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FINAL

DATA EVALUATION REPORT

Surfadone LP-100

Study Type: Subchronic Oral Toxicity in Rats

Prepared for:

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Guideline Series 82-1: Subchronic Oral Toxicity in Rats

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DATA EVALUATION REPORT

STUDY TYPE: Guideline series 82-1, subchronic oral toxicity in rats

TOX CHEM NUMBER: N/A

P.C. NUMBER: N/A

STUDY NUMBER: 3152.4

CAS NUMBER:

MRID NUMBER: 426683-16

TEST MATERIAL: Surfadone LP-100

SYNONYMS: [redacted]*

SPONSOR: GAF Chemicals Corporation
(International Specialty Products, Inc.)
Wayne, NJ

TESTING FACILITY: Springborn Laboratories, Inc. (SLS)
Life Sciences Division
Spencerville, OH

TITLE OF REPORT: Surfadone LP-100 90-day Dietary Toxicity Study in Rats

AUTHOR: James T.F. Liao, D.V.M., Ph.D.

REPORT ISSUED: July 2, 1991

QUALITY ASSURANCE: A signed quality assurance statement, dated July 2, 1991, was included with the study report. A GLP compliance statement and a flagging statement were present.

CONCLUSION: Surfadone LP-100 was administered via the diet to 60 Sprague-Dawley rats (10/sex/dose) for 3 months at dietary levels of 60, 600, and 6000 ppm. When no overt signs of toxicity were observed, the highest dietary level was increased from 6000 to 8000 ppm at day 29, and from 8000 to 10,000 ppm at day 43. Average intakes for males were 3-7 mg/kg/day for the low-dose group, 33-65 mg/kg/day for the mid-dose group, and 492-718 mg/kg/day

Inert ingredient information may be entitled to confidential treatment

for the high-dose group. Average intakes for females were 4-7 mg/kg/day for the low-dose group, 43-69 mg/kg/day for the mid-dose group, and 608-924 mg/kg/day for the high-dose group.

NOEL = 600 ppm (33-65 mg/kg/day in males; 43-69 mg/kg/day in females)

LOEL = 8462 ppm (492-718 mg/kg/day in males; 608-924 mg/kg/day in females), the time-weighted average high dose for the sexes combined. The LOEL was established based on statistically significant ($p<0.01$) increased absolute and relative liver weights in both sexes and mild hepatocyte hypertrophy observed in two males and eight females.

CORE CLASSIFICATION: Core Guideline. This study satisfies the guideline requirements (82-1) for a subchronic oral toxicity study in rodents.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Surfadone LP-100

Chemical formula: Not available

Lot number: KC 90731

Purity: 99.6%

Physical property: Clear colorless liquid

Stability: Stable at room temperature for up to 14 days; expiration date, November 1, 1991

2. Diet Preparation and Analysis

Target dietary concentrations of 60, 600, 6000, 8000, and 10,000 ppm were prepared by dissolving an appropriate amount of the test material in an aliquot of corn oil, adding the mixture to a specified amount of basal diet (Purina Certified Rodent Chow #5002), and blending for 10 minutes. Control animals received basal diet mixed with corn oil; both control and test diets contained 1% corn oil. Diets were prepared every 7 or 14 days, depending on the feeding schedule, and were stored at room temperature.

When no overt signs of toxicity were observed early in the study, the high-dose level was increased from 6000 to 8000 ppm at day 29, and from 8000 to 10,000 ppm at day 43. The 13-week time-weighted average high-dose level calculated by the reviewers was 8462 ppm for the sexes combined.

Stability, homogeneity, and actual concentrations were determined using gas chromatography with flame ionization detection following CH_3OH/CH_3CN extraction of the samples. Stability was evaluated for 60-, 6000-, 8000-, and 10,000-ppm samples of actual test

diets. The 60- and 6000-ppm samples were evaluated 4, 8, and 15 days after diet preparation. Samples containing 8000 ppm and 10,000 ppm were evaluated 8 days and 8 and 15 days, respectively, after diet preparation. Recoveries averaged 96.1-111.0% for low-dose samples; 91.7-108.4% for mid-dose samples; and 95.3-97.1% for 8000-ppm samples. Average recoveries for 10,000-ppm samples were 95.8-102.8%. Sample recoveries were within 11% of target levels, indicating that the test material was stable in the diet for up to 2 weeks at room temperature.

