Framework for Causation Analysis of Toxic Exposure Claims

CLCW SME Training August, 2017

Purpose

- Examiners are frequently asked: is the condition attributable to a specific event?
- It is incumbent on SME clinicians to give a medical opinion after a careful review of:

1. Clinical findings and history (medical, social, genetic, occupational, etc.) reported in the records provided for review
2. Exposure(s)
3. The literature linking (or not) the exposure of concern and the condition(s) being claimed

Definitions

- **Association:** occurrence of two variables more often than would be expected by chance alone.
- **Causal association:** when cause and effect relation is seen.
- Association $\neq$ Causation

What is Cause?

- KJ Rothman defined a cause as an event, condition or characteristic that plays an essential role in producing an occurrence of the disease.
- Risk is the probability that an event will occur…a *risk factor* is an environmental, behavioral or biologic factor confirmed by temporal sequence, that if present, directly increases the likelihood a disease will occur and if absent or removed, reduces the likelihood.
- Causal models are complicated by differences in personal susceptibility, genetic predisposition, repeated exposures at low levels, latency period and severity of exposure.
- To establish medical causation, there must be a cause-and-effect association between the outcome and the postulated cause.

Epidemiological versus Individual Assessments

- Epidemiologically based causal Assessments - evaluate whether a purported "risk factor" is truly a disease determinant or merely an associated factor. If causal, elimination of the risk factor must result in diminished occurrences.
- Individually based causal Assessments – require application of the aforementioned on an individual basis

Hills Original Criteria/Guidelines for Causation

Temporal relation	Does the cause precede the effect? (essential)
Plausibility	Is the association consistent with other knowledge? (mechanism of action; evidence from experimental animals)
Consistency	Have similar results been shown in other studies?
Strength	What is the strength of the association between the cause and the effect? (relative risk)
Dose–response relationship	Is increased exposure to the possible cause associated with increased effect?
Reversibility	Does the removal of a possible cause lead to reduction of disease risk?
Study design	Is the evidence based on a strong study design?
Judging the evidence	How many lines of evidence lead to the conclusion?

Steps for Concluding a Causal Association Exists*

Melhorn et al. Guides to the Evaluation of Disease and Injury Causation*

1. Collect all epidemiological literature on the disorder through exhaustive literature searches
2. Identify the design of each study
3. Assess the methods of each study
    a. Exposure Assessment methods and potential biases
    b. Disease ascertainment methods and potential biases
    c. Absence of significant uncontrolled confounders; residual confounding
    d. Other potential biases
    e. Adequacy of biostatistical methods and analytical techniques
4. Ascertain statistical significance and the degree to which chance may have produced the results

5. Assess studies using **Updated** Hill Criteria:
    a. Temporality – exposure preceded disease
    b. Strength of the Association – higher the RR or OR the more likely the association is causal
    c. Dose-response Relationship – more exposure=more disease
    d. Consistency – same results in differing populations using different study designs/methods
    e. Coherency – collateral information is supportive of association
    f. Specificity – measure of the effectiveness of a test
    g. Plausibility – association considered makes sense
    h. Reversibility – when offending agent is removed the disease or condition improves
    i. Prevention/elimination - if exposure is eliminated disease does not occur
    j. Experiment – animal and/or human experiments lend support to purported association
    k. Analogy – analogous exposure-response relationship known to which the current purported relationship is similar (similar evidence with another similar exposure)
    l. Predictive Performance – predict the morbidity in another location testing accuracy
6. Conclusion about the degree to which causal association is *or* is not present

Modified NIOSH Steps for the Determination of Work-Relatedness of a Disease*

*Glass et al (2004)

1. Identify evidence of disease (is the dx correct, does the history, imaging, laboratory testing etc. support dx? (it's not cancer until pathology reveals cancer)
2. Review and Assess the available epidemiological evidence for a causal relationship (does the data support a relationship with disease?)
3. Obtain and assess the evidence of exposure (ATSDR Water modeling; 2507, MPRs, or STRs)
4. Consider other relevant factors (forensic review of records for other risk factors- post service occupation, Shx, FHx, etc.)
5. Judge the validity of testimony (veteran statement, Nexus letter – are there conflicting dates, Nexus predicated solely on profession?)
6. Evaluation and conclusions (individualized case-by-case basis)

Medical-Legal Standard

- What is probable, not what is possible.
- Medicine is an inexact science-standard is what is probable or likely; if converted to a percentage would indicate something more than 50% (at least as likely as not).
- MO conveyed in terms “In my opinion and based on reasonable medical probability…” or “based on a reasonable degree of medical certainty…”
- Avoid hedge words such as “it seems,” “I think,”” I believe” and absolutes such as “always,” “completely” and “never”.
- State the reasons which justify the opinion in a concise format.
- Make sure the report is internally consistent and consistent with previous MOs you have rendered.
- Use caution when using templates (individualize case-by-case).

