Tributyltin and Dibutyltin Stimulation of Tumor Necrosis Factor α Expression in Human Immune Cells: Role of Toll-like Receptor 4

Tributyltin (TBT) and dibutyltin (DBT) have been found in human blood at concentrations as high as 260 nM and 0.3 μM, respectively. TBT is used as a biocide in various applications and DBT is used in plastic production including polyvinyl chloride (PVC). They enter the human body due to contamination of food and beverages. Both have been shown to stimulate the production/expression of the proinflammatory cytokines, interleukin (IL)-1 beta (β) and IL-6 from human immune cells. Tumor necrosis factor-alpha (TNF-α) is another proinflammatory cytokine that, like IL-1β and IL-6, regulates immune responsiveness. TBT and DBT, at certain exposures, stimulate secretion of TNFα from human immune cells. Toll-like receptors (TLR) regulate production/expression of proinflammatory cytokines such as TNF-α and have been shown to have a role in elevating IL-1β and IL-6 in response to TBT. Elevation of proinflammatory cytokines such as TNFα in the absence of appropriate stimuli (infection or injury) causes chronic inflammation, which is associated with numerous pathologies including cancer. Based on previous studies showing TBT- and DBT-induced production of IL-1β and IL-6 and secretion of TNFα, we hypothesize that they will increase TNFα production/expression (secreted combined with intracellular levels). In this study, we examined whether TBT and DBT increase TNFα production/expression and whether TLR4 is involved. Human peripheral blood mononuclear cells (PBMC) were treated for 1 h with the TLR4 inhibitor (TAK242) or appropriate control, prior to exposure to TBT and DBT. Secreted TNF-α was measured by ELISA and intracellular TNF-α was determined by Western blot. Results indicate that both TBT and DBT induce production/expression of TNFα and that TLR4 is needed for TBT, but not DBT, to cause this increase. Increased production of TNFα stimulated by TBT and DBT has the potential to cause chronic inflammation with its attendant effects on cancer progression.