

Summary of Drinking Water Carcinogenicity Study
of β -Chloropropionic Acid
in F344 Rats

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Japan Bioassay Laboratory

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PREFACE

The tests were contracted and supported by the Ministry of Labour of Japan. The tests were conducted by Japan Bioassay Laboratory (JBL) and the report was prepared by JBL and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Labour of Japan on December 28, 1994.

This English Summary was translated by JBL from Japanese complete report.

Summary of Drinking Water Carcinogenicity Study of β -Chloropropionic acid in F344 Rats

Purpose, materials and methods

β -Chloropropionic acid (CAS No. 107-94-8) is a white plates or leaflets with a melting point of 41°C. It is soluble in water, alcohol, and chloroform.

The carcinogenicity and chronic toxicity of β -chloropropionic acid (purity : greater than 99%) were examined in F344/DuCrj rats. Groups of test animals were administered β -chloropropionic acid in their drinking water for 2 years (104 weeks). Each group consisted of either 50 male or 50 female rats. The drinking water concentrations of β -chloropropionic acid were 0, 800, 2400 or 7200 ppm (w/w). Both sexes were administered each concentration of β -chloropropionic acid. The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in a previous 13-week toxicity study. The identity of the β -chloropropionic acid used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by infrared spectrometry and gas chromatography before and after use to affirm its stability. The concentrations of β -chloropropionic acid in the drinking water were determined by gas chromatography at the time of preparation and on the 4th day after preparation while stored at room temperature. The animals were observed daily for clinical signs and mortality. Body weight, water consumption and food consumption were measured once a week for the first 14 weeks and every 2 weeks thereafter. Animals found dead, in a moribund state, or surviving to the end of the 2-year administration period underwent complete necropsy. Urinalysis was performed near the end of the administration period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five μ m thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of β -chloropropionic acid induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, water consumption, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by

Dunnett's test. The present study was conducted with reference to the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

Results

The survival rates of the males and females administered 2400 ppm and 7200 ppm β -chloropropionic acid were slightly higher than the respective controls. Growth rates of the males and females administered 2400 ppm and 7200 ppm β -chloropropionic acid were suppressed. Water consumption and food consumption were decreased in the males administered 2400 ppm and above throughout most of the 2-year administration period.

The incidences of selected neoplastic lesions of male and female rats are presented in the tables below. The incidences of endometrial stromal polyp, endometrial stromal sarcoma and the combined incidence of endometrial stromal polyp and/or endometrial stromal sarcoma in uterus were increased (Peto test and Cochran-Armitage test) in females. The combined incidence of endometrial stromal polyp and/or endometrial stromal sarcoma in female rats administered 7200 ppm β -chloropropionic acid was increased by Fischer's exact test. The squamous cell papilloma and the squamous cell carcinoma in the stomach in male rats administered 7200 ppm β -chloropropionic acid was observed. They are the rare tumor in rats and might be related to the β -chloropropionic acid administration.

The incidences of adenoma in pituitary gland, chronic nephropathy in kidney and myocardial fibrosis in heart, they were thought age-related lesion were suppressed. The slightly higher survival rate, the suppression of growth rate and food consumption might be caused by the suppression of water consumption.

Conclusions

There was equivocal evidence for carcinogenicity of β -chloropropionic acid in male rats based on the incidences of squamous cell papilloma and squamous cell carcinoma in the stomach, which are rare tumor in rats and might be related to the β -chloropropionic acid administration. There was some evidence for carcinogenicity of β -chloropropionic acid in female rats based on the increased incidences of endometrial stromal polyp and endometrial stromal sarcoma in the uterus.

Incidences of selected neoplastic lesions of male rats in the 2-year drinking water carcinogenicity study of β -chloropropionic acid

Dose (ppm)		0	800	2400	7200	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
subcutis	fibroma	3	6	5	3	↑	↓↓
pituitary	adenoma	22	15	10 *	6 **		
stomach	squamous cell papilloma	0	0	1	2		
testis	interstitial cell tumor	41	47	48	48	↑	
malignant tumor							
spleen	mononuclear cell leukemia	11	2 *	1 **	7		
stomach	squamous cell carcinoma	0	0	0	1		
stomach	squamous cell papilloma+ squamous cell carcinoma	0	0	1	3	↑	↑

Incidences of selected neoplastic lesions of female rats in the 2-year drinking water carcinogenicity study of β -chloropropionic acid

Dose (ppm)		0	800	2400	7200	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
uterus	endometrial stromal polyp	5	5	8	13	↑↑	↑
malignant tumor							
uterus	endometrial stromal sarcoma	0	1	0	3	↑	↑
uterus	endometrial stromal polyp+ endometrial stromal sarcoma	5	6	8	16 *	↑↑	↑↑

Significant difference

*: $p \leq 0.05$

↑: $p \leq 0.05$ increase

↓: $p \leq 0.05$ decrease

** : $p \leq 0.01$

↑↑: $p \leq 0.01$ increase

↓↓: $p \leq 0.01$ decrease

(Fisher test)

(Peto, Cochran-Armitage test)

(Cochran-Armitage test)

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TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN MALE RAT
(TWO-YEAR STUDY)

Week on Study	Control		800 ppm			2400 ppm			7200 ppm		
	Au.Wt.	No.of Surviv. <50>	Au.Wt.	% of cont. <50>	No.of Surviv.	Au.Wt.	% of cont. <50>	No.of Surviv.	Au.Wt.	% of cont. <50>	No.of Surviv.
0	129 (50)	50/50	129 (50)	100	50/50	129 (50)	100	50/50	129 (50)	100	50/50
1	169 (50)	50/50	166 (50)	98	50/50	163 (50)	96	50/50	157 (50)	93	50/50
2	203 (50)	50/50	200 (50)	99	50/50	198 (50)	98	50/50	187 (50)	92	50/50
3	231 (50)	50/50	228 (50)	99	50/50	226 (50)	98	50/50	213 (50)	92	50/50
4	250 (50)	50/50	248 (50)	99	50/50	246 (50)	98	50/50	232 (50)	93	50/50
5	268 (50)	50/50	266 (50)	99	50/50	263 (50)	98	50/50	248 (50)	93	50/50
6	283 (50)	50/50	280 (50)	99	50/50	276 (50)	98	50/50	258 (50)	91	50/50
7	298 (50)	50/50	296 (50)	99	50/50	290 (50)	97	50/50	269 (50)	90	50/50
8	310 (50)	50/50	308 (50)	99	50/50	302 (50)	97	50/50	279 (50)	90	50/50
9	320 (50)	50/50	319 (50)	100	50/50	312 (50)	98	50/50	288 (50)	90	50/50
10	328 (50)	50/50	327 (50)	100	50/50	318 (50)	97	50/50	293 (50)	89	50/50
11	336 (50)	50/50	335 (50)	100	50/50	326 (50)	97	50/50	300 (50)	89	50/50
12	341 (50)	50/50	341 (50)	100	50/50	331 (50)	97	50/50	303 (50)	89	50/50
13	348 (50)	50/50	348 (50)	100	50/50	336 (50)	97	50/50	308 (50)	89	50/50
14	353 (50)	50/50	352 (50)	100	50/50	340 (50)	96	50/50	311 (50)	88	50/50
16	362 (50)	50/50	358 (50)	99	50/50	347 (50)	96	50/50	317 (50)	88	50/50
18	368 (50)	50/50	365 (50)	99	50/50	354 (50)	96	50/50	323 (50)	88	50/50
20	376 (50)	50/50	372 (50)	99	50/50	361 (50)	96	50/50	329 (50)	88	50/50
22	384 (50)	50/50	380 (50)	99	50/50	368 (50)	96	50/50	335 (50)	87	50/50
24	391 (50)	50/50	387 (50)	99	50/50	374 (50)	96	50/50	340 (50)	87	50/50
26	399 (50)	50/50	394 (50)	99	50/50	381 (50)	95	50/50	345 (50)	86	50/50
28	406 (50)	50/50	399 (50)	98	50/50	386 (50)	95	50/50	350 (50)	86	50/50
30	410 (50)	50/50	405 (50)	99	50/50	391 (50)	95	50/50	356 (50)	87	50/50
32	417 (50)	50/50	411 (50)	99	50/50	396 (50)	95	50/50	360 (50)	86	50/50
34	423 (50)	50/50	418 (50)	99	50/50	402 (50)	95	50/50	364 (50)	86	50/50
36	429 (50)	50/50	422 (50)	98	50/50	406 (50)	95	50/50	369 (49)	86	49/50
38	433 (50)	50/50	427 (50)	99	50/50	410 (50)	95	50/50	372 (49)	86	49/50
40	436 (50)	50/50	429 (50)	98	50/50	412 (50)	94	50/50	373 (49)	86	49/50
42	441 (50)	50/50	433 (50)	98	50/50	415 (50)	94	50/50	376 (49)	85	49/50
44	446 (50)	50/50	437 (50)	98	50/50	420 (50)	94	50/50	379 (49)	85	49/50
46	452 (50)	50/50	443 (50)	98	50/50	424 (49)	94	49/50	382 (49)	85	49/50
48	456 (50)	50/50	447 (50)	98	50/50	428 (49)	94	49/50	385 (49)	84	49/50
50	460 (50)	50/50	451 (50)	98	50/50	431 (49)	94	49/50	389 (49)	85	49/50
52	463 (50)	50/50	453 (50)	98	50/50	432 (49)	93	49/50	390 (49)	84	49/50
54	468 (50)	50/50	458 (50)	98	50/50	436 (49)	93	49/50	392 (49)	84	49/50
56	470 (50)	50/50	461 (50)	98	50/50	438 (49)	93	49/50	394 (49)	84	49/50
58	474 (50)	50/50	464 (50)	98	50/50	442 (49)	93	49/50	396 (49)	84	49/50
60	477 (50)	50/50	468 (50)	98	50/50	444 (49)	93	49/50	397 (49)	83	49/50
62	480 (50)	50/50	469 (50)	98	50/50	444 (49)	93	49/50	398 (49)	83	49/50
64	483 (50)	50/50	472 (50)	98	50/50	447 (49)	93	49/50	400 (49)	83	49/50
66	486 (50)	50/50	475 (50)	98	50/50	449 (49)	92	49/50	400 (49)	82	49/50
68	484 (50)	50/50	471 (50)	97	50/50	446 (49)	92	49/50	398 (49)	82	49/50
70	485 (50)	50/50	472 (50)	97	50/50	447 (49)	92	49/50	399 (49)	82	49/50
72	482 (50)	50/50	469 (50)	97	50/50	445 (49)	92	49/50	397 (49)	82	49/50
74	479 (50)	49/50	466 (50)	97	50/50	445 (49)	93	49/50	397 (49)	83	49/50
76	478 (48)	48/50	468 (49)	98	49/50	443 (49)	93	49/50	397 (49)	83	49/50
78	479 (48)	48/50	470 (49)	98	49/50	445 (49)	93	49/50	397 (48)	83	48/50
80	477 (48)	48/50	469 (49)	98	49/50	443 (48)	93	48/50	395 (48)	83	48/50
82	474 (47)	45/50	470 (49)	99	49/50	445 (48)	94	48/50	395 (48)	83	48/50
84	481 (44)	44/50	471 (49)	98	49/50	443 (48)	92	48/50	392 (47)	81	47/50
86	481 (43)	43/50	472 (49)	98	49/50	444 (48)	92	48/50	396 (45)	82	46/50
88	480 (42)	42/50	469 (48)	98	48/50	443 (48)	92	48/50	397 (45)	83	45/50
90	480 (41)	41/50	465 (48)	97	48/50	441 (48)	92	48/50	393 (45)	82	44/50
92	479 (40)	40/50	462 (47)	96	47/50	439 (47)	92	47/50	390 (44)	81	44/50
94	474 (40)	40/50	463 (45)	98	45/50	436 (47)	92	46/50	388 (44)	82	44/50
96	470 (40)	40/50	458 (43)	97	43/50	436 (45)	93	45/50	386 (44)	82	44/50
98	467 (39)	39/50	457 (43)	98	43/50	434 (45)	93	45/50	382 (44)	82	44/50
100	461 (39)	39/50	452 (43)	98	43/50	428 (45)	93	45/50	382 (44)	83	44/50
102	451 (38)	37/50	447 (43)	99	43/50	426 (44)	94	44/50	377 (44)	84	44/50
104	447 (36)	36/50	438 (43)	98	43/50	416 (43)	93	43/50	377 (42)	84	42/50
< >:No.of effective animals,():No.of measured animals											
Au.Wt.: g											

