Summary of Inhalation Carcinogenicity Study of Glycidol in BDF1 Mice

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Japan Bioassay Research Center

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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.

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Purpose, materials and methods

Glycidol (CAS No. 556-52-5) is a 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 Crj:BDF1 mice of both sexes to glycidol vapor at a target concentration of 0 (clean air), 4, 13 or 40 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: 3700 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 13 and 40 ppm-exposed groups of both sexes and the respective controls. The markedly decreased survival rates of the 40 ppm-exposed groups of both sexes were attributed to the increased number of deaths due to nasal cavity tumors in the males and due to uterine tumor in the females. Body weight of the 40 ppm-exposed males was significantly lower than that of the male control.

The incidences of hemangiomas and hemangiosarcomas in the nasal cavity were increased dose-dependently in both sexes. The incidences of adenomas, adenocarcinomas, squamous cell carcinomas and squamous cell papillomas in the nasal cavity were also increased. Additionally, the incidences in the Harderian gland (adenomas), subcutis (histiocytic sarcomas) and peripheral nerves (histiocytic sarcomas) in the males, and in the Harderian gland (adenomas), uterine (histiocytic sarcomas) and mammary gland (adenocarcinomas) in the females were increased. The increased incidences of hemangiomas and hemangiosarcomas in the nasal cavity were noted in the males and females exposed to 13 ppm and above. The incidence of Harderian gland adenomas was increased in the males and females exposed to 40 ppm. In the nasal cavity, the combined incidence of adenomas and adenocarcinomas in the males and females exposed to 40 ppm and the combined incidence of squamous cell carcinomas and squamous cell papillomas in the females exposed to 40 ppm were significantly increased. The incidence of uterine histiocytic sarcomas in the females exposed to 13 ppm and above was significantly increased.

The incidences of squamous cell metaplasia with atypia and squamous cell hyperplasia in the respiratory epithelium, and respiratory metaplasia in the gland and olfactory epithelium were increased in the glycidol-exposed groups of both sexes. The incidence of hyperplasia in the transitional epithelium was also increased in the glycidol-exposed females. These nasal lesions were increased primarily in the males and females exposed to 13 ppm and above, but the incidence of respiratory metaplasia in the submucosal gland and olfactory epithelium was significantly increased in all the glycidol-exposed female groups.

Conclusions

In mice, there was clear evidence of carcinogenic activity of glycidol in males and females, based on the increased incidences of nasal cavity tumors (hemangiomas, hemangiosarcomas, adenomas, adenocarcinomas, squamous cell carcinomas and squamous cell papillomas), and histiocytic sarcomas of subcutis and peripheral nerves in the males, and based on the increased incidences of nasal cavity tumors (hemangiomas, hemangiosarcomas, adenomas, adenocarcinomas, squamous cell carcinomas and squamous cell papillomas) uterine tumors (histiocytic sarcomas) and mammary gland tumors (adenocarcinomas) in the females. Additionally, the incidences of squamous cell metaplasia with atypia and squamous cell

hyperplasia in the respiratory epithelium, and respiratory metaplasia in the submucosal gland and olfactory epithelium were increased in the glycidol-exposed groups of both sexes.

TABLES

TABLES (CONTINUED)

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

Weeks on Study	Control Av.Wt.	Control No.of Surviv. <50>	4ppm Av.Wt.	4ppm % of cont.	4ppm No.of Surviv. <50>	13ppm Av.Wt.	13ppm % of cont.	13ppm No.of Surviv. <50>	40ppm Av.Wt.	40ppm % of cont.	40ppm No.of Surviv. <50>
0	22.3 (50)	50/50	22.3 (50)	100	50/50	22.3 (50)	100	50/50	22.3 (50)	100	50/50
1	23.8 (50)	50/50	23.5 (50)	99	50/50	23.7 (50)	100	50/50	23.1 (50)	97	50/50
2	24.6 (50)	50/50	24.0 (50)	98	50/50	24.6 (50)	100	50/50	23.7 (50)	96	50/50
3	25.4 (50)	50/50	24.6 (50)	97	50/50	25.3 (50)	100	50/50	24.2 (50)	95	50/50
4	25.9 (50)	50/50	25.2 (50)	97	50/50	26.0 (50)	100	50/50	24.9 (50)	96	50/50
5	26.4 (50)	50/50	25.8 (50)	98	50/50	26.5 (50)	100	50/50	25.3 (50)	96	50/50
6	27.4 (50)	50/50	26.4 (50)	96	50/50	27.1 (50)	99	50/50	25.9 (50)	95	50/50
7	27.7 (50)	50/50	26.7 (50)	96	50/50	27.9 (50)	101	50/50	26.1 (50)	94	50/50
8	28.3 (50)	50/50	27.3 (50)	96	50/50	28.2 (50)	100	50/50	26.4 (50)	93	50/50
9	28.9 (50)	50/50	27.7 (50)	96	50/50	28.7 (50)	99	50/50	27.0 (50)	93	50/50
10	29.3 (50)	50/50	28.2 (50)	96	50/50	29.1 (50)	99	50/50	27.4 (50)	94	50/50
11	30.4 (50)	50/50	29.1 (50)	96	50/50	29.9 (50)	98	50/50	27.9 (50)	92	50/50
12	30.8 (50)	50/50	29.5 (50)	96	50/50	30.8 (50)	100	50/50	28.5 (50)	93	50/50
13	31.2 (50)	50/50	30.0 (50)	96	50/50	30.9 (50)	99	50/50	29.0 (50)	93	50/50
14	32.1 (50)	50/50	30.7 (50)	96	50/50	31.5 (50)	98	50/50	29.5 (50)	92	50/50
18	34.9 (50)	50/50	33.1 (50)	95	50/50	33.9 (50)	97	50/50	31.7 (50)	91	50/50
22	36.6 (50)	50/50	35.2 (50)	96	50/50	35.9 (50)	98	50/50	33.7 (50)	92	50/50
26	39.0 (50)	50/50	37.7 (50)	97	50/50	38.3 (50)	98	50/50	35.7 (50)	92	50/50
30	40.5 (50)	50/50	39.0 (50)	96	50/50	39.9 (50)	99	50/50	36.7 (50)	91	50/50
34	41.4 (50)	50/50	40.3 (50)	97	50/50	41.3 (50)	100	50/50	37.5 (50)	91	50/50
38	43.0 (50)	50/50	41.8 (50)	97	50/50	42.5 (50)	99	50/50	38.4 (50)	89	50/50
42	44.4 (50)	50/50	43.4 (50)	98	50/50	43.3 (50)	98	50/50	39.2 (50)	88	50/50
46	45.4 (50)	50/50	43.9 (50)	97	50/50	43.8 (50)	96	50/50	39.7 (50)	87	50/50
50	46.8 (50)	50/50	44.5 (50)	95	50/50	44.9 (50)	96	50/50	40.3 (50)	86	50/50
54	47.7 (49)	49/50	45.9 (48)	96	48/50	45.7 (50)	96	50/50	40.5 (49)	85	49/50
58	47.6 (49)	49/50	46.1 (48)	97	48/50	46.1 (48)	97	48/50	39.8 (48)	84	48/50
62	49.1 (49)	49/50	47.3 (48)	96	48/50	47.1 (47)	96	47/50	40.4 (47)	82	47/50
66	49.1 (49)	49/50	47.7 (48)	97	48/50	47.5 (47)	97	47/50	39.7 (44)	81	44/50
70	49.3 (49)	49/50	48.4 (48)	98	48/50	47.3 (47)	96	47/50	38.2 (44)	77	44/50
74	49.6 (49)	49/50	49.1 (47)	99	47/50	46.8 (47)	94	47/50	37.3 (42)	75	41/50
78	49.8 (49)	49/50	49.7 (45)	100	45/50	46.8 (43)	94	43/50	35.2 (36)	71	36/50
82	50.3 (48)	48/50	50.3 (45)	100	45/50	47.0 (39)	93	39/50	33.9 (29)	67	28/50
86	49.3 (48)	48/50	50.1 (45)	102	45/50	45.5 (38)	92	38/50	35.3 (19)	72	18/50
90	50.2 (43)	43/50	50.2 (43)	100	43/50	43.4 (35)	86	34/50	35.2 (16)	70	16/50
94	49.2 (42)	42/50	50.1 (43)	102	43/50	41.9 (29)	85	29/50	32.4 (12)	66	12/50
98	48.6 (41)	41/50	49.7 (41)	102	41/50	39.0 (26)	80	26/50	30.0 (8)	62	8/50
102	48.3 (39)	39/50	49.3 (37)	102	37/50	37.7 (22)	78	20/50	27.2 (5)	56	5/50
104	47.7 (38)	38/50	49.1 (35)	103	35/50	38.2 (18)	80	18/50	29.0 (3)	61	3/50

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

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

Weeks on Study	Control Av.Wt.	Control No.of Surviv. <50>	4ppm Av.Wt.	4ppm % of cont.	4ppm No.of Surviv. <50>	13ppm Av.Wt.	13ppm % of cont.	13ppm No.of Surviv. <50>	40ppm Av.Wt.	40ppm % of cont.	40ppm No.of Surviv. <49>
0	18.1 (50)	50/50	18.1 (50)	100	50/50	18.1 (50)	100	50/50	18.1 (49)	100	50/50
1	18.9 (50)	50/50	18.7 (50)	99	50/50	18.9 (50)	100	50/50	18.7 (49)	99	49/49
2	19.8 (50)	50/50	19.8 (50)	100	50/50	19.9 (50)	101	50/50	19.5 (49)	98	49/49
3	20.5 (50)	50/50	20.4 (50)	100	50/50	20.5 (50)	100	50/50	20.1 (49)	98	49/49
4	21.4 (50)	50/50	21.2 (50)	99	50/50	21.2 (50)	99	50/50	20.9 (49)	98	49/49
5	21.9 (50)	50/50	21.6 (50)	99	50/50	21.6 (50)	99	50/50	21.2 (49)	97	49/49
6	22.4 (50)	50/50	22.2 (50)	99	50/50	22.0 (50)	98	50/50	21.8 (49)	97	49/49
7	22.6 (50)	50/50	22.4 (50)	99	50/50	22.4 (50)	99	50/50	22.1 (49)	98	49/49
8	22.7 (50)	50/50	22.4 (50)	99	50/50	22.7 (50)	100	50/50	22.2 (49)	98	49/49
9	23.2 (50)	50/50	22.7 (50)	98	50/50	22.7 (50)	98	50/50	22.7 (49)	98	49/49
10	23.1 (50)	50/50	22.9 (50)	99	50/50	22.9 (50)	99	50/50	22.7 (49)	98	49/49
11	24.1 (50)	50/50	24.0 (50)	100	50/50	23.6 (50)	98	50/50	23.5 (49)	98	49/49
12	24.1 (50)	50/50	23.9 (50)	99	50/50	24.1 (50)	100	50/50	23.8 (49)	99	49/49
13	24.3 (50)	50/50	24.1 (50)	99	50/50	24.1 (50)	99	50/50	23.6 (49)	97	49/49
14	24.6 (50)	50/50	24.5 (50)	100	50/50	24.2 (50)	98	50/50	23.9 (49)	97	49/49
18	25.5 (50)	50/50	25.4 (50)	100	50/50	25.0 (50)	98	50/50	24.8 (49)	97	49/49
22	26.0 (50)	50/50	26.0 (50)	100	50/50	25.6 (50)	98	50/50	25.6 (49)	98	49/49
26	27.1 (50)	50/50	27.0 (49)	100	49/50	26.9 (50)	99	50/50	26.2 (49)	97	49/49
30	27.8 (50)	50/50	27.9 (49)	100	49/50	27.2 (50)	98	50/50	26.8 (49)	96	49/49
34	27.5 (50)	50/50	27.8 (49)	101	49/50	27.7 (50)	101	50/50	27.3 (49)	99	49/49
38	28.3 (50)	50/50	28.3 (49)	100	49/50	28.3 (49)	100	49/50	27.3 (49)	96	49/49
42	29.1 (50)	50/50	29.0 (49)	100	49/50	29.2 (49)	100	49/50	28.1 (49)	97	49/49
46	29.1 (50)	50/50	29.1 (49)	100	49/50	29.2 (49)	100	49/50	28.1 (49)	97	49/49
50	29.8 (50)	50/50	30.0 (49)	101	49/50	30.3 (49)	102	49/50	28.9 (48)	97	48/49
54	29.8 (50)	50/50	30.1 (48)	101	48/50	30.4 (49)	102	49/50	28.9 (47)	97	47/49
58	29.5 (50)	50/50	30.3 (48)	103	48/50	30.8 (48)	104	48/50	29.1 (46)	99	46/49
62	29.8 (49)	49/50	31.1 (48)	104	48/50	31.7 (48)	106	48/50	29.6 (44)	99	44/49
66	29.9 (47)	47/50	31.5 (48)	105	48/50	32.3 (47)	108	47/50	28.8 (43)	96	43/49
70	30.1 (47)	47/50	32.1 (47)	107	47/50	32.2 (44)	107	44/50	28.5 (39)	95	38/49
74	30.8 (46)	46/50	31.8 (46)	103	46/50	32.7 (43)	106	43/50	28.7 (35)	93	35/49
78	31.3 (46)	46/50	32.0 (45)	102	45/50	31.7 (37)	101	34/50	28.0 (30)	89	27/49
82	30.8 (43)	43/50	32.9 (43)	107	42/50	33.0 (31)	107	31/50	30.2 (19)	98	19/49
86	31.2 (43)	43/50	32.9 (40)	105	40/50	34.0 (30)	109	30/50	27.9 (16)	89	16/49
90	31.0 (40)	40/50	33.5 (35)	108	35/50	33.8 (26)	109	26/50	28.4 (12)	92	12/49
94	31.7 (37)	37/50	33.7 (30)	106	30/50	32.8 (24)	103	23/50	27.2 (4)	86	4/49
98	31.2 (33)	33/50	32.1 (28)	103	28/50	33.8 (18)	108	18/50	21.4 (3)	69	2/49
102	30.3 (29)	29/50	31.2 (25)	103	25/50	32.4 (14)	107	14/50	21.1 (2)	70	1/49
104	30.8 (28)	28/50	31.8 (22)	103	22/50	33.1 (10)	107	10/50	21.2 (1)	69	1/49

