Scientific Supplement

Claim for Parkinson's disease For Herbicide Exposure & Direct Service Connection

Prepared by:

U.S. Military Veterans with Parkinson's
USMVP

Alan B. Oates
4270 South Ox Rd
Edinburg, Virginia 22824
oldvet@aol.com
540-459-9376
540-325-1232

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Opening Overview

Here I give an overview to the evidence presented in the claim.

Opening (**An executive summary of the Claim is found starting on page**

I am a Vietnam Veteran who has Parkinson's disease. In this portion of my claim I will provide evidence of direct service connection to my Parkinson's disease (PD). PD will be used through out this document to mean Parkinson's disease.

I will show that both my service in Vietnam and my exposures to the presumptive herbicides are connected to my Parkinson's disease.

I will present a Stanford University Study and a study on a group of Vietnam Veterans with Parkinson's disease that link Parkinson's disease to service in Vietnam. I will also present evidence from the Department of Veterans' Affairs of a higher incident of PD in Veterans than in non-veterans. DVA or VA will be used to indicate the Department of Veterans' Affairs.

I will present evidences showing that the two herbicides (2,4-D and 2,4,5-) in Agent Orange are significantly associated with Parkinson's disease.

I will present evidence that shows even with a genetic predisposition for Parkinson's disease chemical exposures play a role in the development of PD and in an earlier onset of PD.

I will present evidence of exposures to other chemicals including Chloroquine, Trichloroethylene, Organophosphates in the form of Malathion, solvents and fuels.

I will present evidence that the chemicals exposures play a role in the development of PD even in those with a genetic predisposition to the disease.

I will show that the combination and mixtures of chemicals can and do impact on the development of PD.

I will show how these chemical cause damage that leads to the development of PD.

I will show how other chemical exposures of the Vietnam War experience play role in the development of PD.

Each of my points and claims are supported by scientific evidence in the exhibits attached to this claim or provided in PDF files on a CD disk or both.

The evidence you will see is credible, it is compelling and it support the one thing before the DVA in this case. That is, does the evidence presented show that it is at least as likely as not that my Parkinson's disease is service connected. To do this you must compare the evidence submitted in this claim against the evidence against an association. To deny this claim you must also show the evidence that outweighs the evidence presented here. The research for this claim encompassed over 18 months and is presented to make it easier for you to approve the claim.

Introduction To This Claim

Here, I will present some important facts and background information. There are legal and procedural considerations addressed in the portion of this claim.

Introduction to the claim.

Why you must evaluate the evidence presented in this Claim.

- Even though this claim is for a disease that the Secretary of Veterans' Affairs has found not presumptive to herbicide exposure under current laws and regulations, that does not prevent a Veteran from presenting evidence of direct service connection.

- Public Law or the Secretary of Veterans' Affairs by regulations establishes diseases or health issues that are presumptive to military service and in the case of some Veterans to herbicide exposure. However the fact that presumptiveness has not been established for a particular disease or health issue does not prevent a Veteran from presenting evidence of direct service connection.

    - *"In the case of Combee v. Brown, 34 F. 3d 1039 (Fed Cir. 1994), the United States Court of Appeals for the Federal Circuit (Federal Circuit) held that a veteran was not precluded from presenting proof of direct service connection between a disorder and exposure even if the disability in question was not among conditions enumerated under the Veterans' Dioxin and Radiation Exposure Compensation Standards Act, the presumption not being the sole method for showing causation."*

This is especially true in regards to new information that has not been evaluated by the VA. With that in mind, the following evidence is submitted in support of my claim of direct service connection for Parkinson's disease.

Due to the scientific nature of the evidence, I request my case be referred the VA Health Neurologists for evaluation and opinion.

It is also important to evaluate the evidence individually and collectively. Is the evidence for the association of military service to Parkinson's disease at least equal to the evidence against an association.

In looking at this claim it is important to recognize that the term *pesticides* include herbicides, insecticides, fungicides, and rodentcides. A herbicide is a pesticide.

"*A pesticide may be defined as any agent used to kill undesired organisms such as insects (insecticide), snails and slugs (molluscicide), rodents (rodenticide), plants (herbicide) or fungi (fungicide)." (*Finlay D. Dick, 2007) (Exhibit 69)

Is there an environmental risk for Parkinson's disease (PD)?

There is a substantial amount of scientific evidence that support the involvement of environmental toxins in etiology of PD.

- "*We investigated associations between Parkinson's disease and other degenerative parkinsonian syndromes and environmental factors in five European countries…….CONCLUSIONS: The association of pesticide exposure with Parkinson's disease suggests a causative role….*" *(Dick FD, et al., 2007) (Exhibit 38)"*

- *"Many epidemiologic studies have examined the relationship between PD and pesticides, but most have been conducted in population-based studies using a broad definition of pesticide exposure. Our findings make three main contributions to the literature supporting pesticide exposure as an important risk factor for PD. First, replication of associations between pesticides and PD in the most extensive family-based study to date suggests that this positive association is not likely confounded by unmeasured genetic and environmental influences on exposure and disease. Secondly, the strongest associations between PD and pesticides were obtained in families with no history of PD thus introducing family history as a potentially important variable to consider in future studies of the effect of pesticides on PD. This finding suggests that sporadic PD cases may be particularly vulnerable to the toxic effects of pesticides, but the possibility of pesticides influencing risk of PD in individuals from families with a history of PD cannot be ruled out. Lastly, our findings add support to the limited data implicating specific classes of pesticides, notably organochlorines, organophosphorus compounds, chlorophenoxy acids/esters, and botanicals, as potential risk factors for PD. "(Dana B Hancock1, et al., 2008) (Exhibit 18*

- "When adjusted for these variables and smoking status, there was a significant association of occupational exposure to herbicides (odds ratio [OR], 4.10; 95% CI, 1.37, 12.24) and insecticides (OR, 3.55; 95% CI, 1.75, 7.18) with PD, but no relation was found with fungicide exposure. ……. The association of occupational exposure to herbicides or insecticides with PD remained after adjustment for farming. …….These results suggest that PD is associated with occupational exposure to herbicides and insecticides and to farming and that the risk of farming cannot be accounted for by pesticide exposure alone." (J. M. Gorell, et al., 1998) (Exhibit 93)

TCDD is an organochlorine, Malathion is an organophosphorus compound, 2-4-D and 2,4,5-T are chlorophenoxy acids/esters. This points to the fact that all three classes of chemicals in agent are a potential risk for PD.

Importantly, these environmental factors need to be viewed in regards to their ability to promote or speed up the development of Parkinson's disease.

- *"Environmental factors have been shown to contribute to the incidence of Parkinson's disease (PD)…….. Furthermore, these chemicals and their environmentally relevant combinations should be evaluated for their ability to promote or accelerate PD and not merely for being singular causative agents."* (Exhibit 13, Jaime M. Hatcher, et. al, 2008)

The VA has failed to look at the total chemical exposure and Vietnam experience and has focused on only some of the herbicides!

Much has been said about Agent Orange in regards to the Vietnam Veterans health issues. Vietnam Veterans exposure to the dioxin 2,3,7,8-TCDD (TCDD) has been the subject of many studies, most notably the U.S. Air Force Ranch Hand Study. Even this study has it flaws and limitations. However little has been done by anyone including the U.S. Government to look at the Vietnam Veterans over all Chemical Experiences or the combined effects of these chemicals.

The [1]Center for Neurodegenerative Disease, Emory University School of Medicine, in a study on PD noted:

- *"Furthermore, these chemicals and their environmentally relevant combinations should be evaluated for their ability to promote or accelerate PD and not merely for being singular causative agents."* (Exhibit 13, Jaime M. Hatcher, et. al, 2008)

Alvin Young is recognized as an expert on Agent Orange and its use during the Vietnam War.

- *"Throughout his career, Dr. Young has been involved with all phases of Agent Orange research, from testing and evaluation of dissemination equipment to environmental fate and health impact studies. He has published four books and more than 70 peer-reviewed publications on herbicides and TCDD. The Alvin L. Young Collection on Agent Orange, located in Special Collections, the National Agricultural Library, is the result of his 30-year effort to collect reports, slides, photographs and other documents and materials on issues associated with the use of Agent Orange and other herbicides during the Vietnam War" (http://wwwnal.usda.gov/speccoll/findaids/agentorange)*

The importance of looking at the total Vietnam experience rather than trying to tie all health issues in the Vietnam Veterans to Agent Orange was noted by Dr. Young.

- *"In hindsight, after all the years of controversy over Agent Orange, perhaps we could have been fairer and more generous to all Vietnam veterans with a program of 'Vietnam experience' benefits rather than Agent Orange benefits. What is really needed is scientific studies of effects of the Vietnam experience on all veterans rather than studies seeking to 'link' more diseases to Agent Orange, which in the present context compromises important scientific principles in the process. It is my hope that the forthcoming articles can contribute significant new data and perspective to the ongoing public dialog on Agent Orange."(Exhibit 1 Young Alvin, 2004)*

Dr. Mark Brown, one of the Department of Veterans' Affairs "Agent Orange Experts", pointed out in an email dated Feb 19, 2009. (Exhibit 2)

- *"I asked Dr. Kang about his Vietnam Veteran mortality study, and he told me that he has not found an increased risk of death from PD in this group. However, he points out that PD may not be well picked up in a mortality study, as you yourself suggested at our recent meeting."*

- *"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!"*

- *I agree that our current approach focuses very much on herbicides and dioxin, which is fine, but it may be a mistake to assume that these exposures explain all the health problems experienced today by veterans of that conflict!"*

The point of PD not being picked up in a mortality study is echo in the 2005 update to the Australian Mortality Study (Exhibit 14).

- "*Mortality from diseases of the nervous system among Vietnam veterans was significantly lower than expected, SMR 0.78 (95% CI 0.62, 0.94). This result is not unexpected amongst a veteran cohort as people with some diseases in this group, such as cerebral palsy, would be ineligible for military service. Mortality from other diseases, such as Parkinson's disease or Alzheimer's disease, would not be generally evident in a cohort of this age."*

The narrow focus of looking at the herbicide exposure and not the complete chemical exposure is a matter of concern. The National Academy of Science interprets the language in the "Agent Orange Act of 1992", Public Law 102-4, to mean that they are limited to looking at only the herbicides or chemical included in the herbicides. Any

chemicals not included in the herbicides are outside of their preview for the Veterans Agent Orange reviews and updates. The independent agency contracted to look at the Health Issues of Vietnam Veterans are in fact not looking for service connection but only if there is a direct association with the herbicides.

- *"1)(B) of this subsection shall be presumed to have been exposed during such service to an herbicide agent containing dioxin or 2,4-dichlorophenoxyacetic acid, and may be presumed to have been exposed during such service to any other chemical compound in an herbicide agent, unless there is affirmative evidence to establish that the veteran was not exposed to any such agent during that service.*
  "(4) For purposes of this section, the term 'herbicide agent' means a chemical in an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during he Vietnam era." (Public Law 102-4)(Exhibit 3)

In a recent email Dr. Mary Paxton, Staff Director for the Agent Orange Vietnam Veterans Health Reviews pointed out: (Exhibit 3)

- "*The Chloroquine info does sound tantalizing, but as you know any effects it may have had do not fall under the VAO committee's charge only to address the herbicides (along with any contaminants) used in Vietnam. The interaction possibility, however, does provide a bit of a talking point."*

After the 2006 VAO Review Update, the VA published in the federal register the following: (Exhibit 4, Federal Register / Vol. 72, No. 112 / Tuesday, June 12, 2007 / Notices)

- "*The study provides some evidence of an association between service in Vietnam and peripheral neuropathy. However, the study does not provide evidence for an association between specific exposure to the compounds of interest and chronic persistent neuropathy*"

In the above the compounds of interest were the herbicides and their contaminants. The flaw is obvious in the tunnel vision methodology which looks only at the herbicides and does not look at the total Vietnam Chemical exposure. The fact that there is an association with Vietnam service is the important point. The causative chemical or mechanism of the association should be secondary to the fact there is a service connection.

