Summary of Inhalation Carcinogenicity Study of Glycidol in F344 Rats

March 2003

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 25 2003.

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

Summary of Inhalation Carcinogenicity Study of Glycidol in F344 Rats

Purpose, materials and methods

Glycidol (CAS No. 556-52-5) is colorless liquid with a boiling point of 166-167°C. It is soluble in water, ethanol and diethyl ether.

The carcinogenicity and chronic toxicity of glycidol were examined by inhalation exposure of groups of 50 F344/DuCrj (Fischer) rats of both sexes to glycidol vapor at a target concentration of 0 (clean air), 3, 10 or 30 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. Glycidol 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. Glycidol vapor-air mixture was generated by bubbling clean air through the glycidol liquid, and supplied to the inhalation exposure chambers. Air concentrations of glycidol 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

There was a significant difference in survival rate between the 30 ppm-exposed groups of both sexes and the respective controls. The decreased survival rates were attributed to the increased number of deaths due to the peritoneal mesothelioma and nasal cavity tumors in the males and due to the uterine tumor in the females. Body weights of the 30 ppm-exposed male and female groups were slightly decreased as compared with the respective controls.

The incidences of nasal cavity tumors (squamous cell carcinomas, adenomas, adenocarcinomas and basal cell carcinomas) and peritoneal tumors (mesotheliomas) were increased markedly in the males. The incidences of mammary gland tumors (fibroadenomas) and skin tumors (squamous cell papillomas) were increased in the males. In females, the incidences of nasal cavity tumors (adenomas, adenocarcinomas, squamous cell carcinomas), uterine tumors (endometrial stromal sarcomas), and mammary gland tumors (fibroadenomas) were increased. The significantly increased incidences of peritoneal tumors (mesotheliomas) occurred in the males exposed to 10 ppm and above, while those of nasal cavity tumors (squamous cell carcinomas, adenomas) and mammary gland tumors (fibroadenomas) appeared in the 30 ppm-exposed males. The increased incidence of mammary gland tumors (fibroadenomas) was observed in the females exposed to 10 ppm and above, while nasal cavity tumors (adenomas) and uterine tumors (endometrial stromal sarcomas) were observed in the 30 ppm-exposed females. As pre-neoplastic lesions, hyperplasia in the transitional and respiratory epithelia, and squamous cell metaplasia and squamous cell hyperplasia in the respiratory epithelium were observed, and those nasal lesions were accompanied by atypia. In addition, inflammation in the respiratory epithelium, thickening of bone in the turbinate and atrophy in the olfactory epithelium were also observed. Those histopathological lesions were observed primarily in the 30ppm-exposed groups, while thickening of bone in the turbinate and hyperplasia in the transitional epithelium were observed at 10 ppm and above.

Conclusions

In rats, there was clear evidence of carcinogenic activity of glycidol in males and females, based on the increased incidences of nasal cavity tumors (squamous cell carcinomas, adenomas, adenocarcinomas and basal cell carcinomas) and peritoneal tumors (mesotheliomas) in the males, and based on the increased incidences of nasal cavity tumors (adenomas, adenocarcinomas and squamous cell carcinomas), and uterine tumors (endometrial stromal sarcomas) in the females. Additionally, hyperplasia in the transitional and respiratory epithelia accompanied by atypia, squamous cell metaplasia and squamous cell hyperplasia in the respiratory epithelium were observed in the glycidol-exposed males and females, and those lesions were thought to be pre-neoplastic. Thickening of bone in the turbinate was also observed.

TABLES

TABLES (CONTINUED)

TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Weeks on Study	Control Av.Wt.	Control No.of Surviv. <50>	3ppm Av.Wt.	3ppm % of cont.	3ppm No.of Surviv. <50>	10ppm Av.Wt.	10ppm % of cont.	10ppm No.of Surviv. <50>	30ppm Av.Wt.	30ppm % of cont.	30ppm No.of Surviv. <50>
0	122 50)	50/50	122 50)	100	50/50	122 50)	100	50/50	122 50)	100	50/50
1	152 50)	50/50	152 50)	100	50/50	152 50)	100	50/50	152 50)	100	50/50
2	180 50)	50/50	180 50)	100	50/50	180 50)	100	50/50	179 50)	99	50/50
3	204 50)	50/50	202 50)	99	50/50	203 50)	100	50/50	201 50)	99	50/50
4	221 50)	50/50	219 50)	99	50/50	219 50)	99	50/50	217 50)	98	50/50
5	242 50)	50/50	238 50)	98	50/50	238 50)	98	50/50	235 50)	97	50/50
6	256 50)	50/50	252 50)	98	50/50	251 50)	98	50/50	249 50)	97	50/50
7	270 50)	50/50	265 50)	98	50/50	264 50)	98	50/50	261 50)	97	50/50
8	280 50)	50/50	276 50)	99	50/50	274 50)	98	50/50	271 50)	97	50/50
9	289 50)	50/50	284 50)	98	50/50	283 50)	98	50/50	279 50)	97	50/50
10	297 50)	50/50	292 50)	98	50/50	291 50)	98	50/50	288 50)	97	50/50
11	304 50)	50/50	299 50)	98	50/50	298 50)	98	50/50	295 50)	97	50/50
12	311 50)	50/50	305 50)	98	50/50	305 50)	98	50/50	300 50)	96	50/50
13	317 50)	50/50	314 50)	99	50/50	312 50)	98	50/50	307 50)	97	50/50
14	324 50)	50/50	319 50)	98	50/50	317 50)	98	50/50	313 50)	97	50/50
18	340 50)	50/50	337 50)	99	50/50	333 50)	98	50/50	328 50)	96	50/50
22	354 50)	50/50	350 50)	99	50/50	347 50)	98	50/50	341 50)	96	50/50
26	368 50)	50/50	365 50)	99	50/50	359 50)	98	50/50	351 50)	95	50/50
30	378 50)	50/50	376 50)	99	50/50	368 50)	97	50/50	360 50)	95	50/50
34	387 50)	50/50	385 50)	99	50/50	378 50)	98	50/50	370 50)	96	50/50
38	393 50)	50/50	393 50)	100	50/50	384 50)	98	50/50	377 50)	96	50/50
42	401 50)	50/50	400 50)	100	50/50	391 50)	98	50/50	385 50)	96	50/50
46	406 50)	50/50	405 50)	100	50/50	395 50)	97	50/50	390 50)	96	50/50
50	412 50)	50/50	411 50)	100	50/50	402 50)	98	50/50	397 50)	96	50/50
54	416 50)	50/50	415 50)	100	50/50	407 50)	98	50/50	401 50)	96	50/50
58	420 50)	50/50	417 49)	99	49/50	409 50)	97	50/50	404 50)	96	50/50
62	422 50)	50/50	420 49)	100	49/50	411 50)	97	50/50	402 50)	95	50/50
66	423 50)	50/50	419 49)	99	49/50	411 50)	97	50/50	401 50)	95	50/50
70	427 49)	49/50	421 48)	99	48/50	414 50)	97	50/50	400 48)	94	48/50
74	427 49)	49/50	419 48)	98	48/50	415 50)	97	50/50	395 47)	93	47/50
78	426 49)	49/50	423 46)	99	46/50	413 50)	97	50/50	389 46)	91	46/50
82	422 47)	47/50	421 46)	100	46/50	408 48)	97	48/50	393 44)	93	43/50
86	421 46)	46/50	423 46)	100	46/50	408 47)	97	46/50	386 42)	92	42/50
90	419 46)	46/50	419 44)	100	44/50	406 46)	97	46/50	376 39)	90	39/50
94	413 44)	44/50	415 43)	100	43/50	403 44)	98	44/50	370 37)	90	36/50
98	412 42)	42/50	415 42)	101	42/50	395 42)	96	42/50	349 33)	85	31/50
102	406 40)	40/50	413 42)	102	42/50	395 39)	97	39/50	347 26)	85	25/50
104	401 40)	40/50	411 42)	102	42/50	392 38)	98	38/50	336 23)	84	23/50

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

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

Weeks on Study	Control Av.Wt.	Control No.of Surviv. <50>	3ppm Av.Wt.	3ppm % of cont.	3ppm No.of Surviv. <50>	10ppm Av.Wt.	10ppm % of cont.	10ppm No.of Surviv. <49>	30ppm Av.Wt.	30ppm % of cont.	30ppm No.of Surviv. <50>
0	96 50)	50/50	96 50)	100	50/50	96 49)	100	50/50	96 50)	100	50/50
1	110 50)	50/50	109 50)	99	50/50	110 49)	100	50/50	110 50)	100	50/50
2	122 50)	50/50	122 50)	100	50/50	122 49)	100	50/50	121 50)	99	50/50
3	133 50)	50/50	132 50)	99	50/50	132 49)	99	50/50	132 50)	99	50/50
4	139 50)	50/50	138 50)	99	50/50	138 49)	99	50/50	137 50)	99	50/50
5	150 50)	50/50	148 50)	99	50/50	148 49)	99	50/50	147 50)	98	50/50
6	156 50)	50/50	154 50)	99	50/50	153 49)	98	50/50	152 50)	97	50/50
7	162 50)	50/50	159 50)	98	50/50	158 49)	98	50/50	157 50)	97	50/50
8	165 50)	50/50	161 50)	98	50/50	161 49)	98	50/50	159 50)	96	50/50
9	170 50)	50/50	166 50)	98	50/50	166 49)	98	50/50	164 50)	96	50/50
10	176 50)	50/50	172 50)	98	50/50	171 49)	97	49/49	168 50)	95	50/50
11	180 50)	50/50	175 50)	97	50/50	174 49)	97	49/49	171 50)	95	50/50
12	182 50)	50/50	178 50)	98	50/50	176 49)	97	49/49	173 50)	95	50/50
13	185 50)	50/50	182 50)	98	50/50	180 49)	97	49/49	177 50)	96	50/50
14	188 50)	50/50	182 50)	97	50/50	182 49)	97	49/49	179 50)	95	50/50
18	192 50)	50/50	188 50)	98	50/50	185 49)	96	49/49	183 50)	95	50/50
22	197 50)	50/50	195 50)	99	50/50	190 49)	96	49/49	188 50)	95	50/50
26	205 50)	50/50	204 50)	100	50/50	198 49)	97	49/49	195 50)	95	50/50
30	211 50)	50/50	209 50)	99	50/50	203 49)	96	49/49	200 50)	95	50/50
34	216 50)	50/50	215 50)	100	50/50	208 49)	96	49/49	206 50)	95	50/50
38	217 50)	50/50	216 50)	100	50/50	211 49)	97	49/49	206 50)	95	50/50
42	221 50)	50/50	220 50)	100	50/50	214 49)	97	49/49	211 50)	95	50/50
46	224 50)	50/50	225 50)	100	50/50	219 49)	98	49/49	215 50)	96	50/50
50	227 50)	50/50	230 50)	101	50/50	222 49)	98	49/49	220 50)	97	50/50
54	232 50)	50/50	234 50)	101	50/50	228 49)	98	49/49	225 50)	97	50/50
58	234 50)	50/50	235 50)	100	50/50	230 49)	98	49/49	226 50)	97	50/50
62	240 49)	49/50	239 50)	100	50/50	233 47)	97	47/49	229 50)	95	50/50
66	243 49)	49/50	244 50)	100	50/50	238 47)	98	47/49	235 50)	97	50/50
70	246 48)	48/50	250 50)	102	50/50	244 47)	99	47/49	239 50)	97	50/50
74	250 47)	47/50	254 49)	102	49/50	247 47)	99	47/49	240 49)	96	49/50
78	254 47)	47/50	259 49)	102	49/50	252 47)	99	47/49	243 47)	96	47/50
82	258 46)	46/50	262 48)	102	48/50	256 47)	99	47/49	249 45)	97	45/50
86	262 46)	46/50	266 48)	102	48/50	262 47)	100	47/49	252 45)	96	45/50
90	266 45)	45/50	267 44)	100	43/50	267 45)	100	45/49	256 43)	96	43/50
94	266 45)	45/50	270 42)	102	41/50	267 45)	100	45/49	256 40)	96	40/50
98	269 42)	42/50	274 38)	102	38/50	266 43)	99	43/49	254 35)	94	34/50
102	270 41)	41/50	272 38)	101	38/50	267 40)	99	39/49	255 33)	94	33/50
104	267 41)	41/50	271 38)	101	38/50	271 39)	101	39/49	251 32)	94	32/50