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

TABLE 3 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF MALE MICE 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	0/49	0/49	1/49	4/42	4/50 (0/12)
4ppm	0/50	0/50	0/50	0/50	1/49	1/48	2/45	5/43	5/50 (1/15)
13ppm	0/50	0/50	0/50	0/50	2/50	1/47	5/42	7/31	9/50 (4/32)
40ppm	0/50	0/50	0/50	0/50	2/49	6/44	11/35	7/15	14/50 (14/47)
Internal mass									
0ppm	0/50	1/50	1/50	2/50	4/49	5/49	7/49	6/42	10/50 (6/12)
4ppm	1/50	2/50	2/50	2/50	2/49	3/48	7/45	9/43	13/50 (9/15)
13ppm	1/50	1/50	1/50	1/50	3/50	3/47	7/42	6/31	10/50 (8/32)
40ppm	0/50	0/50	0/50	0/50	1/49	2/44	1/35	1/15	3/50 (3/47)

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 MICE 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	0/47	0/46	3/39	3/50 (1/22)
4ppm	0/50	0/50	0/49	0/49	0/48	0/48	0/45	1/33	1/50 (1/28)
13ppm	0/50	0/50	0/50	0/49	1/49	3/47	1/34	4/24	7/50 (5/40)
40ppm	0/50	0/49	0/49	0/49	0/47	5/43	5/25	3/7	8/49 (8/48)
Internal mass									
0ppm	1/50	1/50	1/50	1/50	4/50	8/47	11/46	11/39	20/50 (14/22)
4ppm	1/50	3/50	2/49	2/49	3/48	9/48	13/45	9/33	21/50 (21/28)
13ppm	1/50	0/50	0/50	0/49	4/49	10/47	9/34	12/24	22/50 (16/40)
40ppm	0/50	0/49	1/49	1/49	2/47	8/43	7/25	2/7	12/49 (12/48)

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 MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Weeks on Study	Control Av.FC. <50>	4ppm Av.FC. <50>	4ppm % of cont.	13ppm Av.FC. <50>	13ppm % of cont.	40ppm Av.FC. <50>	40ppm % of cont.
1	4.1 (50)	4.1 (50)	100	4.1 (50)	100	3.9 (50)	95
2	4.0 (50)	3.9 (50)	98	4.0 (50)	100	3.9 (50)	98
3	4.1 (50)	4.1 (50)	100	4.1 (50)	100	4.0 (50)	98
4	4.1 (50)	4.1 (50)	100	4.2 (50)	102	4.1 (50)	100
5	4.2 (50)	4.2 (50)	100	4.2 (50)	100	4.0 (50)	95
6	4.4 (50)	4.3 (50)	98	4.3 (50)	98	4.1 (50)	93
7	4.3 (50)	4.3 (50)	100	4.2 (50)	98	4.0 (50)	93
8	4.5 (50)	4.3 (50)	96	4.3 (50)	96	4.2 (50)	93
9	4.5 (50)	4.4 (50)	98	4.3 (50)	96	4.1 (50)	91
10	4.6 (50)	4.5 (50)	98	4.4 (50)	96	4.2 (50)	91
11	4.6 (50)	4.5 (50)	98	4.4 (50)	96	4.3 (50)	93
12	4.7 (50)	4.5 (50)	96	4.5 (50)	96	4.3 (50)	91
13	4.6 (50)	4.5 (50)	98	4.5 (50)	98	4.5 (50)	98
14	4.7 (50)	4.5 (50)	96	4.6 (50)	98	4.4 (50)	94
18	4.8 (50)	4.7 (50)	98	4.7 (50)	98	4.5 (50)	94
22	4.8 (50)	4.7 (50)	98	4.7 (50)	98	4.5 (50)	94
26	4.9 (50)	4.8 (50)	98	4.9 (50)	100	4.7 (50)	96
30	4.9 (50)	4.8 (50)	98	4.8 (50)	98	4.5 (50)	92
34	5.0 (50)	5.0 (50)	100	5.1 (50)	102	4.7 (50)	94
38	5.2 (50)	5.1 (50)	98	5.2 (50)	100	4.9 (50)	94
42	5.0 (50)	4.8 (50)	96	4.9 (50)	98	4.6 (50)	92
46	5.1 (50)	5.0 (50)	98	5.0 (50)	98	4.7 (50)	92
50	5.2 (50)	5.0 (50)	96	5.1 (50)	98	4.8 (50)	92
54	5.2 (49)	5.1 (48)	98	5.2 (50)	100	4.8 (49)	92
58	5.2 (49)	5.1 (48)	98	5.1 (48)	98	4.6 (48)	88
62	5.4 (49)	5.1 (48)	94	5.3 (47)	98	4.7 (47)	87
66	5.4 (49)	5.3 (48)	98	5.3 (47)	98	4.6 (44)	85
70	5.4 (49)	5.2 (48)	96	5.2 (47)	96	4.4 (44)	81
74	5.4 (49)	5.2 (47)	96	5.3 (47)	98	4.5 (42)	83
78	5.4 (49)	5.4 (45)	100	5.2 (43)	96	4.2 (36)	78
82	5.2 (48)	5.3 (45)	102	5.2 (39)	100	4.2 (29)	81
86	5.0 (48)	5.2 (45)	104	5.0 (38)	100	4.2 (19)	84
90	5.2 (43)	5.3 (43)	102	4.8 (35)	92	4.1 (16)	79
94	5.4 (42)	5.5 (43)	102	4.8 (29)	89	4.1 (12)	76
98	5.5 (41)	5.5 (41)	100	4.8 (26)	87	4.0 (8)	73
102	5.4 (39)	5.4 (36)	100	4.8 (22)	89	3.9 (5)	72
104	5.4 (38)	5.4 (36)	100	4.9 (18)	91	4.7 (3)	87

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

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

Weeks on Study	Control Av.FC.		4ppm Av.FC.		% of cont.	13ppm Av.FC.		% of cont.	40ppm Av.FC.		% of cont.
	<50>		<50>			<50>			<49>		
1	3.4	(50)	3.5	(50)	103	3.5	(50)	103	3.4	(49)	100
2	3.5	(50)	3.5	(50)	100	3.5	(50)	100	3.5	(49)	100
3	3.7	(50)	3.7	(50)	100	3.6	(50)	97	3.6	(49)	97
4	3.9	(50)	3.9	(50)	100	3.9	(50)	100	3.7	(49)	95
5	4.1	(50)	4.0	(50)	98	3.9	(50)	95	3.8	(49)	93
6	4.2	(50)	4.2	(50)	100	4.0	(50)	95	3.9	(49)	93
7	4.2	(50)	4.2	(50)	100	4.0	(50)	95	3.9	(49)	93
8	4.3	(50)	4.3	(50)	100	4.1	(50)	95	4.0	(49)	93
9	4.3	(50)	4.2	(50)	98	4.0	(50)	93	4.0	(49)	93
10	4.4	(50)	4.3	(50)	98	4.2	(50)	95	4.1	(49)	93
11	4.4	(50)	4.4	(50)	100	4.2	(50)	95	4.1	(49)	93
12	4.4	(50)	4.3	(50)	98	4.2	(50)	95	4.1	(49)	93
13	4.4	(50)	4.4	(50)	100	4.2	(50)	95	4.1	(49)	93
14	4.4	(50)	4.4	(50)	100	4.2	(50)	95	4.1	(49)	93
18	4.6	(50)	4.5	(50)	98	4.3	(50)	93	4.2	(49)	91
22	4.5	(50)	4.5	(50)	100	4.3	(50)	96	4.2	(49)	93
26	4.5	(50)	4.4	(49)	98	4.4	(50)	98	4.3	(49)	96
30	4.7	(50)	4.6	(49)	98	4.4	(50)	94	4.3	(49)	91
34	4.7	(50)	4.7	(49)	100	4.7	(50)	100	4.6	(49)	98
38	4.8	(50)	4.8	(49)	100	4.7	(49)	98	4.5	(49)	94
42	4.5	(50)	4.5	(49)	100	4.7	(49)	104	4.5	(49)	100
46	4.5	(50)	4.6	(49)	102	4.6	(49)	102	4.4	(49)	98
50	4.7	(50)	4.8	(49)	102	4.8	(49)	102	4.6	(48)	98
54	4.6	(50)	4.6	(48)	100	4.8	(49)	104	4.6	(47)	100
58	4.5	(50)	4.6	(48)	102	4.7	(48)	104	4.4	(46)	98
62	4.4	(49)	4.6	(48)	105	4.8	(48)	109	4.4	(44)	100
66	4.6	(47)	4.8	(48)	104	4.9	(47)	107	4.4	(43)	96
70	4.5	(47)	4.7	(47)	104	4.7	(44)	104	4.3	(39)	96
74	4.7	(46)	4.5	(46)	96	4.7	(43)	100	4.4	(35)	94
78	4.8	(46)	4.8	(45)	100	4.7	(37)	98	4.4	(30)	92
82	4.5	(43)	4.7	(43)	104	4.9	(31)	109	4.4	(19)	98
86	4.5	(43)	4.5	(40)	100	5.0	(30)	111	4.0	(16)	89
90	4.5	(40)	4.8	(35)	107	5.1	(26)	113	4.4	(12)	98
94	4.8	(37)	5.0	(30)	104	4.9	(24)	102	5.0	(4)	104
98	4.9	(33)	5.0	(28)	102	5.1	(18)	104	4.1	(3)	84
102	4.7	(29)	4.9	(25)	104	5.0	(14)	106	4.2	(2)	89
104	4.8	(28)	4.9	(22)	102	5.1	(11)	106	3.8	(1)	79