On 2/17/2009 in a meeting with the VA's health and Agent Orange Experts, the following question was presented.

- Has the VA conducted any study or studies or have knowledge of any study that has been undertaken to look at the impact of the three chemicals in Agent Orange together?

The Answer was no! Dr Brown stated that they do look at the mortality data. So Forty years after the Vietnam War in which approximately 20 million gallons of herbicides were sprayed (mostly Agent Orange), there has not been one study done to look at the combined effects of the three chemicals in Agent Orange. The U.S. Government including the VA has failed the Vietnam Veterans. It is important in the evaluation of this claim to not assume that Agent Orange itself has been the focus of research.

Vietnam Veterans including me were exposed to a multitude of chemicals and drugs. There were many chemical exposures that are not looked by the Institute of Medicine in the VAO Reviews. The combined effects of the multitude of chemicals in unknown combinations in individual Veterans make it more difficult to evaluate this claim. The chemical exposures are compounded again by other factors. The Gulf War Studies pointed out the body's ability to handle chemical exposures is reduced during times of stress.

To fairly evaluate this claim you must give considerations to the facts of these combined exposures and their relationship in the development of Parkinson's disease. You must also evaluate the evidence that I present for association of Parkinson's disease to my service against the evidence against the association. The evidence against the association must exceed my evidence for association.

With that in mind, I will present evidence in this claim that shows that the herbicides used in Vietnam plays a role in the development of Parkinson's disease. I will also show how other non herbicide chemicals used in Vietnam play a role in the development of PD and how service in Vietnam is directly associated with Parkinson's disease.

The information found in this claim is the result of over 18 months of researching this issue of Parkinson's disease in Vietnam Veterans.

The Evidence is broken down into parts.

- Part 1: Parkinson's disease. You must understand something about PD to evaluate this claim.
- Part 2: Supportive actions by the Veterans' Affairs in regards to PD.
- Part 3: Chemical exposures (herbicides and non-herbicides)
- Part 4: Credible studies show Vietnam service and/or chemicals are related to PD.
- Part 5: Genetic Factors and Environmental Exposures Parkinson's disease.
- Part 6: Combination of Chemicals
- Part 7: Oxidative Stress, Antioxidants, Detoxification, PD.
- Part 8: Other Vietnam War Chemical Links
- Closing

Part 1
Parkinson's disease

Here, I will present some important facts about Parkinson's disease. This will help the examiner understand how the evidence of association applies to the disease.

Part 1: Parkinson's disease

In order to evaluate this claim it is important to understand something about Parkinson's disease. The following information is from the National Institute of Health web site. (http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm#What_is) "*What is Parkinson's Disease?*

Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells. The four primary symptoms of PD are tremor, or trembling in hands, arms, legs, jaw, and face; rigidity, or stiffness of the limbs and trunk; Bradykinesia, or slowness of movement; and postural instability, or impaired balance and coordination. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. ….. "

"Is there any treatment?

At present, there is no cure for PD, but a variety of medications provide dramatic relief from the symptoms. Usually, patients are given levodopa combined with carbidopa. Carbidopa delays the conversion of levodopa into dopamine until it reaches the brain. Nerve cells can use levodopa to make dopamine and replenish the brain's dwindling supply. Although levodopa helps at least three-quarters of parkinsonian cases, not all symptoms respond equally to the drug. Bradykinesia and rigidity respond best, while tremor may be only marginally reduced. Problems with balance and other symptoms may not be alleviated at all. Anticholinergics may help control tremor and rigidity. Other drugs, such as bromocriptine, pramipexole, and ropinirole, mimic the role of dopamine in the brain, causing the neurons to react as they would to dopamine. An antiviral drug, amantadine, also appears to reduce symptoms. In May 2006, the FDA approved rasagiline to be used along with levodopa for patients with advanced PD or as a single-drug treatment for early PD. …….."

"What is the prognosis?

PD is both chronic, meaning it persists over a long period of time, and progressive, meaning its symptoms grow worse over time. Although some people become severely disabled, others experience only minor motor disruptions. Tremor is the major symptom for some patients, while for others tremor is only a minor complaint and other symptoms are more troublesome. No one can predict which symptoms will affect an individual patient, and the intensity of the symptoms also varies from person to person."

This helps the claims evaluator to understand Parkinson's disease before evaluating this claim. The points to remember in looking at the development of Parkinson's disease and the connection to the chemicals exposures in Vietnam are:

- That it is the loss of the dopamine cells in the substantia nigra that causes Parkinson's disease. Any showing of a chemical exposure that plays a role in the death of these cells directly or indirectly is evidence of service connection. The roles chemicals play may range from directly killing or damaging the dopamine neuron cells or to inhibiting the body's ability to protect or repair those cells.

That the evidence only needs to show that it is at least likely as not that Parkinson's disease is associated with military service.

Part 2
VA Actions

Here I will show actions by the VA that support the case that Parkinson's disease is associated with military service.

Part 2: VA actions supporting the service connection for PD.

The VA :

- Opened six regional Parkinson's disease centers in 2001. This occurred about 32 years after the mid point of the highest three years of use of Agent Orange in Vietnam (1969);
    - A study being published on Vietnam Veterans with Parkinson's disease shows that the length of time from leaving Vietnam and the diagnoses of Parkinson's disease is 31 to 32 years. (Exhibit 5, Reid C. letter to Veteran in study)
    - The Opening of these PADRECCs was about 31 to 32 years after the largest concentration of troops in Vietnam and the highest quantity of spraying of herbicides.
- The Board of Veterans Appeals approved the claims of two veterans for PD due to herbicide exposures.
    - BVA ruled in favor of the Veteran in (Exhibit 6)`Citation Nr: 0519813 Decision Date: 07/21/05 Archive Date: 08/03/05 DOCKET NO. 94-37 191` (Exhibit 6):
        - *"The VHA neurologist stated that the Institute of Medicine concluded that although an etiologic connection between pesticide/herbicide exposure was "biologically plausible," there was insufficient evidence at present to support a definite association between Parkinson's disease and "2,4-D, 2,4,5-T, or TCDD."*
- Public Law 102-4 provides that a plausible biological mechanism is a causal association between herbicide exposure and the disease (Parkinson's). This is a point of law that is important to this case. The law states:
    - "(C) whither there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease."
    - The Congress used the words "or other" and not the word "and", it is clear in the reading of this that the term plausible biological mechanism is meant to be considered as evidence of a causal relationship. There can certainly be no other interruption of that.
    - They certainly did not mandate that the IOM find if there exists a plausible biological mechanism and other evidence, nor did they mandate that IOM find if there was a plausible biological mechanism or evidence of a causal relationship.
    - By using the term "or other evidence of a causal relationship" the law is clear in its intent that a plausible biological mechanism is evidence of a causal relationship.

- A causal relationship is positive evidence that must be considered in deciding this claim.

- In this summary, the VA acknowledges a biological plausible mechanism in regards to Parkinson's disease and herbicide exposure. The Agent Orange Act provides that a biological plausible mechanism is a causal association.

- BVA Found in favor of the Veteran in Citation Nr: 0515609 Decision Date: 06/09/05 Archive Date: 06/21/05 DOCKET NO. 02-22 169) (Exhibit 7)
  - *"Under the benefit-of-the-doubt rule, in order for a claimant to prevail, there need not be a preponderance of the evidence in the veteran's favor, but only an approximate balance of the positive and negative evidence. In other words, the preponderance of the evidence must be against the claim for the benefit to be denied. Gilbert v. Derwinski, 1 Vet. App. 49, 54 (1990). Thus, in consideration of the aforementioned evidence, the Board finds that the evidence for and against the appellant's claim for service connection for Parkinson's disease is in a state of relative equipoise. With reasonable doubt resolved in the appellant's favor, the Board concludes that service connection is warranted*."

In both of the Appeal cases the evidence presented was far less than the evidence presented in this case.

- The Detroit Michigan Regional Office approved the claim of Parkinson's disease for herbicide exposure for a Vietnam Veteran in December of 2008. (Exhibit 94)

  - "Although Parkinson's Disease is not listed as a presumptive condition related to Agent Orange exposure, you submitted extensive research information from the Mayo Clinic, internet research, and other similar cases submitted to the Board of Veterans' Appeals. We sent your file to the VA Medical Center in Detroit, Mi and requested a full review of the evidence of record and a medical opinion regarding the likelihood of an association between your condition and exposure to Agent Orange."

  - "Dr. Frank reviewed your file and explained that the Parkinsonism symptoms you are experiencing are at least as not related to exposure to gent Orange. It was explained that the extensive research submitted supports a reasonable doubt in your favor. Therefore, we have determined to grant service connection."

- The DVA published as recently as January 2009 that the incidence rate of PD in Veterans is higher than in non-veterans. (Exhibit 8)
    - The VA in January 2009 posting a notice of Clinical Trial. (Exhibit 8) The VA recognizes that there is a higher incidence of PD among Veterans.
        - "*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*."

    The VA already knows that Veterans are at a higher risk for Parkinson's disease.

    The fact that the VA recognizes this increase risk is supported by the fact that the Department of Defense (DOD) also is working on research for the increase risk for PD that face military personnel. In the DOD's Neurotoin Exposure Treament Research Parkinson's points out that PD is induced by a variety of environmental exposures. Since the DOD, the Department of the government that sends military members in harms way agrees that PD can be caused by environmental exposures this provides a clear basis for the acceptance of that fact for the matter of claims in regards to military service.

    "*Parkinson's Disease (PD), as a particularly relevant disorder induced by a variety of environmental exposures, is a central focus of the research program. Basic research on mechanisms of neurodegeneration will lead to better diagnosis, treatment, and prevention." (Exhibit 30)*

In summary:

- PD for herbicides exposure has been approved at the VA's Regional Claims level.
- PD for herbicides exposure has been approved in two cases by Board of Veterans Appeals.
    - In one of the cases VA agrees that a biological plausible mechanism exist between herbicides and PD.
        - Public law 102-4 provides that a biological plausible mechanism is a causal association.
- The VA admits in Medical Clinical Trail notice that Veterans have a higher incidence of PD than non-veterans.

These all support the fact that in the case of Vietnam Veterans, that Parkinson's disease is service related.

Part 3 Chemical Exposures

Here I will present evidence that shows exposure to certain chemicals during my military service.

Part 3: Chemical Exposures

Chemical exposures in Vietnam were not just herbicides and their contaminants. There was a multitude of other chemicals used in Vietnam. Veterans were subjected to the opportunity for multiple exposures and combined exposures. The chemicals on these lists (Exhibit 9 and 10) are only a portion of the chemicals used in Vietnam and elsewhere.