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

TABLE 3 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass										
	0ppm	0/50	0/50	1/50	3/50	5/50	6/50	6/48	12/45	16/50 (4/10)
	3ppm	0/50	0/50	0/50	0/50	2/50	8/49	8/46	11/43	15/50 (3/8)
	10ppm	0/50	0/50	0/50	2/50	4/50	6/50	11/50	11/44	16/50 (6/12)
	30ppm	0/50	0/50	0/50	0/50	3/50	11/50	12/46	22/38	29/50 (15/27)
Internal mass										
	0ppm	0/50	0/50	0/50	0/50	0/50	1/50	2/48	3/45	6/50 (5/10)
	3ppm	0/50	0/50	0/50	0/50	0/50	0/49	0/46	0/43	0/50 (0/8)
	10ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/44	1/50 (0/12)
	30ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/46	2/38	2/50 (1/27)

No. of animals with mass / No. of surviving animals at the first week in each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 4 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass										
	0ppm	0/50	0/50	0/50	0/50	0/50	3/49	5/47	7/45	10/50 (1/9)
	3ppm	0/50	0/50	0/50	0/50	0/50	0/50	4/48	7/43	7/50 (2/12)
	10ppm	0/50	0/49	0/49	0/49	1/49	1/47	6/47	17/45	20/49 (5/10)
	30ppm	0/50	0/50	0/50	1/50	2/50	4/50	10/46	22/42	23/50 (8/18)
Internal mass										
	0ppm	0/50	0/50	0/50	0/50	0/50	1/49	2/47	1/45	2/50 (2/9)
	3ppm	0/50	0/50	0/50	0/50	0/50	0/50	1/48	2/43	3/50 (1/12)
	10ppm	0/50	0/49	0/49	0/49	0/49	0/47	1/47	6/45	7/49 (5/10)
	30ppm	0/50	0/50	0/50	0/50	0/50	1/50	2/46	5/42	8/50 (5/18)

No. of animals with mass / No. of surviving animals at the first week in each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Weeks on Study	Control Av.FC. <50>	3ppm Av.FC. <50>	3ppm % of cont.	10ppm Av.FC. <50>	10ppm % of cont.	30ppm Av.FC. <50>	30ppm % of cont.
1	15.2 (50)	15.4 (50)	101	15.3 (50)	101	15.1 (50)	99
2	15.8 (50)	16.1 (50)	102	16.0 (50)	101	16.1 (50)	102
3	16.9 (50)	17.0 (50)	101	16.9 (50)	100	17.5 (50)	104
4	17.5 (50)	17.1 (50)	98	17.1 (50)	98	17.2 (50)	98
5	17.3 (50)	16.8 (50)	97	16.8 (50)	97	17.1 (50)	99
6	17.1 (50)	16.5 (50)	96	16.3 (50)	95	16.9 (50)	99
7	17.6 (50)	16.9 (50)	96	17.0 (50)	97	17.1 (50)	97
8	17.4 (50)	16.8 (50)	97	16.8 (50)	97	17.1 (50)	98
9	17.1 (50)	16.6 (50)	97	16.6 (50)	97	16.6 (50)	97
10	16.8 (50)	16.4 (50)	98	16.1 (50)	96	16.1 (50)	96
11	16.8 (50)	16.2 (50)	96	16.0 (50)	95	16.5 (50)	98
12	16.4 (50)	15.7 (50)	96	16.1 (50)	98	16.2 (50)	99
13	16.6 (50)	16.2 (50)	98	16.2 (50)	98	16.2 (50)	98
14	16.7 (50)	16.0 (50)	96	16.0 (50)	96	15.9 (50)	95
18	16.4 (50)	16.4 (50)	100	16.2 (50)	99	15.9 (50)	97
22	16.4 (50)	16.2 (50)	99	16.2 (50)	99	16.1 (50)	98
26	16.8 (50)	16.6 (50)	99	16.7 (50)	99	16.4 (50)	98
30	16.4 (50)	16.3 (50)	99	16.2 (50)	99	16.3 (50)	99
34	16.9 (50)	16.7 (50)	99	16.7 (50)	99	16.5 (50)	98
38	17.2 (50)	17.2 (50)	100	16.9 (50)	98	16.7 (50)	97
42	17.4 (50)	17.3 (50)	99	17.0 (50)	98	17.1 (50)	98
46	17.1 (50)	17.0 (50)	99	16.7 (50)	98	16.9 (50)	99
50	17.4 (50)	17.2 (50)	99	16.9 (50)	97	16.9 (50)	97
54	17.4 (50)	17.4 (50)	100	17.0 (50)	98	17.1 (50)	98
58	17.5 (50)	17.3 (49)	99	16.8 (50)	96	16.7 (50)	95
62	17.8 (50)	17.6 (49)	99	17.1 (50)	96	16.9 (50)	95
66	17.8 (50)	17.7 (49)	99	17.3 (50)	97	17.0 (50)	96
70	17.9 (49)	17.8 (48)	99	17.4 (50)	97	16.8 (48)	94
74	17.8 (49)	17.4 (48)	98	17.2 (50)	97	16.6 (47)	93
78	17.9 (49)	17.6 (46)	98	17.2 (50)	96	16.7 (46)	93
82	17.9 (47)	17.9 (46)	100	16.7 (48)	93	16.7 (44)	93
86	17.3 (46)	17.4 (46)	101	16.9 (46)	98	15.8 (42)	91
90	17.1 (46)	17.0 (44)	99	16.4 (46)	96	16.2 (39)	95
94	16.1 (44)	16.9 (43)	105	16.3 (43)	101	16.1 (37)	100
98	17.2 (42)	17.7 (42)	103	16.5 (42)	96	14.7 (33)	85
102	17.4 (39)	18.3 (42)	105	17.0 (39)	98	16.2 (25)	93
104	17.2 (39)	18.1 (42)	105	16.9 (37)	98	16.2 (23)	94

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

TABLE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Weeks on Study	Control Av.FC.		3ppm Av.FC.		% of cont.	10ppm Av.FC.		% of cont.	30ppm Av.FC.		% of cont.
	<50>		<50>			<49>			<50>		
1	11.0	(50)	11.3	(50)	103	11.1	(49)	101	11.0	(50)	100
2	10.8	(50)	10.5	(50)	97	10.7	(49)	99	10.7	(50)	99
3	11.3	(50)	11.4	(50)	101	11.4	(49)	101	11.6	(50)	103
4	11.7	(50)	11.4	(50)	97	11.5	(49)	98	11.3	(50)	97
5	11.8	(50)	11.6	(50)	98	11.6	(49)	98	11.6	(50)	98
6	11.5	(50)	11.2	(50)	97	11.0	(49)	96	11.2	(50)	97
7	11.9	(50)	11.4	(50)	96	11.3	(49)	95	11.2	(50)	94
8	10.9	(50)	10.8	(50)	99	10.9	(49)	100	10.5	(50)	96
9	11.8	(50)	11.4	(50)	97	11.1	(49)	94	11.0	(50)	93
10	12.1	(50)	11.8	(50)	98	11.1	(49)	92	10.9	(50)	90
11	12.2	(50)	11.5	(50)	94	11.2	(49)	92	11.1	(50)	91
12	11.5	(50)	11.1	(50)	97	11.3	(49)	98	11.1	(50)	97
13	11.6	(50)	11.6	(50)	100	11.4	(49)	98	11.2	(50)	97
14	11.7	(50)	11.1	(50)	95	11.3	(49)	97	10.9	(50)	93
18	11.2	(50)	11.2	(50)	100	10.6	(49)	95	10.9	(50)	97
22	11.2	(50)	11.2	(50)	100	10.8	(49)	96	10.7	(50)	96
26	11.6	(50)	11.9	(50)	103	11.5	(49)	99	11.3	(50)	97
30	11.6	(50)	11.6	(50)	100	11.0	(49)	95	11.2	(50)	97
34	11.7	(50)	12.1	(50)	103	11.8	(49)	101	11.8	(50)	101
38	11.8	(50)	11.9	(50)	101	11.6	(49)	98	11.2	(50)	95
42	11.8	(50)	11.8	(50)	100	11.4	(49)	97	11.5	(50)	97
46	11.8	(50)	12.2	(50)	103	11.8	(49)	100	11.6	(50)	98
50	12.1	(50)	12.3	(50)	102	11.8	(49)	98	12.0	(50)	99
54	11.9	(50)	12.1	(50)	102	11.9	(49)	100	11.7	(50)	98
58	12.0	(50)	11.9	(50)	99	11.6	(49)	97	11.6	(50)	97
62	12.6	(49)	12.4	(50)	98	11.7	(47)	93	11.5	(50)	91
66	12.7	(49)	12.8	(50)	101	12.4	(47)	98	12.4	(50)	98
70	13.0	(48)	13.1	(50)	101	12.8	(47)	98	12.3	(50)	95
74	12.8	(47)	12.5	(49)	98	12.2	(47)	95	11.8	(49)	92
78	12.8	(47)	12.8	(49)	100	12.5	(47)	98	12.0	(47)	94
82	12.9	(46)	12.9	(48)	100	12.5	(47)	97	12.4	(45)	96
86	12.9	(46)	12.4	(48)	96	12.7	(47)	98	12.2	(45)	95
90	12.7	(45)	12.1	(44)	95	12.5	(45)	98	12.1	(43)	95
94	12.2	(45)	12.1	(42)	99	12.0	(45)	98	11.7	(40)	96
98	13.0	(42)	13.0	(38)	100	12.6	(43)	97	12.6	(35)	97
102	13.4	(41)	13.2	(38)	99	12.8	(40)	96	12.3	(33)	92
104	12.9	(41)	12.7	(38)	98	13.1	(39)	102	11.9	(32)	92

