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Short Communication

Historical control background incidence of spontaneous thyroid and parathyroid glands lesions of rats and CD-1 mice used in 104-week carcinogenicity studies

Kaori Isobe[1*], Sydney Mukaratirwa[1], Claudio Petterino[1], and Alys Bradley[1]

[1] Charles River Laboratories Edinburgh Ltd., Elphinstone Research Centre, Tranent, East Lothian, EH33 2NE, United Kingdom

Abstract: The incidence and range of spontaneous thyroid and parathyroid glands findings were determined in control Han-Wistar and Sprague-Dawley rats, and CD-1 mice from 104-week carcinogenicity studies carried out between 1998 and 2010 at Charles River Edinburgh. In both strains of rats and in CD-1 mice, non-proliferative lesions of the thyroid or parathyroid glands were generally uncommon apart from some findings in CD-1 mice such as ultimobranchial duct/cyst (5.72%), follicular distension/dilatation (3.84%), and cystic follicles (3.53%). In Han-Wistar rats, thyroid proliferative lesions were slightly more frequent in males than in females, but in Sprague-Dawley rats, they were of similar incidence in both sexes. The most common findings overall in Han-Wistar and Sprague-Dawley rats were C-cell hyperplasia (48.11% and 36.56%, respectively) and adenoma (10.87% and 9.52%, respectively), follicular cell hyperplasia (4.21% and 0.91%, respectively) and adenoma (4.32% and 1.36%, respectively). Secondary neoplastic lesions either in thyroid or parathyroid gland were poorly represented. (DOI: 10.1293/tox.2016-0005; J Toxicol Pathol 2016; 29: 201–206)

Key words: carcinogenicity studies, CD-1, Han-Wistar, Sprague-Dawley, thyroid gland, parathyroid gland

Rodent carcinogenicity studies are an important part of the drug development process. When assessing the risk of carcinogenicity, however, it must be taken into consideration that positive results in a rodent carcinogenicity study cannot always be extrapolated to humans.

Rodents tend to have a higher incidence of thyroid proliferative lesions than humans[1, 2]. The greater sensitivity of the rodent thyroid is related to the shorter plasma half-life of T_4 than in humans due to the considerable differences in the transport proteins for thyroid hormones between these species. In humans, circulating T_4 is bound primarily to thyroxine-binding globulin (TBG), but this high-affinity binding protein is not present in rodents.

Hepatic microsomal enzymes also play an important role in inducing tumors deriving from thyroid follicular cells[1, 2]. Glucuronidation is the rate-limiting step in the biliary excretion of T_4 and sulfation primarily by phenol sulfotransferase for the excretion of T_3. Long-term exposure of rodents to a wide variety of different chemicals, such as phenobarbital, may induce these enzyme pathways and result in chronic stimulation of the thyroid by increased circulation of TSH. This thyroid tumor induction occurs particularly with rodents, firstly because UDP-glucuronyl transferase can easily be induced in rodents and secondly because thyroxine metabolism takes place very rapidly in rats in the absence of TBG. Their promoting effect on thyroid tumors usually is greater in rats than in mice, with males developing a higher incidence of tumors more often than females. On the other hand, there is no convincing evidence that humans treated with drugs or exposed to chemicals that induce hepatic microsomal enzymes are at increased risk for the development of thyroid tumors.

Pathological evaluation of lesions caused by xenobiotics must take into account the recognition of background findings[3]. Therefore, knowledge about species, strain, and/or sex differences and continuous updating of the incidence of spontaneous findings are crucial for proper interpretation of drug-induced lesions.

