

Minutes

Veterans' Advisory Committee on
Environmental Hazards

Subcommittee Study Evaluation Methodology

July 23, 1990

AVJ

At the meeting of the full Committee in May, 1990, it was suggested by several Committee members that the Committee needed to adopt a better method for communicating how it considers the weight of scientific evidence. Additionally, it was thought advisable to devise an approach for giving greater consideration to studies that were deemed to be inconclusive by the Committee. Doctors Yanders, Colton, Lathrop, Bender and Neel volunteered to serve on a subcommittee to address these issues.

The subcommittee members (absent Dr. Neel who was unable to attend the meeting) heard a presentation by Dr. Laurence Freedman, Biometry Branch, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health. Dr. Freedman provided an overview of meta analysis which he defined as "a quantitative method of combining results from different studies pertaining to a specific research question." He noted that meta analysis was appropriate where an investigator wanted to overcome the lack of power of individual studies to detect a small effect; to resolve controversies between apparently contradictory results of different studies, or to investigate the consistency of an observed effect in different settings. He discussed the techniques of meta analysis, providing several examples and answered questions that subcommittee members had.

After Dr. Freedman left, subcommittee members discussed the issues raised by his presentation and ways in which the technique could be applied to assist the Committee in its evaluation of studies. It was noted that one of the key elements of meta analysis was the weighting of particular studies. A concern of the members was that there should be an agreement as to the relative ranking in importance of studies and the relative significance or weight of their findings. It was agreed that the study types reviewed by the Committee fell into the following order ranked from strongest to weakest:

- Cohort studies
- Case control studies
- Cross-sectional analyses
- Standardized mortality ratio studies (SMR)
- Proportional mortality ratio studies (PMR)
- Correlational studies
- Case series
- Case reports
- Animal studies

The subcommittee agreed that this ranking would be applicable to both Agent Orange and radiation related studies.

2.

In addition to this rank ordering of studies, Dr. Lathrop suggested that an a priori numerical range be associated with each type of study to reflect the greater weight that they should have. The subcommittee accepted that idea in principle. The initial ranges proposed were:

<u>Study Type</u>	<u>Range</u>
Cohort studies	5-10
Case control studies	4-8
Cross-sectional analyses	3-7
Standardized mortality ratio studies (SMR)	3-6
Proportional mortality ratio studies (PMR)	2-5
Correlational studies	1-3
Case series	.01
Case reports	.05
Animal studies	--

Dr. Bender suggested that a quality factor should be considered. That is, in addition to considering the relative importance of a study by virtue of its design, there should be taken in to account how well the study was conducted. Some members suggested that this was putting too much elegance into the concept when it was not necessary. It was noted that the range in the weights would be sufficient to give added weight to a well conducted study of a particular type and lesser weight to poorly conducted study.

The subcommittee agreed to attempt to perform a meta analysis of the papers relating to soft tissue sarcoma when it reconvened the following morning.

Whereupon, the subcommittee adjourned.

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July 24, 1990

The subcommittee was provided a list of the studies relating to soft tissue sarcoma that the Committee had characterized as valid positive, valid negative and valid inconclusive. As a preliminary matter, it agreed to amend the weight ranges:

<u>Study Type</u>	<u>Range</u>	<u>Median</u>
Cohort studies	6-10	7
Standardized Incidence Ratio studies (SIR)	5-9	
Case control studies	4-8	5
Cross-sectional analyses	3-7	4
Standardized mortality ratio studies (SMR)	2-6	3
Proportional mortality ratio studies (PMR)	1-5	2
Correlational studies	1-3	
Case series	.01	
Case reports	.05	
Animal studies	--	

The median figure was designed to reflect the weight an average study of a particular type should have. It could be adjusted upwards or downwards depending on a member's assessment of the quality of the study. This suggestion led to a discussion of the necessity for a reviewer of a study to comment upon certain characteristics of the study so as to enable other Committee members to arrive better at a judgment about the study. It was agreed that a primary reviewer should discuss the following characteristics of the study under review:

Study design (type)

Whether the study is valid or invalid. If valid, whether it is positive, negative, or inconclusive.

Quality of exposure information

Quality of diagnosis or disease information

Size of the study

Accounting for latency

Magnitude of effect.

The members then applied their proposed methodology to the valid positive and negative studies relating to soft tissue sarcoma that the Committee had reviewed at its May, 1990 meeting. At the conclusion of their discussion of each study, each member assigned a weight to the study. At the conclusion, the scores from each member were totalled. The result indicated stronger weight had been given to the negative studies than to the positive studies. One explanation offered was that this process had not taken into account the valid inconclusive studies nor those other relevant studies that may have a bearing on the scientific judgment arrived at.

2.

The members agreed to defer any recommendation that meta analysis be employed by the Committee until they had further experience with it. They would report that they believed it to be potentially useful. They did agree to recommend to the full Committee that the reviewers be asked to comments on the factors discussed above when they comment of their assigned studies.

