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A quantitative adverse outcome pathway model for thyroid axis disruption in Xenopus laevis tadpoles

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The development of *Xenopus laevis* tadpoles is tightly controlled by the thyroid hormones tetraiodothyronine (T4) and triiodothyronine (T3). Toxicity testing efforts have shown that several compounds interfere with development in *X. laevis* tadpoles by disrupting the thyroid axis at one or more control points. The goal of this study was to develop a quantitative description of the thyroid axis in prometamorphic (NF stage 54-56) *X. laevis* tadpoles that could be used to simulate the normal sequence of developmental events, as well as observed effects of chemicals interacting with specific cellular targets. Attributes of this model include feedback inhibition of T4 on TSH secretion by the pituitary/hypothalmus, and TSH-stimulated release of T3 and T4 from the thyroid gland. TSH impacts on the thyroid gland are mediated by coordinated upregulation of iodide uptake, thyroglobulin synthesis, organification of iodide by thyroperoxidase (TPO), and thyroglubulin proteolysis. Sustained high levels of TSH also stimulate an increase in gland size. This relatively simple feedback structure confers a high level of stability to model predictions of circulating T3 and T4. Model parameters were derived from detailed observations on test animals (e.g., thyroid follicle cell number per organism), changes in mRNA expression for selected proteins (e.g., thyroid stimulating hormone), studies of *X. laevis* thyroid gland explants, and by fitting simulations to measured levels of T3 and T4 in thyroid glands and plasma. The model accounts for potential chemical impacts on several key processes including competitive inhibition of the sodium-iodide symporter (NIS; as by perchlorate), competitive and non-competitive inhibition of TPO (as by methimazole and 6-propylthiouracil, respectively), displacement of T4 from binding proteins in plasma, and changes in hepatic clearance of T3 and T4. The contents of this abstract do not necessarily constitute or reflect USEPA policy.

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