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Mortality, Body Weight, Food and Water Consumption, and Clinical Signs in F344/DuCrj Rats in Studies of Chronic Toxicity and Carcinogenicity

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In vivo historical control data, including mortality, body weight, food and water consumption, and clinical signs in F 344/DuCrj rats were obtained from 11 long-term toxicity and carcinogenicity studies conducted at the Biosafety Research Center, Foods, Drugs and Pesticides, (An-Pyo Center) during the last five years. Survival at 109 weeks of age was 80.2% (min : 74%, max : 90%) in males and 80.5% (min : 72%, max : 92%) in females. The maximum mean body weights of males and females were 443.3±15.8 g (mean±S. D.) and 295.7±13.3 g respectively. Male rats attained their maximum body weight at 82.6±5.3 weeks of age, the females at 103.5 ±2.5 weeks of age. Clinical symptoms increased with age, particularly after 84 weeks of age, and included : wasting, piloerection, palpable subcutaneous and abdominal masses, and decreased spontaneous movement. Lowered body temperature and auricular pallor occured commonly in moribund animals. The nature and grade of toxicity in the treated animals were generally disclosed by comparing with the behavior and signs in the control animals. The use of in-house, historical control data can be useful in subsequent evaluations of chronic toxicity and carcinogenicity studies. —KEY WORDS : animal care, chronic study, F 344 rat, historical data,

In chronic toxicity and carcinogenicity studies, a wide variety of chemical substances, drugs and pesticides are continuously evaluated for safety in humans and the environment by interpreting and extrapolating findings from commonly used strains of laboratory animals. The type and degree of adverse or toxic findings are obtained by comparing the clinical signs displayed by treated animals with those of untreated, concurrent-control animals. It is also quite useful in evaluating these findings to compare the historical control data bases of the laboratories conducting the study with the experimental findings in the same strain of animal. There are many reports comparing historical control data with the spontaneous occurence of tumors in F 344 rats in long term studies, but there is a paucity of information on clinical signs and symptoms and *in vivo* data in general [13, 15].

Clinical monitoring is important to detect incipient disease unrelated to treatment in test animals and is of greater importance with carcinogenicity studies to help interpreting the significance of histological lesions at the termination of the study [14]. The purpose of this paper is to summarize such data as mortality, body weight, food and water consumption and clinical signs, observed in F 344/DuCrj rats used in long term toxicity and carcinogenicity studies conducted at the Biosafety Research Center during the last five years.

Materials and Methods

Four-week-old F 344/DuCrj rats, purchased from Charles River Japan Inc., Kanagawa, were acclimated for one week and maintained

Table 1. Modified NIH open formula for rat and mouse ration

Ingredient	Percentage by Weight
Dried skim milk	5.00
Fish meal (60% protein)	10.00
Soybean meal (49% protein)	15.00
Alfalfa meal (dehydrated 17% protein)	4.00
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Wheat middlings	10.00
Brewer's dried yeast	2.00
Dry molasses	1.50
Soy oil	2.50
Salt	0.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Pre-mixes	0.25
	100.00

throughout the study under a specific pathogen free environment ; temperature 23± 1 ℃, humidity 55± 5 % and a 12 hour light-dark cycle (225± 75 lux). An automatic control system recorded temperature and humidity once cach hour. Our standards for environmental eare included also : 20 fresh air changes per hour in each animal room and air pressure adjusted so that the animal rooms was slightly higher (3 mm H_2O) than oustide. Animals were individually housed in suspended, stainless steel wire mesh cages (15.8×23.8×16.0 cm) with free access to food (Oriental Yeast Co. Ltd., modified NIH Open Formula Rat and Mouse Diet, sterilized by gamma irradiation, Table 1), and water. Basal diets were analyzed four times a year and found to be free of contaminants such as γ-BHC, heptachlor, DDT, polychlorobiphenyl, dieldrin, estradiol, benzo (a) pyrene and aflatoxins.

