

# Parkinson's Disease Service Related Update

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**San Francisco, CA**



**Parkinson's  
Disease**

Research,  
Education &  
Clinical Center

*San Francisco VA  
PADRECC*



**UCSF**

Weill Institute for  
Neurosciences

Department of  
Neurology

# Parkinson's Disease Service Related Update

- Scientific background
- Presumptions – Service connected
- VA services

What Causes PD?

# Twins: Mother Nature's Controlled Study



- MZ twins share ~100% of genes
- DZ twins share ~50% of genes

**Hypothesis:** If Parkinson's disease is primarily a genetic disorder, then concordance in MZ twins should be > than in DZ twins.

## Results:

Twins aged 72-82:

**MZ & DZ concordance similar;  
Except in young onset MZ > DZ**



*NAS/NRC WWII  
VETERAN TWINS ROSTER  
31,848 TWINS BORN 1917 - 1927*

**Twenty year followup:**

**11 living, 97% valid NDI matches**

# Concordance for Parkinson's Disease in Twins: a 20-year Update

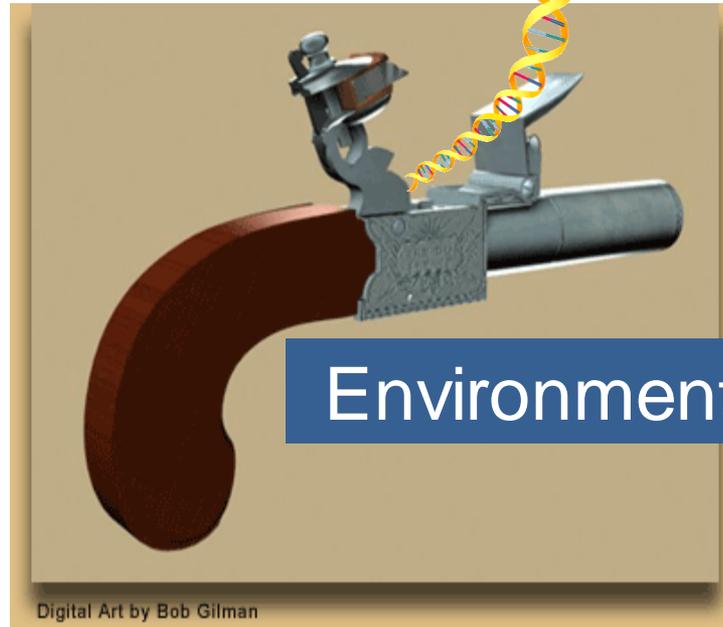
- U.S. National Death Index (NDI) through 12/31/2015
- ICD codes – underlying & all causes of death

PD dx age in twin-1	Zygoty	Concordance		MZ:DZ Concordance Ratio (95% CI) & Heritability (h <sup>2</sup> )		MZ:DZ Hazard Ratio (95% CI)
		Pairwise	Probandwise	Pairwise	Probandwise	
Overall	MZ	<b>0.17</b>	<b>0.20</b>	1.5 (0.8-3.0)	1.6 (0.9-3.0)	1.38 (0.67-2.83)
	DZ	<b>0.11</b>	<b>0.14</b>	<b>h<sup>2</sup>= 0.13</b>	<b>h<sup>2</sup>=0.16</b>	
≤ 50	MZ	<b>0.67</b>	<b>0.75</b>	3.3 (0.9-13.0)	3.75 (1.02-13.8)	3.76 (0.68-20.7)
	DZ	<b>0.20</b>	<b>0.20</b>	h <sup>2</sup> =0.61	h <sup>2</sup> =0.73	
>50	MZ	<b>0.14</b>	<b>0.16</b>	1.4 (0.7-3.1)	1.4 (0.7-2.8)	1.28 (0.57-2.91)
	DZ	<b>0.10</b>	<b>0.11</b>	<b>h<sup>2</sup>=0.11</b>	<b>h<sup>2</sup>=0.10</b>	

**Conclusion: Environment is an important contributor to the cause of PD**

# Parkinson's Disease : A Complex Disorder

Genetics loads the gun



Environment pulls the trigger

Digital Art by Bob Gilman

# Pesticides



# Polychlorinated Biphenyls



# Head Injury



# Solvents



## Some Factors Associated with a Higher Risk of Parkinson's Disease



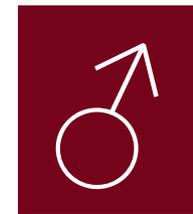
Age



Metals?



