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

MAR 23 1989

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Irgasan: Review of Chronic Feeding / Oncogenicity Study in Rats

Caswell No. 186A EPA ID No. 100-502
EPA Record No. 230991

TO: J. Kempter / W. C. Francis, PM (32)
Registration Division (H7505C)

FROM: Whang Phang, Ph.D. 3/20/89
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THROUGH: K. Clark Swentzel, Toxicologist K. Clark Swentzel 3/21/89
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The registrant, Ciba-Geigy Corp. has submitted a 2-year feeding/ oncogenicity study in rats with Irgasan (Fat 80'023). This study has been reviewed by Dynamac Corp. and approved by Toxicology Branch II. The data evaluation report is attached, and the conclusion is as follows:

1). This study is poorly organized and written. It also contains technical errors in clinical chemistry analyses. In most cases summary data are not prepared.

2). Groups of rats (80/sex/dose) were fed Irgasan at dietary concentrations of 0, 300, 1000, and 3000 ppm for 104 weeks and 6000 ppm for 52 weeks. Under the conditions of the study, the test agent did not show any oncogenic effects.

3). A significant body weight decrease was seen in 6000 ppm females.

4). Consistent and statistically significant decreases in erythrocyte counts were seen in 300, 1000, and 3000 ppm males

1 of 31

at the measuring periods of weeks 78 and 104. Decreases in hemoglobin concentration and hematocrit in treated males were also present, but they were not consistent and sometimes were not statistically significant. Clotting time in 6000 ppm males was consistently increased.

5). A significant increase in the incidence of accumulation of foamy macrophages in pulmonary alveoli of both treated males and females was seen at 104 week.

6). A significant increase in the incidence of non-neoplastic liver changes such as cytoplasmic inclusions and hepatocellular hypertrophy was seen in 3000 ppm males. An increase in the incidence of hepatic necrosis was seen in 300, 1000, and 3000 ppm males relative to the controls. It seemed to be quite odd that clinical chemistry data did not show consistent changes in SGPT or SGOT levels while the above effects on the liver were found in the treated males. In the absence of the historical control incidence of liver necrosis, the increase in the incidence of liver necrosis in 300, 1000, and 3000 ppm males could not be dismissed.

Based upon the increase in the incidence of liver necrosis, the decrease in the erythrocyte count, and the increase in the incidence of accumulation of foamy macrophages in the pulmonary alveoli, the LOEL is established at 300 ppm which was the lowest concentration tested. At the present a NOEL for chronic toxicity can not be established.

The study is classified as supplementary because it contains many technical errors, is incomplete, and is poorly organized.

CONFIDENTIAL BUSINESS INFORMATION
NOT CONTAINED
SECURITY INFORMATION (EO 12065)

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EPA: 68D80056
DYNAMAC No. 136-A
March 2, 1989

DATA EVALUATION RECORD

IRGASAN

Chronic Toxicity/Oncogenicity Feeding Study in Rats

APPROVED BY:

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Dynamac Corporation

Signature: Roman J. Puenta (for)

Date: 3-3-89

3

007098

EPA: 68D80056
DYNAMAC No. 136-A
March 2, 1989

DATA EVALUATION RECORD

IRGASAN

Chronic Toxicity/Oncogenicity Feeding Study in Rats

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4

007098

DATA EVALUATION RECORD

GUIDELINE § 83-5

STUDY TYPE: Chronic toxicity/oncogenicity feeding study in rats.

ACCESSION/MRID NUMBER: 263791-263794.

TEST MATERIAL: Fat 80'023.

SYNONYM(S): Irgasan DP-300; Triclosan.

STUDY NUMBER(S): MIN 833005.

SPONSOR: Dyestuffs and Chemical Division, Ciba-Geigy Corporation, Greensboro, NC.

TESTING FACILITY: Research Department, Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ.

TITLE OF REPORT: Study 1--Fat 80'023. 2 Year Oral administration to Rats; Study 2--Determination of Fat 80'023 in Blood and Tissue Samples Taken during a Two-Year Chronic Oral Toxicity/Oncogenicity Study in Albino Rats (24-Month Final Report).

AUTHOR(S): Study 1--Yau, E. T., and Green, J. D., Study 2--Parkes, D. G.

REPORT ISSUED: Study 1--April 28, 1986; Study 2--April 30, 1986.

5

CONCLUSIONS: Under the conditions of the chronic toxicity study, Fat 80'023 was not oncogenic when fed to male and female Sprague-Dawley rats at levels of 0, 300, 1000, or 3000 ppm for 104 weeks or 6000 ppm for 52 weeks. There were no overt signs of toxicity or dose-related effects on mortality, clinical observations, ophthalmology, urinalysis, gross pathology, palpable mass observations, or neoplastic histopathology. Body weights were significantly decreased in males and females fed 6000 ppm and females fed 3000 ppm. A compensatory increase in food consumption was exhibited in males only. Erythrocyte counts (RBC), hemoglobin (HGB) concentration, and hematocrit (HCT) of males fed 300, 1000, or 3000 ppm, RBC counts of females fed 1000 or 3000 ppm, and HCT levels of females fed 6000 ppm were found to be decreased. SGOT and SGPT indices were increased in males fed 3000 ppm and BUN levels were increased in dosed females when compared to concurrent controls. Compound-related decreases were found in total bilirubin, triglycerides, total protein, SGOT, and glucose indices. Liver weights of males and females fed 6000 ppm were found to be decreased. Nonneoplastic liver changes (cytoplasmic inclusions and hepatocellular hypertrophy) were exhibited in males fed 3000 and 6000 ppm; hepatic necroses were increased in males fed 300, 1000, or 3000 ppm. Residue levels of the test compound recovered in the blood, kidney, and liver tissues were proportional to the dose levels. The predominant amount of residual Fat 80'023 in the blood and kidney was found as the sulfate conjugate while the unconjugated form was predominant in liver tissue. In general, the blood contained the highest concentration of total residual test compound. Female blood levels of residual Fat 80'023 and residual levels in male livers tended to be increased when compared to residual levels in animals of the opposite sex.

Based on the histopathological incidence of hepatic necrosis, the LOEL is 300 ppm, the lowest dose tested.

Classification: CORE Supplementary. The study contained many technical errors, was incomplete and was poorly written (See Reviewers' Discussion and Interpretation of Study Results.)

A. MATERIALS:

1. Test Compound: Fat 80'023; description: white powder; batch No. 5.2.0211.0; purity: 99%.

2. Test Animals: Species: rat; strain: CrL:COBS CD(SD) BR; age: 37 days at study initiation; weight: males--155.5 to 161.1g, females--127.6 to 129.2 g; source: Charles River Breeding Laboratories, Kingston, N.Y.

6

B. STUDY DESIGN:

1. Animal Assignment: Following 2 weeks of acclimation and a physical and ocular examination, animals were assigned to the following test groups with a computerized randomization procedure:

Test Group	Dose in Diet (ppm)	Main Study (104 weeks) Males	Main Study (104 weeks) Females	Interim Sacrifice (52 weeks) Males	Interim Sacrifice (52 weeks) Females	Serial Sacrifice[a] (13, 26, and 78 weeks) Males	Serial Sacrifice[a] (13, 26, and 78 weeks) Females
1 Control[b]	0	60	60	20	20	15	15
2 Low (LDT)	300	60	60	10	10	15	15
3 Mid (MDT)	1000	60	60	10	10	15	15
4 High (HDT)	3000	60	60	10	10	15	15
5 Toxic Level	6000	--	--	20	20	--	--

[a]Animals were used for blood and tissue residue determinations (5 animals sacrificed/interval).

[b]Additional groups of 10 animals/sex were used for clinical biochemistry baseline data prior to study initiation.

The study authors indicated that even though the most probable route of exposure of the test material in humans is dermally, Fat 80'023 was administered orally since its metabolic profile is similar by either the oral or dermal route and a sufficient amount of the test material is absorbed following oral administration to cause systemic effects.

2. Diet Preparation: The test compound was mixed weekly with the basal diet at the appropriate test concentrations. The test diet was stored at room temperature. The purity and stability of the test compound and the test diet mixture were determined by the study sponsor. The stability and homogeneity of the test diet mixture were validated by the study laboratory; the concentration of Fat 80'023 in the test diet was determined on study day 1 and monthly thereafter by the study laboratory. The mean body weight and food consumption values were used to calculate the amount of test material needed to maintain the targeted dosage levels on a mg/kg body weight basis.

1

Results: Homogeneity results of the test diets are presented in Table 1a. The study authors considered the test compound to have been homogeneously distributed in the diet mixtures; dates of homogeneity analyses were not reported. The percent recovery of the low-dose sample was in error for the middle subsample; the corrected range was 98.0 to 131.3%, which is outside the level of acceptability. Other dose mixtures varied only 2 to 8% indicating homogeneity of the subsamples. Stability analyses indicated that the low and high doses of the test diet were stable at room temperature and at 6°C for up to 21 days.

Selected results from the analyses of the diet concentrations at selected months are presented in Table 1b. The mean recovery values of the diets ranged from 94 to 101.7%, 94 to 102.0%, 97 to 103.9%, and 97.4 to 105.2% for 300-, 1000-, 3000- and 6000-ppm diets, respectively. The study authors stated that no test substance was detected in the control feed; however, these control analyses were not presented.

