クロトンアルデヒドのマウスを用いた
吸入によるがん原性試験報告書

試験番号　0319

TABLES

TABLES

TABLES (CONTINUED)

TABLE 1 EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

<Method of Administration>
Inhalation
<Number of Groups>
Male 4, Female 4
<Size of Groups>
50 males and 50 females of each group
<Animals>
Strain and Species
Crj:BDF_1 mouse
Animal Source
Charles River Japan, Inc.
Duration Held Before Study
2 wk
Age When Placed on Study
6 wk
Age When Killed
110～111 wk
<Doses>
Male and Female
0, 3, 6, 12ppm
<Duration of Dosing>
6h/d, 5d/wk, for 104wk
<Animal Maintenance>
Feed
CRF-1 (Oriental Yeast Co., Ltd.)
Sterilized by γ-ray
Available *ad libitum*
Water
Filtrated and sterilized by ultraviolet ray
Automatic watering system
Available *ad libitum*
Animal per Cage
Single (stainless steel wire)
Animal Room Environment
Barrier system
Temperature : 22±2℃
Fluorescent light : 12h/d
Air changes : 15～17 time/h
Chamber Environment
Temperature : 22±2℃
Humidity : 55±15%
Air changes : 12±1 time/h
Pressure : 0～-15mmAq
<Type and Frequency of Observation>
Clinical Sign
Observed 1 per day for mortality, Detailed clinical observation performed on once weekly before exposure.
Body Weight
Weighed 1 per wk for 14wk
Weighed 1 per 4wks thereafter
Food Consumption
Weighed 1 per wk for 14wk
Weighed 1 per 4wks thereafter

TABLE 1 (continued) EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

<Hematology>
Hematological examination performed on scheduled sacrificed animals.
The following measurement parameters were examined;
Red blood cell (RBC), Hemoglobin, Hematocrit,
Mean Corpuscular Volume (MCV),
Mean Corpuscular hemoglobin (MCH),
Mean Corpuscular hemoglobin concentration (MCHC),
Platelet, White blood cell (WBC), Differential WBC.

<Biochemistry>
Biochemistrical examination performed on scheduled sacrificed animals.
The following measurement parameters were examined;
Total protein, Albumin, A/G ratio,
Total bilirubin, Glucose, Total cholesterol
Triglyceride, Phospholipid,
Glutamic oxaloacetic transaminase (GOT),
Glutamic pyruvic transaminase (GPT),
Lactate dehydrogenase (LDH),
Alkaline phosphatase (ALP),
γ -Glutamyl transpeptidase (γ -GTP)
Creatine phosphokinase (CPK),
Urea nitrogen,
Sodium, Potassium, Chloride,
Calcium, Inorganic phosphorus.

<Urinalysis>
Urinalysis performed on all animals that survived to end of dosing period using fresh urine collection.
The following measurement parameters were examined;
pH, Protein, Glucose, Ketone body,
Occult blood, Urobilinogen.

<Necropsy>
Necropsy performed on all animals.

<Organ Weight>
Organ weight measurement performed on scheduled sacrificed animals.
The following organs were weighed;
adrenal, testis, ovary, heart, lung, kidney, spleen, liver, brain.

<Histopathologic Examination>
Histopathologic examination performed on all animals.
The following organs were examined;
skin, nasal cavity, nasopharynx, larynx, trachea, lung, bone marrow,
lymph node, thymus, spleen, heart, tongue, salivary gland, esophagus,
stomach, small intestine, large intestine, liver, gall bladder, pancreas,
kidney, urinary bladder, pituitary, thyroid, parathyroid, adrenal, testis,
epididymis, seminal vesicle, prostate, ovary, uterus, vagina,
mammary gland, brain, spinal cord, peripheral nerve,
eye, Harderian gland, muscle, bone, other organs/tissues with gross lesions.