The aim of this study was to provide the range and incidences of spontaneous thyroid and parathyroid glands lesions in control rodents from 104-week carcinogenicity studies carried out at Charles River Preclinical Service Edinburgh. Of the different strains of rodents available, Han-Wistar rats, Sprague-Dawley rats, and CD-1 mice are regularly used for carcinogenicity studies in Europe. There are few reports that describe the incidence and range of thyroid and parathyroid findings in these strains[4-7], and most of them are focused only on neoplastic lesions, getting out of date, or a mixture of studies conducted at many facilities in different countries. This report presents up-to-date results including non-proliferative and proliferative findings of the thyroid and parathyroid gland and can serve as a historical

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*Corresponding Author: K Isobe (e-mail: kaori.isobe@crl.com)

Table 1. Details of Data Sources

Species/strain	Total number of studies	Route of administration (number of studies)				Total number of animals	
		Oral gavage	Dietary	Subcutaneous injection	Inhalation	Males	Females
Han-Wistar rats	12	5	3	1	3	935	942
Sprague-Dawley rats	4	2	0	1	1	328	334
CD-1 mice	13	7	1	3	2	1,278	1,273

Table 2. Incidence of Spontaneous Thyroid Gland Non-proliferative Lesions in Rats and CD-1 Mice

Findings	Han-Wistar rats			Sprague-Dawley rats			CD-1 mice		
	Males (n = 935)	Females (n = 942)	Total (n = 1,877)	Males (n = 328)	Females (n = 334)	Total (n = 662)	Males (n = 1,278)	Females (n = 1,273)	Total (n = 2,551)
Follicular cell hypertrophy	2 (0.21%)	0	2 (0.11%)	1 (0.30%)	0	1 (0.15%)	0	1 (0.08%)	1 (0.04%)
Atrophy	0	0	0	0	0	0	2 (0.16%)	0	2 (0.08%)
Necrosis	0	0	0	0	0	0	0	2 (0.16%)	2 (0.08%)
Inflammatory cell infiltration[a, c]	4 (0.43%)	1 (0.11%)	5 (0.27%)	7 (2.13%)	4 (1.20%)	11 (1.66%)	14 (1.10%)	41 (3.22%)	55 (2.16%)
Follicular distension/dilatation[a, b, c]	2 (0.21%)	3 (0.32%)	5 (0.27%)	9 (2.74%)	0	9 (1.36%)	63 (4.93%)	35 (2.75%)	98 (3.84%)
Cystic follicles	8 (0.86%)	3 (0.32%)	11 (0.59%)	1 (0.30%)	1 (0.30%)	2 (0.30%)	44 (3.44%)	46 (3.61%)	90 (3.53%)
Pigmentation of follicular cells	0	0	0	0	0	0	0	3 (0.24%)	3 (0.12%)
Ultimobranchial duct/cyst	2 (0.21%)	2 (0.21%)	4 (0.21%)	2 (0.61%)	4 (1.20%)	6 (0.91%)	74 (5.79%)	72 (5.66%)	146 (5.72%)
Abscess	0	0	0	0	0	0	1 (0.08%)	1 (0.08%)	2 (0.08%)
Arteritis/periarteritis	1 (0.11%)	1 (0.11%)	2 (0.11%)	1 (0.30%)	0	1 (0.15%)	4 (0.31%)	6 (0.47%)	10 (0.39%)

Significantly different ($P<0.01$) incidences of lesions: a = males, Han-Wistar rats vs. Sprague-Dawley rats; b = Sprague-Dawley rats, males vs. females; c = CD-1 mice, males vs. females.

control reference for use in correspondence with regulatory authorities.

In this study, thyroid and parathyroid gland samples from a total of 2,539 rats (1,877 Han-Wistar [Crl:WI(Han)], 662 Sprague-Dawley [Crl:CD(SD)]) and 2,551 CD-1 [Crl:CD-1(ICR)] mice) were obtained from control groups of twenty-nine 104-week carcinogenicity studies conducted between 1998 and 2010 at Charles River Edinburgh (Table 1). The animals were purpose-bred for laboratory use and supplied by Charles River UK Ltd. (Margate, Kent, U.K.).

Male mice were housed separately, and female mice were housed in groups of up to 3 animals per cage. Rats were housed in groups of up to 5 animals per cage by sex. Animal room temperature and humidity were automatically controlled at 19°C to 23°C and 40% to 70%, respectively, with a minimum of 15 air changes/hr. An automatic 12-hr light-dark cycle was maintained. Animals had free access to tap water in bottles with sipper tubes and were fed an *ad libitum* commercial rodent diet (Rat and Mouse [modified] No. 1 Diet SQC Expanded, Special Diet Service Ltd., Witham Essex, U.K.). Wooden chewsticks were also offered to all animals for environmental enrichment.