3. Food and Water Consumption: Animals received food (certified Purina Rodent Chow No. 5002) and water ad libitum.

4. Statistics: The following procedures were utilized in analyzing the numerical data. Body weights, food consumption, and organ weights were analyzed using Bartlett's test for homogeneity of variance. Based on this outcome, data were analyzed using Dunnett's test or Behren's t test with Cochran's approximation. The analyses of clinical laboratory data were designed to test each parameter for trends existing between treatment groups. The survival distribution was determined using Kaplan-Meier estimates, the Gehan-Wilcoxon test, and the Mantel-Cox logrank test. Microscopic data were analyzed by Fisher's exact test. The method of Peto, Mantel's time-adjusted trend test, Tukey's exact test and the

4

TABLE 1a. Results of Homogeneity Analyses of Fat 80'023 in Rat Diets

Sample Source	Nominal Concentration (ppm)	Sample Concentration (ppm)	Percent Recovery (%)
Top	300	317	105.7
Middle	300	394	131.3 (98.1)[a]
Bottom	300	294[b]	98.0
Top	1000	934	93.4
Middle	1000	968	96.8
Bottom	1000	980	98.0
Top	3000	2820	94.0
Middle	3000	2977	99.2
Bottom	3000	3086	102.9
Top	6000	5962	99.4
Middle	6000	5953	99.2
Bottom	6000	6061	101.0

[a]Reported by the study authors to be 98.1%; recalculation of the data indicated the percent recovery to be 131.3%.

[b]Possible error in notation.

9

TABLE 1b. Dietary Analyses of Fat & Test Diets as Percent of Targeted Dose in a 2-Year Rat Study

Week	Dietary Level	Target Concentration (ppm)	Percent of Targeted Dose (%)[a]
1	300	302	100.6
	1000	961	96.1
	3000	2961	98.7
	6000	5992	99.9
25	300	305	101.7
	1000	1017	101.7
	3000	3068	102.3
	6000	6141	102.4
53	300	291	97.0
	1000	998	99.8
	3000	3087	102.9
	6000	6101	101.7
105	300	299	100.0
	1000	1003	100.3
	3000	3005	100.2
	6000	NA[b]	NA

[a]Range: Low of 94.3% for 300 ppm at week 61 to high of 105.2% for 6000 ppm at week 9.

[b]NA = Not analyzed.

10

logistic regression method of Dinse and Lagakos were used to evaluate tumor incidence.

5. Quality Assurance: A quality assurance statement was signed and dated April 28, 1986.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for signs of moribundity and mortality. Gross signs of toxicity were recorded monthly. Palpable mass observations were conducted monthly for study months 1 to 12 and biweekly thereafter.

Results: Mortality and percent survival were not significantly different between control and dosed rats of either sex (Table 2).

It was reported that there were no abnormal signs suggestive of a compound-related effect. Chromodacryorrhea, foot and tail sores, and alopecia were observed in control and dosed animals in the second year of study. The incidence of pollakiuria and unkempt appearance was slightly increased in animals receiving 3000 ppm.

Palpation of the skin was reported by the study authors to reveal a similar number of masses in dosed and control mice; individual data for females receiving 6000 ppm was not reported.

2. Body Weight: Rats were weighed at study initiation, weekly to week 12, and monthly thereafter.

Results: Table 3 presents mean body weight data at selected intervals. The mean body weights of males receiving 6000 ppm were significantly ($p<0.01$) decreased from study weeks 3 to 52 (reduction of 10.4%), the date of their terminal sacrifice. Males receiving 3000 ppm exhibited significantly ($p<0.01$) reduced body weights from study initiation to study week 6, although these differences were considered to have been due to initial

11

TABLE 2. Cumulative Mortality and Percent Survival in Rats Fed 80'023 for 104 Weeks

Dose Group (ppm)	Number of Animals		Number of Mortalities (percent mortality) at Week		
	Initial	Termination[a]	52[b]	78[c]	104[a]
			Males		
0	95	22	3 (4.6)	11 (18.3)	38 (63.3)
300	85	18	1 (1.5)	9 (15.0)	42 (70.0)
1000	85	28	(0.0)	8 (13.3)	32 (53.3)
3000	85	22	(3.6)	11 (18.3)	38 (63.3)
6000	20	19	(5.0)	---[d]	---
			Females		
0	95	20	2 (3.1)	11 (18.3)	40 (66.7)
300	85	19	1 (1.5)	21 (35.0)	41 (68.3)
1000	85	21	2 (3.1)	13 (21.6)	39 (65.0)
3000	85	18	3 (4.6)	14 (23.3)	42 (70.0)
6000	20	20	0 (0.0)	---[d]	---

[a]Based on 60 rats/sex/group of the main study.

[b]Percent mortality was based on 65 animals in all groups with the exception of those animals dosed at 6000 ppm; 20 animals/control group are sacrificed at week 52; 10 animals/dose/sex were sacrificed at week 52 for remaining groups.

[c]Percent mortality was based on 60 animals in all groups; 3 to 5 animals/dose/sex were sacrificed at week 78.

[d]Animals were sacrificed at 52 weeks.

17

TABLE 3. Representative Results of Mean Body Weights of Rats Fed 80'023 for 104 Weeks[a]

Dose Group (ppm)	Mean Body Weight (g ± S.E.) at Week					
	0	3	28	52	76	104
			Males			
0	161.1 ± 1.3	317.1 ± 2.4	644.4 ± 8.1	719.9 ± 11.8	797.8 ± 15.1	725.1 ± 36.2
300	157.3 ± 1.2	316.3 ± 2.4	638.3 ± 7.7	715.0 ± 9.8	785.8 ± 15.1	755.8 ± 34.5
1000	157.5 ± 1.2	309.9 ± 2.8	624.6 ± 7.7	705.4 ± 8.8	775.4 ± 14.0	711.4 ± 29.1
3000	155.5 ± 1.4**	303.8 ± 2.8**	619.9 ± 10.0	706.9 ± 11.9	787.3 ± 16.8	763.2 ± 34.5
6000	155.9 ± 2.4	295.8 ± 5.1**	568.3 ± 15.2**	645.1 ± 19.0**	---[b]	---
			Females			
0	128.6 ± 0.9	194.3 ± 1.7	329.4 ± 4.3	396.3 ± 6.8	472.9 ± 15.6	439.6 ± 25.9
300	127.6 ± 1.1	191.9 ± 1.9	328.2 ± 3.8	400.7 ± 6.7	476.1 ± 11.8	414.3 ± 27.3
1000	129.2 ± 1.1	191.4 ± 2.0	328.7 ± 5.1	408.1 ± 8.2	490.7 ± 14.1	442.2 ± 30.2
3000	128.0 ± 0.8	184.9 ± 1.5**	308.2 ± 3.6**	371.7 ± 5.8**	427.1 ± 10.9*	474.3 ± 22.3
6000	128.6 ± 2.0	177.8 ± 3.6**	270.1 ± 4.2**	305.5 ± 7.3**	---	---

[a]Based on rats of the main group.

[b]Animals sacrificed at 52 weeks.

*Significantly different from control values at $p < 0.05$.

**Significantly different from control values at $p < 0.01$.

13

differences in body weights between animals of this dose group and concurrent controls; body weight gain between these groups was comparable. Body weights of males receiving 1000 ppm were slightly but nonsignificantly decreased throughout the study. The mean body weights of females receiving 6000 ppm were significantly ($p<0.01$) decreased from study initiation to week 52 (reduction of 22.9%), the date of their terminal sacrifice. Females receiving 3000 ppm exhibited significantly ($p<0.01$, $p<0.05$) reduced body weights from study weeks 2 to 52 (reduction of 6.3%) and week 76 (reduction of 9.3%); body weights of these females were nonsignificantly decreased to study week 96. All other body weights of dosed males and females were similar to concurrent controls.

3. Food Consumption and Compound Intake: Consumption was determined and mean daily diet consumption was calculated at the same intervals as weighings.

Results: Table 4 presents food consumption data at selected intervals. Food consumption of males receiving 3000 and 6000 ppm Fat 80'023 was increased throughout the study when compared to concurrent controls; these increases were significant ($p<0.05$, $p<0.01$) in both dose groups from study weeks 3 to 48 and in rats receiving 3000 ppm from study weeks 56 to 80. Food consumption was slightly increased in this latter dose group from study weeks 80 to 104. Food consumption in females receiving 3000 ppm was slightly increased from study weeks 48 to 104 when compared to concurrent controls. Food consumption of other dosed females was similar to controls throughout the study with the exception of incidental changes at sporadic weekly intervals.

The average test compound intake in all dosed groups was reported by the study authors to decrease by 41 to 68% during study year 1 and 17 to 41% during study year 2 (Table 5); however, the proportionality between the average doses received by different groups remained approximately constant. Mean test compound intake as calculated by the reviewers was 15.3, 52.4, 168.0, and 415.0 mg/kg/day for males receiving 300-, 1000-, 3000-, and 6000-ppm concentrations, respectively. Mean test compound intake for females receiving 300-, 1000-, 3000-, and 6000-ppm concentrations was 20.0, 66.9, 217.4, and 519.3 mg/kg/day, respectively. It should be noted that the mean test compound intake of each dose group was calculated from the data on average daily dose, which was computed weekly from weeks 1 to 12 and monthly thereafter until study termination. In addition, rats dosed with 6000 ppm Fat 80'023 were sacrificed at week 52, which caused an inflated test compound mean intake due to the greater influence of values for young animals.

TABLE 4. Representative Food Consumption for Rats Fed Fat 80'023 for 104 Weeks

Dose Group (ppm)	Mean Food Consumption (g/day ± S.E.) at Week					
	1	3	6	48	64	104
			Males			
0	23.7 ± 0.2	26.7 ± 0.2	27.0 ± 0.3	28.3 ± 0.3	28.3 ± 0.4	23.0 ± 1.5
300	23.4 ± 0.2	27.0 ± 0.2	27.4 ± 0.3	28.3 ± 0.3	28.9 ± 0.4	23.5 ± 1.0
1000	23.8 ± 0.2	26.5 ± 0.4	27.9 ± 0.3	29.2 ± 0.4	28.8 ± 0.4	24.4 ± 1.3
3000	24.1 ± 0.3	28.0 ± 0.3**	28.8 ± 0.4**	30.2 ± 0.4**	30.1 ± 0.6*	27.0 ± 1.1
6000	23.4 ± 0.5	27.9 ± 0.4*	29.3 ± 0.6**	31.1 ± 0.8**	--[a]	--
			Females			
0	18.9 ± 0.2	19.4 ± 0.2	19.7 ± 0.2	21.3 ± 0.3	22.3 ± 0.4	17.5 ± 1.7
300	18.4 ± 0.2	19.9 ± 0.2	20.0 ± 0.2	21.8 ± 0.5	23.2 ± 0.4	15.4 ± 1.4
1000	18.5 ± 0.2	19.9 ± 0.2	20.4 ± 0.3	22.1 ± 0.3	23.2 ± 0.5	15.6 ± 1.3
3000	18.2 ± 0.2*	19.5 ± 0.2	19.9 ± 0.2	23.3 ± 0.3**	24.1 ± 0.5*	18.2 ± 1.0
6000	16.2 ± 0.3**	19.1 ± 0.5	19.1 ± 0.5	23.0 ± 0.7*	--	--

[a]Animals sacrificed at 52 weeks.