The VA has selected the most used herbicides as the specific chemicals of presumptive exposure, specifically 2,4-D; 2,4,5-T and its contaminant TCDD; cacodylic acid (arsenic); and picloram. The Agent Orange Act of 1991 (Public Law 12-4) provides that "*(4) For purposes of this section, the term 'herbicide agent' means a chemical in an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era.*" Therefore any herbicide or chemical in a herbicide used in Vietnam era is presumptive under this act of law.

- Tactical herbicides included:
  - PURPLE: A formulation of 2,4,-D and 2,4,5,-T
  - GREEN: Contained 2,4,5-T.
  - PINK: Contained 2,4,5-T.
  - ORANGE: A formulation of 2,4,-D and 2,4,5-T. (most used herbicide mixture)
  - WHITE: A formulation of Picloram and 2,4,-D. (contaminate Hexachlorobenzene)
  - BLUE: Contained cacodylic acid (Arsenic)
  - ORANGE II: A formulation of 2,4,-D and 2,4,5-T "Super Orange"
  - DINOXOL: A formulation of 2,4,-D and 2,4,,5-T.
  - TRINOXOL: Contained 2,4,5-T
  - BROMACIL
  - DIQUAT (similar chemical to Paraquat)
  - TANDEX
  - MONURON
  - DIURON
  - DALAPON

These were the herbicides used by the U.S. Forces. (Exhibit 9) There were also exposures from chemicals and herbicides used by our allies. Any herbicides used by allied forces are also presumptive exposures by the Agent Orange Act of 1991(Public Law 103-4).

- Again, Public Law 102-4, the Agent Act of 1991, provides:
  - *"*12 "(3) For the purposes of this subsection, a veteran who, during active military, naval, or air service, served in the Republic of Vietnam during the Vietnam era and has a disease referred to in paragraph (1)(B) of this subsection shall be presumed to have been exposed during such service to an herbicide agent containing dioxin or 2,4-dichlorophenoxyacetic acid, and may be presumed to have been exposed during such service to any other chemical compound in an herbicide agent, unless there is affirmative evidence to establish that the veteran was not exposed to any such agent during that service.*

- *"(4) For purposes of this section, the term 'herbicide agent' means a chemical in an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era."*

Chemicals used by our allies in the form of herbicides are presumptive exposures by this law. Exhibit 9 is a list of some of the chemicals used by U.S. allies in Vietnam. But one of these herbicides Paraquat is of particular interest as it is associated with Parkinson's disease.

The by law presumptive Chemicals that will I will show the associations with PD are:

- 2,3,7,8-TCDD or TCDD
- 2,4-D
- 2,4,5-T
- Picloram and its contaminate Hexachlorobenzene
- Arsenic
- Paraquat
- Diquat

The other chemicals not considered presumptive by the VA, I will first establish that there was an exposure. Those chemicals are the organophosphate Malathion, the anti malaria drug Chloroquine, Trichloroethylene and fuels. I will also address the issue of Paraquat again.

- **Malathion**
  - "Operation Flyswatter, A War Within A War" was co-authored by Alvin Young. This was an operation to limit the number of troops getting malaria by spraying the organophosphate Malathion directly over the troop areas every 9 days weather permitting. (Young Al, 2007) (Exhibit 71)
    - Spraying of Malathion
    - Every 9 days
    - Directly over troop areas
    - Sprayed by same unit as Agent Orange
    - 1.76 million concentrated liters sprayed
    - Sprayed just after dawn or just before dusk
      - Chow times for troops

This provides proof of a global spraying of Malathion in Vietnam.. The association of Malathion to PD will be shown later in this document.

- **Chloroquine is an anti-malaria drug. It use is well known by the Vietnam Veterans. The big orange pill was taken weekly. Use of this drug in Vietnam is documented in Military Preventive Medicine: Mobilization and Deployment, Volume 1, chapter 5. (Exhibit 12)**
  - This military document provides proof of exposure to Chloroquine.

- **Paraquat is a herbicide that is known to be associated with the development of Parkinson's disease. Paraquat was used in Vietnam by our ally Australia. (Exhibit 15 and Exhibit 10)**
    - As mentioned earlier Public Law 102-4 the Agent Orange Act provides presumptiveness for exposure to herbicides used in support of U.S and allied military operations in Vietnam.

    - The use of the herbicide Paraquat by our ally in Vietnam therefore is a presumptive exposures provided for in the Agent Orange Act of 1991.

- **Trichloroethylene (TCE) is a chemical found in various solvents used in Vietnam and in military operations worldwide.** A universal exposure for Vietnam Veterans to this chemical was by the routine cleaning of individual and crew served weapons. The cleaning weapons involved the use of bore cleaning solvents containing Trichloroethylene. There were many other chemical solvents used in Vietnam. In my case solvents were used to clean not only weapons but to clean out the space under the flooring panels of our track vehicles. Exhibit 41 documents that it is present in military solvents.

Some of the chemicals that are known neurotoxins and that were used in Vietnam. This is not a complete list but a list of the most knows chemicals.

- The following Vietnam exposure chemicals are included on the list of neurotoxins found on NeuroReseach Clinics, Inc. (American Medical Association Category 1 Continuing Medical Education) (Exhibit 22)

    - TCDD (2,3,7,8-TCDD)
    - 2,4-D
    - 2,4,5-T
    - Arsenic
    - Chloroquine
    - Dapsone
    - DDT
    - Deet
    - Dieldrin
    - Diquat
    - Hexachlorobenzene
    - Jet Fuels
    - Magnesium Oxide
    - Magnesium Sulfate
    - Malathion
    - Manganese
    - Organic Solvents
    - Organophosphates Pesticides
    - Organochlorine Pesticides
    - Paraquat
    - Trichloroethylene

- Besides being on the above list of neurotoxins, The National Academy Of Science noted the neurotoxicity of TCDD:

- "*Although TCDD, other dioxins, and DLCs have received wide recognition for their potential to cause cancer, birth defects, reproductive disorders, immunotoxicity, and chloracne, animal and human studies have demonstrated other potential toxic end points, including liver disease, thyroid dysfunction, lipid disorders, neurotoxicity, cardiovascular disease, and metabolic disorders, such as diabetes." (Health Risks from Dioxin and Related Compounds: Evaluation of EPA Reassessment (2006), Board on Environmental Studies and Toxicology (Best) National Academy of Science.) (http://books.nap.edu/openbook.php?isbn=0309102588&page=23)*

Combined Effects of Chemicals:

The combined effect of chemical has been presented several times in this paper. Because almost no studies have been undertaken on the combined effects of the multitude of chemicals in the Vietnam War experience, we may never know all the effects. In one study we can see that there are synergic effects of some Vietnam exposures. Sunscreen and alcohol and the Agent Orange herbicide 2,4-D provides a look at this issue. All three of these were present in Vietnam.

- "Xenobiotics absorption is a health concern and skin is a major exposure site for many of these chemicals. Both alcohol consumption and topical sunscreen application act as transdermal penetration enhancers for model xenobiotics …..Comparing 2,4-D transdermal absorption after exposure to both ethanol and sunscreen with a theoretical value (sum of penetration after ethanol or sunscreen treatment) demonstrates that these two treatments enhance additively at the higher doses tested." (R.M. Brand, et al., 2007) (Exhibit 72)

This is just one example showing that dermal absorption of 2,4-D an Agent Orange herbicide was increased for Veterans using alcohol or sunscreen with a synergic absorption effect if using both at the same time.

Part 4
Credible Studies Linking PD with Vietnam Service

Here I will present credible and convincing new evidence that shows Vietnam Service and the chemicals that I and other Vietnam Veterans were exposed are significantly associated to Parkinson's disease.

Part 4: Credible studies show Vietnam service and/or chemicals are related to PD

The Following Studies show that there is a positive association between Vietnam Service and/or the chemicals exposures in Vietnam. The strength of the evidence in this part far exceeds the requirement of "it is as least as likely as not" that my Parkinson's disease is service related.

Before I present those studies I want to quickly to address the issue of the Blood Brain Barrier (BBB). One of the ways the body protects the sensitive brain tissue from toxins is by way of the BBB. It has been said that these chemicals can't cause Parkinson's because they cannot get pass the BBB. 2,4-D and 2,4,5-T the two chemicals in Agent Orange are shown to penetrate in the brain in rats. Also the BBB integrity may be threatened by exercise in a warm environment and alcohol consumption.

- "Protein-unbound fractions of 2,4-D and MCPA in the plasma were clearly higher than those of 2,4,5-T but the highest herbicide concentration increased the protein-unbound fraction of 2,4,5-T more (7-13-fold) than of 2,4-D and MCPA (5-fold). The results suggest that the greater increase in the penetration into the brain of 2,4-D and MCPA than of 2,4,5-T during their intoxication is due to some factors other than the changes in their binding to plasma proteins and mere enhanced diffusion through the blood-brain barrier." (Kristiina Tyynela, et al., 1990) (Exhibit 73)

- Blood-brain barrier integrity may be threatened by exercise in a warm environment… The results of this study demonstrate that serum S100β was elevated after water immersion and prolonged exercise in a warm environment, suggesting that blood-brain barrier permeability may be altered. (Phillip Watson, et al., 2005) (Exhibit 74)

- "Thus, oxidative stress resulting from alcohol metabolism in BMVEC can lead to BBB breakdown in alcohol abuse, serving as an aggravating factor in neuroinflammatory disorders." (J. Haorah, et al., 2005) (Exhibit 75)

In Part 2 there is a VA document that shows an increase incident of Parkinson's disease in Veterans more so than non veterans. This is supported by in Dr. Nelson's Deployment Study.

- **(Stanford Study) Military Deployment and the Risk of Parkinson's disease (Nelson et al. 2005; Laino, Neurology Today. 2005. June (5)6: 48) (Exhibit 16).**

    - When compared to the men who had never served in the military, men that served in the military during peacetime but never during a conflict were not at increased risk of PD (adjusted odds ratio (OR) = 0.9, 95% confidence interval (CI) 0.5-1.7; p-NS). ……., the risk of PD was increased among men who were deployed during the Vietnam war (OR = 2.6, 95% CI 0.9-7.13, p<0.07), but not among men who served at the time of the Vietnam war but were not deployed (OR = 0.9, 95% CI 0.4-1.7; p-NS).

The study establishes a solid connection between serving in Vietnam and developing Parkinson's disease.

This association between Parkinson's disease and Vietnam service is supported in Dr. C. Reid's study on a group of Vietnam Veterans who have Parkinson's disease. I was a member of this group of Vietnam Veterans. Dr. Reid's nexus letter is provided in (Exhibit 5)

- **(USMVP Member Study) Parkinson's disease in a group of Vietnam Veterans (Reid C, et. al, 2009, awaiting publication) Dr. Reid found**,
  - A high rate of diseases that are already presumptive to herbicide exposure in these Vietnam Veterans.
  - An earlier onset of PD was common in these Veterans
  - A mechanism of PD causation distinct from the general U.S. population.
  - Male siblings of these Vietnam Veterans, collectively, had a PD rate of less than 1%. A rate well below the national average.
  - A mechanism of PD causation, other than genetic, appears to be shared by these veterans**.**
    - "*Based on these data, it appears that these self-reported, US veterans with PD share a dramatically increased risk of illnesses associated with agent-orange exposure, as well as a mechanism of PD causation distinct from that of the general U.S. population. Perhaps most significantly, in contrast to the Vietnam veterans, their male siblings, collectively, had a PD rate of less than 1%--below the national average. Therefore, a mechanism of PD causation, other than genetic, appears to be shared by the Vietnam veterans."*

- **A study out of Boston University titled "Herbicide exposure modifies GSTP1 haplotype association to Parkinson onset age" supports an earlier onset in Parkinson's disease with the exposure to herbicides**. (Exhibit 31)
  - Haplotype results also provided evidence that the relation between *GSTP1* and onset age is modified by herbicide exposure. One haplotype was associated with an approximately 8-years-earlier onset in the occupationally exposed group and a 2.8-years-later onset in the nonexposed group.
    - **"Conclusions:** Herbicide exposure may be an effect modifier of the relation between glutathione S-transferase pi gene polymorphisms and onset age in familial PD."

