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# Leap of Faith:

## The Increasingly Murky Line Between Theory And Hypothesis in the Association Between Benzene & Non-Hodgkin's Lymphoma

**By Thomas J. Tobin and Daniel Bodell of Gordon & Rees, LLP**
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**Introduction**

Over the past few years, attorneys have witnessed an increasing wave of "trace benzene" litigation nationwide, in which plaintiffs with various forms of cancer claim that substances which arguably include trace amounts of benzene played some legally significant role in the development of their disease. Primarily, these diseases involve cancers relating to blood and blood-forming organs. Specifically, these cancers include the various forms of leukemia and "pre-leukemic" diseases as well as other forms of cancer. One such group is the collection of cancers known as non-Hodgkin's Lymphoma.

Despite the general recognition that some epidemiologic link exists between certain dose levels of benzene and certain kinds of leukemia, the epidemiology relating to NHL is largely undetermined in the benzene context – or so the words of the published literature addressing the subject indicate. Simply put, a large percentage of the literature on the subject tells us that the jury is still out on whether benzene at any exposure level should be recognized as a risk factor for the development of any kind of NHL.

Nevertheless, a recent trend has gained momentum which tends to minimize these conclusions in order to have NHL become synonymous with those diseases such as Acute Myelogenous Leukemia (AML) that do demonstrate a benzene link at higher dosage/exposure levels. At first blush, this appears logical and, in some cases, admissible as expert testimony by those who are proponents of this hypothesis. However, it does not accurately reflect the stated conclusions of the published literature that address the issue of whether exposure to benzene at any level rises to the level of a recognized risk factor for any of the sub-classes of NHL.

This article will provide a general description of the NHL disease category, a summary of some of its more recognized risk factors and some recommendations on highlighting the lack of scientific consensus on whether benzene should be considered a recognized risk factor for NHL.

**Non-Hodgkins Lymphoma – A Collection of Diseases**

Lymphoma refers to a collection of cancers in which the "cells of the lymphoid

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tissue multiply uncontrollably."[1] Hodgkin's Disease ("HD") is a specific lymphoma with the characteristic Reed-Sternberg cells. All other lymphomas are known as non-Hogkin's Lymphomas ("NHL").[2]

The diseases that comprise NHL represent a diverse group of cancers "whose common link is a characteristic monoclonal expansion of malignant B or T cells, and is the single largest group of neoplasms of the immune system."[3] Some of the most common types of NHL are Burkitt's Lymphoma, B-Cell Follicular Lymphoma, diffuse lymphoma, small lymphocytic lymphoma. However, other types of lymphomas do exist, which have confounded the results of the epidemiologic studies involving this disease category.[4]

According to epidemiologists Chiu and Weisenberger in their 2003 update on the epidemiology of NHL, the incidence of NHL has increased 80 percent since the 1970s and was the fifth most common cancer in the United States by the turn of the century. The incidence of NHL is approximately 50 percent higher among men than women and 35 percent higher among white people than black people. The incidence rates of all subtypes of NHL have increased as well, especially diffuse large-cell and immunoblastic subtypes.[5] Aside from better diagnostic methods, the literature on the types and trends regarding NHL provide little explanation for the increase in incidence. Given the fact that the causes are generally unknown, the increased incidence too is largely unexplained.

**"Risk Factors" for NHL**

As scientists have studied NHL, some recognized risk factors have emerged. However, some have defined these "risk factors" as "potential" and not "recognized." The failure of scientists to agree on the definition of NHL risk factors results in the generally uncertain nature of the etiology of NHL and its sub-classes.[6]

Although scientists have studied the many cellular changes associated with lymphoma, no one really knows why such changes occur. In fact, the vast majority, if not all, of the literature comments that the precise mechanism and/or cause of NHLs is largely unknown. It is likely that certain risk factors make individuals more prone to developing NHL. Many factors - such as age and genetics - are probably beyond our control. Other factors, such as environmental or lifestyle-related variables, may be more correctable.[7]

It is now known that all cancers, including lymphoma, begin as a mutation (change) in the genetic material - the DNA (deoxyribonucleic acid) - within certain cells. The external or internal causes of such change probably add up over a lifetime. DNA errors may occur in the form of translocations - damage produced when part of one chromosome becomes displaced and attached to another chromosome. Translocations disrupt the normal sequencing of the genes. As a result, oncogenes (cancer-promoting genes) on the chromosomes may be switched on, whereas tumor suppressors (cancer-preventing genes) may be switched off. These changes often occur in cases of lymphoma. Physicians test for these translocations to help diagnose the type of lymphoma, determine a patient's prognosis (outcome), and identify cancer recurrence.

Numerous risk factors may be responsible for DNA damage within the body's lymphocytes (specialized white blood cells). The risk factors now believed to have the strongest associations with lymphoma are:[8]

- Age
- Sex
- Infections
- Medical Conditions
- Genetics
- Cancer Therapy
- Drug Use

***Age***

The rate of NHL increases exponentially with age between 20 and 79 years, and the rate of HD is highest in two age groups: young adults (age 15 - 40) and older adults (age 55+).

