Introduction
Endocrine disruptors have attracted much attention in the last decades. Therefore, in research and regulatory toxicology there has been an increasing interest on the effects of this class of compounds on the neuroendocrine system (Gore 2010). Although most of the studies have focused on the hypothalamic-pituitary-gonadal axis, other systems (hypothalamic-pituitary-thyroid axis, and hypothalamic-pituitary-adrenal axis) are vulnerable as well (Gore 2010). The pituitary gland plays a multitude of complex roles as part of the neuroendocrine system. It is responsible for the production of several hormones (ACTH, LH, FSH, TSH, GH, and PRL) which regulate vital functions such as growth, reproduction, lactation, basal metabolism, stress response, immune response, and the state of hydration (Moï and Moï, 2008). Although naturally occurring and direct or indirect toxic-induced pituitary gland lesions are uncommon in rodents (Gopinath and Mowat, 2014, Chandra et al. 2013) the knowledge and continuing update of their incidence is crucial for a proper interpretation of histological findings in pre-clinical toxicity studies (McInnes and Scudamore, 2014) especially for those targeted on endocrine disruptors. The aim of this study was to provide a database of pituitary gland lesions from 104-week carcinogenicity studies carried out at Charles River Preclinical Service Edinburgh.

Materials and Methods
Animals
Pituitary glands were obtained from rats and mice from 104-week non-clinical toxicity studies evaluated between 1998 and 2010 (Table 1). The strains of rats were Wistar, Han Wistar and Sprague Dawley. Only CD-1 (Crl:CD-I) (ICR) BR mice were used in our facility In that period. The animals were purpose-bred for laboratory use and came from Charles River European suppliers (Charles River UK Ltd., Margate, Kent, UK). All control animals enrolled into the study were obtained from groups of animals that had sham dosed with an appropriate vehicle. All studies were conducted in accordance with the UK 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).

Histological Evaluation
Treatment-related lesions detected at necropsy were prepared in 10% neutral buffered formalin, processed for paraffin waxing, sectioned to a 4-μm thickness, and stained with haematoxylin and eosin. They were examined microscopically, and the findings were entered directly into a computerized database. Each study was subjected to an internal peer review. Data presented here are from untreated control groups only.

Statistical Analysis
Statistical analysis of lesions incidence was performed at 1% significance level (p <0.01) using Fischer’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.

Discussion and Conclusion
In both strains of rats (Han Wistar and Sprague Dawley) included in the current study proliferative lesions were more common than non-proliferative lesions. Non-proliferative lesions were more common in males than in females Han Wistar rats. In contrast, proliferative lesions were more common in females than in males of both strains. Infiltrative lesions were uncommon in both sexes of either Han Wistar or Sprague Dawley rats. A few statistically significant differences in the incidence of non-proliferative and proliferative lesions were noted. Pituitary cysts and cholesterol clefts were more common in males than in females Han Wistar rats. Moreover, adenoma and carcinoma of the anterior lobe had a significantly higher incidence in females than in males (within the same strain), and were higher in Sprague Dawley rats when compared to Han Wistar rats. In CD-1 mice non-proliferative lesions were more common in males than in females. In contrast, as observed in rats, proliferative lesions were more common in females than in males of both strains. Infiltrative lesions were uncommon in both sexes of either Han Wistar or Sprague Dawley rats. However, adenoma and carcinoma of the anterior lobe had a significantly higher incidence in males than in females (within the same strain), and were higher in Sprague Dawley rats when compared to Han Wistar rats. In CD-1 mice non-proliferative lesions were more common in males than in females. In contrast, as observed in rats, proliferative lesions were more common in females than in males of both strains. Infiltrative lesions were uncommon in both sexes of either Han Wistar or Sprague Dawley rats.

A few more histological types of lesions were seen at lower incidences in both rats and mice. To the best of our knowledge this is the most comprehensive combined study of the incidence of background lesions in pituitary gland in control rats and CD-1 mice. Spontaneous proliferative and nonlesional lesions were uncommon in both males and females CD-1 mice. The most common lesion was infiltration by malignant lymphoma, followed by hyperplasia of intermediate lobe, adenoma of anterior lobe, and hyperplasia of anterior lobe.

References