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# **Diminished Serum T4 Concentrations Induced by PTU or Brominated Flame Retardants (DE-71) are Necessary But Not Sufficient for a Congenital Malformation of the Brain**

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## **Introduction**

A number of environmental chemicals are capable of interfering with the bioavailability and the action of thyroid hormones (TH), which are essential for healthy brain development. In humans, even mild thyroxine (T4) insufficiency during pregnancy has been linked to lower child IQ, impaired language and motor development and increased risk of neurobehavioral disorders such as autism and schizophrenia. Our understanding of the consequences of TH insufficiency on the developing brain has been shaped by studies with the therapeutic antithyroid drug propylthiouracil (PTU). PTU administered to pregnant and lactating rats induces a wide range of brain malformations in their offspring attributed to low T4 during brain development. Here, we compare the effects of PTU and DE-71 (a commercial mixture of brominated diphenyl ethers) on TH and brain development.

## **Methods**

PTU (0, 1 or 2.5 mg/kg/day) or DE-71 (20 or 40 mg/kg/day) was administered (p.o.) to Sprague-Dawley rat dams from gestation day (GD) 7 through to postnatal day (PD) 22. TH and TSH was measured in dams on GD 15, and male offspring were assessed for TH, TSH, heterotopia formation and cortical gene expression on PD 16.

## **Results/Discussion**

Here, we show that offspring of PTU-exposed dams have congenital malformations of the brain in the form of periventricular heterotopia. They are irreversibly formed clusters of ectopic neurons in the corpus callosum, which are associated with low fetal and perinatal T4 levels. DE-71 induced serum T4 suppressions of a similar magnitude (~75% reduction), yet failed to produce heterotopia in offspring. Unlike PTU, exposure to DE-71 also did not affect expression of TH-regulated genes in the cortex.

## **Conclusions**

Our results show that different mechanisms of perturbing the TH system causing same degree of T4 suppression can result in different outcomes on T3 and the hypothalamic-pituitary-thyroid axis as well as on bioindicators of TH-action in cortex and on an adverse outcome in the brain.

It appears that serum T4 suppression may be necessary, but not sufficient for the induction of heterotopia. Understanding of the sufficient conditions will be essential for protection of the unborn and developing child against thyroid hormone disrupting chemicals.

Topic area: endocrine disruptors, thyroid and brain, development