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Thomas Sanderson

University of Quebec, Canada

The endocrine disrupting potential of neonicotinoid pesticides in humans, using physiologically and toxicologically relevant *in vitro* models of steroidogenesis

In humans, sex steroid hormones are essential for healthy reproduction and pregnancy, but are also involved in diseases such as hormone-dependent breast cancer. Steroidogenic enzymes are increasingly considered to be important targets for endocrine disrupting chemicals. However, little is known about effects of emerging pesticides such as neonicotinoid insecticides on the biosynthesis of androgens and estrogens. Aromatase (CYP19), which converts androgens to estrogens, is of particular interest as, unlike in rodents and lower vertebrates, in which aromatase expression is restricted to gonads and brain, human aromatase is expressed in numerous tissues including mammary gland (where it is overexpressed in hormone-dependent breast cancer) and placenta using alternate promoters. As rodent models are inadequate, we developed several human in vitro models with improved physiological relevance to study the effects of endocrine disrupting chemicals. Cellular co-culture models of the feto-placental unit and the human breast tumor microenvironment were used to determine the effects of imidacloprid, thiacloprid and thiamethoxam on steroid biosynthesis and the promoter-specific regulation of the aromatase gene. We found that these neonicotinoids increased CYP19 gene expression in a promoter-specific manner in our human co-culture models and that this concentration-dependent response was non-monotonic with a decline in gene induction and catalytic activity at higher concentrations. In the feto-placental co-culture model, the neonicotinoids increased estradiol and estrone, but strongly inhibited estriol production. In our breast cancer model, the neonicotinoids induced a promoter-switch in CYP19 expression, with silencing of the normal mammary promoter 1.4 and activation of pro-cancerous promoters PII, 1.3 and 1.7, resulting in aromatase overexpression. These are the first studies to document in vitro, potential adverse effects of neonicotinoids on human steroidogenic processes

Biography

Thomas Sanderson obtained his B.Sc. (Faculty of Chemistry and Pharmacochemistry, 1989) from the Free University of Amsterdam, The Netherlands, followed by a Ph.D. (Faculty of Pharmaceutical Sciences, 1994) from the University of British Columbia in Vancouver, Canada. After a postdoctoral research position at Michigan State University (National Food Safety and Toxicology Center, 1994-1997), he held an Assistant Professorship at Utrecht University, The Netherlands (Institute for Risk Assessment Sciences, 1997-2005) where he was tenured since 2003. Since 2005, Thomas Sanderson holds a position of Associate Professor at the INRS-Institute Armand-Frappier

thomas.sanderson@iaf.inrs.ca

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