Homogeneity of mixing was determined for 60-, 6000-, 8000-, and 10,000-ppm diet samples by analyzing duplicate samples taken from the top, middle, and bottom part of the food storage container. Recoveries from the top, middle, and bottom of the container were 101.2-105.8% for the low-dose samples; 96.5-119.0% for the mid-dose samples; 87.1-103.5% for the 8000-ppm samples; and 89.8-107.0% for the 10,000-ppm samples. Average recoveries for two samples from the top, middle, and bottom of the container were within 11% of each other, indicating that the samples were homogeneous.

Dietary samples of 0, 60, 600, and 6000 ppm were analyzed at weeks 1, 2, and 4 to determine actual concentrations. Samples from 0-, 60-, and 600-ppm diets were also analyzed at months 2 and 3. Samples from 8000-ppm diets were analyzed at weeks 5 and 6. Samples from 10,000-ppm diets were analyzed at week 7 and months 2 and 3. Actual concentrations were 93.3-109.6% of target levels across all dietary levels. Actual concentrations achieved in the test diets for each target dietary level were as follows (data were extracted from chemistry table 3, pages 111–112 of the study report):

Time of Analysis	Target Concentration (ppm)	Average Percent Concentration Achieved
Week 1	0	--
	60	104.7
	600	93.3
	6000	102.9
Week 2	0	--
	60	103.5
	600	103.8
	6000	104.9
Week 4	0	--
	60	96.0
	600	97.7
	6000	97.1
Week 5[a]	8000	94.1
Week 6	8000	100.6
Week 7[a]	10,000	95.6
		101.1
		93.3
Month 2	0	--
	60	107.6
	600	109.6
	10,000	108.5
Month 3	0	--
	60	99.5
	600	104.4
	10,000	93.8

[a] Percent achieved for these weeks was calculated from concentrations from the sample homogeneity analyses.

3. Animals

Sixty male and 60 female (nulliparous, nonpregnant) Sprague-Dawley Crl:CD(BR) VAF/Plus rats, approximately 4 weeks old, were received from Charles River Laboratories, Inc., Portage, Mississippi. Upon arrival, rats were examined for disease and behavior abnormalities, weighed within 1 day of receipt, and uniquely identified by metal ear tags. Rats were acclimated for 14 days under study environmental conditions.

Animals were housed individually in suspended stainless steel cages and were provided rodent chow and water (municipal water supply) *ad libitum*. A 12-hour dark/light cycle was maintained. Room temperature was kept at 64-79°F. Relative humidity was maintained at 40-70%. On 1 day of the study, the room temperature was 1°F below the desired temperature range. On seven occasions, humidity was outside the desired range (from -11% to 8%). Neither condition affected the outcome of the study.

At the end of the acclimation period, all rats were weighed. Healthy animals were assigned to study groups (10/sex/group) using a computer randomization program. The computer program ranked the animals by pre-test body weight and randomly assigned them to study groups using a stratified block design. At initiation of dosing, rats were approximately 6 weeks old and weighed 182-211 g (males) and 127-160 g (females).

Test Group	Dietary Concentration (ppm)	Number of Rats	
		Males	Females
1 (control)	0	10	10
2 (low dose)	60	10	10
3 (mid dose)	6000	10	10
4 (high dose)	10,000[a]	10	10

[a] Dietary levels for this group were 6000 ppm for days 1-28, 8000 ppm for days 29-42, and 10,000 ppm for days 43-91.

Rationale for dose selection: Dietary levels were chosen based on data received from the sponsor; however, the selection criteria were not discussed in the study report.

