

A Basic Introduction

By Eric K. Falk

The most important point for the defense practitioner to remember is that the cause of NHL in the vast majority of cases remains “unexplained.”

The Epidemiology of Non-Hodgkin’s Lymphoma

Defense practitioners have recently seen an increase in litigation involving non-Hodgkin’s lymphoma allegedly caused by exposure to various solvents. For example, on June 12, 2008, the Mississippi Supreme

Court affirmed the granting of a judgment notwithstanding the verdict (JNOV) where the expert testimony was held to be scientifically unreliable on the issue of the causation of the plaintiff’s non-Hodgkin’s lymphoma. *Watts v. Radiator Specialty Co. and United States Steel Corp.*; ___ So. 2d ___; 2008 WL 2372694 (Miss.). Why are we seeing more cases involving non-Hodgkin’s lymphoma? What are the causal factors? The purpose of this article is to provide a basic primer on the epidemiology of non-Hodgkin’s lymphoma (NHL) and its alleged association with solvent exposures.

NHL is a generic term for a diverse group of cancers that begin in cells of the immune system, or lymphatic system. Multiple sites are frequently involved. See Lister, *et al.*, Chapter 112, “Non-Hodgkin’s Lymphoma,” in *Clinical Oncology*. (Abeloff *et al.*, eds. Elsevier, Churchill and Livingstone, 3rd ed., 2004). NHL (and Hodgkin’s disease, which differs from NHL and will not be the subject of this article) account for the most common hematological malignancies in the

United States, representing approximately five percent of all new cancer cases. They are the fifth leading cause of cancer death in the United States, and the second fastest growing cancer in terms of mortality. Fisher, *et al.*, Section 2, Chapter 41, “Lymphomas—Non-Hodgkin’s Lymphoma,” in *Cancer: Principles and Practice of Oncology*, (DeVita, *et al.*, eds., Lippincott, Williams and Wilkins, 7th ed., 2005). Medically speaking, “A striking increase in NHL incidence rates has occurred over the last four decades that has been referred to as an epidemic of NHL.” *Id.*

Thus, the increased rate of NHL has resulted in an increase in litigation concerning the causes of NHL, which is unsurprising, given our litigious society. Most commonly, allegations are raised that exposures to solvents caused a particular plaintiff’s NHL. Most studies have found little evidence for an association between benzene exposure and NHL. See, e.g., *Eleventh Report on Carcinogens*, National Toxicology Program, U.S. Dept.



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of Health and Human Services. See also Savitz & Andrews, "Review of Epidemiologic Evidence on Benzene and Lymphatic and Hematopoietic Cancers," 31 *American Journal of Industrial Medicine* 287 (1997). But see, Smith, *et al.*, "Benzene Exposure and Risk of Non-Hodgkin's Lymphoma," 16 *Cancer Epidemiology and Biomarkers* 385 (2007) (the authors concluded, based on review of certain epidemiological studies, that the evidence did support an association between occupational benzene exposure and NHL). Most allegations claim that exposure to "solvents," a group of substances as diverse as NHL itself, caused a plaintiff's NHL

Classification of Non-Hodgkin's Lymphoma

As one researcher noted, "A number of difficulties have been associated with the performance and review of epidemiological studies of NHL and related hematopoietic cancers. Foremost has been the constantly evolving nomenclature and confusing array of complex classification systems for NHL." Weisenburger, "Pathological Classification of Non-Hodgkin's Lymphoma for Epidemiological Studies," 52 *Cancer Research Supplement* 5456s (1992). In response to the confusing nomenclature for NHL diseases, the World Health Organization (WHO) published a new classification system for hematological and lymphoid malignancies in 2001. Jaffe, *et al.*, eds., *World Health Organization Classification of Tumours of Hematopoietic and Lymphoid Tissues* (International Agency for Research on Cancer Press, 2001). As the WHO states, "within the category of 'non-Hodgkin's lymphomas, there are a large number of distinct diseases. These are associated with distinctive epidemiology, aetiology, clinical features and, often, distinctive responses to therapy." *Id.* at 13. The classification system for malignant lymphomas includes the following: follicular lymphoma; diffuse large B-cell lymphoma; Burkitt's lymphoma; mantle cell lymphoma; mucosa-associated lymphoid tissue (MALT) lymphoma; mature T-cell lymphoma; chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); mediastinal large B-cell lymphoma; anaplastic large-cell lymphoma; nodal marginal zone lymphoma; precursor T-lymphoblastic lymphoma; and other types.

