Introduction

• Polychlorinated biphenyls (PCBs) are legacy pollutants that were used until the 1970s, but banned by the Stockholm Convention on Persistent Organic Pollutants and they are a group of known toxic substances that have environmental ramifications (Wu, Kammerer, & Lehmler, 2014).
• Cytochrome P450 enzymes are involved in the metabolism of PCBs in the human body and convert PCBs into hydroxylated metabolites, either directly or via a PCB epoxide (Grimm et al., 2015).
• Human microsomal epoxide hydrolase (mEH) has been shown to metabolize many polyaromatic hydrocarbons into carcinogenic and toxic products (Hosagrahara, Rette, Hassett, & Omiecinski, 2004).
• PCBs have been associated with a variety of health problems including neurological disorders, such as stunted brain development, and various forms of cancer (Lin & Lu, 1998).
• Two major sources of PCB intake in humans include air and diet contaminated with PCBs (Grimm et al., 2015).

Objectives

• To determine the effect of inhibition of mEH on the metabolic profile of PCBs following metabolism by human liver microsomes in vitro.

Hypothesis

• As concentration of cyclohexene oxide (mEH inhibitor) increases, the formation of the hydroxylated metabolites will increase while the production of PCB dihydrodiol will decrease.

Methods

Step 1: Incubation
Human Liver Microsomes, NADPH, phosphate buffer, PCB (20 µM) and cyclohexene oxide (CHO) in DMEM (total volume 250µl) for 30 minutes at 37°C.

Step 2: Extraction
Headspace-ATR C S W/G.

Step 3: Derivationization
Gaseous phase, oven.

Step 4: Clean up
Sulfuric acid and tert-butylmethylsulfinyl solution.

Step 5: Analysis
GC-ECID-DR5: screening colum.

Results - Effect of different concentrations of cyclohexene oxide on the formation of hydroxylated metabolites of PCB 95

Conclusions

• Levels of 4’-95, 4-95 and 3-103 increase initially as the CHO concentration increases.
• Production of metabolites decreases at higher levels of CHO concentrations, potentially due to inhibition of the P450 cytochrome enzymes.
• 5-95 decreases in production as the concentration of CHO increases.
• 4,5-95 is a secondary metabolite as the concentration stays relatively constant over time.
• 3-140 showed a trend of increasing in concentration until 500 µM.
• 5-132 and 4-132 metabolites decrease in concentration which may be due to inhibition of cytochrome P450 enzymes.
• The overall effect of CHO on metabolism of PCBs is still unclear due to the differences between PCB 95 and PCB 132.

Implications and Future Directions

• Inhibition of mEH has different effects on the metabolic profile of different PCB congeners.
• Further investigation on different PCB congeners is needed for more conclusive effect of mEH inhibition on PCB metabolism.

Selected References


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