Executive Summary

Vietnam Service, Chemical Exposure and Parkinson’s disease (PD)
Executive Summary: Vietnam Veterans, Chemical Exposures, Parkinson’s Disease

Veterans from all wars served their country in extreme conditions and with unique challenges. The Vietnam Veterans' war experience included a quagmire of chemical exposures with dioxins and herbicides like Agent Orange at the top of the list.

The interactions and synergic effects of these herbicides between themselves and in conjunction with other chemical exposures created a complex hazardous environment for these Veterans. These exposures were further complicated by physical and mental stressors, important factors in the body’s ability to handle chemical exposures. These stress factors were discovered in the Gulf War studies. (Exhibit 28)

These chemical exposures are linked to numerous health issues and diseases. Some of these diseases occur shortly after exposure, like skin diseases, but other diseases, like cancers, may have long latency periods and may occur in Veterans many years after the exposures. Many degenerative neurological diseases including PD fall into the later category.

One troubling fact that must be considered in reviewing the issue of diseases with exposures to “Agent Orange” is; there have been no studies undertaken to look at the possible impacts of the dioxin TCDD and the two herbicides in Agent Orange in combination with each other. When this question was presented in a meeting on February 17, 2009 with the VA, Dr. Brown explained that the VA looks at mortality data. Forty (40) years after the fact and not one study to determine the combined effects of the three chemicals in Agent Orange. This is an extenuating factor to consider in the issue of diseases associated with chemical exposures in Vietnam. The lack of appropriate actions should be considered in making a presumptive decision.

The primary method the Department of Veterans’ Affairs employs to look at health issues in Vietnam Veterans is the mortality studies. PD normally appears later in life and is considered to be an old age related disease. This coupled with the relative young age of Vietnam Veteran and the fact that Parkinson’s is a progressive disease that in many cases worsens over decades makes it unlikely that it would show up in a mortality study.

Dr. Kang, VA’s own expert on mortality in Veterans agrees that PD may not show up in a mortality study.

Dr. Brown, VA’s own Agent Orange expert expressed in an email dated February 19, 2009:

- “The fact is, nobody is doing a long-term morbidity study of Vietnam veterans, that would be checking for health effects not necessarily leading to increased mortality rates, which would include PD. I have always thought that such a study would be a good idea, as a way to evaluate the actual health problems experienced by Vietnam veterans. Right now, nobody really knows too much about this, due to a lack of such a longitudinal epidemiologic study!”

Over the past two years many studies have come to light connecting Vietnam War time service and the presumptive herbicides to PD.
The National Institute of Medicine (IOM) finding of positive association between Agent Orange and Parkinson’s.

- IOM found in its 2008 Veterans Agent Orange review (released 24 July 2009) (Exhibit 111) that:
  - “With respect to PD, previous VAO reports have concluded that there was inadequate or insufficient evidence of an association between exposure to the compounds of interest and PD. In this report, we review both new data published after Update 2006 and older studies investigating the relationship between herbicide exposure and PD risk. Although a compelling biologic mechanism has not been identified, the bulk of evidence suggests a risk of herbicide exposure in general with regard to PD. This impression is strengthened by recent studies that report a specific risk of compounds of interest. Thus, the committee now concludes that there is limited or suggestive evidence of an association between exposure to compounds of interest and the development of PD.”

- IOM provides the Veterans Agent Orange review as a result of a contract between the Department of Veterans Affairs and the National Academy of Sciences. IOM reports are used by the VA to help decide presumptive issues.

- This is certainly competent and credible input that is relevant to all veterans who served in Vietnam and have Parkinson’s. Since it shows positive association there must be credible offsetting negative association that out weighs this evidence.