All studies were conducted in accordance with the U.K. Animals (Scientific Procedures) Act 1986, which conforms to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, Council of Europe).

Animals were humanely euthanized by a rising concentration of carbon dioxide and exsanguinated via femoral veins. Comprehensive necropsy was performed, and tissues were fixed by immersion in 10% neutral-buffered formalin, embedded in paraffin wax, sectioned to a thickness of 4 to 5 µm, mounted onto glass slides, stained with hematoxylin and eosin (H&E), and coverslipped. Data from all studies were recorded by direct computer entry by the study pathologist using PLACES and PLACES 2000 (Instem; Apoloco Limited Systems, Conshohocken, PA, USA). Generally accepted terms were used in the diagnosis of proliferative and non-proliferative lesions (STP/ARP/AFIP SSNDC Guides for Toxicologic Pathology)[8, 9]. All neoplastic findings in each study underwent pathology peer review, and all data were reviewed by the Quality Assurance Department at Charles River's Edinburgh facility prior to the release of the final pathology report.

Statistical analysis of lesion incidence was performed at the 1% significance level ($p<0.01$) using Fisher's exact test comparing males versus females within the same species or strain and comparing different strains of rats (Han-Wistar versus Sprague-Dawley) for the same sex.

Table 2 presents a summary of thyroid gland non-proliferative findings with their incidences. Overall incidences were not high either in rats or mice.

In rats, non-proliferative lesions of the thyroid gland were less common compared with in mice. Among the findings of rats, inflammatory cell infiltration and follicular distension/dilatation of Sprague-Dawley rats were noted with an incidence higher than 1%. When the 2 strains of rats were compared for the same sex, the incidences of both findings in males were significantly higher in Sprague-Dawley rats than Han-Wistar rats. Also, when males versus females were

Table 3. Incidence of Spontaneous Thyroid Gland Proliferative Lesions in Rats and CD-1 Mice

Findings	Han-Wistar rats			Sprague-Dawley rats			CD-1 mice		
	Males (n = 935)	Females (n = 942)	Total (n = 1,877)	Males (n = 328)	Females (n = 334)	Total (n = 662)	Males (n = 1,278)	Females (n = 1,273)	Total (n = 2,551)
Follicular cell									
Follicular cell hyperplasia[a, c]	60 (6.42%)	19 (2.02%)	79 (4.21%)	5 (1.52%)	1 (0.30%)	6 (0.91%)	2 (0.16%)	11 (0.86%)	13 (0.51%)
Follicular cell adenoma[a, c]	55 (5.88%)	26 (2.76%)	81 (4.32%)	7 (2.13%)	2 (0.60%)	9 (1.36%)	5 (0.39%)	2 (0.16%)	7 (0.27%)
Follicular cell carcinoma[a, c]	23 (2.46%)	7 (0.74%)	30 (1.60%)	0	0	0	1 (0.08%)	2 (0.16%)	3 (0.12%)
C-cell									
C-cell hyperplasia[a, b]	449 (48.02%)	454 (48.20%)	903 (48.11%)	110 (33.54%)	132 (39.52%)	242 (36.56%)	3 (0.23%)	2 (0.16%)	5 (0.20%)
C-cell adenoma	100 (10.70%)	104 (11.04%)	204 (10.87%)	37 (11.28%)	26 (7.78%)	63 (9.52%)	0	0	0
C-cell carcinoma	3 (0.32%)	9 (0.96%)	12 (0.64%)	1 (0.30%)	1 (0.30%)	2 (0.30%)	0	0	0
Secondary tumor									
Sarcoma	0	0	0	1 (0.30%)	0	1 (0.15%)	0	0	0
Histiocytic sarcoma	0	0	0	0	1 (0.30%)	1 (0.15%)	0	2 (0.16%)	2 (0.08%)
Lymphoma	4 (0.43%)	3 (0.32%)	7 (0.37%)	1 (0.30%)	0	1 (0.15%)	20 (1.56%)	34 (2.67%)	54 (2.12%)
Leukemia	0	0	0	0	0	0	0	1 (0.08%)	1 (0.04%)