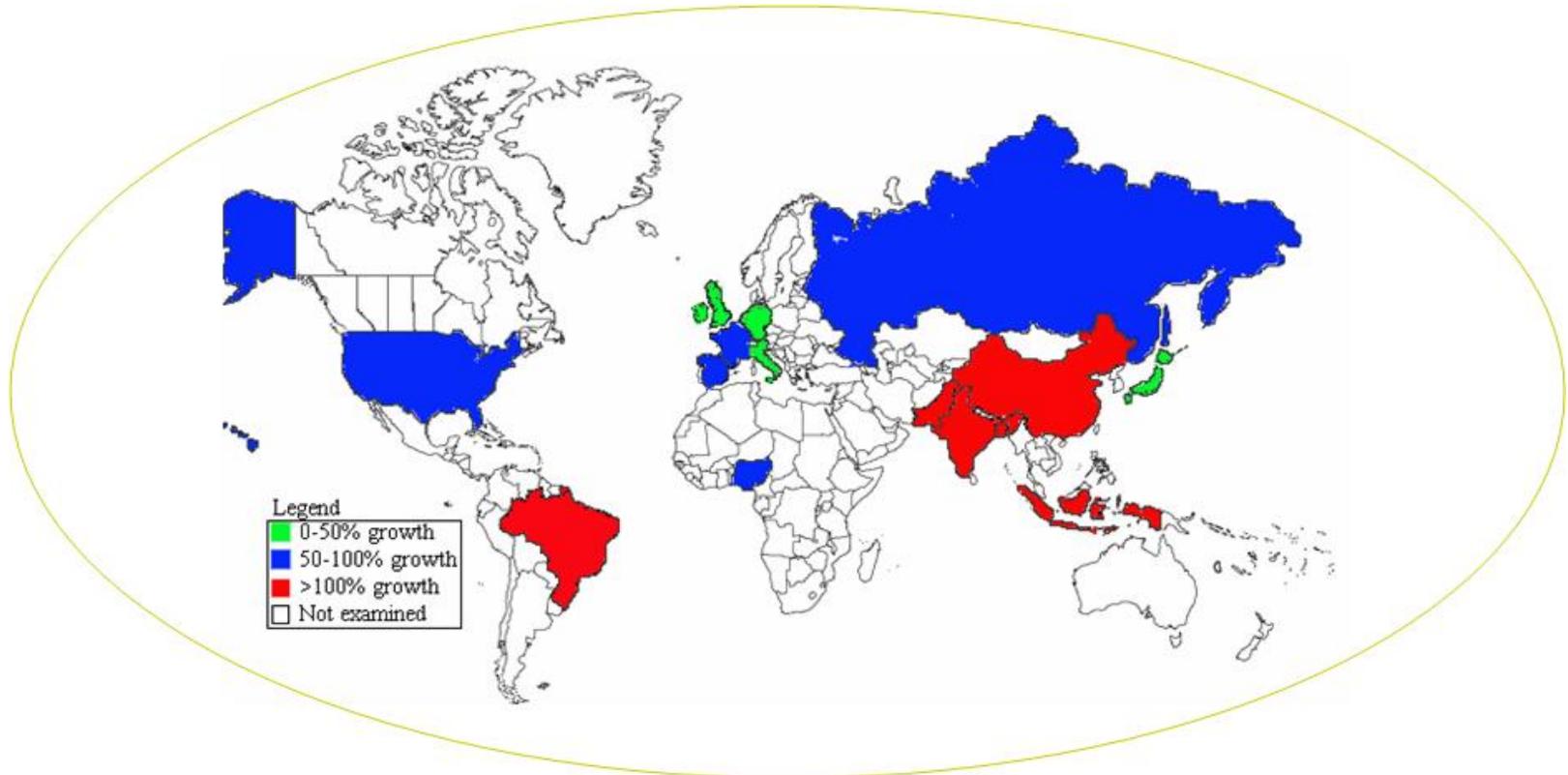
Air Pollution



Male Gender

The global burden of Parkinson's disease is expected to increase with increasing life expectancy worldwide

**Change in number of people with Parkinson's disease in the world's most populous nations from 2005 to 2030\***



\*Among individuals over 50 in the world's ten most and Western Europe's five most populous nations

Source: Dorsey et al, Neurology 2007;68:384-6

# The Economic Burden of PD in the U.S.A. 2017 - 2037

## Excess Medical Costs Due to PD, 2017: \$25,348 Billion

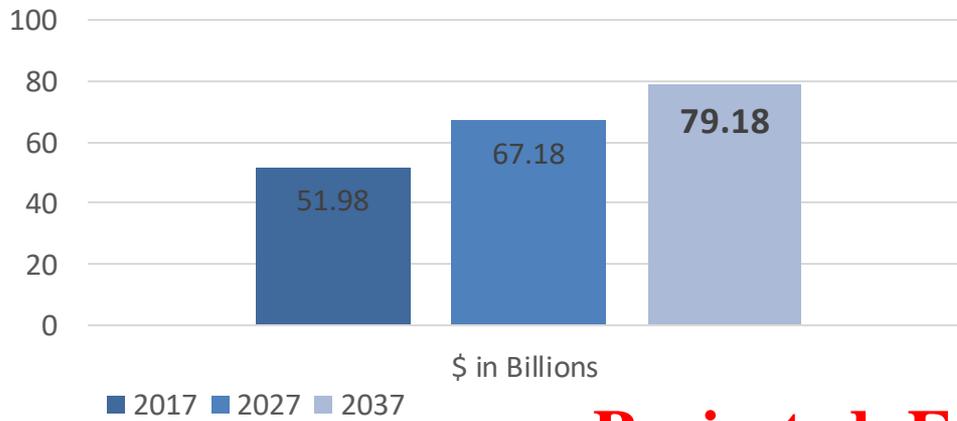
Age	Total Excess Medical Cost due to PD		Mean Excess Cost due to PD (\$, Billions)
	Cost in Billions	Percentage of the Total	
≤49	490	2%	29,346
50-64	4,153	16%	22,598
65-74	8,858	35%	23,011
≥75	11,847	47%	26,222
<b>Overall</b>	<b>25,348</b>	<b>100%</b>	<b>24,439</b>