TABLE 3 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN FEMALE RAT
(TWO--YEAR STUDY)

Week on Study	Control		800 ppm			2400 ppm			7200 ppm		
	Au.Wt.	No.of Surviv. <50>	Au.Wt.	% of cont. <50>	No.of Surviv.	Au.Wt.	% of cont. <50>	No.of Surviv.	Au.Wt.	% of cont. <50>	No.of Surviv.
0	104 (50)	50/50	103 (50)	99	50/50	103 (50)	99	50/50	104 (50)	100	50/50
1	124 (50)	50/50	123 (50)	99	50/50	122 (50)	98	50/50	118 (50)	95	50/50
2	140 (50)	50/50	139 (50)	99	50/50	138 (50)	99	50/50	134 (50)	96	50/50
3	151 (50)	50/50	152 (50)	101	50/50	149 (50)	99	50/50	144 (50)	95	50/50
4	160 (50)	50/50	161 (50)	101	50/50	158 (50)	99	50/50	151 (50)	94	50/50
5	168 (50)	50/50	170 (50)	101	50/50	166 (50)	99	50/50	158 (50)	94	50/50
6	176 (50)	50/50	177 (50)	101	50/50	173 (50)	98	50/50	163 (50)	93	50/50
7	182 (50)	50/50	184 (50)	101	50/50	179 (50)	98	50/50	168 (50)	92	50/50
8	187 (50)	50/50	189 (50)	101	50/50	185 (50)	99	50/50	172 (50)	92	50/50
9	192 (50)	50/50	195 (50)	102	50/50	189 (50)	98	50/50	176 (50)	92	50/50
10	195 (50)	50/50	197 (50)	101	50/50	192 (50)	98	50/50	178 (50)	91	50/50
11	197 (50)	50/50	202 (50)	103	50/50	196 (50)	99	50/50	183 (50)	93	50/50
12	198 (50)	50/50	201 (50)	102	50/50	195 (50)	98	50/50	182 (50)	92	50/50
13	202 (50)	50/50	206 (50)	102	50/50	200 (50)	99	50/50	186 (50)	92	50/50
14	205 (50)	50/50	208 (50)	101	50/50	202 (50)	99	50/50	188 (50)	92	50/50
16	205 (50)	50/50	209 (50)	102	50/50	203 (50)	99	50/50	188 (50)	92	50/50
18	209 (50)	50/50	211 (50)	101	50/50	205 (50)	98	50/50	189 (50)	90	50/50
20	213 (50)	50/50	215 (50)	101	50/50	207 (50)	97	50/50	191 (50)	90	50/50
22	216 (50)	50/50	217 (50)	100	50/50	210 (50)	97	50/50	194 (50)	90	50/50
24	219 (50)	50/50	222 (50)	101	50/50	213 (50)	97	50/50	198 (50)	90	50/50
26	222 (50)	50/50	225 (50)	101	50/50	216 (50)	97	50/50	200 (50)	90	50/50
28	225 (50)	50/50	228 (50)	101	50/50	219 (50)	97	50/50	202 (50)	90	50/50
30	227 (50)	50/50	230 (50)	101	50/50	221 (50)	97	50/50	204 (50)	90	50/50
32	231 (50)	50/50	234 (50)	101	50/50	224 (50)	97	50/50	205 (50)	89	50/50
34	233 (50)	50/50	236 (50)	101	50/50	227 (50)	97	50/50	208 (50)	89	50/50
36	235 (50)	50/50	240 (50)	102	50/50	230 (50)	98	50/50	210 (50)	89	50/50
38	238 (50)	50/50	242 (50)	102	50/50	233 (50)	98	50/50	212 (50)	89	50/50
40	240 (50)	50/50	244 (50)	102	50/50	234 (50)	98	50/50	212 (50)	88	50/50
42	245 (50)	50/50	248 (50)	101	50/50	236 (50)	96	50/50	215 (50)	88	50/50
44	247 (50)	50/50	251 (50)	102	50/50	239 (50)	97	50/50	217 (50)	88	50/50
46	249 (50)	50/50	256 (50)	103	50/50	243 (50)	98	50/50	220 (50)	88	50/50
48	254 (50)	50/50	259 (50)	102	50/50	247 (50)	97	50/50	222 (50)	87	50/50
50	259 (50)	50/50	264 (50)	102	50/50	251 (50)	97	50/50	226 (50)	87	50/50
52	261 (50)	50/50	268 (50)	103	50/50	252 (50)	97	50/50	226 (50)	87	50/50
54	266 (50)	50/50	273 (50)	103	50/50	256 (50)	96	50/50	228 (49)	86	49/50
56	268 (50)	50/50	276 (50)	103	50/50	260 (50)	97	50/50	231 (49)	86	49/50
58	275 (49)	49/50	282 (50)	103	50/50	265 (50)	96	50/50	234 (49)	85	49/50
60	278 (49)	49/50	287 (50)	103	50/50	269 (50)	97	50/50	236 (49)	85	49/50
62	283 (48)	48/50	292 (50)	103	50/50	273 (50)	96	50/50	238 (49)	84	49/50
64	287 (48)	48/50	296 (50)	103	50/50	277 (50)	97	50/50	242 (49)	84	49/50
66	291 (48)	48/50	300 (50)	103	50/50	281 (50)	97	50/50	244 (49)	84	49/50
68	291 (47)	47/50	299 (50)	103	50/50	281 (50)	97	50/50	243 (49)	84	49/50
70	291 (47)	47/50	301 (50)	103	50/50	283 (50)	97	50/50	245 (49)	84	49/50
72	294 (45)	45/50	303 (50)	103	50/50	286 (50)	97	50/50	245 (49)	83	49/50
74	298 (45)	45/50	304 (50)	102	50/50	289 (50)	97	50/50	248 (49)	83	48/50
76	303 (44)	44/50	307 (50)	101	50/50	291 (50)	96	50/50	251 (48)	83	48/50
78	310 (44)	44/50	308 (49)	99	49/50	295 (50)	95	50/50	257 (48)	83	48/50
80	311 (44)	44/50	309 (48)	99	48/50	296 (50)	95	50/50	257 (48)	83	48/50
82	316 (44)	44/50	310 (48)	98	48/50	299 (50)	95	50/50	260 (48)	82	48/50
84	320 (43)	43/50	311 (48)	97	48/50	302 (50)	94	50/50	260 (48)	81	48/50
86	324 (43)	43/50	312 (46)	96	45/50	303 (50)	94	50/50	263 (48)	81	48/50
88	324 (42)	42/50	314 (45)	97	45/50	306 (50)	94	50/50	265 (48)	82	48/50
90	326 (41)	41/50	321 (43)	98	43/50	308 (50)	94	50/50	267 (47)	82	47/50
92	325 (41)	41/50	321 (43)	99	43/50	310 (49)	95	49/50	268 (47)	82	47/50
94	327 (40)	40/50	321 (43)	98	43/50	310 (49)	95	49/50	269 (47)	82	47/50
96	327 (39)	39/50	321 (43)	98	43/50	310 (49)	95	49/50	270 (47)	83	47/50
98	333 (37)	37/50	322 (41)	97	41/50	312 (47)	94	47/50	269 (47)	81	47/50
100	336 (37)	37/50	319 (41)	95	41/50	314 (47)	93	47/50	270 (47)	80	47/50
102	334 (37)	37/50	320 (39)	96	39/50	314 (46)	94	45/50	269 (46)	81	46/50
104	330 (37)	37/50	316 (38)	96	38/50	313 (43)	95	43/50	267 (45)	81	45/50
<div>< >:No.of effective animals,():No.of measured animals</div> <div>Au.Wt.: g</div>											

TABLE 4 INCIDENCE AND TIME OF MASS OCCURRENCE IN CLINICAL OBSERVATION :RAT :MALE

Time of mass occurrence (week)	0~13	14~26	27~39	40~52	53~65	66~78	79~91	92~104	0~104
The kind of mass									
External mass									
Control	0/50	0/50	0/50	2/50	3/50	6/50	13/48	12/40	16/50 (3/14)
800 ppm	0/50	0/50	0/50	2/50	2/50	4/50	10/49	17/47	20/50 (4/ 7)
2400 ppm	0/50	0/50	0/50	0/50	1/49	3/49	7/49	11/47	12/50 (2/ 7)
7200 ppm	0/50	0/50	2/50	2/49	2/49	4/49	5/48	9/44	14/50 (3/ 8)
Internal mass									
Control	0/50	0/50	0/50	0/50	0/50	0/50	0/48	1/40	1/50 (1/14)
800 ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/49	0/47	0/50 (0/ 7)
2400 ppm	0/50	0/50	0/50	2/50	1/49	0/49	0/49	0/47	2/50 (1/ 7)
7200 ppm	0/50	0/50	0/50	0/49	0/49	0/49	1/48	0/44	1/50 (1/ 8)

No. of animals with mass/No. of survival animals at first week on each period.
(No. of dead and moribund animals with mass/No. of dead and moribund animals.)

TABLE 5 INCIDENCE AND TIME OF MASS OCCURRENCE IN CLINICAL OBSERVATION :RAT :FEMALE

Time of mass occurrence (week)	0~13	14~26	27~39	40~52	53~65	66~78	79~91	92~104	0~104
The kind of mass									
External mass									
Control	0/50	0/50	0/50	0/50	3/50	6/48	8/44	9/41	13/50 (5/13)
800 ppm	0/50	1/50	1/50	3/50	1/50	5/50	5/49	11/43	16/50 (4/12)
2400 ppm	0/50	0/50	0/50	1/50	2/50	2/50	5/50	5/49	7/50 (3/ 7)
7200 ppm	0/50	1/50	0/50	0/50	1/50	2/49	3/48	4/47	8/50 (2/ 5)
Internal mass									
Control	0/50	0/50	0/50	0/50	0/50	1/48	0/44	0/41	1/50 (1/13)
800 ppm	0/50	0/50	0/50	0/50	0/50	0/50	1/49	1/43	2/50 (2/12)
2400 ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/49	1/50 (0/ 7)
7200 ppm	0/50	0/50	0/50	1/50	2/50	1/49	0/48	1/47	3/50 (2/ 5)

No. of animals with mass/No. of survival animals at first week on each period.
(No. of dead and moribund animals with mass/No. of dead and moribund animals.)

