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Dibutyltin Stimulation of Tumor Necrosis Factor α in Human Immune Cells: Role of Toll-Like Receptor 4.

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The environmental contaminant dibutyltin (DBT) has been found in human blood at concentrations as high as 0.3 μM. DBT is used in the stabilization of plastics including polyvinyl chloride (PVC) and as a de-wormer in poultry. DBT can be found in the body due to the consumption of water and other beverages that are stored in plastic piping/containers and has been shown to stimulate the production of the proinflammatory cytokines, interleukin (IL)-1 beta (β) and IL-6 from human immune cells. Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that, like IL-1β and IL-6, regulates immune responsiveness. Toll-like receptors (TLR) are responsible for initiating the production of proinflammatory cytokines such as TNF-α and have been shown to have a role in elevating other pro-inflammatory cytokines (IL-1β and IL-6) in response to another organotin contaminant, tributyltin (TBT). Elevation of proinflammatory cytokines such as TNFα in the absence of appropriate stimuli (infection or injury) can cause chronic inflammation. There is a known link between the abnormal elevation of inflammatory cytokines and cancer. Previous work has shown that DBT, at certain exposures, increases the secretion of TNFα from human immune cells. Based on previous studies showing DBT-induced production of IL-1β and IL-6 and DBT-induced secretion of TNFα, we hypothesize that DBT will increase TNFα production (secreted plus intracellular levels). In this study, we examined whether DBT increases TNFα production and whether TLR4 is involved in DBT's ability to do so. Human peripheral blood mononuclear cells (PBMC) were treated for 1 h with a selective TLR4 inhibitor (TAK242) or appropriate control, prior to exposure to 0.5, 0.25, and 0.1 μM DBT. Secreted TNF-α was measured by ELISA and intracellular TNF-α was determined by Western blot. Results indicate that DBT-induces increased production of TNFα but that TLR4 is not appreciably responsible for this elevation. Increased production of TNFα stimulated by DBT has the potential to cause chronic inflammation with its attendant effects on cancer progression.