**Total  
Economic  
Burden Of  
PD, 2017:  
\$51.9  
Billion**

## Indirect Costs Due to PD, 2017: \$26,509 Billion

	PWP Loss	Care Partner Loss	PWP & Care Partner
<b>Attributable Death</b>	2,508	NA	2,508
<b>Reduced Employment</b>	1,873	802	2,675
<b>Absenteeism</b>	1,395	3,655	5,050
<b>Presenteeism</b>	1,263	1,684	2,946
<b>Social Productivity Loss</b>	623	410	1,034
<b>Disability Income</b>			
Supplemental security income (SSI)	561	NA	561
Social security disability insurance (SSDI)	1,677	NA	1,677
Other disability income	2,521	NA	2,521
<b>Non-Medical Costs</b>			
Paid daily non-medical care	3,847	NA	3,847
Home modification	2,232	NA	2,232
Motor vehicle modification	931	NA	931
Other expenses	527	NA	527
<b>Overall</b>	<b>19,958</b>	<b>6,551</b>	<b>26,509</b>

## Projected Increase in Total Economic Burden 2017-2037



**Projected Economic Burden Of PD, 2037:  
\$79.18 Billion**

# Parkinson's Disease at VA

- Estimated number receiving care with Parkinson's Disease: 80,000\* ~ 110,000 in 2017 & at least 130,000 Veterans or surviving spouses

**Estimates do not include veterans receiving care outside of VAHCS.**

\*<http://www.va.gov>

# Veterans with Parkinsonism

## Taking an Exposure History

- **Service history**
  - Years/ages, branch, rank, occupation, locations,
  - Combat? POW?
- **Exposure assessment**
  - Jobs, tasks? Known exposures? Where? When? Duration? Route(s) of exposure? Precautions?
  - Symptoms? Treatments?
- **Traumatic Brain Injury**
  - How many? When? Where? Loss of consciousness? How long? Hospitalized? Signs/symptoms?
- **Documentation? Witnessed? Others exposed?**

# Parkinson's Disease – Presumptive Relationship to Qualifying Military Service

**Presumptive diseases:** Certain diseases assumed by VA to be related to a Veteran's qualifying military service.

## **Parkinson's disease:**

Agent Orange (qualifying service in Vietnam, Korea, other) + *Parkinsonism 2021*

Camp Lejeune residence (Cl solvents in H<sub>2</sub>O)

Traumatic brain injury (2ary)

# Exposure Related Health Concerns

Veterans may be exposed to a wide variety of hazards and potentially harmful substances during military service that may cause health problems.



## Agent Orange Related Diseases

Certain cancers and other diseases linked to Agent Orange



## Birth Defects

Certain birth defects in Veterans' biological children associated with military service in Vietnam or Korea



## Gulf War Veterans' Illnesses

Medical conditions linked to service during the Gulf War Era (Aug. 2, 1990 to present)



## Infectious Diseases

Nine infectious diseases associated with Southwest Asia and Afghanistan military service



## Radiation Related Diseases

Certain cancers linked to ionizing radiation exposure during military service



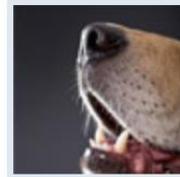
## Vaccinations & Medications During Service

Possible health effects of certain military vaccinations and medications



## Toxic Embedded Fragments

Shrapnel and other metals that remain in the body after injury



## Rabies

Disease transmitted by bite or saliva from an infected warm-blooded animal



## Traumatic Brain Injury

Often caused by explosions among Veterans who served in Iraq and Afghanistan



## Heat Injuries

Health problems that could be caused by extremely hot temperatures



## Cold Injuries

Health problems associated with extremely cold temperatures



## Occupational Hazards

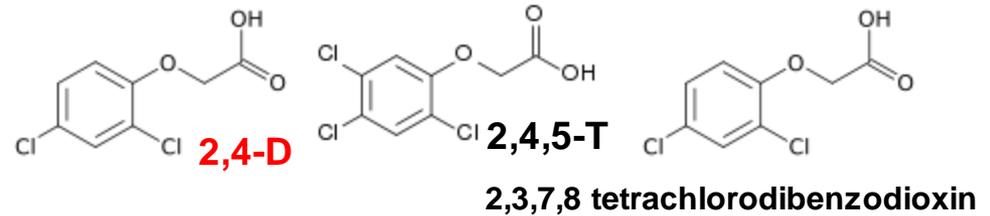
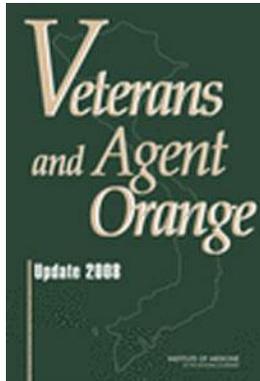
Exposures from working with chemicals, paints, and machinery during service

# Agent Orange & Parkinson's Disease Risk

Operation Ranch Hand:

1962-1971

20 x 10<sup>6</sup> gallons Agent Orange



UNITED STATES  
DEPARTMENT OF VETERANS AFFAIRS



- 2009: Agent Orange Linked to Parkinson's Disease established service-connection:
  - Certain Vietnam Veterans may be eligible for: [disability compensation](#) and [health care benefits](#).