TABLE 6 WATER CONSUMPTION IN MALE RAT(TWO-YEAR STUDY)

Week-Day on Study	Control		800 ppm			2400 ppm			7200 ppm		
	Au.WC.	No.of Surviv. <50>	Au.WC.	% of cont. <50>	No.of Surviv.	Au.WC.	% of cont. <50>	No.of Surviv.	Au.WC.	% of cont. <50>	No.of Surviv.
1-3	18.8 (50)	50/50	17.5 (50)	93	50/50	15.8 (50)	84	50/50	12.9 (50)	69	50/50
1-7	19.5 (50)	50/50	18.1 (50)	93	50/50	16.0 (50)	82	50/50	14.7 (50)	75	50/50
2-3	20.8 (50)	50/50	19.1 (50)	92	50/50	16.7 (50)	80	50/50	15.2 (50)	73	50/50
2-7	21.4 (50)	50/50	20.0 (50)	93	50/50	17.2 (50)	80	50/50	15.2 (50)	71	50/50
3-3	22.1 (50)	50/50	20.7 (50)	94	50/50	18.3 (50)	83	50/50	15.5 (50)	70	50/50
3-7	22.7 (49)	50/50	22.1 (50)	97	50/50	18.4 (49)	81	50/50	16.3 (50)	72	50/50
4-7	23.1 (50)	50/50	21.7 (50)	94	50/50	19.4 (50)	84	50/50	15.8 (50)	68	50/50
5-3	23.6 (50)	50/50	22.7 (50)	96	50/50	18.4 (50)	78	50/50	16.8 (50)	71	50/50
5-7	23.1 (50)	50/50	22.3 (49)	97	50/50	18.2 (50)	79	50/50	16.3 (50)	71	50/50
6-3	22.8 (50)	50/50	21.7 (50)	95	50/50	18.3 (50)	80	50/50	15.8 (50)	69	50/50
6-7	23.5 (50)	50/50	23.2 (50)	99	50/50	18.6 (49)	79	50/50	16.3 (50)	69	50/50
7-3	22.8 (50)	50/50	21.9 (50)	96	50/50	18.4 (50)	81	50/50	16.0 (50)	70	50/50
7-7	22.5 (50)	50/50	21.8 (50)	97	50/50	18.4 (50)	82	50/50	16.0 (50)	71	50/50
8-3	22.3 (49)	50/50	21.7 (50)	97	50/50	18.4 (50)	83	50/50	16.3 (50)	73	50/50
8-7	23.0 (50)	50/50	21.6 (49)	94	50/50	18.8 (50)	82	50/50	16.3 (50)	71	50/50
9-3	23.3 (50)	50/50	22.1 (50)	95	50/50	18.8 (50)	81	50/50	18.1 (50)	78	50/50
9-7	23.3 (50)	50/50	22.3 (50)	96	50/50	19.0 (50)	82	50/50	17.5 (50)	75	50/50
10-3	22.0 (50)	50/50	21.7 (50)	99	50/50	18.5 (50)	84	50/50	16.5 (50)	75	50/50
10-7	22.0 (50)	50/50	21.4 (50)	97	50/50	18.4 (50)	84	50/50	16.3 (50)	74	50/50
11-3	22.0 (50)	50/50	20.9 (50)	95	50/50	18.8 (50)	85	50/50	16.1 (50)	73	50/50
11-7	22.1 (50)	50/50	21.4 (50)	97	50/50	18.4 (50)	83	50/50	15.7 (50)	71	50/50
12-3	21.1 (50)	50/50	20.0 (50)	95	50/50	18.6 (50)	88	50/50	15.5 (50)	73	50/50
12-7	22.0 (50)	50/50	20.7 (50)	94	50/50	18.6 (50)	85	50/50	16.0 (49)	73	50/50
13-3	21.5 (50)	50/50	20.4 (50)	95	50/50	18.2 (50)	85	50/50	16.6 (50)	77	50/50
13-7	21.9 (50)	50/50	21.1 (49)	96	50/50	18.8 (49)	86	50/50	16.8 (50)	77	50/50
14-3	20.8 (50)	50/50	20.2 (50)	97	50/50	18.0 (50)	87	50/50	15.9 (50)	76	50/50
14-7	21.4 (50)	50/50	21.0 (49)	98	50/50	18.2 (49)	85	50/50	16.2 (49)	76	50/50
16-7	19.7 (50)	50/50	19.2 (50)	97	50/50	17.0 (50)	86	50/50	14.8 (50)	75	50/50
18-7	19.4 (50)	50/50	19.3 (50)	99	50/50	16.8 (50)	87	50/50	15.5 (50)	80	50/50
20-7	18.9 (50)	50/50	18.6 (50)	98	50/50	16.7 (50)	88	50/50	14.8 (50)	78	50/50
22-7	18.4 (50)	50/50	17.9 (50)	97	50/50	16.3 (50)	89	50/50	14.5 (50)	79	50/50
24-7	18.7 (50)	50/50	18.6 (50)	99	50/50	16.9 (50)	90	50/50	15.1 (50)	81	50/50
26-7	18.9 (50)	50/50	18.7 (50)	99	50/50	16.8 (50)	89	50/50	15.2 (50)	80	50/50
28-7	18.8 (50)	50/50	18.4 (50)	98	50/50	17.4 (50)	93	50/50	15.1 (50)	80	50/50
30-7	18.8 (50)	50/50	18.3 (50)	97	50/50	17.3 (50)	92	50/50	15.2 (50)	81	50/50
32-7	19.0 (50)	50/50	18.4 (50)	97	50/50	17.0 (50)	89	50/50	15.2 (49)	80	50/50
34-7	19.0 (50)	50/50	19.1 (50)	101	50/50	18.2 (50)	96	50/50	15.6 (50)	82	50/50
36-7	18.8 (50)	50/50	18.7 (50)	99	50/50	17.1 (50)	91	50/50	15.7 (49)	84	49/50
38-7	19.1 (50)	50/50	18.8 (50)	98	50/50	17.3 (50)	91	50/50	15.7 (49)	82	49/50
40-7	18.6 (50)	50/50	18.2 (50)	98	50/50	17.5 (50)	94	50/50	15.3 (49)	82	49/50
42-7	18.9 (50)	50/50	18.2 (50)	96	50/50	17.0 (50)	90	50/50	15.4 (49)	81	49/50
44-7	18.8 (50)	50/50	18.1 (50)	96	50/50	17.2 (50)	91	50/50	15.4 (49)	82	49/50
46-7	18.9 (50)	50/50	18.2 (50)	96	50/50	17.6 (49)	93	49/50	15.4 (49)	81	49/50
48-7	18.9 (50)	50/50	18.3 (50)	97	50/50	17.1 (49)	90	49/50	15.7 (49)	83	49/50
50-7	19.2 (50)	50/50	18.7 (50)	97	50/50	17.4 (49)	91	49/50	15.8 (49)	82	49/50
52-7	19.3 (50)	50/50	18.9 (49)	98	50/50	17.4 (49)	90	49/50	15.8 (49)	82	49/50
54-7	19.0 (50)	50/50	18.7 (50)	98	50/50	17.5 (49)	92	49/50	15.7 (49)	83	49/50
56-7	19.6 (50)	50/50	19.0 (50)	97	50/50	17.7 (49)	90	49/50	16.0 (49)	82	49/50
58-7	19.2 (50)	50/50	18.6 (50)	97	50/50	17.9 (49)	93	49/50	16.0 (49)	83	49/50
60-7	19.7 (50)	50/50	19.2 (50)	97	50/50	18.4 (49)	93	49/50	16.2 (49)	82	49/50
62-7	20.5 (50)	50/50	19.6 (50)	96	50/50	18.2 (49)	89	49/50	16.5 (49)	80	49/50
64-7	20.4 (50)	50/50	19.5 (50)	96	50/50	18.0 (49)	88	49/50	16.2 (49)	79	49/50
66-7	20.5 (50)	50/50	19.5 (50)	95	50/50	17.9 (49)	87	49/50	16.0 (49)	78	49/50
68-7	19.6 (50)	50/50	18.9 (50)	96	50/50	17.5 (49)	89	49/50	15.7 (49)	80	49/50
70-7	20.2 (50)	50/50	19.3 (50)	96	50/50	17.6 (49)	87	49/50	15.9 (49)	79	49/50
72-7	20.1 (50)	50/50	19.6 (50)	98	50/50	18.0 (49)	90	49/50	15.9 (49)	79	49/50
74-7	19.8 (50)	49/50	19.7 (50)	99	50/50	17.8 (49)	90	49/50	15.1 (49)	76	49/50
76-7	22.0 (48)	48/50	21.0 (49)	95	49/50	18.4 (49)	84	49/50	16.0 (49)	73	49/50
78-7	22.5 (48)	48/50	20.8 (49)	92	49/50	18.3 (49)	81	49/50	16.1 (49)	72	48/50
80-7	22.5 (48)	48/50	20.8 (49)	92	49/50	18.2 (48)	81	48/50	15.5 (48)	69	48/50
82-7	23.0 (47)	45/50	21.3 (49)	93	49/50	18.8 (48)	82	48/50	15.9 (48)	69	48/50
84-7	23.7 (44)	44/50	21.7 (49)	92	49/50	19.0 (48)	80	48/50	15.2 (47)	64	47/50
86-7	22.4 (43)	43/50	21.0 (49)	94	49/50	17.8 (48)	79	48/50	15.5 (46)	69	46/50
88-7	22.8 (41)	42/50	22.3 (48)	98	48/50	19.0 (48)	83	48/50	15.9 (45)	70	45/50
90-7	22.5 (41)	41/50	21.1 (48)	94	48/50	18.3 (48)	81	48/50	15.3 (45)	68	44/50
92-7	23.4 (39)	40/50	20.5 (46)	88	47/50	18.8 (47)	80	47/50	15.1 (42)	65	44/50
94-7	23.7 (40)	40/50	21.7 (45)	92	45/50	18.7 (47)	79	46/50	15.3 (44)	65	44/50
96-7	24.6 (40)	40/50	23.8 (40)	97	43/50	18.8 (42)	76	45/50	16.3 (44)	66	44/50
98-7	25.0 (39)	39/50	22.8 (43)	91	43/50	19.2 (45)	77	45/50	15.2 (44)	61	44/50
100-7	26.3 (39)	39/50	23.0 (42)	87	43/50	19.3 (45)	73	45/50	16.6 (44)	63	44/50
102-7	28.2 (38)	37/50	25.4 (42)	90	43/50	20.7 (43)	73	44/50	16.8 (44)	60	44/50
104-7	29.1 (34)	36/50	27.1 (42)	93	43/50	21.2 (42)	73	43/50	16.7 (42)	57	42/50

< >:No.of effective animals,():No.of measured animals

Au.WC.:g

TABLE 7 WATER CONSUMPTION IN FEMALE RAT(TWO-YEAR STUDY)