- **(Mayo Clinic Study) Alpha-Synuclein, pesticides, and Parkinson disease (L. Brighina, et al., 2008, 10.1212/01.wnl.0000304049.31377.f) (Exhibit 18). The study provides a significant association between 2,4-D and Parkinson's disease**. (L. Brighina, et al., 2008) (Exhibit 18)

- Shows that the alpha synuclein and pesticides operated independently of each other to increase the risk of Parkinson's disease.

- Shows that in the pesticides, herbicides were significantly associated with Parkinson's disease.

- 2,4-D, one of the herbicides in Agent Orange, was the most reported herbicide reported by the study group.

    - *"The chlorophenoxy herbicide most commonly reported by our subjects was 2,4-D. This agent is contained in several broad leaf herbicide products and was a component of Agent Orange.33 Laboratory experiments have shown that 2,4-D may induce _-synuclein fibrillation in vitro34 and may delay ontogeny of dopamine levels in utero in animals.35 Intracerebral administration of 2,4-D in the basal ganglia induces behavioral and neurochemical alterations consistent with other adult animal models of parkinsonism"*

- Those exposed to herbicides were 2.43 time more likely to have Parkinson's disease. The "p" value for this study was .004. That is only 4 tenth of one percent of a chance that it was something other than herbicides that caused the Parkinson's disease in those in the study group exposed to herbicides.

The Mayo Clinic is a world renowned medical and research facility its creditability is unquestionably first class. This study by itself provides credible significant association between the herbicide 2,4-D and Parkinson's disease. This Mayo Clinic Study was cited by the Detroit Regional VA Office in their approved of a claim for Parkinson's disease for Agent Orange exposure. (Exhibit 27)

❖ **(NIH) Iowa Agriculture Health Study (Exhibit 17 & 17A)**

- The Iowa Agriculture Health Study update 2007 (Exhibit 17A) provides evidence linking 2,4,5-T (A herbicide in Agent Orange) directly to an increase in Parkinson's disease. This is highly credible study. It shows that a statistical association of Parkinson's with herbicide exposure exists.

    - ***"****Using information from the entire AH, we found that:" "Individual who used paraquat, cyanazine, trifluralin or 2,4,5-T had an increase risk for Parkinson's disease."*

    - This study provides a direct scientific link between the chemical 2,4,5-T (Agent Orange) and Parkinson's disease.

    - The study also provides a controlled and detail approach to data gathering, measuring exposure, and examining the subject for diagnoses of Parkinson's disease.

- The study identified the chemical 2,4,5-T as increasing the risk of Parkinson's. 2, 4,5-T is one of the herbicides in Agent Orange.

This is strong evidence that supports this claim and must be offset by evidence that outweighs it. This study alone provides a positive association connecting Agent Orange and service in Vietnam to my Parkinson's disease.

In Part 3 exposure to the organophosphate Malathion while serving in Vietnam was established. The organophosphate Malathion is significantly associated with Parkinson's disease.

- The Pesticides exposure and the risk of Parkinson's disease study organophosphate with Malathion one of the most common one is the study are significantly associated with Parkinson's disease.

    - "*However, application of only the organochlorine and organophosphorus chemical classes were found to also be significantly associated with PD. In our sample, chlordane and dichloro-diphenyl-trichloroethane (DDT) were the most common of the 10 organochlorine chemicals, while chlorpyrifos, diazinon, and malathion were the most common of the eight organophosphorus chemicals." (Dana B Hancock1, et al,, 2008) (Exhibit 32)*

- Agent Orange and 2,4-D was also associated with Parkinson's disease. There were strong OR estimates but the association did not reach the level of significant.

    - Two less common classes, the botanical class (including rotenone) and 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.

    - "*Our findings make three main contributions to the literature supporting pesticide exposure as an important risk factor for PD. First, replication of associations between pesticides and PD in the most extensive family-based study to date suggests that this positive association is not likely confounded by unmeasured genetic and environmental influences on exposure and disease. Secondly, the strongest associations between PD and pesticides were obtained in families with no history of PD thus introducing family history as a potentially important variable to consider in future studies of the effect of pesticides on PD. This finding suggests that sporadic PD cases may be particularly vulnerable to the toxic effects of pesticides, but the possibility of pesticides influencing risk of PD in individuals from families with a history of PD cannot be ruled out. Lastly, our findings add support to the limited data implicating specific classes of pesticides, notably organochlorines, organophosphorus compounds, chlorophenoxy acids/esters, and botanicals, as potential risk factors for PD. Further investigation of these specific pesticides and others may lead to identification of pertinent biological pathways influencing PD development*"

In this Part the credible evidence shows that Parkinson's disease has been significantly linked to the presumptive herbicides, 2,4-D, 2,4,5-T, and in two studies to service in Vietnam. Also a major credible study links Parkinson's disease to the organophosphate Malathion a proven chemical exposure of Vietnam Veterans through "Operation Flyswatter".

The evidence so far is credible, substantial and verifiable in showing my service in Vietnam and the chemicals I was exposed to are significantly associated with my Parkinson's disease.

Part 5
Vietnam Service & Genetics Increase Risk for PD

Here I will present evidence showing why genetics or a family member having PD should not be used to deny a Veterans claim for Parkinson's disease for service or chemical exposure.

Part 5: Genetics Factors, Environmental Exposures and Parkinson's disease.

In reviewing some denied claims the issue of Genetics has been called in to question. In this Part of this claim that issue is addressed. A genetic factor in a Vietnam Veteran is an added risk they carry with them during military service.

There are studies that point to the fact that individuals with a genetic risk for PD have an increase risk to develop the disease and/or develop it at an earlier age when exposed to environmental agents. Genetics in the cases of chemically exposed veterans should not be a factor in denying the Veterans claim. There is a volume of evidence that an environmental trigger coupled with a genetic factor more than likely plays a role in the development of PD. The gene-environmental interaction has more and more become accepted in studies and scientific literature.

- "Environmental factors along with gene-environment interactions are considered to be major contributing factors for the development of sporadic PD, which represents more than 90% of PD cases." (Tanner *et al.*, 1999).

- We already saw in the Boston University Study titled "Herbicide exposure modifies GSTP1 haplotype association to Parkinson onset age" that in those people with a certain gene that exposure to herbicides could result in an earlier on set of the disease.

    - Herbicide exposure may be an effect modifier of the relation between glutathione S-transferase pi gene polymorphisms and onset age in familial PD.

- This gene-environment factor is pointed out again in these studies:

    - "We performed a case-control study of Parkinson's disease (PD) in a population characterized by a high prevalence of pesticide exposure and studied the joint effect of pesticide exposure and CYP2D6. Although they are based on a small group of subjects with the joint exposure, our findings are consistent with a gene-environment interaction disease model according to which (1) pesticides have a modest effect in subjects who are not CYP2D6 poor metabolizers, (2) pesticides' effect is increased in poor metabolizers (approximately twofold), and (3) poor metabolizers are not at increased PD risk in the absence of pesticide exposure". (Alexis Elbaz, et. al, 2004, Ann Neurol 2004) (Exhibit 36)

    - "Our findings suggest that inherited interactive weakness of AChE and PON1 expression increases the insecticide-induced occurrence of Parkinson's disease." (Liat Benmoyal-Segal, et al., 2005) (Exhibit 76)

    - "These studies also suggest that, although genetic and environmental factors can hasten its onset, Parkinson's disease stems from a distinctive

neuronal design common to all human beings, making its appearance simply a matter of time." (Prof D James Surmeier PhD, 2007) (Exhibit 62)

- "Pesticide exposure and a positive family history were risk factors for Parkinson's disease. Interpretation GSTP1-1, which is expressed in the blood-brain barrier, may influence response to neurotoxins and explain the susceptibility of some people to the parkinsonism-inducing effects of pesticides" (Menegon A, et al., 1998) (Exhibit 94)

- "CONCLUSIONS: Many small studies have reported associations between genetic polymorphisms and PD. Fewer have examined gene-environment interactions. This large study was sufficiently powered to examine these aspects. GSTM1 null subjects heavily exposed to solvents appear to be at increased risk of PD." (Dick FD, et al., 2007) (Exhibit 37)

❖ Using the benefit of the doubt legal mandate, the risk of developing Parkinson's from a genetic factor alone would have to exceed fifty percent. If the genetic risk is 50% or less then it is more likely than not that the Veteran more likely than not would have not developed Parkinson's disease from a genetic factor alone. In one study the accumulative risk of developing Parkinson's disease to the age of 75 for first-degree relatives of people with Parkinson's was only 2%. Another study the accumulative risk for Parkinson's disease to the age 90 was 7.5 %.

- *"Objective: To determine the relative risk (RR) and cumulative incidence of idiopathic Parkinson's disease (PD) in first-degree relatives of PD patients compared with relatives of controls from the same geographic region. …. The cumulative incidence of PD to age 75 among first-degree relatives of PD patients was 2% compared with 1% among first-degree relatives of controls……Risk for siblings and parents of probands was similar. Conclusions: Susceptibility to PD is increased in first-degree relatives of both sporadic and familial cases. The pattern of inheritance and the relationship between genetic and environmental risk factors warrant further study." (Marder, et al., 1996) (Exhibit 60)*

- *"Overall the cumulative risk of developing parkinsonism by age 90 was found to be 7.5 per cent." (Bower, James H., et al. 1999) (Exhibit 19)*

It is clear that most cases of PD are sporadic and the risk of developing PD in small even when a first-degree family member has the disease. Given these considerations it is clear that this claim for PD cannot be denied based on genetic considerations.

Part 6
Combination of Chemicals

Here I will show the importance of looking at the combination of chemicals and their interactions.

Part 6: Combination of Chemicals

Combinations of chemicals play an important role in our health, both good and bad. The combination of drug given by health care providers can help cure come illness and disease and control the symptoms of others. Some drugs interact with each other for wanted or unwanted results. Doctors look at medications a person is taking before prescribing a new one. It would never be acceptable to prescribe a mixture of drugs with out knowing their interactions.

- **That is what has happened with military Veterans and in this case with Vietnam Veterans. Vietnam Veterans were exposed to so many chemicals and drugs that is very clear that:**
  - **It will never be know which chemicals in which combination in which dosage that each individual service member was exposed.**
  - **It would take years of research to even evaluate that multitude of chemical combinations. How many groups of unique combination are in just 7 chemicals? That is only 5,040 different groups of chemical to evaluate in unknown number of dosages.**

The Mathematical Association of New South Wales, Inc (Exhibit 79) shows:

" Line permutation

1. *All items, each unique*

Q. In how many ways can seven students be arranged in a line?

Order important - line permutation, without restriction.

All 7 items arranged and unique.

No. of arrangements = 7! = 5040."

