendix I. Those animals which died on test showed a slight weight loss prior to death. All surviving animals demonstrated body weight gains by the end of the observation period.

d. Necropsy. Gross necropsy findings on animals which died on test included altered color of the lungs, brain, liver, bladder, intestines and/or heart and distention of the caecum, stomach, bladder and/or small intestine. These findings, however, were not noted among animals which survived the observation period and were sacrificed at the termination of the study.

IV. QUALITY ASSURANCE

The final draft report was audited on July 31, 1980 by Josephine M. Reed. This study was found to be in compliance with Life Sciences Quality Assurance criteria. All raw data generated during the course of this study will be retained in the Life Sciences Archives as specified by government regulations.

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Pub/Journal Name		9							
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Author(s)		10							
Organ. Name		11							
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Contractor		21							
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TABLE I

MORTALITY DATA IN MALE AND FEMALE RATS
FOLLOWING A SINGLE DOSE OF

<u>Dose</u> (mg/kg)	<u>Number of</u> <u>Animals/Sex</u>	<u>Number of</u> <u>Deaths by Day 15</u>	<u>Approximate</u> <u>Time to</u> <u>Death (hour)</u>
MALES			
875	10	1	21
1307	10	3	4-45
1952	10	6	21
2915	10	5	21-45
4353	10	9	4-21
6500	10	10	21
FEMALES			
263	10	0	—
392	10	0	—
586	10	4	21-49
875	10	6	3-45
1307	10	8	3-21
1952	10	10	3-21
		<u>MALE</u>	<u>FEMALE</u>
LD ₅₀ (mg/kg)		1982	785
95% Confidence Interval of LD ₅₀ (mg/kg)		1414-2778	566-1088
Slope (probit/log dose)		3.50	4.67

TABLE II

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**INCIDENCE OF CLINICAL OBSERVATIONS
IN FEMALE RATS* FOLLOWING
A SINGLE ORAL DOSE OF**

DOSE (mg/kg)

	263	392	586	875	1307	1952
	F	F	F	F	F	F
COMA	0	0	5	9	5	8
MOTOR ACTIVITY DECREASED	0	3	4	2	1	0
ATAXIA	1	2	1	0	1	1
LABORED BREATHING	0	0	1	0	0	0

*Each dosage group consists of 10 animals

TABLE III

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**INCIDENCE OF CLINICAL OBSERVATIONS
IN MALE RATS* FOLLOWING
A SINGLE ORAL DOSE OF**

	DOSE (mg/kg)					
	875	1307	1952	2915	4353	6500
	M	M	M	M	M	M
COMA	1	3	5	4	9	10
MOTOR ACTIVITY DECREASED	0	2	4	4	1	1
ATAXIA	0	0	1	5	5	5

*Each dosage group consists of 10 animals

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APPENDIX

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INDIVIDUAL BODY WEIGHT MEASUREMENTS IN RATS FOLLOWING A SINGLE ORAL DOSE OF **PUBLIC COPY**

Sex: MALE Test Day:	1	2	8	11		
Dose: 875 mg/kg						
Animal Number:						
1	90 *					
2	94	107	153	176		
3	85	100	139	158		
4	112	136	177	202		
5	93	106	144	165		
6	91	105	138	160		
7	96	106	147	167		
8	72	77	112	131		
9	92	107	147	169		
10	100	119	154	176		
Dose: 1307 mg/kg						
Animal Number:						
11	88 *					
12	87	103	146	168		
13	96 *					
14	94	112	152	173		
15	90	103	142	157		
16	81	77 *				
17	95	115	165	189		
18	85	99	140	155		
19	104	122	168	198		
20	100	116	160	182		
Dose: 1952 mg/kg						
Animal Number:						
21	97	112	150	170		
22	93	106	146	165		
23	110	130	174	194		
24	88 *					
25	99	107	146	167		
26	74 *					
27	87 *					
28	82 *					
29	89 *					
30	89 *					

* FINAL WEIGHT PRIOR TO DEATH

INDIVIDUAL BODY WEIGHT MEASUREMENTS IN RATS FOLLOWING
A SINGLE ORAL DOSE OF**PUBLIC COPY**

Sex: MALE					
Test Day:	1	2	8	11	
Dose: 2915 mg/kg					
Animal Number:					
31	104	110	155	181	
32	83	77*			
33	88	98	130	147	
34	104*				
35	98	106	147	171	
36	89	86*			
37	96*				
38	78	91	120	143	
39	86*				
40	92	103	139	162	
Dose: 4353 mg/kg					
Animal Number:					
41	93*				
42	96*				
43	81*				
44	92*				
45	80	88	125	148	
46	101*				
47	102*				
48	104*				
49	79*				
50	90*				
Dose: 6500 mg/kg					
Animal Number:					
51	97*				
52	93*				
53	86*				
54	113*				
55	86*				
56	78*				
57	93*				
58	97*				
59	97*				
60	83*				

* FINAL WEIGHT PRIOR TO DEATH

INDIVIDUAL BODY WEIGHT MEASUREMENTS IN RATS FOLLOWING **PUBLIC** ~~CONF~~
A SINGLE ORAL DOSE OF

Sex: FEMALE					
Test Day:	1	6	8	11	
Dose: 263 mg/kg					
Animal Number:					
261	75	106	112	115	
262	90	123	129	134	
263	86	121	129	135	
264	86	121	130	143	
265	83	118	128	140	
266	100	138	147	151	
267	93	124	129	136	
268	82	117	127	137	
269	85	125	134	158	
270	94	128	134	137	
Dose: 392 mg/kg					
Animal Number:					
251	94	134	140	156	
252	89	118	124	133	
253	88	120	129	140	
254	89	125	135	143	
255	85	124	130	146	
256	80	115	121	131	
257	81	116	127	143	
258	97	134	140	150	
259	96	133	138	146	
260	83	120	126	137	
Dose: 586 mg/kg					
Animal Number:					
241	86	120	127	134	
242	79*				
243	104	141	150	160	
244	85*				
245	81	116	128	138	
246	92*				
247	84	115	125	136	
248	94	123	132	140	
249	90	125	133	140	
250	86*				

* FINAL WEIGHT PRIOR TO DEATH

INDIVIDUAL BODY WEIGHT MEASUREMENTS IN RATS FOLLOWING
 A SINGLE ORAL DOSE OF

PUBLIC COPY

Sex: FEMALE						
Test Day:	1	2	8	11		
Dose: 875 mg/kg						
Animal Number:						
61	75*					
62	86	76				
63	74	80	113	125		
64	87	78	131	148		
65	79*					
66	62*					
67	76	68				
68	70	79	112	124		
69	84	98	131	142		
70	78*					
Dose: 1307 mg/kg						
Animal Number:						
71	85	96	131	148		
72	77*					
73	75*					
74	84*					
75	79*					
76	60*					
77	72	80	117	129		
78	83*					
79	67*					
80	88*					
Dose: 1952 mg/kg						
Animal Number:						
81	80*					
82	70*					
83	73*					
84	85*					
85	79*					
86	82*					
87	69*					
88	76*					
89	93*					
90	71*					

* FINAL WEIGHT PRIOR TO DEATH

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