Week-Day on Study	Control		800 ppm		2400 ppm		7200 ppm	
	Au.WC.	No.of Surviv. <50>	Au.WC.	% of cont. <50>	Au.WC.	% of cont. <50>	Au.WC.	% of cont. <50>
1-3	16.3 (50)	50/50	15.3 (50)	94	50/50	12.9 (50)	79	50/50
1-7	17.9 (49)	50/50	16.6 (50)	93	50/50	13.8 (50)	77	50/50
2-3	19.5 (50)	50/50	18.3 (50)	94	50/50	13.9 (50)	71	50/50
2-7	19.5 (48)	50/50	18.6 (50)	95	50/50	13.9 (50)	71	50/50
3-3	22.2 (50)	50/50	18.3 (50)	82	50/50	14.1 (50)	64	50/50
3-7	19.8 (44)	50/50	18.8 (48)	95	50/50	14.9 (50)	75	50/50
4-7	23.1 (49)	50/50	19.6 (48)	85	50/50	15.0 (50)	65	50/50
5-3	24.6 (48)	50/50	19.7 (50)	80	50/50	14.7 (50)	60	50/50
5-7	23.5 (46)	50/50	20.9 (50)	89	50/50	14.5 (50)	62	50/50
6-3	21.6 (48)	50/50	18.7 (50)	87	50/50	14.3 (49)	66	50/50
6-7	21.2 (43)	50/50	20.9 (49)	99	50/50	14.7 (50)	69	50/50
7-3	25.0 (49)	50/50	19.7 (50)	79	50/50	15.7 (50)	63	50/50
7-7	23.1 (48)	50/50	19.8 (49)	86	50/50	15.8 (50)	68	50/50
8-3	23.2 (49)	50/50	20.6 (50)	89	50/50	15.3 (50)	66	50/50
8-7	24.1 (48)	50/50	19.5 (50)	81	50/50	15.2 (50)	63	50/50
9-3	22.7 (48)	50/50	19.5 (50)	86	50/50	14.6 (50)	64	50/50
9-7	23.3 (48)	50/50	21.1 (50)	91	50/50	15.2 (50)	65	50/50
10-3	23.5 (50)	50/50	20.8 (48)	89	50/50	14.6 (50)	62	50/50
10-7	22.9 (47)	50/50	20.0 (50)	87	50/50	15.0 (50)	66	50/50
11-3	25.7 (49)	50/50	19.9 (50)	77	50/50	14.7 (50)	57	50/50
11-7	25.1 (48)	50/50	21.6 (48)	86	50/50	14.8 (50)	59	50/50
12-3	23.5 (49)	50/50	19.5 (50)	83	50/50	14.1 (50)	60	50/50
12-7	- (-)	50/50	- (-)	-	50/50	- (-)	-	50/50
13-3	24.7 (50)	50/50	18.4 (50)	74	50/50	13.6 (50)	55	50/50
13-7	24.5 (45)	50/50	21.8 (49)	89	50/50	14.6 (50)	60	50/50
14-3	28.0 (46)	50/50	22.0 (50)	79	50/50	14.9 (50)	53	50/50
14-7	24.7 (42)	50/50	21.1 (50)	85	50/50	15.0 (50)	61	50/50
16-7	24.7 (49)	50/50	20.8 (50)	84	50/50	14.9 (50)	60	50/50
18-7	27.1 (49)	50/50	20.9 (50)	77	50/50	14.9 (50)	55	50/50
20-7	23.8 (46)	50/50	18.3 (50)	77	50/50	14.3 (49)	60	50/50
22-7	23.1 (49)	50/50	19.5 (50)	84	50/50	13.9 (50)	60	50/50
24-7	24.7 (47)	50/50	19.1 (49)	77	50/50	14.3 (50)	58	50/50
26-7	25.4 (49)	50/50	20.9 (50)	82	50/50	14.6 (50)	57	50/50
28-7	22.2 (49)	50/50	19.8 (50)	89	50/50	14.1 (50)	64	50/50
30-7	23.0 (48)	50/50	19.3 (50)	84	50/50	14.0 (50)	61	50/50
32-7	22.1 (49)	50/50	19.0 (50)	86	50/50	14.6 (50)	66	50/50
34-7	21.6 (47)	50/50	19.6 (50)	91	50/50	14.4 (50)	67	50/50
36-7	22.3 (50)	50/50	19.0 (50)	85	50/50	13.9 (50)	62	50/50
38-7	21.4 (49)	50/50	18.4 (48)	86	50/50	14.0 (50)	65	50/50
40-7	20.3 (50)	50/50	18.3 (50)	90	50/50	13.8 (50)	68	50/50
42-7	20.9 (49)	50/50	18.2 (50)	87	50/50	13.8 (50)	66	50/50
44-7	20.4 (50)	50/50	17.9 (50)	88	50/50	14.1 (50)	69	50/50
46-7	19.6 (50)	50/50	18.8 (50)	96	50/50	14.1 (50)	72	50/50
48-7	19.4 (49)	50/50	18.2 (50)	94	50/50	14.1 (50)	73	50/50
50-7	21.3 (50)	50/50	18.5 (50)	87	50/50	13.8 (50)	65	50/50
52-7	18.6 (50)	50/50	18.1 (50)	97	50/50	13.7 (50)	74	50/50
54-7	17.4 (50)	50/50	17.7 (50)	102	50/50	13.6 (50)	78	50/50
56-7	17.4 (50)	50/50	17.3 (49)	99	50/50	14.5 (50)	83	50/50
58-7	18.1 (49)	49/50	17.2 (50)	95	50/50	13.6 (50)	75	50/50
60-7	17.2 (49)	49/50	16.3 (50)	95	50/50	13.7 (50)	80	50/50
62-7	17.5 (47)	48/50	17.5 (50)	100	50/50	14.1 (50)	81	50/50
64-7	16.9 (48)	48/50	17.5 (50)	104	50/50	14.2 (50)	84	50/50
66-7	17.5 (48)	48/50	16.5 (50)	95	50/50	14.1 (50)	81	50/50
68-7	16.4 (47)	47/50	16.7 (50)	102	50/50	13.6 (50)	83	50/50
70-7	17.8 (47)	47/50	17.7 (50)	99	50/50	14.0 (50)	79	50/50
72-7	17.3 (46)	45/50	18.2 (50)	105	50/50	14.5 (50)	84	50/50
74-7	17.1 (45)	45/50	18.4 (50)	108	50/50	14.6 (50)	85	50/50
76-7	18.2 (44)	44/50	18.8 (50)	103	50/50	14.9 (50)	82	50/50
78-7	19.4 (44)	44/50	18.2 (49)	94	49/50	15.3 (50)	79	50/50
80-7	19.1 (44)	44/50	19.8 (48)	104	48/50	15.3 (50)	80	50/50
82-7	20.0 (44)	44/50	18.7 (48)	94	48/50	15.7 (50)	79	50/50
84-7	18.9 (43)	43/50	18.5 (48)	98	48/50	16.0 (50)	85	50/50
86-7	18.9 (43)	43/50	18.6 (46)	98	45/50	15.3 (50)	81	50/50
88-7	19.6 (41)	42/50	20.7 (44)	106	45/50	17.0 (50)	87	50/50
90-7	19.9 (41)	41/50	20.5 (43)	103	43/50	16.2 (50)	81	50/50
92-7	20.1 (41)	41/50	20.8 (43)	103	43/50	16.1 (49)	80	49/50
94-7	20.6 (40)	40/50	19.4 (43)	94	43/50	16.0 (49)	78	49/50
96-7	20.7 (39)	39/50	20.9 (43)	101	43/50	16.0 (49)	77	49/50
98-7	21.6 (37)	37/50	21.2 (41)	98	41/50	16.2 (47)	75	47/50
100-7	23.2 (37)	37/50	21.8 (41)	94	41/50	17.0 (47)	73	47/50
102-7	23.1 (37)	37/50	22.9 (38)	99	39/50	18.4 (46)	80	45/50
104-7	22.8 (37)	37/50	23.6 (38)	104	38/50	17.8 (41)	78	43/50

< >:No.of effective animals, ():No.of measured animals

Au.WC.: g

TABLE 8 FOOD CONSUMPTION IN MALE RAT(TWO-YEAR STUDY)

Week on Study	Control			800 ppm			2400 ppm			7200 ppm		
	Au.FC.	No.of Surviv. <50>		Au.FC.	% of cont. <50>	No.of Surviv.	Au.FC.	% of cont. <50>	No.of Surviv.	Au.FC.	% of cont. <50>	No.of Surviv.
1	15.2 (50)	50/50		14.7 (50)	97	50/50	14.1 (50)	93	50/50	13.0 (50)	86	50/50
2	17.0 (50)	50/50		16.6 (50)	98	50/50	16.0 (50)	94	50/50	14.3 (50)	84	50/50
3	17.3 (50)	50/50		17.0 (50)	98	50/50	16.9 (50)	98	50/50	15.4 (50)	89	50/50
4	17.4 (50)	50/50		17.2 (50)	99	50/50	17.2 (50)	99	50/50	16.5 (50)	95	50/50
5	17.3 (50)	50/50		16.9 (49)	98	50/50	16.7 (50)	97	50/50	15.5 (50)	90	50/50
6	17.5 (50)	50/50		17.3 (50)	99	50/50	16.8 (50)	96	50/50	15.4 (50)	88	50/50
7	17.5 (50)	50/50		17.3 (50)	99	50/50	17.1 (50)	98	50/50	15.4 (50)	88	50/50
8	17.7 (50)	50/50		17.8 (50)	101	50/50	17.0 (50)	96	50/50	15.7 (50)	89	50/50
9	17.8 (50)	50/50		17.8 (50)	100	50/50	17.3 (50)	97	50/50	16.1 (50)	90	50/50
10	17.4 (50)	50/50		17.6 (50)	101	50/50	16.6 (50)	95	50/50	15.5 (50)	89	50/50
11	17.2 (50)	50/50		17.2 (50)	100	50/50	16.7 (50)	97	50/50	15.6 (50)	91	50/50
12	17.0 (50)	50/50		16.9 (50)	99	50/50	16.4 (50)	96	50/50	15.2 (50)	89	50/50
13	16.8 (50)	50/50		16.7 (50)	99	50/50	16.1 (50)	96	50/50	15.2 (50)	90	50/50
14	16.4 (50)	50/50		16.4 (50)	100	50/50	15.8 (50)	96	50/50	14.7 (50)	90	50/50
18	16.5 (50)	50/50		16.7 (50)	101	50/50	15.9 (50)	96	50/50	15.3 (50)	93	50/50
22	16.3 (50)	50/50		16.3 (50)	100	50/50	15.8 (50)	97	50/50	14.9 (50)	91	50/50
26	16.3 (50)	50/50		16.2 (50)	99	50/50	16.0 (50)	98	50/50	15.2 (50)	93	50/50
30	16.8 (50)	50/50		16.4 (50)	98	50/50	15.8 (50)	94	50/50	15.3 (50)	91	50/50
34	16.4 (50)	50/50		16.8 (50)	102	50/50	16.1 (50)	98	50/50	15.1 (50)	92	50/50
38	16.5 (50)	50/50		16.2 (50)	98	50/50	16.1 (50)	98	50/50	15.4 (49)	93	49/50
42	16.6 (50)	50/50		16.6 (50)	100	50/50	16.4 (50)	99	50/50	15.6 (49)	94	49/50
46	16.6 (50)	50/50		16.4 (50)	99	50/50	16.1 (49)	97	49/50	15.1 (49)	91	49/50
50	16.8 (50)	50/50		16.7 (50)	99	50/50	16.2 (49)	96	49/50	15.4 (49)	92	49/50
54	16.7 (50)	50/50		16.9 (50)	101	50/50	16.2 (49)	97	49/50	15.2 (49)	91	49/50
58	17.1 (50)	50/50		16.9 (50)	99	50/50	16.7 (49)	98	49/50	15.4 (49)	90	49/50
62	16.7 (50)	50/50		16.5 (50)	99	50/50	16.0 (49)	96	49/50	14.8 (49)	89	49/50
66	16.7 (50)	50/50		16.5 (50)	99	50/50	15.9 (49)	95	49/50	14.7 (49)	88	49/50
70	16.9 (50)	50/50		16.7 (50)	99	50/50	16.1 (49)	95	49/50	15.3 (49)	91	49/50
74	16.9 (50)	49/50		17.3 (49)	102	50/50	16.6 (49)	98	49/50	15.2 (49)	90	49/50
78	17.4 (48)	48/50		17.3 (49)	99	49/50	16.6 (49)	95	49/50	15.7 (49)	90	48/50
82	17.8 (47)	45/50		17.8 (49)	100	49/50	17.3 (48)	97	48/50	15.7 (48)	88	48/50
86	17.6 (43)	43/50		17.7 (49)	101	49/50	16.6 (48)	94	48/50	15.5 (46)	88	46/50
90	17.5 (41)	41/50		17.6 (48)	101	48/50	16.5 (48)	94	48/50	15.4 (45)	88	44/50
94	17.4 (40)	40/50		17.6 (45)	101	45/50	16.4 (47)	94	46/50	15.3 (43)	88	44/50
98	17.2 (39)	39/50		17.3 (43)	101	43/50	16.2 (45)	94	45/50	14.8 (44)	86	44/50
102	17.3 (38)	37/50		17.9 (43)	103	43/50	16.5 (44)	95	44/50	15.0 (44)	87	44/50
104	17.2 (36)	36/50		17.1 (43)	99	43/50	16.1 (43)	94	43/50	15.0 (42)	87	42/50
< >:No.of effective animals,():No.of measured animals Au.FC.: g												