Body weights were recorded weekly, for the first 26 weeks of each study (31 weeks of age) and every two weeks thereafter. Food consumption was measured weekly throughout the studies. Cage-side observations for gross signs of pharmacologic/toxicologic effects and mortality were conducted twice daily, AM and PM, throughout the study. Detailed physical and clinical examinations and palpation for tissue masses were performed on individual animals each time they were weighed.

Results

Survival : Survival in both sexes at the end of 52 weeks of study (57 weeks of age) was nearly 100%. At the end of 104 weeks (109 weeks of age), the mean survival was 80.2% (min : 74.0%, max : 90.0%) in 500 males and 80.5% (min : 72.0%, max : 92.0%) in 550 females. The survival rate was not significantly different between males and females. The first deaths occurred at 39 weeks of age in males and 47 weeks in females (Fig. 1).

Body Weight : Males and females typically, grew rapidly (body weight gain) from weeks 5 through 19. The maximum mean body weights were 443.3± 15.8 g (mean ± S. D.) in males and 295.7± 13.3 g in females. Male rats attained a maximum mean body weight at 82.6 ±5.3 g weeks of age, and females at 103.5± 2.5 weeks.

Differences in mean body weights between the 11 control groups were minimal at each interval. Therefore, the combined mean body weights of all groups are presented (Fig. 2). However, as would be expected, marked variability in individual body weight became evident as rats of either sex grew older.

Food Consumption (g/day) : The mean food consumption was approximately 16 g/day for males and 14 g/day for females. In both sexes food consumption increased slightly with age

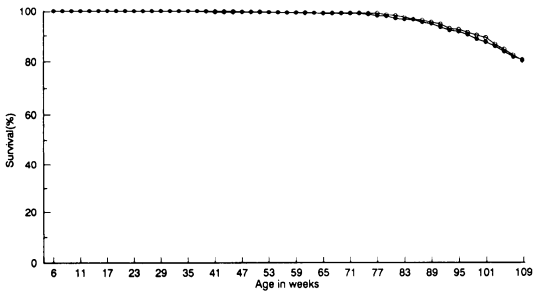

Fig. 1. Survival curves of male and female F 344/ DuCrj (Fischer) rats ○——○ Males (n=500) ●——● Females (n=550)

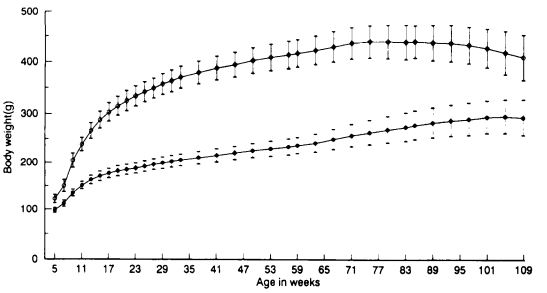

Fig. 2. Mean body weight in F 344/DuCrj (Fischer) rats ○——○ Males ●——● Females The vertical bars represent the standard deviations from the mean.

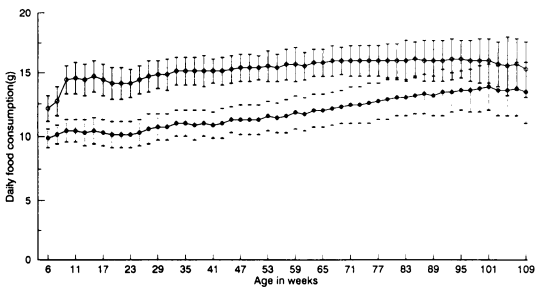

Fig. 3. Mean daily food consumption in F 344/ DuCrj (Fischer) rats ○——○ Males ●——● Females The vertical bars represent the standard deviations from the mean.