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

TABLE 7 ORGAN WEIGHT OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group Name	Control	3 ppm	10 ppm	30 ppm	
No. of examined animals	40	42	38	23	
Body weight (g)	376 ± 50	384 ± 52	365 ± 48	313 ± 36	**
Adrenals (g)	0.081 ± 0.024	0.078 ± 0.013	0.079 ± 0.015	0.076 ± 0.011	
Adrenals (%)	0.022 ± 0.007	0.021 ± 0.004	0.022 ± 0.005	0.025 ± 0.006	*
Testes (g)	3.360 ± 1.462	3.577 ± 1.744	4.051 ± 1.426	4.043 ± 1.752	
Testes (%)	0.917 ± 0.421	0.943 ± 0.480	1.140 ± 0.464	1.282 ± 0.514	**
Heart (g)	1.167 ± 0.098	1.190 ± 0.107	1.179 ± 0.121	1.177 ± 0.110	
Heart (%)	0.313 ± 0.031	0.314 ± 0.045	0.325 ± 0.027	0.382 ± 0.063	**
Lung (g)	1.421 ± 0.171	1.391 ± 0.104	1.400 ± 0.135	1.493 ± 0.306	
Lung (%)	0.381 ± 0.050	0.367 ± 0.046	0.387 ± 0.035	0.482 ± 0.107	**
Kidneys (g)	2.680 ± 0.224	2.701 ± 0.240	2.681 ± 0.275	2.779 ± 0.365	
Kidneys (%)	0.720 ± 0.080	0.711 ± 0.079	0.741 ± 0.080	0.898 ± 0.150	**
Liver (g)	11.254 ± 2.244	11.201 ± 1.654	10.938 ± 1.569	10.865 ± 1.906	
Liver (%)	3.013 ± 0.601	2.937 ± 0.403	3.009 ± 0.370	3.488 ± 0.621	**
Brain (g)	1.955 ± 0.050	1.957 ± 0.061	1.940 ± 0.057	1.932 ± 0.070	
Brain (%)	0.527 ± 0.055	0.516 ± 0.052	0.539 ± 0.063	0.626 ± 0.084	**

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

TABLE 8 ORGAN WEIGHT OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group Name	Control	3 ppm	10 ppm	30 ppm	
No. of examined animals	41	38	39	32	
Body weight (g)	249 ± 25	251 ± 22	252 ± 25	235 ± 22	*
Kidneys (g)	1.721 ± 0.112	1.797 ± 0.270	1.788 ± 0.147	1.874 ± 0.167	**
Kidneys (%)	0.698 ± 0.067	0.723 ± 0.141	0.713 ± 0.060	0.803 ± 0.096	**
Spleen (g)	0.628 ± 0.840	0.611 ± 0.500	0.648 ± 0.972	0.836 ± 0.935	*
Spleen (%)	0.252 ± 0.326	0.248 ± 0.222	0.255 ± 0.368	0.362 ± 0.410	*
Heart (g)	0.834 ± 0.067	0.836 ± 0.054	0.838 ± 0.061	0.854 ± 0.075	
Heart (%)	0.338 ± 0.033	0.335 ± 0.029	0.335 ± 0.024	0.366 ± 0.050	**
Lung (g)	1.014 ± 0.176	0.990 ± 0.071	0.978 ± 0.071	1.055 ± 0.187	
Lung (%)	0.411 ± 0.074	0.397 ± 0.038	0.391 ± 0.038	0.453 ± 0.100	*
Liver (g)	6.434 ± 1.080	6.695 ± 0.890	6.507 ± 0.880	6.593 ± 0.933	
Liver (%)	2.596 ± 0.392	2.683 ± 0.367	2.583 ± 0.225	2.817 ± 0.423	**
Brain (g)	1.792 ± 0.057	1.785 ± 0.057	1.790 ± 0.050	1.797 ± 0.048	
Brain (%)	0.728 ± 0.079	0.717 ± 0.061	0.717 ± 0.068	0.771 ± 0.075	*

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

TABLE 9 INCIDENCES OF SELECTED LESIONS OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group		Control	3ppm	10ppm	30ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	50		
Organ / Findings	Grade of Nonneoplastic lesion						
Skin/Appendage							
Squamous cell papilloma		0	0	1	3	**	
Subcutis							
Fibroma		10	2 *	10	9		
Nasal cavity							
Inflammation: transitional epithelium	+	9	15	3	0 **		
Hyperplasia: transitional epithelium	+	0	0	11 **	5 *		
	2+	0	0	0	1		
Hyperplasia with atypia: transitional epithelium	+	0	0	3	4		
Inflammation: respiratory epithelium	+	7	6	5	9 **		
	2+	0	0	1	23		
Necrosis: respiratory epithelium	+	0	0	1	4		
	2+	0	0	0	2		
	3+	0	0	0	1		
Hyperplasia: respiratory epithelium	+	0	0	0	6 *		
	2+	0	0	0	1		
Hyperplasia with atypia: respiratory epithelium	+	0	0	0	5		
Squamous cell metaplasia: respiratory epithelium	+	1	2	3	1		
	2+	0	0	0	0		
	3+	0	0	0	1		
Squamous cell metaplasia with atypia: respiratory epithelium	+	0	1	5	9 **		
	2+	0	0	0	38		
Squamous cell hyperplasia	+	0	0	0	2		
	2+	0	0	0	2		
Squamous cell hyperplasia with atypia	+	0	0	0	15 **		
	2+	0	0	0	15		
Hyperplasia with atypia: nasal gland	2+	0	0	0	3		
Necrosis: olfactory epithelium	+	0	1	0	3		
Atrophy: olfactory epithelium	+	0	0	0	11 *		
Eosinophilic change: olfactory epithelium	+	24	28	19	33 **		
	2+	17	15	16	2		
	3+	3	2	5	0		
Thickening of bone: turbinate	+	0	3	24 **	15 **		
	2+	0	0	14	6		
Adenoma 1)		0	0	3	5 *	**	**
Adenocarcinoma 2)		0	0	0	1		
1) +2)		0	0	3	6 *	**	**
Squamous cell carcinoma		0	0	0	14 **	**	**
Basal cell carcinoma		0	0	0	1		
Bone marrow							
Erythropoiesis: increased	+	0	3	3	5 **		
	2+	3	1	4	8		

TABLE 9 INCIDENCES OF SELECTED LESIONS OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group		Control	3ppm	10ppm	30ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	50		
Organ / Findings	Grade of Nonneoplastic lesion						
Spleen							
Deposit of hemosiderin	+	17	4 **	2 **	9		
	2+	1	0	0	1		
Extramedullary hematopoiesis	+	18	29	23	19 *		
	2+	3	2	7	9		
	3+	1	3	3	6		
Fibrosis	+	0	5	3	10 **		
	2+	0	0	0	0		
	3+	0	0	0	1		
Heart							
Myocardial fibrosis	+	18	34 **	29	35 **		
	2+	28	15	16	9		
Liver							
Acidophilic cell focus	+	6	16	4	5		
	2+	1	1	1	0		
Basohilic cell focus	+	3	21 **	16 **	3		
	2+	1	0	2	1		
Hepatocellular adenoma		0	2	1	0		
Hepatocellular carcinoma		1	0	0	0		
Pancreas							
Islet cell adenoma 1)		4	0	1	2		
Islet cell adenocarcinoma 2)		2	0	0	0		
1)+2)		6	0 *	1	2		
Pituitary							
Hyperplasia	+	11	7	6	1 **		
	2+	2	2	5	1		
Thyroid							
Follicular adenoma 1)		0	1	2	0		
Follicularl adenocarcinoma 2)		0	1	0	4	**	**
1)+2)		0	2	2	4	*	
Testis							
Interstitial cell tumor		41	37	44	47	**	*
Mammary gland							
Adenoma 1)		0	0	0	1		
Fibroadenoma 2)		0	0	0	6 *	**	**
1)+2)		0	0	0	7 **	**	**
Eye							
Retinal atrophy	+	45	46	40	34 **		
	2+	0	0	0	0		
	3+	2	0	1	2		
Peritoneum							
Mesothelioma		2	3	12 **	22 **	**	**

Grade +: Slight 2+: Moderate 3+: Marked 4+: Severe

Significant difference * : $p<0.05$ ** : $p<0.01$ Chi square test

TABLE 10 INCIDENCES OF SELECTED LESIONS OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group		Control	3ppm	10ppm	30ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	49	50		
Organ / Findings	Grade of Nonneoplastic lesion						
Nasal cavity							
Inflammation: transitional epithelium	+	6	16 *	13	7		
	2+	1	0	0	0		
Hyperplasia: transitional epithelium	+	0	2	8 **	13 **		
	2+	0	0	0	2		
Hyperplasia with atypia: transitional epithelium	+	0	0	0	4		
Inflammation: respiratory epithelium	+	1	1	3	21 **		
	2+	0	0	0	5		
Necrosis: respiratory epithelium	+	0	0	2	3		
	2+	0	0	0	1		
Squamous cell metaplasia: respiratory epithelium	+	0	0	2	6 *		
Squamous cell metaplasia with atypia: respiratory epithelium	+	0	0	2	10 **		
	2+	0	0	0	26		
Squamous cell hyperplasia	+	0	0	0	3		
Squamous cell hyperplasia with atypia	+	0	0	0	8 **		
	2+	0	0	0	2		
Eosinophilic change: respiratory epithelium	+	36	36	37	27 *		
	2+	6	2	1	2		
Hyperplasia: nasal gland	+	0	0	0	1		
Hyperplasia with atypia: nasal gland	+	0	0	0	1		
Necrosis: olfactory epithelium	+	0	0	0	2		
Atrophy: olfactory epithelium	+	0	0	0	12 **		
	2+	0	0	0	1		
Eosinophilic change: olfactory epithelium	+	10	1 **	2 *	9		
	2+	29	18	27	37		
	3+	10	30	20	3		
Thickening of bone: turbinate	+	0	0	17 **	20 **		
	2+	0	0	0	22		
Mineralization	+	43	13 **	21 **	38		
Adenoma 1)		0	0	4	8 **	**	**
Adenocarcinoma 2)		0	0	0	2		
1) +2)		0	0	4	10 **	**	**
Squamous cell carcinoma		0	0	0	2		
Nasolacrimal duct							
Inflammation	+	22	13	8 **	4 **		
	2+	6	6	0	0		
Spleen							
Deposit of hemosiderin	+	40	41	41	28 *		
	2+	0	0	1	0		

TABLE 10 INCIDENCES OF SELECTED LESIONS OF FEMALE RATS
IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group		Control	3ppm	10ppm	30ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	49	50		
Organ / Findings	Grade of Nonneoplastic lesion						
Mononuclear cell leukemia		3	3	1	8	**	*
Liver							
Granulation	+	28	22	23	12 **		
	2+	2	6	4	4		
	3+	0	1	0	0		
Herniation	+	15	4 *	14	4 *		
Kidney							
Mineralization: pelvis	+	9	2	1 *	2		
Adrenal							
Peliosis-like lesion	+	23	28	29 *	27 **		
	2+	19	11	7	6		
	3+	1	0	0	0		
Focal fatty change: cortex	+	8	12	11	10 *		
	2+	2	1	6	10		
	3+	0	0	0	1		
Pheochromocytoma 1)		3	3	1	0		
Pheochromocytoma: malignant 2)		0	2	0	0		
1)+2)		3	5	1	0		*
Uterus							
Endometrial stromal polyp		6	11	11	13	*	
Endometrial stromal sarcoma		1	4	4	7 *	*	*
Mammary gland							
Adenoma 1)		2	1	3	2		
Fibroadenoma 2)		8	6	18 *	17 *	**	*
Adenocarcinoma 3)		2	1	1	2		
1)+2)		10	7	20 *	17	*	*
1)+2)+3)		10	8	21 *	19 *	**	*