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

Weeks on Study	Control		3ppm			6ppm			12ppm		
	Av.Wt.	No.of Surviv. <50>	Av.Wt.	% of cont.	No.of Surviv. <50>	Av.Wt.	% of cont.	No.of Surviv. <50>	Av.Wt.	% of cont.	No.of Surviv. <49>
0	22.1 (50)	50/50	22.1 (50)	100	50/50	22.1 (50)	100	50/50	22.1 (49)	100	50/50
1	23.6 (50)	50/50	23.3 (50)	99	50/50	23.4 (50)	99	50/50	22.3 (49)	94	50/50
2	24.2 (50)	50/50	23.9 (50)	99	50/50	23.9 (50)	99	50/50	22.0 (49)	91	50/50
3	24.8 (50)	50/50	24.3 (50)	98	50/50	24.4 (50)	98	50/50	22.2 (49)	90	50/50
4	25.5 (50)	50/50	24.9 (49)	98	49/50	25.2 (49)	99	49/50	22.5 (49)	88	50/50
5	26.1 (50)	50/50	25.5 (49)	98	49/50	25.8 (49)	99	49/50	23.2 (49)	89	50/50
6	26.8 (50)	50/50	26.1 (49)	97	49/50	26.0 (49)	97	49/50	23.9 (49)	89	50/50
7	27.2 (50)	50/50	26.6 (49)	98	49/50	26.3 (49)	97	49/50	23.8 (49)	88	50/50
8	27.8 (50)	50/50	27.1 (49)	97	49/50	27.0 (49)	97	49/50	24.6 (49)	88	50/50
9	28.5 (50)	50/50	27.6 (49)	97	49/50	27.3 (49)	96	49/50	24.2 (49)	85	50/50
10	29.1 (50)	50/50	28.3 (49)	97	49/50	28.0 (49)	96	49/50	24.3 (49)	84	50/50
11	29.7 (50)	50/50	29.0 (49)	98	49/50	28.2 (49)	95	49/50	24.2 (49)	81	50/50
12	30.3 (50)	50/50	29.5 (49)	97	49/50	28.7 (49)	95	49/50	24.9 (49)	82	50/50
13	30.9 (50)	50/50	30.1 (49)	97	49/50	29.4 (49)	95	49/50	24.8 (49)	80	50/50
14	31.5 (50)	50/50	30.9 (49)	98	49/50	30.3 (49)	96	49/50	25.3 (49)	80	50/50
18	34.0 (49)	49/50	33.3 (49)	98	49/50	31.9 (49)	94	49/50	26.1 (49)	77	50/50
22	35.9 (49)	49/50	35.1 (49)	98	49/50	33.3 (49)	93	49/50	26.7 (48)	74	49/50
26	37.6 (49)	49/50	36.8 (49)	98	49/50	35.1 (49)	93	49/50	27.7 (48)	74	49/50
30	38.8 (48)	48/50	38.1 (49)	98	49/50	36.1 (49)	93	49/50	27.8 (48)	72	49/50
34	40.6 (47)	47/50	40.2 (48)	99	48/50	37.3 (49)	92	49/50	28.0 (48)	69	48/49
38	42.2 (47)	47/50	41.8 (48)	99	48/50	38.7 (49)	92	49/50	29.1 (48)	69	48/49
42	43.1 (47)	47/50	42.9 (47)	100	47/50	39.6 (49)	92	49/50	29.1 (48)	68	48/49
46	44.0 (47)	47/50	43.8 (47)	100	47/50	40.6 (49)	92	49/50	29.4 (48)	67	48/49
50	44.7 (47)	47/50	44.9 (46)	100	46/50	41.2 (49)	92	49/50	30.6 (48)	68	48/49
54	45.6 (47)	47/50	46.1 (45)	101	45/50	41.9 (49)	92	49/50	30.4 (46)	67	46/49
58	46.3 (47)	47/50	46.5 (44)	100	44/50	43.3 (48)	94	48/50	31.6 (46)	68	46/49
62	47.2 (47)	47/50	47.5 (43)	101	43/50	43.4 (48)	92	48/50	31.1 (46)	66	46/49
66	47.9 (47)	47/50	48.8 (43)	102	43/50	44.7 (48)	93	48/50	31.5 (46)	66	46/49
70	48.8 (47)	47/50	50.0 (42)	102	42/50	45.1 (47)	92	47/50	31.7 (46)	65	46/49
74	50.1 (47)	47/50	51.0 (42)	102	42/50	46.6 (45)	93	45/50	32.5 (46)	65	46/49
78	50.7 (47)	47/50	51.1 (41)	101	41/50	46.9 (44)	93	44/50	32.6 (45)	64	45/49
82	50.7 (45)	45/50	51.5 (40)	102	40/50	47.0 (44)	93	44/50	32.4 (44)	64	44/49
86	50.4 (45)	45/50	52.3 (38)	104	38/50	46.6 (44)	92	44/50	32.4 (44)	64	44/49
90	49.6 (43)	43/50	52.5 (38)	106	38/50	47.0 (42)	95	42/50	33.6 (43)	68	43/49
94	50.4 (40)	40/50	52.3 (38)	104	38/50	47.1 (41)	93	41/50	33.5 (43)	66	43/49
98	49.5 (37)	35/50	52.2 (34)	105	34/50	46.8 (41)	95	40/50	33.6 (43)	68	43/49
102	49.6 (34)	34/50	50.7 (31)	102	31/50	45.8 (38)	92	38/50	33.0 (43)	67	43/49
104	49.0 (33)	33/50	49.4 (30)	101	30/50	44.3 (38)	90	38/50	32.1 (43)	66	43/49

