Summary of Inhalation Carcinogenicity Study of Propiononitrile in F344 Rats

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Japan Bioassay Research Center

Japan Industrial Safety and Health Association

PREFACE

The tests were contracted and supported by the Ministry of Health, Labour and Welfare of Japan. The tests were conducted by Japan Bioassay Research Center (JBRC) and the report was prepared by JBRC and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Health, Labour and Welfare of Japan on March 27, 2007.

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

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Purpose, materials and methods

Propiononitrile (CAS No. 107-12-0) is a colorless liquid with a boiling point of 97.2°C. It is soluble in water and miscible with alcohol and ether.

The carcinogenicity and chronic toxicity of propiononitrile were examined by inhalation exposure of groups of 50 F344/DuCrlCrlj rats of both sexes to propiononitrile vapor at a target concentration of 0 (clean air), 25, 50 or 100 ppm (v/v) for 6 hours/day, 5 days/week for 2 years (104 weeks). The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in the previous 13-week toxicity study. Propiononitrile was analyzed for purity and stability by both infrared spectrometry and gas chromatography before and after its use. Stainless-steel inhalation exposure chambers (volume: 7600 L) were used throughout the 2-year exposure period. Propiononitrile vapor-air mixture was generated by bubbling clean air through the propiononitrile liquid and supplied to the inhalation exposure chambers. Air concentrations of propiononitrile vapor in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. Animals found dead, in a moribund state, or surviving to the end of the 2-year exposure period underwent complete necropsy. Urinalysis was performed near the end of the exposure period. For hematology and blood biochemistry, the surviving animals were bled under ether anesthesia, after they were fasted overnight, at the terminal necropsy. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were fixed and embedded in paraffin. Tissue sections of 5 μm thick were prepared and stained with hematoxylin and eosin and examined for histopathology. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. A positive trend of the dose-response relation for the neoplastic incidence was analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies were conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and with reference to the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

Results

Survival rates of the 100 ppm-exposed males were slightly decreased as compared with the respective controls. Terminal body weight of the 100 ppm-exposed males was suppressed to 92% as compared with the male control. However, there was no significant difference in survival rate or body weight between any propiononitrile-exposed female group and the respective control. Reticulocyte counts were increased in the females exposed to 50 ppm and above.

No significant increase in the incidence of neoplastic lesions was found in any propiononitrile-exposed group of either sex as compared with the respective control. Increased weights of liver and spleen were observed in the females exposed to 50 ppm and above, but the incidences of non-neoplastic lesions in the liver and spleen were not increased in any propiononitrile-exposed group of either sex.

Conclusions

In rats, there was no evidence of carcinogenic activity of propiononitrile in males or females.

TABLES

TABLES (CONTINUED)

TABLE 1　CONCENTRATIONS OF PROPIONONITRILE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
25 ppm	25.1 ± 0.2
50 ppm	50.1 ± 0.4
100 ppm	100.0 ± 2.0

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Week on Study	Control		25 ppm			50 ppm			100 ppm		
	Av. Wt.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>
0	122 (50)	50 / 50	122 (50)	100	50 / 50	122 (50)	100	50 / 50	121 (50)	99	50 / 50
1	151 (50)	50 / 50	150 (50)	99	50 / 50	150 (50)	99	50 / 50	146 (50)	97	50 / 50
2	182 (50)	50 / 50	181 (50)	99	50 / 50	181 (50)	99	50 / 50	170 (50)	93	50 / 50
3	206 (50)	50 / 50	205 (50)	100	50 / 50	205 (50)	100	50 / 50	190 (50)	92	50 / 50
4	225 (50)	50 / 50	226 (50)	100	50 / 50	225 (50)	100	50 / 50	209 (50)	93	50 / 50
5	243 (50)	50 / 50	242 (50)	100	50 / 50	243 (50)	100	50 / 50	227 (50)	93	50 / 50
6	259 (50)	50 / 50	256 (50)	99	50 / 50	257 (50)	99	50 / 50	238 (50)	92	50 / 50
7	271 (50)	50 / 50	268 (50)	99	50 / 50	270 (50)	100	50 / 50	250 (50)	92	50 / 50
8	284 (50)	50 / 50	282 (50)	99	50 / 50	282 (50)	99	50 / 50	261 (50)	92	50 / 50
9	294 (50)	50 / 50	292 (50)	99	50 / 50	292 (50)	99	50 / 50	270 (50)	92	50 / 50
10	302 (50)	50 / 50	300 (50)	99	50 / 50	301 (50)	100	50 / 50	277 (50)	92	50 / 50
11	310 (50)	50 / 50	307 (50)	99	50 / 50	309 (50)	100	50 / 50	286 (50)	92	50 / 50
12	316 (50)	50 / 50	313 (50)	99	50 / 50	314 (50)	99	50 / 50	291 (50)	92	50 / 50
13	321 (50)	50 / 50	319 (50)	99	50 / 50	321 (50)	100	50 / 50	297 (50)	93	50 / 50
17	341 (50)	50 / 50	334 (50)	98	50 / 50	340 (50)	100	50 / 50	315 (50)	92	50 / 50
21	356 (50)	50 / 50	352 (50)	99	50 / 50	353 (50)	99	50 / 50	329 (50)	92	50 / 50
25	368 (50)	50 / 50	364 (50)	99	50 / 50	366 (50)	99	50 / 50	342 (50)	93	50 / 50
29	381 (50)	50 / 50	376 (50)	99	50 / 50	376 (50)	99	50 / 50	351 (50)	92	50 / 50
33	390 (50)	50 / 50	386 (50)	99	50 / 50	386 (50)	99	50 / 50	359 (50)	92	50 / 50
37	391 (50)	50 / 50	388 (50)	99	50 / 50	388 (50)	99	50 / 50	362 (50)	93	50 / 50
41	385 (50)	50 / 50	383 (50)	99	50 / 50	383 (49)	99	50 / 50	358 (50)	93	50 / 50
45	395 (50)	50 / 50	392 (50)	99	50 / 50	392 (50)	99	50 / 50	367 (50)	93	50 / 50
49	409 (49)	49 / 50	405 (50)	99	50 / 50	405 (50)	99	50 / 50	379 (50)	93	50 / 50
53	416 (49)	49 / 50	410 (50)	99	50 / 50	411 (49)	99	49 / 50	385 (50)	93	50 / 50
54	416 (49)	49 / 50	411 (50)	99	50 / 50	412 (49)	99	49 / 50	386 (50)	93	50 / 50
58	418 (49)	49 / 50	415 (50)	99	50 / 50	416 (49)	100	49 / 50	389 (50)	93	50 / 50
62	423 (49)	49 / 50	418 (50)	99	50 / 50	417 (49)	99	49 / 50	393 (50)	93	50 / 50
66	425 (49)	49 / 50	420 (50)	99	50 / 50	418 (49)	98	49 / 50	394 (50)	93	50 / 50
70	428 (49)	49 / 50	423 (50)	99	50 / 50	420 (48)	98	48 / 50	398 (50)	93	50 / 50
74	430 (48)	48 / 50	426 (50)	99	50 / 50	422 (47)	98	47 / 50	401 (50)	93	50 / 50
78	430 (48)	48 / 50	425 (49)	99	49 / 50	420 (47)	98	47 / 50	402 (50)	93	50 / 50
82	428 (47)	47 / 50	422 (49)	99	49 / 50	415 (46)	97	46 / 50	399 (48)	93	48 / 50
86	427 (47)	47 / 50	422 (48)	99	48 / 50	418 (44)	98	44 / 50	399 (48)	93	48 / 50
90	425 (47)	47 / 50	420 (48)	99	48 / 50	417 (44)	98	44 / 50	395 (45)	93	45 / 50
94	421 (47)	47 / 50	422 (47)	100	47 / 50	413 (43)	98	43 / 50	390 (43)	93	43 / 50
98	416 (46)	46 / 50	414 (44)	100	44 / 50	407 (43)	98	43 / 50	383 (39)	92	39 / 50
102	412 (45)	45 / 50	410 (44)	100	44 / 50	400 (43)	97	43 / 50	382 (37)	93	37 / 50
104	408 (44)	44 / 50	406 (44)	100	44 / 50	395 (42)	97	42 / 50	377 (36)	92	36 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. Wt. : Averaged body weight (Unit : g).