Daubert vs Merrell Dow Pharmaceuticals Inc.

1. Pre-Daubert: expert was a “really smart person” – opinion was acceptable because a smart person said so.
2. Now:

a. Method on which opinion is based centered on a testable hypothesis

b. There is a known or potential rate of error associated with method

c. Method subject to peer review

d. Method is generally accepted in the scientific community

- What does this all mean?

As a SME document a detailed and reliable reasoning (rationale) for opinion(s) predicated on current peer-reviewed evidence based literature.

Federal Rule 702

- Expert witnesses must have “knowledge, skill, experience, training, or education” may testify in the form of an opinion or otherwise if

a. the expert’s scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;

b. the testimony is based on sufficient facts or data;

c. the testimony is the product of reliable principles and methods; and

d. the expert has reliably applied the principles and methods to the facts of the case.

Three-step Process for Analyzing Toxic Exposures

1. Establish or verify the diagnosis claimed.

a. Whether an exposure occurred is irrelevant until the presence of disease or illness has been established.

b. Its not cancer until there is a confirmatory pathology report or overwhelming anecdotal evidence (imaging, specialist reports, surveillance exams, etc.).

c. Determining evidence of disease is a clinical and pathological process.

d. If unable to "reasonably" establish a diagnosis; then opine in the negative due to an absence of primary source records; *"There are no primary source treatment records, no OR notes, no oncology records, no exact dates of cancer diagnosis and no specific pathologic or tissue diagnosis is found. Therefore a proper forensic review cannot be done and the claimed condition cannot be found to be related to service absent any definitive diagnosis and a timeline of diagnosis."*

(PEARL: check to see if the veteran is already service connected or has a presumptive condition which requires no MO i.e. Prostate cancer and AO exposure)

2. Determine if a cause and effect relationship exists.

a. Research and evaluate current peer-reviewed literature.

b. Conclusions about toxic effects of chemicals depend on epidemiological surveys of exposed vs. non-exposed populations and on animal data.

c. Resources include: National Library of Medicine, Haz-Map, Environmental Health and Toxicology, CDC, EPA, ATSDR, IARC; professional journals and current textbooks.

3. Implement the hazard evaluation process when the diagnosis has been established and there is credible evidence that a cause-effect relationship *could* exist.

a. Exposure history: When, where, how long, post-service occupation/activities
b. Latent period: acute, months, years or decades
c. Toxic agents: TCE, PERC, VC, Benzene; what about AO, etc.
d. Toxicological information: Profile of each agent
e. Dose response model: synthesis of clinical, industrial hygiene, and toxicological information to determine if estimated dose was sufficient to explain observed effects known to be associated with the agent in question

