Developmental Thyroid Hormone (TH) Disruption: In Search of Sensitive Bioindicators of Altered TH-Dependent Signaling in Brain. C Wood[1], A Johnstone[1], ME Gilbert[1]. [1]Toxicity Assessment Division, US EPA, RTP, NC

Thyroid hormones (TH) are essential for brain development, yet clear indicators of disruption at low levels of TH insufficiency have yet to be identified. Brain TH is difficult to measure, but TH-responsive genes can serve as sensitive indicators of TH action in brain. A large number of TH-responsive genes have been identified, yet very limited data are available under conditions of moderate TH insufficiency characteristic of environmental TH disruptors. The present study identified TH-responsive genes in neonatal rat cortex in a low dose model of TH insufficiency based on propylthiouracil (PTU, 0 1 2 3 10 ppm in drinking water to dams GD6-PN21). A suite of genes were examined including genes previously shown to be responsive to TH deprivation or activated by T3 in vivo or in vitro, and genes implicated in brain development. PTU dose-dependently reduced serum T4 in dams and pups on postnatal day (PN) 4 to a maximum of ~30% of control, with more severe reductions seen in neonates on PN14 (T4 <10% of control at the highest dose). Expression of several genes was dose-dependently down-regulated by PTU (*Mog, Parv, Hr, Bteb, NGF, Arc*) while others critically involved in brain development or previously identified with severe hypothyroidism or T3 administration were not altered (*BDNF, Reelin, CamkIV, Sox2, Pax6, Nurr1*). Gene targets altered at the lowest dose of PTU (T4 of 85, 63, 54% of control in dams at weaning, PN4, PN14 pups) included *Col11a2, Itih3,Gjb6, Agt, Erg1* and *Parv*. A number of genes in 'compensatory pathways' (*Mct8, Oatpc, Dio2*) remained unchanged. These data indicate that many genes previously implicated as "TH-responsive" may not be involved in brain dysfunction associated with moderate TH insufficiencies. They further suggest that compensatory 'protective' mechanisms may either be insufficiently activated or immature in the neonatal brain. The most sensitive gene targets identified here will be used to evaluate the fidelity of serum TH induced by environmental contaminants to predict disruption of TH action in brain. *(Does not reflect EPA policy).*