TABLE 3 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Week on Study	Control		25 ppm			50 ppm			100 ppm		
	Av. Wt.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>
0	95 (50)	50 / 50	95 (50)	100	50 / 50	95 (50)	100	50 / 50	95 (50)	100	50 / 50
1	109 (50)	50 / 50	109 (50)	100	50 / 50	109 (50)	100	50 / 50	108 (50)	99	50 / 50
2	123 (50)	50 / 50	123 (50)	100	50 / 50	123 (50)	100	50 / 50	120 (50)	98	50 / 50
3	132 (50)	50 / 50	133 (50)	101	50 / 50	132 (50)	100	50 / 50	129 (50)	98	50 / 50
4	140 (50)	50 / 50	142 (50)	101	50 / 50	141 (50)	101	50 / 50	138 (50)	99	50 / 50
5	148 (50)	50 / 50	148 (50)	100	50 / 50	148 (50)	100	50 / 50	146 (50)	99	50 / 50
6	154 (50)	50 / 50	155 (50)	101	50 / 50	154 (50)	100	50 / 50	150 (50)	97	50 / 50
7	157 (50)	50 / 50	159 (50)	101	50 / 50	158 (50)	101	50 / 50	155 (50)	99	50 / 50
8	162 (50)	50 / 50	164 (50)	101	50 / 50	162 (50)	100	50 / 50	160 (50)	99	50 / 50
9	166 (50)	50 / 50	170 (50)	102	50 / 50	166 (50)	100	50 / 50	164 (50)	99	50 / 50
10	170 (50)	50 / 50	173 (50)	102	50 / 50	169 (50)	99	50 / 50	167 (50)	98	50 / 50
11	174 (50)	50 / 50	177 (50)	102	50 / 50	173 (50)	99	50 / 50	171 (50)	98	50 / 50
12	176 (50)	50 / 50	178 (50)	101	50 / 50	176 (50)	100	50 / 50	173 (50)	98	50 / 50
13	178 (50)	50 / 50	182 (50)	102	50 / 50	179 (50)	101	50 / 50	176 (50)	99	50 / 50
17	186 (50)	50 / 50	190 (50)	102	50 / 50	188 (50)	101	50 / 50	183 (50)	98	50 / 50
21	190 (50)	50 / 50	194 (50)	102	50 / 50	190 (50)	100	50 / 50	188 (50)	99	50 / 50
25	196 (50)	50 / 50	200 (50)	102	50 / 50	195 (50)	99	50 / 50	194 (50)	99	50 / 50
29	199 (50)	50 / 50	203 (50)	102	50 / 50	197 (50)	99	50 / 50	197 (50)	99	50 / 50
33	200 (50)	50 / 50	202 (50)	101	50 / 50	197 (50)	99	50 / 50	195 (50)	98	50 / 50
37	209 (50)	50 / 50	212 (50)	101	50 / 50	207 (50)	99	50 / 50	206 (50)	99	50 / 50
41	213 (50)	50 / 50	216 (50)	101	50 / 50	210 (50)	99	50 / 50	210 (50)	99	50 / 50
45	215 (50)	50 / 50	219 (50)	102	50 / 50	212 (50)	99	50 / 50	212 (50)	99	50 / 50
49	218 (50)	50 / 50	222 (50)	102	50 / 50	215 (50)	99	50 / 50	215 (50)	99	50 / 50
53	221 (50)	50 / 50	225 (50)	102	50 / 50	219 (50)	99	50 / 50	217 (50)	98	50 / 50
54	221 (50)	50 / 50	226 (50)	102	50 / 50	219 (50)	99	50 / 50	217 (50)	98	50 / 50
58	224 (50)	50 / 50	230 (50)	103	50 / 50	221 (49)	99	49 / 50	221 (49)	99	49 / 50
62	228 (50)	50 / 50	236 (50)	104	50 / 50	224 (49)	98	49 / 50	225 (49)	99	49 / 50
66	233 (50)	50 / 50	241 (50)	103	50 / 50	228 (47)	98	47 / 50	228 (49)	98	49 / 50
70	238 (50)	50 / 50	246 (50)	103	50 / 50	233 (47)	98	47 / 50	234 (49)	98	49 / 50
74	243 (50)	50 / 50	250 (50)	103	50 / 50	238 (47)	98	47 / 50	239 (48)	98	48 / 50
78	246 (49)	49 / 50	254 (50)	103	50 / 50	243 (46)	99	46 / 50	244 (48)	99	48 / 50
82	249 (47)	47 / 50	257 (50)	103	50 / 50	245 (45)	98	45 / 50	246 (47)	99	47 / 50
86	253 (45)	45 / 50	260 (50)	103	50 / 50	249 (44)	98	44 / 50	250 (47)	99	47 / 50
90	257 (44)	44 / 50	264 (49)	103	49 / 50	254 (43)	99	43 / 50	253 (46)	98	46 / 50
94	259 (44)	44 / 50	268 (47)	103	47 / 50	254 (40)	98	40 / 50	255 (45)	98	45 / 50
98	257 (42)	42 / 50	269 (47)	105	47 / 50	260 (39)	101	39 / 50	254 (42)	99	42 / 50
102	258 (40)	40 / 50	272 (45)	105	45 / 50	261 (37)	101	37 / 50	257 (39)	100	39 / 50
104	259 (37)	37 / 50	271 (45)	105	45 / 50	259 (36)	100	36 / 50	256 (39)	99	39 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. Wt. : Averaged body weight (Unit : g).

