Toll-like Receptors in the Mechanism of Hexabromocyclododecane-induced Production of Pro-inflammatory Cytokines, IL-1β, IL-6, and TNF-α

Hexabromocyclododecane (HBCD) is used extensively as brominated flame-retardant in a variety of materials and is resistant to natural decomposition. HBCD has been identified as a persistent bioaccumulating toxin and is found in many tissues including human blood. Previous research has demonstrated that exposure to HBCD increases the generation of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α by peripheral blood mononuclear cells (PBMCs). Inappropriate increases in these cytokines by HBCD has the potential to lead to chronic inflammation, which is associated with an increasing number of diseases including cancer. The mitogen-activated protein kinase (MAPK) pathway appears to be involved in the increased pro-inflammatory cytokines generation seen with HBCD. Toll-like receptors (TLRs) trigger immune cells to produce pro-inflammatory cytokines, resulting in MAPK activation and modulation of other intracellular components regulating cytokine production. This research explores the potential involvement of TLR4 in HBCD stimulation of pro-inflammatory cytokine production (combination of changes in intracellular and secreted levels). PBMCs were treated for 1-hour with a selective TLR4 inhibitor (TAK242) before a 24-hour exposure to HBCD at concentrations ranging from 1 to 5 μM. Intracellular levels were measured using western blot and secreted level using ELISA. Results from the study reveal that targeted inhibition of TLRs 4 diminishes the HBCD's capacity to induce IL-1β, IL-6, and TNF-α production. These findings represent a significant advancement in comprehending HBCD-induced stimulation of IL-1β, IL-6, and TNF-α, with potential implications for chronic inflammation and associated pathologies.