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

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

Weeks on Study	Control		3ppm			6ppm			12ppm		
	Av.Wt.	No.of Surviv. <50>	Av.Wt.	% of cont. <50>	No.of Surviv. <50>	Av.Wt.	% of cont. <50>	No.of Surviv. <50>	Av.Wt.	% of cont. <50>	No.of Surviv. <50>
0	18.6 (50)	50/50	18.6 (50)	100	50/50	18.6 (50)	100	50/50	18.6 (50)	100	50/50
1	19.7 (50)	50/50	19.4 (50)	98	50/50	19.5 (50)	99	50/50	19.0 (50)	96	50/50
2	20.3 (50)	50/50	20.0 (50)	99	50/50	20.1 (50)	99	50/50	18.9 (50)	93	50/50
3	20.9 (50)	50/50	20.7 (50)	99	50/50	20.7 (50)	99	50/50	19.4 (50)	93	50/50
4	21.6 (50)	50/50	21.4 (50)	99	50/50	21.5 (50)	100	50/50	19.8 (50)	92	50/50
5	22.2 (50)	50/50	22.1 (50)	100	50/50	22.0 (50)	99	50/50	20.5 (50)	92	50/50
6	22.7 (50)	50/50	22.6 (50)	100	50/50	22.4 (50)	99	50/50	21.3 (50)	94	50/50
7	23.1 (50)	50/50	23.1 (50)	100	50/50	22.8 (50)	99	50/50	21.5 (50)	93	50/50
8	23.8 (50)	50/50	23.3 (50)	98	50/50	23.6 (50)	99	50/50	22.5 (50)	95	50/50
9	23.9 (50)	50/50	23.6 (50)	99	50/50	23.4 (50)	98	50/50	22.2 (50)	93	50/50
10	24.4 (50)	50/50	23.8 (50)	98	50/50	23.8 (50)	98	50/50	22.2 (50)	91	50/50
11	24.7 (50)	50/50	24.3 (50)	98	50/50	24.3 (50)	98	50/50	22.3 (50)	90	50/50
12	24.8 (50)	50/50	24.5 (50)	99	50/50	24.4 (50)	98	50/50	22.7 (50)	92	50/50
13	25.4 (50)	50/50	24.9 (50)	98	50/50	24.7 (50)	97	50/50	23.0 (50)	91	50/50
14	25.3 (50)	50/50	25.1 (50)	99	50/50	25.3 (50)	100	50/50	23.4 (50)	92	50/50
18	27.0 (50)	50/50	26.2 (50)	97	50/50	26.0 (50)	96	50/50	23.7 (50)	88	50/50
22	27.5 (50)	50/50	27.0 (49)	98	49/50	27.1 (50)	99	50/50	24.4 (50)	89	50/50
26	28.4 (50)	50/50	27.4 (49)	96	49/50	27.7 (50)	98	50/50	24.7 (50)	87	50/50
30	28.7 (50)	50/50	28.5 (49)	99	49/50	28.4 (50)	99	50/50	25.0 (50)	87	50/50
34	29.7 (50)	50/50	28.9 (49)	97	49/50	28.8 (50)	97	50/50	25.0 (49)	84	49/50
38	30.7 (50)	50/50	29.8 (49)	97	49/50	29.9 (50)	97	50/50	25.7 (49)	84	49/50
42	31.2 (50)	50/50	29.9 (49)	96	49/50	30.4 (50)	97	50/50	25.3 (49)	81	49/50
46	31.7 (50)	50/50	30.4 (49)	96	49/50	30.7 (50)	97	50/50	25.6 (49)	81	49/50
50	31.8 (50)	50/50	31.0 (49)	97	49/50	30.9 (50)	97	50/50	26.1 (49)	82	49/50
54	32.4 (50)	50/50	31.4 (49)	97	49/50	31.3 (50)	97	50/50	25.9 (49)	80	49/50
58	32.3 (50)	50/50	32.2 (49)	100	49/50	32.1 (49)	99	49/50	26.8 (49)	83	49/50
62	33.1 (49)	49/50	32.7 (49)	99	49/50	32.7 (49)	99	49/50	26.3 (48)	79	48/50
66	33.6 (49)	49/50	33.0 (48)	98	48/50	33.1 (49)	99	49/50	26.5 (48)	79	48/50
70	33.8 (49)	49/50	33.2 (46)	98	46/50	33.6 (48)	99	48/50	26.3 (47)	78	47/50
74	34.9 (47)	47/50	34.8 (45)	100	45/50	34.6 (48)	99	48/50	27.0 (47)	77	47/50
78	34.8 (45)	45/50	35.3 (44)	101	44/50	34.1 (48)	98	47/50	26.5 (46)	76	46/50
82	34.1 (43)	43/50	35.2 (42)	103	41/50	35.5 (45)	104	45/50	27.2 (46)	80	46/50
86	34.1 (41)	41/50	35.8 (39)	105	39/50	35.4 (44)	104	44/50	27.5 (43)	81	42/50
90	34.1 (39)	39/50	36.0 (37)	106	37/50	35.8 (43)	105	43/50	27.4 (41)	80	41/50
94	34.5 (35)	35/50	36.0 (34)	104	34/50	36.4 (40)	106	40/50	27.5 (41)	80	41/50
98	34.2 (33)	33/50	35.9 (31)	105	31/50	36.1 (36)	106	36/50	27.7 (39)	81	39/50
102	34.2 (31)	31/50	36.2 (29)	106	29/50	35.1 (32)	103	32/50	27.4 (34)	80	34/50
104	34.3 (30)	30/50	35.2 (25)	103	25/50	34.5 (30)	101	30/50	27.0 (34)	79	34/50