TABLE 4 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Week on Study	Control		25 ppm			50 ppm			100 ppm		
	Av. FC.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>
1	14.4 (50)	50 / 50	14.3 (50)	99	50 / 50	14.1 (50)	98	50 / 50	13.2 (50)	92	50 / 50
2	15.7 (50)	50 / 50	15.7 (50)	100	50 / 50	15.4 (50)	98	50 / 50	13.9 (50)	89	50 / 50
3	16.8 (50)	50 / 50	16.9 (50)	101	50 / 50	16.6 (50)	99	50 / 50	14.8 (50)	88	50 / 50
4	16.9 (50)	50 / 50	16.7 (50)	99	50 / 50	16.7 (50)	99	50 / 50	15.5 (50)	92	50 / 50
5	16.9 (50)	50 / 50	16.9 (50)	100	50 / 50	17.0 (50)	101	50 / 50	16.4 (50)	97	50 / 50
6	16.6 (50)	50 / 50	16.4 (50)	99	50 / 50	16.6 (50)	100	50 / 50	15.4 (50)	93	50 / 50
7	16.7 (50)	50 / 50	16.5 (50)	99	50 / 50	16.3 (50)	98	50 / 50	15.0 (50)	90	50 / 50
8	17.2 (50)	50 / 50	17.3 (50)	101	50 / 50	16.9 (50)	98	50 / 50	15.9 (50)	92	50 / 50
9	16.9 (50)	50 / 50	16.8 (50)	99	50 / 50	16.7 (50)	99	50 / 50	15.5 (50)	92	50 / 50
10	16.9 (50)	50 / 50	16.8 (50)	99	50 / 50	16.8 (50)	99	50 / 50	15.9 (50)	94	50 / 50
11	16.4 (50)	50 / 50	16.2 (50)	99	50 / 50	16.4 (50)	100	50 / 50	15.5 (50)	95	50 / 50
12	16.1 (50)	50 / 50	15.9 (50)	99	50 / 50	16.2 (50)	101	50 / 50	15.3 (50)	95	50 / 50
13	15.9 (50)	50 / 50	15.7 (50)	99	50 / 50	16.0 (50)	101	50 / 50	15.0 (50)	94	50 / 50
17	16.0 (50)	50 / 50	15.5 (50)	97	50 / 50	15.9 (50)	99	50 / 50	15.2 (50)	95	50 / 50
21	16.3 (50)	50 / 50	16.0 (50)	98	50 / 50	16.0 (50)	98	50 / 50	15.3 (50)	94	50 / 50
25	16.0 (50)	50 / 50	15.8 (50)	99	50 / 50	15.7 (50)	98	50 / 50	15.3 (50)	96	50 / 50
29	16.6 (50)	50 / 50	16.5 (50)	99	50 / 50	16.4 (50)	99	50 / 50	15.8 (50)	95	50 / 50
33	16.4 (50)	50 / 50	16.3 (50)	99	50 / 50	16.2 (50)	99	50 / 50	15.2 (50)	93	50 / 50
37	15.4 (50)	50 / 50	15.0 (50)	97	50 / 50	15.5 (50)	101	50 / 50	15.0 (50)	97	50 / 50
41	15.7 (50)	50 / 50	15.6 (50)	99	50 / 50	15.6 (50)	99	50 / 50	15.3 (50)	97	50 / 50
45	15.7 (50)	50 / 50	15.9 (50)	101	50 / 50	15.6 (50)	99	50 / 50	15.0 (50)	96	50 / 50
50	16.5 (49)	49 / 50	16.4 (50)	99	50 / 50	16.3 (49)	99	49 / 50	15.5 (25)	94	50 / 50
53	16.5 (49)	49 / 50	16.5 (50)	100	50 / 50	16.1 (49)	98	49 / 50	15.8 (50)	96	50 / 50
54	16.5 (49)	49 / 50	16.4 (50)	99	50 / 50	16.2 (49)	98	49 / 50	15.9 (50)	96	50 / 50
58	16.2 (49)	49 / 50	16.3 (50)	101	50 / 50	16.3 (49)	101	49 / 50	15.7 (50)	97	50 / 50
62	17.1 (49)	49 / 50	16.9 (50)	99	50 / 50	16.6 (49)	97	49 / 50	16.3 (50)	95	50 / 50
66	16.9 (49)	49 / 50	16.8 (50)	99	50 / 50	16.6 (49)	98	49 / 50	16.1 (50)	95	50 / 50
70	17.2 (49)	49 / 50	17.0 (50)	99	50 / 50	17.0 (48)	99	48 / 50	16.6 (50)	97	50 / 50
74	16.7 (48)	48 / 50	16.5 (50)	99	50 / 50	16.5 (47)	99	47 / 50	16.1 (50)	96	50 / 50
78	16.7 (48)	48 / 50	16.4 (49)	98	49 / 50	16.6 (47)	99	47 / 50	16.4 (50)	98	50 / 50
82	16.3 (47)	47 / 50	16.1 (49)	99	49 / 50	16.1 (46)	99	46 / 50	15.9 (48)	98	48 / 50
86	16.6 (47)	47 / 50	16.3 (48)	98	48 / 50	16.7 (44)	101	44 / 50	16.2 (48)	98	48 / 50
90	16.2 (47)	47 / 50	16.3 (48)	101	48 / 50	16.8 (44)	104	44 / 50	15.9 (45)	98	45 / 50
94	16.3 (47)	47 / 50	16.4 (47)	101	47 / 50	16.7 (43)	102	43 / 50	15.4 (43)	94	43 / 50
98	16.5 (46)	46 / 50	16.7 (44)	101	44 / 50	16.9 (43)	102	43 / 50	15.5 (39)	94	39 / 50
102	16.5 (45)	45 / 50	16.7 (44)	101	44 / 50	16.4 (43)	99	43 / 50	16.2 (37)	98	37 / 50
104	16.5 (44)	44 / 50	16.7 (44)	101	44 / 50	16.9 (42)	102	42 / 50	15.9 (36)	96	36 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. FC. : Averaged food consumption (Unit : g).