L. Nelson found that Vietnam Veterans who deployed to Vietnam had a 2.6 times higher incidence of PD than did veterans who served at the same time but who had not deployed to Vietnam. (Nelson et al. 2005; Laino, Neurology Today. 2005. June (5)6: 48)

This increase incident of PD in is also supported by a new study on a group of Vietnam Veterans, who in fact have PD. (Reid C, et. al, 2009). Some of the findings from this study were presented by Dr. Reid at the Institute of Medicine VAO review committee’s public meeting in June 2008. This study shows that these Vietnam Veterans:

- have a high rate of diseases already presumptive for Vietnam Veterans.
- have earlier onset of the disease compared to the normal PD population,
  - In 1996 IOM’s VAO update; “Cases of early-onset parkinsonism are particularly important to testing the hypothesis that the disease relates to a toxic exposure.”
- share a common mechanism of causation;
- Sibling brothers have a lower rate of PD than siblings of PD cases in the general population. indicating a common mechanism of causation and that genetics appears not to be a factor in these Veterans.
Mayo Clinic found in their “Alpha-synuclein, Pesticides, PD” study that both pesticides and alpha-synuclein increases the risk of PD independent of each other. People in the study who were exposed to herbicides developed PD 2.43 times more than people who were not exposed. The study points to the fact that the Agent Orange herbicide 2,4-D is significantly linked to PD. (L. Brighina, MD, et al., Neurology 70 April 15, 2008)

The Iowa and N.C. agriculture health study (AHS) update 2007 showed that the other herbicide in Agent Orange 2,4,5-T also increased the risk of PD. (Michael C. R. Alavanja, Dr. P.H., et al, Iowa and North Carolina Agricultural Health Study, update 2007)

The Effect of Dioxins on regulation tyrosine hydroxylase gene expression by way aryl hydrocarbon receptors: a neurotoxicology study shows how TCDD (dioxin in Agent Orange) impact dopamine system. Parkinson’s disease is the result of loss of dopamine.

The above studies are credible, they are compelling and they are convincing in showing that PD is significantly associated with service in Vietnam and to the herbicides in Agent Orange.

The VA already acknowledges that Veterans have a higher incident of Parkinson’s than do non-Veterans. This is support by Dr. Nelson’s deployment study mentioned earlier. According to VA’s “Effect of Robot-Assisted Gait Training on Freezing of Gait in PD” clinic trail document:

- “There are approximately 1 million Americans with PD in the US. There is a higher incidence of PD among Veterans than non-Veterans, with nearly 2% of Veterans suffering from PD. PD is a significant cause for reduced functional ability and quality of life, progressive disability.”

These studies are only a few of many that connect the numerous chemicals used in Vietnam to PD. Research shows that numerous other studies point to the connection between the chemicals used in Vietnam and Parkinson’s disease.

Vietnam Veterans and most Americans are aware of the spraying of “Agent Orange” in Vietnam, but few including Veterans are unaware of “Operation Flyswatter”. This was a global operation that sprayed the organophosphate insecticide Malathion direct over the troops in Vietnam every 9 to 11 days. This war against the mosquitoes subjected Veterans to a neurotoxin that is now significantly associated with PD.

In the March 2008 “Pesticide exposure and risk of PD: A family-based case-control study” organophosphate including Malathion was found to be significantly associate with PD.

- “However, application of only the organochlorine and organophosphorus chemical classes were found to also be significantly associated with PD……chlorpyrifos, diazinon, and malathion were the most common of the eight organophosphorus chemicals.” (Dana B Hancock, et al., March 2008, BMC Neurology 2008, 8:6 doi:10.1186/1471-2377-8-6)
In this same study the herbicides in Agent Orange showed strong odd ratios indicating possible association with

- “the chlorophenoxy acid/ester class [including 2,4-dichlorophenoxyacetic acid (2,4-D) and Agent Orange], showed strong OR estimates possibly indicative of a positive association with PD, but these associations were not significant.” (Dana B Hancock, et al., March 2008, *BMC Neurology* 2008, 8:6 doi:10.1186/1471-2377-8-6)

There are important considerations to look at in Vietnam Veterans exposures ------- the dose levels in some chemicals were much higher than the same chemical used in civilian operations. The IOM VAO update indicates that the dioxin in Agent Orange varied up to 1,000 times the levels in civilian type herbicides.

- “When we (military scientists) initiated the herbicide program in the 1960’s, we were aware of the potential for damage due to dioxin contamination in the herbicide. We were even aware that the ‘military’ formulation had a higher dioxin concentration than the ‘civilian’ version, due to the lower cost and speed of manufacture. “(22 Nov 1989, U. S. Congressional Records)

The end result was trading the lives and health of our service members in Vietnam for a cheaper product that could be quickly produced.

As mention earlier unlike the controlled environment of a lab, chemical exposures in Vietnam could have been in combination with other chemical with a multitude of dosages. Those chemical include not only the VA designated presumptive herbicides but medicine and other neurotoxins.