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

TABLE 4 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

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	0/49	0/47	0/47	0/47	1/47	2/41	3/50(1/17)
	3ppm	0/50	0/49	0/49	0/48	0/45	0/43	0/41	2/38	2/50(1/20)
	6ppm	0/50	0/49	0/49	0/49	0/49	0/48	3/44	2/41	3/50(2/12)
	12ppm	0/49	0/49	0/48	0/48	0/47	0/46	0/45	1/43	1/49(0/ 6)
Internal mass										
	0ppm	2/50	6/50	4/49	5/47	5/47	6/47	11/47	9/41	16/50(9/17)
	3ppm	2/50	7/49	9/49	8/48	5/45	4/43	7/41	8/38	17/50(12/20)
	6ppm	0/50	2/49	3/49	3/49	4/49	4/48	2/44	3/41	8/50(6/12)
	12ppm	1/49	7/49	6/48	6/48	5/47	6/46	7/45	7/43	11/49(4/ 6)

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

TABLE 5 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

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	2/49	3/43	4/38	7/50(3/20)
	3ppm	0/50	0/50	0/49	0/49	1/49	1/48	2/42	1/38	3/50(2/25)
	6ppm	0/50	0/50	0/50	0/50	0/50	0/49	1/46	5/41	5/50(2/20)
	12ppm	0/50	0/50	0/50	1/49	2/49	2/48	2/46	2/41	5/50(4/16)
Internal mass										
	0ppm	0/50	0/50	0/50	0/50	1/50	5/49	7/43	10/38	17/50(11/20)
	3ppm	0/50	2/50	2/49	3/49	4/49	5/48	7/42	13/38	18/50(12/25)
	6ppm	0/50	0/50	1/50	2/50	3/50	5/49	8/46	13/41	18/50(11/20)
	12ppm	1/50	1/50	2/50	2/49	3/49	8/48	12/46	7/41	13/50(8/16)