TABLE 9 FOOD CONSUMPTION IN FEMALE RAT(TWO-YEAR STUDY)

Week on Study	Control		800 ppm			2400 ppm			7200 ppm		
	Au.FC.	No.of Surviv. <50>	Au.FC.	% of cont. <50>	No.of Surviv.	Au.FC.	% of cont. <50>	No.of Surviv.	Au.FC.	% of cont. <50>	No.of Surviv.
1	12.1 (50)	50/50	11.6 (50)	96	50/50	11.3 (50)	93	50/50	10.3 (50)	85	50/50
2	12.4 (50)	50/50	12.3 (50)	99	50/50	11.7 (50)	94	50/50	11.2 (50)	90	50/50
3	12.4 (50)	50/50	12.5 (50)	101	50/50	11.9 (50)	96	50/50	11.2 (50)	90	50/50
4	12.3 (50)	50/50	12.5 (50)	102	50/50	11.9 (50)	97	50/50	11.4 (50)	93	50/50
5	12.4 (50)	50/50	12.3 (50)	99	50/50	11.6 (50)	94	50/50	10.7 (50)	86	50/50
6	12.2 (50)	50/50	12.4 (50)	102	50/50	11.5 (50)	94	50/50	10.8 (50)	89	50/50
7	12.4 (33)	50/50	12.5 (50)	101	50/50	11.7 (50)	94	50/50	10.8 (50)	87	50/50
8	12.2 (50)	50/50	12.4 (50)	102	50/50	11.7 (50)	96	50/50	10.7 (50)	88	50/50
9	12.1 (50)	50/50	12.3 (50)	102	50/50	11.8 (50)	98	50/50	10.9 (50)	90	50/50
10	11.8 (50)	50/50	11.9 (50)	101	50/50	11.3 (50)	96	50/50	10.6 (50)	90	50/50
11	11.7 (50)	50/50	12.2 (50)	104	50/50	11.7 (50)	100	50/50	10.9 (50)	93	50/50
12	11.0 (50)	50/50	11.2 (50)	102	50/50	10.5 (50)	95	50/50	10.0 (50)	91	50/50
13	11.4 (50)	50/50	11.6 (50)	102	50/50	11.0 (50)	96	50/50	10.4 (50)	91	50/50
14	11.8 (50)	50/50	11.9 (50)	101	50/50	11.3 (50)	96	50/50	10.6 (50)	90	50/50
18	11.9 (50)	50/50	12.0 (50)	101	50/50	11.3 (49)	95	50/50	10.4 (50)	87	50/50
22	11.5 (50)	50/50	11.7 (50)	102	50/50	10.8 (50)	94	50/50	10.2 (50)	89	50/50
26	11.7 (50)	50/50	11.9 (50)	102	50/50	11.0 (50)	94	50/50	10.4 (50)	89	50/50
30	11.7 (50)	50/50	11.8 (50)	101	50/50	11.1 (50)	95	50/50	10.3 (50)	88	50/50
34	11.8 (50)	50/50	12.1 (50)	103	50/50	11.3 (48)	96	50/50	10.4 (50)	88	50/50
38	11.4 (50)	50/50	12.1 (50)	106	50/50	11.2 (50)	98	50/50	10.4 (50)	91	50/50
42	12.1 (50)	50/50	12.4 (50)	102	50/50	11.5 (50)	95	50/50	10.9 (50)	90	50/50
46	11.6 (50)	50/50	12.2 (50)	105	50/50	11.6 (50)	100	50/50	10.7 (50)	92	50/50
50	12.3 (50)	50/50	12.3 (50)	100	50/50	11.5 (50)	93	50/50	10.6 (50)	86	50/50
54	11.9 (50)	50/50	12.3 (50)	103	50/50	11.5 (50)	97	50/50	10.7 (50)	90	49/50
58	12.7 (49)	49/50	12.9 (50)	102	50/50	12.1 (50)	95	50/50	11.1 (49)	87	49/50
62	11.8 (49)	48/50	12.4 (50)	105	50/50	11.6 (50)	98	50/50	10.5 (49)	89	49/50
66	12.1 (48)	48/50	12.3 (50)	102	50/50	11.7 (50)	97	50/50	10.7 (49)	88	49/50
70	12.7 (46)	47/50	13.0 (50)	102	50/50	12.4 (50)	98	50/50	11.2 (49)	88	49/50
74	13.0 (45)	45/50	13.5 (50)	104	50/50	12.5 (50)	96	50/50	11.5 (49)	88	48/50
78	14.0 (44)	44/50	13.5 (49)	96	49/50	13.1 (50)	94	50/50	12.3 (48)	88	48/50
82	14.4 (44)	44/50	14.1 (48)	98	48/50	13.3 (50)	92	50/50	12.3 (48)	85	48/50
86	14.1 (43)	43/50	14.2 (47)	101	45/50	12.9 (50)	91	50/50	12.2 (48)	87	48/50
90	14.2 (42)	41/50	14.7 (43)	104	43/50	13.6 (50)	96	50/50	12.7 (47)	89	47/50
94	14.4 (40)	40/50	14.5 (43)	101	43/50	13.3 (49)	92	49/50	12.4 (47)	86	47/50
98	14.5 (37)	37/50	14.6 (41)	101	41/50	13.2 (47)	91	47/50	12.0 (47)	83	47/50
102	14.6 (37)	37/50	14.6 (39)	100	39/50	13.9 (45)	95	45/50	12.1 (45)	83	46/50
104	13.9 (37)	37/50	14.1 (38)	101	38/50	13.3 (43)	96	43/50	12.3 (45)	88	45/50
< >:No.of effective animals,():No.of measured animals Au.FC.: g											

TABLE 10 NEOPLASTIC LESIONS (UTERUS) INCIDENCE AND STATISTICAL ANALYSIS : RAT : FEMALE

Group Name	Control	800 ppm	2400 ppm	7200 ppm
SITE : uterus TUMOUR : endometrial stromal polyp				
Tumor Rates				
Overall Rates(a)	5/50 (10.0)	5/50 (10.0)	8/50 (16.0)	13/50 (26.0)
Adjusted Rates(b)	11.11	11.63	22.22	31.58
Terminal Rates(c)	3/37 (8.1)	4/38 (10.5)	8/43 (18.6)	12/45 (26.7)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=1.0000 ?			
Prevalence Method(d)	P=0.0083**			
Combined analysis(d)	P=0.0148*			
Cochran-Armitage Test(e)	P=0.0113*			
Fisher Exact Test(e)		P=0.3710	P=0.3141	P=0.0676
SITE : uterus TUMOUR : endometrial stromal sarcoma				
Tumor Rates				
Overall Rates(a)	0/50 (0.0)	1/50 (2.0)	0/50 (0.0)	3/50 (6.0)
Adjusted Rates(b)	0.0	0.0	0.0	2.63
Terminal Rates(c)	0/37 (0.0)	0/38 (0.0)	0/43 (0.0)	1/45 (2.2)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.0859			
Prevalence Method(d)	P=0.1587			
Combined analysis(d)	P=0.0286*			
Cochran-Armitage Test(e)	P=0.0300*			
Fisher Exact Test(e)		P=0.4950	P=0.5000	P=0.1325
SITE : uterus TUMOUR : endometrial stromal polyp, endometrial stromal sarcoma				
Tumor Rates				
Overall Rates(a)	5/50 (10.0)	6/50 (12.0)	8/50 (16.0)	16/50 (32.0)
Adjusted Rates(b)	11.11	11.63	22.22	31.58
Terminal Rates(c)	3/37 (8.1)	4/38 (10.5)	8/43 (18.6)	13/45 (28.9)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.2063			
Prevalence Method(d)	P=0.0038**			
Combined analysis(d)	P=0.0027**			
Cochran-Armitage Test(e)	P=0.0013**			
Fisher Exact Test(e)		P=0.4872	P=0.3141	P=0.0238*

(a):Number of tumor-bearing animals/number of animals examined at the site.

(b):Kaplan-Meire estimate tumor incidence at the end of study after adjusting for intercurrent mortality.

(c):Observed tumor incidence at terminal kill.

(d):Beneath the control incidence are the P-values associated with the trend test.

Standard method : Death analysis

Prevalence method : Incidental tumor test

Combined analysis : Death analysis + Incidental tumor test

(e):The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.

? :The conditional probabilities of the largest and smallest possible outcomes can not be estimated or this P-value beyond the estimated P-value.