*Significantly different from control values at $p<0.05$ as evaluated by the study authors.

**Significantly different from control values at $p<0.01$ as evaluated by the study authors.

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TABLE 5. Calculated Average Intake of Fat 80'023 at Representative Weeks

Dietary Level in Feed (ppm)	Mean Daily Dose (mg/kg/day ± S.D.) at Week				
	1	12	52	80	104
			Males		
300	36.37 ± 2.10	15.51 ± 1.28 (42.6)[a]	11.99 ± 1.30 (33.0)	10.91 ± 1.39 (30.0)	9.31 ± 1.89 (25.6)
1000	129.27 ± 6.74	53.67 ± 2.86 (41.5)	40.49 ± 4.27 (31.3)	36.73 ± 5.99 (28.4)	33.57 ± 9.07 (26.0)
3000	400.19 ± 29.84	171.85 ± 9.10 (42.9)	127.15 ± 13.58 (31.8)	119.81 ± 25.89 (29.9)	107.22 ± 26.53 (26.8)
6000	784.84 ± 55.25	360.54 ± 16.71 (45.9)	246.91 ± 27.59 (31.5)	--[b]	--
			Females		
300	39.87 ± 3.25	21.71 ± 2.21 (54.5)	16.54 ± 2.58 (41.5)	14.24 ± 3.30 (35.7)	10.65 ± 4.01 (26.7)
1000	131.53 ± 9.60	73.70 ± 7.36 (56.0)	55.65 ± 8.07 (42.3)	45.51 ± 10.71 (34.6)	33.98 ± 11.76 (25.8)
3000	394.67 ± 27.72	235.50 ± 25.25 (60.0)	189.91 ± 24.80 (48.1)	151.20 ± 53.12 (38.3)	113.90 ± 25.47 (28.9)
6000	714.74 ± 49.96	453.63 ± 67.78 (63.5)	421.90 ± 69.57 (59.0)	--	--

[a]Number in parentheses is the percent mean daily dose compared to mean daily dose at week 1.

[b]Animals sacrificed at week 52.

007098

4. Ophthalmological: Ophthalmological examinations were performed during the acclimation period and study weeks 52 and 104.

Results: Ophthalmological findings (chromodacryorrhea, corneal stippling, corneal opacity, and lens and retinal abnormalities) were observed in control and dosed males and females and were considered to be normal age- and strain-related changes.

5. Hematology and Clinical Chemistry: Blood was collected following a 12-hour fasting period from the periorbital sinus prior to study initiation from a group of 10 rats/sex and at 13, 26, 52, 78, and 104 weeks from 20 rats/sex/group (assigned as clinical test animals) for hematology analyses. Clinical chemistry analyses were determined from 10 of the 20 rats/sex/group designed as clinical test animals. The CHECKED (X) parameters were examined:

a. Hematology:

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Reticulocyte count (RETIC)[a,b]
Red cell morphology
X Leukocyte differential count
X Mean corpuscular HGB (MCH)[c]
X Mean corpuscular HGB concentration (MCHC)[c]
X Mean corpuscular volume (MCV)
Coagulation: thromboplastin time (PT)
X Clotting time[a]

Results: Selected hematology results are presented in Tables 6 and 7. Erythrocyte counts (RBC), hemoglobin concentration (HGB), and hematocrit (HCT) were found to be slightly decreased in males fed 300, 1000, or 3000 ppm Fat 80'023 at 78 and 104 weeks (Table 6). These levels differed significantly ($p<0.05$, $p<0.01$) from concurrent controls at several intervals. Erythrocyte parameters of males fed 6000 ppm were similar to controls or only slightly decreased at weeks 13, 26, and 52 with the exception of a slight but significantly ($p<0.05$) decreased RBC count at week 13. Red cell indices (MCV, MCH, MCHC) were concurrently altered with erythrocytic parameters. RETICS were decreased in males but not females fed 6000 ppm. WBC counts were slightly but nonsignificantly increased

*Recommended by Subdivision F (October 1982) Guidelines.
[a]Not examined in animals bled prior to study initiation for baseline data.
[b]Evaluated in control and 6000-ppm groups only.
[c]Not consistently reported at all intervals.

17

TABLE 6. Hematology Parameters (± S.E.) at Selected Intervals in Male Rats Fed Fat 80'023 for 104 Weeks

Parameter/Week	Dietary Level (ppm) 0	300	1000	3000	6000[a]
Hemoglobin (g/dL)					
13	16.07 ± 0.18	16.17 ± 0.12	16.07 ± 0.11	16.06 ± 0.11	15.98 ± 0.11
26	16.16 ± 0.20	15.91 ± 0.15	16.20 ± 0.17	16.53 ± 0.14	16.25 ± 0.20
52	15.13 ± 0.23	15.08 ± 0.19	15.25 ± 0.16	15.50 ± 0.17	15.44 ± 0.16
78	15.27 ± 0.24	14.90 ± 0.14	14.49 ± 0.39	14.32 ± 0.53*	--
104	14.58 ± 0.34	13.45 ± 0.56	13.31 ± 0.53	13.71 ± 0.46	--
Erythrocytes (10^6/cu mm)					
13	8.376 ± 0.09	8.568 ± 0.11	8.347 ± 0.10	8.293 ± 0.09	8.166 ± 0.09*
26	8.374 ± 0.10	8.474 ± 0.11	8.425 ± 0.11	8.483 ± 0.08	8.103 ± 0.11
52	7.824 ± 0.13	7.757 ± 0.10	7.727 ± 0.10	7.847 ± 0.12	7.871 ± 0.07
78	8.039 ± 0.15	7.700 ± 0.11	7.368 ± 0.22*	7.175 ± 0.30**	--
104	7.277 ± 0.21	6.465 ± 0.31*	6.242 ± 0.26*	6.457 ± 0.24*	--
Hematocrit (%)					
13	47.9 ± 0.80	47.5 ± 0.61	46.9 ± 0.43	46.7 ± 0.42	47.2 ± 0.33
26	48.9 ± 0.54	47.7 ± 0.45	47.8 ± 0.51	48.5 ± 0.35	47.5 ± 0.58
52	46.2 ± 0.71	45.6 ± 0.41	45.3 ± 0.46	45.2 ± 0.59	45.1 ± 0.46
78	46.2 ± 0.76	43.9 ± 0.38	42.0 ± 1.05**	42.0 ± 1.40**	--
104	43.9 ± 0.85	40.4 ± 1.64	40.3 ± 1.41	41.1 ± 1.19	--
Clotting Time (Sec)					
13	119.2 ± 8.86	119.6 ± 7.43	130.6 ± 7.64	133.4 ± 7.50	143.6 ± 5.82*
26	114.2 ± 8.59	118.2 ± 6.90	113.1 ± 7.81	144.4 ± 7.99*	150.0 ± 10.08**
52	145.9 ± 17.06	197.5 ± 13.89*	198.8 ± 17.70*	191.0 ± 11.49*	196.9 ± 12.11*
78	152.0 ± 13.11	148.5 ± 8.52	174.5 ± 11.94	151.5 ± 9.90	--
104	112.2 ± 9.71	150.5 ± 11.80	134.3 ± 11.97	173.5 ± 8.21**	--

[a]Sacrificed at week 52.

*Significantly different from controls at $p<0.05$ as evaluated by the study authors.

**Significantly different from controls at $p<0.01$ as evaluated by the study authors.

18

TABLE 7. Hematology Parameters (± S.E.) at Selected Intervals in Female Rats Fed Fat 89-023 for 104 Weeks

Parameter/Week	Dietary Level (ppm) 0	300	1000	3000	6000[a]
Hemoglobin (g/dL)					
13	16.02 ± 0.11	16.05 ± 0.08	16.12 ± 0.12	16.12 ± 0.13	15.41 ± 0.15**
26	15.89 ± 0.15	15.82 ± 0.17	15.69 ± 0.12	16.20 ± 0.17	15.61 ± 0.14
52	15.10 ± 0.12	14.97 ± 0.22	14.66 ± 0.40	15.43 ± 0.19	15.01 ± 0.16
78	14.89 ± 0.15	14.65 ± 0.18	14.32 ± 0.43	14.85 ± 0.29	--
104	13.47 ± 0.49	13.74 ± 0.43	13.16 ± 0.46	14.51 ± 0.23	--
Erythrocytes (10^6/cu mm)					
13	7.780 ± 0.10	7.815 ± 0.10	7.602 ± 0.12	7.860 ± 0.09	7.698 ± 0.10
26	7.411 ± 0.12	7.381 ± 0.09	7.157 ± 0.14	7.476 ± 0.11	7.426 ± 0.08
52	7.225 ± 0.08	6.953 ± 0.11	6.812 ± 0.24	7.268 ± 0.12	7.234 ± 0.09
78	7.263 ± 0.10	6.997 ± 0.11	6.673 ± 0.20*	6.810 ± 0.18*	--
104	6.001 ± 0.22	6.217 ± 0.16	5.631 ± 0.25	6.523 ± 0.14	--
Hematocrit (%)					
13	46.6 ± 0.72	46.9 ± 0.57	45.9 ± 0.55	46.3 ± 0.44	45.1 ± 0.54*
26	47.4 ± 0.57	46.3 ± 0.47	46.2 ± 0.41	46.3 ± 0.49	45.5 ± 0.44**
52	44.7 ± 0.47	43.4 ± 0.57	42.0 ± 1.07	44.2 ± 0.52	42.4 ± 0.44*
78	43.8 ± 0.46	42.9 ± 0.56	41.6 ± 1.22	43.2 ± 0.70	--
104	39.8 ± 1.30	40.6 ± 1.12	39.0 ± 1.15	42.9 ± 0.68	--
Clotting Time (sec)					
26	94.6 ± 10.01	110.3 ± 8.73	134.5 ± 10.74	115.0 ± 11.65	121.6 ± 12.02
52	128.2 ± 9.54	149.3 ± 12.69	146.8 ± 13.74	156.8 ± 10.84	192.8 ± 10.06
78	140.1 ± 6.50	151.2 ± 9.13	155.7 ± 10.14	141.5 ± 9.46	--
104	144.9 ± 14.93	125.7 ± 9.77	143.3 ± 12.19	147.4 ± 6.15	--

[a]Sacrificed at week 52.