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

TABLE 6 FOOD CONSUMPTION CHANGES OF MALE MICE
IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

Weeks on Study	Control Av.FC.	<50>	3ppm Av.FC.	<50>	% of cont.	6ppm Av.FC.	<50>	% of cont.	12ppm Av.FC.	<49>	% of cont.
1	4.1	(50)	3.9	(50)	95	4.0	(50)	98	3.7	(49)	90
2	3.7	(50)	3.7	(50)	100	3.7	(50)	100	3.2	(49)	86
3	3.9	(50)	3.9	(50)	100	3.7	(50)	95	3.4	(49)	87
4	4.0	(50)	4.0	(49)	100	3.9	(49)	98	3.5	(49)	88
5	4.1	(50)	4.1	(49)	100	4.0	(49)	98	3.8	(49)	93
6	4.2	(50)	4.1	(49)	98	4.0	(49)	95	3.8	(49)	90
7	4.2	(50)	4.2	(49)	100	4.0	(49)	95	3.8	(49)	90
8	4.3	(50)	4.2	(49)	98	4.1	(49)	95	3.9	(49)	91
9	4.4	(50)	4.3	(49)	98	4.2	(49)	95	3.9	(49)	89
10	4.4	(50)	4.4	(49)	100	4.1	(49)	93	3.8	(49)	86
11	4.4	(50)	4.4	(49)	100	4.1	(49)	93	3.7	(49)	84
12	4.4	(50)	4.5	(49)	102	4.2	(49)	95	3.9	(49)	89
13	4.4	(50)	4.4	(49)	100	4.3	(49)	98	3.7	(49)	84
14	4.5	(50)	4.5	(49)	100	4.4	(49)	98	3.8	(49)	84
18	4.6	(49)	4.6	(49)	100	4.4	(49)	96	3.9	(49)	85
22	4.8	(48)	4.6	(49)	96	4.5	(49)	94	3.9	(48)	81
26	4.6	(49)	4.5	(49)	98	4.4	(49)	96	3.9	(48)	85
30	4.7	(48)	4.6	(49)	98	4.3	(49)	91	3.8	(48)	81
34	4.7	(47)	4.7	(48)	100	4.5	(49)	96	3.8	(48)	81
38	4.9	(47)	4.8	(48)	98	4.6	(49)	94	3.9	(48)	80
42	4.9	(47)	4.9	(47)	100	4.6	(49)	94	3.9	(48)	80
46	5.0	(47)	4.9	(47)	98	4.7	(49)	94	3.9	(48)	78
50	5.0	(47)	4.9	(46)	98	4.8	(49)	96	4.2	(48)	84
54	5.1	(47)	5.1	(45)	100	4.8	(49)	94	4.0	(46)	78
58	5.2	(47)	5.0	(44)	96	5.0	(48)	96	4.3	(46)	83
62	5.2	(47)	5.1	(43)	98	4.8	(48)	92	4.0	(46)	77
66	5.2	(47)	5.2	(43)	100	4.9	(48)	94	4.0	(46)	77
70	5.3	(47)	5.3	(42)	100	5.0	(47)	94	4.2	(46)	79
74	5.4	(47)	5.3	(42)	98	5.3	(45)	98	4.3	(46)	80
78	5.2	(47)	5.2	(41)	100	4.9	(44)	94	4.1	(45)	79
82	5.4	(45)	5.3	(40)	98	5.1	(44)	94	4.2	(44)	78
86	5.4	(45)	5.5	(38)	102	5.2	(44)	96	4.4	(44)	81
90	5.2	(43)	5.3	(38)	102	5.0	(42)	96	4.2	(43)	81
94	5.3	(40)	5.3	(38)	100	5.1	(41)	96	4.3	(43)	81
98	5.3	(37)	5.4	(34)	102	5.0	(41)	94	4.3	(43)	81
102	5.3	(34)	5.1	(31)	96	5.0	(38)	94	4.3	(43)	81
104	5.1	(33)	4.9	(30)	96	4.7	(38)	92	4.0	(43)	78

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

TABLE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE
IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