Table 1. World Health Organization Classification of Lymphoid Neoplasms

B-Cell Neoplasms	T-Cell and Nk-Cell Neoplasms
Precursor B-Cell Neoplasms	Precursor T-Cell Neoplasms
—Precursor B-lymphoblastic leukemia/lymphoma	—Precursor T lymphoblastic leukemia/lymphoma —Blastic NK-cell lymphoma
Mature (Peripheral) B-Cell Neoplasms	Mature T-Cell and Nk-Cell Neoplasms
—Chronic lymphocytic leukemia —Small lymphocytic lymphoma —B-cell prolymphocytic leukemia —Lymphoplasmacytic lymphoma —Splenic marginal zone lymphoma —Hairy cell leukemia —Plasma cell myeloma —Solitary plasmacytoma of bone —Extrasosseous plasmacytoma —Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma) —Nodal marginal zone B-cell lymphoma —Follicular lymphoma —Mantle cell lymphoma —Diffuse large B-cell lymphoma —Mediastinal (thymic) large B-cell lymphoma —Intravascular large B-cell lymphoma —Primary effusion lymphoma —Burkitt lymphoma/leukemia	T-cell prolymphocytic leukemia —T-cell large granular lymphocytic leukemia —Aggressive NK-cell leukemia —Adult T-cell leukemia/lymphoma —Extranodal NK/T-cell lymphoma, nasal type —Enteropathy-type T-cell lymphoma —Hepatosplenic T-cell lymphoma —Subcutaneous panniculitis-like T-cell lymphoma —Mycosis fungoides —Sezary syndrome —Primary cutaneous anaplastic large cell lymphoma —Peripheral T-cell lymphoma, unspecified —Angioimmunoblastic T-cell lymphoma —Anaplastic large cell lymphoma
B-Cell Proliferations of Uncertain Malignant Potential	T-Cell Proliferation of Uncertain Malignant Potential
—Lymphomatoid granulomatosis —Post-transplant lymphoproliferative disorder, polymorphic	—Lymphomatoid papulosis

See Table 1. The most common types are follicular and diffuse large B-cell lymphomas, which together, account for approximately 50 percent of all non-Hodgkin's lymphomas.

Risk Factors for NHL

While the causes of most cases of NHL remain unknown, several risk factors have been identified. Immunodeficiency, whether congenital or acquired, has been shown to create a statistically significant increased risk of NHL. Identified immunodeficiency conditions include AIDS/the HIV virus; Epstein-Barr virus; Hypogammaglobulinemia; autoimmune disorders, such as rheumatoid arthritis; Sjogren's syndrome; and Wiskott-Aldrich syndrome. Several of these autoimmune deficiency conditions have been linked to specific types of NHL. Sjogren's syndrome has been linked with MALT lymphoma, while

Epstein-Barr virus has a strong association with Burkitt's lymphoma.

Various retroviruses have also been linked with NHL. Human T-cell lymphotropic virus type 1 (HTLV-1) is an established cause of adult T-cell leukemia/lymphoma. Evidence also suggests a link between Hepatitis C and NHL. A detailed review of the extensive epidemiological literature on NHL must bear in mind the cautionary instruction of the WHO when it reclassified the various NHLs. Each different form of NHL is associated with distinct epidemiological and etiological features. Moreover, the causes of the majority of the individual NHL subtypes "remain unexplained." Hartge, *et al.*, *supra*. See also Fisher, *et al.*

Occupational Exposures

Epidemiological studies have been undertaken concerning various occupational



exposures and NHL risk, with various results. As one treatise explained:

Studies of occupational and environmental NHL risk are frequently inconsistent and contradictory. Difficulties in estimating risk are often related to sample size and other methodological difficulties in addition to difficulties in quantifying exposure. The risk of NHL

The association between NHL and organic solvents is controversial, due to studies that are inconsistent and contradictory.

is increased in several occupations including farmers, forestry workers and agricultural workers. Several studies have shown an increased risk of NHL in relation to herbicide exposure, especially phenoxy herbicides such as 2, 4-dichlorophenoxyacetic acid, although this is controversial. The development of NHL has also been linked to hair dyes, especially darker and permanent markers used before 1980. Furthermore, NHL has been associated with organic solvents and high level of nitrates in drinking water.

Fisher, *et al.*, at 1959.