***Sex***

In general, NHL affects more men than women.

***Infections***

In addition, the chance of developing NHL is increased among people who have been exposed to:

- human T-lymphotrophic virus type I (HTLV-1);
- Epstein-Barr (EBV) virus;
- Helicobacter pylori, a bacteria that may infect the gastrointestinal tract and can cause lymphomas of the stomach;
- human immunodeficiency virus (HIV), the "AIDS" virus; and
- malaria, especially in areas of Africa, where Burkitt's lymphoma is common.

It is important to note that there is no evidence of infection in many HD and NHL patients, so the role of infection in cancer development remains uncertain.

***Medical Conditions***

Specific medical conditions may make a person more likely to develop Hogkins Disease or NHL. In particular, HD and NHL are more common among people

with a weakened immune system, such as those with:

- autoimmune disease (e.g., HIV/AIDS), disease caused by the body's immunologic attacks against its own tissues;
- inherited immune deficiency syndromes (e.g., ataxia telangiectasia); or
- organ transplants that require the use of immunosuppressant drugs.

Some experts believe that HD is caused by a complex deficiency in cellular immunity. Such a deficiency may be due to chronic overstimulation by cytokines - substances that draw germ-fighting white blood cells to areas of infection.

***Recreational or Prescribed Drugs***

The risk of NHL is increased among individuals exposed to chemicals such as cocaine or other recreational drugs, although the association is generally only an elevated risk as opposed to a risk more statistically significant.[9] In addition, some have associated some increased risk with the use of the antiepileptic medicine Phenytoin, which may cause overgrowth of lymphoid tissues.

***Genetics***

The rates of lymphoma and leukemia (e.g., chronic lymphocytic leukemia, CLL) are especially high in some Jewish populations, whereas Asian populations rarely develop CLL. Among first-degree relatives (parents, children, siblings) of CLL patients there is a two- to four-fold increased risk for this cancer.

***Cancer Therapy***

Individuals who have received chemotherapy and/or radiotherapy (radiation therapy) for previous cancers have a slightly greater chance of developing NHL or secondary leukemia (leukemia that arises after therapy) at some later date.[10]

Again, the above list of risk factors should not be considered rising to the level of a recognized risk factor, given the uncertainty of scientists in ascribing causes of the various types of NHL.[11] As the etiology is largely unexplained, scientists are hesitant to draw any firm conclusions but rather call for further study, as we will see below.

**Highlighting the Uncertainty of the Association Between NHL and Benzene**

As the battle continues over whether it is scientifically recognized or arguably admissible to offer opinion evidence that exposure to some quantum of benzene can cause one of the various types of NHL, there are numerous examples of language in the literature that underscore the uncertainty. Depending on the state or jurisdiction in which one litigates, there is little doubt that the conclusions of a number of the scientists who have written on the topic will be persuasive in raising doubt as to general causation either in the mind of the judge or the jury.

One such example is the recent conclusion of Wong & Fu in their 2005 epidemiologic overview and ongoing case

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control study in Shanghai. In this article, they conclude:

> The epidemiologic overview presented earlier shows that there is little epidemiologic evidence supporting an association between benzene exposure and NHL. The record-linkage investigation reported by Vianna and Polan was a classic example of misleading results derived from linking health data to administrative databases that were not set up for research purposes … Similarly, as discussed earlier, other cohort studies and case-control studies provide ample evidence supporting the finding of Rinsky et al., that is, no increased risk of NHL in benzene-exposed workers.[12]

As a result, the Wong & Fu study not only declined to list benzene exposure as a risk factor for NHL but actually goes so far as to indicate that benzene presents no increased risk of NHL in benzene-exposed workers.

Aside from the Wong & Fu study, there are some articles that mention an increased risk of NHL for benzene-exposed workers. However, the general conclusion of these papers is undetermined at best. For example, in their recent update of the epidemiology of NHL, Chiu and Weisenberger chronicle a number of risk factors for NHL and summarize the current status of the literature. In describing their conclusions on the scientific reliability on considering the numerous associations (including benzene) as risk factors, Chiu and Weisenberger conclude:

> The incidence of NHL has increased 80 percent in the United States since the 1970s. Although the overall NHL incidence rates stabilized in the early 1990s and then began to decrease between 1996 and 1999, primarily because of a decrease in the incidence of AIDS, the incidence of NHL types not associated with AIDS and NHL in groups at low risk of AIDS has continued to increase throughout the 1990s. The effects of the AIDS epidemic, use of immunosuppressive therapies, and improved diagnostic techniques account for only approximately one third of the increase in NHL incidence. **The etiology of most of the remaining cases of NHL is essentially unexplained; however, data concerning certain occupational, environmental, and lifestyle factors provide the framework for a hypothesis that may explain the increase in incidence of NHL.** Similar common exposures with weak relative risks in the general population are more likely to explain the increase in NHL than are rare exposures with high relative risks **Epidemiologic studies of such common exposures are needed to validate this hypothesis.** *[Emphasis added]*[13]