Weeks on Study	Control Av.FC. <50>	3ppm Av.FC. <50>	3ppm % of cont.	6ppm Av.FC. <50>	6ppm % of cont.	12ppm Av.FC. <50>	12ppm % of cont.
1	3.6 (50)	3.4 (50)	94	3.4 (50)	94	3.4 (50)	94
2	3.2 (50)	3.1 (50)	97	3.2 (50)	100	3.0 (50)	94
3	3.5 (50)	3.5 (50)	100	3.4 (50)	97	3.2 (50)	91
4	3.7 (50)	3.7 (50)	100	3.7 (50)	100	3.4 (50)	92
5	3.9 (50)	3.9 (50)	100	3.9 (50)	100	3.6 (50)	92
6	3.9 (50)	3.9 (50)	100	3.9 (50)	100	3.8 (50)	97
7	4.0 (50)	4.1 (50)	103	4.0 (50)	100	3.8 (50)	95
8	4.2 (50)	4.1 (50)	98	4.2 (50)	100	4.0 (50)	95
9	4.1 (50)	4.2 (50)	102	4.1 (50)	100	4.0 (50)	98
10	4.2 (50)	4.2 (50)	100	4.2 (50)	100	3.9 (50)	93
11	4.2 (50)	4.3 (50)	102	4.2 (50)	100	3.9 (50)	93
12	4.2 (50)	4.2 (50)	100	4.2 (50)	100	4.0 (50)	95
13	4.3 (50)	4.3 (50)	100	4.2 (50)	98	3.9 (50)	91
14	4.2 (50)	4.2 (50)	100	4.2 (50)	100	3.9 (50)	93
18	4.4 (50)	4.4 (50)	100	4.3 (50)	98	4.1 (50)	93
22	4.4 (50)	4.5 (49)	102	4.5 (50)	102	4.1 (50)	93
26	4.4 (50)	4.3 (49)	98	4.3 (50)	98	4.0 (50)	91
30	4.4 (50)	4.4 (49)	100	4.3 (50)	98	3.9 (50)	89
34	4.6 (50)	4.5 (49)	98	4.4 (50)	96	3.9 (49)	85
38	4.6 (50)	4.7 (49)	102	4.5 (50)	98	4.1 (49)	89
42	4.6 (50)	4.6 (49)	100	4.5 (50)	98	4.0 (49)	87
46	4.6 (50)	4.6 (49)	100	4.5 (50)	98	4.0 (49)	87
50	4.6 (50)	4.7 (49)	102	4.6 (50)	100	4.1 (49)	89
54	4.7 (50)	4.7 (49)	100	4.8 (50)	102	4.0 (49)	85
58	4.7 (50)	4.7 (49)	100	4.6 (49)	98	4.2 (49)	89
62	4.8 (49)	4.7 (49)	98	4.7 (49)	98	3.9 (48)	81
66	4.8 (49)	4.9 (48)	102	4.6 (49)	96	4.0 (48)	83
70	4.8 (49)	4.7 (46)	98	4.9 (48)	102	4.0 (47)	83
74	4.9 (47)	4.8 (45)	98	4.9 (48)	100	4.0 (47)	82
78	4.6 (45)	4.8 (44)	104	4.5 (47)	98	3.8 (46)	83
82	4.8 (43)	4.8 (42)	100	4.9 (45)	102	3.9 (46)	81
86	4.9 (41)	5.0 (39)	102	5.2 (44)	106	4.3 (43)	88
90	4.9 (39)	4.9 (37)	100	4.8 (43)	98	4.0 (41)	82
94	5.0 (35)	4.9 (34)	98	5.0 (40)	100	4.1 (37)	82
98	5.1 (33)	5.1 (31)	100	5.3 (36)	104	4.2 (39)	82
102	5.1 (31)	4.9 (29)	96	4.9 (32)	96	4.3 (34)	84
104	4.9 (30)	4.6 (25)	94	4.6 (30)	94	3.9 (34)	80

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

TABLE 8 SELECTED NASAL CAVITY LESIONS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

Group Name	0ppm				3 ppm				6 ppm				12 ppm			
No. of Animals	50				50				50				49			
Findings Grade [a]	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
non-neoplastic lesions																
respiratory epithelium																
necrosis	0	0	0	0	0	0	0	0	0	0	0	0	12	4	0	0 **
atrophy	0	0	0	0	0	0	0	0	0	0	0	0	9	2	0	0 **
inflammation	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0
hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
cuboidal change	0	0	0	0	0	1	0	0	6	12	0	0 **	13	18	0	0 **
squamous cell metaplasia	0	0	0	0	0	0	0	0	0	0	0	0	19	15	0	0 **
eosinophilic change	8	3	0	0	5	0	1	0	1	1	0	0 *	4	2	1	0
olfactory epithelium																
necrosis	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0
atrophy	0	0	0	0	0	0	0	0	0	0	0	0	30	12	0	0 **
respiratory metaplasia	18	2	0	0	18	1	0	0	7	1	0	0 *	18	28	1	0 **
eosinophilic change	20	6	0	0	10	4	0	0 *	12	2	0	0 *	16	9	0	0
others																
exudate	0	0	2	0	0	0	1	0	0	1	0	0	2	19	7	0 **
edema of lamina propria	0	0	0	0	0	0	0	0	0	0	0	0	19	0	0	0 **
hyperplasia of glands	0	0	0	0	0	0	0	0	0	0	0	0	19	0	0	0 **
respiratory metaplasia of glands	13	4	0	0	8	5	0	0	10	2	0	0	16	25	0	0 **

[a] 1 : Slight 2 : Moderate 3 : Marked 4 : Severe

Significant difference ; * : $P \leqq 0.05$ ** : $P \leqq 0.01$ Test of Chi Square

TABLE 9 SELECTED NASAL CAVITY LESIONS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