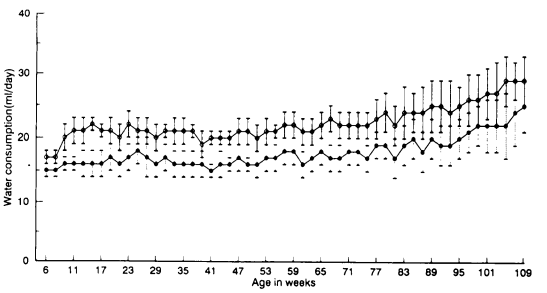

Fig. 4. Mean water consumption in F 344/ DuCrj (Fischer) rats ○——○ Males ●——● Females The vertical bars represent the standard deviations from the mean.

(Fig. 3).

Water Consumption (ml/day) : Mean water consumption ranged from 17 to 29 ml/day in males and 15 to 25 ml/day in females. The water consumption of both sexes also increased with age (Fig. 4).

Clinical Signs : Clinical signs were recorded from 5 through 109 weeks of age and presented at 6 month intervals. Those appearing most frequently are presented in Table 2, those seen less frequently are presented in Table 3.

Clinical observations for the first 52 weeks included : wasting, piloerection, poor grooming (dirty coat), decreased body temperatures, palpable surface, subcutaneous and abdominal tissue masses, ocular opacities, decreased spontaneous motor activity, and eyeball hypertrophy. The incidences of clinical findings for the first 52 weeks ranged from 0.2 to 1.3%. The most common finding during this period was ocular opacities with an incidence of 1.2 and 1.3% in males and females respectively.

The incidence of clinical findings increased with age. The following signs were most evident from 52 to 78 weeks : wasting, piloerection, auricular pallor palpable tissue masses and decreased spontaneous motor activity.

The distribution of body-surface masses is presented in Table 4. They appeared most frequently on the backs (dorsal surfaces), and lower abdomens of both male and female rats (Table 5). Masses in the axillary regions and on the sides of the abdomen followed by peritoneal and inguinal regions were the most common sites of appearance in males ; the axillary regions, lower abdominal and inguinal regions were the most common in females.

The incidence of ocular opacities increased

Table 2. Historical control data of clinical observation in F 344/DuCrj (Fischer) rats—High-incidence clinical signs—

Age (weeks)	5 – 31		32 – 57		58 – 83		84 – 109	
Sex	M[1]	F[2]	M	F	M	F	M	F
No. of animals	500	550	500	550	497	547	488	532
Signs	Incidence (%)[3]							
wasting	0	0	0.6	0.2	1.4	2.0	18.6	18.6
piloerection	0	0	0.6	0	1.2	1.5	14.1	12.2
alopecia	0	0	0	0	0	0.7	2.0	4.9
dirty coat	0	0	0.2	0.2	0.6	0.5	4.7	1.9
pallor of the auricles	0	0	0	0	0.8	0.5	7.2	12.0
lowered body temperature	0	0	0.2	0	0.4	0.4	3.9	6.0
tissue-mass/surface	0	0	0.2	0.2	1.4	0.4	8.6	2.1
tissue-mass/subcutaneous site	0	0	0.2	0.5	0.8	1.1	9.6	11.5
tissue-mass/abdomen	0	0	0	0.2	0.2	0.7	5.1	9.6
ocular discharge	0	0	0	0	0.8	0.7	4.5	4.7
ocular opacity	0.2	0.4	1.2	1.3	2.0	2.0	4.1	3.0
decreased spontaneous motor activity	0	0	0.2	0	1.2	1.3	10.7	10.9

1) Male 2) Female
3) percent (No. of affected animals/No. of animals examined)

Table 3. Historical control data of clinical observation in F 344/DuCrj (Fischer) rats—Low-incidence clinical signs—