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

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

Group Name	Control	4 ppm	13 ppm	40 ppm
No. of examined animals	38	35	18	3
Body weight (g)	43.2 ± 7.5	44.9 ± 7.9	34.3 ± 7.4 **	25.4 ± 2.4 **
Testes (g)	0.214 ± 0.034	0.204 ± 0.048	0.197 ± 0.033	0.196 ± 0.016
Testes (%)	0.508 ± 0.105	0.467 ± 0.130	0.598 ± 0.164 *	0.776 ± 0.087 **
Heart (g)	0.235 ± 0.040	0.235 ± 0.027	0.211 ± 0.026 *	0.176 ± 0.023 **
Heart (%)	0.561 ± 0.148	0.540 ± 0.115	0.633 ± 0.109	0.690 ± 0.052
Lung (g)	0.230 ± 0.059	0.254 ± 0.102	0.216 ± 0.027	0.224 ± 0.055
Lung (%)	0.550 ± 0.177	0.583 ± 0.249	0.652 ± 0.136 *	0.880 ± 0.181 *
Kidneys (g)	1.514 ± 3.370	1.012 ± 2.035	0.631 ± 0.065	0.560 ± 0.054
Kidneys (%)	3.457 ± 7.180	2.346 ± 4.791	1.889 ± 0.276 **	2.200 ± 0.009 *
Spleen(g)	0.128 ± 0.141	0.149 ± 0.203	0.063 ± 0.029 **	0.048 ± 0.006 *
Spleen(%)	0.317 ± 0.371	0.354 ± 0.493	0.189 ± 0.097	0.193 ± 0.043
Liver (g)	1.661 ± 0.445	1.870 ± 0.743	1.457 ± 0.221	1.046 ± 0.091 *
Liver (%)	3.970 ± 1.166	4.401 ± 2.513	4.436 ± 1.304	4.114 ± 0.084
Brain (g)	0.457 ± 0.017	0.456 ± 0.017	0.453 ± 0.018	0.439 ± 0.007
Brain (%)	1.093 ± 0.214	1.052 ± 0.219	1.378 ± 0.294 **	1.740 ± 0.196 **

Mean ± S.D.

Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

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

Group Name	Control	4 ppm	13 ppm	40 ppm
No. of examined animals	28	22	10	1
Body weight (g)	26.4 ± 3.4	27.8 ± 4.7	28.6 ± 3.3	18.7
Ovaries(g)	0.080 ± 0.080	0.034 ± 0.019 **	0.043 ± 0.021	0.011
Ovaries(%)	0.294 ± 0.281	0.126 ± 0.076 **	0.150 ± 0.062	0.059

Mean ± S.D.

Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

TABLE9 INCIDENCES OF SELECTED LESIONS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group		Control	4ppm	13ppm	40ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	50		
Organ / Findings	Grade of Nonneoplastic lesion						
Subcutis							
Histiocytic sarcoma		1	1	3	3	**	
Nasal cavity							
Hemorrhage	+	0	0	2 **	2 **		
	2+	0	0	3	11		
	3+	0	0	8	8		
Exudate	+	0	1	4 **	7 **		
	2+	0	0	7	12		
	3+	0	0	3	5		
Squamous cell metaplasia: respiratory epithelium	+	0	1	7 **	8 **		
	2+	0	1	24	18		
	3+	0	0	1	4		
Squamous cell metaplasia with atypia: respiratory epithelium	+	0	0	2 *	4 **		
	2+	0	0	6	11		
	3+	0	0	0	1		
Squamous cell hyperplasia	+	0	0	2	3		
	2+	0	1	0	0		
Squamous cell hyperplasia with atypia	+	0	0	5 *	12 **		
	2+	0	0	1	5		
Respiratory metaplasia: gland	+	26	9 **	41 **	9 **		
	2+	0	1	6	41		
Respiratory metaplasia: olfactory epithelium	+	11	2 *	37 **	8 **		
	2+	0	0	12	40		
	3+	0	0	0	1		
Hemangioma 1)		0	3	13 **	7 **	**	
Hemangiosarcoma 2)		0	0	17 **	33 **	**	**
1) +2)		0	3	30 **	40 **	**	**
Adenoma 3)		0	0	3	2	*	
Adenocarcinoma 4)		0	0	0	3	**	**
3) +4)		0	0	3	5 *	**	**
Squamous cell papilloma		0	0	1	0		
Squamous cell carcinoma		0	0	0	1		
Lung							
Bronchiolar-alveolar carcinoma		4	7	3	4	*	
Lymph node							
Malignant lymphoma		5	8	9	4	*	
Salivary gland							
Lymphocytic infiltration	+	35	33	26	23 *		
Stomach							
Hyperplasia: forestomach	+	0	0	1	4 *		
	2+	0	0	2	3		
	3+	0	0	1	0		
Liver							
Granulation	+	18	22	9	5 **		
	2+	1	0	0	0		
Hepatocellular adenoma 1)		11	11	5	3 *		*
Hepatocellular carcinoma 2)		4	8	5	0		*
1) +2)		15	18	10	3 **		**

TABLE9 INCIDENCES OF SELECTED LESIONS OF MALE MICE
IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group		Control	4ppm	13ppm	40ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	50		
Organ / Findings	Grade of Nonneoplastic lesion						
Liver							
Hemangioma 3)		3	2	3	2	*	
Hemangiosarcoma 4)		1	0	0	0		
3) +4)		4	2	3	2		
Kidney							
Lymphocytic infiltration	+	8	7	2	0 **		
Mineralization: cortex	+	16	12	29 *	32 **		
	2+	0	0	0	1		
Brain							
Mineralization	+	34	36	29	21 *		
Peripheral nerves							
Histiocytic sarcoma		1	0	3	3	*	
Harderian gland							
Adenoma		2	6	7	10 *	*	*
All SITE							
Histiocytic sarcoma		7	9	12	13	**	
Malignant lymphoma		6	10	10	4		

Grade +: Slight 2+: Moderate 3+: Marked 4+: Severe
Significant difference * : $p<0.05$ ** : $p<0.01$ Chi square test

TABLE10 INCIDENCES OF SELECTED LESIONS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group		Control	4ppm	13ppm	40ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	49		
Organ / Findings	Grade of Nonneoplastic lesion						
Nasal cavity							
Hemorrhage	+	0	0	4 *	7 **		
	2+	0	0	4	11		
	3+	0	0	2	10		
	4+	0	0	0	1		
Exudate	+	1	0	2	2 **		
	2+	1	0	3	7		
	3+	0	0	0	7		
Squamous cell metaplasia: respiratory epithelium	+	0	0	11 **	4 **		
	2+	0	0	9	11		
	3+	0	0	0	1		
Squamous cell metaplasia with atypia: respiratory epithelium	+	0	0	1 *	3 **		
	2+	0	0	5	23		
	3+	0	0	0	1		
Squamous cell hyperplasia:	+	0	0	3	6 *		
	2+	0	0	0	1		
Squamous cell hyperplasia with atypia	+	0	0	1	3 *		
	2+	0	0	0	4		
Hyperplasia: transitional epithelium	+	0	1	6 *	1		
Respiratory metaplasia: gland	+	7	27 **	21 **	0 **		
	2+	0	1	29	44		
	3+	0	0	0	5		
Respiratory metaplasia: olfactory epithelium	+	1	33 **	19 **	0 **		
	2+	1	0	29	42		
	3+	0	0	2	7		
Eosinophilic change: olfactory epithelium	+	11	9	3 *	4		
	2+	0	1	0	0		
Eosinophilic change: respiratory epithelium	+	19	15	10 *	22 *		
	2+	18	17	33	9		
	3+	6	6	1	2		
	4+	1	1	0	0		
Hemangioma 1)		0	0	5 *	10 **	**	**
Hemangiosarcoma 2)		0	1	16 **	21 **	**	**
1) +2)		0	1	21 **	31 **	**	**
Adenoma 3)		0	0	0	3	**	**
Adenocarcinoma 4)		0	0	0	2		
3) +4)		0	0	0	5 *	**	**
Squamous cell papilloma 5)		0	0	1	1		
Squamous cell carcinoma 6)		0	0	0	4	**	**
5) +6)		0	0	1	5 *	**	**
Sarcoma:NOS		0	0	0	1		
Lung							
Inflammatory infiltration	+	5	3	4	0 *		
	2+	0	0	1	1		
Bronchiolar-alveolar adenoma 1)		2	1	1	3	*	
Bronchiolar-alveolar carcinoma 2)		2	0	2	1		
1) +2)		4	1	3	4	**	

TABLE10 INCIDENCES OF SELECTED LESIONS OF FEMALE MICE
IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL (CONTINUED)

Group		Control	4ppm	13ppm	40ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	49		
Organ / Findings	Grade of Nonneoplastic lesion						
Lymph node							
Malignant lymphoma		17	14	14	6 **		*
Liver							
Granulation	+	21	18	8 **	2 **		
	2+	0	0	0	1		
Kidney							
Hyaline droplet	+	8	11	21 *	10		
	2+	3	1	1	1		
Uterus							
Cystic endometrial hyperplasia	+	18	8	10	8 *		
	2+	5	6	8	2		
Histiocytic sarcoma		12	15	22 *	18	**	
Mammary gland							
Adenocarcinoma		2	0	5	4	*	
Brain							
Mineralization	+	20	22	20	9 *		
Harderian gland							
Adenoma		1	1	6	7 *	**	**
All SITE							
Histiocytic sarcoma		12	17	27 **	21 *	**	
Malignant lymphoma		21	17	16	7 **		**

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 MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group Name	Control	4ppm	13ppm	40ppm
SITE : subcutis				
TUMOR : histiocytic sarcoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	2.63	2.86	16.67	7.69
Terminal rates(c)	1/38(2.6)	1/35(2.9)	3/18(16.7)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0254* f)			
Prevalence method(d)	P=0.0341*			
Combined analysis (d)	P=0.0039**			
Cochran-Armitage test(e)	P=0.2569			
Fisher Exact test(e)		P=0.7525	P=0.3087	P=0.3087
SITE : nasal cavity				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	0.0	0.0	13.64	12.50
Terminal rates(c)	0/38(0.0)	0/35(0.0)	2/18(11.1)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0103*			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.1655			
Fisher Exact test(e)		P=N.C.	P=0.1212	P=0.2475
SITE : nasal cavity				
TUMOR : hemangioma				
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	13/50(26.0)	7/50(14.0)
Adjusted rates(b)	0.0	7.14	38.89	20.00
Terminal rates(c)	0/38(0.0)	2/35(5.7)	7/18(38.9)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0006**			
Prevalence method(d)	P=0.0122*			
Combined analysis (d)	P=0.0001**			
Cochran-Armitage test(e)	P=0.0582			
Fisher Exact test(e)		P=0.1212	P<0.0001**	P=0.0062**
SITE : nasal cavity				
TUMOR : adenocarcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	0.0	8.00
Terminal rates(c)	0/38(0.0)	0/35(0.0)	0/18(0.0)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.1204			
Prevalence method(d)	P=0.0038**f)			
Combined analysis (d)	P=0.0005**f)			
Cochran-Armitage test(e)	P=0.0040**			
Fisher Exact test(e)		P=N.C.	P=N.C.	P=0.1212