Group Name	0ppm				3 ppm				6 ppm				12 ppm			
No. of Animals	50				50				50				50			
Findings Grade [a]	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
non-neoplastic lesions																
respiratory epithelium																
necrosis	1	0	0	0	0	0	0	0	0	0	0	0	14	5	0	0 **
atrophy	0	0	0	0	0	0	0	0	0	0	0	0	7	2	0	0 **
inflammation	0	0	0	0	0	0	0	0	0	0	0	0	11	1	0	0 **
hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0 *
cuboidal change	0	0	0	0	0	0	0	0	3	3	0	0 *	12	21	3	0 **
squamous cell metaplasia	0	0	0	0	0	0	0	0	0	0	0	0	14	16	0	0 **
eosinophilic change	29	10	0	0	13	33	1	0 **	14	12	0	0 **	23	4	0	0 *
olfactory epithelium																
necrosis	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0
atrophy	1	0	0	0	0	0	0	0	0	0	0	0	35	10	0	0 **
respiratory metaplasia	8	0	0	0	10	0	0	0	5	0	0	0	5	43	1	0 **
eosinophilic change	19	2	1	0	8	5	0	0 *	3	0	0	0 **	9	5	0	0
others																
exudate	0	0	0	0	0	0	0	0	1	1	0	0	1	30	14	0 **
edema of lamina propria	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
hyperplasia of glands	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
respiratory metaplasia of glands	4	0	0	0	6	0	0	0	8	3	0	0	16	14	0	0 **

[a] 1 : Slight 2 : Moderate 3 : Marked 4 : Severe

Significant difference ; * : $P \leqq 0.05$ ** : $P \leqq 0.01$ Test of Chi Square

TABLE 10 NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

Group Name	Control	3ppm	6ppm	12ppm
SITE : lung				
TUMOR : bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	10/50(20.0)	8/50(16.0)	9/50(18.0)	0/49(0.0)
Adjusted rates(b)	27.27	17.65	21.05	0.0
Terminal rates(c)	9/33(27.3)	5/30(16.7)	8/38(21.1)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.8626			
Prevalence method(d)	P=0.9996			
Combined analysis (d)	P=0.9998			
Cochran-Armitage test(e)	P=0.0033**			
Fisher Exact test(e)		P=0.3976	P=0.5000	P=0.0007**
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	12/50(24.0)	13/50(26.0)	11/50(22.0)	0/49(0.0)
Adjusted rates(b)	29.41	30.00	26.32	0.0
Terminal rates(c)	9/33(27.3)	9/30(30.0)	10/38(26.3)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.8626			
Prevalence method(d)	P=0.9999			
Combined analysis (d)	P=1.0000			
Cochran-Armitage test(e)	P=0.0006**			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.0001**
SITE : lymph node				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	11/50(22.0)	6/50(12.0)	9/50(18.0)	3/49(6.1)
Adjusted rates(b)	11.43	15.63	15.79	6.98
Terminal rates(c)	3/33(9.1)	4/30(13.3)	6/38(15.8)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.9977			
Prevalence method(d)	P=0.7821			
Combined analysis (d)	P=0.9903			
Cochran-Armitage test(e)	P=0.0493*			
Fisher Exact test(e)		P=0.1434	P=0.4016	P=0.0223*
SITE : liver				
TUMOR : hemangioma				
Tumor rate				
Overall rates(a)	5/50(10.0)	9/50(18.0)	4/50(8.0)	0/49(0.0)
Adjusted rates(b)	12.12	10.81	10.53	0.0
Terminal rates(c)	4/33(12.1)	3/30(10.0)	4/38(10.5)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.9038			
Prevalence method(d)	P=0.9876			
Combined analysis (d)	P=0.9957			
Cochran-Armitage test(e)	P=0.0165*			
Fisher Exact test(e)		P=0.1940	P=0.5000	P=0.0296*

TABLE 10 NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE (continued)