Age (weeks)	5 – 31		32 – 57		58 – 83		84 – 109	
Sex	M[1]	F[2]	M	F	M	F	M	F
No. of animals	500	550	500	550	497	547	488	532
Signs	Incidence (%)[3]							
trauma	0	0	0	0	0	0	0	0.2
sleek disappearing hair	0	0	0	0	0	0	0.6	0
tissue-mass/oral cavity	0	0	0	0	0	0	0.2	0
lacrimation	0	0	0	0	0	0	0	1.5
corneal abnormality	0	0	0	0	0	0	0.4	0.2
nodule of eyelid	0	0	0	0	0	0	0.2	0
hypertrophy of eyeball	0	0.2	0	0.7	0	0.5	0	0.4
nodule at nasal site	0	0	0	0	0	0	0.6	0
nodule of auricle	0	0	0	0	0.2	0	0.2	0
salivation	0	0	0	0	0	0	0.4	0
loose stool	0	0	0	0	0	0	0.4	0
vaginal prolapse	0	0	0	0	0	0.2	0	0
urogenital hemorrhage	0	0	0	0	0	0	0.4	0.6
prone position	0	0	0	0	0	0	0.4	0.6
lateral position	0	0	0	0	0	0	0.4	0.4
wryneck	0	0	0	0	0.2	0.2	0.6	0.6
staggering gait	0	0	0	0	0	0	0.2	0
shuffling gait	0	0	0	0	0	0	0.4	0.2
gait difficulty	0	0	0	0	0.2	0	1.2	1.1
tachypnea	0	0	0	0	0	0	2.0	1.3
hyperventilation	0	0	0	0	0.2	0	0.4	0
dyspnea	0	0	0	0	0	0	0.8	0
abdominal distention	0	0	0	0	0	0	0.8	1.3
labial nodule	0	0	0	0	0	0	0.2	0

1) Male 2) Female
3) percent (No. of affected animals/No. of animals examined)

Table 4. Tumor masses on the body surface of F 344/DuCrj (Fischer) rats

Sex	Male	Female
No. of animals	500	550
Local site	No. of abnormal animals	
nasal region	1	0
peri-otic region	2	0
peri-oral region	1	0
mandible	2	0
neck	1	0
shoulder	0	1
chest	2	0
back or dorsal surface	13	3
axillary region	1	0
abdomen	2	0
side-abdomen	3	0
lower-abdomen	5	7
waist	2	0
anterior limb	2	0
posterior limb	2	0
tail	1	1

Table 5. Tumor masses at subcutaneous sites in F 344/DuCrj (Fischer) rats

Sex	Male	Female
No. of animals	500	550
Local site	No. of abnormal animals	
nasal region	1	0
peri-otic region	4	0
mandible	2	1
neck	1	1
shoulder	0	1
chest	2	2
back	3	1
axillary region	16	34
abdomen	2	2
side-abdomen	9	5
lower-abdomen	2	19
inguinal region	3	8
anterior limb	1	1
posterior limb	1	3
scrotum	1	0
anal region	1	0

with age, reaching a maximum of 4.1% in males and 3.0% in females up to 109 weeks of age. Other findings appeared infrequently : trauma, masses in the oral cavity, nodules in the nasal area, auricle and labia, vaginal prolapse and staggering gait.

Discussion

Properly designed, well controlled and well conducted experiments using healthy animals are essential for an accurate pathological

Table 6. Comparison of the food consumption per kg body weight between F 344/DuCrj (Fischer) rats and Slc : SD rats

Strain	F344		SD	
Age (Weeks)	Male	Female	Male	Female
6	124	120	99	102
7	87	89	85	89
11	63	66	62	71
15	52	58	53	59
19	44	55	49	59
23	42	53	46	57
27	43	56	45	54
31	41	54	40	50
45	38	50		
57	39	52		
71	37	47		
83	36	47		
97	37	48		
109	37	44		

review and evaluation of chronic toxicity and carcinogenicity in rodents.

Daily records of the various environmental parameters, e. g., temperature, humidity, are important when assessing the etiology of clinical signs since the environmental conditions may influence the physiological and behavioral status of the animals [5, 14].