~~Four Seasons~~

Tahiti
Center



70 do
10M Antee starts in April
7/8 May Tues/Wed
Jun 5/6
Aug 5/6
July 10/11

Chem 10
Ward
EPA - Fitzpatrick
10M - Turner

Agenda
Veterans' Advisory Committee on
Environmental Hazards

March 13, 1991

- ✓ 9:00 Opening Remarks.....Oliver Meadows
Chairman
- ✓ 9:10 Remaining Obligations of the Advisory
Committee.....Jack Thompson
Assistant General Counsel
- ✓ 9:45 Review of Papers
 - Assennato, et al., "Follow-up of Subjects Who Developed
Chloracne Following TCDD Exposure at Seveso,"
Amer. J. Indust. Med. 16: 119-125 (1989).....Dr. Kurland
Dr. Melvin
 - ✓ Filippini, et al., "Relationship between clinical and
electrophysiological findings and indicators of heavy
exposure to 2,3,7,8-tetrachlorodibenzo-dioxin," Scand.
J. Work Environ. Health 7: 257-262 (1981).....Dr. Melvin
Dr. Yanders
 - ✓ Eriksson, et al., "Exposure to Dioxins as a Risk Factor
for Soft Tissue Sarcoma: A Population-Based Case-Control
Study," JNCI 82: 486-490 (1990).....Dr. Lathrop
Dr. Colton
- 10:15 - 10:30 Break
- ✓ Lynge, et al., "Evaluation of Trends in Soft Tissue
Sarcoma According to Diagnostic Criteria and Consumption
of Phenoxy Herbicides," Cancer 60: 1896-1901 (1987).....Dr. Lathrop
Dr. Colton
- ✓ Olsson & Brandt, "Risk of non-Hodgkin's lymphoma among
men occupationally exposed to organic solvents," Scan.
J. Work Environ. Health 14: 246-251 (1988).....Dr. Lathrop
Dr. Colton
- ✓ Wiklund, et al., "Risk of cancer in pesticide applicators
in Sweden," Br. J. Indust. Med. 46: 809-814 (1989).....Dr. Lathrop
Dr. Colton

Agenda
Veterans' Advisory Committee on
Environmental Hazards

March 14, 1991

9:00 Discussion of Contents of Final Committee Report and
of Soft Tissue Sarcoma Meta Analysis.....Members

12:00 1:15 Lunch

4:30 Adjourn

*Enter B1 data - Jan 516 birth defects

May - diah 7000 prog

Get copies re BSMC vs Army
statements for final review

Disease/Condition for Consideration by the
Veterans' Advisory Committee on Environmental Hazards

<u>Disease/Condition</u>	<u>VACEH</u>	<u>Agent Orange Scientific Task Force</u>	<u>Zumwalt Report</u>
Chloracne	Yes	SSA ¹	Yes
Soft Tissue Sarcoma	Yes	SSA	Yes
Non-Hodgkin's Lymphoma	No	SSA	Yes
Porphyria Cutanea Tarda	No	SSA	Yes
Brain Cancer	No	SSE ²	Yes
Liver Cancer	No	---	Yes
Testicular Cancer	No	SSE	Yes
Nasal/Nasopharyngeal Cancer	No	No	Yes
Immunological Disorders	No	Yes	Yes
Hodgkin's Disease	No	50-50	Yes
Neurologic Defects/Disorders	-- H ✓	50-50	Yes
Leukemia	-- L	SSE	Yes
Kidney Cancer	-- L	SSE	Yes
Stomach Cancer	-- L	SSE	Yes
Prostate Cancer	-- L	SSE	Yes

*Multiple myeloma
myeloma
leukemia
skin*

-
1. SSA - Significant Statistical Association
 2. SSE - Sound Scientific Evidence

tip

<u>Disease/Condition</u>	<u>VACEH</u>	<u>Agent Orange Scientific Task Force</u>	<u>Zumwalt Report</u>
Colon Cancer	-- L	SSE	Yes
Cancer of the Hepatobiliary Tract	NO	SSE	---
Psychosocial Effects	-- N	SSE	Yes
Gastrointestinal Ulcer	-- N	SSE	---
Gastrointestinal Diseases	-- N	---	Yes
Multiple Myeloma	-- L	--	Yes
Lip Cancer	-- N	---	Yes
Bone Cancer	-- L	---	Yes
Lung Cancer	-- H ✓	---	Yes
Hematopoetic Diseases	-- N	---	Yes
Esophageal Cancer	-- L	---	Yes
Malignant Melanoma	-- L	---	Yes
Liver Disorders	-- N	---	Yes
Skin Cancer <i>B&K cell</i>	-- L	---	Yes
Cardiovascular Disorder	-- N	---	Yes
Altered Lipid Metabolism <i>Diabetes</i>	-- H ✓	SSE	---
Birth Defects <i>untoward pregnancy outcome</i>	-- H ✓	50-50	Yes
Subclinical Hepatotoxic Effects	-- N	SSA	---