Group Name	Control	3ppm	6ppm	12ppm
SITE : liver				
TUMOR : hemangioma, hemangiosarcoma				
Tumor rate				
Overall rates(a)	5/50(10.0)	10/50(20.0)	4/50(8.0)	0/49(0.0)
Adjusted rates(b)	12.12	13.51	10.53	0.0
Terminal rates(c)	4/33(12.1)	4/30(10.0)	4/38(10.5)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.9038			
Prevalence method(d)	P=0.9906			
Combined analysis (d)	P=0.9967			
Cochran-Armitage test(e)	P=0.0139*			
Fisher Exact test(e)		P=0.1312	P=0.5000	P=0.0296*
SITE : liver				
TUMOR : hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	6/50(12.0)	6/50(12.0)	2/50(4.0)	1/49(2.0)
Adjusted rates(b)	15.15	19.35	5.26	2.33
Terminal rates(c)	5/33(15.2)	5/30(16.7)	2/38(5.3)	1/43(2.3)
Statistical analysis				
Peto test				
Standard method(d)	P=----------			
Prevalence method(d)	P=0.9946			
Combined analysis (d)	P=----------			
Cochran-Armitage test(e)	P=0.0278*			
Fisher Exact test(e)		P=0.3798	P=0.1343	P=0.0590
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	13/50(26.0)	15/50(30.0)	11/50(22.0)	6/49(12.2)
Adjusted rates(b)	33.33	43.75	28.21	13.95
Terminal rates(c)	11/33(33.3)	12/30(40.0)	10/38(26.3)	6/43(14.0)
Statistical analysis				
Peto test				
Standard method(d)	P=----------			
Prevalence method(d)	P=0.9952			
Combined analysis (d)	P=----------			
Cochran-Armitage test(e)	P=0.0475*			
Fisher Exact test(e)		P=0.4120	P=0.4076	P=0.0684

(a):Number of tumor-bearing animals/number of animals examined at the site.
(b):Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c):Observed tumor incidence at terminal kill.
(d):Beneath the control incidence are the P-values associated with the trend test.
Standard method :Death analysis
Prevalence method :Incidental tumor test
Combined analysis :Death analysis + Incidental tumor test
(e):The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? :The conditional probabilities of the largest and smallest possible out comes can not be estimated or this P-value is beyond the estimated P-value.
------:There is no data which should be statistical analysis.
Significant difference; *:P≦0.05 **:P≦0.01

TABLE 11 NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

Group Name	Control	3ppm	6ppm	12ppm
SITE : lymph node				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	17/50(34.0)	17/50(34.0)	21/50(42.0)	6/50(12.0)
Adjusted rates(b)	29.03	24.00	30.00	11.76
Terminal rates(c)	8/30(26.7)	6/25(24.0)	9/30(30.0)	4/34(11.8)
Statistical analysis				
Peto test				
Standard method(d)	P=0.9823			
Prevalence method(d)	P=0.9531			
Combined analysis (d)	P=0.9965			
Cochran-Armitage test(e)	P=0.0137*			
Fisher Exact test(e)		P=0.4165	P=0.2684	P=0.0082**
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	5/50(10.0)	2/50(4.0)	0/50(0.0)
Adjusted rates(b)	13.33	12.00	4.35	0.00
Terminal rates(c)	4/30(13.3)	3/25(12.0)	1/30(3.3)	0/34(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.5991			
Prevalence method(d)	P=0.9898			
Combined analysis (d)	P=0.9913			
Cochran-Armitage test(e)	P=0.0316*			
Fisher Exact test(e)		P=0.5000	P=0.3389	P=0.0587

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

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

(c):Observed tumor incidence at terminal kill.

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

Standard method :Death analysis

Prevalence method :Incidental tumor test

Combined analysis :Death analysis + Incidental tumor test

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

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

------:There is no data which should be statistical analysis.

Significant difference; *:P≦0.05 **:P≦0.01

TABLE 12 CAUSE OF DEATH OF MICE IN THE 2-YEAR INHALATION STUDY OF CROTONALDEHYDE

	Male				Female			
Group	0ppm	3ppm	6ppm	12ppm	0ppm	3ppm	6ppm	12ppm
Number of dead or moribund animals	17	20	12	6	20	25	20	16
Hepatic lesion	2	0	0	0	0	0	0	0
Renal lesion	0	0	1	1	1	2	0	0
Central nervous system lesion	0	0	0	1	1	0	0	0
Urinary retention	0	2	1	1	0	0	0	0
Arteritis	0	0	0	0	1	1	0	0
Hydronephrosis	4	7	3	2	0	0	1	2
Tumor death : leukemia	7	1	4	0	9	11	12	3
subcutis	0	0	0	0	0	1	0	0
lung	1	2	1	0	0	0	0	0
spleen	1	0	1	0	0	0	0	1
liver	1	6	1	0	1	1	0	0
urinary bladder	0	1	0	0	0	0	0	1
pituitary	0	0	0	0	1	3	1	1
uterus	-	-	-	-	5	6	4	7
mammary gland	0	0	0	0	1	0	1	1
peripheral nerves	0	1	0	1	0	0	1	0
peritoneum	1	0	0	0	0	0	0	0