Grade +: Slight 2+: Moderate 3+: Marked 4+: Severe

Significant difference * : $p<0.05$ ** : $p<0.01$ Chi square test

TABLE 11 NEOPLASTIC LESIONS INCIDENCES AND STATISTICAL ANALYSIS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group Name	Control	3ppm	10ppm	30ppm
SITE : skin/appendage				
TUMOR : squamous cell papilloma				
Tumor rate				
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	2.63	8.70
Terminal rates(c)	0/40(0.0)	0/42(0.0)	1/38(2.6)	2/23(8.7)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0069**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0138*			
Fisher Exact test(e)		P=N.C.	P=0.5000	P=0.1212
SITE : nasal cavity				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	3/50(6.0)	5/50(10.0)
Adjusted rates(b)	0.0	0.0	7.89	17.39
Terminal rates(c)	0/40(0.0)	0/42(0.0)	3/38(7.9)	4/23(17.4)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0006**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0037**			
Fisher Exact test(e)		P=N.C.	P=0.1212	P=0.0281*
SITE : nasal cavity				
TUMOR : squamous cell carcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	14/50(28.0)
Adjusted rates(b)	0.0	0.0	0.0	34.78
Terminal rates(c)	0/40(0.0)	0/42(0.0)	0/38(0.0)	8/23(34.8)
Statistical analysis				
Peto test				
Standard method(d)	P<0.0001**f)			
Prevalence method(d)	P<0.0001**f)			
Combined analysis (d)	P<0.0001**f)			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=N.C.	P=N.C.	P<0.0001**
SITE : nasal cavity				
TUMOR : adenoma, adenocarcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	3/50(6.0)	6/50(12.0)
Adjusted rates(b)	0.0	0.0	7.89	21.74
Terminal rates(c)	0/40(0.0)	0/42(0.0)	3/38(7.9)	5/23(21.7)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P<0.0001**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P<0.0010**			
Fisher Exact test(e)		P=N.C.	P=0.1212	P=0.0133*

TABLE 11 NEOPLASTIC LESIONS INCIDENCES AND STATISTICAL ANALYSIS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group Name	Control	3ppm	10ppm	30ppm
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	4/50(8.0)	5/50(10.0)	3/50(6.0)
Adjusted rates(b)	4.76	8.33	13.16	10.34
Terminal rates(c)	1/40(2.5)	3/42(7.1)	5/38(13.2)	2/23(8.7)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.3220			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.9716			
Fisher Exact test(e)		P=0.3389	P=0.2180	P=0.5000
SITE : lung				
TUMOR : bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	3/50(6.0)	2/50(4.0)	0/50(0.0)
Adjusted rates(b)	10.00	4.76	2.63	0.0
Terminal rates(c)	4/40(10.0)	2/42(4.8)	1/38(2.6)	0/23(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.5903			
Prevalence method(d)	P=0.9683			
Combined analysis (d)	P=0.9624			
Cochran-Armitage test(e)	P=0.0481*			
Fisher Exact test(e)		P=0.5000	P=0.3389	P=0.0587
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	6/50(12.0)	7/50(14.0)	7/50(14.0)	3/50(6.0)
Adjusted rates(b)	14.29	12.77	15.79	10.34
Terminal rates(c)	5/40(12.5)	5/42(11.9)	6/38(15.8)	2/23(8.7)
Statistical analysis				
Peto test				
Standard method(d)	P=0.5903			
Prevalence method(d)	P=0.7406			
Combined analysis (d)	P=0.7756			
Cochran-Armitage test(e)	P=0.2091			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.2435
SITE : thyroid				
TUMOR : follicular adenocarcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	1/50(2.0)	0/50(0.0)	4/50(8.0)
Adjusted rates(b)	0.0	2.38	0.0	14.29
Terminal rates(c)	0/40(0.0)	1/42(2.4)	0/38(0.0)	3/23(13.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0014**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0073**			
Fisher Exact test(e)		P=0.5000	P=N.C.	P=0.0587

TABLE 11 NEOPLASTIC LESIONS INCIDENCES AND STATISTICAL ANALYSIS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group Name	Control	3ppm	10ppm	30ppm
SITE : thyroid				
TUMOR : follicular adenoma, follicular adenocarcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	2/50(4.0)	2/50(4.0)	4/50(8.0)
Adjusted rates(b)	0.0	4.76	5.26	14.29
Terminal rates(c)	0/40(0.0)	2/42(4.8)	2/38(5.3)	3/23(13.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0114*			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0640			
Fisher Exact test(e)		P=0.2475	P=0.2475	P=0.0587
SITE : testis				
TUMOR : interstitial cell tumor				
Tumor rate				
Overall rates(a)	41/50(82.0)	37/50(74.0)	44/50(88.0)	47/50(94.0)
Adjusted rates(b)	90.91	80.95	97.44	97.30
Terminal rates(c)	36/40(90.0)	34/42(81.0)	37/38(97.4)	22/23(95.7)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0001**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0159*			
Fisher Exact test(e)		P=0.2348	P=0.2883	P=0.0606
SITE : mammary gland				
TUMOR : fibroadenoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	6/50(12.0)
Adjusted rates(b)	0.0	0.0	0.0	16.67
Terminal rates(c)	0/40(0.0)	0/42(0.0)	0/38(0.0)	3/23(13.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0805			
Prevalence method(d)	P<0.0001**f)			
Combined analysis (d)	P<0.0001**f)			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=N.C.	P=N.C.	P=0.0133*
SITE : mammary gland				
TUMOR : fibroadenoma, adenoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	7/50(14.0)
Adjusted rates(b)	0.0	0.0	0.0	20.00
Terminal rates(c)	0/40(0.0)	0/42(0.0)	0/38(0.0)	4/23(17.4)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0805			
Prevalence method(d)	P<0.0001**f)			
Combined analysis (d)	P<0.0001**f)			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=N.C.	P=N.C.	P=0.0062**

TABLE 11 NEOPLASTIC LESIONS INCIDENCES AND STATISTICAL ANALYSIS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONYINUED)

Group Name	Control	3ppm	10ppm	30ppm
SITE : peritoneum				
TUMOR : mesothelioma				
Tumor rate				
Overall rates(a)	2/50(4.0)	3/50(6.0)	12/50(24.0)	22/50(44.0)
Adjusted rates(b)	5.00	4.76	25.00	32.00
Terminal rates(c)	2/40(5.0)	2/42(4.8)	9/38(23.7)	7/23(30.4)
Statistical analysis				
Peto test				
Standard method(d)	P<0.0001**			
Prevalence method(d)	P=0.0003**			
Combined analysis (d)	P<0.0001**			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=0.5000	P=0.0038**	P<0.0001**

(a):Number of tumor-bearing animals/number of animals examined.
(b):Kaplan-Meire-estimated tumor incidence at the time of terminal necropsy after adjusting for intercurrent mortality.
(c):Observed tumor incidence at the time of terminal necropsy.
(d):P-value of the trend tests was given in the colum of control incidence.
Standard method :Death analysis
Prevalence method :Incidental tumor test
Combined analysis :Death analysis + Incidental tumor test
(e):Cochran-Armitage test and Fisher exact test were applied to directly with the overall incidence rates.
f) :indicates either the case that the upper or lower limit of the probability is not given or the case that the P-value exceeds the expected one.
------:The P-value can not be caluculated because the number of tumor-bearing animals was zero.
Significant difference; *:P≦0.05 **:P≦0.01
N.C. :Statistical value cannot be calculate.
Significant difference; *:P≦0.05 **:P≦0.01
N.C. :Statistical value cannot be calculated and was not significant.

TABLE 12 NEOPLASTIC LESIONS INCIDENCES AND STATISTICAL ANALYSIS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group Name	Control	3ppm	10ppm	30ppm
SITE : nasal cavity				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	4/49(8.2)	8/50(16.0)
Adjusted rates(b)	0.0	0.0	9.52	21.21
Terminal rates(c)	0/41(0.0)	0/38(0.0)	3/39(7.7)	6/32(18.8)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0001**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0001**			
Fisher Exact test(e)		P=N.C.	P=0.0563	P=0.0029**
SITE : nasal cavity				
TUMOR : adenoma, adenocarcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	4/49(8.2)	10/50(20.0)
Adjusted rates(b)	0.0	0.0	9.52	21.43
Terminal rates(c)	0/41(0.0)	0/38(0.0)	3/39(7.7)	6/32(18.8)
Statistical analysis				
Peto test				
Standard method(d)	P=0.1407			
Prevalence method(d)	P<0.0001**			
Combined analysis (d)	P<0.0001**			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=N.C.	P=0.0563	P=0.0006**
SITE : spleen				
TUMOR : mononuclear cell leukemia				
Tumor rate				
Overall rates(a)	3/50(6.0)	3/50(6.0)	1/49(2.0)	8/50(16.0)
Adjusted rates(b)	4.88	2.63	0.0	12.50
Terminal rates(c)	2/41(4.9)	1/38(2.6)	0/39(0.0)	4/32(12.5)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0599			
Prevalence method(d)	P=0.0398*			
Combined analysis (d)	P=0.0097**			
Cochran-Armitage test(e)	P=0.0252*			
Fisher Exact test(e)		P=0.6611	P=0.3163	P=0.0999
SITE : adrenal gland				
TUMOR : pheochromocytoma				
Tumor rate				
Overall rates(a)	3/50(6.0)	3/50(6.0)	1/49(2.0)	0/50(0.0)
Adjusted rates(b)	7.32	7.89	2.56	0.0
Terminal rates(c)	3/41(7.3)	3/38(7.9)	1/39(2.6)	0/32(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.9717			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0647			
Fisher Exact test(e)		P=0.6611	P=0.3163	P=0.1212

TABLE 12 NEOPLASTIC LESIONS INCIDENCES AND STATISTICAL ANALYSIS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group Name	Control	3ppm	10ppm	30ppm
SITE : adrenal gland				
TUMOR : pheochromocytoma, pheochromocytoma: malignant				
Tumor rate				
Overall rates(a)	3/50(6.0)	5/50(10.0)	1/49(2.0)	0/50(0.0)
Adjusted rates(b)	7.32	10.53	2.56	0.0
Terminal rates(c)	3/41(7.3)	4/38(10.5)	1/39(2.6)	0/32(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.5280			
Prevalence method(d)	P=0.9796			
Combined analysis (d)	P=0.9855			
Cochran-Armitage test(e)	P=0.0367*			
Fisher Exact test(e)		P=0.3575	P=0.3163	P=0.1212
SITE : uterus				
TUMOR : endometrial stromal polyp				
Tumor rate				
Overall rates(a)	6/50(12.0)	11/50(22.0)	11/49(22.4)	13/50(26.0)
Adjusted rates(b)	14.63	26.19	26.83	34.29
Terminal rates(c)	6/41(14.6)	9/38(23.7)	9/38(23.1)	10/23(31.3)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0471*			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.1685			
Fisher Exact test(e)		P=0.1434	P=0.1330	P=0.0624
SITE : uterus				
TUMOR : endometrial stromal sarcoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	4/50(8.0)	4/49(8.2)	7/50(14.0)
Adjusted rates(b)	0.0	5.26	2.56	3.13
Terminal rates(c)	0/41(0.0)	2/38(5.3)	1/39(2.6)	1/32(3.1)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0152*			
Prevalence method(d)	P=0.3505			
Combined analysis (d)	P=0.0201*			
Cochran-Armitage test(e)	P=0.0454*			
Fisher Exact test(e)		P=0.1811	P=0.1748	P=0.0297*
SITE : mammary gland				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	1/50(2.0)	3/49(6.1)	2/50(4.0)
Adjusted rates(b)	4.26	2.56	7.14	6.25
Terminal rates(c)	1/41(2.4)	0/38(0.0)	2/39(5.1)	2/32(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.3835			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.8301			
Fisher Exact test(e)		P=0.5000	P=0.4903	P=0.6913

