Agent Orange Exposure and Monoclonal Gammopathy of Undetermined Significance An Operation Ranch Hand Veteran Cohort Study

Presented by Joel Michalek, PhD

9 November 2015

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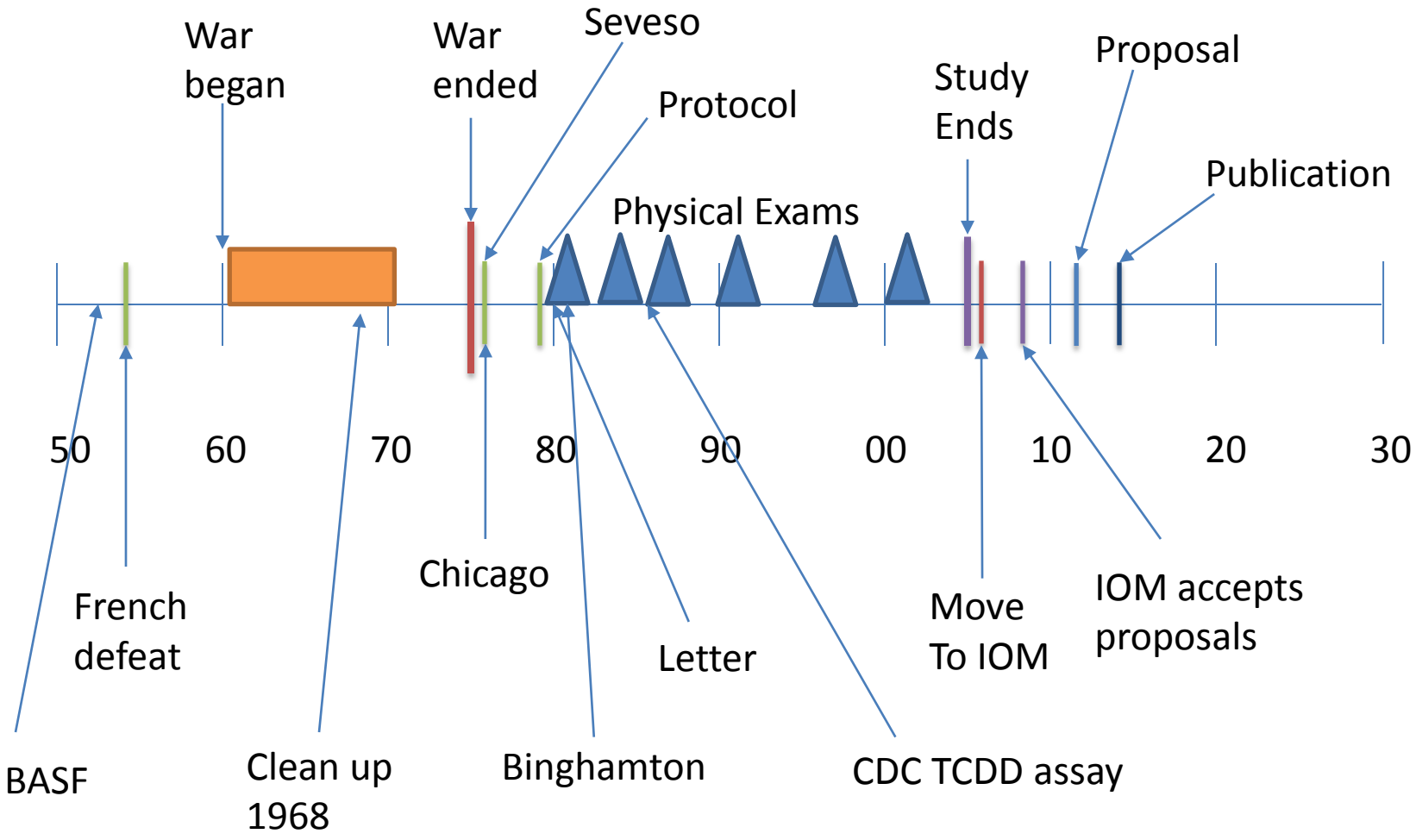
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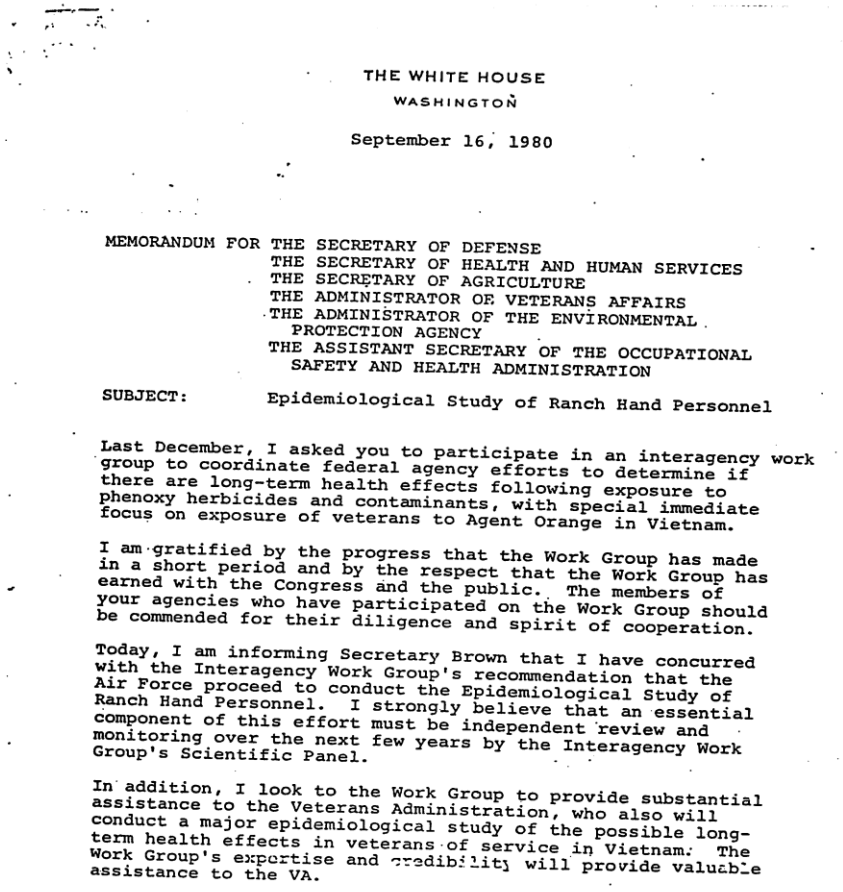
Reference