*Significantly different from controls at $p<0.05$ as evaluated by the study authors.

**Significantly different from controls at $p<0.01$ as evaluated by the study authors.

19

in dosed males at 78 and 104 weeks. Clotting time was sporadically increased in dosed males throughout the study. The study authors reported that red cell morphology appeared altered (increased incidence of polychromasia, hypochromia, poikilocytosis, anisocytosis, and targeting) in males receiving 1000 and 3000 ppm.

RBCs were slightly but significantly ($p < 0.05$) decreased in females fed 1000 and 3000 ppm Fat 80'023 at week 78 and nonsignificantly decreased at week 104; HGB and HCT levels of these animals were similar to concurrent controls throughout the study. Females fed 6000 ppm exhibited slightly but significantly ($p < 0.05$, $p < 0.01$) decreased HCT levels at weeks 13, 26, and 52; HGB and RBC counts of these animals were similar to concurrent controls from study initiation to sacrifice at week 52. Red cell indices (MCV, MCH, MCHC) were concurrently altered with erythrocytic parameters. The reductions in erythrocytic parameters and red cell indices exhibited in dosed males and females were within the range of values for those parameters in historical laboratory controls.[1]

b. Clinical Chemistry

	Electrolytes
X	Calcium+
	Chloride+
	Magnesium+
	Phosphorus+
	Potassium+
	Sodium+

	Enzymes
X	Alkaline phosphatase (ALP)
	Cholinesterase
	Creatinine phosphokinase+
	Lactic acid dehydrogenase
X	Serum alanine aminotransferase (SGPT)+
X	Serum aspartate aminotransferase (SGOT)+
X	Gamma glutamyltransferase (GGT)

	Other
X	Albumin+
X	Albumin/globulin ratio
	Blood creatinine+
X	Blood urea nitrogen+
X	Cholesterol+
	Globulins
X	Glucose+
X	Total bilirubin+
	Direct bilirubin
X	Total protein+
X	Triglycerides

[1]Hazleton Laboratories. 1984. Hematology Reference Ranges --Sprague-Dawley Rats. In: Representative Historical Control Data for Rats and Mice.
+Recommended by Subdivision F (October 1982) Guidelines.

30

Results: Selected clinical biochemistry results are presented in Tables 8 and 9. Mean SGPT levels were found to be significantly ($p < 0.05$) increased in males fed 3000 ppm at 78 weeks when compared to concurrent controls. There were nonsignificant increases at other intervals. SGOT was also significantly ($p < 0.05$) increased at 78 weeks in males but there were significant decreases at 13 ($p < 0.01$) and 52 ($p < 0.05$) weeks and essentially no change at 104 weeks. Even though these increases were dose related, they were not consistent at other test intervals between sexes. Blood-urea-nitrogen (BUN) levels were slightly but significantly ($p < 0.05$, $p < 0.01$) increased at 13 and 26 weeks in females fed 6000 ppm and in all dosed females at 52 weeks. These values were generally similar to control values at 78 weeks; BUN levels were not increased in dose males.

Significant ($p < 0.05$, $p < 0.01$) decreases were found in total bilirubin, triglycerides, and total protein parameters in dosed males and SGOT, glucose, triglycerides, and total bilirubin in dosed females. Many of these decreases were dose related and consistent over time; generally, these decreased levels recovered prior to study termination. These decreased parameters were considered by the study reviewers to be compound related even though the level of decrease generally remained within the range of values for that parameter in historical laboratory controls.[2] Even though these changes were not biologically significant, they were considered to be the result of toxic effects of the test compound.

6. Urinalysis: Urine was collected from 10 fasted rats/sex/dose at 13, 26, 52, 78, and 104 weeks. The CHECKED (X) parameters were examined:

	Appearance*	X	Glucose*
	Volume*	X	Ketones
X	Specific Gravity*	X	Bilirubin*
X	pH	X	Blood*
	Sediment (microscopic)*		Nitrate
X	Protein*		Urobilinogen

*Recommended by Subdivision F (October 1982) Guidelines.
[2]Hazleton Laboratories. 1984. Clinical Chemistry Reference Ranges--Sprague-Dawley Rats. In: Representative Historical Control Data for Rats and Mice.

21

TABLE 8. Selected Clinical Chemistry Data (± S.E.) for Male Rats Fed Far 80'023 for 104 Weeks

007098

Parameter/Week	Dietary Level (ppm) 0	300	1000	3000	6000[a]
SGPT (U/L)					
13	27.0 ± 1.23	28.1 ± 2.19	26.5 ± 1.66	26.0 ± 1.26	25.9 ± 1.64
26	34.6 ± 2.05	34.0 ± 1.65	44.2 ± 7.65	38.1 ± 2.82	31.3 ± 1.60
52	34.5 ± 5.78	28.3 ± 1.45	50.5 ± 9.65	53.3 ± 12.40	40.3 ± 6.22
78	36.9 ± 4.04	37.4 ± 3.95	47.4 ± 10.60	68.1 ± 10.57**	--
104	33.5 ± 4.10	46.3 ± 13.37	36.9 ± 6.74	40.3 ± 10.09	--
SGOT (U/L)					
13	112.2 ± 5.04	93.2 ± 6.78*	89.3 ± 7.10**	74.5 ± 2.61**	73.9 ± 3.66**
26	65.8 ± 4.72	86.7 ± 7.03	85.2 ± 8.13	88.1 ± 11.52	63.6 ± 4.20
52	108.3 ± 6.61	96.1 ± 5.90	97.1 ± 7.56	85.1 ± 12.41*	83.6 ± 4.59*
78	102.9 ± 9.23	112.1 ± 11.26	117.3 ± 14.18	150.0 ± 14.04*	--
104	104.0 ± 9.33	118.8 ± 21.53	105.9 ± 8.86	98.4 ± 10.34	--
JUN (mg/dL)					
13	12.7 ± 0.65	13.8 ± 0.39	13.0 ± 0.39	13.0 ± 0.33	14.1 ± 0.59
26	12.6 ± 0.45	14.5 ± 0.56	13.7 ± 0.56	14.3 ± 0.65	14.2 ± 0.51
52	13.4 ± 0.52	14.5 ± 0.48	12.8 ± 0.61	13.4 ± 0.78	11.2 ± 0.44**
78	13.8 ± 0.99	19.1 ± 3.37	17.8 ± 1.48	14.5 ± 0.22	--
104	20.8 ± 3.78	31.0 ± 10.54	23.1 ± 7.89	15.9 ± 1.86	--
Triglycerides (mg/dL)					
13	96.1 ± 7.06	79.5 ± 11.74	151.7 ± 43.82	47.9 ± 4.32	29.3 ± 2.58*
26	114.3 ± 9.81	118.7 ± 14.13	207.1 ± 40.11	81.4 ± 14.81	57.3 ± 10.29*
52	179.0 ± 28.27	276.5 ± 85.14	366.0 ± 111.13	233.0 ± 132.62	78.2 ± 9.15[b]
78	298.3 ± 74.66	419.4 ± 113.44	446.0 ± 155.08	157.9 ± 21.60	--
104	292.6 ± 89.56	217.4 ± 29.24	187.8 ± 39.86	181.9 ± 31.89	--
Total Protein (gm/dL)					
13	6.77 ± 0.11	6.55 ± 0.08	6.74 ± 0.13	6.29 ± 0.08**	6.27 ± 0.09**
26	6.65 ± 0.11	6.59 ± 0.08	7.14 ± 0.11	6.47 ± 0.10	6.49 ± 0.08
52	7.09 ± 0.15	6.94 ± 0.10	7.17 ± 0.12	6.86 ± 0.26	6.79 ± 0.09
78	7.84 ± 0.17	7.78 ± 0.10	7.96 ± 0.18	7.31 ± 0.12*	--
104	7.02 ± 0.23	7.30 ± 0.15	7.09 ± 0.17	6.77 ± 0.21	--
Albumin/Globuin Ratio					
13	1.51 ± 0.05	1.56 ± 0.03	1.53 ± 0.06	1.59 ± 0.04	1.64 ± 0.02*
26	1.69 ± 0.08	1.67 ± 0.05	1.55 ± 0.07	1.73 ± 0.10	1.91 ± 0.08*
52	1.33 ± 0.08	1.17 ± 0.03	1.19 ± 0.06	1.32 ± 0.11	1.51 ± 0.04*
78	1.17 ± 0.06	1.03 ± 0.05	1.03 ± 0.05	1.24 ± 0.06	--
104	1.04 ± 0.06	0.86 ± 0.04	0.94 ± 0.05	1.06 ± 0.09	--
Total Bilirubin (mg/dL)					
13	0.371 ± 0.02	0.289 ± 0.03*	0.249 ± 0.03**	0.214 ± 0.02**	0.177 ± 0.01**
26	0.171 ± 0.02	0.205 ± 0.02	0.216 ± 0.02	0.245 ± 0.02	0.184 ± 0.02
52	0.415 ± 0.04	0.327 ± 0.03	0.375 ± 0.06	0.306 ± 0.06	0.173 ± 0.03**
78	0.318 ± 0.04	0.387 ± 0.06	0.371 ± 0.03	0.322 ± 0.03	--
104	0.390 ± 0.03	0.324 ± 0.03	0.377 ± 0.05	0.311 ± 0.03	--

[a]Sacrificed at week 52.