TABLE 11 NEOPLASTIC LESIONS (STOMACH) INCIDENCE AND STATISTICAL ANALYSIS : RAT : MALE

Group Name	Control	800 ppm	2400 ppm	7200 ppm
SITE : stomach				
TUMOUR : squamous cell papilloma, squamous cell carcinoma				
Tumor Rates				
Overall Rates(a)	0/50 (0.0)	0/50 (0.0)	1/50 (2.0)	3/50 (6.0)
Adjusted Rates(b)	0.0	0.0	5.88	9.09
Terminal Rates(c)	0/36 (0.0)	0/43 (0.0)	1/43 (2.3)	3/42 (7.1)
Statistical Analysis				
Peto Test				
Standard metod(d)	P=-----			
Prevalence method(d)	P=0.0114*			
Combined analysis(d)	P=-----			
Cochran-Armitage Test(e)	P=0.0139*			
Fisher Exact Test(e)		P=0.5000	P=0.4950	P=0.1325

TABLE 12 NEOPLASTIC LESIONS (PITUITARY GLAND) INCIDENCE AND STATISTICAL ANALYSIS : RAT : MALE

Group Name	Control	800 ppm	2400 ppm	7200 ppm
SITE : pituitary gland				
TUMOUR : adenoma				
Tumor Rates				
Overall Rates(a)	22/50 (44.0)	15/50 (30.0)	10/50 (20.0)	6/50 (12.0)
Adjusted Rates(b)	43.33	29.55	17.65	16.00
Terminal Rates(c)	14/36 (38.9)	12/43 (27.9)	7/43 (16.3)	4/42 (9.5)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.8041			
Prevalence Method(d)	P=0.9998			
Combined analysis(d)	P=0.9998			
Cochran-Armitage Test(e)	P=0.0008**			
Fisher Exact Test(e)		P=0.2145	P=0.0484*	P=0.0056**

SITE : pituitary gland				
TUMOUR : adenoma, adenocarcinoma				
Tumor Rates				
Overall Rates(a)	22/50 (44.0)	15/50 (30.0)	11/50 (22.0)	6/50 (12.0)
Adjusted Rates(b)	43.33	29.55	22.53	16.00
Terminal Rates(c)	14/36 (38.9)	12/43 (27.9)	8/43 (18.6)	4/42 (9.5)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.8041			
Prevalence Method(d)	P=0.9998			
Combined analysis(d)	P=0.9998			
Cochran-Armitage Test(e)	P=0.0008**			
Fisher Exact Test(e)		P=0.2145	P=0.0707	P=0.0056**

- (a):Number of tumor-bearing animals/number of animals examined at the site.
(b):Kaplan-Meire estimate tumor incidence at the end of study after adjusting for intercurrent mortality.
(c):Observed tumor incidence at terminal kill.
(d):Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e):The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
-----:There is no data which should be statistical analysis.

TABLE 13 CAUSE OF DEATH :RAT

Group	Male					Female				
	Control	800ppm	2400ppm	7200ppm	7200ppm	Control	800ppm	2400ppm	7200ppm	
Number of dead/moribund animal	14	7	7	7	8	13	12	7	5	
No microscopical confirmation	0	0	1	0	0	0	0	0	0	
Hematopoetic lesion	0	0	0	0	0	0	1	0	0	
Cardiovascular lesion	0	1	0	0	0	0	0	0	0	
Body cavity lesion	0	0	0	0	0	0	1	0	0	
Other system lesion	0	0	1	0	0	0	0	0	0	
Ileus	2	0	0	0	0	0	0	0	0	
Chronic nephropathy	1	0	0	0	0	0	0	0	0	
Tumor death : leukemia	2	2	1	2	2	3	2	3	2	
: subcutis	0	1	1	3	0	2	1	0	0	
: lung	0	0	0	0	0	1	0	0	0	
: large intestine	0	0	0	0	0	0	1	0	0	
: liver	0	0	0	1	0	0	0	0	0	
: pituitary gland	5	2	3	2	2	4	3	2	0	
: uterus	0	0	0	0	0	1	1	1	3	
: mammary gland	0	0	0	0	0	0	0	1	0	
: prep./cli. gland	1	0	0	0	0	2	1	0	0	
: spinal cord	1	0	0	0	0	0	0	0	0	
: Zymbal gland	1	1	0	0	0	0	0	0	0	
: peritoneum	1	0	0	0	0	0	0	0	0	
: retroperitoneum	0	0	0	0	0	0	1	0	0	

SELECTED FIGURES

FIGURE 1	SURVIVAL ANIMAL RATE : RAT MALE (TWO-YEAR STUDIES)
FIGURE 2	SURVIVAL ANIMAL RATE : RAT FEMALE (TWO-YEAR STUDIES)
FIGURE 3	BODY WEIGHT CHANGES : RAT MALE (TWO-YEAR STUDIES)
FIGURE 4	BODY WEIGHT CHANGES : RAT FEMALE (TWO-YEAR STUDIES)
FIGURE 5	WATER CONSUMPTION : RAT MALE (TWO-YEAR STUDIES)
FIGURE 8	WATER CONSUMPTION : RAT FEMALE (TWO-YEAR STUDIES)
FIGURE 7	FOOD CONSUMPTION : RAT MALE (TWO-YEAR STUDIES)
FIGURE 8	FOOD CONSUMPTION : RAT FEMALE (TWO-YEAR STUDIES)

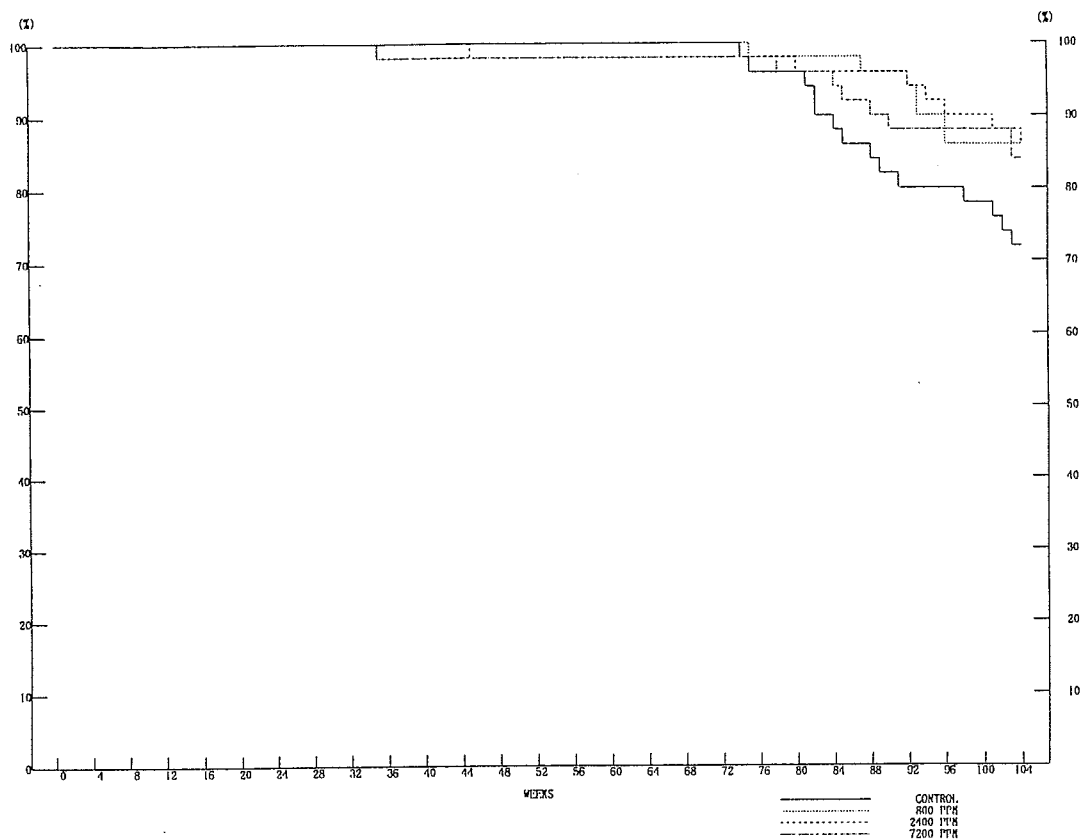


FIGURE 1 SURVIVAL ANIMAL RATE : RAT:MALE(TWO-YEAR STUDY)

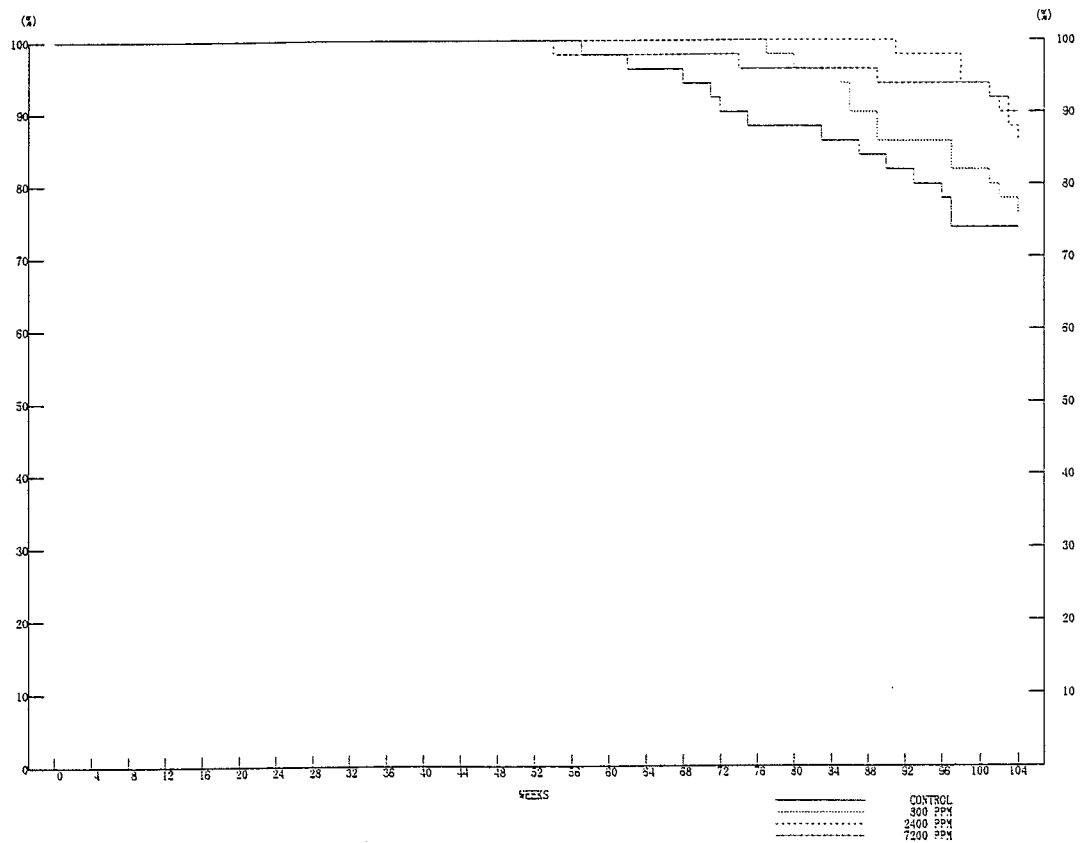


FIGURE 2 SURVIVAL ANIMAL RATE : RAT:FEMALE(TWO-YEAR STUDY)