- **When we increase the number chemicals to 10 the groupings of chemicals the number of unique groupings zoom to 3,628,800** without consideration for the unlimited number of dosages. This is easily calculated on an excel spread sheet using =PERMUT(10,10).

There can be no doubt that these combinations will never be evaluated. As shown earlier, it is forty (40) years after Vietnam and not one evaluation has been done on the even combined effect of the three chemicals in most sprayed herbicide combination used in Vietnam, Agent Orange. Given this history all Vietnam Veterans and generations of their lineage will be dead before any of this will be evaluated.

Take look at a few studies that open the eyes to the combined effect of chemicals.

In one study we can see that there are synergic effects of some Vietnam exposures. Sunscreen and alcohol and the Agent Orange herbicide 2,4-D provides a look at this issue. All three of these were present in Vietnam.

- "Xenobiotics absorption is a health concern and skin is a major exposure site for many of these chemicals. Both alcohol consumption and topical sunscreen application act as transdermal penetration enhancers for model xenobiotics …..Comparing 2,4-D transdermal absorption after exposure to both ethanol and sunscreen with a theoretical value (sum of penetration after ethanol or sunscreen treatment) demonstrates that these two treatments enhance additively at the higher doses tested." (R.M. Brand, et al., 2007) (Exhibit 72)

This is just one example showing that dermal absorption of 2,4-D an Agent Orange herbicide was increased for Veterans using alcohol or sunscreen with a synergic absorption effect if using both at the same time.

The following study relates to Parkinson's disease and demonstrates the complex issue at hand. Vietnam Veterans were exposed to solvents and in those solvents the chemical trichloroethylene. The following study show how trichloroethylene. Trichloroethylene is readily metabolized by mammals to produce chloral hydrate (LIPSCOMB J. C, et al., 1996) (Exhibit 80).

- "Trichloroethylene (TRI), a common groundwater contaminant, is readily metabolized by mammals to produce chloral hydrate (CH), trichloroacetic acid (TCA), and trichloroethanol (TCOH). Cytochrome P450 (CYP) and other enzymes are responsible for formation of these metabolites, which are implicated in TRI's toxicity and carcinogenicity." (LIPSCOMB J. C, et al., 1996) (Exhibit 80).

Tryptamine is found in animals, plants and fungi. It is found in the human brains and is thought to play a role in the central neurotransmission. (**Jones RS**. , 1982) (Exhibit 81)

"Whatever the role of tryptamine in the CNS it is clear that it not simply present as an accident of metabolism or a "biological artefact." The indications are that it possesses important functions in central neurotransmission." (Jones RS. , 1982) (Exhibit 81)

To this point we have Chloral Hydrate a metabolite of Trichloroethylene and tryptamine found in the brain. What is the interaction of these two chemicals? Chloral hydrate condenses with tryptamine (in vivo) to TaClo with a structure analogy to the MPTP. MPTP is known to causes the onset of Parkinson's disease symptoms in humans and animals.

"Trichloroethylene, a common industrial solvent and a metabolic precursor of chloral hydrate, occurs widely in the environment. Chloral hydrate, which is also used as a hypnotic, 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 N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (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 line, SK-N-SH, involving the translocation of mitochondrial cytochrome c to the cytosol and activation of caspase 3. TaClo-induced apoptosis shows considerable differences from that mediated by other Parkinson-inducing agents such as MPTP, rotenone and manganese. 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 Parkinson's disease, the spontaneous in vivo formation of TaClo and its pro-apoptotic properties, as shown in this report, should be considered."(Akundi RS, et al., 2004) (Exhibit 43)

While the above study is not clear if this combination clinically could lead to the on set of Parkinson's disease. A 2008 study indicates that Trichloroethylene should join MPTP as a risk factor for parkinsonism.

- Trichloroethylene, used extensively in industry and the military and a common environmental contaminant, joins other mitochondrial neurotoxins, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and some pesticides, as a risk factor for parkinsonism." (Gash Don M, et al., 2008)(Exhibit 26)

An example of how combinations of chemicals in varying dosages can have two opposite impacts is with the case of Malathion in the study below.

- *"Inhibition of acetylcholinesterase increased with the time of exposure to malathion and its inhibiting by-products within the interval from 0 to 5 minutes. Through simultaneous exposure of the enzyme to Malaoxon and isomalathion, an additive effect was achieved for lower concentrations of the inhibitors (in the presence of malaoxon/isomalathion at concentrations 2 × 10- 7 M/2 × 10- 7 M, 2 × 10- 7 M/3 × 10- 7 M and 2 × 10- 7 M/4.5 × 10- 7 M), while an antagonistic effect was obtained for all higher concentrations of inhibitors." (Krstic, Danijela, et al., 2008) (Exhibit 83)*

The Vietnam experience resulted in Veterans being exposed to untold multitude of chemicals and chemical mixtures in unknown combinations and dosage. This is a valid factor in considering a Veteran's claim for service connection to chemical exposures. Given the fact that no combined studies have been undertaken in the past 40 years, it is reasonable and prudent to believe none will be undertaken on the combinations of the chemicals of exposures for Vietnam Veterans. In this case the benefit of the doubt should go to the Veteran.

Part 7
Oxidative Stress
Antioxidants
PD

Here I will show that Oxidative Stress plays a leading role in the etiology of PD; that chemicals used in Vietnam can create this oxidative stress; that antioxidants are neuroprotective to dopamine cells; that Vietnam chemicals inhibit and inhibit these antioxidants; and that Vietnam chemicals impair the body's detoxification system.

Part 6: Oxidative Stress, Antioxidant, Detoxification, PD.

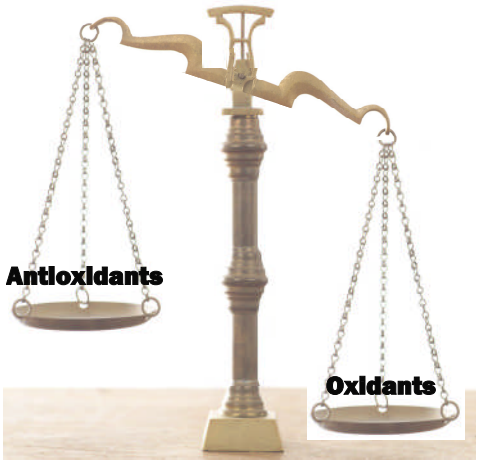
The body including the brain is subjected to oxidants both from within the body (endogenous) and from toxicants from the environment. The human body has an antioxidant system that combats these damaging oxidants.

Oxidative stress describes a condition in which cellular antioxidant defenses are insufficient to keep the levels of Reactive Oxidative Species (ROS) below a toxic threshold.

The balance of oxidants (free radicals/Reactive Oxidative Species created by oxidative stress) and antioxidants plays an important role in the development of diseases including Parkinson's disease.

- "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) (Exhibit 23)

The proper balance between the oxidants and the antioxidants prevent damage to the cells that may result in their death. A disruption of this balance may occur when the oxidants overwhelm the antioxidant system. This can occur either by an inhibition of the antioxidants or an increase in oxidative stress above the level that the antioxidant system can handle.



While normal oxidative stress can be counteracted by the body's antioxidant system. An overload of oxidants or a depletion or inhibition of antioxidants creates an unbalanced antioxidant/oxidant situation that can result in cell damage and death. It is this type of damage and death that is involved in the development of Parkinson's disease.

- "It is still unclear whether oxidative stress is the primary initiating event that is associated with neurodegeneration in PD, AD and ALS. However, a growing body of evidence implicates it as being involved in at least the propagation of cellular injury that leads to neuropathology in these various conditions. It is intimately linked with an integrated series of cellular phenomena, which all seem to contribute to neuronal demise. Interaction between these various components is not necessarily a cascade but might be a cycle of events, of which oxidative stress is a major component. Inhibition of oxidative stress therapeutically might act to 'break the cycle' of cell death." (JULIE K ANDERSEN, 2004) (EXHIBIT 66).

Many of the mutated genes associated with famila Parkinson's disease have an association with the oxidative stress process.

Oxidative stress, free radicals and mitochondrial dysfunction and GSH depletion are known to be involved in the death of neuron cells and the development of Parkinson's disease. There are many studies that point this out. As the oxidative stress is so widely accepted as associated with the development of Parkinson's disease, only a few studies will be used to document this.

- "*The objective of the present research is to determine whether there is a coherent body of evidence implicating oxidative damage in the pathogenesis of* ***Parkinson's*** *Disease and the MPTP model of Parkinsonism. We carried out initial studies in the Parkinsonian Syndrome known as Progressive Supranuclear Palsy. These studies showed that there is significant increase in lipid peroxidation in the subthalamic nucleus. We developed a novel column switching assay for measurement of an oxidative marker of damage to DNA in human body fluids. We found that both overexpression of manganese*

superoxide dismutase, a major free radical scavenging enzyme, as well as Bc12 and a dominant negative inhibitor of interleukin converting enzyme all significantly attenuate NPTP induced dopaminergic ***neurotoxicity****. This is accompanied by reductions in markers of oxidative stress. We also found that a number of therapeutic interventions, which may modulate oxidative stress, are effective in the NPTP model. We found that several novel free radical spin traps attenuate MPTP induced* ***neurotoxicity*** *and also attenuate oxidative damage. Lastly, we found that oral administration of creatine or cyclocreatine are neuroprotective against MPTP* ***neurotoxicity****."* (M.F. Beal, et al., 1999) (Exhibit97)

- *"A growing body of evidence indicates crucial implications for oxidative stress in several steps of the pathogenesis of many neurodegenerative diseases. The current idea is that it could have a causative role,….. However, the vast majority of PD is sporadic, resulting from gene–gene and gene–environment interactions superimposed on slow and sustained neuronal death due to aging ……. There is evidence of mitochondrial dysfunction and increased oxidative damage to lipids, proteins and nucleic acids in PD brains. Moreover, oxidative damage has been largely observed also in peripheral tissues of PD individuals." (Lucia Migliorea, et. al, 2008) (Exhibit 20)*

- *"The literature has seemingly reached a consensus that the neuronal cell death in PD is due to oxidatative stress. In particular, GSH depletion has been targeted as the source of this increased oxidative stress [8, 38]. Many studies have focused on the repletion of GSH as a means to prevent the oxidative death of DA neuronal cells." (Kashiwaya Y., et al., 2000) (Exhibit 35)*

- *"The action of toxins or the altered metabolism of dopamine may lead to oxidative stress in substantia nigra, thereby inducing dopamine cell death and the onset of Parkinson's disease. Postmortem studies showing a depletion of reduced glutathione and increased mitochondrial superoxide dismutase activity suggest the occurrence of an ongoing toxic process in substantia nigra involving free radical mechanisms." (Jenner P, 1992) (Exhibit 47)*

- *"Importantly, the role of mitochondrial function and oxidative stress in disease pathogenesis is not specific to PD. There is evidence that these pathways are also involved in other neurodegenerative diseases such as Friedreich ataxia, Alzheimer disease, amyotrophic lateral sclerosis, and Huntington disease, among others. Potential exists, therefore, for considerable 'cross-talk' in the development of improved treatments for each of these conditions…"A growing body of evidence now indicates that mitochondrial dysfunction and oxidative stress have central roles in PD pathogenesis. Recent advances in understanding the genetics of PD in humans, as well as the use of animal models of PD, have enabled us to make important steps not only in identifying the proteins involved in the pathways of PD pathogenesis, but also in determining how these proteins interact, both of which have enabled us to link oxidative stress and mitochondrial dysfunction with abnormal UPS function." (Claire Henchclifee, et. al, 2008) (Exhibit 21)*

- *In this study we see the oxidative stress in associated not just with Parkinson's disease by also with ALS. The Secretary of Veterans' Affairs just recently issued presumptiveness for ALS to military service.*

❖ *"In summary, our studies showed further evidence linking oxidative damage to dopaminergic neurons in the* ***substantia nigra*** *as well as in the MPTP model of PD." (M.F. Beal, et al., 2003)(Exhibit 22*)

❖ "The altered GSH/GSSG ratio in the substantia nigra in Parkinson's disease is consistent with the concept of oxidative stress as a major component in the pathogenesis of nigral cell death in Parkinson's disease." (Sian J., et at., 1994) (Exhibit 65)

I have shown ample evidence to support the association between Parkinson's disease and oxidative stress. The question now is can any of the chemical exposures from Vietnam Service cause this type of oxidative damage in neuron cells by increasing oxidants or decreasing antioxidants? .