TABLE 5 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Week on Study	Control		25 ppm			50 ppm			100 ppm		
	Av. FC.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>
1	10.5 (50)	50 / 50	10.2 (50)	97	50 / 50	10.1 (50)	96	50 / 50	10.0 (50)	95	50 / 50
2	11.0 (50)	50 / 50	11.1 (50)	101	50 / 50	11.0 (50)	100	50 / 50	10.5 (50)	95	50 / 50
3	11.0 (50)	50 / 50	11.3 (50)	103	50 / 50	11.0 (50)	100	50 / 50	10.9 (50)	99	50 / 50
4	11.2 (50)	50 / 50	11.4 (50)	102	50 / 50	11.3 (50)	101	50 / 50	11.1 (45)	99	50 / 50
5	11.5 (50)	50 / 50	11.6 (50)	101	50 / 50	11.7 (50)	102	50 / 50	11.8 (50)	103	50 / 50
6	11.1 (50)	50 / 50	11.2 (50)	101	50 / 50	10.9 (50)	98	50 / 50	10.6 (50)	95	50 / 50
7	10.8 (50)	50 / 50	11.3 (50)	105	50 / 50	10.9 (50)	101	50 / 50	10.7 (50)	99	50 / 50
8	10.9 (50)	50 / 50	10.9 (50)	100	50 / 50	10.7 (50)	98	50 / 50	10.6 (50)	97	50 / 50
9	10.9 (50)	50 / 50	11.5 (50)	106	50 / 50	10.9 (50)	100	50 / 50	10.8 (50)	99	50 / 50
10	10.7 (50)	50 / 50	11.1 (50)	104	50 / 50	10.8 (50)	101	50 / 50	10.4 (50)	97	50 / 50
11	11.0 (50)	50 / 50	11.2 (50)	102	50 / 50	10.8 (50)	98	50 / 50	11.0 (50)	100	50 / 50
12	10.4 (50)	50 / 50	10.5 (50)	101	50 / 50	10.6 (50)	102	50 / 50	10.4 (50)	100	50 / 50
13	10.7 (50)	50 / 50	11.3 (50)	106	50 / 50	11.0 (50)	103	50 / 50	10.7 (50)	100	50 / 50
17	10.9 (50)	50 / 50	11.2 (50)	103	50 / 50	11.0 (50)	101	50 / 50	10.7 (50)	98	50 / 50
21	10.4 (50)	50 / 50	10.6 (50)	102	50 / 50	10.3 (50)	99	50 / 50	10.4 (50)	100	50 / 50
25	11.1 (50)	50 / 50	11.4 (50)	103	50 / 50	10.7 (50)	96	50 / 50	10.7 (50)	96	50 / 50
29	10.8 (50)	50 / 50	11.1 (50)	103	50 / 50	10.6 (50)	98	50 / 50	11.1 (50)	103	50 / 50
33	10.5 (50)	50 / 50	10.5 (50)	100	50 / 50	10.4 (50)	99	50 / 50	10.0 (50)	95	50 / 50
37	12.4 (50)	50 / 50	12.5 (49)	101	50 / 50	12.1 (50)	98	50 / 50	12.4 (50)	100	50 / 50
41	11.1 (50)	50 / 50	11.3 (50)	102	50 / 50	11.0 (50)	99	50 / 50	11.5 (50)	104	50 / 50
45	11.3 (50)	50 / 50	11.5 (50)	102	50 / 50	10.8 (50)	96	50 / 50	11.1 (50)	98	50 / 50
50	10.5 (50)	50 / 50	10.8 (50)	103	50 / 50	10.1 (50)	96	50 / 50	10.5 (50)	100	50 / 50
53	11.2 (50)	50 / 50	11.4 (50)	102	50 / 50	11.1 (50)	99	50 / 50	10.8 (50)	96	50 / 50
54	10.8 (50)	50 / 50	11.2 (50)	104	50 / 50	10.8 (50)	100	50 / 50	10.7 (50)	99	50 / 50
58	11.0 (50)	50 / 50	11.3 (50)	103	50 / 50	10.6 (49)	96	49 / 50	10.8 (49)	98	49 / 50
62	11.5 (50)	50 / 50	11.8 (50)	103	50 / 50	11.5 (49)	100	49 / 50	11.4 (49)	99	49 / 50
66	11.6 (50)	50 / 50	11.8 (50)	102	50 / 50	11.2 (47)	97	47 / 50	11.5 (49)	99	49 / 50
70	11.7 (50)	50 / 50	12.0 (50)	103	50 / 50	11.6 (47)	99	47 / 50	11.8 (49)	101	49 / 50
74	11.5 (50)	50 / 50	11.8 (50)	103	50 / 50	11.5 (47)	100	47 / 50	11.4 (48)	99	48 / 50
78	11.5 (49)	49 / 50	12.0 (50)	104	50 / 50	11.6 (46)	101	46 / 50	11.7 (48)	102	48 / 50
82	11.4 (47)	47 / 50	11.8 (50)	104	50 / 50	11.6 (45)	102	45 / 50	11.6 (47)	102	47 / 50
86	11.8 (45)	45 / 50	12.1 (50)	103	50 / 50	12.0 (44)	102	44 / 50	11.9 (47)	101	47 / 50
90	12.0 (44)	44 / 50	12.2 (49)	102	49 / 50	12.0 (43)	100	43 / 50	11.8 (46)	98	46 / 50
94	11.7 (44)	44 / 50	12.2 (47)	104	47 / 50	11.9 (40)	102	40 / 50	11.6 (45)	99	45 / 50
98	11.9 (42)	42 / 50	12.5 (47)	105	47 / 50	12.6 (39)	106	39 / 50	12.0 (42)	101	42 / 50
102	11.6 (40)	40 / 50	12.4 (44)	107	45 / 50	12.3 (37)	106	37 / 50	12.3 (39)	106	39 / 50
104	12.2 (37)	37 / 50	12.4 (45)	102	45 / 50	12.0 (36)	98	36 / 50	11.9 (39)	98	39 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. FC. : Averaged food consumption (Unit : g).