Despite the above statement, the association between NHL and organic solvents is controversial, due to studies that are inconsistent and contradictory. For example, the Institute of Medicine (IOM) of the National Academy of Science (NAS), at the request of Congress, undertook a series of studies reviewing the health effects of many of the biological, chemical and environmental agents to which Gulf War I veterans were exposed. The IOM appointed a 37-member committee composed of epidemiologists, industrial hygienists, toxicologists and physicians from various fields charged with examining the insecticides and solvents to which Gulf War I veterans may have been exposed. The committee reviewed all of the available literature and “focused on human

studies of long term effects that might follow exposure to these agents, inasmuch as veterans’ symptoms have continued long after the war.” That committee concluded that there was “limited/suggestive evidence of an association between chronic exposure to benzene and non-Hodgkin’s lymphoma.” *Gulf War and Health—Volume 2—Insecticides and Solvents*; (National Academies Press, 2003). The IOM came to a rather different conclusion from that of the National Toxicology Program’s *Eleventh Report on Carcinogens, supra*.

Turning toward solvents generally, excluding benzene:

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the solvents under review, other than benzene, and non-Hodgkin’s lymphoma.

Id.

The IOM then provided a comprehensive listing in table format of the epidemiological studies to date examining NHL and exposure to organic solvents, further subdivided studies into four categories: trichloroethylene, benzene, certain specified solvents, and unspecified mixtures of organic solvents. This listing provides the names of the authors, the study population, the number of exposed cases, and the estimated relative risk with the 95 percent confidence interval for each such study. *Id.* at Table 6.34. This table is strongly recommended to the practitioner as a handy reference for most of the literature available at that time.

The defense practitioner should be mindful that many of the epidemiological studies on NHL predated the WHO classifications of the various subtypes and, thus, do not take into account the separate etiological agents for each subtype.

Etiology of Certain NHL Subtypes

According to the *World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues*, the etiology of the following NHL classifications are unknown: precursor B-lymphoblastic leukemia/lymphoblastic lymphoma; precursor T-lymphoblastic leukemia/lymphoblastic lymphoma; diffuse large B-cell lymphoma; mediastinal large B-cell lymphoma; extra-

nodal NK/T-cell lymphoma, nasal type; blastic NK-cell lymphoma; T-cell lymphoproliferative disorder/lymphomatoid papulosis; peripheral T-cell lymphoma, unspecified; and anaplastic large cell lymphoma.

The WHO classification does set forth etiological risk factors for certain other forms of NHL, but does not mention exposures to solvents. These other forms of NHL include lymphoplasmacytic lymphoma (associated with Hepatitis C. The WHO also states that “occupational exposures have also been postulated,” without further elaboration than to cite to one additional article); extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, or MALT-lymphoma (associated with *Helicobacter pylori*); primary effusion lymphoma (associated with Epstein-Barr virus); Burkitt lymphoma (associated with the Epstein-Barr HIV viruses); lymphomatoid granulomatosis (associated with the Epstein-Barr HIV viruses); enteropathy-type T-cell lymphoma (associated with the Epstein Barr virus and Coeliac disease); hepatosplenic T-cell lymphoma (associated with immunosuppressed patients following certain organ transplants); subcutaneous panniculitis-like T-cell lymphoma (immunosuppression appears to be the predisposing factor, although Epstein-Barr virus is absent]; and angioimmunoblastic T-cell lymphoma (in the majority of cases, cells are positive for Epstein-Barr virus, although such cells are for the most part B-cells rather than T-cells).

In short, assessing the causal relationship between solvents and NHL is confusing in any case involving allegations that exposure to solvents led to NHL. Much of the NHL literature, as set forth in Table 6.34 of the IOM Report, *Gulf War and Health, Volume 2*, simply predated the WHO classifications of various NHL types. The practitioner has to be mindful that much of the literature used by both plaintiffs and defendants will predate the WHO classifications, yet at the same time, understand those classifications as well as the epidemiological research that predates the 2001 WHO classifications.

Discussion of Select Epidemiology Literature on NHL

The NHL literature is extensive. The fol-

lowing discussion focuses on certain recent articles of interest to the practitioner.