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

Group Name	Control	4ppm	13ppm	40ppm
SITE : nasal cavity				
TUMOR : hemangiosarcoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	17/50(34.0)	33/50(66.0)
Adjusted rates(b)	0.0	0.0	31.82	66.67
Terminal rates(c)	0/38(0.0)	0/35(0.0)	4/18(22.2)	2/ 3(66.7)
Statistical analysis				
Peto test				
Standard method(d)	P<0.0001**(f)			
Prevalence method(d)	P<0.0001**			
Combined analysis (d)	P<0.0001**(f)			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=N.C.	P<0.0001**	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)	5/50(10.0)
Adjusted rates(b)	0.0	0.0	13.64	14.29
Terminal rates(c)	0/38(0.0)	0/35(0.0)	2/18(11.1)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.1204			
Prevalence method(d)	P=0.0016**			
Combined analysis (d)	P=0.0004**			
Cochran-Armitage test(e)	P=0.0038**			
Fisher Exact test(e)		P=N.C.	P=0.1212	P=0.0281*
SITE : nasal cavity				
TUMOR : hemangioma, hemangiosarcoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	30/50(60.0)	40/50(80.0)
Adjusted rates(b)	0.0	7.14	65.22	75.00
Terminal rates(c)	0/38(0.0)	2/35(5.7)	11/18(61.1)	2/ 3(66.7)
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=0.1212	P<0.0001**	P<0.0001**
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma				
Tumor rate				
Overall rates(a)	3/50(6.0)	5/50(10.0)	5/50(10.0)	5/50(10.0)
Adjusted rates(b)	7.89	13.89	13.79	25.00
Terminal rates(c)	3/38(7.9)	4/35(11.4)	2/18(11.1)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0533			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.6516			
Fisher Exact test(e)		P=0.3575	P=0.3575	P=0.3575

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

Group Name	Control	4ppm	13ppm	40ppm
SITE : lung				
TUMOR : bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	7/50(14.0)	3/50(6.0)	4/50(8.0)
Adjusted rates(b)	6.52	17.14	5.56	33.33
Terminal rates(c)	2/38(5.3)	6/35(17.1)	1/18(5.6)	1/ 3(33.3)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0253*			
Prevalence method(d)	P=0.4185			
Combined analysis (d)	P=0.0725			
Cochran-Armitage test(e)	P=0.6402			
Fisher Exact test(e)		P=0.2623	P=0.5000	P=0.6425
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	7/50(14.0)	11/50(22.0)	8/50(16.0)	9/50(18.0)
Adjusted rates(b)	13.16	27.78	19.05	40.00
Terminal rates(c)	5/38(13.2)	9/35(25.7)	3/18(16.7)	1/ 3(33.3)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0253*			
Prevalence method(d)	P=0.1039			
Combined analysis (d)	P=0.0200*			
Cochran-Armitage test(e)	P=0.9121			
Fisher Exact test(e)		P=0.2178	P=0.5000	P=0.3929
SITE : lymph node				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	5/50(10.0)	8/50(16.0)	9/50(18.0)	4/50(8.0)
Adjusted rates(b)	7.89	17.14	22.22	20.00
Terminal rates(c)	3/38(7.9)	6/35(17.1)	4/18(22.2)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.2001			
Prevalence method(d)	P=0.0487*			
Combined analysis (d)	P=0.0405*			
Cochran-Armitage test(e)	P=0.4070			
Fisher Exact test(e)		P=0.2768	P=0.1940	P=0.5000
SITE : liver				
TUMOR : hemangioma				
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	5.26	4.44	5.88	0.0
Terminal rates(c)	2/38(5.3)	1/35(2.9)	0/18(0.0)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0279*			
Prevalence method(d)	P=0.7360			
Combined analysis (d)	P=0.1787			
Cochran-Armitage test(e)	P=0.7471			
Fisher Exact test(e)		P=0.5000	P=0.6611	P=0.5000

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

Group Name	Control	4ppm	13ppm	40ppm
SITE : liver				
TUMOR : hepatocellular adenoma				
Tumor rate				
Overall rates(a)	11/50(22.0)	11/50(22.0)	5/50(10.0)	3/50(6.0)
Adjusted rates(b)	23.40	28.57	22.22	9.38
Terminal rates(c)	8/38(21.1)	10/35(28.6)	4/18(22.2)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.3343			
Prevalence method(d)	P=0.7838			
Combined analysis (d)	P=0.7745			
Cochran-Armitage test(e)	P=0.0117*			
Fisher Exact test(e)		P=0.5952	P=0.0857	P=0.0204*
SITE : liver				
TUMOR : hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	8/50(16.0)	5/50(10.0)	0/50(0.0)
Adjusted rates(b)	4.88	13.95	20.00	0.0
Terminal rates(c)	1/38(2.6)	3/35(8.6)	3/18(16.7)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.9176			
Prevalence method(d)	P=0.6486			
Combined analysis (d)	P=0.8513			
Cochran-Armitage test(e)	P=0.0182*			
Fisher Exact test(e)		P=0.1783	P=0.5000	P=0.0587
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	15/50(30.0)	18/50(36.0)	10/50(20.0)	3/50(6.0)
Adjusted rates(b)	28.89	37.21	38.89	9.38
Terminal rates(c)	9/38(23.7)	12/35(34.3)	7/18(38.9)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.8523			
Prevalence method(d)	P=0.9211			
Combined analysis (d)	P=0.9603			
Cochran-Armitage test(e)	P=0.0003**			
Fisher Exact test(e)		P=0.3355	P=0.1779	P=0.0017**
SITE : peripheral nerves				
TUMOR : histiocytic sarcoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	0.0	0.0
Terminal rates(c)	0/38(0.0)	0/35(0.0)	0/18(0.0)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0232*			
Prevalence method(d)	P=---------			
Combined analysis (d)	P=0.0232*			
Cochran-Armitage test(e)	P=0.1438			
Fisher Exact test(e)		P=0.5000	P=0.3087	P=0.3087

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

Group Name	Control	4ppm	13ppm	40ppm
SITE : Harderian gland				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	6/50(12.0)	7/50(14.0)	10/49(20.4)
Adjusted rates(b)	4.26	12.50	24.00	22.22
Terminal rates(c)	0/38(0.0)	3/35(8.6)	2/18(11.1)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0146*			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0256*			
Fisher Exact test(e)		P=0.1343	P=0.0798	P=0.0126*
SITE : ALL SITE				
TUMOR : histiocytic sarcoma				
Tumor rate				
Overall rates(a)	7/50(14.0)	9/50(18.0)	12/50(24.0)	13/50(26.0)
Adjusted rates(b)	13.16	14.29	27.78	33.33
Terminal rates(c)	5/38(13.2)	5/35(14.3)	5/18(27.8)	1/ 3(33.3)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0003**			
Prevalence method(d)	P=0.0075**			
Combined analysis (d)	P<0.0001**			
Cochran-Armitage test(e)	P=0.1513			
Fisher Exact test(e)		P=0.3929	P=0.1540	P=0.1054
SITE : ALL SITE				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	6/50(12.0)	10/50(20.0)	10/50(20.0)	4/50(8.0)
Adjusted rates(b)	10.53	22.86	22.22	20.00
Terminal rates(c)	4/38(10.5)	8/35(22.9)	4/18(22.2)	0/ 3(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.1886			
Prevalence method(d)	P=0.0872			
Combined analysis (d)	P=0.0595			
Cochran-Armitage test(e)	P=0.2157			
Fisher Exact test(e)		P=0.2070	P=0.2070	P=0.3703

(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 MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

Group Name	Control	4ppm	13ppm	40ppm
SITE : nasal cavity				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	3/49(6.1)
Adjusted rates(b)	0.0	0.0	0.0	100.00
Terminal rates(c)	0/28(0.0)	0/22(0.0)	0/10(0.0)	1/ 1(100.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0007**f)			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0036**			
Fisher Exact test(e)		P=N.C.	P=N.C.	P=0.1175
SITE : nasal cavity				
TUMOR : hemangioma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	5/50(10.0)	10/49(20.4)
Adjusted rates(b)	0.0	0.0	20.00	13.04
Terminal rates(c)	0/28(0.0)	0/22(0.0)	2/10(20.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0001**			
Prevalence method(d)	P=0.0023**			
Combined analysis (d)	P<0.0001**			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=N.C.	P=0.0281*	P=0.0005**
SITE : nasal cavity				
TUMOR : squamous cell carcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	4/49(8.2)
Adjusted rates(b)	0.0	0.0	0.0	100.00
Terminal rates(c)	0/28(0.0)	0/22(0.0)	0/10(0.0)	1/ 1(100.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0078**f)			
Prevalence method(d)	P<0.0001**f)			
Combined analysis (d)	P<0.0001**f)			
Cochran-Armitage test(e)	P=0.0008**			
Fisher Exact test(e)		P=N.C.	P=N.C.	P=0.0563
SITE : nasal cavity				
TUMOR : hemangiosarcoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	1/50(2.0)	16/50(32.0)	21/49(42.9)
Adjusted rates(b)	0.0	2.50	33.33	50.00
Terminal rates(c)	0/28(0.0)	0/22(0.0)	1/10(10.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P<0.0001**f)			
Prevalence method(d)	P<0.0001**			
Combined analysis (d)	P<0.0001**f)			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=0.5000	P<0.0001**	P<0.0001**

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

Group Name	Control	4ppm	13ppm	40ppm
SITE : nasal cavity				
TUMOR : squamous cell papilloma, squamous cell carcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	1/50(2.0)	5/49(10.2)
Adjusted rates(b)	0.0	0.0	2.94	100.00
Terminal rates(c)	0/28(0.0)	0/22(0.0)	0/10(0.0)	1/ 1(100.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0078**f)			
Prevalence method(d)	P=0.0005**			
Combined analysis (d)	P<0.0001**			
Cochran-Armitage test(e)	P=0.0006**			
Fisher Exact test(e)		P=N.C.	P=0.5000	P=0.0267*
SITE : nasal cavity				
TUMOR : adenoma, adenocarcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	5/49(10.2)
Adjusted rates(b)	0.0	0.0	0.0	100.00
Terminal rates(c)	0/28(0.0)	0/22(0.0)	0/10(0.0)	1/ 1(100.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0851			
Prevalence method(d)	P=0.0003**f)			
Combined analysis (d)	P<0.0001**f)			
Cochran-Armitage test(e)	P=0.0002**			
Fisher Exact test(e)		P=N.C.	P=N.C.	P=0.0267*
SITE : nasal cavity				
TUMOR : hemangioma, hemangiosarcoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	1/50(2.0)	21/50(42.0)	31/49(63.3)
Adjusted rates(b)	0.0	2.50	46.67	50.00
Terminal rates(c)	0/28(0.0)	0/22(0.0)	3/10(30.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P<0.0001**f)			
Prevalence method(d)	P<0.0001**			
Combined analysis (d)	P<0.0001**f)			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=0.5000	P<0.0001**	P<0.0001**
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	1/50(2.0)	1/50(2.0)	3/49(6.1)
Adjusted rates(b)	7.14	4.55	7.69	14.29
Terminal rates(c)	2/28(7.1)	1/22(4.5)	0/10(0.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0198*			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.3443			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.4903