First let's look at TCDD the dioxin in Agent Orange and its ability to create oxidative stress in the brain cells and how it also impairs the body's antioxidant and detoxification systems.

First TCDD accumulates in the brain tissue and creates oxidative stress.

❖ TCDD is a ubiquitous and most notorious environmental pollutant that accumulates in the brain as well as other organs (Kakeyama *et al.,* 2003).

❖ TCDD decreases the ability of brain cells to live, increase damage to DNA, and increases intracellular calcium levels by way of oxidative stress.

❖ *"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,) (Exhibit 48)*

❖ *"The abilities of single doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to induce oxidative stress in hepatic and some extra-hepatic tissues of animals, are well documented. The results of the study suggest that subchronic exposures to TCDD, PeCDF and PCB126 induce significant oxidative damage in the hepatic and brain tissues of rats, with more damage observed in the brain as compared to the hepatic tissues ." (HASSOUN E. A., et al., 2000) (Exhibit 50)*

❖ *"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." (HASSOUN E. A., et al., 2000****) (Exhibit 50)***

- *"Excellent inverse correlations between lipid peroxidation and membrane fluidity were observed. Thus, decreased membrane fluidity and increased membrane damage may contribute to the toxic manifestations of TCDD as a consequence of an oxidative stress." (N. Z. Alsharif, et al., 1990) (Exhibit 51)*

Second TCCD impairs the body's Antioxidant and detoxification systems.

- Melatonin is a neuroprotective hormone created in the pineal gland in the brain. TCDD reduces the serum level of this neuroprotective antioxidant. It has the ability to lessen the impact of neurotoxins in Parkinson's disease models and to rescue dopamine cells from cells death associated with oxidative stress.

  - "To find out whether this effect is related to the mechanism of acute lethality of TCDD, serum melatonin levels were measured at the nocturnal peak phase in the most TCDD-resistant rat strain variant, Han/Wistar rats, 6 hr to 28 days after TCDD exposure. The same dose as used in the previous study, 50 micrograms/kg, decreased serum melatonin levels to approximately half the control values by the first day after the treatment. Melatonin concentrations remained at this reduced level over the whole observation period."

  - *"We conclude that TCDD decreases serum melatonin levels in rats by enhancing the peripheral, evidently extrahepatic, metabolism of the hormone" (melatonin) (Raimo Pohjanvirta, et al., 1999) (Exhibit 52)*

  - "The same dose as used in the previous study, 50 micrograms/kg, decreased serum melatonin levels to approximately half the control values by the first day after the treatment. Melatonin concentrations remained at this reduced level over the whole observation period." (Linden J. et al., 1991) (Exhibit 70)

  - *"These results indicate that melatonin possesses the remarkable ability to rescue DA neurons from cell death in several experimental paradigms associated with oxidative stress." (Loraine Lacovitti, et al., 1997) (Exhibit 53)*

  - *"These findings support a physiological role for melatonin in protecting against parkinsonian neurodegeneration in the nigrostriatal system." (Shrma Rohita, et al., 2006) (Exhibit 54)*

  - *"The process by which melatonin and its metabolites successively scavenge ROS/RNS is referred as the free radical scavenging cascade. This cascade reaction is a novel property of melatonin and explains how it differs from other conventional antioxidants. This cascade reaction makes melatonin highly effective, even at low concentrations," (Tan, et al., 2007) (Exhibit 55)*

- TCDD is a contaminate found in 2,4,5-T. Both herbicides in Agent Orange (2,4-D and 2,4,5-T) inhibit Glutathione (GSH). Glutathione is a powerful antioxidant. Studies show that GSH level are depleted in Parkinson's diseased brains.

- *"GSH levels were reduced in substantia nigra in Parkinson's disease patients (40% compared to control subjects) and GSSG levels were marginally (29%) but insignificantly elevated; there were no changes in other brain areas……. The altered GSH/GSSG ratio in the substantia nigra in Parkinson's disease is consistent with the concept of oxidative stress as a major component in the pathogenesis of nigral cell death in Parkinson's disease." (Sian J, et al., 1994)(Exhibit 57)*

- *"The phenoxyacid herbicides, 2,4-dichlorophenoxyacetate (2,4-D) and 2,4,5-trichlorophenoxyacetate (2,4,5-T), inhibit all known isoenzymes of human liver and erythrocyte glutathione (GSH) S-transferase." (Shivendra V. Singh and Yogesh C. Awasthi, 2004) (Exhibit 56)*

- *Oxidative stress appears to play an important role in neuronal degeneration associated with PD (Beal. 1992; Burke, 1998; Adams et al.. 2001; Sayreet al., 2001). The depletion of glutathione (GSH) in the brain is the earliest know indicator of oxidative stress in presymptomatic PD. (Jenner, 1993)*

- *"Herbicide metabolism, especially paraquat and 2,4-D, rapidly depletes GSH and protein thiols. Paraquat and 2,4-D (1-10 mM) decrease the GSH/GSSG ratio, promote loss of protein thiol contents and induce lipid peroxidation." (Palmeira C.M., et al., 1995) (Exhibit 58)*

Malathion, an organophosphate, is neurotoxin that creates oxidative stress and depletes the GSH a major antioxidant in the body.

- "Besides AchE inhibition, malathion may act as a pro-oxidative agent by interfering with antioxidant defences, as shown by a decrease of glutathione peroxidase and glutathione reductase activity in the cerebral cortex (100 mg/kg malathion)." (Trevesan R, et al., 2008) (Exhibit 84)

- Variation activity of the enzymes involved in OPT metabolism could be expected to contribute to differences in susceptibility to OPT toxic effects, either due to genetic polymorphism or environmental influence, altering the bioactivation/detoxication ratio. (F. M. Buratti, *et al.) (Exhibit 85)*

- *Increasing evidence suggests excess illness in Persian Gulf War veterans (GWV) can be explained in part by exposure of GWV to organophosphate and carbamate acetylcholinesterase inhibitors (AChEis), including pyridostigmine bromide (PB), pesticides, and nerve agents.(* **Beatrice Alexandra Golomb, 2008) (Exhibit 86)**

- In Part 4, the Duke University Study showed a significant association between Malathion and Parkinson's disease. Malathion creates oxidative stress and depletes the GSH.

- "Malathion is an organophosphate compound, and like other organophosphates, is detoxified via conjugation reactions with glutathione (Malik and Summer 1982). In a study on rat hepatocytes, increasing concentrations of malathion (0.25 mM to 30 mM) depleted GSH in a dose-dependent manner and carboxylesterase activity was inhibited. This type of inhibition, of the carboxylesterase-mediated malathion degradation, could direct malathion metabolism toward GSH-dependent metabolism and result in further depletion of cellular GSH. The lack of GSH availability could have considerable influence on the metabolism and rate of detoxification of Malathion, as well as other xenobiotics (Malik and Summer, 1982). (Exhibit 49)

Chloroquine and anti-malaria drugs. A routine drug given to almost ever Vietnam Veteran was the anti-malaria pill. These pills are shown to inhibit the P450 2E6 phase I detoxification enzyme. This enzyme metabolizes neurotoxins.

- "The results imply that oxamniquine, primaquine and chloroquine could be substrates of cytochrome P4502 D6 or that they are potent non-substrate inhibitors of the enzyme similar to quinidine. In either case, the inhibition of CYP2D6 by these agents could lead to interference with in vivo population-phenotyping procedures in the tropical regions where treatment with the drugs is common." (J. A. Hasler, et al., 1994) (Exhibit 89)

- "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*) (Exhibit 90)

Vietnam Veterans served in an environment with a large number of neurotoxins while at the same time receiving anti-malaria drugs that inhibited the body's ability to metabolize the neurotoxins. This is an important factor to consider in looking at the Vietnam chemical experience and Parkinson's.

Hexachlorobenzene a contaminate in the Picloram, Agent White herbicide creates oxidative stress in the brain and also inhibits the GSH antioxidants.

- The evidence of neurotoxicity in humans following oral exposure to hexachlorobenzene was provided by studies of people in southeast Turkey who consumed contaminated bread in the late 1950s. ….Following ingestion of bread contaminated with hexachlorobenzene, observed neurological effects included profound weakness, loss of muscle control (inability to handle utensils, myotonia [delayed muscle relaxation after an initial contraction], and cogwheeling [irregular jerkiness of movement due to increased muscle tone as seen in

Parkinson's disease]), paresthesia (spontaneous tingling or burning sensations), and sensory shading (graded sensory loss indicative of polyneuropathy) (Cam and Nigogosyan 1963; Gocmen et al. 1989; Peters et al. 1982, 1987).

- "*In brain, HCB also significantly elevated the contents of reactive oxygen species (ROS), thiobarbituric acid- reactive substances (TBARS, as an indicator of lipid peroxidation products), glutathione disulfide (GSSG), and activities of nitric oxide synthase (NOS), glutathione peroxidase (GPx), and glutathione reductase (GR), and inhibited activities of acetylcholinesterase (AchE) and glutathione S-transferase (GST). The results clearly demonstrated that environmentally possible level of HCB could result in oxidative stress in fish and brain was a sensitive target organ of HCB toxicity." (S.B. Song, et al., 2006) (Exhibit 63)*

The evidence is extensive on the issue of oxidative stress in PD and in the chemicals related to military and Vietnam War service. Other studies exist on SOD and other antioxidants that are not presented here due to the length of this claim already.

Part 8
Other Vietnam War Chemical Links

In this Part, I will show how various chemical used in Vietnam have the ability to play a role in the development of Parkinson's disease.

Part 8: Other Links To Vietnam Service Chemicals

TCDD or 2,3,7,8-TCDD is an organochlorine. Organochlorine chemical have been found in the substantia nigra of people with Parkinson's disease.

- "These findings are not inconsistent with the hypothesis derived from epidemiological work and animal studies that organochlorine insecticides produce a direct toxic action on the dopaminergic tracts of the substantia nigra and may contribute to the development of PD in those rendered susceptible by virtue of cytochrome P-450 polymorphism, excessive exposure, or other factors." (F.M. Corrigan, et al., 2000) (Exhibit 91).