Significantly different ($P<0.01$) incidences of lesions: a = males, Han-Wistar rats vs. Sprague-Dawley rats; b = females, Han-Wistar rats vs. Sprague-Dawley rats; c = Han-Wistar rats, males vs. females.

compared within the same strain, follicular distension/dilatation in Sprague-Dawley rats was more frequent in males than in females. In CD-1 mice, the most common non-proliferative lesions were, in decreasing order and with an incidence higher than 1%, ultimobranchial duct/cyst (5.72%), follicular distension/dilatation (3.84%), cystic follicles (3.53%, Fig. 1), and inflammatory cell infiltration (2.16%). When these lesions in males were compared with those in females, inflammatory cell infiltration was observed to have a significantly higher incidence in females than in males, but follicular distension/dilatation showed a countertrend in terms of sex difference. Other thyroid non-proliferative lesions with an incidence below 1% in both rats and mice were hypertrophy of follicular cells, atrophy, necrosis, mononuclear cell infiltration, lymphocytic thyroiditis, pigmentation of follicular cells, abscess, and arteritis/periarteritis.

The incidences of thyroid proliferative lesions are summarized in Table 3. Across all studies, thyroid neoplastic lesions were more frequently encountered in rats than in mice.

In rats, follicular and C-cell proliferative lesions were highly presented in Han-Wistar rats compared with Sprague-Dawley rats. When the 2 strains of rats were compared for the same sex, the incidences of follicular proliferative lesions (hyperplasia, adenoma, and carcinoma) in male Han-Wistar rats were significantly higher than those in male Sprague-Dawley rats, and when males versus females were compared within Han-Wistar rats, the incidence was higher in males than females (Fig. 2, 3). The incidence of C-cell proliferative lesions (hyperplasia, adenoma, and carcinoma) did not show any significant differences between sexes (Fig. 4, 5). However, the incidence of C-cell hyperplasia in male and female Han-Wistar rats was significantly higher than that of Sprague-Dawley rats when compared within the same sex. In CD-1 mice, both follicular and C-cell proliferative lesions were uncommon, and no C-cell tumors were observed. Lymphoma was the most common secondary tumor in both sexes. Other secondary tumors noted with an incidence below 1% in both rats and mice were sarcoma, histiocytic sarcoma, and leukemia.

The incidences of spontaneous parathyroid gland findings are presented in Table 4.

Non-proliferative lesions of the parathyroid gland were uncommon in both rats and mice. Among the findings of rats, hypertrophy of Sprague-Dawley rats was noted with an incidence higher than 1%. When the 2 strains of rats were compared for the same sex, the incidence of parathyroid gland hypertrophy in female Sprague-Dawley rats was significantly higher than that in female Han-Wistar rats, and when males versus females were compared within Sprague-Dawley rats, the incidence was higher in females than males. Other parathyroid non-proliferative lesions with an incidence below 1% in both rats and mice were inflammatory cell infiltration, interstitial fibrosis, and cysts. Among them, inflammatory cell infiltration and cysts were slightly more frequently observed in mice than in rats.

In rats, parathyroid hyperplasia was noted with a relatively high incidence in both Han-Wistar (4.58%) and Sprague-Dawley (4.02%) rats compared with CD-1 mice (0.57%). In Han-Wistar rats, the incidence of hyperplasia was significantly higher in males than in females. However, in both rats and mice, parathyroid gland tumors were uncommon (Fig. 6), and no malignant tumors were observed in this study. The only secondary tumor noted in the parathyroid gland was lymphoma.

