

Concern that it would be extremely difficult for EPA model TCDD actions

I. AhR and Nuclear Receptor Interactions

Modeling the actions of TCDD would be difficult because of the many mechanisms through which liganded AhR acts. The arylhydrocarbon receptor (AhR) mediates most, if not all TCDD effects and the AhR is a nuclear transcription factor. Thus, the simplest model is that ligand binding promotes AhR binding to AhREs (XREs, DREs) and activates gene transcription. Unfortunately, this mechanism ignores the toxicological effects of TCDD-dependent AhR cross-talk with other nuclear transcription factors (reviewed in E. Swedenborg and I. Pongratz; *Toxicology* 268 (2010):132-138).

A) Most notably, TCDD interferes with estrogen receptor (ER) pathways in a number of ways listed below and reviewed previously (Swedenborg and Pongratz, 2010 and Safe et al, 2000; *J. Mammary Gland Biol Neoplasia* 5:295-306):

- 1) TCDD acts through AhR to downregulate levels of ER α : Romkes, M. and Safe, S. (1988) *Toxicol Appl Pharmacol* 87:306-314; Devito, M.J., et al (1992) *Toxicol. Appl. Pharmacol.* 113:284-292; Wang, X. et al (1993) *Mol Cell Endocrinol* 96:159-166; Wormke, et al (2000) *FEBS Letters* 478:109-112.

Recent work suggests that TCDD decreases ER α levels by activating proteosomal degradation (Safe et al, 2001; *Pharmacol Toxicol* 69:400-409). 2

- 2) TCDD acts through AhR to inhibits ER α induction of ER β (Kietz, S. et al, 2004, *Biochem Biophys Res Comm* 76-82)
- 3) TCDD increases estradiol metabolism by inducing CYP1A1 and CYP 1B1: Hayes, C.L. (1996) *PNAS*: 93: 9776-9781; Spink, D.C. et al *Arch Biochem Biophys* 293:342-348.
- 4) Activated AhR competes for cofactors important for ER transactivation of gene expression (see Matthews and Gustafsson, 2006: *Nucl. Recept Signal* 4:e016.
- 5) AhR interferes with ER transactivation of gene expression estrogen response elements (EREs): Safe and Wormke, 2003. *Chem Res Toxicol* 16:807-816

B) TCDD also affects androgen signaling.

- 1) TCDD-liganded AhR acts as an E3 ubiquitin ligase to promote proteolysis of ER α and androgen receptor. (Ohtake, Fujii-Kuriyama and Kato, *Biochem. Pharmacol.* 77(4):474-484.

C) TCDD indirectly affects thyroid hormone receptor (TR) activity.

- 1) AhR-induction of CYP1A1 metabolizes PCB congeners to compounds that act as thyroid hormone receptor agonists (Gauger, et al., *EHP* 115(11):1623-1630.

II. Neural effects of TCDD

A) TCDD effects in the brain, particularly the developing brain, have not been as extensively studied as in breast cancer cell or liver cells because the receptors were not mapped in the brain until ten years ago (Petersen et al., 2000; *JCN* 427(3):428-439). Since then, TCDD actions have been identified in the nervous system:

Additional Preliminary Comments From Dr. Petersen

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1) Both ER and AhR are found in GABAergic neurons throughout the brain (Hays, Carpenter and Petersen, 2002; EHP 110:369-376). It is likely that TCDD activation of the AhR interferes with sexual differentiation of the brain by interfering with ER activity. (Petersen, Krishnan and Hudgens, Endocrinology (2006) 147:s33-s42).

2) TCDD exposure interferes with sexual differentiation of the neural substrate controlling non-reproductive behaviors (Weiss, B. EHP (2002) 3:387-391)

3) TCDD alters sex-specific spatial and visual reversal learning in rats (Widholm, JJ et al Neurotoxicol Teratol (2003) 25:459-471)

Thus, it seems likely that TCDD activation of AhR in the nervous system interferes with ER and/or androgen receptor actions in the central nervous system as it does in other tissues.

III. Summary

A number of studies show that TCDD activation of AhR results in cross-talk with ER and other nuclear transcription factors. Nuclear receptors and AhR are found in a number of tissues, including brain. Therefore, if modeling of TCDD action is to be meaningful for risk assessment, it would have to include all of these “endocrine disrupting” effects.