# Agent Orange Exposure: Qualifying Military Service

## Exposure to Agent Orange by Location

- **Exposure to Agent Orange in Vietnam**

Presumed exposure on land in Vietnam, on a vessel operating on the inland waterways of Vietnam, or on a vessel operating not more than 12 nautical miles seaward from the demarcation line of the waters of Vietnam and Cambodia as defined in [Public Law 116-23](#) (Blue Water Navy Vietnam Veterans Act 2019) between January 9, 1962 and May 7, 1975

- **C-123 Airplanes and Agent Orange Residue**

Possible exposure of C-123 flight, ground maintenance, and aeromedical crew members to herbicide residue in C-123 planes flown during and after the Vietnam War

- **Korean Demilitarized Zone**

Presumed exposure for units determined by VA and DoD to have operated along the demilitarized zone in Korea between Sept. 1, 1967, and August 31, 1971.

- **Thailand Military Bases**

VA considers disability benefits claims based on exposure to herbicides on a U.S. military base in Thailand or Royal Thai Air Force base between January 9, 1962, and May 7, 1975, on a case-by-case basis.

- **Herbicide Tests and Storage Outside Vietnam**

Possible exposure due to Department of Defense herbicide tests and storage at military installations in the United States and at locations in other countries.



Aircraft spraying herbicides

# William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021

## SEC. 9109. ADDITIONAL DISEASES ASSOCIATED WITH EXPOSURE TO CERTAIN HERBICIDE AGENTS FOR WHICH THERE IS A PRESUMPTION OF SERVICE CONNECTION FOR VETERANS WHO SERVED IN THE REPUBLIC OF VIETNAM.

Section 1116(a)(2) of title 38, United States Code, is amended by adding at the end the following new subparagraphs:

“(I) Parkinsonism. “(J) Bladder cancer. “(K) Hypothyroidism.”.

- Passed [House](#) and [Senate](#) with veto-proof majorities 12\11\2020.
- President Trump [vetoed](#) on 12\23\20..
- House & Senate voted to override veto 12\28 & 1\1\21, respectively.
- First and only veto override of Trump's presidency.

History: IOM 2016 report included the term “Parkinson’s-like symptoms” under PD as presumptive disease associated with Agent Orange. OMB objected & VA leadership changed - did not go forward.

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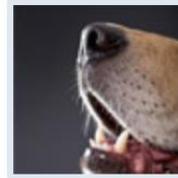
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Health problems associated with extremely cold temperatures



**Occupational Hazards**  
Exposures from working with chemicals, paints, and machinery during service

# Traumatic Brain Injury (TBI) & Parkinsonism

## 2<sup>ary</sup> Service Connection

- [December, 2013: 38 CFR 3.310\(d\)](#) was amended to establish an association between TBI and certain illnesses:

In the absence of clear evidence to the contrary, Parkinsonism, including Parkinson's disease, following moderate or severe TBI is held to be a secondary result of TBI.

# Head Injury and PD Risk in WWII Veteran Twins

Goldman, Tanner et al, Annals of Neurology 2006

Subjects: 93 discordant pairs with complete information  
→ 26 pairs with at least one head injury

Results: 14.7% with head injury; 7.8% hospitalized

Head injury 37.4 yrs (mean) *before* PD onset

	<u>OR</u>	<u>95% CI</u>	<u>p-value*</u>
<b>Overall</b>	<b>3.0</b>	<b>1.14-9.2</b>	<b>0.023</b>
<b>MZ</b>	<b>3.3</b>	<b>0.86-19</b>	<b>0.092</b>
<b>DZ</b>	<b>2.7</b>	<b>0.64-16</b>	<b>0.23</b>

→ PD risk further increased with > 1 head injury:

1 injury: OR 2.6 (1.07, 6.5; p = 0.035)

2 injuries: OR 5.1 (0.54, 48; p = 0.16)

Test for trend 0.042

# VA & DOD Definitions of TBI Severity

	Mild	Moderate	Severe
Structural Imaging	NL	NL or ABNL	NL or ABNL
Loss of consciousness	0 to 30 min	30 min – 24 hrs	> 24 hrs
Alteration of consciousness	1 min – 24 hrs	> 24 hrs	> 24 Hrs
Posttraumatic amnesia	< 24 hrs	24 hrs – 1 week	> 1 week
GCS*	13 to 15	9 to 12	< 9

Glasgow Coma Scale (GCS):