Among the non-proliferative lesions of the thyroid gland, ultimobranchial duct/cyst, follicular distension/dila-

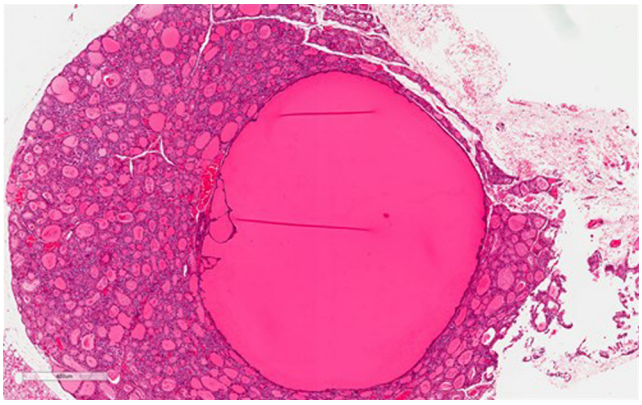

Fig. 1. Cystic follicles are present in the periphery of the thyroid gland. The lesion is many times larger than normal follicles. Han-Wistar rat. H&E. Bar = 400 µm.

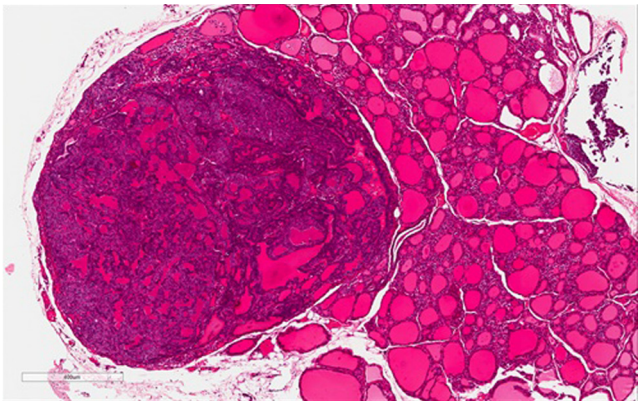

Fig. 2. Well-demarcated follicular cell adenoma is present in the thyroid gland. No penetration of the thyroid gland capsule, local invasion of adjacent tissues and/or vessels, or metastasis is found. Sprague-Dawley rat. H&E. Bar = 400 µm.

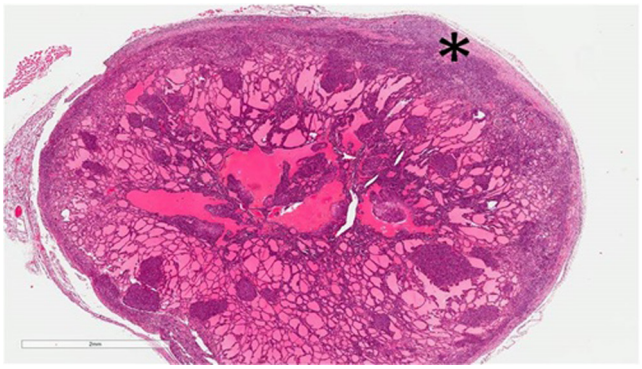

Fig. 3. Follicular cell carcinoma. This tumor shows penetration of the thyroid gland capsule (*). Sprague-Dawley rat. H&E. Bar = 2 mm.

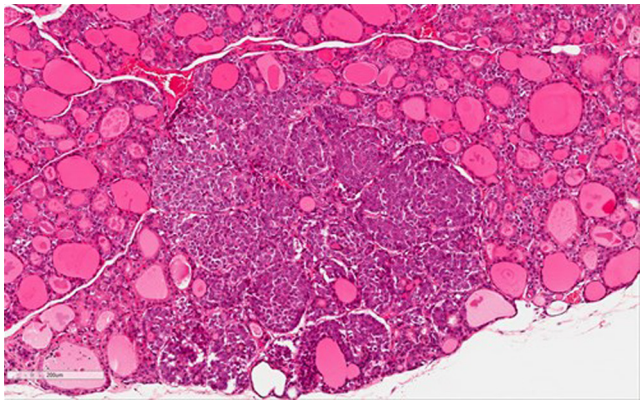

Fig. 4. C-cell adenoma. The lesion is well circumscribed and larger than the area of five average thyroid follicles. Han-Wistar rat. H&E. Bar = 200 µm.