- Agent Orange Exposure and Monoclonal Gammopathy of Undetermined Significance An Operation Ranch Hand Veteran Cohort Study. *JAMA Oncol.* *doi:10.1001/jamaoncol.2015.2938*

Background


War began
War ended
Seveso
Protocol
Physical Exams
Study Ends
Proposal
Publication
50
60
70
80
90
00
10
20
30
BASF
French defeat
Clean up 1968
Chicago
Binghamton
Letter
CDC TCDD assay
Move To IOM
IOM accepts proposals

Letter



THE WHITE HOUSE

WASHINGTON

September 16, 1980

MEMORANDUM FOR THE SECRETARY OF DEFENSE
THE SECRETARY OF HEALTH AND HUMAN SERVICES
THE SECRETARY OF AGRICULTURE
THE ADMINISTRATOR OF VETERANS AFFAIRS
THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY
THE ASSISTANT SECRETARY OF THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

SUBJECT: Epidemiological Study of Ranch Hand Personnel

Last December, I asked you to participate in an interagency work group to coordinate federal agency efforts to determine if there are long-term health effects following exposure to phenoxy herbicides and contaminants, with special immediate focus on exposure of veterans to Agent Orange in Vietnam.

I am gratified by the progress that the Work Group has made in a short period and by the respect that the Work Group has earned with the Congress and the public. The members of your agencies who have participated on the Work Group should be commended for their diligence and spirit of cooperation.

Today, I am informing Secretary Brown that I have concurred with the Interagency Work Group's recommendation that the Air Force proceed to conduct the Epidemiological Study of Ranch Hand Personnel. I strongly believe that an essential component of this effort must be independent review and monitoring over the next few years by the Interagency Work Group's Scientific Panel.

In addition, I look to the Work Group to provide substantial assistance to the Veterans Administration, who also will conduct a major epidemiological study of the possible long-term health effects in veterans of service in Vietnam. The Work Group's expertise and credibility will provide valuable assistance to the VA.