4. Statistical Analyses

Statistical analyses were two-tailed with a minimal significance level of 5%. Body weight, body weight gain, food consumption, organ weight, and clinical pathology data were analyzed by one-way analysis of variance (ANOVA). If data were significantly differently from control values, a group-by-group comparison was conducted using Dunnett's Test.

5. General Observations

(a) Mortality/moribundity/survival

Animals were checked twice daily for mortality and moribundity.

Results: No treatment-related deaths were observed.

(b) Clinical observations

Animals were observed daily for general appearance, behavior, and overt signs of toxicity.

Results: No clinical signs of toxicity were observed.

(c) Body weight/food consumption/test article intake

Body weight/body weight gain--Individual body weights were measured before assignment to study groups, just prior to initiation of dosing, weekly during dosing, and at terminal sacrifice.

Results: Mean body weight data are summarized in Table 1. No statistically significant changes were observed. Body weights were slightly reduced in high-dose females (92-101% of controls) and in high-dose males (97-99% of controls). Body weights for low- and mid-dose animals were comparable to or in excess of controls.

Body weight gain data are summarized in Table 2. No statistically significant changes were observed in any dose group. A slight reduction in body weight gain was observed in high-dose males (90-97% of controls) and high-dose females (80-90% of controls); at week 13, body weight gains for high-dose males and females were 97% and 83% of controls, respectively.

Food consumption--Food consumption in g/kg/day and g/animal/day was calculated weekly until study day 91.

Results: Table 3 summarizes food consumption in g/kg/day. Statistically significant ($p<0.05$) increases in food consumption (g/kg/day) were observed in mid-dose males at weeks 4-5 and 7-9 and in high-dose males at weeks 4-5, 6-7, 8-9, and 13-14. At week 14, consumption in high-dose males was 107% of controls.

Food consumption was significantly increased in high-dose females at weeks 12-13 only; at week 14, consumption was 112% of control values. Food consumption in low- or mid-dose females was generally comparable to or in excess of controls.

Test article intake--Dietary levels of 60, 600, and 10,000 ppm Surfadone LP-100 corresponded to average intakes for males of 3-7 mg/kg/day for the 60-ppm group, 33-65 mg/kg/day for the 600-ppm group, and 492-718 mg/kg/day for the 10,000-ppm group. Average intakes for females were 4-7 mg/kg/day for the 60-ppm group, 43-69 mg/kg/day for the 600-ppm group, and 608-924 mg/kg/day for the 10,000-ppm group.

TABLE 1. Mean Body Weights (g ± S.D.) for Rats Ingesting Surfadone LP-100 in the Diet for 90 Days[a,b]

Week	Dietary Level (ppm)			
	0	60	600	10,000[c]
		Males		
1	197 ± 7	197 ± 8 (100)	196 ± 7 (99)	195 ± 9 (99)
3	286 ± 10	290 ± 20 (101)	286 ± 14 (100)	274 ± 19 (96)
5	344 ± 14	356 ± 26 (103)	350 ± 24 (102)	337 ± 21 (98)
7	384 ± 22	402 ± 34 (105)	396 ± 34 (103)	373 ± 27 (97)
9	413 ± 24	430 ± 39 (104)	441 ± 31 (107)	404 ± 30 (98)
11	436 ± 31	455 ± 38 (104)	467 ± 34 (107)	425 ± 34 (97)
13	458 ± 33	471 ± 29 (103)	488 ± 38 (107)	445 ± 39 (97)
		Females		
1	143 ± 8	144 ± 9 (101)	145 ± 8 (101)	144 ± 7 (101)
3	181 ± 16	179 ± 11 (99)	182 ± 12 (101)	177 ± 14 (98)
5	208 ± 26	207 ± 14 (100)	210 ± 20 (101)	200 ± 12 (96)
7	225 ± 27	226 ± 14 (100)	229 ± 23 (102)	218 ± 19 (97)
9	241 ± 36	241 ± 16 (100)	241 ± 31 (100)	225 ± 18 (93)
11	251 ± 38	244 ± 17 (97)	250 ± 31 (100)	230 ± 18 (92)
13	259 ± 41	253 ± 18 (98)	256 ± 35 (99)	238 ± 19 (92)

[a] Data extracted from Study No. 3152.4, Table 2, pages 27–32.
[b] Numbers in parentheses represent percent control.
[b] Dietary levels were 6000 ppm for test days 1–28, 8000 ppm for test days 29–42, and 10,000 ppm for test days 43–91.