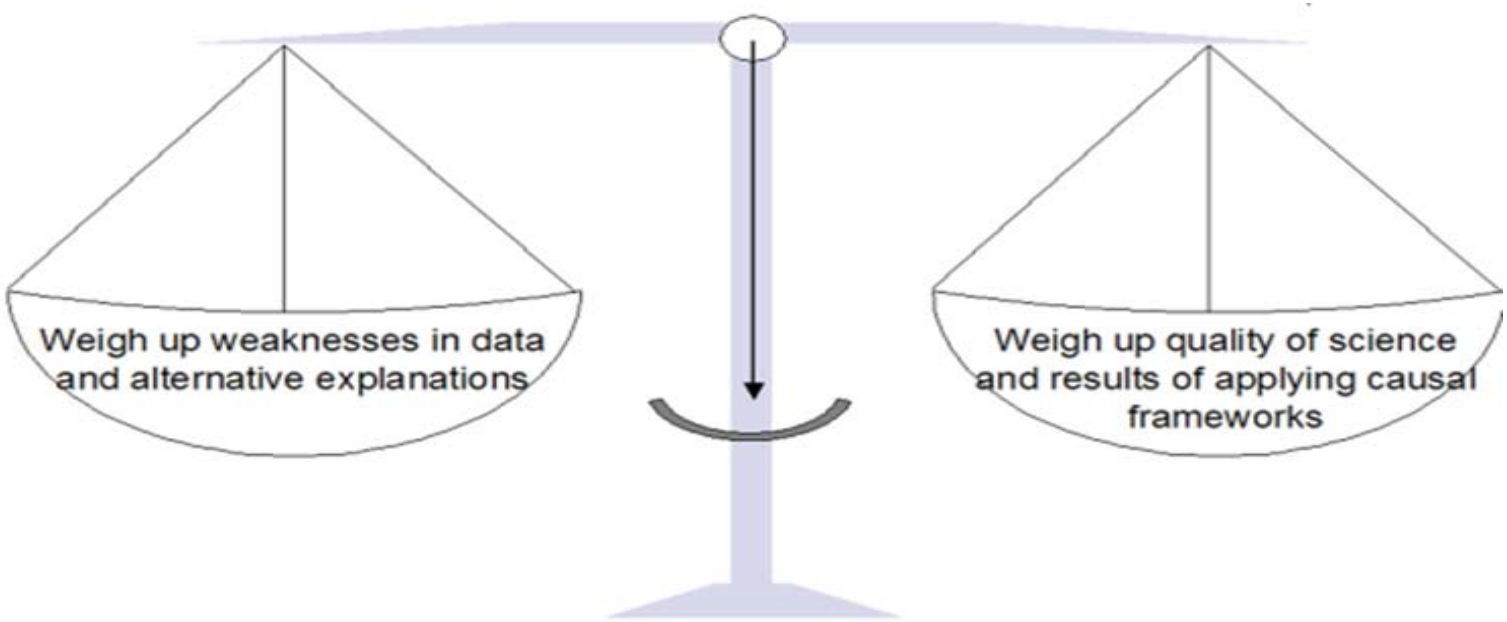
"All substances are poisons. The right dose differentiates a poison from a remedy."
Paracelsus (1493-1541)

Causality (Nexus) Decision

- Causality: based on review of the **probative evidence** of record, current clinical evaluation and applicable medical facts/principles
- Probative evidence:
  - Tendency of a given item of evidence to prove or disprove a legal element of the case
  - Having the effect of proof, tending to prove, or actually proving
- Association does not equate to causation

- No single study is sufficient for causal inference
- It is always necessary to consider multiple alternate explanations before making conclusions about the causal relationship between any two items under investigation.
- Causal inference is not a simple process
  - consider weight of evidence
  - requires judgment and interpretation
  - open to change with new evidence
  - SMEs are expert witnesses not judge or jury

Scale of Causal Judgment



Outline/Template

Date:
Name:
SSN:
Date of Birth:
Sex: Male
Dates of service at Camp Lejeune per 2507:
Veteran's duties and the locations where he/she worked on base per 2507: Not provided
Veteran's residence on base or off base per 2507: Not provided

Reviewer: Dr.
Member, Subject Matter Expert Panel
Camp Lejeune Contaminated Water Project
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The following report was based on record review. The veteran claims the following condition(s) as secondary to exposure to CLCW:

Contention 1: Choose an item.
Diagnosis 1:
Nexus: The claimed condition is/is not at least-as-likely-as not (50/50 probability) caused by or a result of the Veteran's prior exposure to CLCW of 30 days or more between 08/01/1953-12/31/1987.

Case Specific Discussion (a brief summary of the individual claim):
Mr. / Miss NAME, a USMC veteran was exposed to CLCW for a period of XX as indicated by the 2507 provided. He was subsequent diagnosed with the condition claimed above on XXXX., at age XX, and approximately XX years after service at Camp Lejeune.

Rationale: (relevance of literature identified- i.e. risk factors, occurrence rates, occupational and environmental literature review and relevance)
Bibliography:
Evidence review (a list of all pertinent records reviewed/date/source including: history, tests, treatment, prognosis, etc.)
-Was the Veteran's VA claims file reviewed? X Yes 0 No
-VBMS/VVA review:
-JLV/VVA/VistAweb review:

Putting it all Together

- Know your audience (written for VBA-RVSR, veteran, legal, BVA, public interest groups, etc.).
- Requires meticulous attention (SME seen as expert, MO will be viewed potentially by many).
- Proof MO for mistakes, each and every mistake made will lessen the report's value and credibility of the SME.
- The report is not for a "patient"-no doctor/patient relationship; use the term Veteran, Mr. or Ms. XXXX.
- Must be thorough (no stone unturned).
- A complete explanation must be given for conclusion.
- Conclusion must be predicated on valid scientific methods.
- Study reports of colleagues and adapt best features.
- Report can be your best friend or worst enemy.