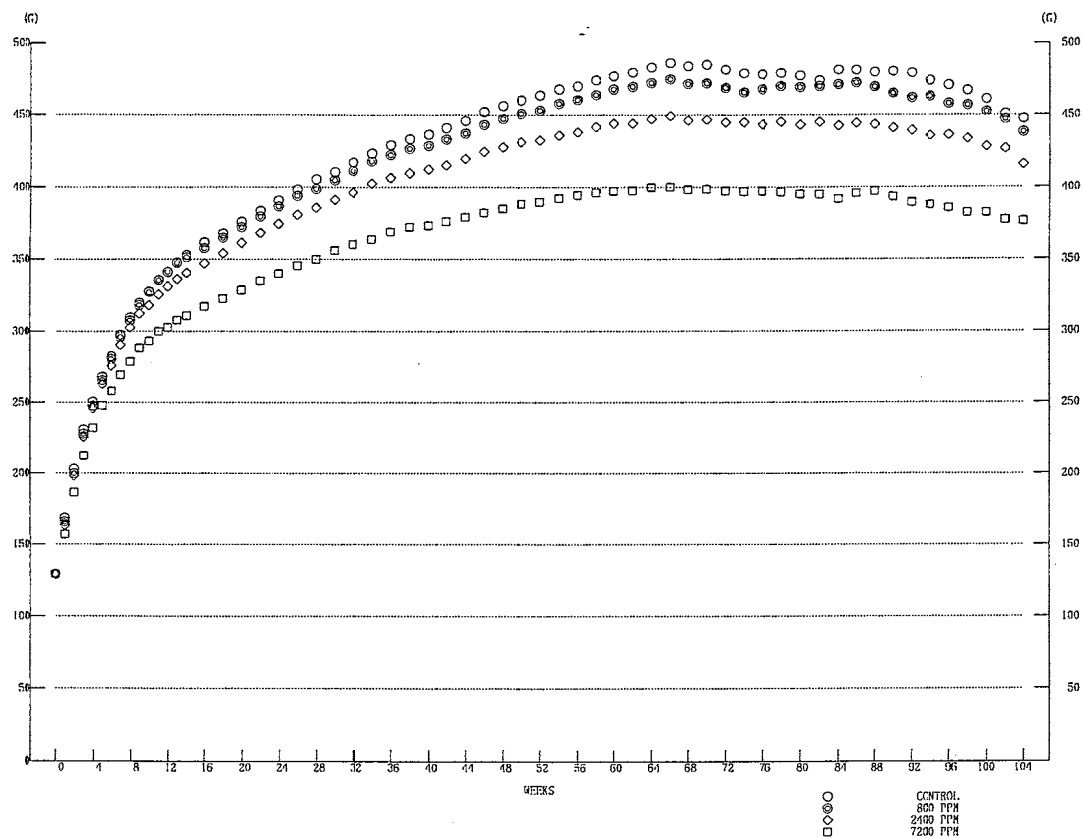


FIGURE 3 BODY WEIGHT CHANGES : RAT:MALE(TWO-YEAR STUDY)

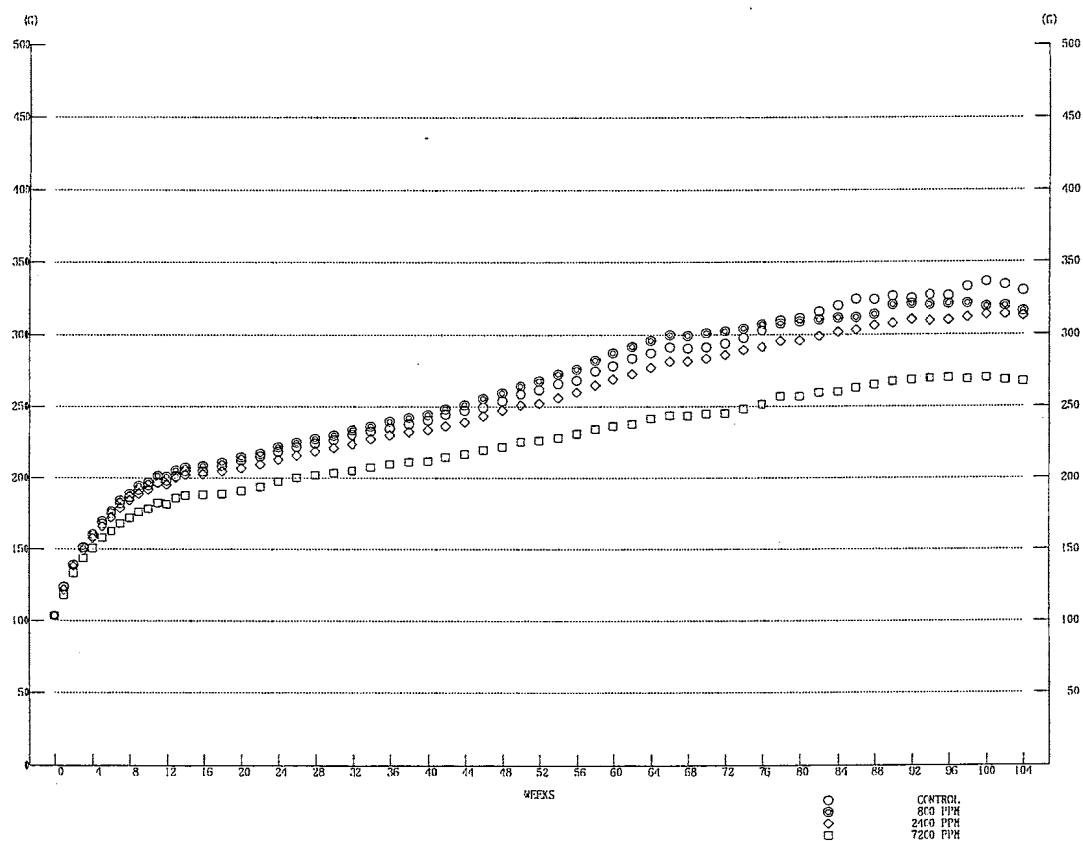


FIGURE 4 BODY WEIGHT CHANGES : RAT:FEMALE(TWO-YEAR STUDY)

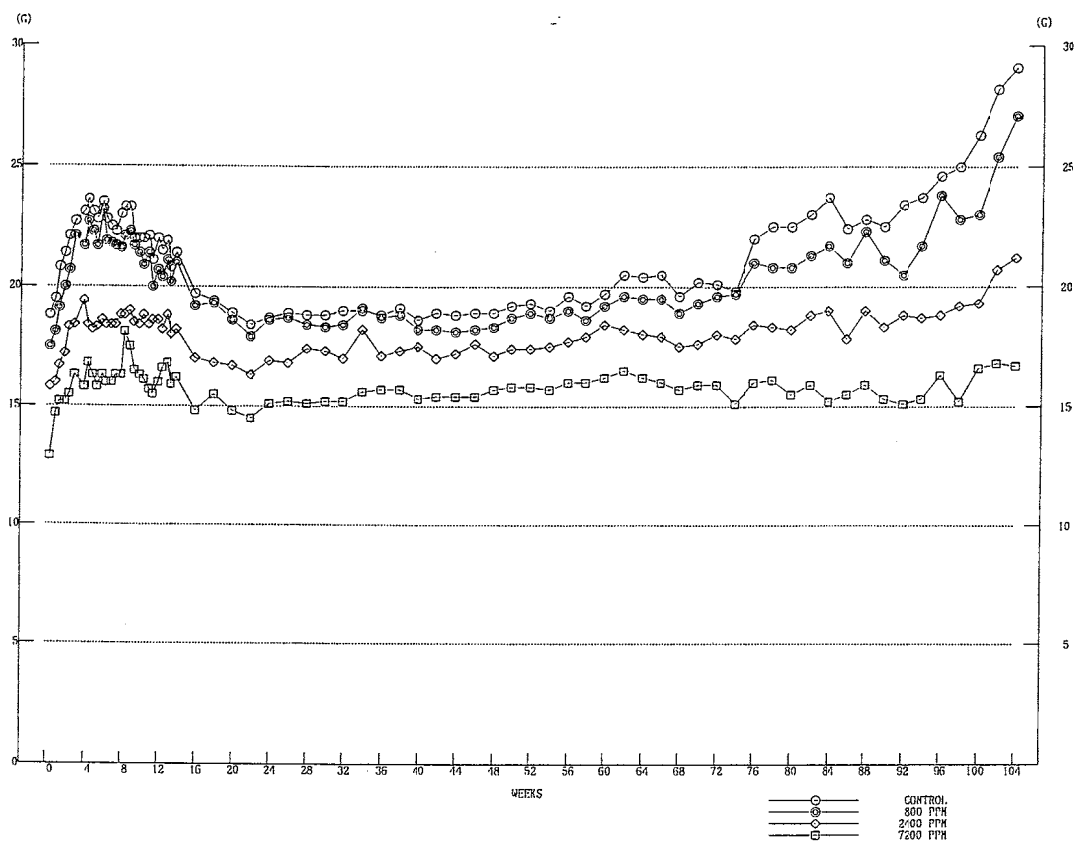


FIGURE 5 WATER CONSUMPTION : RAT:MALE(TWO-YEAR STUDY)

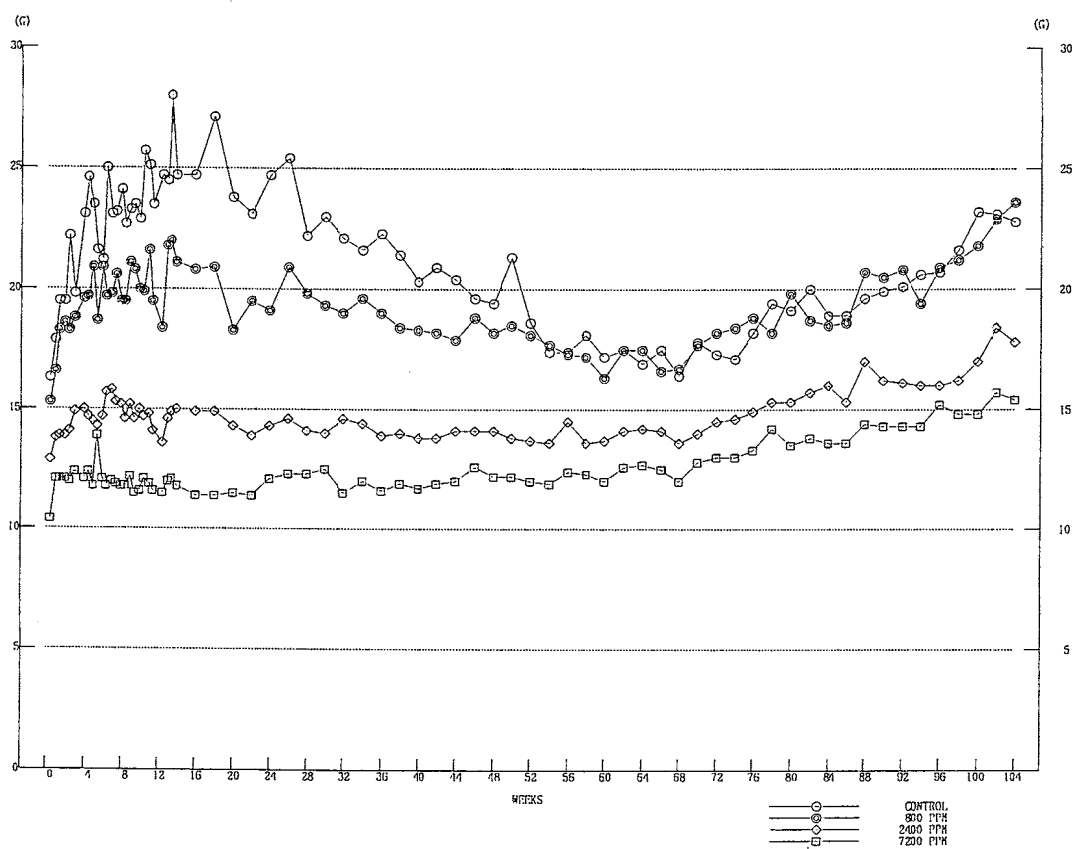


FIGURE 6 WATER CONSUMPTION : RAT:FEMALE(TWO-YEAR STUDY)