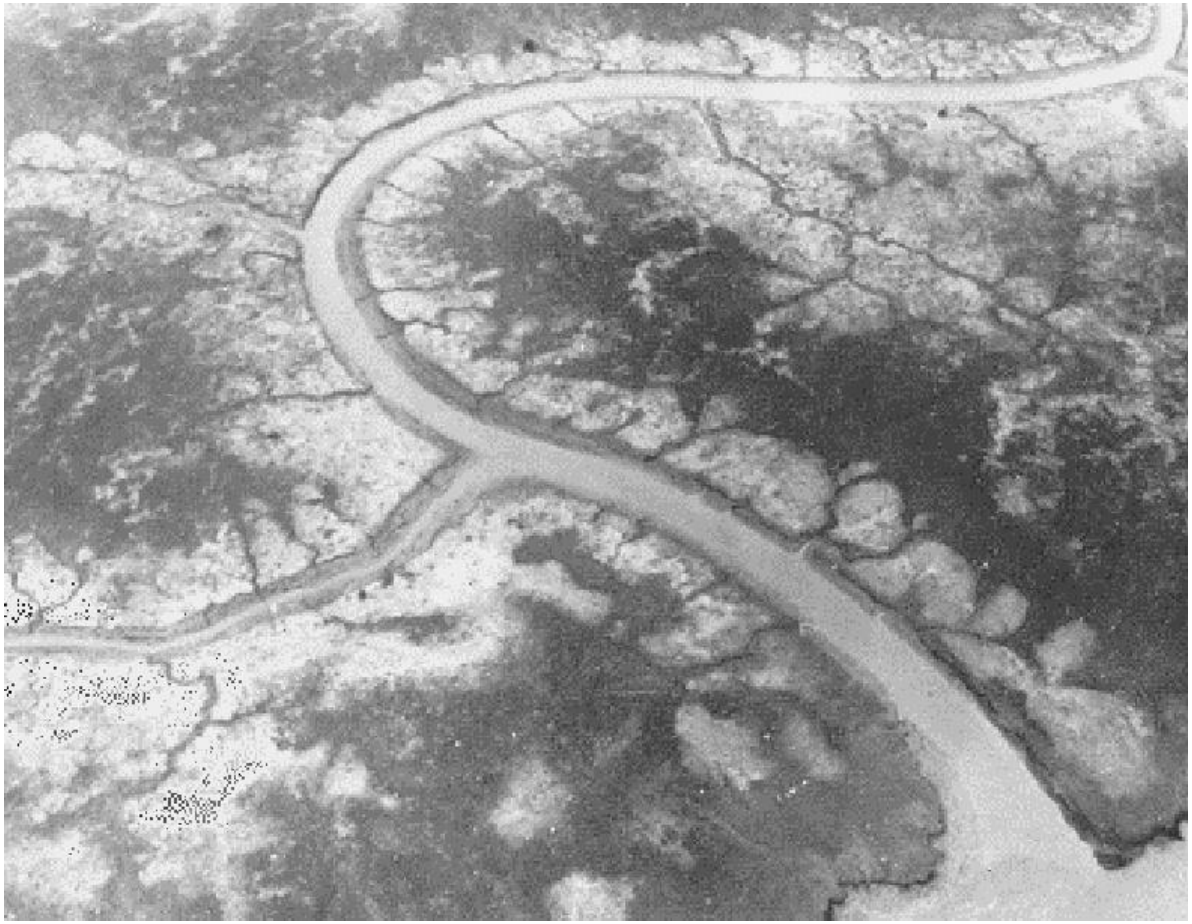
Herbicides in Vietnam: 1962-71



Before



After



TCDD-contaminated herbicides[1,2]

Code name	Gallons sprayed	Period	TCDD (pm)
Purple	145,000	1962-1964	32.8
Pink	122,792	1962-1964	65.6
Green	8,208	1962-1964	65.6
Orange	11,261,429	1965-1970	2-3 ppm

1. Containing 2,4,5-T
2. Veterans and Agent Orange. National Academy Press, 1994, Table 3-4

Design

- Matched cohort study
  - ~1200 Ranch Hand veterans
  - ~19,000 Comparison veterans
    - ~1600 matched to Ranch Hands (age, race, occupation)
- Repeated
  - Physical examinations
  - Questionnaires
  - TCDD assays