Summation of historical control data : mortality, body weight, food and water consumption and clinical signs, obtained from 11 long-term studies with F 344 rats, conducted at the Biosafety Research Center, Foods, Drugs and Pesticides (An-Pyo Center) during the last 5 years were evaluated by comparing inter-laboratory differences as follows :

Survival data : The survival rates at the An-Pyo Center were similar to those reported by NTP from 1984 to 1989 [12, 15]. A higher survival rate was reported by UFAW for group-housed animals, as compared to individual housing [17]. All NTP studies were conducted using group housing with 3 to 5 rats per cage. The An-Pyo Center used individual housing.

Boody Weight : Growth curves of control animals of the An-Pyo facility were similar to those reported by other laboratories [12, 13, 15]. The mean, maximum body weight data of the An-Pyo Center corresponded to that reported over an 11 year period from 1971 to 1981 in carcinogenicity studies of NCI-NTP[13], and to that reported by Fujimoto *et al* [6]. Rats, in the Fujimoto study, were purchased from the same supplier as those in this paper, Charles River Japan, Inc., but were housed 2 rats per cage. No marked interlaboratory differences were evident in maximum mean body weight data between the An-Pyo studies and those reported in the literature. The maximum mean body weight occurred between 75-85 weeks in males and at approximately 110 weeks in females.

Food Consumption : Although variations by sex and age were evident, food consumption ranged between 12.0-16.0 g/day in males and 10.0-14.0 g/day in females. According to Fujimoto *et al* [6], food consumption of F 344/DuCrj rats ranged between 13.7-17.3 g/day in males and 11.2-14.7 g/day in female and their survival was similar to that of our rats. Absolute food consumption, on a g/day basis, of F 344 rats was less than that of SD and Wistar rats [10], probably because F 344 rats are smaller than SD and Wistar rats.

However, as shown in Table 6 , relative food consumption (g/kg/day) was similar in the F 344 and SD rats in our laboratory.

Although absolute food consumption (g of food/day) did not change appreciably throughout the 104 weeks of the study, relative food consumption (g of food/kg of body weight/day) decreased with age. As would be expected, this was most evident during the first 10 weeks, the period of rapid growth ; after

which it remained relatively constant and then deceased very gradually with age. The relative food consumption (g/kg/day) was slightly greater by females than by males throughout the study.

Water Consumption : Daily water consumption ranged between 17-29 ml in males and 15-25 ml in females in this study. This was similar to that reported by Fujimoto *et al* [6]. However, there were other laboratories, which reported greater daily water consumption in rats, ranging from 30-35 ml [4, 10]. The reason for this interlaboratory difference in water consumption between our laboratory and the others is not readily clear. However, differences in the measurement of water consumption may be a contributory factor. Although there were no definite differences in the effects of single versus group housing on the physical parameters, such as body weight, food consumption and water consumption.

Clinical Signs : In the first 52 weeks of the study, the physical observations for clinical signs of pharmacologic/toxicologic effects were of the type commonly seen in the laboratory rat. The most common finding during this period was the ocular opacities with an incidence of 1.2% in males and 1.3% in females.

There were no other signs or symptoms which were considered to be of toxicologic or pathologic significance during the first 52 weeks of the study.

A variety of clinical signs became evident after 78 weeks and included : wasting, piloerection, decreased spontaneous motor activity, the appearance of subcutaneous and abdominal masses, body surface masses, pallor of the auricles and lowered body temperature. Most of these signs were prevalent in moribund animals as well as in many surviving animals near the end of the study.

Histopathological evaluations revealed a correlation with the occurrence of clinical, in-life observations attributable to age-associated changes. Wasting of animals with accompanying loss in body weight and decreased food consumption occurs commonly in the spontaneous, age-associated diseases of the laboratory rat, such as chronic nephropathy syndrome, leukemia and tumors of the pituitary [7, 9]. Piloerection and a rough coat is a common finding in aged rats. Decreases in spontaneous movement is frequently seen in animals with disorders of the central nervous system, such as pressure effects that can be produced by growth of tumors in the pituitary gland. Hypertrophy or bulging of the eyeballs can also be produced by such pressure effects. Decreased motor activity can be caused by progressive peripheral nerve degeneration resulting in hind-limb paralysis. Large subcutaneous and/or abdominal masses can also impede movement.