TABLE 12 NEOPLASTIC LESIONS INCIDENCES AND STATISTICAL ANALYSIS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group Name	Control	3ppm	10ppm	30ppm
SITE : mammary gland				
TUMOR : fibroadenoma				
Tumor rate				
Overall rates(a)	8/50(16.0)	6/50(12.0)	18/49(36.7)	17/50(34.0)
Adjusted rates(b)	19.51	15.79	38.46	43.75
Terminal rates(c)	8/41(19.5)	6/38(15.8)	15/39(38.5)	14/32(43.8)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0014**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0110*			
Fisher Exact test(e)		P=0.3871	P=0.0167*	P=0.0317*
SITE : mammary gland				
TUMOR : adenoma, fibroadenoma				
Tumor rate				
Overall rates(a)	10/50(20.0)	7/50(14.0)	20/49(40.8)	17/50(34.0)
Adjusted rates(b)	21.95	17.95	42.55	43.75
Terminal rates(c)	9/41(22.0)	6/38(15.8)	16/39(41.0)	14/32(43.8)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0112*			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0409*			
Fisher Exact test(e)		P=0.2977	P=0.0205*	P=0.0880
SITE : mammary gland				
TUMOR : adenoma, fibroadenoma, adenocarcinoma				
Tumor rate				
Overall rates(a)	10/50(20.0)	8/50(16.0)	21/49(42.9)	19/50(38.0)
Adjusted rates(b)	21.95	20.51	44.68	46.88
Terminal rates(c)	9/41(22.0)	7/38(18.4)	17/39(43.6)	15/32(46.9)
Statistical analysis				
Peto test				
Standard method(d)	P=0.1346			
Prevalence method(d)	P=0.0073**			
Combined analysis (d)	P=0.0038**			
Cochran-Armitage test(e)	P=0.0164*			
Fisher Exact test(e)		P=0.3976	P=0.0123*	P=0.0385*

(a):Number of tumor-bearing animals/number of animals examined.
(b):Kaplan-Meire-estimated tumor incidence at the time of terminal necropsy after adjusting for intercurrent mortality.
(c):Observed tumor incidence at the time of terminal necropsy.
(d):P-value of the trend tests was given in the colum of control incidence.
Standard method :Death analysis
Prevalence method :Incidental tumor test
Combined analysis :Death analysis + Incidental tumor test
(e):Cochran-Armitage test and Fisher exact test were applied to directly with the overall incidence rates.
f) :indicates either the case that the upper or lower limit of the probability is not given or the case that the P-value exceeds the expected one.
------:The P-value can not be caluculated because the number of tumor-bearing animals was zero.
Significant difference; *:P≦0.05 **:P≦0.01
N.C. :Statistical value cannot be calculate.
Significant difference; *:P≦0.05 **:P≦0.01
N.C. :Statistical value cannot be calculated and was not significant.

TABLE 13 CAUSE OF DEATH OF MALE AND FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

	Male				Female			
Group	0ppm	3ppm	10ppm	30ppm	0ppm	3ppm	10ppm	30ppm
Number of dead or moribund animals	10	8	12	27	9	12	10	18
No microscopical confirmation	0	1	0	2	2	2	0	0
Central nervous system lesion	0	0	1	0	0	0	0	1
Renal lesion	0	0	0	1	0	0	0	0
Thrombosis	0	0	0	0	0	0	0	1
Tumor death : peritoneum	0	1	2	12	0	0	0	0
nasal cavity	0	0	0	5	0	0	0	1
leukemia	5	1	3	2	1	2	2	4
skin/appendage	0	1	0	0	0	0	0	0
subcutis	2	0	1	0	0	0	0	1
lung	0	1	1	0	0	0	0	0
spleen	1	0	0	0	0	0	0	0
oral cavity	0	0	1	0	0	0	0	0
tongue	0	0	0	0	0	0	0	1
salivary gland	0	1	0	0	0	0	0	0
pancreas	0	0	0	0	1	0	0	1
urinary bladder	0	0	0	0	1	0	0	0
pituitary gland	1	0	0	1	3	4	1	1
adrenal gland	0	1	1	0	0	1	1	0
uterus					1	2	4	6
ovary					0	1	0	0
mammary gland	0	0	0	1	0	0	0	1
preputial/clitoral gland	0	0	1	0	0	0	0	0
brain	0	0	0	1	0	0	1	0
Zymbal gland	0	1	1	1	0	0	1	0
retroperitoneum	1	0	0	1	0	0	0	0

TABLE 14 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrj MALE RATS

Organs / Tumors	No. of animals examined	No. of tumor-bearing animals	Incidence (%)	Min. - Max. (%)
Skin/Appendage	<1248>			
Squamous cel papilloma		14	1.1	0 - 4
Nasal cavity	<1249>			
Adenoma		2	0.2	0 - 2
Adenocarcinoma		0	0.0	0 - 0
Squamous cell carcinoma		0	0.0	0 - 0
Basal cell carcinoma		0	0.0	0 - 0
Lung	<1249>			
Bronchiolar-alveolar carcinoma		12	1.0	0 - 4
Pancreas	<1249>			
Islet cell adenoma 1)		75	6.0	0 - 14
Islet cell adenocarcinoma 2)		5	0.4	0 - 2
1)+2)		80	6.4	0 - 14
Thyroid	<1243>			
Follicular adenoma 1)		12	1.0	0 - 4
Follicular adenocarcinoma 2)		27	2.2	0 - 8
1)+2)		39	3.1	0 - 8
Testis	<1249>			
Interstitial cell tumor		1099	88.0	74 - 98
Mammary gland	<1249>			
Adenoma 1)		8	0.6	0 - 4
Fibroadenoma 2)		27	2.2	0 - 6
1)+2)		35	2.8	0 - 8
Subcutis	<1249>			
fibroma		90	7.2	2 - 14
Peritoneum	<1249>			
Mesothelioma		31	2.5	0 - 8

25 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, 0267, 0269, 0284, 0288, 0294, 0296, 0318

TABLE 15 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrj FEMALE RATS

Organs / Tumors	No. of animals examined	No. of tumor-bearing animals	Incidence (%)	Min. - Max. (%)
Nasal cavity	<1197>			
Adenoma		0	0.0	0 - 0
Adenocarcinoma		0	0.0	0 - 0
Squamous cell carcinoma		0	0.0	0 - 0
Spleen	<1197>			
Mononuclear cell leukemia		160	13.4	2 - 26
Adrenal	<1197>			
Pheochromocytoma		48	4.0	0 - 16
Pheochromocytoma : malignant		13	1.1	0 - 6
1)+2)		61	5.1	0 - 18
Uterus	<1197>			
Endometrial stromal polyp		172	14.4	2 - 28
Endometrial stromal sarcoma		7	0.6	0 - 2
Mammary gland	<1197>			
Adenoma		45	3.8	0 - 18
Fibroadenoma		130	10.9	0 - 20
Adenocarcinoma		19	1.6	0 - 6

24 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, 0267, 0269, 0284, 0296, 0303, 0318