Endpoints

- Cancer
- Diabetes
- Cardiovascular disease
- Reproductive outcomes
- Mortality
- Clinical, psychological, reproductive abnormalities

Methods

- Binary, continuous, time-to-event outcomes
- Group contrasts
- TCDD category contrasts
- Main effects ANCOVA, PH, LR models
- Some interaction exploration in 1992
- All disease endpoints verified by record review
- Many covariates

MGUS Methods

- MGUS measured in 2002 serum in 2014
- Goals
  - Contrast cohorts on MGUS prevalence
  - Assess MGUS risk versus TCDD in the exposed cohort
- Inclusion criteria
  - At least 50 years of age at 2002 follow-up
  - Saved serum from 2002
  - Consented to use of data and specimens

MGUS Methods

- At total of 1349 veterans met inclusion criteria
  - 560 Ranch Hand
  - 789 Comparison
- We systematically selected
  - the oldest 480 Ranch Hands
  - Oldest 480 Comparisons stratified random sampling by the age distribution of the Ranch Hand age distribution 50-59, 60-69, 70-79, 80+

MGUS Methods

- Excluded veterans with
  - Waldenstrom macroglobulinemia
  - Solitary plasmacytoma
  - amyloidosis
- Final sample size[1]
  - Ranch Hand 479
  - Comparison 479

1. After excluding one veteran in each cohort with multiple meloma

MGUS Methods

- Covariates
  - Birth year
  - Military occupation
  - Body mass index
  - Drinking history
  - Smoking history
  - Serum creatinine levels
  - History of radiation therapy or exposure

MGUS Methods

- IRB approved
- All data de-identified
- Access to specimens approved by IOM
- Protein assays conducted at NIH

MGUS Methods

- MGUS defined by case definition
  - Landgren O. Hematology Am Soc Hematol Educ Program 2013:2013;478-487.

Results

Demographic Characteristics

	No. (%)				P Value[b]
	Ranch Hand (n=479)[a]		Comparison (n=479)[a]		
Age in 2002, y					
Median (IQR)	65.0	(58.0–70.0)	65.0	(59.0–70.0)	.76
55–59	143	(29.9)	144	(30.1)	
60–64	91	(19.0)	90	(18.8)	
65–69	120	(25.1)	120	(25.1)	
70–74	97	(20.3)	98	(20.5)	
75–89	28	(5.8)	27	(5.6)	
Men	479	(100)	479	(100)	
Race					
Black	23	(4.8)	20	(4.2)	.75
Non-black	456	(95.2)	459	(95.8)	
Body mass index[c]					
Median (IQR)	28.2	(25.7–31.2)	28.4	(26.1–31.0)	
Under weight	1	(0.2)	0	(0)	
Normal	90	(18.8)	77	(16.1)	.36
Over weight	225	(47.1)	246	(51.4)	
Obese	162	(33.9)	156	(32.6)	

a. Numbers may not total due to missing data
b. Kruskal-Wallis and Fishers Exact testing

Results

Demographic Characteristics

	No. (%)				P Value[b]
	Ranch Hand (n=479)[a]		Comparison (n=479)[a]		
Received treatment for cancer within 5 years[c]	9	(1.9)	7	(1.5)	.80
Tested positive for HIV infection[c]	1	(0.2)	0	(0)	
Occupation group					
Officer	236	(49.3)	228	(47.6)	
Enlisted flyer	94	(19.6)	78	(16.3)	.18
Enlisted ground	149	(31.1)	173	(36.1)	
Lifetime cigarette smoking, pack-yrs[c]					
Median (IQR)	8.0	(0–29.3)	7.5	(0–24.0)	.28
Lifetime drinking, drink-yrs[c]					
Median (IQR)	21.6	(7.4–48.9)	23.0	(9.1–53.5)	.30
Lipid-adjusted TCDD, ppt[d]					
Median (IQR)	10.5	(6.2–21.4)	4.1	(2.9–5.8)	
≤3.65	45	(9.4)	196	(40.9)	
3.66-5.80	68	(14.2)	169	(35.3)	<.0001
5.81-10.92	138	(28.9)	102	(21.3)	
>10.92	227	(47.5)	12	(2.5)	
Received treatment for cancer within 5 years[c]	9	(1.9)	7	(1.5)	.80

a. Numbers may not total due to missing data
b. Kruskal-Wallis and Fishers Exact testing