TABLE 2. Cumulative Mean Body Weight Gain (g ± S.D.) for Rats Ingesting Surfadone LP-100 in the Diet for 90 Days[a,b]

Weeks	Dietary Level (ppm)			
	0	60	600	10,000[c]
		Males		
1-3	88 ± 8	93 ± 17 (106)	90 ± 13 (102)	79 ± 13 (90)
1-5	147 ± 14	159 ± 23 (108)	154 ± 23 (105)	142 ± 17 (97)
1-7	187 ± 22	205 ± 31 (110)	200 ± 33 (107)	178 ± 22 (95)
1-9	216 ± 25	233 ± 37 (108)	245 ± 29 (113)	208 ± 26 (96)
1-11	239 ± 30	258 ± 36 (108)	270 ± 33 (113)	230 ± 31 (96)
1-13	260 ± 33	274 ± 25 (106)	292 ± 36 (112)	250 ± 35 (96)
1-14	269 ± 37	284 ± 26 (106)	302 ± 38 (112)	260 ± 35 (97)
		Females		
1-3	38 ± 8	35 ± 5 (92)	36 ± 6 (95)	33 ± 8 (87)
1-5	65 ± 20	63 ± 7 (97)	65 ± 14 (100)	56 ± 8 (86)
1-7	82 ± 21	82 ± 9 (100)	84 ± 18 (102)	74 ± 14 (90)
1-9	98 ± 30	97 ± 10 (99)	96 ± 25 (98)	81 ± 13 (83)
1-11	108 ± 32	100 ± 12 (93)	105 ± 26 (97)	86 ± 14 (80)
1-13	116 ± 34	109 ± 11 (94)	111 ± 30 (96)	94 ± 15 (81)
1-14	120 ± 35	114 ± 13 (95)	117 ± 28 (98)	100 ± 15 (83)

[a] Data extracted from study No. 3152.4, Table 4, pages 39-44.
[b] Numbers in parentheses represent percent control.
[c] Dietary levels were 6000 ppm for test days 1-28, 8000 ppm for test days 29-42, and 10,000 ppm for test days 43-91.

TABLE 3. Mean Food Consumption (g/kg/day ± S.D.) for Rats Ingesting Surfadone LP-100 in the Diet for 90 Days[a,b]

Week	Dietary Level (ppm)			
	0	60	600	10,000[c]
		Males		
1-2	106 ± 7.5	111 ± 5.7 (105)	108 ± 6.7 (102)	95 ± 21.4 (90)
3-4	87 ± 4.4	90 ± 3.4 (103)	87 ± 6.2 (100)	92 ± 4.9 (106)
5-6	74 ± 3.3	78 ± 2.8 (105)	77 ± 5.2 (104)	77 ± 3.4 (104)
7-8	66 ± 2.8	67 ± 3.5 (102)	70 ± 5.3* (106)	69 ± 2.5 (105)
9-10	67 ± 3.3	65 ± 5.9 (97)	67 ± 3.5 (100)	69 ± 3.8 (103)
11-12	63 ± 2.7	61 ± 8.5 (97)	64 ± 5.6 (102)	66 ± 3.0 (105)
13-14	53 ± 2.1	55 ± 3.8 (104)	55 ± 5.1 (104)	57 ± 2.2* (107)
		Females		
1-2	117 ± 9.3	119 ± 6.0 (102)	116 ± 5.7 (99)	112 ± 6.7 (96)
3-4	108 ± 9.4	111 ± 4.5 (103)	105 ± 4.7 (97)	110 ± 15.6 (102)
5-6	95 ± 7.8	101 ± 7.2 (106)	94 ± 4.6 (99)	93 ± 6.3 (98)
7-8	87 ± 5.0	91 ± 5.0 (105)	86 ± 3.6 (99)	86 ± 10.9 (99)
9-10	87 ± 7.5	86 ± 6.2 (99)	87 ± 6.0 (100)	92 ± 12.7 (106)
11-12	80 ± 5.3	85 ± 5.4 (106)	80 ± 3.1 (100)	85 ± 11.0 (106)
13-14	69 ± 7.2	72 ± 4.1 (104)	72 ± 5.7 (104)	77 ± 8.1 (112)

