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Technical Report

Transition of Historical Control Data for High Incidence Tumors in F344 Rats

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Abstract: Historical control data of tumor incidence were collected from the control groups (215 animals of each sex) in four recent carcinogenicity studies that were started between 2005 to 2009 (terminally sacrificed between 2007 and 2011) at BoZo Research Center Inc. (Gotemba, Shizuoka, Japan) using Fischer 344 rats (F344/DuCrlCrlj). These data were compared to the previous historical control data (from 1990 to 2004, previously reported) in the same facility. In the results, the incidence of C-cell adenoma in the thyroid tended to increase in both sexes in recent years (30.8% for males and 24.4% for females in 2005-2009) as compared with the previous data (17.4% and 20.1% for males and 11.5% and 11.8% for females in 1990–1999 and 2000–2004, respectively). In addition, the incidences of pancreatic islet cell adenoma in males and uterine adenocarcinoma tended to increase from around 2000 and remained high in recent years (incidences of islet cell adenoma in males of 10.5%, 17.1% and 20.5% in 1990–1999, 2000–2004 and 2005–2009; incidences of uterine adenocarcinoma of 3.3%, 12.0% and 13.5% in 1990–1999, 2000–2004 and 2005–2009, respectively). There was no apparent difference in the incidence of other tumors. (DOI: 10.1293/tox.26.227; J Toxicol Pathol 2013; 26: 227–230)

Key words: historical control data, F344 rat, high incidence tumor

Introduction

It is important to maintain the validity of historical control data for assessment of toxicities, especially carcinogenicity. In carcinogenicity studies for novel pharmaceuticals and chemicals, Peto's test is commonly employed as one of the tools of statistical analysis for evaluation of the carcinogenicity of test chemicals[1,2]. In such a statistical analysis for carcinogenicity, the types of tumors observed should be categorized as common or rare tumors based on the incidence from the historical control data in the test facility. Gotemba Laboratory, BoZo Research Center Inc. (Gotemba, Shizuoka, Japan), has used Fischer 344 rats for carcinogenicity studies since the 1990s, as well as other major strains including Sprague-Dawley (SD) and Wistar rats. The historical control data for common tumors in F344 rats in our facility were reported previously[3]. In the present report, we update the data from the last 5 years and compare them with previous data to examine the transition of tumor incidences over the years.

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Materials and Methods

Animals and husbandry in each carcinogenicity study

Data were newly collected from the control groups of 4 carcinogenicity studies using F344 rats that were started between 2005 and 2009 (terminally sacrificed between 2007 and 2011) at Gotemba Laboratory, BoZo Research Center Inc. (Table 1). In each carcinogenicity study, male and female specific pathogen-free (SPF) rats of the Fischer F344 strain, F344/DuCrlCrlj, were obtained from Atsugi Breeding Center, Charles River Laboratories Japan, Inc. The animals were 4 or 5 weeks old on arrival and used at 6 weeks of age after 1 or 2 weeks of quarantine/acclimatization. All animals were housed in animal rooms in an SPF rodent barrier facility with periodic microbiological monitoring. Animals rooms were maintained at a temperature of 23 ± 3°C with a relative humidity of 50 ± 20%, air ventilation at 10 to 17 times per hour and 12-hour illumination (07:00 to 19:00). Male and female rats were housed individually in bracket-type stainless steel wire mesh cages (W254×D350×H170 mm). The animals were allowed free access to powdered diet (radiation sterilized CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water. Each study was conducted in compliance with laws and guidelines concerning animal welfare as follows; the Law for the Humane Treatment and Management of Animals (Law No. 105), the Standards Relating to the Care and Management of Labora-

Table 1. Outline of the Studies

Study	Year of study start	Year of scheduled necropsy	Route of administration	Number of control rats	Survival rate (Males)	Survival rate (Females)
A	2005	2007	Diet	50 males and 50 females	84.0	82.0
B	2008	2010	Gavage	55 males and 55 females	81.8	78.2
C	2008	2010	Gavage	55 males and 55 females	87.3	80.0
D	2009	2011	Gavage	55 males and 55 females	83.6	70.9

Table 2. Comparison of Tumor Incidence in Male Fischer 344 Rats

	Data set	Previously reported 1990–1999	Previously reported 2000–2004	Present data 2005–2009
	No. of study	11[a]	5	4
	No. of rats	873	275	215
Prostatic adenoma	Mean (%)	16.8	10.6	9.8
	Range (%)	4–28	7 –15	7–14
Leydig cell tumor	Mean (%)	92.9	85.5	87.4
	Range (%)	76–98	78–91	82–93
Pituitary anterior adenoma	Mean (%)	28.0	20.0	20.5
	Range (%)	13–52	13–31	16–27
Adrenal pheochromocytoma	Mean (%)	15.5	7.3 *	11.2
	Range (%)	7 –22	2–13	5–16
Large granular lymphocytic leukemia	Mean (%)	19.1	13.1	12.1
	Range (%)	4–30	7–20	8 –16
Hepatocellular adenoma	Mean (%)	5.0	3.6	2.8
	Range (%)	0 –12	0–7	0–5
Islet cell adenoma	Mean (%)	10.5	17.1	20.5 *
	Range (%)	0 –18	9–25	15–31
Cutanenous fibroma	Mean (%)	4.6	5.8	3.7
	Range (%)	0–10	2–9	0–9
Thyroid C-cell adenoma	Mean (%)	17.4	20.1	30.8 *
	Range (%)	6 –25	13–27	22–45