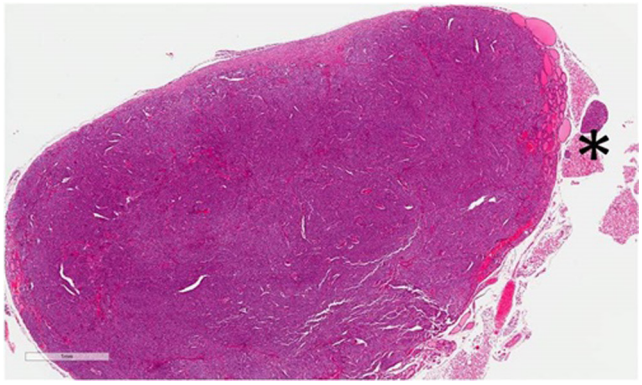

Fig. 5. C-cell carcinoma. Invasion of adjacent tissue (*) is present. Sprague-Dawley rat. H&E. Bar = 1 mm.

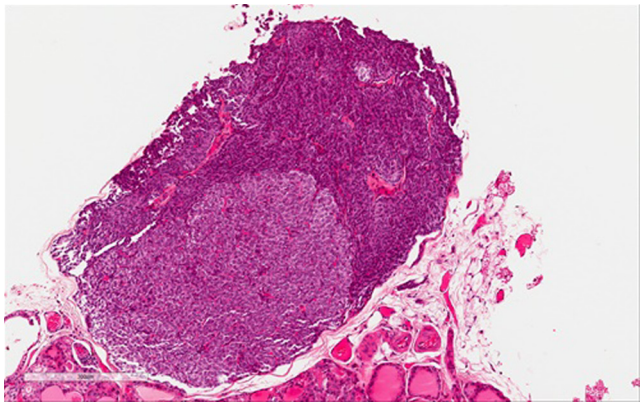

Fig. 6. Parathyroid gland adenoma. A solitary, well-demarcated proliferation of chief cells with compression of adjacent tissues is present in the parathyroid gland. Sprague-Dawley rat. H&E. Bar = 300 µm.

Table 4. Incidence of Spontaneous Parathyroid Gland Non-proliferative and Proliferative Lesions in Rats and CD-1 Mice

Findings	Han-Wistar rats			Sprague-Dawley rats			CD-1 mice		
	Males (n = 885)	Females (n = 884)	Total (n = 1,769)	Males (n = 309)	Females (n = 313)	Total (n = 622)	Males (n = 972)	Females (n = 944)	Total (n = 1,916)
Non-proliferative lesions									
Hypertrophy[a, c]	2 (0.23%)	0	2 (0.11%)	1 (0.32%)	12 (3.83%)	13 (2.09%)	0	0	0
Inflammatory cell infiltration	0	0	0	1 (0.32%)	0	1 (0.16%)	6 (0.62%)	10 (1.06%)	16 (0.84%)
Interstitial fibrosis	0	1 (0.11%)	1 (0.06%)	1 (0.32%)	3 (0.96%)	4 (0.64%)	0	0	0
Cyst	0	1 (0.11%)	1 (0.06%)	0	0	0	4 (0.41%)	2 (0.21%)	6 (0.31%)
Proliferative lesions									
Primary lesion									
Hyperplasia[b]	61 (6.89%)	20 (2.26%)	81 (4.58%)	17 (5.50%)	8 (2.56%)	25 (4.02%)	3 (0.31%)	8 (0.85%)	11 (0.57%)
Adenoma	9 (1.02%)	3 (0.34%)	12 (0.68%)	2 (0.65%)	1 (0.32%)	3 (0.48%)	1 (0.10%)	0	1 (0.05%)
Secondary tumor									
Lymphoma	2 (0.23%)	1 (0.11%)	3 (0.17%)	0	0	0	10 (1.03%)	18 (1.91%)	28 (1.46%)