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

Group Name	Control	4ppm	13ppm	40ppm
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	3/50(6.0)	4/49(8.2)
Adjusted rates(b)	14.29	4.55	15.38	22.22
Terminal rates(c)	4/28(14.3)	1/22(4.5)	1/10(10.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.3010			
Prevalence method(d)	P=0.0080**			
Combined analysis (d)	P=0.0122*			
Cochran-Armitage test(e)	P=0.5199			
Fisher Exact test(e)		P=0.1811	P=0.5000	P=0.6311
SITE : lymph node				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	17/50(34.0)	14/50(28.0)	14/50(28.0)	6/49(12.2)
Adjusted rates(b)	21.43	27.27	31.25	14.29
Terminal rates(c)	6/28(21.4)	6/22(27.3)	3/10(30.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.2409			
Prevalence method(d)	P=0.1526			
Combined analysis (d)	P=0.1378			
Cochran-Armitage test(e)	P=0.0113*			
Fisher Exact test(e)		P=0.3329	P=0.3329	P=0.0094**
SITE : spleen				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	2/50(4.0)	2/50(4.0)	1/49(2.0)
Adjusted rates(b)	10.71	9.09	0.0	0.0
Terminal rates(c)	3/28(10.7)	2/22(9.1)	0/10(0.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.2841			
Prevalence method(d)	P=0.8503			
Combined analysis (d)	P=0.4353			
Cochran-Armitage test(e)	P=0.2435			
Fisher Exact test(e)		P=0.3389	P=0.3389	P=0.1874
SITE : uterus				
TUMOR : histiocytic sarcoma				
Tumor rate				
Overall rates(a)	12/50(24.0)	15/50(30.0)	22/50(44.0)	18/49(36.7)
Adjusted rates(b)	17.86	13.64	33.33	13.64
Terminal rates(c)	5/28(17.9)	3/22(13.6)	3/10(30.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P<0.0001**			
Prevalence method(d)	P=0.0371*			
Combined analysis (d)	P<0.0001**			
Cochran-Armitage test(e)	P=0.2466			
Fisher Exact test(e)		P=0.3264	P=0.0283*	P=0.1230

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

Group Name	Control	4ppm	13ppm	40ppm
SITE : mammary gland				
TUMOR : adenocarcinoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	0/50(0.0)	5/50(10.0)	4/49(8.2)
Adjusted rates(b)	7.14	0.0	15.79	22.22
Terminal rates(c)	2/28(7.1)	0/22(0.0)	1/10(10.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0264*			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.1639			
Fisher Exact test(e)		P=0.2475	P=0.2180	P=0.3292
SITE : Harderian gland				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	6/50(12.0)	7/49(14.3)
Adjusted rates(b)	3.57	4.55	17.86	25.00
Terminal rates(c)	1/28(3.6)	1/22(4.5)	0/10(0.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=---------			
Prevalence method(d)	P=0.0025**			
Combined analysis (d)	P=---------			
Cochran-Armitage test(e)	P=0.0094**			
Fisher Exact test(e)		P=0.7525	P=0.0559	P=0.0277*
SITE : ALL SITE				
TUMOR : histiocytic sarcoma				
Tumor rate				
Overall rates(a)	12/50(24.0)	17/50(34.0)	27/50(54.0)	21/49(42.9)
Adjusted rates(b)	17.86	13.64	41.67	18.18
Terminal rates(c)	5/28(17.9)	3/22(13.6)	4/10(40.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P<0.0001**			
Prevalence method(d)	P=0.0123*			
Combined analysis (d)	P<0.0001**			
Cochran-Armitage test(e)	P=0.1075			
Fisher Exact test(e)		P=0.1891	P=0.0019**	P=0.0375*
SITE : ALL SITE				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	21/50(42.0)	17/50(34.0)	16/50(32.0)	7/49(14.3)
Adjusted rates(b)	32.14	36.36	31.25	14.29
Terminal rates(c)	9/28(32.1)	8/22(36.4)	3/10(30.0)	0/ 1(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.2430			
Prevalence method(d)	P=0.2629			
Combined analysis (d)	P=0.1855			
Cochran-Armitage test(e)	P=0.0025**			
Fisher Exact test(e)		P=0.2684	P=0.2038	P=0.0020**

(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 MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

	Male				Female			
Group	0ppm	4ppm	13ppm	40ppm	0ppm	4ppm	13ppm	40ppm
Number of dead or moribund animals	12	15	32	47	22	28	40	48
No microscopical confirmation	0	0	1	0	0	1	0	0
Urinary retention	0	2	1	2	0	0	0	0
Hydronephrosis	1	1	1	0	0	2	0	2
Cardiovascular resion	0	0	0	0	0	0	0	1
Arteritis	1	0	0	0	0	0	0	0
Hepatic lesion	0	0	0	0	1	0	0	0
Central nervous system lesion	0	0	0	0	1	0	0	0
Peripheral nerves system lesion	0	1	0	0	0	0	0	0
Amyloidosis	0	0	0	0	0	0	0	1
Tumor death : nasal cavity	0	0	12	29	0	0	7	21
leukemia	2	2	6	1	12	9	11	5
subcutis	0	0	1	2	0	0	0	0
lung	1	0	2	2	0	0	1	0
spleen	0	2	0	0	0	0	0	0
tooth	0	0	1	0	0	0	0	0
stomach	0	0	0	1	0	0	0	0
small intestine	0	0	0	1	0	0	0	0
large intestine	0	0	0	1	0	0	0	0
liver	4	5	3	4	1	3	1	1
kidney	1	0	0	1	0	0	0	0
urinary bladder	1	0	0	0	0	0	0	0
epididymis	0	0	1	0				
seminal vesicle	0	1	0	0				
prostate	0	1	0	0				
uterus					7	12	17	15
pituitary gland	0	0	0	0	0	1	0	0
peripheral nerve	1	0	3	3	0	0	2	0
Zymbal gland	0	0	0	0	0	0	0	1
mediastinum	0	0	0	0	0	0	1	1

TABLE 14 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : Crj:BDF$_1$ MALE MICE

Organs / Tumors	No. of animals examined	No. of tumor-bearing animals	Incidence (%)	Min. - Max. (%)
Subcutis	<1047>			
Histiocytic sarcoma		4	0.4	0 - 4
Nasal cavity	<1047>			
Adenoma		1	0.1	0 - 2
Adenocarcinoma		0	0.0	0 - 0
Squamous cell papilloma		0	0.0	0 - 0
Squamous cell carcinoma		0	0.0	0 - 0
Hemangioma		0	0.0	0 - 0
Hemangiosarcoma		0	0.0	0 - 0
Lung	<1046>			
Bronchiolar-alveolar adenoma		74	7.1	2 - 18
Bronchiolar-alveolar carcinoma		120	11.5	0 - 24
Liver	<1047>			
Hepatocellular adenoma		179	17.1	4 - 34
Hepatocellular carcinoma		224	21.4	2 - 42
Hemangioma		14	1.3	0 - 10
Hemangiosarcoma		50	4.8	0 - 12
Lymph node	<1047>			
Malignant lymphoma		111	10.6	2 - 22
Peripheral nerves	<1047>			
Histiocytic sarcoma		3	0.3	0 - 2
Harderian gland	<1047>			
Adenoma		45	4.3	0 - 10

21 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. 0044, 0060, 0062, 0064, 0066, 0068, 0096, 0105, 0116, 0140, 0159, 0163, 0190, 0206, 0211, 0225, 0243, 0270, 0285,0297, 0319

TABLE 15 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : Crj:BDF$_1$ FEMALE MICE

Organs / Tumors	No. of animals examined	No. of tumor-bearing animals	Incidence (%)	Min. - Max. (%)
Nasal cavity	<1048>			
Adenoma		0	0.0	0 - 0
Adenocarcinoma		0	0.0	0 - 0
Squamous cell papilloma		0	0.0	0 - 0
Squamous cell carcinoma		0	0.0	0 - 0
Hemangioma		0	0.0	0 - 0
Hemangiosarcoma		0	0.0	0 - 0
Sarcoma NOS+C25		0	0.0	0 - 0
Lung	<1048>			
Bronchiolar-alveolar adenoma		42	4.0	0 - 10
Bronchiolar-alveolar carcinoma		32	3.1	0 - 8
Lymph node	<1048>			
Malignant lymphoma		277	26.4	12 - 44
Uterus	<1046>			
Histiocytic sarcoma		207	19.8	10 - 30
Mammay gland	<1048>			
Adenocarcinoma		16	1.5	0 - 8
Harderian gland	<1048>			
Adenoma		32	3.1	0 - 12

21 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. 0044, 0060, 0062, 0064, 0066, 0068, 0096, 0105, 0116, 0140, 0159, 0163, 0190, 0206, 0211, 0225, 0243, 0270, 0285,0297, 0319

