INVESTIGATION OF THE EFFECTS OF POLYBROMINATED DIPHENYL ETHERS AND THEIR DERIVATIVES ON STEROIDOGENESIS IN THE H295R CELL LINE

HE YU HE

何宇鶴

MASTER OF PHILOSOPHY

CITY UNIVERSITY OF HONG KONG

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CITY UNIVERSITY OF HONG KONG

香港城市大學

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多溴聯苯醚及其衍生物在 H295R 細胞系中對類固醇生成影響的研究

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He Yuhe

何宇鶴

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ABSTRACT

Polybrominated diphenyl ethers (PBDEs) and tetrabromobisphenol A (TBBPA) are produced in large quantities for use as brominated flame retardants (BFRs) that are commonly used in construction materials, textiles, and as polymers in electronic equipment. Environmental and human levels of PBDEs have been increasing in the past 30 years. Hydroxylated (OH-) and methoxylated (MeO-) PBDEs have also been reported in the adipose tissue, blood and milk of wild animals and humans.

The toxicity of PBDEs is not fully understood. Studies on their effects are relatively limited, and show that PBDEs are neurotoxins and potential endocrine disruptors. Exposures to specific congeners affect brain development, behavior and learning ability in rats, and PBDEs and their metabolites were also found to be able to disrupt thyroid hormone function. However, conclusive data are currently lacking, and thus further studies are needed to more fully understand the toxicities of these compounds.

In the first study, 15 PBDEs metabolites, two BDE mixtures (DE71 and DE79), and TBBPA were studied individually to determine their effects on ten steroidogenic genes and aromatase activity in the H295R human adrenocortical carcinoma cell line. Exposure to 0.05 μM 2'-OH-BDE-68 significantly induced the expression of CYP11A, CYP11B2, CYP17, CYP21, 3βHSD2, 17βHSD1, and

17βHSD4, and the expression of StAR was induced by 6-OH-BDE-90 at three concentrations. Exposure to DE71 and DE79 caused a trend towards induction with increasing dosed concentrations. Moreover, exposure to 0.5 μM 2-OH-BDE-123 and 2-MeO-BDE-123 also resulted in significantly higher aromatase activity. Generally, OH-BDEs had a much stronger ability to affect steroidogenic gene expression than MeO-BDEs, and most chemicals tested in this study did not significantly affect aromatase activity.

In the second study, 20 OH-, MeO- and/or chlorinated PBDE derivatives were studied at both the gene and enzyme levels at higher exposure concentrations. Moreover, sex steroid (testosterone (T) and 17β-estradiol (E2)) concentrations in the culture medium were also measured. CYP11B2 was the most sensitive gene and was induced by most of the compounds tested in this study. Several PBDE metabolites showed some potential ability to interfere with steroidogenesis, including 5-Cl-6-OH-BDE-47, a biologically relevant BDE-47 metabolite, which significantly decreased aromatase activity and E2 production at a concentration of 10 μM. The results of this study indicate that PBDE metabolites affect steroidogenesis *in vitro* and that they may have the potential to affect steroidogenesis and reproduction in whole organisms.

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Ah-R	Aryl hydrocarbon receptor
BFR	Brominated flame retardant
BSEF	Bromine Science Environmental Forum
DDT	Dichlorodiphenyl trichloroethane
DMSO	Dimethyl sulfoxide
E2	17β-estradiol
EDTA	Ethylenedinitrilotetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EROD	Ethoxyresorufin-*O*-deethylase
MAPKs	Mitogen activated protein kinases
MeO-	Methoxylated
OH-	Hydroxylated
PBDE	Polybrominated diphenyl ether
PBS	Phosphate buffered saline
PCB	Polychlorinated biphenyl
PKC	Protein kinase C
Q-RT-PCR	Quantitative real-time PCR
SRB	Sulforhodamine B
T	Testosterone
T2	3,5-diiodothyronine
T3	3,3,5-triiodothyronine
T4	3,3,5,5-tetraiodothyronine
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-Dioxin
TTR	Transthyretin
TBBPA	Tetrabromobisphenol A
UDPGT	Uridine diphosphate-glucuronosyl transferase
WHO/ICPS	World health organization / International programme on chemical safety