Malathion, an organophosphate, is a neurotoxin that creates oxidative stress and depletes the GSH a major antioxidant in the body. Studies show that Malathion and organophosphates are significantly associated with Parkinson disease. (Exhibit 49)

- Organophosphates were developed in the late 1930's by Nazi Germany for use as chemical warfare agents. These agents are quite toxic to the brain. Chronic brain damage can occur from exposure to organophosphates.(L. Rosenstock, et al., 1991) (F.H. Duffy, et al., 1979) (R. Repetto, et al., 1996)

- Organophosphates interfere with the function of the nervous system, interfering with nerve transmitters. (Exhibit 77)

    - Nicotinic nerve interference can cause twitching, cramping, weakness and fatigue. Delayed effects can occur as well following both chronic and acute exposures. These can involve the peripheral nerves. This can result in poor balance and cause reduced control of bladder and bowel functions.

    - Many of these symptoms are comparable to symptoms in Parkinson's.

- The Gulf War Studies have looked at the issue of organophosphates in Gulf War Veterans and found these Veterans have association with neurodegenerative disease like ALS. In regards to Parkinson's the study noted.
    - "Parkinson's disease, a related neurodegenerative condition, has also been linked to pesticides (69, 70) and PON genotype (26, 71), suggesting that monitoring for excess age-adjusted Parkinson's in GWV may be prudent." (Beatrice Alexandra , et al, 2008) (Exhibit 86)
- In Part 4, the Duke University Study showed a significant association between Malathion and Parkinson's disease. (Dana B. Hancock, et al., 2008) (Exhibit 32)
- Exhibit 82 presents information that impact upon the exposure to Malathion.
    - The technical grade malathion (the type we are exposed to) contains approximately 11 impurities. It is these impurities which scientists state are the main poisoning ingredients in malathion. One impurity has been shown to be approximately 500 times more toxic than purified malathion (based on the amount needed to kill test animals - LD-50 is 20 mg/kg compared to 10,000 mg/kg for purified malathion)
    - Malathion undergoes a chemical reaction in sunlight called "photolysis" which results in increasing the formation of the highly toxic trimethyl impurities. ***-Journal of Agricultural Food & Chemistry, 27(6):1423***
- Malathion as are all organophosphates is a known inhibitor of AChE.
    - *"Neurotoxic organophosphorous compounds are known to modulate their biological effects through the inhibition of a number of esterases including acetylcholinesterase (AChE), the enzyme responsible for the degradation of the neurotransmitter acetylcholine."(Jamal El Yazal, et al.,2001) (Exhibit 88)*
- Reduced levels of AChE combined with mutated genes are associated with Parkinson's disease.
    - "Our findings suggest that inherited interactive weakness of AChE and PON1 expression increases the insecticide-induced occurrence of Parkinson's disease." (Liat Benmoyal-Segal, et al., 2005) (Exhibit 76)

Diquat an herbicide used in Vietnam.

- Diquat is an herbicide used by the U.S. Military and their allies in Vietnam. While much has been written about Paraquat in regards to Parkinson's disease less has

been written about Diquat. Both Diquat and Paraquat are redox cycling herbicides. The study below point to redox cycling in the degeneration of dopaminergic cells. It is the loss of these cells that leads to PD. Diquat is shown to be more toxic than Paraquat in triggering redox cycling reactions.

- "*A loss of nigrostriatal dopaminergic neurons is the primary neurodegenerative feature of Parkinson's disease. Paraquat, a known redox cycling herbicide, has recently been shown to kill selectively nigrostriatal dopaminergic cells in the mouse model. The purpose of this study was to test the ability of paraquat and other redox cycling pesticides to damage dopaminergic neurons in primary mesencephalic cultures. Addition of paraquat, diquat, or benzyl viologen to mesencephalic cultures induced morphological changes (e.g., dystrophic neuronal processes) consistent with dopaminergic cell injury. The three pesticides also caused cell death as assessed by a reduction of the number of tyrosine hydroxylase-immunoreactive neurons and a dose-dependent decrease in [(3)H]dopamine uptake. Quite interestingly, diquat and benzyl viologen were significantly more toxic than paraquat, probably reflecting their more pronounced ability to trigger redox cycling reactions. The data support a role of redox cycling as a mechanism of dopaminergic cell degeneration and suggest that the property of redox cycling should be taken into consideration when evaluating putative environmental risk factors for Parkinson's disease." (Bonneh-Barkay D, et. al, 2005) (Exhibit 42)*

Paraquat an herbicide used by our allies in Vietnam has been connected to the development of Parkinson's disease.

- "We propose that the relatively hydrophobic pesticides preferentially bind to a partially folded intermediate conformation of alpha-synuclein, accounting for the observed conformational changes, and leading to association and subsequent fibrillation. These observations suggest one possible underlying molecular basis for Parkinson's disease."

- *"Genetic variability in the α-synuclein gene and long-term exposure to the pesticide paraquat constitute possible risk factors for sporadic Parkinson's disease…… However, paraquat markedly increased proteinase-K-resistant α-synuclein aggregates in substantia nigra of the transgenic mice. The data further validate the use of paraquat to model Parkinson's disease in mice and show that although paraquat and α-synuclein over-expression act synergistically to increase protein aggregation in vivo, this interaction does not result in short-term neuroprotection or increased vulnerability of nigrostriatal neurons.(P.O. Fernagut, et al., 2007) (Exhibit 68)*

- In 1990, Hertzmann already found a significant association between PD development and paraquat exposure by comparing personal histories of 57 cases and 122 age matched controls (Hertzmann et al. 1990).

- Paraquat crosses the blood-brain barrier (BBB) through neutral amino acid transporters (McCormack & Di Monte, 2003) (Exhibit 94) and then exerts its toxicity to dopaminergic neurons through a dopamine transporter (DAT) (Shimizu et al., 2003) (Exhibit 45)
- "*Paraquat, N-methyl-4-phenyl-1,2,3,6 tetrahydropyridine, and rotenone have been shown to reproduce several features of Parkinson's disease in animal and cell culture models. Although these chemicals are known to perturb dopamine homeostasis and induce dopaminergic cell death, their molecular mechanisms of action are not well defined.……We have previously shown that paraquat does not require functional dopamine transporter and does not inhibit mitochondrial complex I in order to mediate its toxic action (Richardson et al., 2005). In this study, we show that paraquat specifically oxidized the cytosolic form of thioredoxin and activated Jun N-terminal kinase (JNK), followed by caspase-3 activation.…… .Paraquat induced cytosolic oxidative stress followed by caspase-3–mediated cell death*." (Sampath Ramachandiran, 2006) (Exhibit 67)

- "*We have previously shown that paraquat does not require functional dopamine transporter and does not inhibit mitochondrial complex I in order to mediate its toxic action (Richardson et al., 2005). In this study, we show that paraquat specifically oxidized the cytosolic form of thioredoxin and activated Jun N-terminal kinase (JNK), followed by caspase-3 activation. Conversely, 1-methyl-4-phenylpyridinium (MPP^+) and rotenone oxidized the mitochondrial form of thioredoxin but did not activate JNK-mitogen–activated protein kinase and caspase-3. Loading cells with exogenous dopamine did not exacerbate the toxicity of any of these compounds. These data suggest that oxidative modification of cytosolic proteins is critical to paraquat toxicity, while oxidation of mitochondrial proteins is important for MPP^+ and rotenone toxicity." (**Sampath Ramachandiran et al.,**

- *We compared personal histories of 57 cases and 122 age-matched controls to identify possible environmental determinants of Parkinson's disease (PD). Odds ratios (OR) adjusted for sex, age, and smoking were computed using stepwise logistic regression. We found a statistically significant increased risk for working in orchards (OR = 3.69, p = 0.012, 95% CI = 1.34, 10.27) and a marginally significant increased risk associated with working in planer mills (OR = 4.11, p = 0.065, 95% Cl = 0.91, 18.50). A Fisher's exact test of the association between PD development and (1) paraquat contact, and (2) postural tremor gave statistically significant probability estimates of 0.01 and 0.03, respectively. (SEIDLER A, et. al, 1996) (Exhibit 39)*

- "the PD risk was greater among subjects who had used paraquat and other herbicides than those who had used herbicides other than Paraquat" (Liou et al. 1997, p.1583).(Exhibit 87)

- "*Taken together, these findings support the hypothesis that paraquat produces oxidative stress and proteasomal dysfunction mediated toxicity in SY5Y cells. Thus, current findings suggest that paraquat may induce the pathogenesis of dopaminergic neurons through oxidative stress and proteasomal dysfunction*." (Wonsuk Yang, 2005) (Exhibi 44)

- Bonneh-Barkay D, Reaney SH, Langston WJ, Di Monte DA. 005. Redox cycling of the herbicide paraquat in microglial cultures. molecular Brain Research 134 (1):52-56. Mechanisms involved in paraquat neurotoxicity that selectively target nigrostriatal dopaminergic neurons remain relatively unknown. In this study, we tested the hypotheses that paraquat exposure leads to the production of reactive oxygen species (ROS) through a process of redox cycling and that microglia represent an important site for the initiation of redox cycling reactions. Addition of paraquat to N9 microglial cultures resulted in a dose- and time-dependent release of superoxide radicals. Other agents that share with paraquat the property of redox cycling, i.e., benzyl viologen and diquat, also induced a marked production of superoxide radicals by microglia. The ability of paraquat, benzyl viologen, and diquat to induce superoxide release was correlated to their one electron reduction potentials and thus their tendency to redox cycle. Nitric oxide synthase and NADPH oxidase were identified as enzymatic sources of electrons that triggered paraquat redox cycling by microglia. Taken together, these data provide evidence in favor of a new mechanism by which microglia could play a role in oxidative injury during neurodegenerative processes. Microglial NOS and NADPH oxidase could promote the generation of ROS via the redox cycling of paraquat-like toxicants. (Bonneh-Bakay D, et al., 2005) (Exhibit 42)

Trichloroethylene (TCE) is a chemical in many solvents that were used by the military in Vietnam and elsewhere. Solvents are significantly associated with PD.

Cleaning and degreasing of airplanes, metal parts, weapons, and vehicles are some of the uses. Also it was in many of the solvent used on Navy ships. It is a known neurotoxin. In a 2004 study (Akudi, et al.) it was unclear if the TCE could lead to an onset of Parkinson's. However a 2008 study (Gash Don M., el at.) shows that TCE joins the other known Parkinson's developing neurotoxins as a risk factor for PD. The military recognize the dangers of these chemical and are working to find safer alternatives.

- *"Recent Environmental Protection Agency (EPA) mandates stipulate that products procured for Department of Defense utilization by the Defense Supply Center Richmond (DSCR) will be free of toxic and hazardous components. As a result of these mandates, studies were begun on MIL-C-372C (Cleaning Compound, Solvent for Bore of Small Arms and Automatic Aircraft Weapons). This work was conducted as part of DSCR's Hazardous Materials Minimization Program. This report summarizes the findings for replacement and field evaluation of candidate replacements." (Bernard R. Wright, et al., 1997) (Exhibit 25)*

- *"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) (Exhibit 78)

- "*Trichloroethylene, a common industrial solvent and a metabolic precursor of chloral hydrate, occurs widely in the environment. Chloral hydrate, which is also used as a hypnotic, 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 N-methyl-4-phenyl-,2,3,6-tetrahydropyridine (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 line, SK-N-SH, involving the translocation of mitochondrial cytochrome c to the cytosol and activation of caspase 3. TaClo-induced apoptosis shows considerable differences from that mediated by other Parkinson-inducing agents such as MPTP, rotenone and manganese. 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 Parkinson's disease, 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) (Exhibit 43) Also see Part 6 Combination of Chemicals.*

- *"The experiments specifically analyzed complex 1 mitochondrial neurotoxicity because this is a mechanism of action of other known environmental dopaminergic neurotoxins. Results: The three workers with workstations adjacent to the trichloroethylene source and subjected to chronic inhalation and dermal exposure from handling trichloroethylene-soaked metal parts had Parkinson's disease. Coworkers more distant from the trichloroethylene source, receiving chronic respiratory exposure, displayed many features of parkinsonism, including significant motor slowing. Neurotoxic actions of trichloroethylene were demonstrated in accompanying animal studies showing that oral administration of trichloroethylene for 6 weeks instigated selective complex 1 mitochondrial impairment in the midbrain with concomitant striatonigral fiber degeneration and loss of dopamine neurons. Interpretation: Trichloroethylene, used extensively in industry and the military and a common environmental contaminant, joins other mitochondrial neurotoxins, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and some pesticides, as a risk factor for parkinsonism." (Gash Don M, et al., 2008)(Exhibit 26)*

Agent Blue one of the presumptive herbicides and contains Arsenic. There are a number of studies that indicates arsenic may play a role in the development of Parkinson's disease.