FIGURES

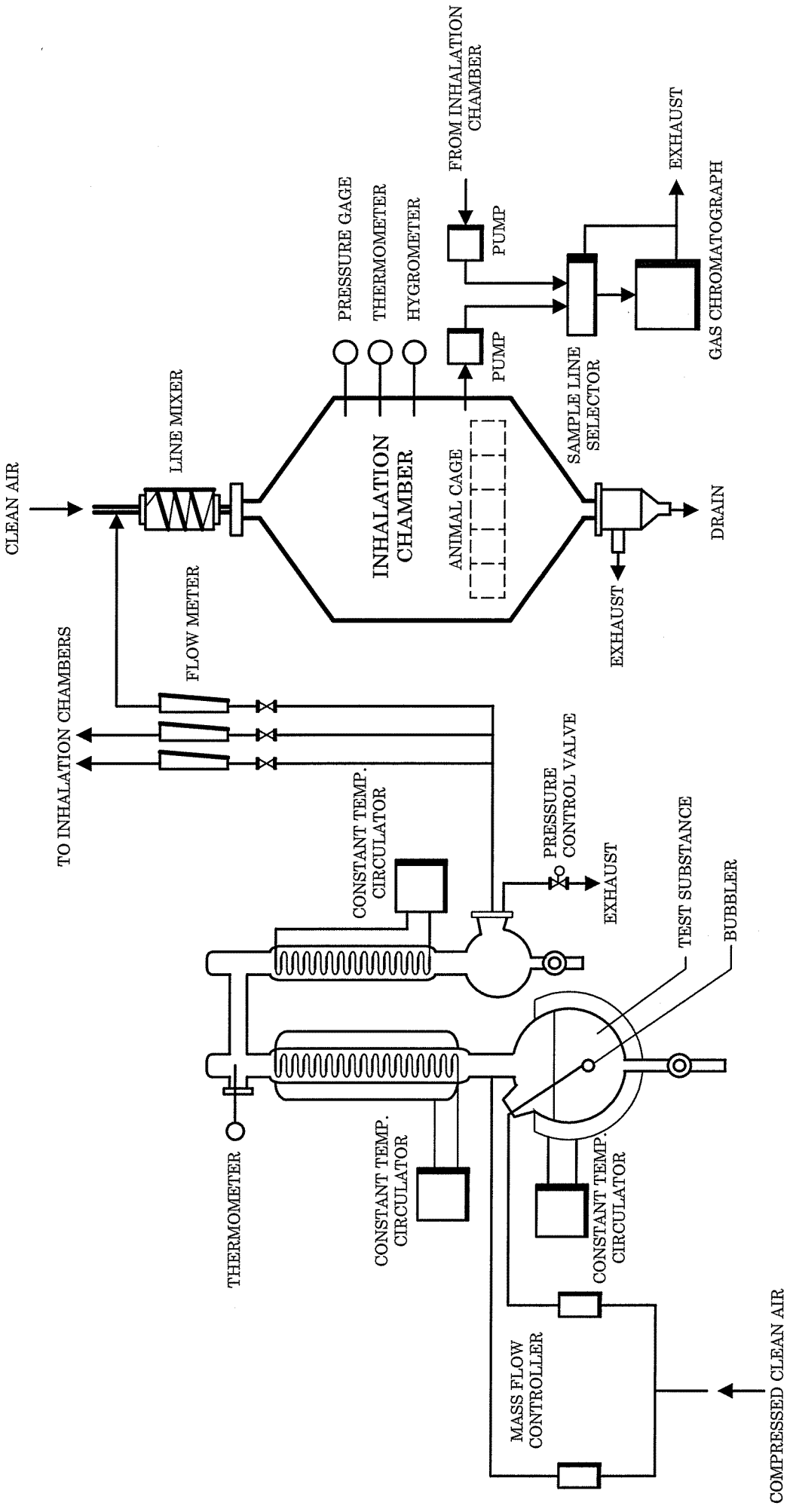


FIGURE 1 GLYCIDOL VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

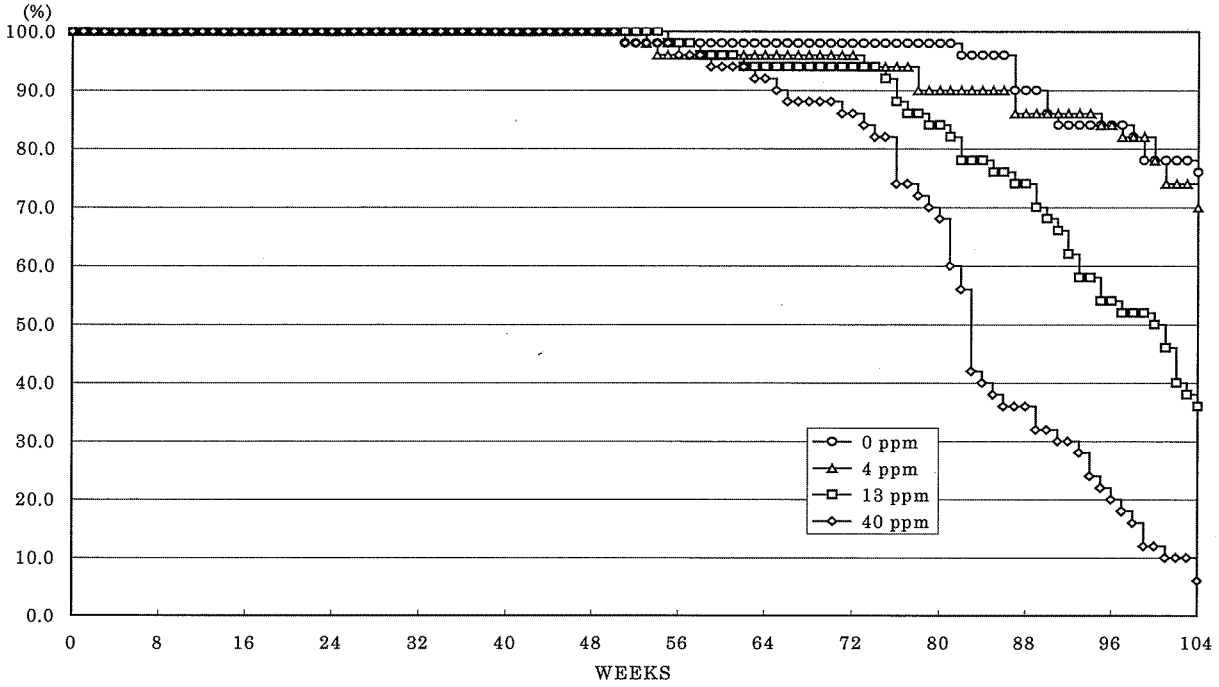


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

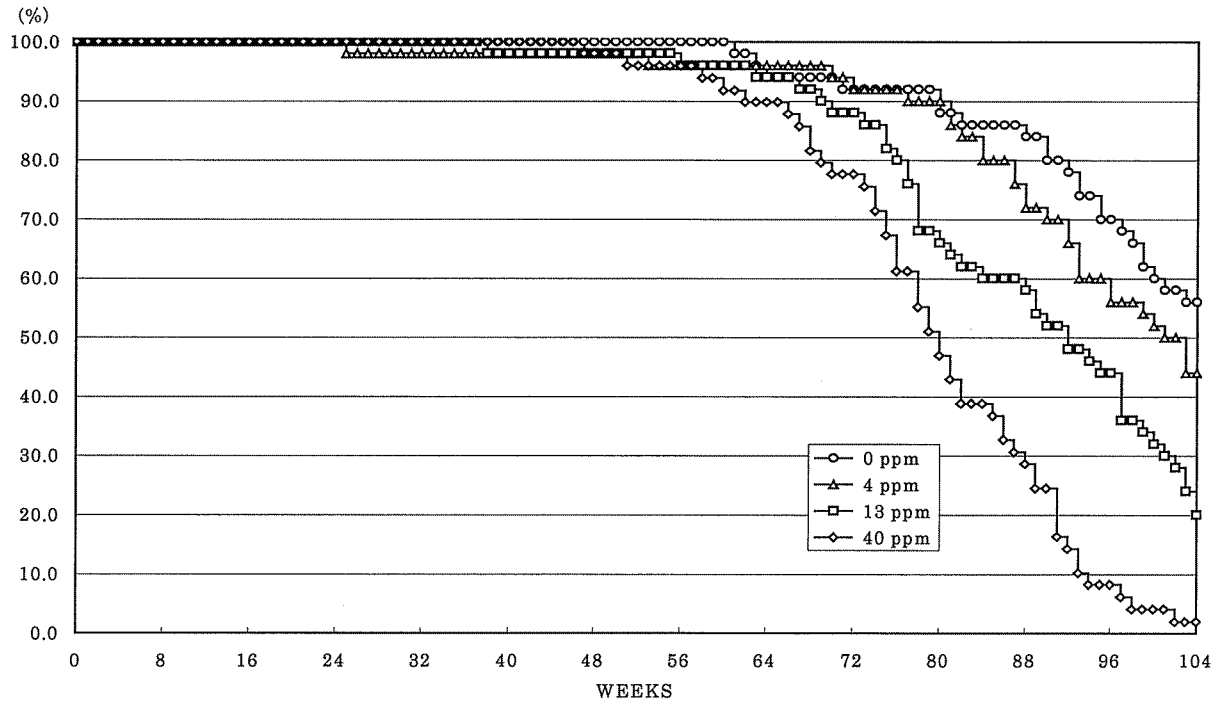


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

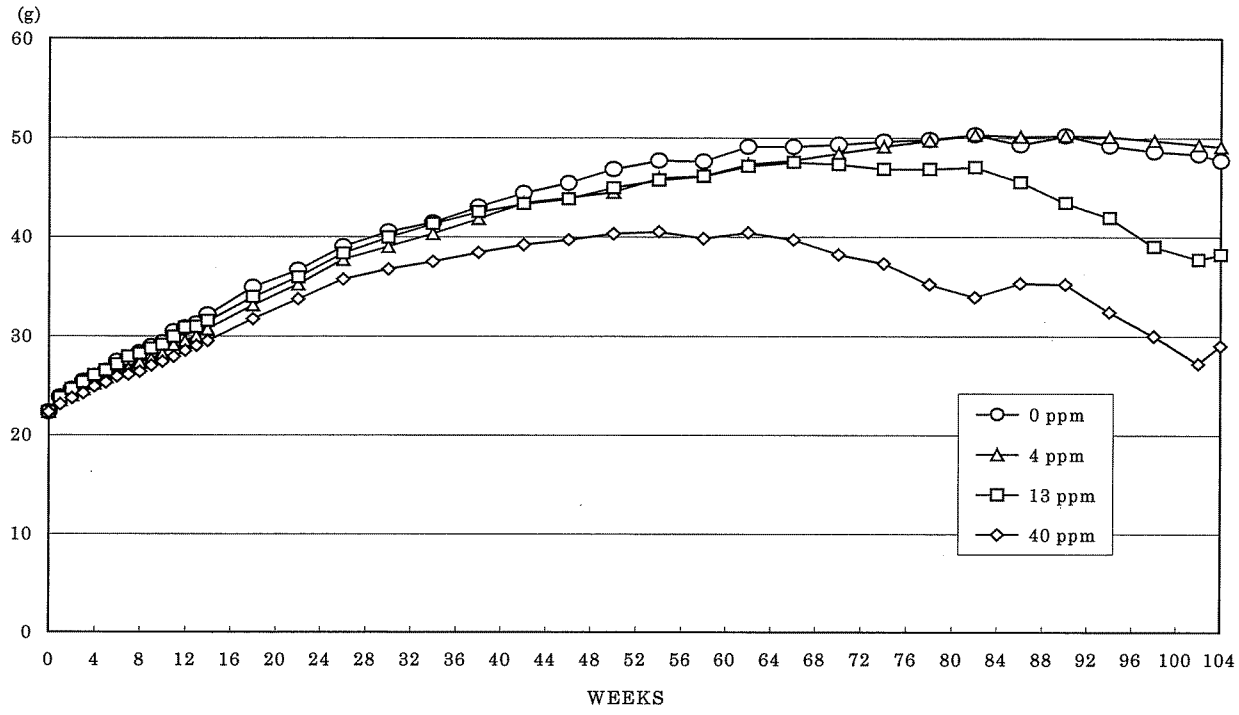


FIGURE 4 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

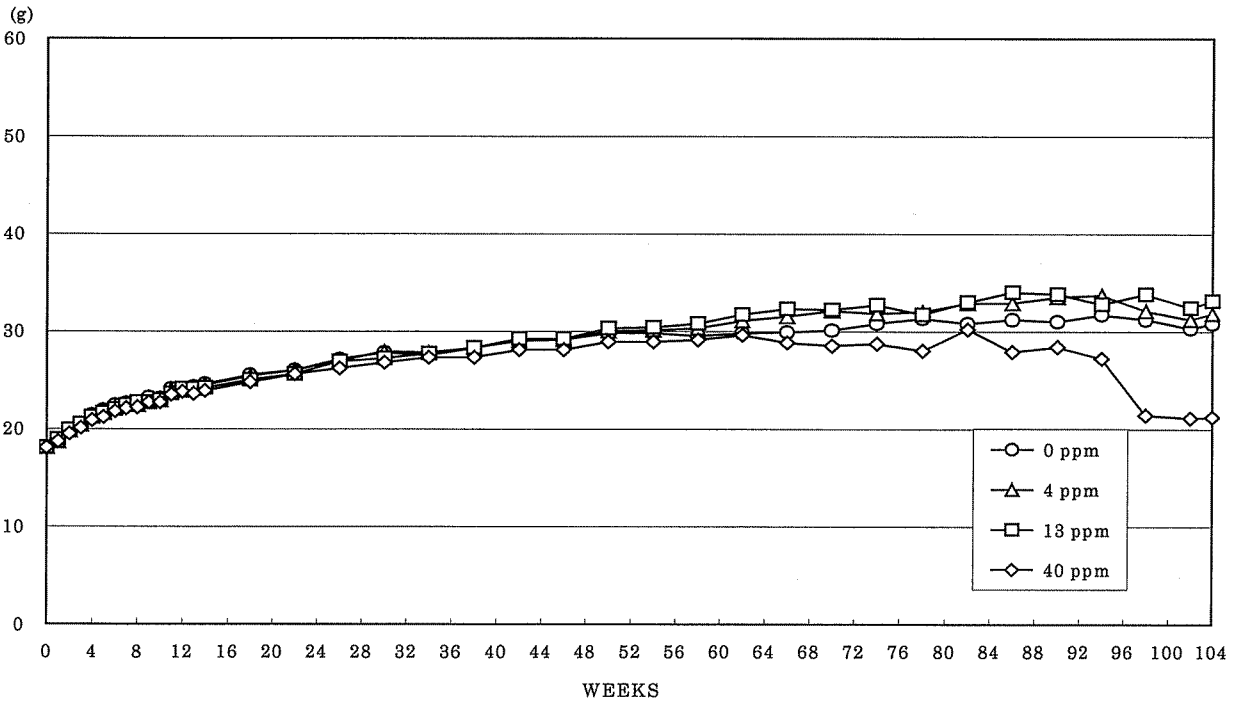


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

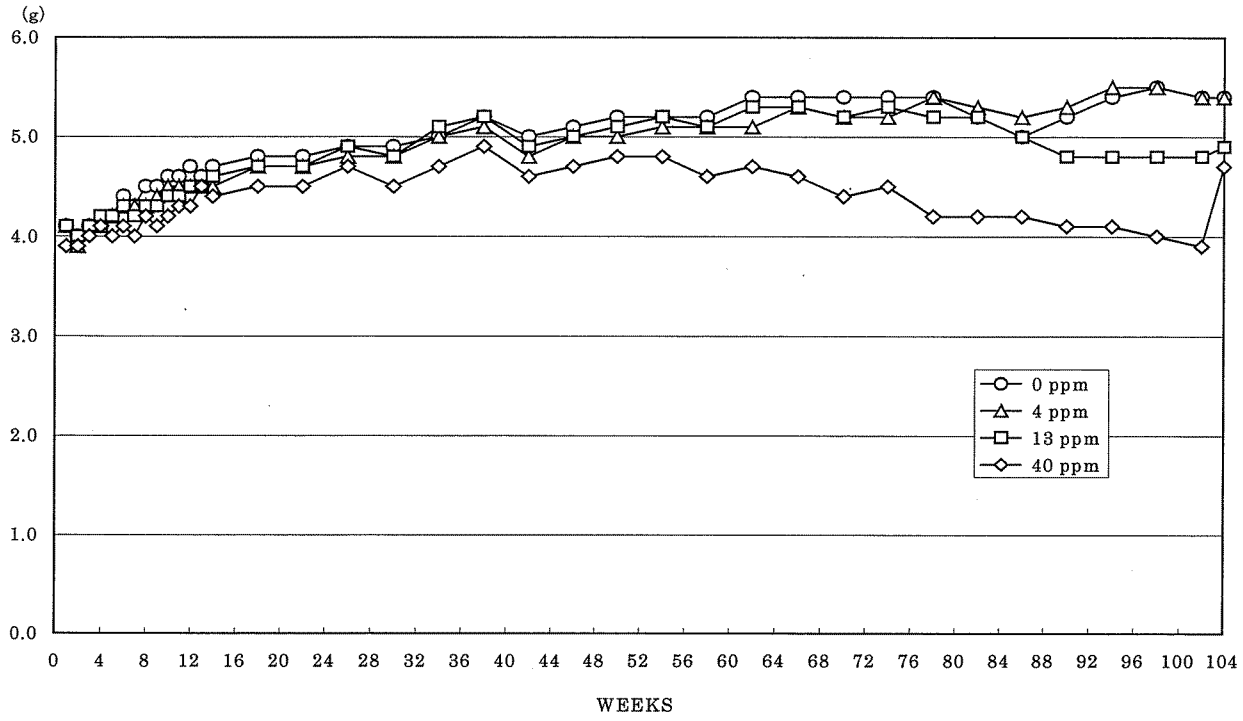


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

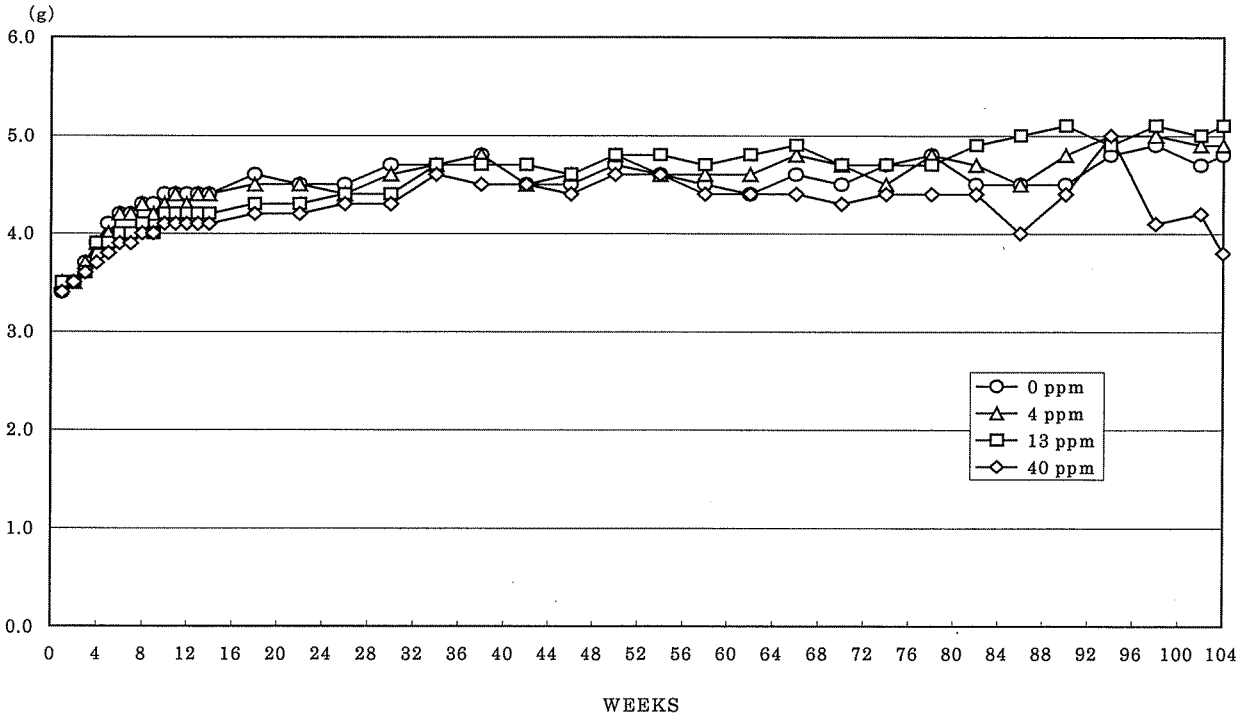


FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF GLYCIDOL

PHOTOGRAPHS

PHOTOGRAPH 1 NOSE: NODULE (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1320

PHOTOGRAPH 2 NASAL CAVITY : HEMANGIOMA (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1329 (H&E)

PHOTOGRAPH 3 NASAL CAVITY : HEMANGIOSARCOMA (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1335 (H&E)

PHOTOGRAPH 4 NASAL CAVITY : HEMANGIOSARCOMA
HIGHER MAGNIFICATION OF PHOTOGRAPH 3
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1335 (H&E)

PHOTOGRAPH 5 NASAL CAVITY : ADENOMA (ARROW)
MOUSE, FEMALE, 40ppm, ANIMAL No. 0343-2333 (H&E)

PHOTOGRAPH 6 NASAL CAVITY : ADENOCARCINOMA
MOUSE, FEMALE, 40ppm, ANIMAL No. 0343-2326 (H&E)

PHOTOGRAPH 7 NASAL CAVITY : SQUAMOUS CELL CARCINOMA (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1310 (H&E)