[a] Data extracted from study No. 3152.4, Table 6, pages 51-53.
[b] Numbers in parentheses represent percent control.
[c] Dietary levels were 6000 ppm for test days 1-28, 8000 ppm for test days 29-42, and 10,000 ppm for test days 43-91.

* Significantly different from control; $p<0.05$.

(d) Ophthalmoscopic examination

Eyes were examined just prior to initiation of dosing and near the end of the study period.

Results: No treatment-related lesions were found.

6. Clinical Pathology

One day before initiation of dosing, blood was collected from 10 male and 10 female rats to determine overall health. These 20 rats were then sacrificed and discarded. Just prior to sacrifice at day 92 or 93 of the study, blood was collected from all surviving animals for hematology and clinical chemistry tests. Blood was drawn from the orbital plexus of fasted rats. The checked (X) parameters were examined.

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Leukocyte count, differential*
X Erythrocyte count (RBC)*
X Platelet count*
X Mean corpuscular HGB (MCH)
X Mean corpusc. volume (MCV)
X Mean corpusc. HGB concentration (MCVH)
X Nucleated red blood cells
X Reticulocyte count

*Recommended by Subdivision F (November 1984) Guidelines

Results: The following statistically significant changes were observed in males: reduced erythrocyte counts in low- and high-dose males (95% and 94% of controls, respectively); reduced hemoglobin in low- and mid-dose males (96% of control); reduced hematocrit in high-dose males ($p<0.01$; 95% of control), and reduced reticulocytes in mid-dose males (16% of controls; $p<0.01$). Statistically significant changes in females included reduced reticulocytes in mid- and high-dose females ($p<0.05$; 17% and 27% of controls, respectively) and reduced monocytes in mid-dose females ($p<0.05$; 44% of control). However, the changes observed in hematology parameters were within the range of historical controls and were considered incidental findings.

(b) Blood (clinical) chemistry

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	X Albumin/globulin ratio
X Phosphorus*	X Creatinine*
X Potassium*	X Blood urea nitrogen*
X Sodium*	X Glucose (fasting)*
Magnesium*	X Globulins
	X Total serum protein (TP)*
	X Total bilirubin
Enzymes	Cholesterol*
	Triglycerides
Creatinine phosphokinase*	Serum protein electrophoresis
X Alkaline phosphatase (ALK)	
X Serum alanine aminotransferase (SGPT)*	
X Serum aspartate aminotransferase (SGOT)*	
X Gamma glutamyl transferase (GGT)	

*Recommended by Subdivision F (November 1984) Guidelines

Results: Statistically significant changes included increased total protein in high-dose females (106% of control), reduced chloride in low- and high-dose females (97% of control), increased total bilirubin in mid-dose males (131% of control), and decreased glucose in low-dose males (87% of control). These values were within historical control ranges and the changes were not considered biologically significant.

(c) Urinalysis

Urinalysis determinations were not performed.

7. Sacrifice and Pathology

Complete gross examinations were conducted on all rats surviving until terminal sacrifice. One-half the animals from each sex/dose group were sacrificed by CO_2 inhalation at day 92, and the remainder were sacrificed in the same manner at day 93. Animals sacrificed moribund during the study were also necropsied. Tissues checked below (X) were collected from all rats and were placed in 10% neutral buffered formalin. Double-checked tissues were also weighed for all animals (paired organs were weighed together).

