

Occupational Medicine Clinical Update

Dedicated to the prevention of occupational illness and injuries, and promoting the well-being of all workers

Occupational Health Clinics for Ontario Workers Inc, Samia-Lambton

This Issue:

- Nuts and Bolts of Evaluating Causality

Coming Issues:

- Heat Illness
- Parkinson's Disease
- Terminology in Occupational Epidemiology

Weighing the Evidence for Causality

As discussed last month, proving causality is doomed to failure from the outset. Strictly speaking, nothing can ever be proven irrefutably, only disproved. Science is a process of presenting the best theory possible with the information available until it is replaced with a better theory.

Philosophical arguments aside, we are still faced with making a decision: is a disease work related? The current tool of choice is commonly known as the 'Bradford Hill' method.

Despite Hill's cautioning that his rules (published in 1965) not be used as "hard and fast rules for evidence" they have, ironically, become the gold standard for arriving at judgments of causation.

A modified version of his original criteria are presented below, using benzene as an example. It has been relatively extensively studied and is well established as a cause of acute myelogenous leukemia (AML), and strongly suspected of causing a wide spectrum of related diseases.



Table 1 provides a quick reference to the criteria of causality, and Table 2 (on page 2) summarizes the relative weight of these in arriving at judgments regarding causation.

Perhaps the most important caveat when assessing research should be: who is paying for it? As has been found with industries like the pharmaceutical industry, funding (overt or covert) can have a profound influence on published conclusions. Knowing who paid for a study may sometimes be the most important weighting factor of all.

Table 1: Summary of Criteria

1. Is there evidence from *true experiments* in humans?
2. Is the association *strong*?
3. Is the association *consistent* from study to study?
4. Is the *temporal relationship* correct?
5. Is there a *dose-response* gradient?
6. Does the association make *epidemiologic sense*?
7. Does the association make *biologic sense*?
8. Is the association *specific*?
9. Is the association *analogous* to a previously proven causal association?

Criteria for Causality Applied to Benzene and Hematologic Malignancies

True experiments in humans?

Ideally a randomized controlled trial (RCT) exposing one group to the substance of interest (benzene) and a matched group of controls without the exposure, would be followed for the outcome of interest (leukemia). Obviously, this is not done with substances like benzene but prior to 1913 it was ironically used as a *treatment* for leukemia. Its use was stopped due to bone marrow toxicity.

How strong is the association?

Simply speaking, the greater the odds favouring the outcome of interest, the greater the strength of the association. There are three different types of studies used: **RCT, cohort studies, case-control studies**. The confidence that can be placed in each of these coincides with the order in which they are listed.

Most often in occupational medicine we are dealing with case-control studies and less frequently cohort analyses. This reflects the cost and relative difficulty in doing these studies. Cohorts are difficult and time consuming to assemble. Often these analyses are undertaken by industries as they have the necessary financial and demographic resources.

One should be wary however, of the conclusions drawn in industry-sponsored cohort analyses. Methods have to be scrutinized carefully (in any study) as it has been the case that the experimental design may not be able to answer the actual research question being asked. This may reflect the motivation behind some of these studies. Many are produced to defend against lawsuits (the tobacco industry being a prime example).

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There are a number of study designs and methods that can be used to produce a desired result. We will review some of these techniques in a future issue of the *Update*.

Back to *strength of the association*. In the case of AML, the association is strong. Risks elevations range typically from 2 or 3 times, up to 98 times (95% CI:20-288), in one cohort. This risk has depended on the level of exposure to benzene.

How consistent is the association?

Repeatedly demonstrating an association using different methods, investigators, and settings, results in consistency. This has been shown with benzene and acute leukemias. Evidence is still accumulating for chronic leukemias, lymphomas, and multiple myelomas due to longer latencies and other factors.

Is the temporal relationship correct?

Generally, a consistent finding of exposure to benzene, followed by development of hematological disease in a latent period consistent with the commonly accepted time-course of the disease, satisfies this criterion.

Is there a dose-response gradient?

This harkens back to the old toxicologist's adage, 'the dose makes the poison'. The observation that increasing quantity or duration of exposure to the substance of interest results in increased risk of the disease satisfies this test. Dose-response has been demonstrated for benzene and leukemia's, lymphomas, myelodysplastic syndrome and aplastic anemia.

Does the association make epidemiologic sense?

If, for example, the worldwide 'epidemic' in lymphoma was attributed conclusively to exposure to organic solvents or pesticides (which is currently only suspected), then the association between NHL and benzene would be said to make *epidemiologic sense*.

Does the association make biologic sense?

Does the association make sense in terms of the way cells and subcellular elements, tissues, organs and organisms are under-

Table 1: Relative weight given to criteria in judging causation

Criteria*	Consistent with Causation	Neutral or Inconclusive	Opposes Causation
Human experiments	++++	---	----
Strength of association			
- randomized trial	++++	---	----
- cohort study	+++	--	----
- case-control study	+	0	-
Consistency	+++	--	----
Temporality	++	--	----
Dose-response	++	-	--
Epidemiologic sense	+	-	--
Biologic sense	+	0	-
Specificity	+	0	-
Analogy	+	0	-

* Listed in decreasing order of importance. '+' = causation supported; '0' = causal decision not affected; '-' = causation rejected.

stood to respond to various exposures? Benzene's well-known myelotoxic properties readily fulfills this criteria, on a number of different levels.

Is the association specific?

A single cause, limited to a single effect, is an exceedingly uncommon scenario in medicine and does not apply to any known lymphoproliferative disorders.

Is there an analogous previously proven causal association?

The acceptance in the scientific community (and even the petrochemical industry after legal battles) that benzene causes AML and aplastic anemia has paved the way for more ready acceptance of like diseases being related to benzene exposure. It is becoming increasingly clear that benzene (and other solvents) are likely responsible for a wide range of hematologic malignancies including other acute/chronic leukemias, NHL, multiple myeloma, Hodgkin's disease, and myelofibrosis (covered last month).

"Read not to contradict, nor to believe, but to weigh and consider."

- Sir Francis Bacon, 1597

Conclusion

These nine criteria form a framework for evaluating evidence for causal relationships. Like all tools in science, they currently represent the best theory we have for evaluating this type of information - until a better group of criteria come along to replace them.

Although the value of these specific criteria will likely fade, some ideas can stand the test of time. Perhaps the most valuable criterion for evaluating scientific information was created over 300 years ago by Sir Francis Bacon when he advised, "Read not to contradict, nor to believe, but to weigh and consider".

References

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