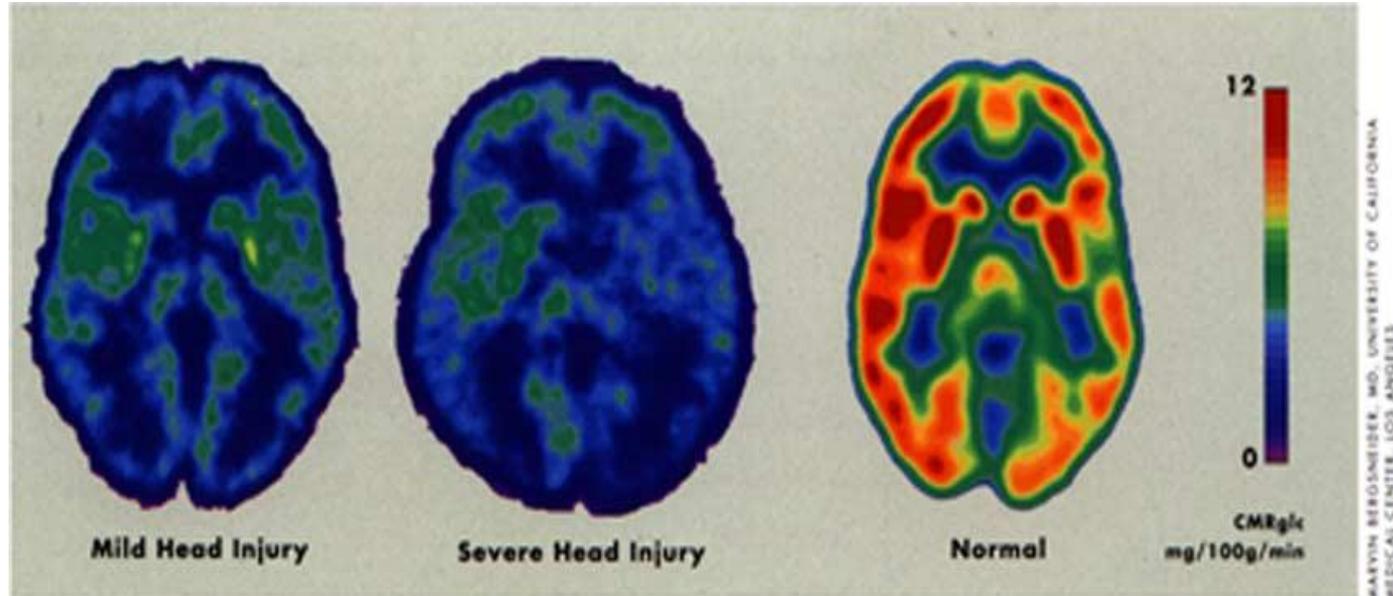
Eye opening: NI = 4...No response = 1

Best verbal response: Oriented = 5...No response = 1

Best motor response: Obeys commands for movement = 6... No response = 1

# Clinically defined head injury “severity” is poorly correlated with metabolic derangement

[<sup>18</sup>F]deoxyglucose PET Scan in Mild & Severe Head Injury



Bergsneider, et al. J Neurotrauma, 17(5), 2000.

- Est. 90% of military head injuries are mild.
- Interval between mild head injury and PD can be decades.

Is there more to understand?

# Chemicals

Veterans' exposure to the chemicals listed below potentially could be linked to certain health problems, depending on a number of other factors.



## Agent Orange or Other Herbicides

Herbicides used during the Vietnam era to destroy foliage and crops



## Pesticides (Gulf War)

Substances used to repel or destroy pests such as insects and pathogens



## Burn Pits

Open-air pit waste disposal at military sites



## Depleted Uranium

Uranium used in military tank armor and some bullets



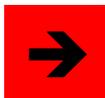
## Sulfur Fire (Al Mishraq, Iraq)

Sulfur plant burned almost a month in June 2003; large amounts of sulfur dioxide released into the air



## Chromium (Qarmat Ali)

Hexavalent chromium in sodium dichromate dust; water treatment plant in 2003



## Camp Lejeune Water Supplies

Tap water contaminated by industrial chemicals at Marine Corps Base Camp in the 1950s to 1980s



## PCBs

Polychlorinated biphenyl used as coolant and insulating fluid



## Industrial Solvents

Usually liquid, used to dissolve, degrease, clean, strip paint, etc.



## PFAS

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) found in products, including fire-fighting foams

# Camp Lejeune N.C.

## History:

1953-1985 - Water contaminated with TCE & PCE (i.e., PERC)

1980 – Contaminants discovered

1987- Wells closed

1989 - EPA Superfund

**500,000 – 1 million exposed**

Military: Marines, National Guard, reservists

Civilian: Family members, employees

**Sources of exposure:** Drinking water, bathing, inhalation, swimming, recreation

## Exposure levels:

Est. monthly median (max. mean) ug/L:

PCE: 85 (158); TCE: 366 (783)

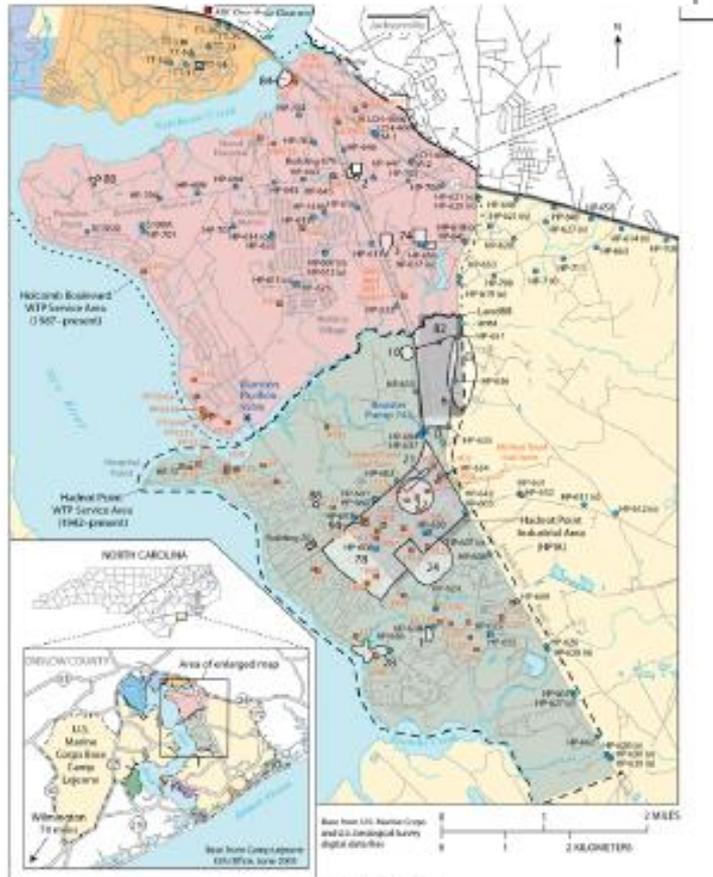
**vs. US max. contaminant level: 5 ug/l**