PHOTOGRAPH 8 NASAL CAVITY :
A: NORMAL RESPIRATORY EPITHELIUM (TRANSITIONAL TYPE)
B: SQUAMOUS METAPLASIA OF THE RESPIRATORY EPITHELIUM
MOUSE, MALE, 13ppm, ANIMAL No. 0343-1231 (H&E)

PHOTOGRAPH 9 NASAL CAVITY: SQUAMOUS METAPLASIA WITH ATYPIA OF THE RESPIRATORY EPITHELIUM (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1328 (H&E)

PHOTOGRAPH 10 NASAL CAVITY : SQUAMOUS CELL HYPERPLASIA WITH ATYPIA (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1335 (H&E)

PHOTOGRAPH 11 NASAL CAVITY : RESPIRATORY METAPLASIA OF THE GLAND (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1301 (H&E)

PHOTOGRAPH 12 NASAL CAVITY : RESPIRATORY METAPLASIA OF THE OLFACTORY EPITHELIUM (ARROW)
MOUSE, MALE, 13ppm, ANIMAL No. 0343-1214 (H&E)

PHOTOGRAPHS (CONTINUED)

PHOTOGRAPH 13 SUBCUTIS: HISTIOCYTIC SARCOMA (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1335 (H&E)

PHOTOGRAPH 14 PERIPHERAL NERVE: HISTIOCYTIC SARCOMA
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1348 (H&E)

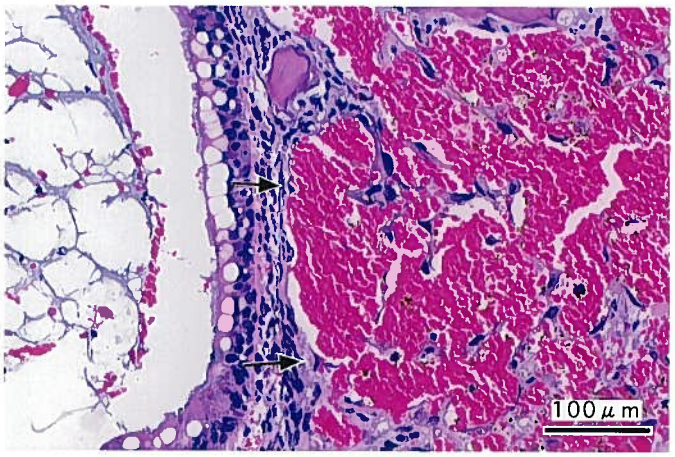
PHOTOGRAPH 15 HARDERIAN GLAND : ADENOMA (ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1306 (H&E)

PHOTOGRAPH 16 UTERUS : HISTIOCYTIC SARCOMA
MOUSE, FEMALE, 40ppm, ANIMAL No. 0343-2339 (H&E)

PHOTOGRAPH 17 MAMMARY GLAND : ADENOCARCINOMA
MOUSE, FEMALE, 40ppm, ANIMAL No. 0343-2333 (H&E)

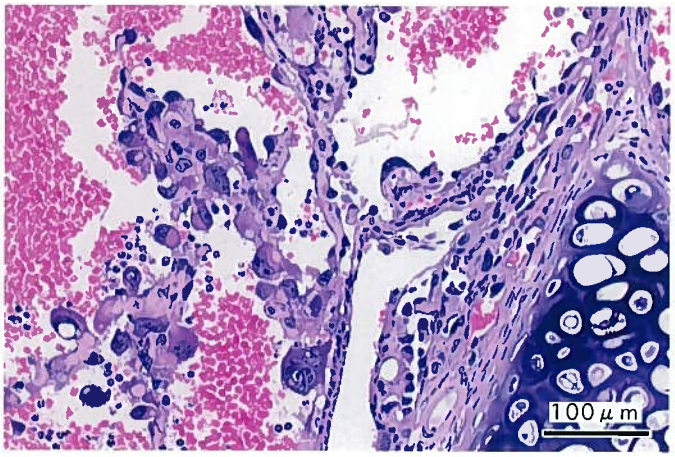
PHOTOGRAPH 18 STOMACH : HYPERPLASIA OF THE FORESTOMACH(ARROW)
MOUSE, MALE, 40ppm, ANIMAL No. 0343-1349 (H&E)