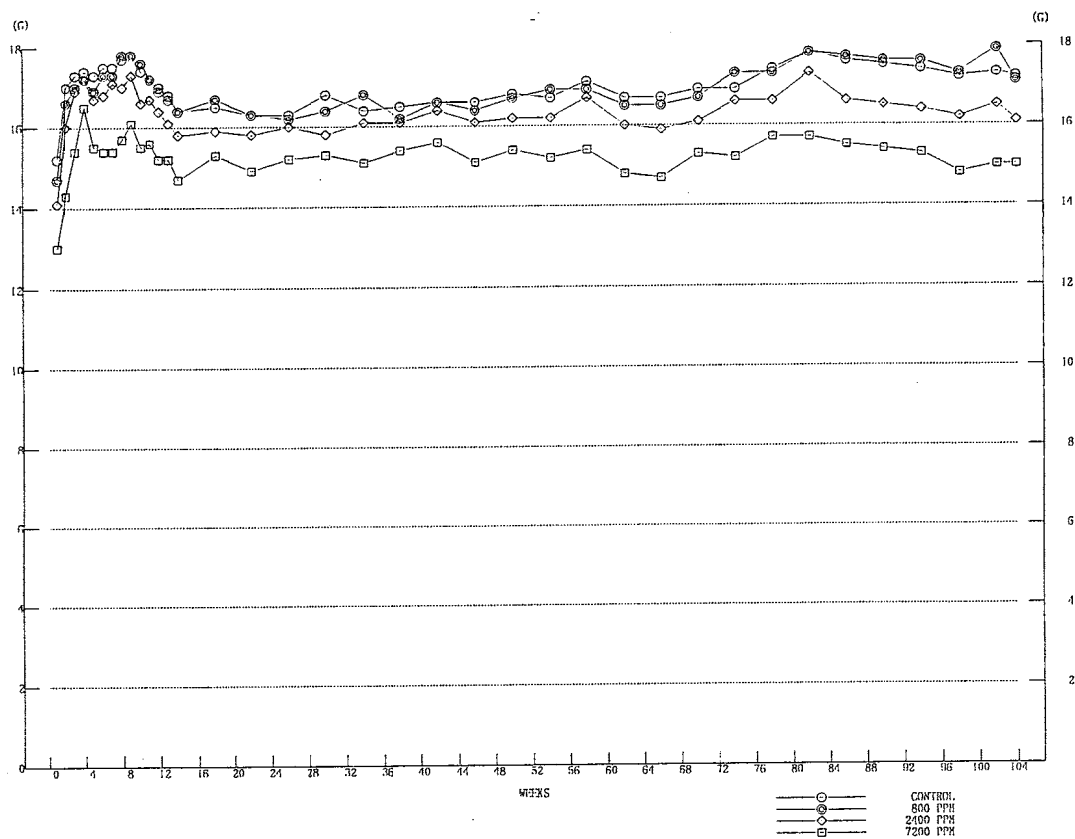


FIGURE 7 FOOD CONSUMPTION : RAT:MALE(TWO-YEAR STUDY)

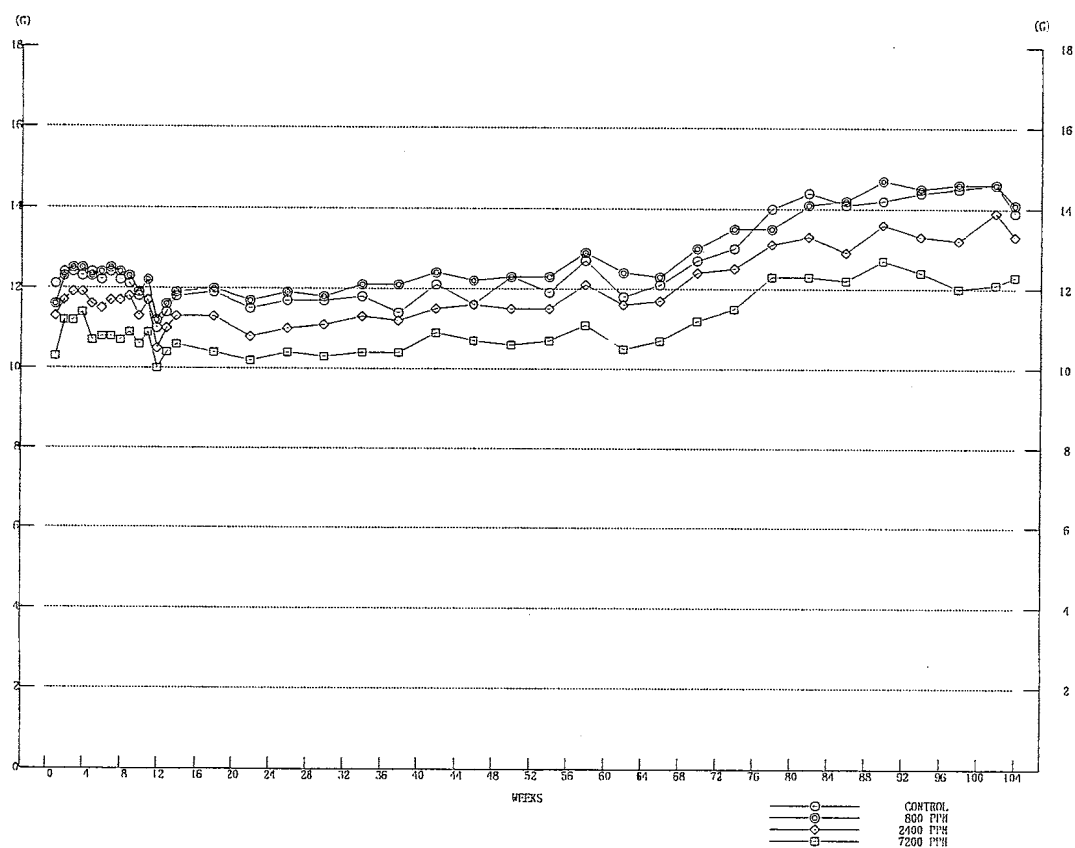
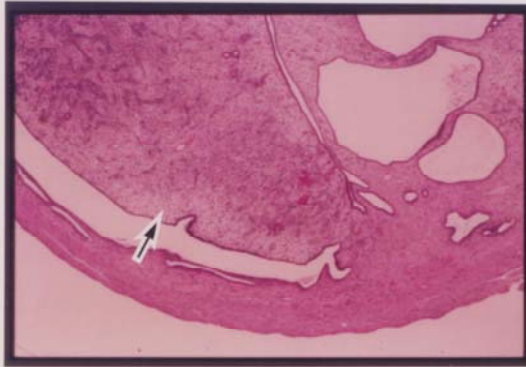


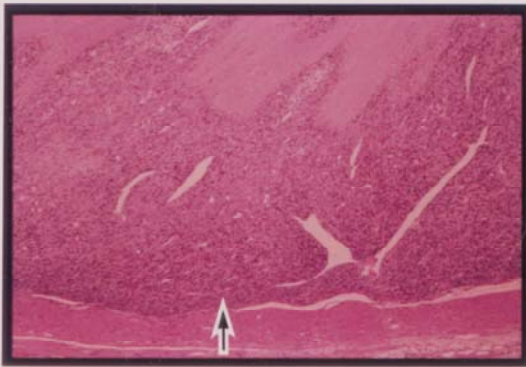
FIGURE 8 FOOD CONSUMPTION : RAT:FEMALE(TWO-YEAR STUDY)



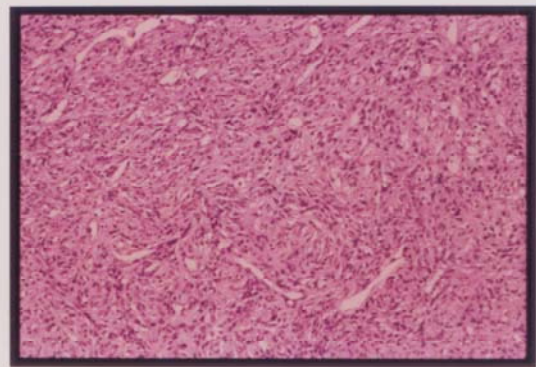
PHOTOGRAPH 1
UTERUS, ENDOMETRIAL STROMAL
POLYP, FEMALE, 7200ppm,
ANIMAL No. 0141-2306 (H. E., X16)



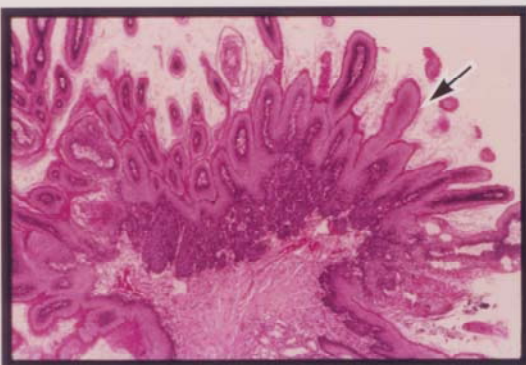
PHOTOGRAPH 2
UTERUS, ENDOMETRIAL STROMAL
SARCOMA, FEMALE, 7200ppm,
ANIMAL No. 0141-2321



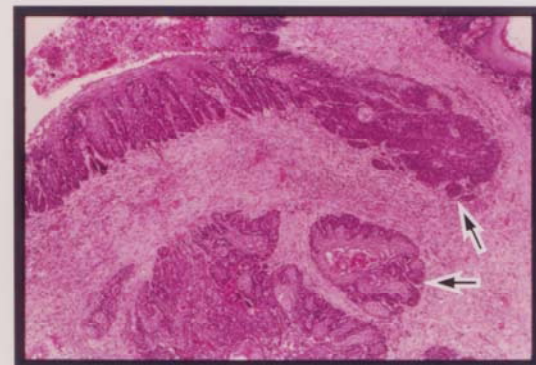
PHOTOGRAPH 3
UTERUS, ENDOMETRIAL STROMAL
SARCOMA, FEMALE, 7200ppm,
ANIMAL No. 0141-2321 (H. E., X32)



PHOTOGRAPH 4
UTERUS, ENDOMETRIAL STROMAL
SARCOMA, FEMALE, 7200ppm,
ANIMAL No. 0141-2321 (H. E., X80)



PHOTOGRAPH 5
STOMACH (FORESTOMACH),
SQUAMOUS CELL PAPPILOMA
MALE, 7200ppm,
ANIMAL No. 0141-1317 (H. E., X32)



PHOTOGRAPH 6
STOMACH (FORESTOMACH),
SQUAMOUS CELL CARCINOMA ,
MALE, 7200ppm,
ANIMAL No. 0141-1331 (H. E., X32)