Significantly different (P<0.01) incidences of lesions: a =females, Han-Wistar rats vs. Sprague-Dawley rats; b = Han-Wistar rats, males vs. females; c = Sprague-Dawley rats, males vs. females.

tation, and cystic follicles were relatively common, especially in CD-1 mice. When these lesions in the 2 strains of rats were compared for the same sex, follicular distension/dilatation was observed with a significantly higher incidence in male Sprague-Dawley rats than in male Han-Wistar rats. When males were compared with females within CD-1 mice, the incidence of this finding in males was higher than in females. On the other hand, there was no difference in the incidence of cystic follicles either between strains for the same sex or between males and females for the same species/strain. Although cystic follicles are defined as follicles many times larger than normal[8], there is no clear threshold between follicular distension/dilatation and cystic follicles. Thus, we must take into consideration that the variance of incidences was likely to be a result of differences in diagnostic thresholds between pathologists. Aside from the findings mentioned above, non-proliferative lesions of the thyroid were seldom encountered. In Wistar Hannover GALAS rats, it has been reported that vacuolar change of thyroid follicular cells sometimes occurs as a spontaneous lesion[10], and this change was termed *thyroid dysplasia* by Weber *et al.*[11] In the present study, however, we did not observe this lesion in any strains of rodents.

As reported by previous studies, spontaneous proliferative lesions of the thyroid are more common in rats than mice, and the incidence increases with age[9, 12, 13]. This is particularly true in the male rat, which has higher circulating levels of TSH than females[1, 2]. The results of this study were in line with the previous literature. Interestingly, follicular cell hyperplasia, adenoma, and carcinoma occurred at significantly higher incidence in male Han-Wistar rats (6.42%, 5.88%, and 2.46%, respectively) than in male Sprague-Dawley rats (1.52%, 2.13%, and 0%, respectively). This difference may be due to the high TSH levels in Han-Wistar rats compared with Sprague-Dawley rats, although supporting data is unavailable. It is known that proliferation of C-cells is common in the rat but quite rare in the mouse[9] and that this occurs with advancing age and in response to long-term hypercalcemia[2]. In this study, the incidences of C-cell hyperplasia, adenoma, and carcinoma were 48.11%, 10.87%, and 0.64% in Han-Wistar rats and 36.56%, 9.52%, and 0.30% in Sprague-Dawley rats. These incidences were evidently higher than in CD-1 mice, in which C-cell hyperplasia was noted with an incidence of only 0.20% and no neoplastic lesions were observed, which coincided with data from the previous report. C-cell hyperplasia was more frequently noted in Han-Wistar rats than in Sprague-Dawley rats when compared within the same sex. This might be related to the difference in the incidence of chronic progressive nephropathy between the strains. Further examinations, including serum calcitonin levels to clarify the pathogenesis of this strain difference, are needed.

Histological findings in the parathyroid glands are infrequently seen, whereas the thyroid gland is commonly affected by pathological changes in preclinical toxicity studies[12, 14]. In this study, non-proliferative findings were rarely found either in rats or mice. Hyperplasia of the parathyroid gland was more common in rats than in mice, and the incidence in Han-Wistar rats was significantly higher in males than in females; a similar tendency was noted in Sprague-Dawley rats as well, although there was no statistically significant difference. These results could be explained as being associated with the high incidence of chronic progressive nephropathy in rats, especially in the male[15, 16]. As reported in the literature, parathyroid neoplastic lesions are very rare in all laboratory animals[12, 13], and this was confirmed in this study as well. Although the incidence of parathyroid hyperplasia was relatively high in rats, adenoma was rarely encountered, and no carcinoma was observed either in rats or mice. It is considered that parathyroid gland hyperplasia does not increase the development of chief cell tumors in rats, as already mentioned in a previous report[2].

To the best of our knowledge, this is the most comprehensive combined study of the incidences of background lesions in thyroid and parathyroid glands in control rats and CD-1 mice. References to the incidences reported here should facilitate the differentiation of spontaneous lesions from induced lesions in toxicological safety studies in these strains of rodents.

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Disclosure of Potential Conflicts of Interest: There are no conflicts of interest to declare.

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