All tissues collected from rats in the control and high-dose groups and from rats with unscheduled deaths were examined histologically. Tissue from the lungs, livers, kidneys, and gross lesions from all low- and mid-dose rats were also examined.

Respiratory	Cardiovascular/ Hematologic	Neurologic
X Nose	X Spleen	XX Brain*
X Trachea*	X Heart*	X Peripheral (sciatic) nerve*
X Lung*	X Aorta*	X Spinal cord (three) levels)*
X Pharynx	X Bone marrow*	X Pituitary*
Larynx	X Thymus*	X Eyes (optic nerve)*
	X Lymph nodes*	
Digestive		**Glandular**
X Stomach*		
X Duodenum*	**Urogenital**	X Parathyroids*
Gall bladder*		X Lachrymal gland
X Jejunum*	XX Kidneys*	XX Adrenal gland*
X Ileum*	X Urinary Bladder*	X Thyroids*
X Cecum*	XX Testes/ovaries*	X Mammary gland*
X Colon*	X Uterus*	
X Rectum*	X Epididymides	**Other**
XX Liver*	X Seminal vesicles	
X Pancreas*	X Prostate	X Bone* (femur)
Salivary glands*		X Skeletal muscle (thigh)*
X Esophagus*		X Skin*
Tongue		X Tissues with gross lesions*

* Recommended by Subdivision F (November 1984) Guidelines

(a) Organ weights

Absolute and relative organ weights are summarized in Tables 4 and 5. Statistically significant changes included increased absolute kidney weights in mid-dose males ($p<0.05$) and increased absolute liver weights in mid- and high-dose males and high-dose females ($p<0.01$). In addition, relative liver and kidney weights were significantly ($p<0.01$) increased in high-dose animals. Because they correspond to mild hepatocyte hypertrophy in several animals, the changes in absolute and relative liver weights were considered to be related to treatment with Surfadone LP-100. Absolute and relative ovary weights in high-dose females were also increased compared to controls; however, there was no corresponding histopathology of the ovaries.

(b) Gross pathology

No treatment-related changes were observed.

(c) Microscopic pathology

Treatment-related changes included minimal-to-mild hepatocyte hypertrophy observed in two high-dose males and eight high-dose females.

TABLE 4. Absolute Organ Weights (g ± S.D.) for Rats Ingesting Surfadone LP-100 in the Diet for 90 Days[a,b]

Organ	Dietary Level (ppm)			
	0	60	600	10,000[c]
Brain	2.20 ± 0.09	2.22 ± 0.06 (101)	2.29 ± 0.13 (104)	2.20 ± 0.09 (100)
Testes	3.38 ± 0.32	3.30 ± 0.15 (98)	3.28 ± 0.32 (97)	3.26 ± 0.21 (96)
Kidneys	3.50 ± 0.32	3.74 ± 0.23 (107)	3.93 ± 0.30* (112)	3.86 ± 0.41 (110)
Adrenal Glands	0.061 ± 0.016	0.060 ± 0.010 (100)	0.063 ± 0.008 (100)	0.062 ± 0.011 (100)
Liver	13.20 ± 1.86	14.22 ± 1.97 (108)	15.64 ± 1.81* (118)	16.08 ± 1.78** (122)
		Females		
Brain	2.01 ± 0.10	2.01 ± 0.11 (100)	2.05 ± 0.08 (102)	2.00 ± 0.10 (100)
Ovaries	0.085 ± 0.015	0.086 ± 0.013 (100)	0.080 ± 0.010 (89)	0.107 ± 0.015** (119)
Kidneys	1.96 ± 0.22	2.04 ± 0.25 (104)	2.09 ± 0.13 (107)	2.14 ± 0.16 (109)
Adrenal Glands	0.071 ± 0.013	0.068 ± 0.009 (100)	0.064 ± 0.013 (86)	0.066 ± 0.012 (93)
Liver	7.55 ± 1.24	7.37 ± 1.03 (98)	7.62 ± 0.62 (101)	9.56 ± 1.07** (127)

[a] Data extracted from Study No. 3152.4, Table 11, pages 81–82.
[b] Numbers in parentheses represent percent control.
[c] Dietary levels were 6000 ppm for test days 1–28, 8000 ppm for test days 29–42, and 10,000 ppm for test days 43–91.