Results

Age-specific prevalence of MGUS among Ranch Hand and Comparison veterans

	MGUS and LC MGUS N/Total N Prevalence % (95% CI)				
Age Range, y	Ranch Hand Veterans		Comparison Veterans		P Value [a]
55-59	5/143	3.5 (1.1–8.0)	0/144	0	
60-69	18/211	8.5 (5.1–13.2)	7/210	3.3 (1.4–6.8)	
≥70	11/125	8.8 (4.5–15.2)	8/125	6.4 (2.8–12.2)	
All	34/479	7.1 (5.0–9.8)	15/479	3.1 (1.8–5.1)	.008

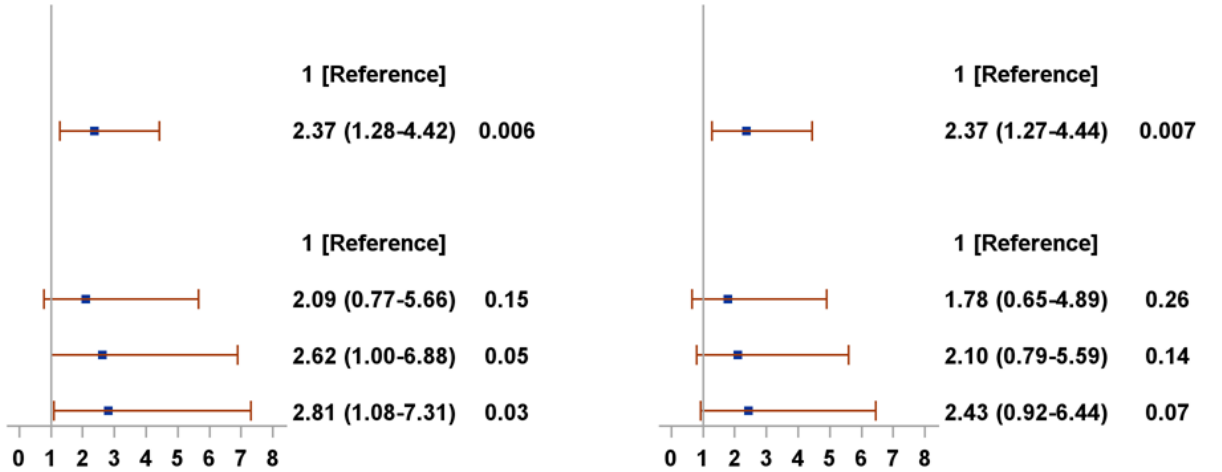
a. P-value by Fishers exact test

MGUS Summary

- MGUS risk was increased in the exposed cohort [Exposed 7.1% 95% CI 5.0-9.8, Control 3.1% 95% CI 1.8-5.1, p=0.008]
- When compared with veterans in the lowest TCDD level (≤3.65 ppt), the crude Ors for having MGUS were 2.09, 2.62. and 2.81 for veterans with TCDD levels of 3.66-5.8 ppt, 5.81-10.92 ppt, and >10.92 ppt; p=0.03. This became non-significant after adjustment (p=0.07).

TCDD Dose Response

	N (% MGUS)	Unadjusted Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)	P Value
Cohort Status					
Comparison	479 (3.1)	1 [Reference]		1 [Reference]	
Ranch Hand	477 (7.1)	2.37 (1.28-4.42)	0.006	2.37 (1.27-4.44)	0.007
Lipid-adjusted TCDD, ppt					
≤ 3.65	241 (2.5)	1 [Reference]		1 [Reference]	
3.66-5.80	237 (5.1)	2.09 (0.77-5.66)	0.15	1.78 (0.65-4.89)	0.26
5.81-10.92	239 (6.3)	2.62 (1.00-6.88)	0.05	2.10 (0.79-5.59)	0.14
> 10.92	239 (6.7)	2.81 (1.08-7.31)	0.03	2.43 (0.92-6.44)	0.07



Conclusions

- These results are consistent with patterns seen in industrial and agricultural sprayers
- To our knowledge this is the first observation and MGUS association with TCDD and Agent Orange exposure in Vietnam Veterans.



The End

- Questions?