Inhibition of the thyroid hormone pathway in Xenopus by mercaptobenzothiazole.

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Amphibian metamorphosis is a thyroid hormone-dependent process that provides a potential model system to assess chemicals for their ability to disrupt the hypothalamic-pituitary-thyroid (HPT) axis. Several studies have demonstrated the sensitivity of this system to a variety of known thyroid disrupting chemicals and a standardized 21-day protocol has been developed which is being used by the US EPA in their Endocrine Disrupter Screening Program. More recently, additional studies have shown that this system responds quickly to thyroid hormone (TH) synthesis inhibitors when molecular and biochemical endpoints are considered. This study evaluated the effects of mercaptobenzothiazole (MBT) at nominal aqueous concentrations ranging from 31 to 500 ppb on HPT function using both 7 and 21 day protocols. The shorter protocol evaluated thyroid histology, circulating TH, thyroidal concentrations of TH and its synthetic precursors, thyroidal sodium-iodide symporter (NIS) gene expression, and circulating thyroid stimulating hormone (TSH). The longer protocol evaluated development and thyroid histology. The results of these two *in vivo* studies were internally consistent and demonstrate that MBT is a potent inhibitor of thyroid hormone synthesis, confirming previous *in vitro* studies that indicated that MBT inhibits TH synthesis and release in this species. In the 7 d study, MBT inhibited synthesis of T4 which resulted in reduced circulating T4 concentrations, increased circulating TSH concentrations, up-regulated NIS gene expression in thyroid tissue, and histological responses typical of HPT compensatory activity, such as follicular cell hypertrophy and hyperplasia, and diffuse glandular hypertrophy. In the 21 d study, MBT retarded metamorphic development and resulted in the same histological observations seen in the 7 d study. Sensitivities of the two protocols were similar when comparing comparable endpoints. Thyroid histology was affected in both studies at the lowest test concentrations (31 ppb), whereas development was retarded at 250 ppb. Within the endpoints evaluated in the 7 d protocol, thyroidal TH reductions, NIS gene upregulation, and compensatory changes in thyroid histology were all observed at the lowest test concentration, suggesting that these endpoints are the most sensitive measures of HPT disruption in this model.

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