[a] A study for background data (n=238) was included, and the two control groups in one study were combined into one control group. *: $p<0.05$ vs. 1990–1999 (Bonferroni t-test).

tory Animals and Relief of Pain (Notification No. 88 of the Ministry of the Environment, Japan), Guidelines for Proper Conduct of Animal Experiments (Science Council of Japan) and the Guide for Animal Care and Use of our facility.

Experimental procedure in each carcinogenicity study

Animals were inspected at least twice daily for gross abnormalities or mortality and given a detailed physical examination weekly. The animals in gavage studies were also handled at the daily oral gavage administration. Body weights and food consumption were recorded at least once each week for the first 13 weeks and at least once every 4 weeks thereafter until the end of the study. After 104 weeks of treatment, all surviving animals were euthanized. All animals, including dead or moribund animals, were subjected to detailed necropsy. All gross lesions were recorded, and all organs and tissues of all animals were taken for routine histopathological examination. Histopathological peer review was conducted by an eminent veterinary pathologist (DACVP) in all studies shown in Table 1 except for Study A.

Collection of historical control data

Before the collection of control data, all neoplastic and preneoplastic lesions were reviewed by one pathologist in order to ensure consistency of the diagnostic criteria. First, in-house historical control data for the incidences of all tumors were collected (data not shown), and then the tumors showing incidences of more than 5% in either the present or previous historical data were listed (Tables 2 and 3).

Statistical analysis

For the incidence (percentage) of each tumor, statistical analysis was performed with the analysis of variance (ANOVA) followed by the Bonferroni t-test among the 3 periods (1990–1999, 2000–2004 and 2005–2009).

Results and Discussion

The tumors with incidences of more than 5% in the past and present data are indicated in Table 2 (males) and Table 3 (females). The two left columns are our previous data[3] and the right column is the present data. The incidences of C-cell adenoma in the thyroid were 17.4% and 20.1% for males and 11.5% and 11.8% for females in 1990–1999 and 2000–2004, respectively, and 30.8% for males and 24.4% for females in 2005–2009, and the incidence tended to increase in both sexes in recent years. The incidence of pancreatic islet cell adenoma in males was 10.5% in 1990–1999, 17.1%

Table 3. Comparison of Tumor Incidence in Female Fischer 344 Rats

	Data set	Previously reported 1990–1999	Previously reported 2000–2004	Present data 2005–2009
	No. of study	11[a]	5	4
	No. of rats	873	275	215
Uterine endometrial stromal polyp	Mean (%)	31.0	29.1	28.8
	Range (%)	18–44	24–35	24–35
Uterine adenocarcinoma	Mean (%)	3.3	12.0 **	13.5 **
	Range (%)	0–8	9–16	9–22
Pituitary anterior adenoma	Mean (%)	37.5	29.9	32.7
	Range (%)	29–52	27–31	20–42
Mammary fibroadenoma	Mean (%)	6.9	6.5	9.8
	Range (%)	2–15	2–15	2–13
Large granular lymphocytic leukemia	Mean (%)	21.3	20.7	17.2
	Range (%)	5–34	13–27	10–29
Thyroid C-cell adenoma	Mean (%)	11.5	11.8	24.4 **††
	Range (%)	7–22	7–13	21–25

[a] A study for background data (n=238) was included, and the two control groups in one study were combined into one control group. **: $p<0.01$ vs. 1990–1999 (Bonferroni t-test). ††: $p<0.01$ vs. 2000–2004 (Bonferroni t-test).

in 2000–2004 and 20.5% in 2005–2009. The incidence of uterine adenocarcinoma was 3.3% in 1990–1999, 12.0% in 2000–2004 and 13.5% in 2005–2009. Thus the incidences of pancreatic islet cell adenoma in males and uterine adenocarcinoma tended to increase from around 2000 as stated in the previous report[3].

In the historical control data that were published between 1987 and 2011, the incidences of C-cell adenoma in the thyroid of F344 rats were 9.2 to 15.42% in males and 6.7 to 12.14% in females[4-7]. The incidence in 2005–2009 in the present survey was higher than those data. It was reported that C-cell tumor developed with a high incidence in Wistar and F344 rats but that it developed with a low incidence in SD rats[8]. Meanwhile, the incidence of C-cell tumor in female Harlan SD rats (25.43%) in the National Toxicology Program (NTP)[9] was far higher than that in the historical control data in female Charles River SD rats (7.21%)[10] and the above data from F344 rats[4-7]. Therefore, it seems that there are differences in tumor incidence between the substrains of suppliers.