TABLE 6 HEMATOLOGY OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Group Name	Control	25 ppm	50 ppm	100 ppm
No. of examined animals	37	45	36	39
MCV (fL)	51.3 ± 2.1	51.4 ± 3.1	52.7 ± 7.9	53.4 ± 5.0 **
MCH (pg)	18.3 ± 0.5	18.2 ± 1.0	18.5 ± 1.7	18.6 ± 0.9 *
MCHC (g/dL)	35.7 ± 1.1	35.4 ± 1.6	35.4 ± 1.7	35.0 ± 2.0 **
RETICULOCYTE (%)	3.1 ± 4.2	3.3 ± 3.8	4.8 ± 8.0 *	3.9 ± 3.5 **

Mean ± S.D.
Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 7 BIOCHEMISTRY OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Group Name	Control	25 ppm	50 ppm	100 ppm	
No. of examined animals	37	45	36	39	
PHOSPHOLIPID (mg/dL)	221 ± 39	227 ± 38	231 ± 46	250 ± 57	*

Mean ± S.D.
Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 8 ORGAN WEIGHTS OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Group Name	Control	25 ppm	50 ppm	100 ppm
No. of examined animals	44	44	42	36
Body weight (g)	382 ± 31	380 ± 24	367 ± 28 *	352 ± 29 **
Kidneys (g)	2.710 ± 0.320	2.649 ± 0.214	2.704 ± 0.355	2.592 ± 0.199
Kidneys (%)	0.714 ± 0.112	0.700 ± 0.062	0.740 ± 0.103	0.741 ± 0.079 *
Liver (g)	10.727 ± 1.801	10.903 ± 1.375	10.879 ± 1.498	10.537 ± 1.089
Liver (%)	2.801 ± 0.319	2.871 ± 0.296	2.972 ± 0.413	3.002 ± 0.298 *
Brain (g)	2.074 ± 0.046	2.069 ± 0.043	2.057 ± 0.044	2.057 ± 0.046
Brain (%)	0.546 ± 0.042	0.547 ± 0.036	0.564 ± 0.047	0.588 ± 0.051 **

Mean ± S.D.
Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 9 ORGAN WEIGHTS OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Group Name	Control	25 ppm	50 ppm	100 ppm
No. of examined animals	37	45	36	39
Body weight (g)	240 ± 21	252 ± 27	241 ± 27	238 ± 24
Heart (g)	0.822 ± 0.063	0.881 ± 0.073 **	0.878 ± 0.079 **	0.854 ± 0.076
Heart (%)	0.343 ± 0.030	0.351 ± 0.034	0.368 ± 0.054 *	0.361 ± 0.045
Spleen (g)	0.553 ± 0.250	0.681 ± 0.851	1.017 ± 1.818 *	0.995 ± 1.866 *
Spleen (%)	0.232 ± 0.108	0.275 ± 0.363	0.473 ± 1.037	0.432 ± 0.874
Liver (g)	6.101 ± 0.822	6.477 ± 0.992	6.543 ± 0.876 *	6.711 ± 1.338 *
Liver (%)	2.542 ± 0.295	2.569 ± 0.305	2.737 ± 0.452 **	2.824 ± 0.505 **

Mean ± S.D.
Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 10 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Group Name	Control	25 ppm	50 ppm	100 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage test
subcutis	<50>	<50>	<50>	<50>		
fibroma	1 (2 %)	8 (16 %) *	2 (4 %)	3 (6 %)		
pituitary gland	<50>	<50>	<50>	<50>		
adenoma	6 (12 %)	4 (8 %)	7 (14 %)	8 (16 %)	↑	

Significant difference: * : p≦0.05 ** : p≦0.01 Fisher's exact test for neoplastic lesion
↑(↓) : p≦0.05 ↑↑(↓↓) : p≦0.01 Peto or Cochran-Armitage test for neoplastic lesion
< > : Number of animals examined at the site

TABLE 11 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

Group Name	Control	25 ppm	50 ppm	100 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage test
uterus	<50>	<50>	<50>	<50>		
endometrial stromal sarcoma	4 (8 %)	0 (0 %)	2 (4 %)	2 (4 %)	↑	

Significant difference: * : p≦0.05 ** : p≦0.01 Fisher's exact test for neoplastic lesion
↑(↓) : p≦0.05 ↑↑(↓↓) : p≦0.01 Peto or Cochran-Armitage test for neoplastic lesion
< > : Number of animals examined at the site

TABLE 12 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj MALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Subcutis	2099			
Fibroma		159	7.6	2 - 20
Pituitary gland	2093			
Adenoma		682	32.6	14 - 66

42 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. : 0043, 0059, 0061, 0063, 0065, 0067, 0095, 0104, 0115, 0130, 0141, 0158, 0162, 0189, 0205, 0210, 0224, 0242, 0246, 0267, 0269, 0278, 0284, 0288, 0294, 0296, 0318, 0328, 0342, 0347, 0365, 0371, 0396, 0399, 0401, 0407, 0417, 0421, 0437, 0448, 0457, 0461

TABLE 13 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj FEMALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Uterus	1947			
Endometrial stromal sarcoma		23	1.2	0 - 8

39 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. : 0043, 0059, 0061, 0063, 0065, 0067, 0095, 0104, 0115, 0130, 0141, 0158, 0162, 0189, 0205, 0210, 0224, 0242, 0246, 0267, 0269, 0278, 0284, 0296, 0303, 0318, 0328, 0342, 0347, 0365, 0371, 0399, 0401, 0417, 0421, 0437, 0448, 0457, 0461

TABLE 14 CAUSE OF DEATH OF RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

		Male				Female			
Group name		Control	25 ppm	50 ppm	100 ppm	Control	25 ppm	50 ppm	100 ppm
Number of dead or moribund animals		6	6	8	14	13	5	14	11
no microscopical confirmation		0	0	0	1	0	0	2	2
tumor death :	leukemia	2	3	3	3	5	2	4	6
	skin/appendage	0	1	0	1	0	0	0	0
	subcutis	1	1	0	2	0	0	0	1
	stomach	0	1	0	0	0	0	0	0
	kidney	0	0	1	0	0	0	0	1
	pituitary gland	0	0	1	2	2	1	1	0
	thyroid	0	0	1	0	0	0	0	0
	adrenal gland	0	0	0	1	0	0	0	0
	ovary	—	—	—	—	0	0	1	0
	uterus	—	—	—	—	6	0	2	0
	mammary gland	0	0	0	1	0	1	2	0
	clitorel gland	—	—	—	—	0	0	0	1
	brain	0	0	1	0	0	1	1	0
	peripheral nerves	1	0	0	0	0	0	0	0
	Zymbal gland	0	0	0	2	0	0	0	0
	bone	2	0	0	0	0	0	1	0
	vertebra	0	0	1	0	0	0	0	0
	peritoneum	0	0	0	1	0	0	0	0