To be brief, present below are only two examples of how combination of chemicals play a role in the development of PD.

Vietnam Veterans were given weekly dosages of the anti-Malaria drug Chloroquine and they were subject to exposure on routine and random bases to neurotoxins including Malathion and Agent Orange. Chloroquine inhibits the P450 2D6 enzyme. This is a phase one detoxification enzyme that helps metabolize neurotoxins. Bottom line, Vietnam Veterans were taking prescribed medication that reduced their body’s ability to detoxify itself while being subjected to exposures to neurotoxins.

- “Chloroquine caused a progressive and significant decrease in CYP2D6 activity as measured by debrisoquine metabolism from first to seventh dose and the activity returned to baseline gradually over 14 days after stopping administration.” (Adedayo Adedoyin, et al. 2002)

Another chemical exposure for Vietnam Veterans and many other Veterans was trichloroethylene found in many solvent. There can be no doubt that this is a troubling toxin. You only have to look at the recent problems with the water at Camp Lejune, North Carolina. These solvents are associated with PD and an earlier onset of PD.

- “One study examined exposure to organic solvents and found a statistically significant relationship to the development of PD (Smargiassi et al. 1998). In
addition to the possibility of solvents causing PD. Pezzoli et al. (2000, 2004) found that exposure to hydrocarbon solvents increased PD severity and earlier age at onset; another showed suggestive evidence of an association between solvents and PD (Seidler et al. 1996)." (Rebecca Brown, et al., 2005)

Some chemicals can interact with existing chemicals in the body and produce unwanted effects that may impact the onset of PD. One of those is trichloroethylene.

- "Trichloroethylene… a metabolic precursor of chloral hydrate…….. Chloral hydrate………has been found to condense spontaneously with tryptamine, in vivo, to give rise to a highly unpolar 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo) that has a structural analogy to the dopaminergic neurotoxin ……. (MPTP). Earlier studies have revealed the relative permeability of the molecule through the blood-brain barrier and its ability to induce Parkinson-like symptoms in rats. In this study, we report that TaClo induces an apoptotic pathway in the human neuroblastoma cell……. Although it is not clear if the clinically administered dosage of chloral hydrate or the relatively high environmental levels of trichloroethylene could lead to an onset of PD, the spontaneous in vivo formation of TaClo and its pro-apoptotic properties, as shown in this report, should be considered. (Akudi RS, et. al, 2004)"

PD results from the loss of dopamine producing neurons in the substantia nigra. When 70 to 80% of these cells are lost the symptoms of PD appears. Aging and oxidative stress has been sited as factors. Third, the aggregation of two proteins alpha-synuclein and tau are known to create neurofibrilllas associated with PD.

- "Oxidative stress has been associated with damage and progressive cell death that occurs in neurodegenerative disorders such as Parkinson’s disease (PD)……The results showed that in the SN of parkinsonian’s brain the balance between production of free radicals and the neutralization by a complex antioxidant system is disturbed." (E.Sofic, et. al, Journal of Neural Transmission. Supplementa, 10.1007/978-3-211-33328-0_5)

- "These results clearly indicate that subchronic exposure to low doses of TCDD can induce oxidative tissue damage in brain tissues which may at least in part play a role in the effects of TCDD on the central nervous system." (Ezdihar A, et al., 1997)

- "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." (Donggun Sul, et al., October 2008,)

Presented in this executive summary are only some of the scientific data that supports the facts that:

- Vietnam Veterans have a higher incident of PD;
- the chemicals in the VA designated presumptive herbicides are significantly associated with PD;
- Other Vietnam chemical exposures are associated with the development of PD.
the combined effects of these chemicals in any combinations have never been evaluated in a scientific study by the VA or any other organization.

Public Law 102-4, the Agent Orange Act of 1991 allows the Secretary of the Department of Veterans' Affairs to add a disease or health issue to the list of diseases that are associated with herbicide exposures. The law also mandates that the Secretary give the benefit of the doubt to the veteran using the standard “is it as least as likely as not” to evaluate a presumptive decision.

The evidence presented in this summary alone is credible, compelling and directly shows that the chemicals used during the Vietnam War are associated with the development of PD in these Veterans.