**As the battle continues over whether it is scientifically recognized or arguably admissible to offer opinion evidence that exposure to some quantum of benzene can cause one of the various types of NHL, there are numerous examples of language in the literature that underscore the uncertainty.**

Therefore, Chiu and Weisenberger conclude that the etiology of most cases of NHL, even in 2003, are largely unexplained and require further study to evaluate any hypothesis as to what causes NHL, especially in the benzene context. This conclusion is also consistent with the 2002 Zheng article (in which Weisenberger participated) summarizing risks with various occupations, which concluded, "Although the relatively small numbers of subjects grouped by the histological type limit the interpretation of the results in this study, further investigation of these associations is warranted."[14]

Finally, in one of the studies often cited by proponents of the benzene-NHL, the concluding language further reflects the uncertainty and undetermined nature of the hypothesis that benzene-exposed workers are at a statistically significant increased risk for developing NHL. In the oft-cited 1997 Hayes study, the conclusion of the study is not that benzene has risen to or was currently at the level of a recognized risk factor for NHL. Rather, the study concluded:

> Nevertheless, the observation of doubled risk for ANLL/MDS at an average exposure of less than 10 ppm benzene, the proportionally smaller increases in risk with increasing exposure, the elevated risk for ANLL/MDS with recent exposure, and the **possible links with NHL are all provocative new observations that should enhance our efforts to understand benzene carcinogenesis in human populations.** *[Emphasis added]*[15]

Given this conclusion, it is not at all clear that one should consider benzene a recognized risk factor for NHL – only that it is a "possible", yet undetermined, risk factor. As a result, despite what one may offer as opinion relative to the degree to which benzene may or may not be considered a risk factor for NHL, the language of the literature on the topic is equivocal at best. Highlighting this less than definitive language will serve defendants well in challenging either the

admissibility or persuasiveness of experts offering opinion in favor of finding a causal link.

**Conclusion — The Battle Continues**

The discussion above provides material useful in one attack on the attempt to associate NHL with leukemia or other diseases where a clearer causal picture exists. As the literature addressing the suspect link between benzene-exposed workers and NHL concludes, no clear scientific consensus or majority exists at this time.

In challenging a plaintiff's causation theory in cases alleging benzene exposure and NHL, not only is the lack of consensus helpful, but other methods exist to assist defendants in attacking the causation case. First, given the many different types of NHL, it is useful to highlight the different varieties of NHL in attacking the statistical findings of the studies addressing NHL. Many studies deal with the class as a whole and do not differentiate between the different types of NHL, which have different ways of developing and require further study. Second, it is also helpful in a "trace" benzene case, which does not involve pure benzene but rather organic solvents or some other substance alleged to contain benzene, to note the lack of a carcinogenic classification of these substances which are not pure benzene. The various organizations that issue such classifications (IARC, etc.) have not designated organic solvents as a carcinogen, which can be helpful in attacking general causation.

Despite the numerous methods of attack and the lack of consensus in the literature, it is still quite possible that plaintiffs will be able to offer expert opinion on the subject at trial. While there was a defense verdict in the *Hooper v. Chevron* case in California in 2005, the plaintiff was allowed to offer opinion testimony in favor of general causation. The jury agreed with the defense that the exposure in that case could not have caused plaintiff's NHL in that case. This demonstrated the judicial hesitance in excluding such opinion testimony, even though no consensus has been reached among the community of epidemiologists evaluating the issue of benzene as a recognized risk factor for NHL. Some courts in the United States would rather have the jury decide general causation, even when scientists have not.

As a result, given the wide array of occupations and products that could arguably lead to exposure to trace benzene, we expect this battle to continue until a definitive scientific conclusion exists —- and possibly even beyond that time.

**Footnotes**

[1] Wong & Fu, "Exposure to Benzene and Non-Hogkin Lymphoma" (2005) *Chemico-Biological Interactions* at 34.
[2] *Ibid.*
[3] *Ibid.*
[4] Zheng, et al., "Occupation & Risk of Non-Hogkin's Lymphoma and Chronic Lymphocytic Leukemia" (2002) *JOEM* at 471.
[5] Chiu & Weisenberger, "An Update of the Epidemiology of Non-Hodgkin's Lymphoma (2002) *Clinical Lymphoma* at 161.
[6] Wong & Fu, *supra*, at 34.
[7] Nelson, Levine, et al., *British Journal of Cancer* (1997) 1532-1537.
[8] *Ibid.* at 1532-1537.
[9] *Ibid.* at 1533.
[10] Wong & Fu, *supra*, at 34-35.
[11] *Ibid.*.
[12] Wong & Fu, *supra*, at 40.
[13] Chiu & Weisenberger, *supra*, at 165.
[14] Zheng, at 473.
[15] Hayes, et al., "Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China" (1997) *Journal of the National Cancer Institute* at 1070.