The cause of the increased incidence in C-cell adenoma in the present survey was unclear. Calcium and vitamin D content in the diet was not responsible because identical formula diets were used consistently in our facility. Chronic progressive nephropathy (CPN), a common age-related lesion in rats, is known to induce secondary hyperparathyroidism[11, 12]. However, the incidences of CPN in 2005–2009, which were graded as moderate/severe, were 6% in males and 2% in females, and they were comparable to or lower than those in our previous data[3]. Therefore, a relationship between CPN and increased C-cell adenoma could be ruled out.

Our series of surveys demonstrated that the historical control data for spontaneous tumors fluctuated over the years. In our survey, all the rats came from the same breeder, and were housed under the same laboratory conditions. The fluctuations of tumor incidences might be caused by some sort of factor from animals other than environmental factors, although genetic drift is rarer in the inbred F344 strain than in the outbred Wistar and SD strains[13]. We hope that our historical control data will help in the evaluation of carcinogenicity studies at other facilities.

References

1. Peto R, Pike MC, Day NE, Lee PN, Parish S, Peto J, Richard S, and Wahrendorf J. Guidelines for simple, sensitive tests for carcinogenic effects in long-term animal experiments. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Suppl. **2**: 365–367. 1980.
2. Guidance for industry: Statistical aspect of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals. Draft guidance. U.S. Department of Health and Human Services, FDA and CDER. 2001.
3. Ando R, Nakamura A, Nagatani M, Yamakawa S, Ohira T, Takagi M, Matsushima K, Aoki A, Fujita Y, and Tamura K. Comparison of past and recent historical control data in relation to spontaneous tumors during carcinogenicity testing in Fischer 344 rats. J Toxicol Pathol. **21**: 53–60. 2008. [CrossRef]
4. Maita K, Hirano M, Harada T, Mitsumori K, Yoshida A, Takahashi K, Nakashima N, Kitazawa T, Enomoto A, Inui K, and Shirasu Y. Spontaneous tumors in F344/DuCrj rats from 12 control groups of chronic and oncogenicity studies. J Toxicol Sci. **12**: 111–126. 1987. [Medline] [CrossRef]
5. Iwata H, Hirouchi Y, Koike Y, Yamakawa S, Kobayashi K, Yamamoto T, Kobayashi K, Inoue H, and Enomoto M. Historical control data of non-neoplastic and neoplastic lesions in F344/DuCrj rats. J Toxicol Pathol. **4**: 1–24. 1991. [CrossRef]
6. Haseman JK, Hailey JR, and Morris RW. Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F1 mice in two-year carcinogenicity studies: a National Toxicology Program update. Toxicol Pathol. **26**: 428–441. 1998. [Medline] [CrossRef]
7. NTP Historical controls Report. All routes and vehicles, F344/N rats. May 2011, from National Toxicology Program

website: http://ntp.niehs.nih.gov/ntp/Historical_Controls/NTP2000_2011/HistCont2011_Rats_AllRoutes.pdf.
8. Hagiwara A, Tamano S, Kurata Y, and Shibata M. Spontaneous thyroid, parathyroid, and pancreatic islet tumors in F344 rats and B6C3F1 mice. J Toxicol Pathol. **2**: 73–83. 1989 (in Japanese). [CrossRef]
9. Dinse GE, Peddada SD, Harris SF, and Elmore SA. Comparison of NTP historical control tumor incidence rates in female Harlan Sprague Dawley and Fischer 344/N rats. Toxicol Pathol. **38**: 765–775. 2010. [Medline] [CrossRef]
10. Giknis MLA, and Clifford CB. Compilation of spontaneous neoplastic lesions and survival in Crl:CD(SD) rats from control groups. March 2004, from Charles River Laboratories. website: http://www.criver.com/sitecollectiondocuments/rm_rm_r_lesions_survival_crlcd_sd_rats.pdf.
11. Owen RA, and Heywood R. Age-related variations in renal structure and function in Sprague-Dawley rats. Toxicol Pathol. **14**: 158–167. 1986. [Medline] [CrossRef]
12. Seely JC, and Hard GC. Chronic progressive nephropathy (CPN) in the rat: Review of pathology and relationsip to renal tumorigenesis. J Toxicol Pathol. **21**: 199–205. 2008. [CrossRef]
13. Tennekes H, Kaufmann W, Dammann M, and van Ravenzwaay B. The stability of historical control data for common neoplasms in laboratory rats and the implications for carcinogenic risk assessment. Regul Toxicol Pharmacol. **40**: 293–304. 2004. [Medline] [CrossRef]