* Significantly different from control; $p<0.05$.
** Significantly different from control; $p<0.01$.

TABLE 5. Relative Organ (to Body) Weights (g/100 g ± S.D.) for Rats Ingesting Surfadone LP-100 in the Diet for 90 Days[a,b]

Organ	Dietary Level (ppm)			
	0	60	600	10,000[c]
Brain	0.503 ± 0.0317	0.488 ± 0.0299 (97)	0.487 ± 0.0196 (97)	0.517 ± 0.0403 (103)
Testes	0.773 ± 0.0663	0.725 ± 0.0522 (94)	0.699 ± 0.0794 (90)	0.768 ± 0.0800 (99)
Kidneys	0.799 ± 0.0392	0.823 ± 0.0600 (103)	0.836 ± 0.0646 (105)	0.904 ± 0.0483** (113)
Adrenal Glands	0.014 ± 0.0038	0.013 ± 0.0020 (93)	0.013 ± 0.0015 (93)	0.015 ± 0.0026 (107)
Liver	3.004 ± 0.2734	3.115 ± 0.3442 (104)	3.315 ±0.2112 (110)	3.765 ± 0.2760** (125)
		Females		
Brain	0.835 ± 0.1058	0.842 ± 0.0630 (101)	0.855 ± 0.1074 (102)	0.886 ± 0.0437 (106)
Ovaries	0.035 ± 0.0067	0.036 ± 0.0060 (103)	0.034 ± 0.0083 (97)	0.047 ± 0.0061** (134)
Kidneys	0.809 ± 0.0785	0.847± 0.0695 (105)	0.871 ± 0.1048 (108)	0.949 ± 0.0708** (117)
Adrenal Glands	0.029 ± 0.0053	0.029 ± 0.0046 (100)	0.027 ± 0.0077 (93)	0.029 ± 0.0051 (100)
Liver	3.107 ± 0.4604	3.066 ± 0.3466 (99)	3.175 ± 0.4207 (102)	4.243 ± 0.4770** (137)

[a] Data extracted from Study No. 3152.4, Table 12, pages 83–84.
[b] Numbers in parentheses represent percent control.
[c] Dietary levels were 6000 ppm for test days 1–28, 8000 ppm for test days 29–42, and 10,000 ppm for test days 43–91.

** Significantly different from control; $p<0.01$.

B. DISCUSSION

This study is classified Core Guideline and satisfies the guideline requirements (82-1) for a subchronic oral toxicity study in rodents.

No treatment-related clinical signs of toxicity, changes in hematology or clinical chemistry parameters, or gross pathological effects were observed in any dose group. The LOEL of 8462 ppm (492-718 mg/kg/day in males; 608-924 mg/kg/day in females) was established based on statistically significant ($p<0.01$) increased absolute and relative liver weights in high-dose animals and mild hepatocyte hypertrophy observed in two high-dose males and eight high-dose females. Slight reductions in body weight and body weight gain were observed in high-dose females.

The potential hepatotoxicity of Surfadone observed in the current study is supported by signs of liver toxicity observed in a subchronic oral toxicity study in Beagle dogs (Study no. SLS 3152.3; MRID No. 426683-17). In the dog study, increased absolute and relative liver weights and hepatocellular hypertrophy were observed at the LOEL of 90 mg/kg/day. In addition, serum alkaline phosphatase and globulin levels were increased, while albumin/globulin ratios and levels of GGT and albumin were reduced.

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R113587

Chemical:	**2-Pyrrolidinone, 1-octyl-**
PC Code:	**911690**
HED File Code	**13000 Tox Reviews**
Memo Date:	**11/17/1993**
File ID:	**00000000**
Accession Number:	**412-06-0006**

HED Records Reference Center
09/28/2005