## Dept. of Veterans Affairs 2017

- 30 or more days of service  
8/1/1953 to 12/31/1987
- Entitled to benefits



Figure 1. The Hadnot Point-Holcomb Boulevard Water Distribution Areas, U.S. Marine Corps Base Camp Lejeune, North Carolina



# Other Hazards Associated with PD but No VA Presumption

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# Trichloroethylene: Parkinsonism and Complex 1 Mitochondrial Neurotoxicity

Don M. Gash, PhD,<sup>1,2</sup> Kathryn Rutland, MPH, MD,<sup>3</sup> Naomi L. Hudson, MPH,<sup>1</sup> Patrick G. Sullivan, PhD,<sup>1,4</sup>  
Guoying Bing, MD, PhD,<sup>1</sup> Wayne A. Cass, PhD,<sup>1,2</sup> Jignesh D. Pandya, PhD,<sup>4</sup> Mei Liu, MD,<sup>1</sup>  
Dong-Yong Choi, MS,<sup>1</sup> Randy L. Hunter, MS,<sup>1</sup> Greg A. Gerhardt, PhD,<sup>1,2,5</sup> Charlie D. Smith, MD,<sup>1,5</sup>  
John T. Slevin, MD,<sup>2,5</sup> and T. Scott Prince, MD<sup>3</sup>

3 PD patients, small industry, all exposed to TCE

65/134 coworkers responded to questionnaire

21 endorsed symptoms

14 with clinical signs of parkinsonism on exam

# PD & Occupational Solvent Exposure in 99 Discordant Twin Pairs

Goldman, Tanner, Quinlan, et al, Ann Neurol 2012

- NAS/NRC WWI Veteran Twins
- Male twins discordant for PD
- NIH criteria by consensus of 2 movement disorder neurologists (CMT, GWR)
- Lifelong job task specific occupational history
- Exposure assigned by industrial hygienist unaware of case status

Solvent	Odds Ratio Ever/Never	95% Confidence Interval	p-value
TCE	6.1	1.2-33	0.034
PERC	10.5	0.97-113	0.053

# Pesticides used in the Gulf War

Pesticides used in the Gulf War fall into several major categories:

- Methyl carbamate organochlorine pesticides (lindane), used to treat uniforms
- DEET, used on the skin as an insect repellent
- Organophosphorus (OP) pesticides
- Pyrethroid pesticides (primarily permethrin)



Lindane and DEET were used as personal insect repellents, lindane to treat uniforms and DEET on the skin. All other pesticides shipped to the Gulf region were to be used only by specially trained individuals or for specific applications.

Visit the Deployment Health and Family Readiness Library to learn how DEET and permethrin-impregnated clothing are used during service.

# Head Injury, Paraquat Use and Risk of PD

Goldman et al 2012

**83 PD and 328 controls with complete data in FAME**

- **Head injury in 19%**
- **Paraquat used by 17%, all men**

Head injury	Paraquat Use	Odds Ratio
No	No	1.0 (ref)
Yes	No	1.2
No	Yes	1.8
<u>Yes</u>	<u>Yes</u>	<u>4.2</u>