[b]Reevaluated by the reviewers using Bartlett's test of homogeneity, the Wilcoxon logrank test, and Dunnett's test and found to be significantly different from controls at $p < 0.05$.

*Significantly different from controls at $p<0.05$ as evaluated by the study authors.

**Significantly different from controls at $p<0.01$ as evaluated by the study authors.

TABLE 9. Selected Clinical Chemistry Data (± S.E.) for Female Rats Fed Fat 80'023 for 104 Weeks

Parameter/Week	Dietary Level (ppm) 0	300	1000	3000	6000[a]
SGPT (U/L)					
13	31.4 ± 2.70	30.3 ± 1.28	31.5 ± 2.69	26.9 ± 1.58	26.1 ± 2.67
26	47.4 ± 8.52	33.1 ± 4.47	48.9 ± 9.10	37.9 ± 5.14	18.5 ± 1.19**
52	33.6 ± 3.33	44.2 ± 8.04	40.1 ± 4.49	39.3 ± 5.03	29.0 ± 2.47
78	38.9 ± 3.06	35.8 ± 3.12	40.7 ± 6.14	36.3 ± 3.14	--
104	47.3 ± 9.40	30.1 ± 4.14	33.7 ± 3.35	40.6 ± 4.75	--
Glucose (mg/dL)					
13	104.9 ± 2.60	111.0 ± 4.10	101.6 ± 3.89	87.3 ± 3.19**	89.1 ± 6.51**
26	119.4 ± 6.30	114.8 ± 3.14	124.3 ± 5.22	111.8 ± 4.33	104.5 ± 4.48*
52	105.1 ± 5.25	115.2 ± 8.61	128.2 ± 5.21	117.8 ± 3.09	108.0 ± 6.57
78	123.8 ± 8.58	128.0 ± 4.94	114.4 ± 7.74	111.8 ± 6.74	--
104	101.2 ± 11.06	107.9 ± 11.34	110.5 ± 12.86	127.8 ± 5.32	--
BUN (mg/dL)					
13	16.1 ± 0.82	18.1 ± 0.43	18.1 ± 0.89	18.3 ± 0.70*	19.0 ± 0.83**
26	14.2 ± 0.59	15.2 ± 0.39	17.1 ± 0.98	15.6 ± 0.52	16.2 ± 0.81*
52	10.3 ± 0.34	13.2 ± 0.63**	14.8 ± 0.68**	12.8 ± 0.81**	14.0 ± 0.89**
78	13.1 ± 1.11	13.0 ± 0.67	17.0 ± 2.65	12.6 ± 0.58	--
104	18.1 ± 1.82	20.3 ± 5.17	12.9 ± 0.75	11.2 ± 0.39*	
SGOT (U/L)					
13	87.5 ± 4.68	82.1 ± 4.02	78.1 ± 4.43	78.8 ± 2.99	72.0 ± 3.24**
26	102.6 ± 10.0	74.2 ± 5.37	96.1 ± 11.96	99.5 ± 9.96	72.2 ± 3.48
52	83.0 ± 6.18	83.1 ± 14.30	94.8 ± 7.38	78.2 ± 5.68	81.4 ± 4.29
78	101.5 ± 4.94	97.1 ± 8.12	105.2 ± 15.12	104.5 ± 11.46	--
104	158.9 ± 21.17	129.6 ± 18.92	98.6 ± 10.67**	102.7 ± 6.11**	--
Triglycerides (mg/dL)					
13	81.7 ± 13.84	54.9 ± 6.31*	47.4 ± 4.41**	39.2 ± 5.10**	36.2 ± 2.08**
26	114.8 ± 18.94	109.8 ± 12.62	108.7 ± 20.36	85.1 ± 12.78	44.7 ± 2.43**
52	164.1 ± 33.71	159.2 ± 37.41	169.7 ± 39.08	78.3 ± 15.10	37.5 ± 1.99**
78	288.2 ± 56.05	271.5 ± 53.97	324.9 ± 67.38	176.8 ± 43.95	--
104	210.8 ± 65.46	181.4 ± 37.72	647.4 ± 485.01[b]	213.6 ± 71.71	--
Total Bilirubin (mg/dL)					
13	0.304 ± 0.02	0.212 ± 0.01	0.267 ± 0.02	0.303 ± 0.01	0.191 ± 0.03**
26	0.377 ± 0.02	0.224 ± 0.01**	0.224 ± 0.01**	0.251 ± 0.03**	0.165 ± 0.02**
52	0.318 ± 0.02	0.310 ± 0.03	0.201 ± 0.02**	0.190 ± 0.02**	--
78	0.350 ± 0.04	0.321 ± 0.03	0.358 ± 0.03	0.312 ± 0.02	--
104	0.337 ± 0.03	0.290 ± 0.01	0.287 ± 0.03	0.317 ± 0.02	--

[a]Sacrificed at week 52.

[b]Abnormal group value due to one female (No. 599) with turbid lipemic serum, which may have interferred with assaying method; if this animal is excluded, the group value is 164.4 ± 49.87 mg/dL.

*Significantly different from controls at $p<0.05$ as evaluated by the study authors.

**Significantly different from controls at $p<0.01$ as evaluated by the study authors.

23

Results: Slight changes were found in the urinary parameters (specific gravity, pH, urinary protein) of males and females receiving 1000, 3000, and 6000 ppm; however, these changes were considered sporadic and were not accompanied by any significant gross or microscopic renal pathology.

7. Residue Analysis: Blood (2 mL minimum) and tissue samples (0.5 g kidney, 3 g liver, 0.5 g spleen, 0.5 g heart, 1 g brain, 1 g skeletal muscle and 1 g retroperitoneal fat) were collected from five designated rats/sex/dose at 13, 26, and 78 (3 to 5 rats/sex/dose) weeks, all interim animals sacrificed at 52 weeks and 50% of the surviving rats at 104 weeks. Samples were sent to the sponsor for residue determinations of free and conjugated Fat 80'023 content. Residue determinations were performed at week 52 only for rats receiving 6000 ppm.

Results: Residue levels of Fat 80'023 found in the blood of dosed animals were proportional to the feeding levels with the largest amount found as the sulfate conjugate (Table 10). Less than 1% existed in the unconjugated form. Females tended to have higher levels of sulfate conjugate at each testing interval; levels remained high until 104 weeks, at which time they were found to decrease. The blood of dosed males exhibited a gradual decrease in sulfate conjugate over the duration of the study. Blood generally contained the highest concentrations of total Fat 80'023 when compared to liver and kidney.

Residue levels of Fat 80'023 found in the kidneys of dosed animals were also proportional to the feeding levels with the largest amount found as the sulfate conjugate (Table 11). Residue levels of the test compound in the kidney appeared to increase over the duration of the study to week 104 when levels appeared slightly decreased. Generally, residue levels were similar in dosed males and females with the exception of slightly increased levels in females fed 3000 ppm at week 104. Unexpected increases were exhibited in conjugated and unconjugated levels of Fat 80'023 in male and female rats dosed with 3000 ppm at 78 weeks; the study authors considered these increases to be a reflection of technical errors and did not regard these values to be an accurate representation of the kidney content of Fat 80'023. The kidney samples of control animals were found to exhibit slight residue levels of the test material at 13, 26, and 52 weeks; these findings were considered to be the result of contamination of the samples following animal sacrifice and were not the result of improper diets.

34

TABLE 10. Mean Residue Levels of Unconjugated and Conjugated Fat 80'023 in the Blood of Rats Fed the Test Compound for 104 Weeks

Week	Dietary Level (ppm)	Fat 80'023 Content (µg/mL ± SD)							
		Males				Females			
		Unconjugated	Glucuronide Conjugate	Sulfate Conjugate	Total (Acid)	Unconjugated	Glucuronide Conjugate	Sulfate Conjugate	Total (acid)
13[a]	0	0.01 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	300	0.91 ± 0.71	5.57 ± 2.41	12.45 ± 2.15	18.93 ± 4.79	0.62 ± 0.36	3.19 ± 1.47	12.79 ± 3.09	16.88 ± 4.31
	1000	0.52 ± 0.22	11.22 ± 4.24	33.74 ± 10.31	45.48 ± 12.50	0.30 ± 0.08	9.04 ± 4.00	41.11 ± 4.81	50.45 ± 5.16
	3000	0.75 ± 0.33	17.10 ± 5.45	78.38 ± 17.09	96.22 ± 20.39	0.69 ± 0.28	20.91 ± 5.68	81.70 ± 22.79	103.50 ± 24.96
	6000[b]	---	---	---	---	---	---	---	---
52[c]	0	0.00 ± 0.00	NA[d]	NA	0.00 ± 0.00	0.00 ± 0.00	NA	NA	0.00 ± 0.00
	300	0.11 ± 0.06	7.15 ± 3.27	6.36 ± 3.11	13.63 ± 5.63	0.06 ± 0.04	5.78 ± 3.25	11.77 ± 5.05	17.60 ± 8.08
	1000	0.21 ± 0.10	12.38 ± 3.68	21.80 ± 7.04	34.39 ± 7.91	0.17 ± 0.08	9.70 ± 4.57	34.27 ± 10.46	44.14 ± 14.21
	3000	0.30 ± 0.07	16.54 ± 4.21	58.39 ± 27.92	75.23 ± 27.79	0.44 ± 0.11	20.52 ± 4.56	85.70 ± 18.14	106.66 ± 20.58
	6000	1.10 ± 0.25	31.68 ± 8.04	101.71 ± 16.87	134.48 ± 20.85	1.58 ± 0.48	25.00 ± 11.01	143.04 ± 37.49	169.62 ± 38.49
78[e]	0	0.00 ± 0.00	NA	NA	0.00 ± 0.00	0.00 ± 0.00	NA	NA	0.00 ± 0.00
	300	0.25 ± 0.19	4.50 ± 1.87	5.13 ± 2.45	9.87 ± 4.04	0.16 ± 0.09	6.10 ± 2.86	14.25 ± 4.32	20.51 ± 7.18
	1000	0.18 ± 0.03	15.96 ± 4.71	18.05 ± 4.72	34.19 ± 9.11	0.29 ± 0.33	16.63 ± 11.26	41.87 ± 10.33	58.79 ± 19.82
	3000	0.45 ± 0.17	20.68 ± 6.84	57.86 ± 25.32	78.99 ± 30.04	0.37 ± 0.10	16.28 ± 3.44	101.50 ± 18.13	118.16 ± 19.56
	6000[b]	---	---	---	---	---	---	---	---
104[f]	0	0.00 ± 0.00	NA	NA	0.01 ± 0.01	0.00 ± 0.01	NA	NA	0.00 ± 0.01
	300	0.05 ± 0.02	3.33 ± 1.33	3.24 ± 1.06	6.61 ± 2.12	0.04 ± 0.03	4.28 ± 4.33	10.56 ± 5.66	16.56 ± 11.27
	1000	0.41 ± 0.31	10.84 ± 3.40	15.84 ± 7.57	27.06 ± 9.85	0.15 ± 0.12	7.70 ± 5.63	18.43 ± 14.70	26.28 ± 19.93
	3000	0.46 ± 0.39	20.31 ± 10.82	33.80 ± 13.95	54.24 ± 16.51	0.32 ± 0.12	18.22 ± 5.8[illegible]	68.06 ± 22.06	86.60 ± 27.28

