5 Nongenotoxic Mechanisms in Thyroid Carcinogenesis

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5.1 Introduction

Nongenotoxic mechanisms of thyroid carcinogenesis are of general application and also of potential importance to regulatory toxicology. To understand the way in which administration of xenobiotics can lead
to thyroid tumours through a nongenotoxic mechanism it is necessary first to consider the pathophysiology of the thyroid gland.

The thyroid gland normally weighs about 20 mg in a rat of 150 g body weight and is of the order of about 0.01% of the body weight in a number of mammals. It is an unusual endocrine gland as its function is dependent on the dietary supply of a single element, iodine, and its main epithelial component, the follicular cells, are derived embryologically from endoderm. A second, minor epithelial component, the C cells, derive from the neural crest and are responsible for the secretion of calcitonin. Their function is moderated by serum calcium.

Benign thyroid tumours are commonly found in 4%–7% of the human population, but cancer of the thyroid is relatively rare – about 1% of total cancer cases in the USA (Hill et al. 1989). Spontaneous tumours of the follicular cells are rare in rodents; the majority of spontaneous thyroid tumours in aged rats are of C cell origin (Thomas and Williams 1994). However, proliferative thyroid lesions of the follicular cell, including carcinomas, are a relatively common finding in toxicological studies on animals. It is therefore important that the relevance of these animal lesions in terms of human risk assessment is evaluated carefully.

### 5.2 Structure

The thyroid is a bilobed organ and histologically each lobe is composed of multiple lobules which are composed of numerous spherical follicles. Each follicle is a closed sac lined by epithelial cells. In the unstimulated gland, the follicular epithelial cells are cuboidal in shape and form a single layer, linked at their apical surfaces by tight junctions. The follicular lumen containing the thyroid-specific protein thyroglobulin acts as a reservoir for thyroid hormones. The follicles are supported by a stromal network which is largely composed of fibroblasts and capillaries.

Structure is linked to function, and under the influence of the trophic hormone thyroid stimulating hormone (TSH), the flattened or cuboidal epithelial cells are modified to become columnar. The increase in pinocytosis by the follicular cells stimulated by TSH leads to a depletion of central colloid and the stimulated gland shows small colloid spaces lined by follicular cells containing many colloid droplets.