**Head injury and paraquat use were synergistically associated with increased PD risk**

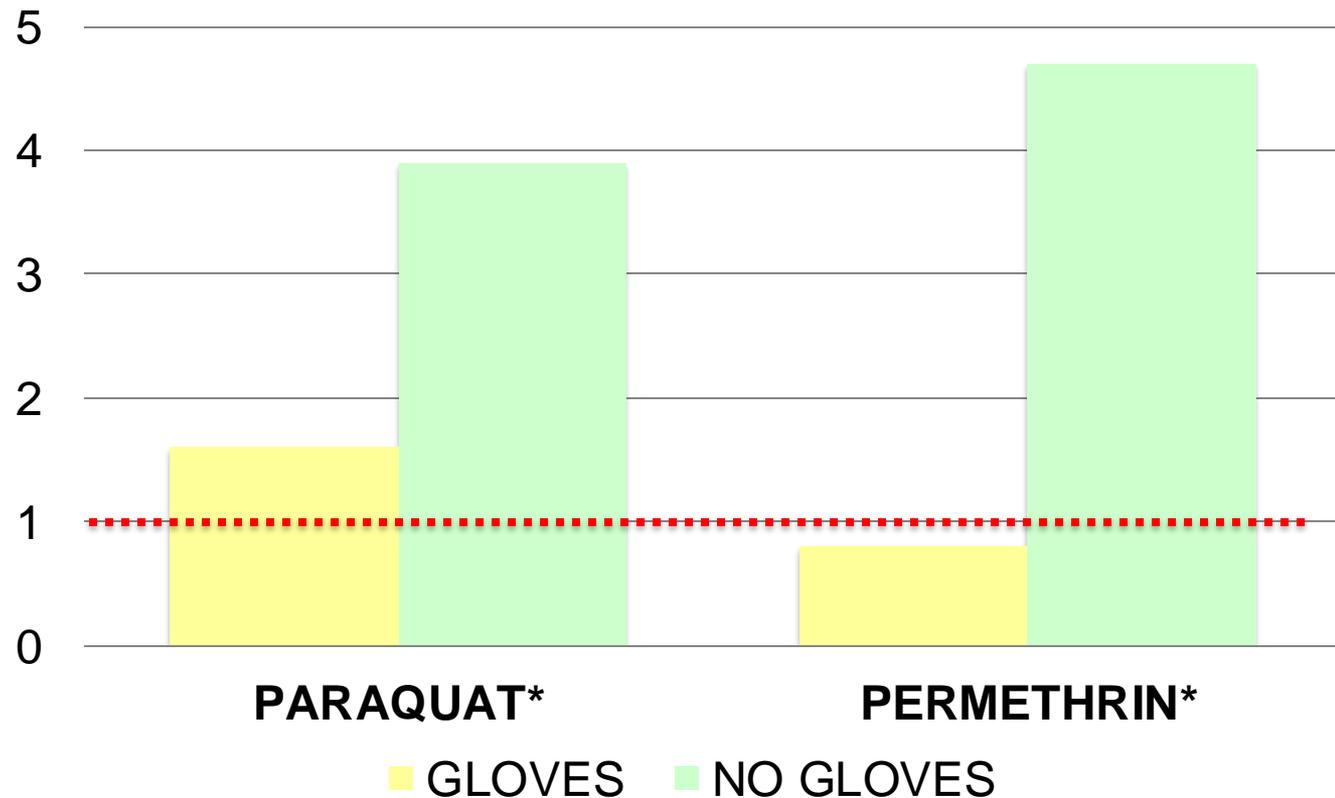
**Both cause oxidative stress**

**Joint effects are synergistic in animal model (Hutson, 2011).**

# Is Preventing PD Possible?

## *Preliminary Results*

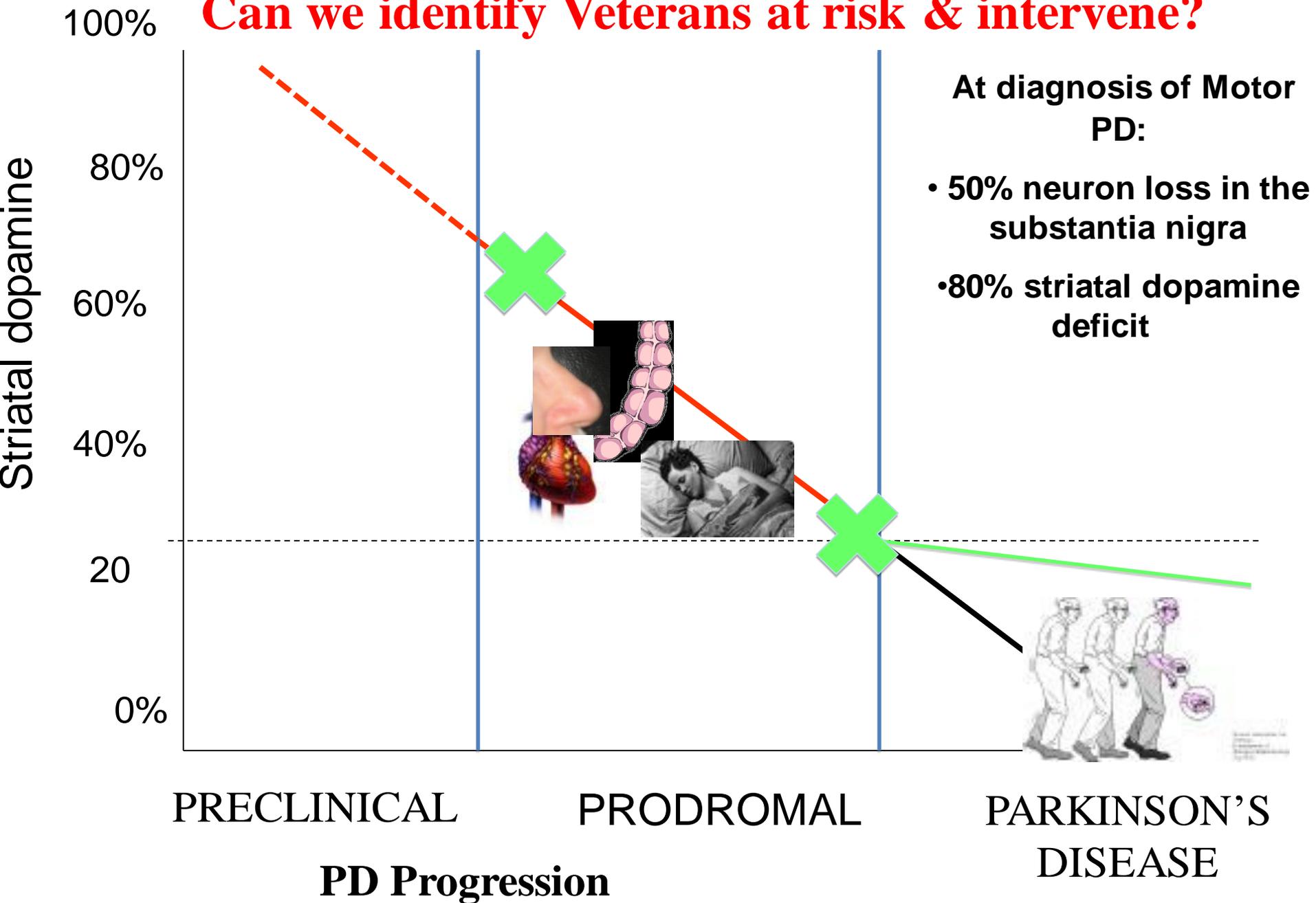
**Increased Risk of PD Was Not Observed in Farmers Using Gloves During Pesticide Application**