[a]Based on five rats/sex/dose.

[b]Determination performed at week 52 only.

[c]Based on 20 animals/sex in control group, 10 animals/sex in 300-, 1000-, and 3000-ppm dose groups, and 19 males and 20 females in 6000-ppm dose group.

[d]NA = not analyzed.

[e]Based on three to five rats/sex/dose.

[f]Based on 9 to 14 males/dose and 8 to 10 females/dose.

007098

TABLE 11. Mean Residue Levels of Unconjugated and Conjugated Fat 80'023 in the Kidneys of Rats Fed the Test Compound for 104 Weeks

Week	Dietary Level (ppm)	FAT 80'023 (µg/g) Males: Unconjugated	Males: Glucuronide Conjugate	Males: Sulfate Conjugate	Males: Total (Acid)	Females: Unconjugated	Females: Glucoronide Conjugate	Females: Sulfate Conjugate	Females: Total (Acid)
13[a]	0[b]	0.05 ± 0.06	0.00 ± 0.00	0.01 ± 0.02	0.06 ± 0.06	0.29 ± 0.17	0.02 ± 0.03	0.05 ± 0.04	0.34 ± 0.16
	300	6.06 ± 2.40	0.81 ± 0.84	4.52 ± 1.30	11.29 ± 2.92	2.52 ± 0.90	1.02 ± 0.86	4.44 ± 2.67	7.97 ± 3.25
	1000	9.86 ± 3.33	2.60 ± 2.52	9.12 ± 2.64	21.58 ± 6.93	5.07 ± 1.16	2.49 ± 1.90	11.31 ± 3.48	18.87 ± 5.27
	3000	17.89 ± 2.01	5.45 ± 5.36	29.56 ± 5.46	52.32 ± 11.11	11.36 ± 2.99	5.95 ± 4.02	33.60 ± 13.20	50.86 ± 14.68
	6000[c]	---	---	---	---	---	---	---	---
52[d]	0	0.01 ± 0.02	NA	NA	0.02 ± 0.03	0.20 ± 1.27	NA	NA	0.01 ± 0.02
	300	2.96 ± 1.38	7.27 ± 2.80	6.20 ± 2.46	16.43 ± 5.03	1.25 ± 0.36	3.62 ± 0.56	6.31 ± 1.67	11.19 ± 2.00
	1000	10.79 ± 3.55	11.20 ± 4.07	13.74 ± 4.23	35.73 ± 8.55	8.07 ± 2.62	10.80 ± 4.86	15.82 ± 6.05	34.69 ± 10.81
	3000	13.74 ± 4.60	26.62 ± 10.79	37.24 ± 10.21	77.60 ± 22.41	5.36 ± 2.02	26.86 ± 8.57	28.35 ± 13.33	60.58 ± 20.34
	6000	16.09 ± 9.12	40.95 ± 16.05	37.71 ± 16.79	93.38 ± 32.18	14.33 ± 6.89	30.48 ± 8.97	76.43 ± 19.97	121.24 ± 25.64
78[e]	0	0.00 ± 0.00	NA	NA	0.01 ± 0.01	0.00 ± 0.00	NA	NA	0.00 ± 0.01
	300	1.53 ± 0.52	3.78 ± 0.69	6.19 ± 4.70	11.49 ± 5.80	1.03 ± 0.51	3.60 ± 1.64	6.65 ± 3.72	11.28 ± 5.64
	1000	5.14 ± 3.34	13.46 ± 1.67	16.38 ± 9.92	34.92 ± 14.09	3.88 ± 1.72	13.70 ± 8.66	21.19 ± 7.18	38.77 ± 16.36
	3000[f]	45.42 ± 8.86	70.00 ± 16.37	125.25 ± 16.23	240.68 ± 12.97	25.29 ± 16.82	63.69 ± 10.07	123.04 ± 20.28	212.02 ± 43.09
	6000[c]	---	---	---	---	---	---	---	---
104[g]	0	0.00 ± 0.01	NA	NA	0.03 ± 0.02	0.01 ± 0.02	NA	NA	0.06 ± 0.07
	300	1.59 ± 0.08	3.79 ± 2.24	6.90 ± 4.76	12.28 ± 7.42	0.97 ± 0.39	3.34 ± 1.68	5.58 ± 3.62	9.89 ± 5.51
	1000	6.09 ± 2.38	9.85 ± 3.38	18.96 ± 8.15	34.89 ± 19.13	4.09 ± 2.89	8.34 ± 5.46	17.87 ± 10.38	30.86 ± 22.82
	3000	13.00 ± 9.02	19.41 ± 8.74	26.15 ± 12.84	58.35 ± 29.55	7.32 ± 4.01	27.81 ± 8.30	51.87 ± 19.15	86.40 ± 25.31
	6000[c]	---	---	---	---	---	---	---	---

[a]Based on five animals/sex/dose.

[b]Residual Fat 80'023 was found in the control samples at 13, 26, and 52 weeks.

[c]Determinations performed at week 52 only.

[d]Based on 20 animals/sex in control group; 10 animals/sex in 300-, 1000-, and 3000-ppm dose groups; and 19 males and 20 females in the 6000-ppm dose group.

[e]Based on three to five animals/sex/dose.

[f]Technical errors involved in resulting high values for males and females at 78 weeks.

[g]Based on 9 to 14 animals/sex/dose.

007098

As with blood and kidney residues, the residue levels of Fat 80'023 found in the livers of dosed males and females were proportional to the dose levels; however, the predominant amount of residual Fat 80'023 was found in the unconjugated form (Table 12). Male livers generally contained higher residual levels; residual levels tended to decline at 104 weeks in males and females. An increased level of the glucuronide conjugate at 52 weeks in males fed 6000 ppm was reported to be a technical error. As with kidney samples, the liver samples of control animals were found to exhibit slight residue levels of the test material at 13, 26, and 52 weeks.

Results of analyses for spleen, heart, brain, skeletal muscle, and retroperitoneal fat were not reported.

8. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

Digestive System	Cardiovasc./Hemat.	Neurologic
Tongue	X Aorta+	XX Brain+
X Salivary glands+	XX Heart+	X Peripheral nerve (sciatic nerve)+
X Esophagus+	X Bone marrow (sternum)+	X Spinal cord (3 levels)
X Stomach+	X Lymph nodes+	X Pituitary+
X Duodenum+	X Spleen+	X Eyes (optic nerve)+
X Jejunum+	X Thymus+	
X Ileum+		
X Cecum+		
X Colon+		
X Rectum		
XX Liver+	Urogenital	Glandular
Gallbladder+	XX Kidneys+	XX Adrenals+
X Pancreas+	X Urinary bladder+	Lacrimal gland+
	XX Testes+	X Mammary gland+
Respiratory	X Epididymides	X Thyroids+
X Trachea+	X Prostate	X Parathyroids+
X Lung+	Seminal vesicle	Harderian glands
	XX Ovaries	
	X Uterus+	Other
	X Cervix	X Bone [vertebra/ femur w/marrow]+
		X Skeletal muscle+
		X Skin
		X All gross lesions and masses

+Recommended by Subdivision F (October 1982) Guidelines.