FIGURES

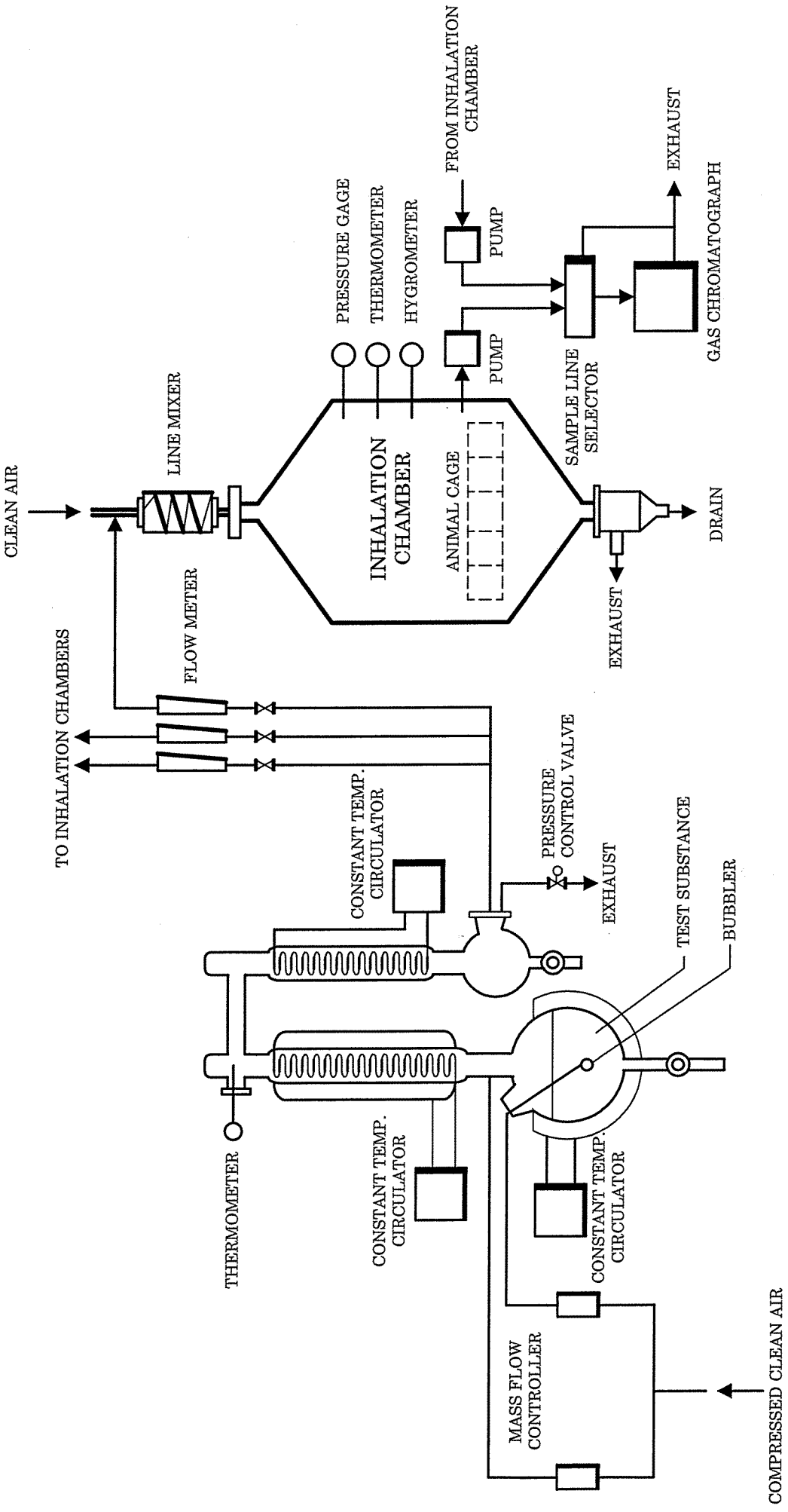


FIGURE 1 GLYCIDOL VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

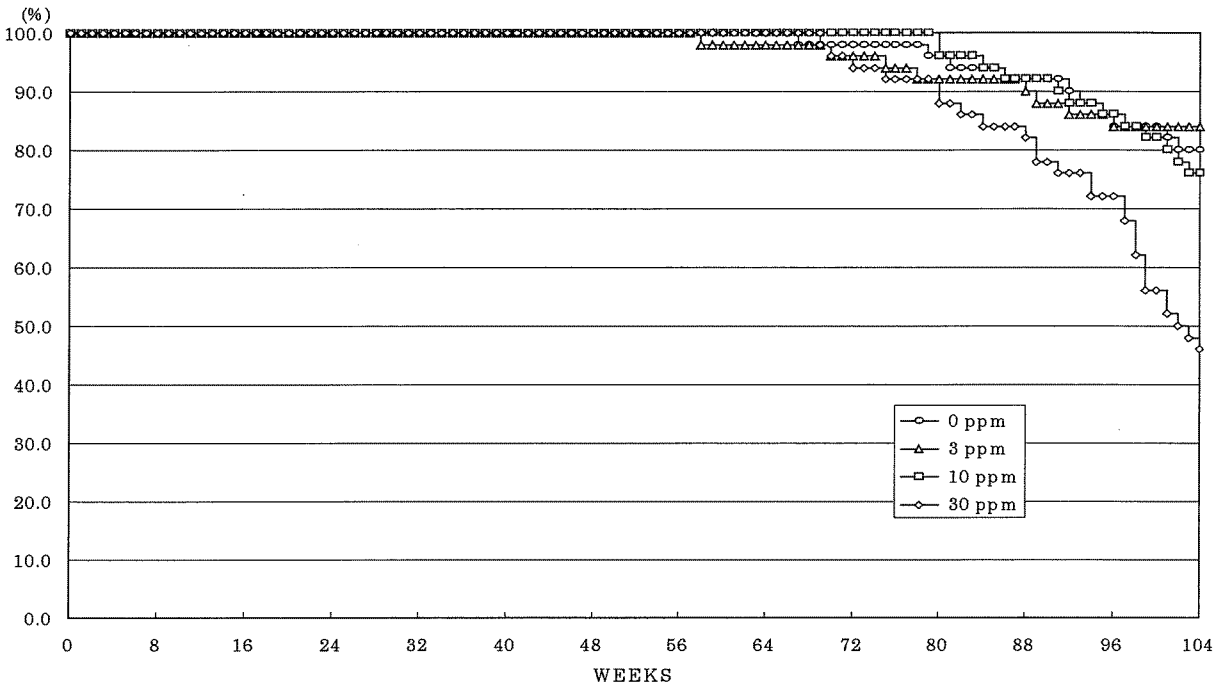


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

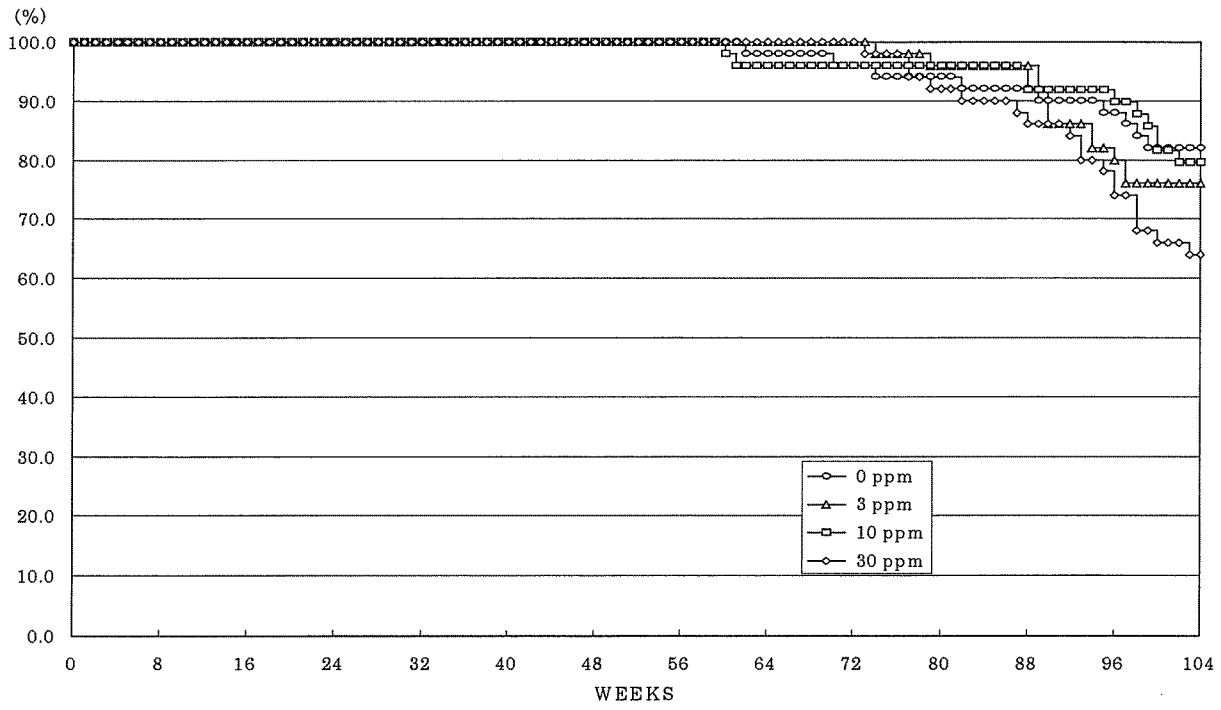


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

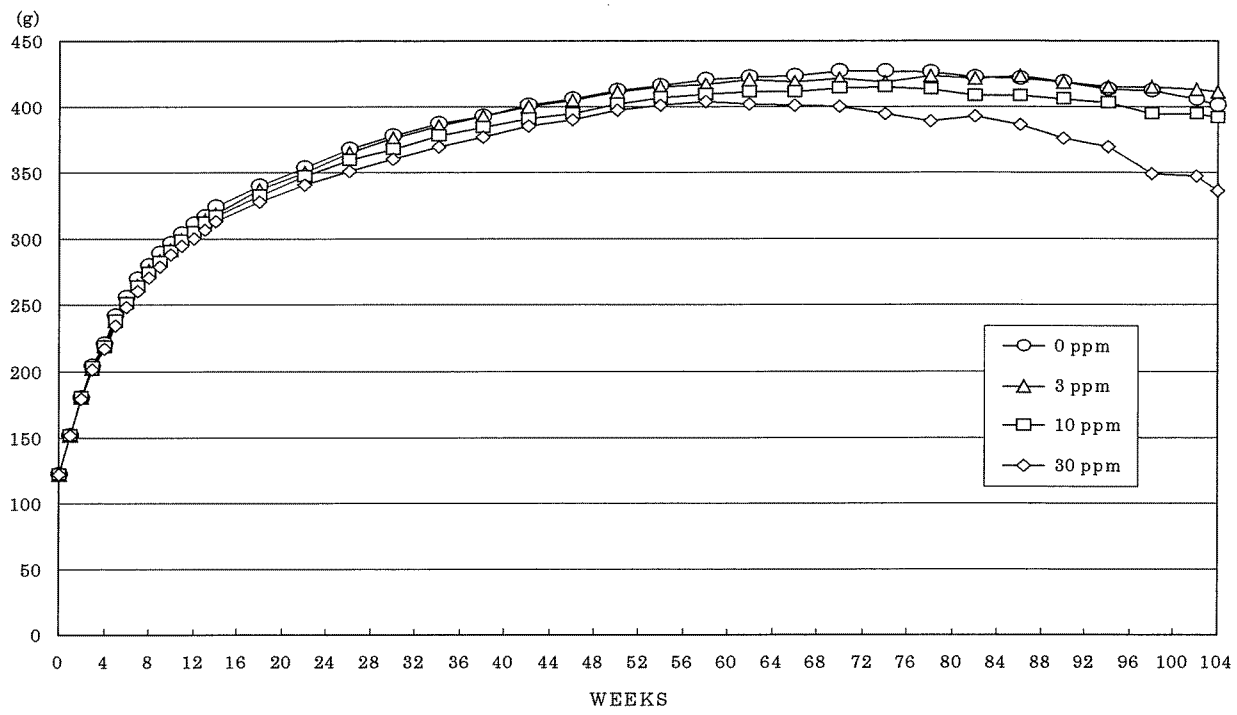


FIGURE 4 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

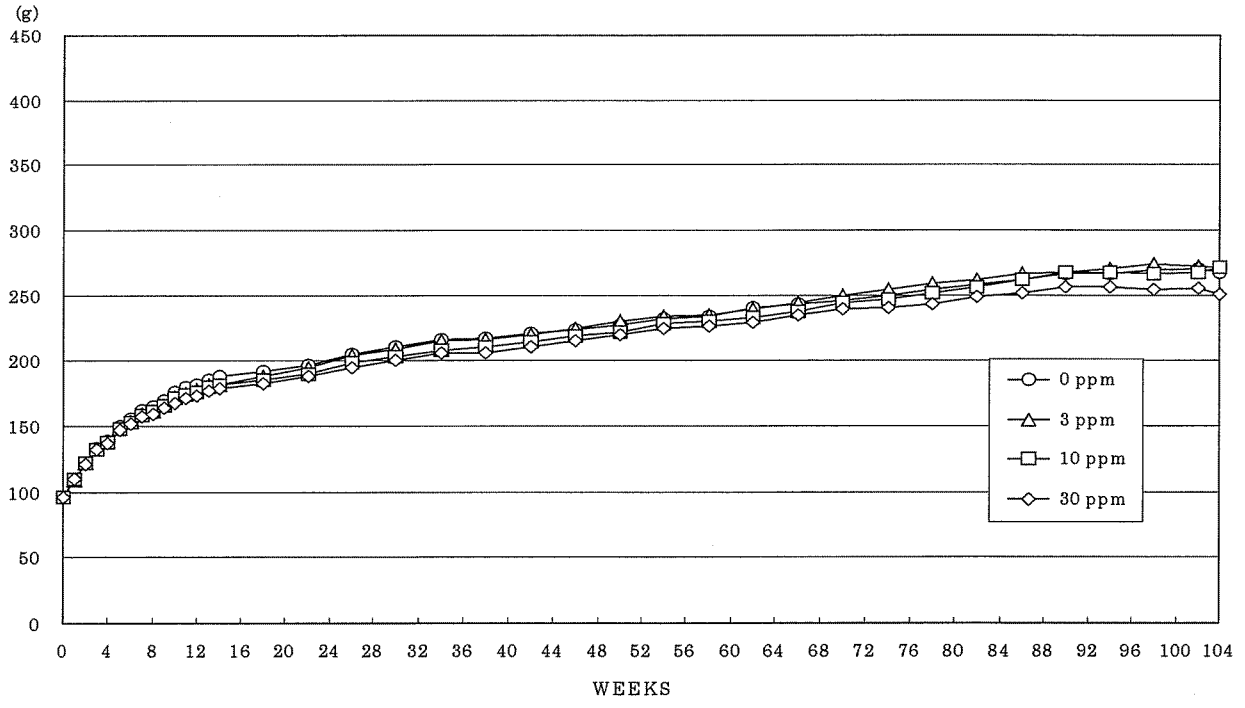


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

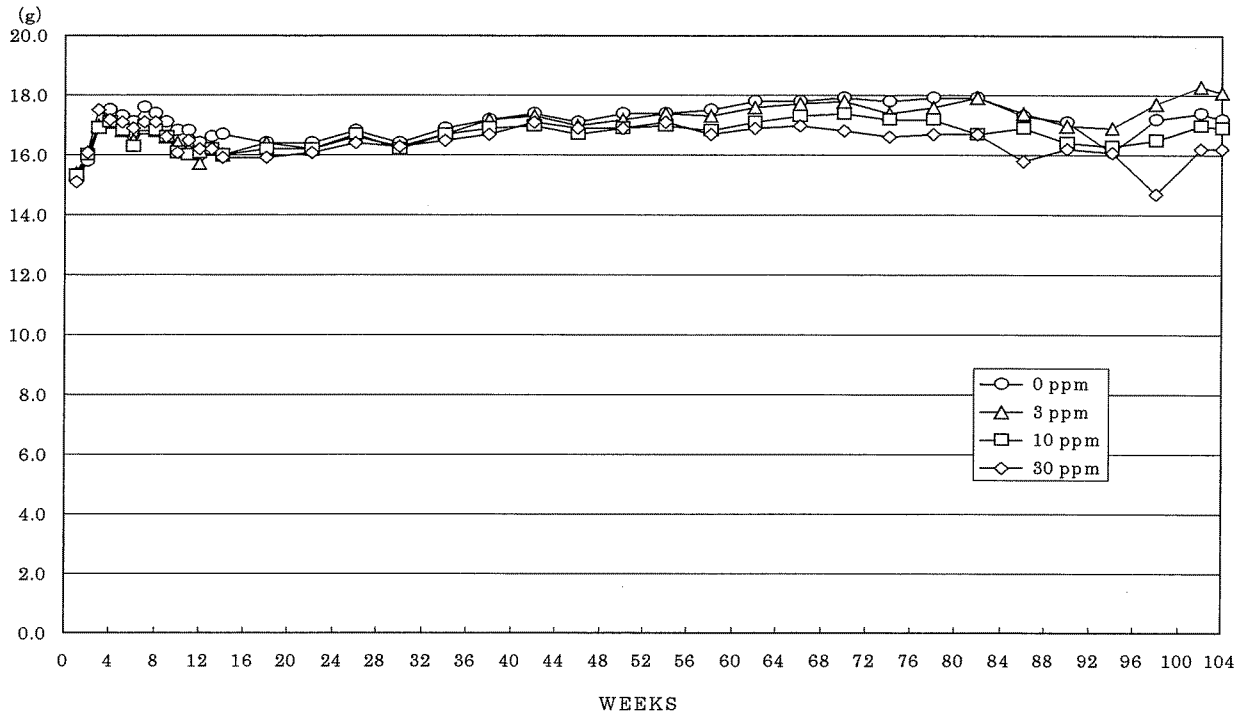


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

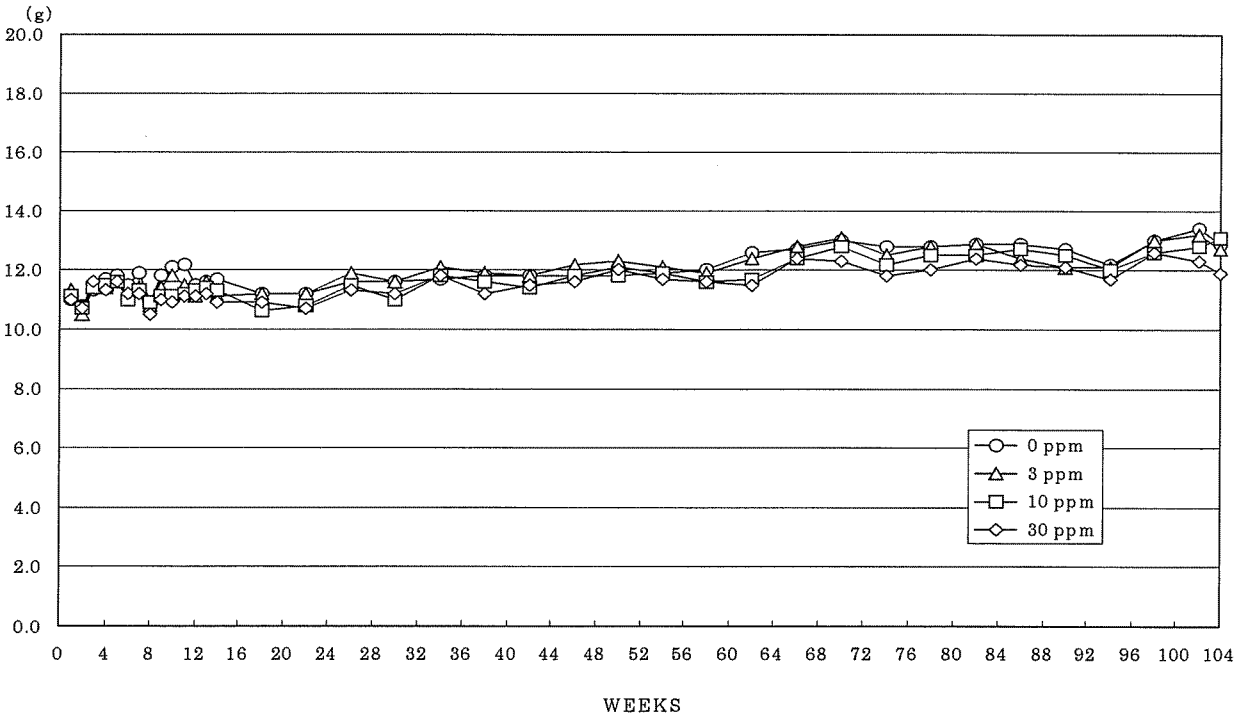


FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

PHOTOGRAPHS

PHOTOGRAPH 1 NOSE : NODULE (ARROW)
RAT, MALE, 30ppm, ANIMAL No. 0342-1347

PHOTOGRAPH 2 NASAL CAVITY : SQUAMOUS CELL CARCINOMA (ARROW)
RAT, MALE, 30ppm, ANIMAL No. 0342-1345 (H&E)

PHOTOGRAPH 3 NASAL CAVITY : SQUAMOUS CELL CARCINOMA
HIGHER MAGNIFICATION OF PHOTOGRAPH 2
RAT, MALE, 30ppm, ANIMAL No. 0342-1345 (H&E)

PHOTOGRAPH 4 NASAL CAVITY : ADENOMA
RAT, MALE, 30ppm, ANIMAL No. 0342-1330 (H&E)

PHOTOGRAPH 5 NASAL CAVITY : ADENOCARCINOMA
RAT, MALE, 30ppm, ANIMAL No. 0342-1317 (H&E)

PHOTOGRAPH 6 NASAL CAVITY : BASAL CELL CARCINOMA