FIGURES

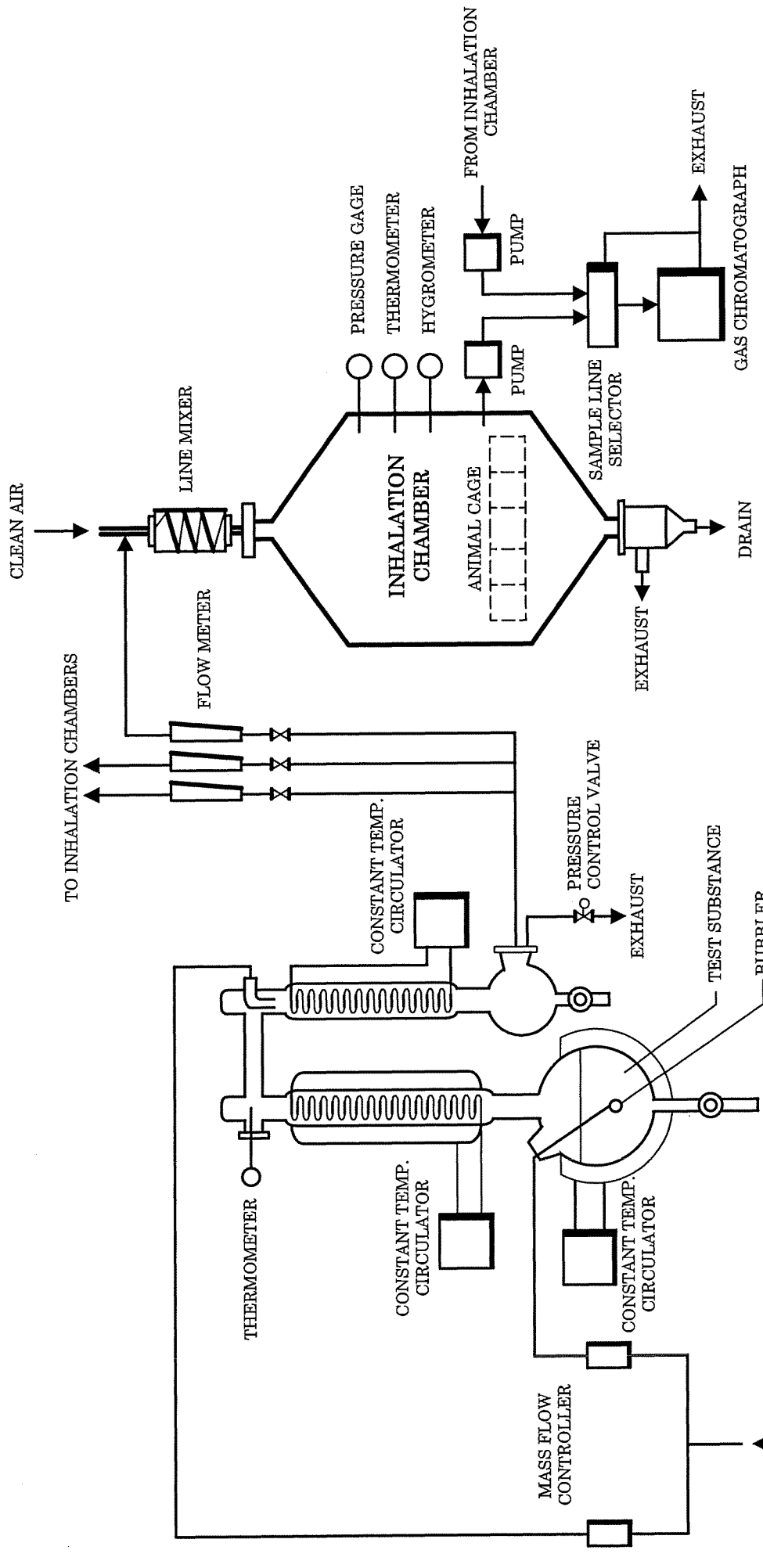

FIGURE 1 PROPIONONITRILE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

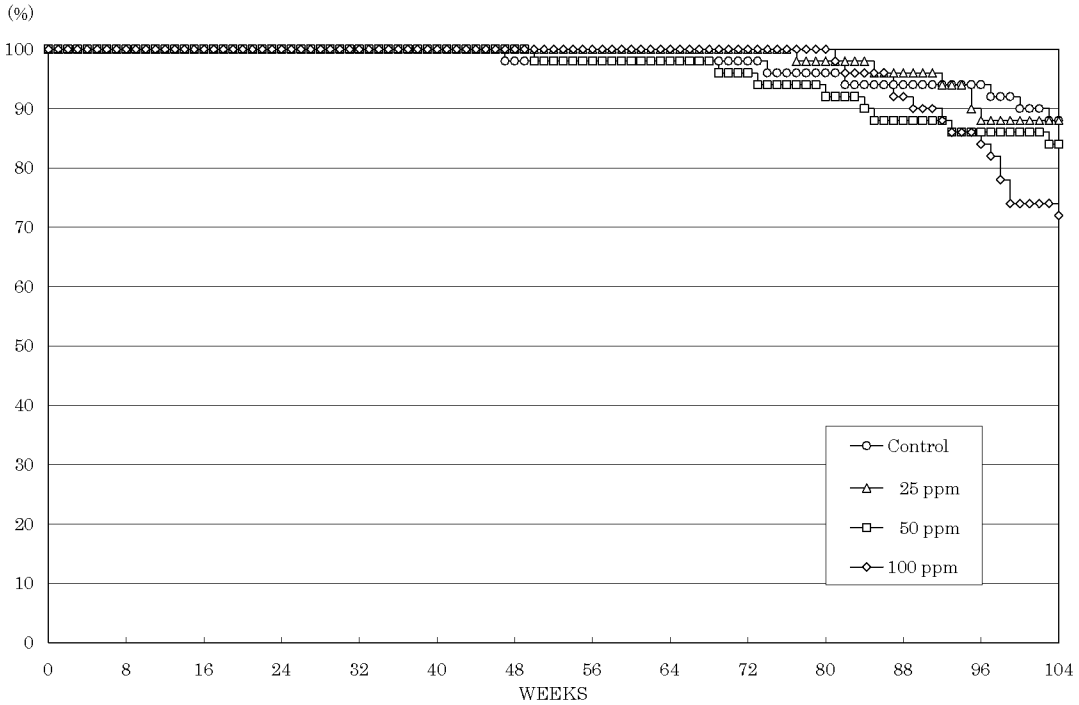

FIGURE 2 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