Primary Prevention:

- Remove causative factors
- Disease process never initiated

# Can we identify Veterans at risk & intervene?



# VA Services

# Public Health

## Public Health

Public Health Home

## Military Exposures

Military Exposures Home

4 Ways to Find Exposures

Agent Orange

Gulf War Veterans' Illnesses

Airborne Hazards and Burn Pits

Radiation

Benefits

## Military Exposures



Veterans may have been exposed to a range of chemical, physical, and environmental hazards during military service.

### MILITARY EXPOSURES & YOUR HEALTH NEWSLETTER

Read the latest issue of [Military Exposures & Your Health](#), a biannual newsletter for Veterans with service from 1990 to the present. This issue covers news on environmental exposures and health, environmental health registries, research, and more.

## 4 Ways to Find Exposures

### Registry Evaluation

A free [medical assessment](#) for possible health problems related to specific environmental hazards

### Health Care

[Health care services](#) for eligible Veterans, how to qualify and apply

### Research Studies

Find out about [military exposure-related research studies](#)

### Publications & Reports

Use these [resources and media materials](#) on military exposures and Veterans

### Provider Resources



[Exposure Ed App](#)

[Health Registry Programs](#)

[Exposure Assessment](#)

[Agent Orange for Providers](#)

[Gulf War Veterans' Illnesses for Providers](#)

[Diagnosis and Treatment of Exposure Health Effects](#)

Good resource for patients & providers:  
[Publichealth.va.gov](http://Publichealth.va.gov)

## Discuss VA services with the Veteran

VA offers specialized programs to address health issues related to deployment. Providers should encourage their patients to [enroll in VA health care](#) in order to take advantage of these services as part of their overall health care plan.

- **VA Environmental Health Clinics**

Environmental Health Clinicians provide specialized knowledge about potential environmental exposures and conduct [exams for registry programs](#): Ionizing Radiation, Agent Orange, Gulf War (includes Operations Iraqi Freedom and New Dawn), and Depleted Uranium. Find local [VA Environmental Health Coordinator](#).

- **War Related Illness and Injury Study Center (WRIISC)**

Three locations nationwide provide telephone or inter-facility consultations: Washington, DC; East Orange, NJ; and Palo Alto, CA. WRIISC provides medical evaluations and treatment plans for chronic, difficult-to-diagnose conditions related to deployment.



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# Public Health

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Birth Defects

Benefits

Exposure Locations

Provider Resources

## Benefits Overview for Agent Orange Exposure

VA offers health registry exams, health care, disability compensation and other benefits to eligible Veterans. Their dependents and survivors also may be eligible for benefits.

### Health care for Veterans

Veterans who were exposed to Agent Orange or other herbicides during military service may be eligible for:

- [Agent Orange Registry health exam](#), a free exam for possible long-term health problems related to herbicide exposure. Veterans who served in Vietnam, the Korean demilitarized zone or other areas where Agent Orange was sprayed may be eligible.
- [Health care benefits](#), a full range of medical benefits. There are many ways a Veteran may qualify.

### Disability compensation for Veterans

VA HEALTH CARE

Apply Now



4 WAYS TO FIND MILITARY EXPOSURES

### CONTACT

Health Care  
877-222-8387

# Benefits for Camp Lejeune Exposure

## Disability compensation

VA has established a presumptive service connection for Veterans, Reservists, and National Guard members exposed to contaminants in the water supply at Camp Lejeune from August 1, 1953 through December 31, 1987 who later developed one of the following eight diseases:

- Adult leukemia
- Aplastic anemia and other myelodysplastic syndromes
- Bladder cancer
- Kidney cancer
- Liver cancer
- Multiple myeloma
- Non-Hodgkin's lymphoma
- Parkinson's disease

Presently, these conditions are the only ones for which there is sufficient scientific and medical evidence to support the creation of presumptions; however, VA will continue to review relevant information as it becomes available.

The registry data helps VA understand and respond to these health problems more effectively.

You may be eligible to participate in one or more of these health registries:

- [Agent Orange Registry](#)
- [Airborne Hazards and Open Burn Pit Registry](#)
- [Gulf War Registry](#) (includes Operations Iraqi Freedom and New Dawn)
- [Ionizing Radiation Registry](#)
- [Depleted Uranium Follow-Up Program](#)
- [Toxic Embedded Fragment Surveillance Center](#)

Use the chart below to help determine your eligibility.

Period of Military Service	Agent Orange	Airborne Hazards and Open Burn Pit	Depleted Uranium Follow-up	Gulf War	Ionizing Radiation	Toxic Embedded Fragments
1940s–1950s					●	
1960s	●				●	
1970s	●					
1990s		●	●	●		
2000s–Present		●	●	●		●

Contact your local [VA Environmental Health Coordinator](#) about getting a registry evaluation. You do not need to enroll in VA's health care system to take part.

Thank You