RAT, MALE, 30ppm, ANIMAL No. 0342-1306 (H&E)

PHOTOGRAPH 7 NASAL CAVITY :
A: NORMAL TRANSITIONAL EPITHELIUM
B: NORMAL RESPIRATORY EPITHELIUM
RAT, MALE, CONTROL, ANIMAL No. 0342-1001 (H&E)

PHOTOGRAPH 8 NASAL CAVITY : TRANSITIONAL CELL HYPERPLASIA WITH ATYPIA
RAT, MALE, 30ppm, ANIMAL No. 0342-1307 (H&E)

PHOTOGRAPH 9 NASAL CAVITY : SQUAMOUS CELL METAPLASIA WITH ATYPIA OF THE RESPIRATORY EPITHELIUM (ARROW)
RAT, MALE, 30ppm, ANIMAL No. 0342-1341 (H&E)

PHOTOGRAPH 10 NASAL CAVITY : SQUAMOUS CELL HYPERPLASIA WITH ATYPIA (ARROW)
RAT, MALE, 30ppm, ANIMAL No. 0342-1336 (H&E)

PHOTOGRAPH 11 NASAL CAVITY (NASOTURBINATE) : NORMAL (ARROW)
RAT, MALE, CONTROL, ANIMAL No. 0342-1001 (H&E)

PHOTOGRAPH 12 NASAL CAVITY (NASOTURBINATE) : THICKENING OF THE BONE (ARROW)
RAT, MALE, 30ppm, ANIMAL No. 0342-1302 (H&E)

PHOTOGRAPHS (CONTINUED)

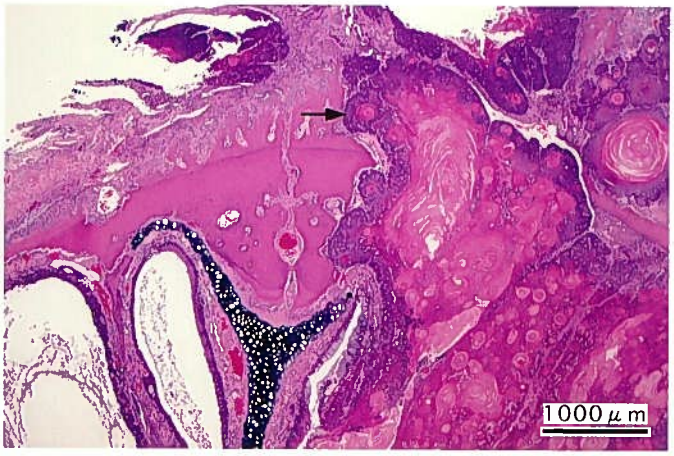
PHOTOGRAPH 13 PERITONEUM : MESOTHELIOMA
RAT, MALE, 30ppm, ANIMAL No. 0342-1312 (H&E)

PHOTOGRAPH 14 UTERUS: ENDOMETRIAL STROMAL SARCOMA
RAT, FEMALE, 30ppm, ANIMAL No. 0342-2331 (H&E)

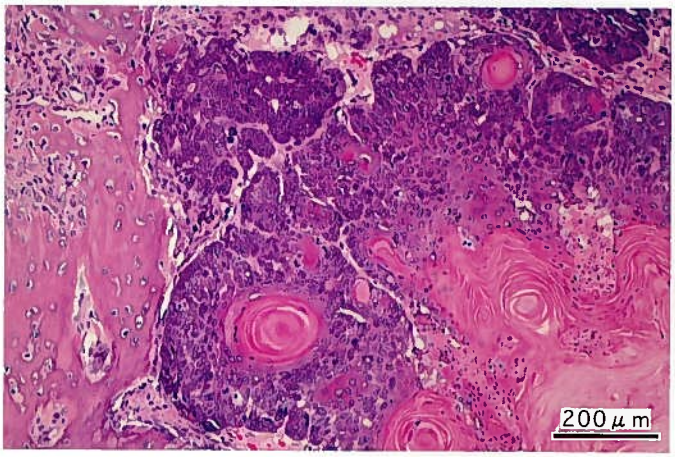
PHOTOGRAPH 15 MAMMARY GLAND : FIBROADENOMA
RAT, FEMALE, 30ppm, ANIMAL No. 0342-2334 (H&E)

PHOTOGRAPH 16 SKIN : SQUAMOUS CELL PAPILLOMA
RAT, MALE, 30ppm, ANIMAL No. 0342-1330 (H&E)