PHOTOGRAPH 1



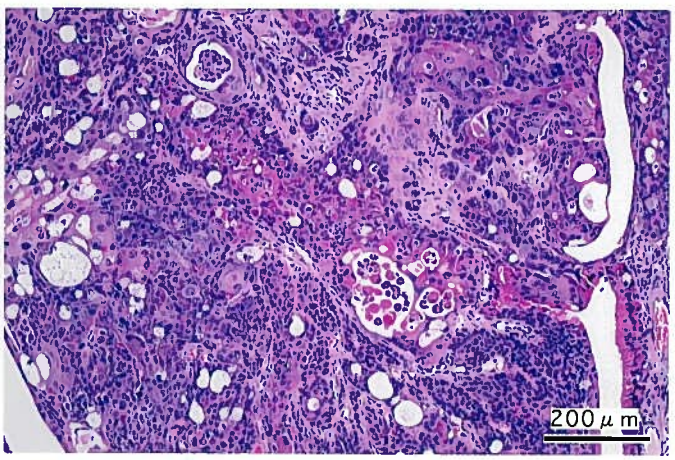
PHOTOGRAPH 2

PHOTOGRAPH 3



PHOTOGRAPH 4

PHOTOGRAPH 5



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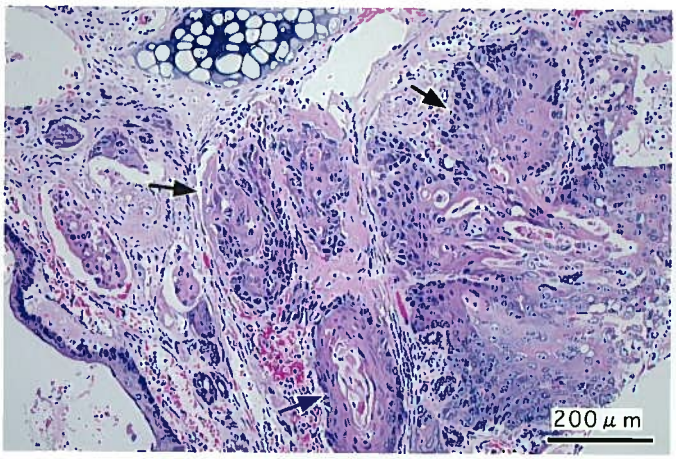

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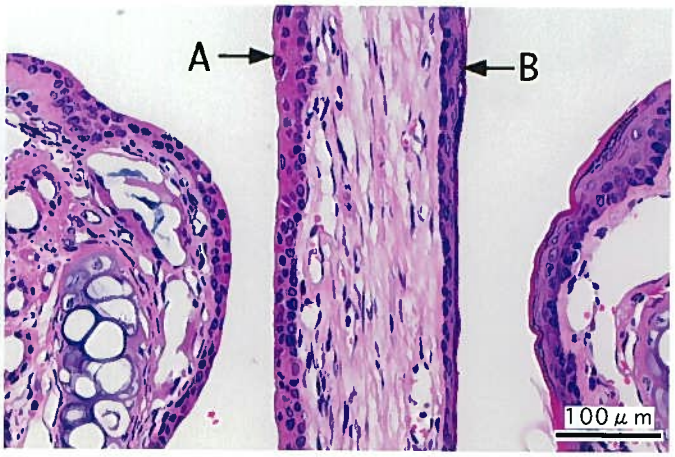

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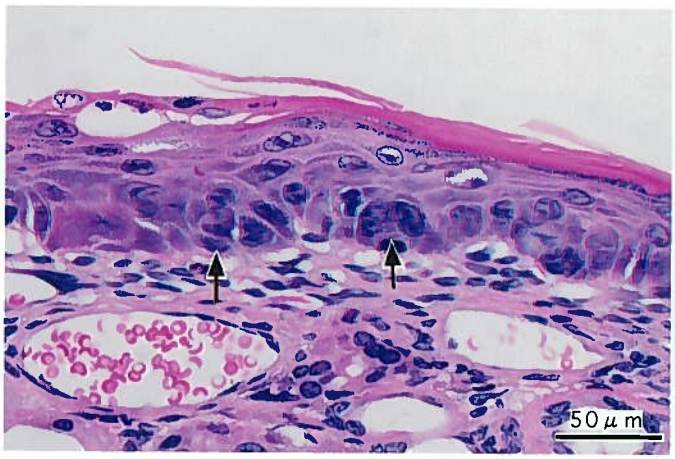

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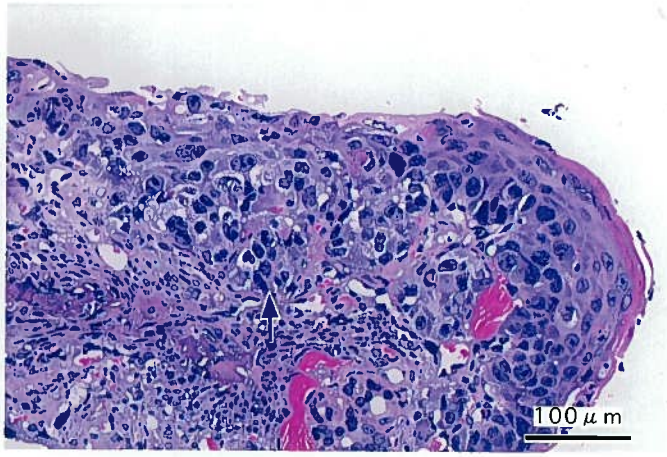

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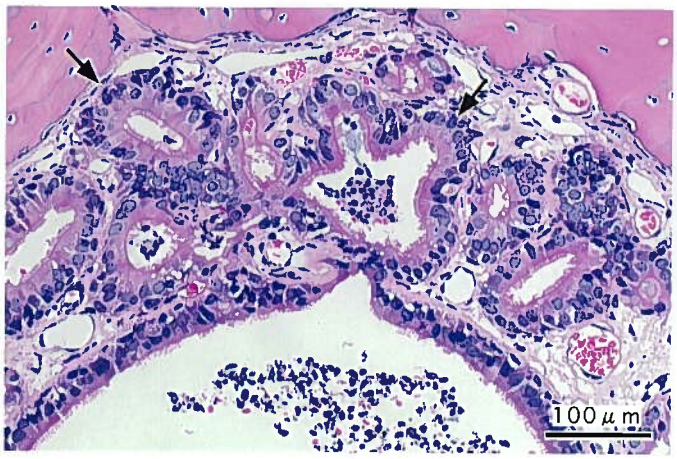

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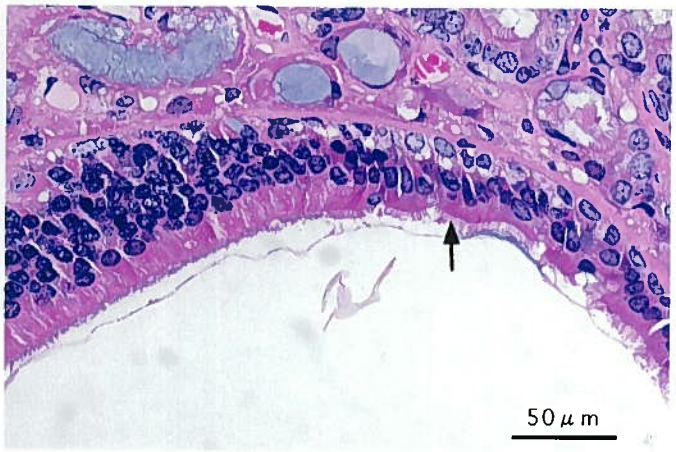

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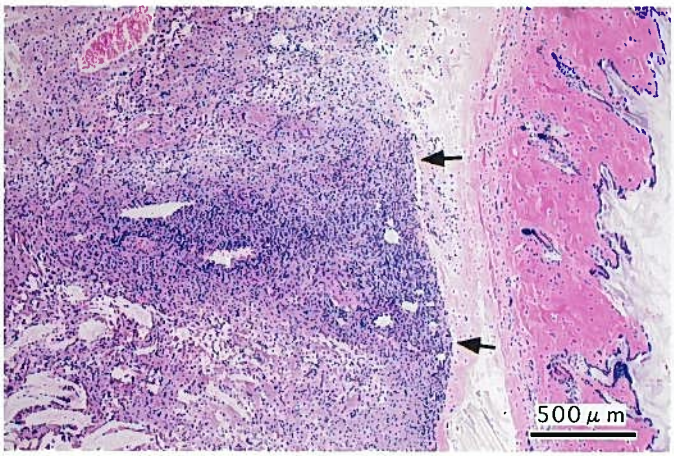

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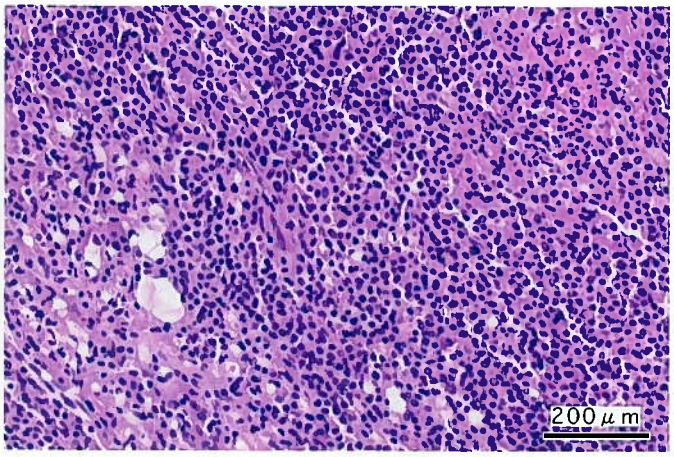

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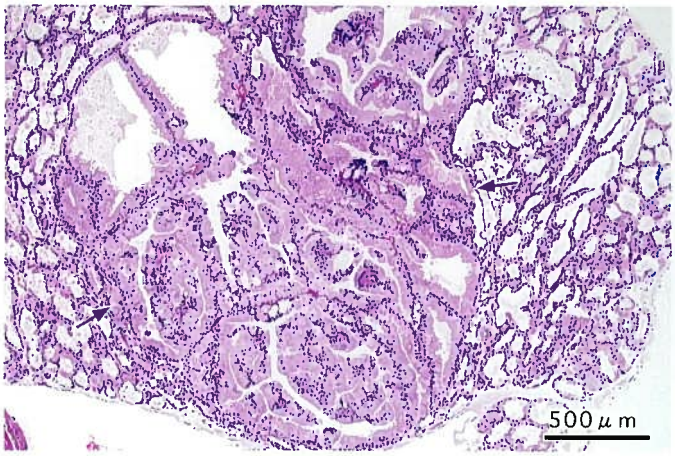

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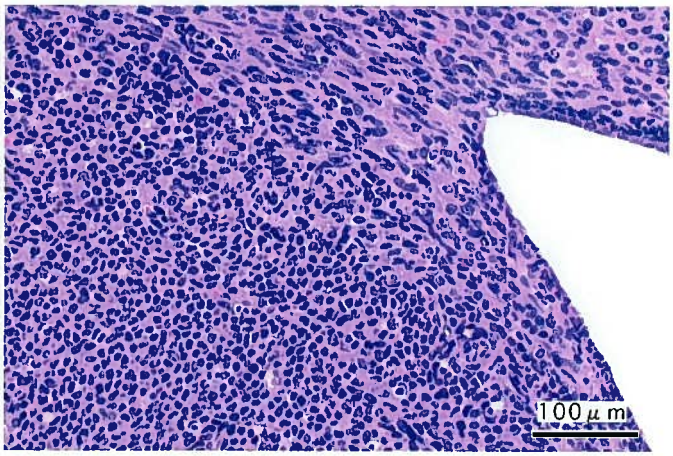

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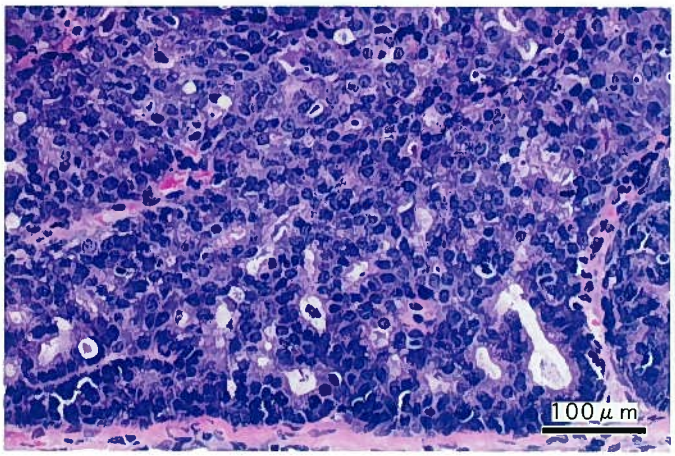

PHOTOGRAPH 17

PHOTOGRAPH 18