- "Parkinson's disease is an environmentally influenced, neurodegenerative disease of unknown origin that is characterized by the progressive loss of dopaminergic neurons in the ***substantia nigra*** pars compacta of the brain. ***Arsenic*** is an environmental contaminant found naturally in ground water, industrial waste, and fertilizers… The initial goal of the present study was to determine if a mixture of arsenite (As^{+3}) and dopamine (DA) could cause enhanced degeneration of dopaminergic neuronal cells…... The results demonstrated that a mixture of As^{+3} and DA was synergistic in producing the death of the SH-SY5Y cells when compared with exposure to either agent alone. It was shown that necrosis, and not apoptosis, was the mechanism of cell death produced by exposure of the SH-SY5Y cells to the mixture of As^{+3} and DA. …….This study provides initial evidence that As^{+3} and DA synergistically can cause enhanced toxicity in cultured neuronal cells possessing dopaminergic differentiation." (Shaik Shavali, et al., 2007) (Exhibit 59)

- "These results showed that deprenyl inhibits As toxicity potentiated by cellular GSH depletion, but not the toxicity induced by As alone." (Sang Geon Kim, et al., 2004) (Exhibit 34)

Hexachlorobenzene is a contaminant found in Picloram (one of the presumptive herbicides). It is also found in ammunition and explosives used in Vietnam by U.S. military and its allies. We showed earlier that HCB creates oxidative stress while at the same time inhibiting antioxidant response.

- "*The evidence of neurotoxicity in humans following oral exposure to hexachlorobenzene was provided by studies of people in southeast Turkey who consumed contaminated bread in the late 1950s. ….Following ingestion of bread contaminated with hexachlorobenzene, observed neurological effects included profound weakness, loss of muscle control (inability to handle utensils, myotonia [delayed muscle relaxation after an initial contraction], and cogwheeling [irregular jerkiness of movement due to increased muscle tone as seen in Parkinson's disease]), paresthesia (spontaneous tingling or burning sensations), and sensory shading (graded sensory loss indicative of polyneuropathy) (Cam and Nigogosyan 1963; Gocmen et al. 1989; Peters et al. 1982, 1987)." (U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Agency for Toxic Substances and Disease Registry, 2002) (Exhibit 64)*

- *"Human data have shown that the developing central nervous system is a target of Hexachlorobenzene toxicity. Many breast-fed infants of mothers who ingested hexachlorobenzene-contaminated bread during an epidemic of hexachlorobenzene poisoning in Turkey between 1955 and 1959 showed symptoms of pembe yara, which included weakness, convulsions, and annular erythema prior to death (Cripps et al. 1984; Peters et al. 1982, 1987). In children exposed (at an average age of 7 years) to hexachlorobenzene contaminated grain, neurological effects persisted into adulthood (weakness, paresthesia, sensory shading, myotonia, and cogwheeling [irregular jerkiness of movement due to increased muscle tone as seen in Parkinson's disease]) (Cripps et al. 1984; Peters et al. 1982). Additionally, a preliminary report of infants from Flix, Spain,*

found an association between high hexachlorobenzene levels in milk and blood and impaired development of locomotor skills (Sala et al. 1999)." (Exhibit 64)

Calcium over expression plays a role in the death of neuron cells. TCDD increases the intracellular calcium levels in a number of studies. Calcium blockers such as isradipine are being evaluated in the treatment of PD.

- *"Collectively, these findings suggest that mitochondrial calcium overload is a critical event in both apoptotic and necrotic cell death." (II Krugman, et al., 1999) (Exhibit 61)*

- *"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,) (Exhibit 48)*

- "*The Ca^{2+} channels underlying autonomous activity in dopaminergic neurons are closely related to the L-type channels found in the heart and smooth muscle. Systemic administration of isradipine, a dihydropyridine blocker of L-type channels, forces dopaminergic neurons in rodents to revert to a juvenile, Ca^{2+}-independent mechanism to generate autonomous activity. More importantly, reversion confers protection against toxins that produce experimental parkinsonism, pointing to a potential neuroprotective strategy for Parkinson's disease with a drug class that has been used safely in human beings for decades." (Prof D James Surmeier PhD, 2007) (Exhibit 62)*

Fuels: JP4, Kerosene & diesel fuels.

The spraying of Agent Orange included mixing the Agent Orange with a fuel product like kerosene. So exposure to these fuels should be presumptive as it was part of the spray mixture. There should be no argument that Vietnam Veterans were exposed to the fuels used in planes, trucks, tanks and other track vehicles and in the normal day to day operations of every unit in Vietnam.

This fuels and mixtures can have an impact on the Central Nervous System (CNS).

- "Jet fuels can produce central nervous system impairment in humans by all routes of exposure, characterized by effects such as fatigue, coordination and concentration difficulties, headache, intoxication, anorexia, depressed mood, lack of initiative, dizziness, sleep disturbances, changes in posture, and reduced sensorimotor speed (ATSDR 1995b, 1998, 1999)…… Central nervous system depression, as observed for jet fuels, is an effect common to many organic solvents. It is generally thought to occur when the lipophilic parent compound partitions into the nerve cell membranes and disrupts function of membrane proteins by disturbing their lipid environment or by directly altering protein conformation (ATSDR 1999). Oxidative metabolism of the parent compounds reduces their lipophilicity and counteracts their central nervous system depressive effects."

Closing

Closing

In Closing it is important for you to look at:

- The total chemical exposures created in the Vietnam experience.
  - Vietnam Veterans were placed in a situation with the possibility for multiple exposures in combinations that can never be individually investigated or the impact fully known. This chemical environment was created knowingly and unknowingly by U.S. Military and their allies.

- Dr. Reid's letter on the only study that evaluates a group of Vietnam Veterans with Parkinson's disease.
  - This study shows an earlier onset of PD is common in these Veterans, that it appears there is a mechanism of causation distinct from the general population and that the siblings of these Vietnam Veterans had a lower rate of PD well below the national average indicating causation other than genetics is share by these Vietnam Veterans.

- Combining the studies and looking at the results. Just using three studies it is easy to connect the dots and show a more likely than not association.
  - One study says Vietnam Veterans had 2.6 time higher rate of Parkinson's than Veterans who served at the same time but did not go to Vietnam.
  - One study says people who were exposed to an Agent Orange herbicides have 2.43 times higher rate of Parkinson's disease than those not exposed
  - One study shows a significant connection between the Agent Orange herbicide 2,4,5-T and Parkinson's disease.

- The different ways scientific study show that various chemicals can cause oxidative stress or impair the antioxidant system both of which are shown to be associated with the development of Parkinson's disease.

- The ways that these chemicals individually or in combination play a role in damage to the brain. Damage that can take a person one step closer to losing that magical 70 to 80% of the dopamine cell and to Parkinson's disease.
  - Each individual exposure potentially damages more cells or setting up the body so a concurrent exposure or later exposure of same or different chemical can eliminate more dopamine cells.
- Part 6 and the complexity of the issue of multiple and combined exposures. Remember just 10 chemicals can give over 3.5 million combination of groups of chemicals depending on the order of the chemical exposures.

- The fact that the VA has recognized that the incidence of Parkinson's disease is higher in Veterans than non-Veterans.

- What evidence the VA has against the association and then weighs it against the evidence presented in this claim.

Keep in mind that what is presented here is only a portion of the studies available to support the connection between Parkinson's disease and my military service. Issues about the aggregation of alapha-synuclein and the tau nor was the issues surrounding the mitochondria.

After looking at what is presented and you feel there is not enough information please contact me and I will provide more.

Once you review the evidence.

Then give the benefit of the doubt to the Veteran. If you do, there can only be one fair and logical decision -------- Approval of this claim. Thank you in advance for your time and efforts in reviewing and acting on this lengthy claim.

Exhibit List

List of Exhibits cited:

Exhibit	*Citation for study*
1	*Alvin Young, TCDD Biomonitoring and Exposure to Agent Orange: Still the Gold Standard, 2004, ESPR – Environ Sci & Pollut Res 11 (3) 2004*
2	*Dr. Mark Brown, DVA Agent Orange Expert,email dtd 19 Feb 2009*
3	*Dr Mary Paxton, IOM Staff Director VAO Review, email dtd 19 Feb 2009*
4	*Federal Register / Vol. 72, No. 112 / Tuesday, June 12, 2007 / Notices*
5	*Dr. C. Reid Letter dtd 10 March 2009*
6	*Board of Veterans Appeal Citation Nr: 0519813 Decision Date 07/21/05 Docket NO. 94-37 191*
7	*Board of Veterans Appeal Citation Nr: 0515609 Decision Date 06/09/05 Docket NO. 02-22 169*
8	*DVA Clinic Trail Effect of Robot-Assisted Gait Training on Freezing of Gait in Parkinson's Disease, received date Jan 2009*
9	*List Chemicals Used In Vietnam War (source Vietnam Veterans of America)*
10	*List Chemicals Used In Vietnam War (source Vietnam Veterans of Australia)*
11	*Public Law 102-4*
12	*J.F. Brundage, CONSERVING THE FIGHTING STRENGTH: MILESTONES OF OPERATIONAL MILITARY PREVENTIVE MEDICINE RESEARCHMilitary Preventive Medicine: Mobilization and Deployment, Volume 1*
13	*Jaime M. Hatcher, et al.,Parkinson's disease and pesticides: a toxicological perspective 2008,doi:10.1016/j.tips.2008.03.007*
14	*Australia, The Third Vietnam Veteran Mortality Study 2005*
15	*Dr Eileen J Wilson, et al.,Health effects of Vietnam service, ADF Health 2003; 4: 59-65*
16	*Nelson L M, et al. 2005; Laino, Neurology Today. 2005. June (5)6: 48)*
17	*F. Kamel,et al, Pesticide Exposure and Self-reported Parkinson's Disease in the Agricultural Health Study, American Journal of Epidemiology Vol. 165, No. 4 DOI: 10.1093/aje/kwk024,November 20, 2006*
17A	*Michael C. R. Alavanja, et al. Agricultural Health Study (AHS) Iowa Study Update 2007 www.aghealth.org*
18	*L. Brighina, et al. -Synuclein, pesticides, and Parkinson disease A case– control study Published Ahead of Print on March 5, 2008 as 10.1212/01.wnl.0000304049.31377.f2*
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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.

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 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.

- Dr. 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 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 neurofribillas 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.