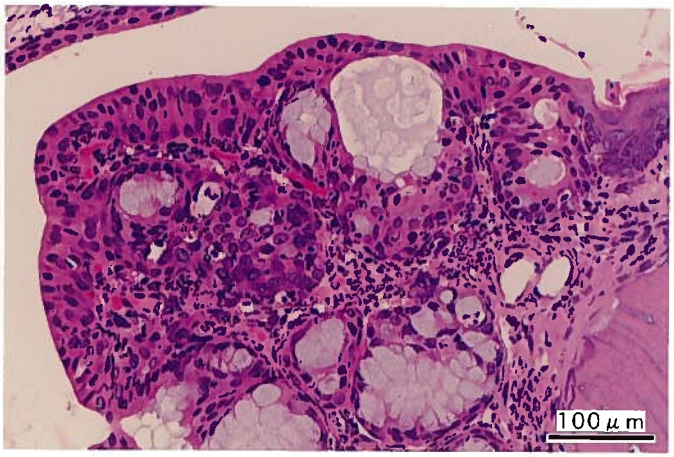
PHOTOGRAPH 1



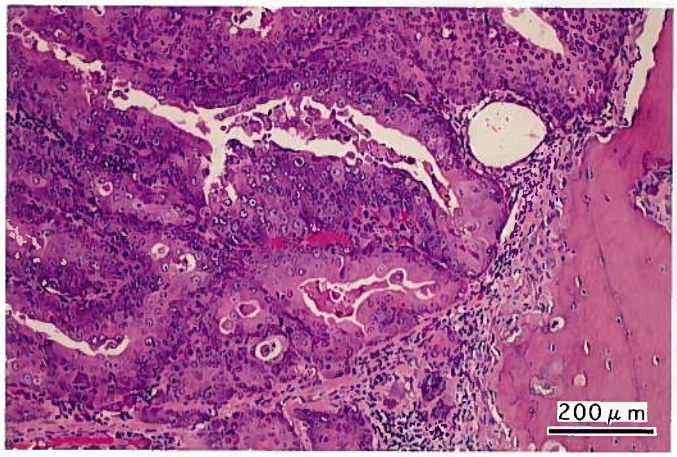
PHOTOGRAPH 2



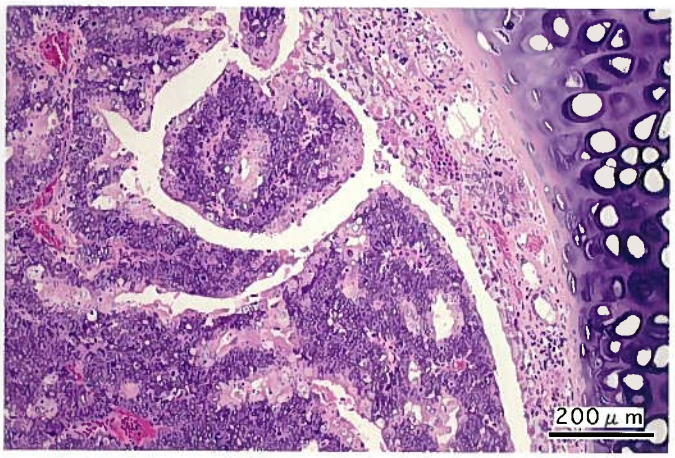
PHOTOGRAPH 3



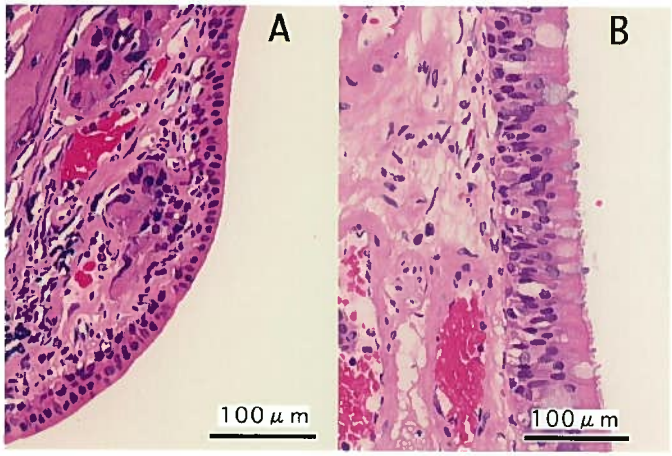
PHOTOGRAPH 4



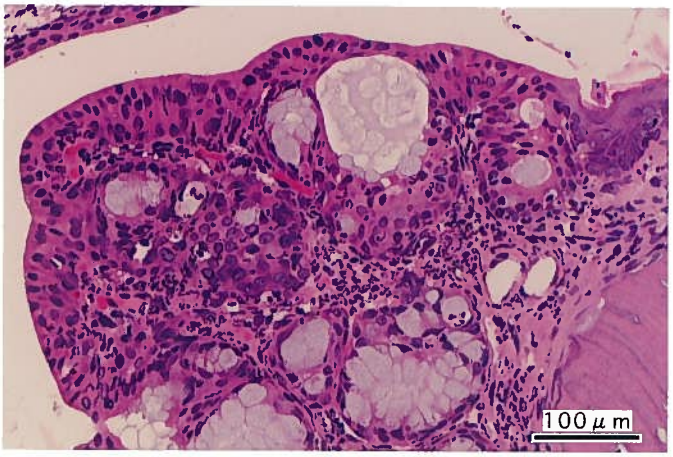
PHOTOGRAPH 5



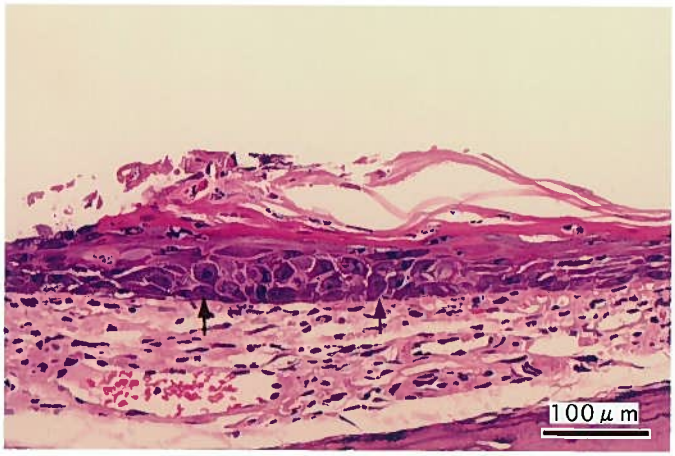
PHOTOGRAPH 6



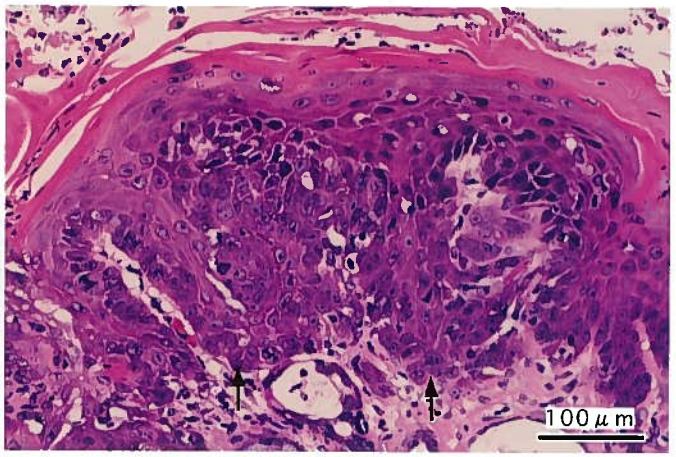
PHOTOGRAPH 7



PHOTOGRAPH 8



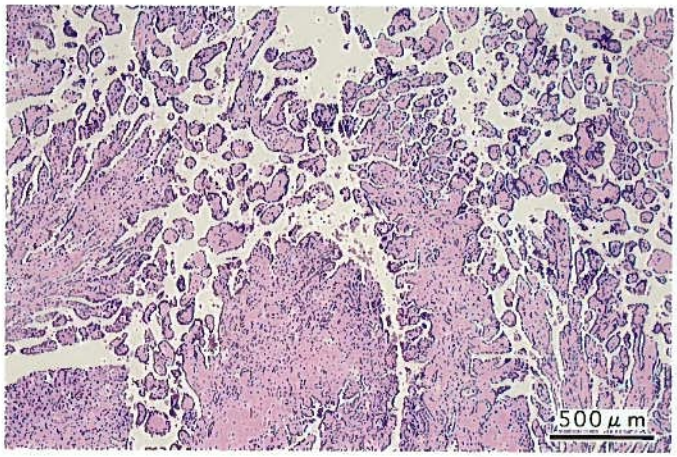
PHOTOGRAPH 9



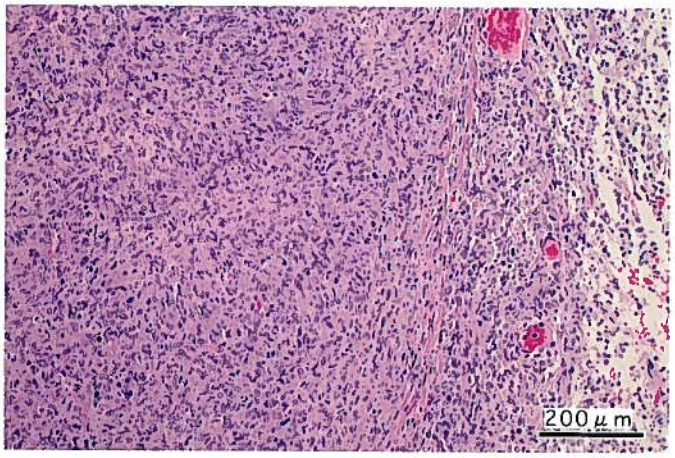
PHOTOGRAPH 10

PHOTOGRAPH 11

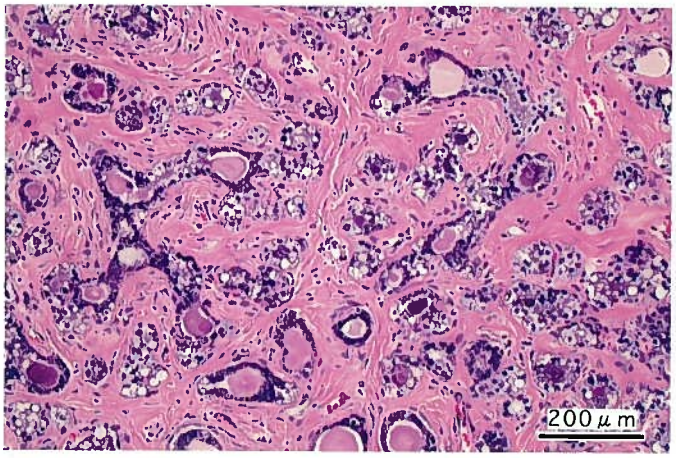
PHOTOGRAPH 12



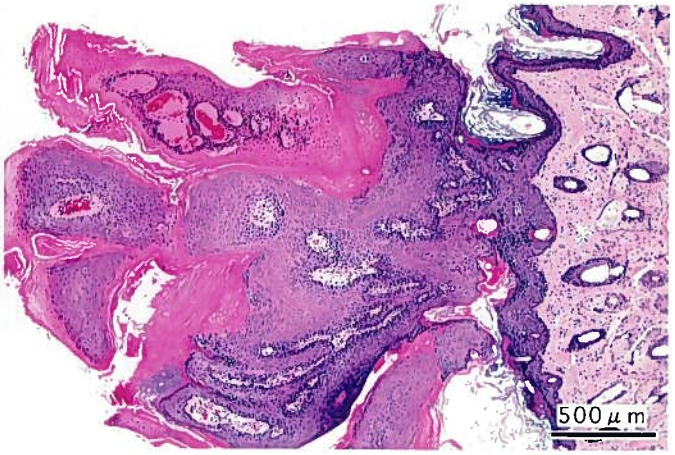
PHOTOGRAPH 13



PHOTOGRAPH 14



PHOTOGRAPH 15



PHOTOGRAPH 16