Both benign and malignant masses which are found subcutaneously or on the body surface originate primarily from tissues of the integumentary system, such as, the skin and subcutaneous tissue, the preputial and clitoral glands, and musculoskeletal or mammary tissue. A variety of these tumors were examined and evaluated histopathologically [9].

Plantar decubitus ulcers causing anemia due to hemorrhage or enlargement of the regional lymph node are commonly found in carcinogenicity studies in rats [7, 8]. No such cases were evident in this study, because of the strain difference between F 344 and SD rats or differences in types of cages [8].

Since one of the endpoints in a long-term study is histopathologic evaluation, every effort must be obtained to present the pathologist with the best samples of tissue from the experimental subject [16]. It is appropriate to increase the frequency of measuring body weight and food consumption to check early warnings of the onset of disease or debilitation in aged animals [11, 16]. In the An-Pyo Center, body weights are recorded weekly for the first 26 weeks and every two weeks thereafter. Food consumption is measured weekly throughout the study.

Arnold *et al* suggested that persistent anorexia, advanced debilitation and obvious pain indicate that the animal should be euthanized [1]. However, lowered body temperature and pallor of the auricles were frequently observed in agonal animals near death in our study. Therefore, these signs were selected as the preferred criteria for defining moribund conditions and selection for euthanasia.

The F 344 rat was adopted as the standard rat for the carcinogenicity bioassay program in the U. S. A., 1970, because this rat was easy to maintain, sensitive to various types of chemical carcinogens and had a relatively low spontaneous tumor rate [2]. The present

analysis of historical control data from F 344 rats in our Laboratory seems to have confirmed again the appropriateness of the selection of this rat strain for long-term toxicity and carcinogenicity studies based on their characteristic good survival, relative uniformity of physiological parameters including body weight, food consumption and water consumption, and higher resistance to infectious diseases. The results of the histopathological obsevations of these rats revealed also the similar or relatively lower rate of spontaneous tumor in this strain than the rates reported in other laboratories [3, 9].

Environmental and nutritional conditions including the caging of single animals, and the use of the basal diet prepared by following the modified NIH Open Formula for rat and mouse diet sterilized by gamma irradiation, may have avoided the apparent influences of shortened longevity or increased rate of spontaneous neoplastic or non-neoplastic lesion in the aged rats.

Finally, the most important contribution of a well-controlled and well-conducted study can be accomplished by the continuing efforts to train and educate personnel for better daily care of animals and clinical observation.

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長期の毒性試験におけるF344/DuCrjラットの死亡率，体重変化，摂餌量，摂水量および一般状態

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F334/DuCrjラットを用い，（財）食品農医薬品安全性評価センターで最近5年間におこなった11の長期毒性試験や発癌性試験の対照群動物の死亡率，体重，摂餌量，摂水量および一般状態のデータを集計した。その結果，109週齢時の生存率は雄で80.2％（最小：74.0％，最大：90.0％），雌で80.5％（最小：72.0％，最大：92.0％）であった。平均体重の最大値は雄で443.3±15.8g（平均±標準偏差），雌で295.7±13.3g（平均±標準偏差）であり，それらは雄で82.6±5.3週齢（平均±標準偏差），雌で103.5±2.5週齢（平均±標準偏差）であった。一般状態では特に生後84週齢以降で雌雄とも加齢に伴う所見が観察され，痩削，立毛，皮下部の腫瘤，腹腔内の腫瘤および自発運動低下が高い発現率を示した。また，切迫屠殺動物には体温低下と耳介の蒼白がもっともしばしば観察された。被験物質処置群動物に観察される毒性発現の種類と程度は一般に対照群動物と行動や症状を比較して解析されている。しかし，それに加えて試験実施機関それぞれに背景データを備えることは慢性毒性試験や発癌性試験の成績を評価するに当って非常に有用である。