Agent Orange/Dioxin &
Other Toxic Substances Committee
(AO/DOTS)
1/15/2010

Draft proposed AO/DOTS Committee position paper: Alzheimer's disease: (discuss and action)

Alzheimer's disease (AD) is a progressive and fatal brain disease affecting over five million Americans. It is reported to be the 7th leading cause of death in the U.S. Alzheimer's disease is the loss of brain cells that result in the loss of memory and causes problems in thinking and behavior. Plaque and tangles of protein in the brain cells are found in the brains of people who have died of AD. The tangles are twisted fibers of a protein called tau.

Background:

AD is not a condition that the Veterans Agent Orange (VAO) Review Committee has looked at individually. The latest 2008 VAO review points out:

"Examples of diseases that result from degeneration of specific brain areas include Parkinson's disease (PD), Alzheimer's disease (AD), spinocerebellar degeneration, or amyotrophic lateral sclerosis (ALS). All of these diseases occur in the absence of any toxicant exposure; however, all may be triggered by different aspects of the environment, including toxicant exposures."

Other than the a few mentions of AD in the review, there was no evaluation of existing studies on Alzheimer's disease by the Review Committee.

Alzheimer's disease is characterized by abnormal hyperphosphorylation of the tau protein is well know in AD research.

New information:

Given the connection between AD and the aggregation of tau protein and a growing body of information implicating oxidative stress in the etiology of neurological conditions, a recent study has put AD on the AO/DOTS committee's radar screen. In the study (abstract below), "*2,3,7,8-TCDD neurotoxicity in neuroblastoma cells is caused by increased oxidative stress, intracellular calcium levels, and tau phosphorylation*", Donggun Sul, 2008, TCDD dioxin exposure to the neuroblastoma cells created DNA damage, hyperphosphorylation of the tau and oxidative stress.

"One of the most notorious environmental toxicants, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), easily accumulates in the environment and most organisms, including humans, because of its high lipophilicity and resistance to degradation. TCDD exposure causes a

variety of adverse health effects in humans including immunotoxicity, hepatotoxicity, neurotoxicity, and carcinogenesis. For the most part, studies regarding the adverse effects of TCDD on the central nervous system (CNS) have been limited to neurodevelopmental processes. In this study, we investigated the neurotoxicity of TCDD in neuronal cells using a neuroblastoma cell line (clone N2a) and explored the possible mechanisms of action. MTT and Comet assays were conducted to determine if TCDD is cytotoxic and if it causes DNA damage, respectively. The results of these assays revealed that treatment with 100, 300, 500 and 1000nM TCDD decreased the viability of N2a cells and increased DNA damage in a dose-dependent manner compared to controls. Additionally, a malondialdehyde (MDA) assay was performed to determine if TCDD induces lipid peroxidation. The results of this assay revealed that 100, 300 and 500 nM TCDD induced lipid peroxidation in a dose-dependent manner. Finally, TCDD neurotoxicity (300 nM or higher) in N2a cells was accompanied by elevated intracellular calcium levels. These increased calcium levels increased the phosphorylation of tau via up-regulation of phospho-glycogen synthase kinase-3_ (GSK-3_). Taken together, these results indicate that TCDD exposure induces neurotoxicity in N2a cells by increasing DNA damage, oxidative stress and intracellular calcium levels. The TCDD-mediated increase of tau phosphorylation in particular indicates an important role for tau hyperphosphorylation in TCDD-induced neurotoxicity."

AO/DOTS Committee's Position:

Both oxidative stress (lipid peroxidation) and tau hyperphosphorylation have been implicated in the etiology of AD. Since a new study now implicates the dioxin in Agent Orange in both lipid peroxidation and the tau phosphorylation, it is the position of this committee:

- That VVA ask the IOM and the Veterans Agent Orange Review Committee to break out Alzheimer disease (AD) in its upcoming 2010 review and its search for scientific information related to the health effects of the herbicides in Vietnam Veterans.
- That the AO/DOTS Committee mine data and existing research on the association between Vietnam War service and Alzheimer's disease.

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