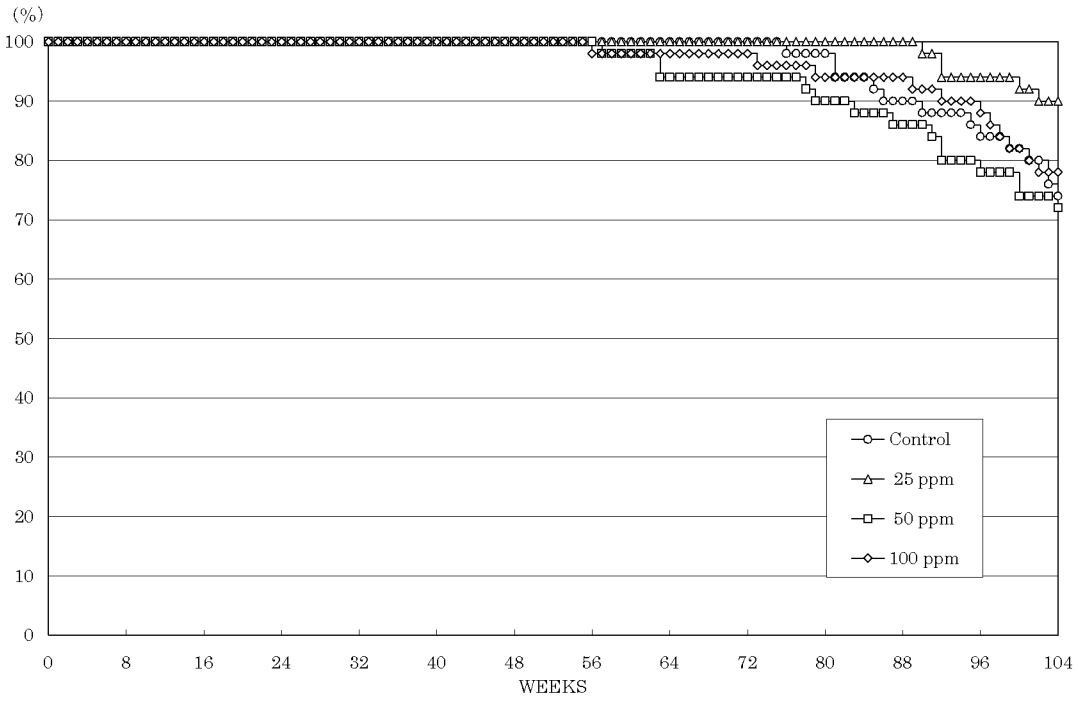

FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

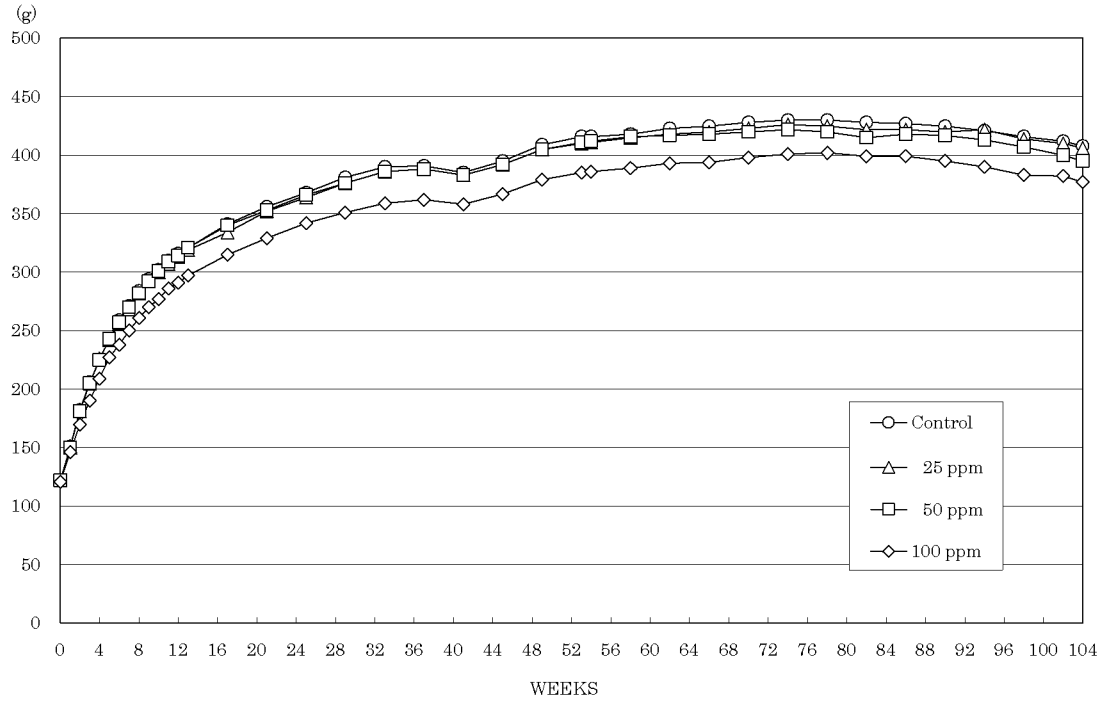

FIGURE 4 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

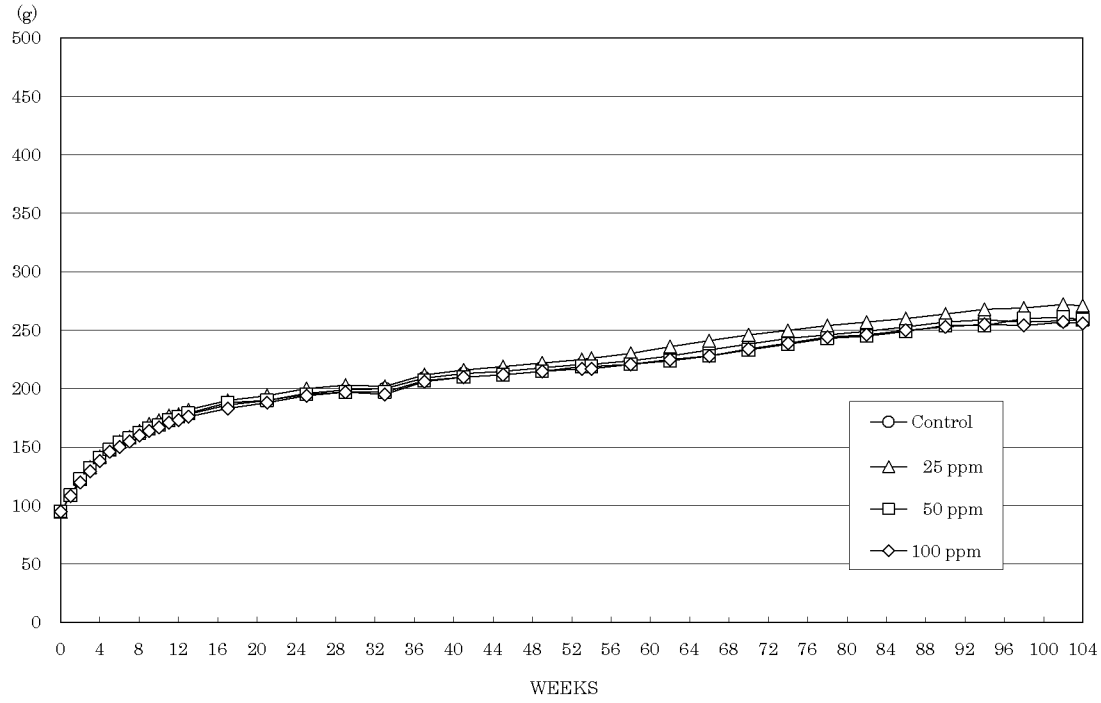