27

TABLE 12. Mean Residue Levels of Unconjugated and Conjugated Fat 80'023 in the Liver of Rats Fed the Test Compound for 104 Weeks

Week	Dietary Level (ppm)	Males: Fat 80'023 Content (µg/ml ± SD)				Females: Fat 80'023 Content (µg/ml ± SD)			
		Unconjugated	Glucuronide Conjugate	Sulfate Conjugate	Total (Acid)	Unconjugated	Glucuronide Conjugate	Sulfate Conjugate	Total (acid)
13[a]	0[b]	0.05 ± 0.02	0.00 ± 0.01	0.00 ± 0.00	0.05 ± 0.03	0.16 ± 0.13	0.00 ± 0.00	0.01 ± 0.01	0.15 ± 0.12
	300	11.87 ± 2.27	0.68 ± 1.10	0.45 ± 0.53	12.23 ± 2.73	6.56 ± 2.10	0.78 ± 1.37	0.21 ± 0.27	6.54 ± 1.97
	1000	19.14 ± 11.88	0.93 ± 1.21	5.61 ± 5.71	22.96 ± 13.44	18.11 ± 5.88	0.76 ± 1.00	3.87 ± 2.51	21.02 ± 5.72
	3000	69.06 ± 10.39	7.03 ± 5.56	12.89 ± 9.15	87.89 ± 11.38	47.38 ± 8.23	2.03 ± 3.07	11.07 ± 4.59	57.77 ± 13.25
	6000[c]	---	---	---	---	---	---	---	---
52[d]	0	0.02 ± 0.09	NA	NA	0.01 ± 0.05	0.01 ± 0.02	NA	NA	0.01 ± 0.02
	300	9.21 ± 3.36	0.26 ± 0.23	0.41 ± 0.32	9.56 ± 3.51	6.73 ± 2.33	1.28 ± 0.96	1.66 ± 1.11	9.45 ± 3.10
	1000	19.24 ± 3.73	5.05 ± 3.12	1.95 ± 1.52	26.19 ± 6.39	15.36 ± 3.82	0.54 ± 1.23	1.14 ± 1.36	16.71 ± 4.10
	3000	50.12 ± 7.61	10.79 ± 7.17	17.08 ± 9.27	77.99 ± 17.77	41.64 ± 10.59	6.60 ± 7.02	19.45 ± 9.51	67.08 ± 15.63
	6000	76.17 ± 23.40	33.24 ± 63.11[e]	24.69 ± 11.69	120.02 ± 25.82	72.60 ± 13.56	7.83 ± 7.56	36.84 ± 12.28	114.83 ± 20.88
78[f]	0	0.00 ± 0.01	NA	NA	0.02 ± 0.02	0.00 ± 0.00	NA	NA	0.02 ± 0.01
	300	6.82 ± 2.13	0.05 ± 0.10	0.64 ± 0.53	7.15 ± 1.95	6.92 ± 1.68	0.30 ± 0.39	0.90 ± 0.72	7.91 ± 2.54
	1000	12.86 ± 2.99	0.36 ± 0.41	0.83 ± 0.80	13.96 ± 3.68	16.33 ± 5.22	0.86 ± 0.84	2.01 ± 0.92	18.98 ± 5.17
	3000	47.28 ± 8.55	8.09 ± 3.40	6.70 ± 8.96	60.80 ± 21.05	27.55 ± 7.69	8.66 ± 3.43	9.09 ± 5.30	45.24 ± 10.57
	6000	---	---	---	---	---	---	---	---
104[g]	0	0.00 ± 0.01	NA	NA	0.01 ± 0.02	0.01 ± 0.03	NA	NA	0.12 ± 0.30
	300	4.85 ± 1.53	0.20 ± 0.21	0.80 ± 0.41	5.82 ± 1.76	5.19 ± 2.38	0.52 ± 0.46	0.68 ± 0.55	6.37 ± 3.00
	1000	16.65 ± 6.80	1.89 ± 0.95	4.00 ± 2.66	22.51 ± 9.03	7.93 ± 4.59	0.84 ± 0.83	1.37 ± 1.38	9.96 ± 5.78
	3000	31.48 ± 8.97	5.26 ± 2.56	9.50 ± 4.12	46.24 ± 13.20	21.67 ± 9.05	7.28 ± 3.79	8.83 ± 5.25	36.95 ± 15.27

[a] Based on five animals/sex/dose.

[b] Residual Fat 80'023 was found in control samples at 13, 26, and 52 weeks.

[c] Determinations were performed at week 52 only.

[d] Based on 20 animals/sex in control group; 10 animals/sex in 300-, 1000-, 3000-ppm dose group; and 19 males and 20 females in the 6000-ppm dose group.

[e] High variation due to suspected technical error.

[f] Based on three to five animals/sex/dose.

[g] Based on 9 to 14 animals/sex/dose.

007098

At 52 weeks and terminal sacrifice, all tissues for control and high-dose (6000 ppm at 52 weeks, 3000 ppm at 104 weeks) males and females were examined histologically. The liver, pancreas, and gross lesions were examined histologically for low- and mid-dose rats at 52 weeks; the liver, kidney, lung, and gross lesions were examined for low- and mid-dose rats at 104 weeks. Only the liver and gross lesions were examined histologically for all dosed rats at 13, 26 and 78 weeks. All tissues were examined from animals dying during the study or sacrificed moribund. One female receiving 300 ppm (animal No. 573) died on the day of scheduled sacrifice (day 184); the liver was reported to be the only organ examined histologically for this animal.

Results:

a. Organ Weights: Decreased liver weights of males fed 3000 and 6000 ppm at week 52 were considered a reflection of body weight changes at that study interval since weights appeared similar to concurrent controls in males fed 3000 ppm at 78 and 104 weeks; absolute and relative (organ to body weight ratio) liver weights of females fed 3000 ppm were found to be slightly decreased throughout the study (Table 13). Other changes in organ weights (spleen, adrenals, ovaries) of dosed males and females were considered to be a reflection of body weight changes at those study intervals and were not considered to be of toxicological significance.

b. Gross Pathology: There were no compound-related increases in any gross lesion in dosed animals when compared to concurrent controls.

c. Microscopic Pathology:

1) Nonneoplastic: Table 14 summarizes nonneoplastic findings in the liver, pancreas, kidney, and lung of dosed and control males and females. The incidence of toxic liver changes [cytoplasmic inclusions (ring-shaped or spherical structures) of hepatocytes and centrilobular hepatocytic hypertrophy (enlargement to 1.3 times normal size with flocculent eosinophilic cytoplasm)] in males fed 3000 and 6000 ppm was found to be increased at 13, 52, and 78 weeks when compared to concurrent controls; these increases (incidence of 4/5 for cytoplasmic inclusions and 5/5 for hepatocellular hypertrophy) were found to be significant at 13 weeks for males fed 3000 ppm ($p<0.05$) and 52 weeks for males fed 6000 ppm ($p<0.05$, $p<0.001$).

59

TABLE 13. Absolute and Relative Mean Liver Weights of Rats Fat 80'023 for 104 Weeks

Dose Group (ppm)	Mean Liver Weights at Week 26 Absolute (g ± S.E.)	26 Relative (%)	52 Absolute (g ± S.E.)	52 Relative (%)	78 Absolute (g ± S.E.)	78 Relative (%)	104 Absolute (g ± S.E.)	104 Relative (%)
Males								
0	22.54 ± 1.91	3.497	25.84 ± 1.18	3.448	24.11 ± 2.94	3.163	21.57 ± 0.89	2.948
300	23.56 ± 2.60	3.910	23.87 ± 0.63	3.454	24.44 ± 1.30	2.888	23.13 ± 1.00	3.069
1000	22.29 ± 1.91	3.598	23.44 ± 1.43	3.180	21.95 ± 0.90	3.009	21.75 ± 0.80	3.067
3000	19.90 ± 0.88	3.244	21.54 ± 1.01*	2.899**	25.44 ± 3.74	2.807	21.19 ± 1.03	2.772
6000	---[a]	---	21.26 ± 0.53**	3.304	---	---	---	---
Females								
0	11.92 ± 0.43	3.281	13.24 ± 0.55	3.301	14.31 ± 1.39	3.817	15.11 ± 0.90	3.439
300	10.47 ± 1.41	3.370	14.06 ± 0.50	3.470	13.99 ± 1.83	3.022	13.86 ± 0.70	3.337
1000	13.17 ± 0.69	3.841	14.66 ± 0.67	3.318	15.87 ± 1.18	3.490	15.10 ± 0.95	3.243
3000	11.20 ± 0.96	3.582	11.86 ± 0.60	3.223	12.61 ± 0.82	3.024	13.92 ± 0.78	2.951
6000	---	---	11.05 ± 0.27**	3.615	---	--	---	---

[a]Relative weights designate organ to body weight ratio.

b...indicates liver weights were not measured.

*Significantly different from controls at p <0.05 as evaluated by the study authors.

**Significantly different from controls at p <0.01 as evaluated by the study authors.

007698

30

TABLE 14. Selected Nonneoplastic Lesion in Rats Fed Fat 80'023 for 104 Weeks

Organ/Finding	Dose Level (ppm)									
	Males					Females				
	0	300	1000	3000	6000[c]	0	300	1000	3000	6000[c]
Liver[a]	(95)[b]	(85)	(85)	(85)	(20)	(95)	(85)	(85)	(85)	(20)
Cytoplasmic inclusions of hepatocytes	0	0	0	4	4*[d]	0	0	0	0	0
Centrilobular hepatocyte hypertrophy	0	0	0	7	12***[d]	0	0	0	0	0
Cellular alteration	13	17	18	14	0	13	15	9	15	0
Hyperplasia of liver and bile duct	19	13	19	7	0	11	13	11	11	0
Necrosis	1	5	4	4	0	0	0	0	2	0
Telangiectasis	12	21*[e]	24**[e]	16	0	0	2	6	1	0
Congestion	12	18	14	10	0	14	9	8	7	0
Vacuolation	15	3	10	19	9	16	12	9	12	0
Pancreas[f]	(80)			(70)	(20)	(80)			(70)	(20)
Focal atrophy of acinar tissue	19	9[g]	13[g]	18	2	13	4[g]	5[g]	10	5
Hyperplasia of pancreatic islets	3	1[g]	1[g]	4	5	1	0[g]	0[g]	0	0
Kidney[f]	(80)	(60)	(60)	(60)	(20)	(79)	(60)	(60)	(60)	(20)
Microscopic renal calculi	3	5	9	12**[e]	0	19	21	19	9	0
Mineralization	1	3	4	5	0	8	10	20**[e]	10	0

(continued)

007098

TABLE 14. Continued

Organ/Finding	Dose Level (ppm)									
	Males					Females				
	0	300	1000	3000	6000[c]	0	300	1000	3000	6000
Lung[f]	(80)	(60)	(60)	(60)	(20)	(80)	(60)	(60)	(60)	(20)
Accumulation of foamy macrophages (alveoli)	15	29**[e]	22	26*[e]	0	6	16*[e]	19**[e]	14*[e]	0

[a]Includes animals at the 13-, 26-, and 78-week serial sacrifices, at the 52-week interim sacrifice, at terminal sacrifice, and those that died or were sacrificed moribund during the study.