FIGURE 5 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

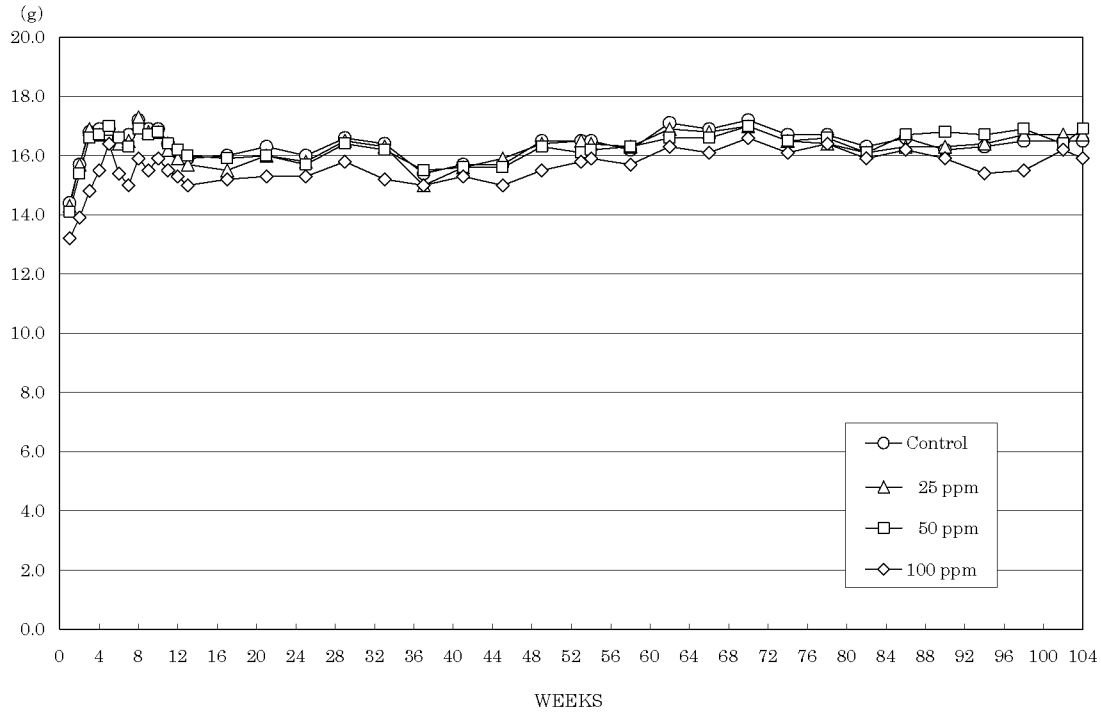

FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE

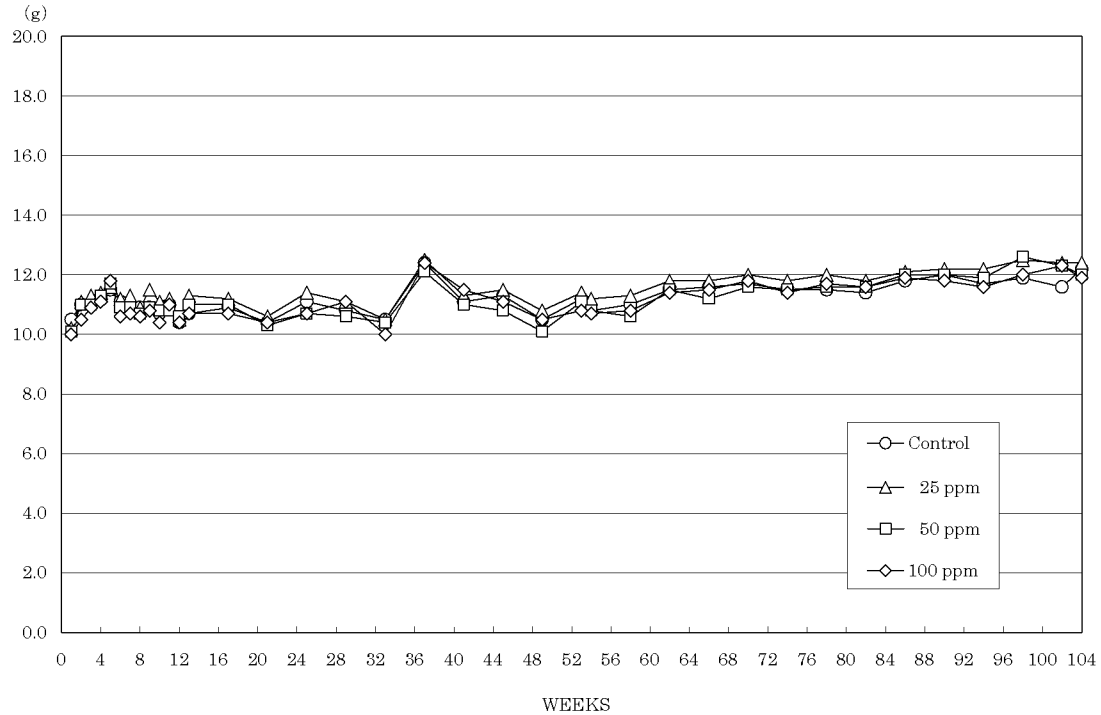

FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF PROPIONONITRILE