[b]Number in parentheses equals number of tissues examined.

[c]All high-dose animals were sacrificed at 52 weeks.

[d]Significant effect at week 52 as evaluated by the study authors.

[e]Significant effect at week 104 as evaluated by the study authors.

[f]Includes animals at the 52-week interim sacrifice, at the terminal sacrifice, and those that died or were sacrificed moribund during the study.

[g]Finding observed in nonroutine organs; only animals with finding were examined histologically.

*Significantly different from controls at $p < 0.05$ as evaluated by the study authors.

**Significantly different from controls at $p < 0.01$ as evaluated by the study authors.

***Significantly different from controls at $p < 0.001$ as evaluated by the study authors.

007098

The incidence of hepatic necrosis and telangiectasis was found to be increased in males fed 300, 1000, and 3000 ppm; however, the study authors did not consider these findings to be compound related since the incidence was not dose related. The incidence of renal calculi (unilateral, very small) was significantly ($p<0.01$) increased in males fed 3000 ppm while the incidence of renal mineralization was significantly ($p<0.01$) increased in females fed 1000 ppm at week 104; however, these findings were not considered to be compound related by the study authors since the relative incidence was not significant among rats of the opposite sex.

The accumulation of foamy macrophages in the alveoli of dosed males and females was generally found to be significantly increased ($p<0.05$, $p<0.01$) when compared to concurrent controls; however, the study authors considered this finding to be a normal age-related lesion and not related to compound administration.

2) Neoplastic: Table 15 summarizes the incidence of neoplastic lesions in rats that died, were sacrificed at study termination, or were sacrificed at 52 weeks. The study authors reported that the incidence of neoplastic lesions was similar in dosed and control animals. In addition, the incidence of the neoplastic lesions found was within the range of incidence for historical laboratory controls of this strain[3] with the exception of a slight increase in islet cell adenomas of the pancreas in females fed 3000 ppm. There were no lesions of the pancreas exhibited in females fed 6000 ppm which were sacrificed at 52 weeks.

D. STUDY AUTHORS' CONCLUSIONS:

Dietary administration of Fat 80'023 to male and female rats at concentrations of 0, 300, 1000, or 3000 ppm for 104 weeks and 6000 ppm for 52 weeks resulted in toxic changes in the liver, designated as the primary target organ. This is based

[3]Hazleton, 1984. Neoplasia in Sprague Dawley rats--Untreated Controls. In: Representative Historical Control Data for Rats and Mice.

TABLE 15. Incidence of Neoplastic Lesions in Rats Fed Fat 80'023 for 104 weeks[a]

Organ/Neoplasm	Dose Level									
	Males					Females				
	0	300	1000	3000	6000	0	300	1000	3000	6000
Adrenal	(79)[b]			(60)	(20)	(80)			(60)	(20)
Cortex--adenoma	1	--[c]	2[d]	2	0	3	4	1	2	0
Pheochromocytoma, benign	6	8	8	7	0	3	1	1	1	0
Liver	(80)	(70)	(70)	(70)	(20)	(80)	(70)	(70)	(70)	(20)
Hepatocarcinoma	1	3	2	3	0	0	0	1	0	0
Hepatocellular adenoma	2	2	1	1	0	4	3	2	2	0
Mammary	(74)			(57)	(20)	(80)			(60)	(20)
Adenocarcinoma	0	--	1	1	0	5	7	11	2	0
Adenoma	0	--	--	0	0	3	3	6	4	0
Pancreas	(80)			(60)	(20)	(80)			(60)	(20)
Islet cell adenoma	2	3	3	4	0	3	1	--	5	0
Parathyroid	(79)			(60)	(20)	(73)			(54)	(20)
Adenoma	0	2	--	1	0	0	--	1	0	0
Pituitary	(77)			(56)	(20)	(80)			(60)	(20)
Pars distalis--adenoma	36	23	31	35	3	52	50	52	50[e]	1
Pars distalis--carcinoma	2	1	1	0	0	2	1	1	3	0
Systemic	(80)			(60)	(20)	(80)			(60)	(20)
Histocytic sarcoma	2	3	1	2	0	1	2	--	2	0
Thyroid	(80)			(60)	(20)	(79)			(60)	(20)
Follicle--adenoma	0	--	1	3	0	2	1	--	1	0

[a] Includes animals at the 52-week interim sacrifice, at the terminal sacrifice, and those that died or were sacrificed moribund during the study.
[b] Number in parentheses equals number of tissues examined.
[c] --indicates no lesions found in nonroutine organs of animals found dead or sacrificed moribund during the study.
[d] Incidence of lesions found in nonroutine organs of animals found dead or sacrificed moribund during the study.
[e] Three additional adenomas found at week 52; pancreas considered nonroutine organ at this interval.

007098

on slight changes in clinical biochemistry, liver weight data, and nonneoplastic histological evaluation. A dose-related reduction was exhibited in the erythrocytic parameters and indices of all dose groups. However, since the magnitude of these changes was small with the low-dose groups, they were not considered to be of toxicological significance. Clinically significant increases in SGPT and SGOT and decreases in total bilirubin, triglycerides, glucose, total protein, and albumin concentrations occurred at doses ≥ 3000 ppm over the initial 52 study weeks. Significant changes in clinical chemistry parameters at lower dose levels (≤ 1000 ppm) were transient and were not considered of toxicologic importance. At 52 weeks, males fed 3000 ppm were found to exhibit decreased mean relative liver weights when compared to concurrent controls.

Nonneoplastic changes were found in the liver (enlarged centrilobular hepatocytes containing hyaline-appearing cytoplasmic "inclusions") of males fed 3000 and 6000 ppm Fat 80'023 at 13 and 52 weeks. Hepatocellular hypertrophy was found in 2/5 males fed 3000 ppm at 78 weeks. These lesions were not found in rats maintained after 78 weeks, suggesting that such compound-induced effects were reversible, repaired through intrinsic mechanisms during continuous exposure to lower relative amounts of the test compound. Tumor incidence was similar in dosed and control animals at 104 weeks. Body weights were significantly decreased in males fed 6000 ppm and females fed 3000 ppm. The percent body weight difference, relative to the control group, was greater for females than for males. A compensatory increase in food consumption was exhibited in males only. Based on body weight data and histological liver findings in males, the maximum tolerated dose and LOEL of dietary Fat 80'023 is 3000 ppm and the NOEL is 1000 ppm.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

The study design was adequate although there were some deficiencies in the conduct of the study and in data reporting. In many areas, the study was poorly reported and written in a confusing manner. Technical and calculation errors were made in homogeneity analyses (Table 1a). The corrected range of source sample recovery at 300 ppm was 98.0 to 131.3%; this is considered to be outside the level of acceptability. Dates and times of testing of homogeneity and stability analyses were not reported. The mean test compound intake over the duration of the study was calculated by the reviewers.

The SGOT level of control males at week 26 varied substantially from the levels reported for these animals at weeks 13 and 52;

25

the reviewers consider these differences to be the results of technical error. Several clinical chemistry parameters (chloride, phosphorus, potassium, sodium, creatinine phosphokinase) as suggested in EPA Pesticide Assessment Guidelines for combined chronic toxicity/oncogenicity studies, 1982, were not measured. Technical errors in residue analyses of kidney tissue resulted in abnormally high levels of conjugated and unconjugated residues in males and females fed 3000 ppm at 78 weeks (Table 11). Technical errors resulted in abnormally high levels of glucuronide conjugate in the livers of males fed 6000 ppm at 52 weeks (Table 12). Technical errors resulted in residue levels of the test compound in control samples of kidney and liver tissues at 13, 26, and 52 weeks (Tables 11 and 12). Absolute liver weights of males and females fed 6000 ppm were significantly decreased ($p<0.01$) at 52 weeks when compared to concurrent controls. Since liver weights were measured at only 52 weeks it was difficult to determine if these reduced liver weights were an effect of decreased body weights in these animals as reported by the study authors. This explanation, however, appears correct for the reduced liver weights of males and females fed 3000 ppm.

A complete tissue inventory was not included in the study. Histopathological results of neoplastic and nonneoplastic lesions were evaluated and computed by the reviewers. Tissues examined histologically differed for mid-dose rats at each sacrifice interval; the liver was the only tissue consistently examined. In a deviation from the protocol, a complete histopathology was performed on sporadic animals designated for residue analysis at 78 weeks. The results of these complete histopathological examinations in rats fed 300 and 1000 ppm were not reported in summary tables but only as individual data.

The method of statistical analysis utilized by the study authors for clinical biochemistry parameters appears to be incorrect. Our reviewers evaluated triglyceride data for males (Table 8) using Bartlett's test of homogeneity, the Wilcoxon logrank test, and Dunnett's test and found that values reported to be nonsignificant by the study authors were significantly different from controls at $p<0.05$. The accuracy of the results of many other statistical analyses (e.g., trends) reported by the study authors were questioned by the reviewers but were not recalculated due to time limitations.

The study authors did not consider the incidence of hepatocellular necrosis, renal calculi, and the accumulation of foamy macrophages in the alveoli of male and female rats to be

compound related. Since rats fed 6000 ppm were sacrificed at 52 weeks and the historical incidence of these nonneoplastic findings is unavailable, it is difficult to determine the cause of these findings. However, the reviewers cannot dismiss the increased incidence of liver necrosis in males fed 300-, 1000-, and 3000-ppm Fat 80'023 (5/85, 4/85 and 4/85, respectively, as compared to 1/95 in concurrent controls) when determining the NOEL for the study. Liver enzyme parameters in many of these individual animals were found to be increased.

We agree with the study authors that Fat 80'023 was not oncogenic under the conditions of the study; however, contrary to the study authors who reported the NOEL to be 1000 ppm, we have found the LOEL to be 300 ppm based on the histopathological incidence of hepatic necrosis.