Seidler, et al., “Solvent Exposure and Malignant Lymphoma: A Population Based Case Control Study in Germany,”

JOURNAL OF OCCUPATIONAL MEDICINE AND TOXICOLOGY (2007)

This article provides an update to a 2006 study (to be discussed, *infra*), Mester, et al., “Occupation and Malignant Lymphoma: A Population Based Case Control Study in Germany”, 63 *Occupational and Environmental Medicine*, 17 (2006). Both studies utilized the 2001 WHO classification system for NHL. The purpose of the 2007 study was to specifically examine the association between chlorinated and aromatic hydrocarbons generally, and specific subtypes of the same, with NHL and certain NHL classifications. The study population was all newly diagnosed patients with both NHL and Hodgkin’s disease, between the ages of 18 and 80, in certain defined regions of Germany. The patients were assessed to determine their exposure to chlorinated hydrocarbons (trichloroethylene, tetrachloroethylene, dichloromethane, and carbon tetrachloride) and aromatic hydrocarbons (benzene, toluene, xylene and styrene). Cumulative lifetime exposures were calculated in terms of parts per million years. The authors did find an increased risk for NHL in the “high” exposure category for chlorinated hydrocarbons, which was defined as exposures greater than 47.3 parts per million years. The OR was 2.1, with a 95 percent confidence interval of 1.1–4.3. No association was found for exposure to aromatic hydrocarbons, either generally or for the specific, aromatic hydrocarbons studied.

The authors also presented specific analyses for Hodgkin’s disease, B-cell NHL and T-cell NHL. Again, at the highest exposure levels, they found significant associations between chlorinated hydrocarbons and B-cell NHL, but no such association for Hodgkin’s disease or T-cell NHL. For B-cell NHL and the specific chlorinated hydrocarbon studied, elevated ORs were reported. Furthermore, with trichloroethylene exposure, elevated ORs were reported for both Hodgkin’s disease and T-cell NHL, but the confidence intervals included 1.0 and the numbers were small, thus raising the question of whether the findings are statistically significant.

The authors also subdivided B-cell NHL into the specific subentities of diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia and marginal zone lymphoma. With chlorinated hydrocarbons exposures generally, elevated ORs were found at the highest exposure levels for diffuse large B-cell, follicular lymphoma, chronic lymphocytic leukemia, and marginal zone lymphoma, with confidence intervals that excluded 1.0 for follicular lymphoma and marginal zone lymphoma. Despite the authors’ earlier conclusions that no association was found between aromatic hydrocarbons and NHL, the authors did find elevated ORs at the study’s medium exposure levels for toluene, xylene, and styrene, but not for benzene. Of even more interest is that the authors did not find elevated risks at the highest exposure levels for toluene, xylene and styrene, thus raising a substantial question about whether the findings are scientifically valid based on the lack of a dose-response relationship. The authors state in conclusion that their study “does not support a strong association between aromatic hydrocarbons (benzene, toluene, xylene, or styrene) and the diagnosis of a malignant lymphoma,” which perhaps, recognizes the dose-response relationship deficiency.

Mester, et al., “Occupation and Malignant Lymphoma: A Population Based Case Control Study in Germany,” 63 OCCUPATIONAL AND ENVIRONMENTAL MEDICINE 17 (2006)

This study generated the data relied on by Seidler, et al. The purpose of this study was to identify occupations that the authors anticipated would be associated with lymphoma risks, based on the new WHO classification system. The authors refer to NHL risks reported in studies of painters, farmers, female physicians, metal workers, machine fitters, shoemakers, furniture makers, dairy workers, printers and chemical industry workers, with appropriate citations to the relevant articles.

Turning to solvents, the authors found increased ORs in several industries/occupations where solvent exposures “can occur,” namely, pulp paper, paper products, publishing and printing; basic metals and fabricated metal products; shoemakers and leather goods; printers; rubber and

plastic product makers. However, many of the ORs reported were just barely above 1.0, and almost all of the confidence intervals include 1.0. The authors noted that “several occupations which can be expected to be prone to solvent exposure (for example drycleaners, painters) are not associated with lymphoma diagnosis.”

The authors also studied the specific NHL subentities: diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and plasma cell myeloma. Increased risks were found for diffuse large B-cell lymphoma among architects, engineers and related technicians; cooks, waiters, bartenders and maids; and metal processors, but the confidence intervals for metal processors, cooks, waiters and bartenders included 1.0. Relevant to follicular lymphoma, elevated ORs were found for numerous occupations, such as architects, engineers and related technicians; chemical processors and related workers; food and beverage processors; machinery fitters, machine assemblers, and precision instrument makers (excluding electrical precision instrument makers); printers; electrical fitters and related electrical and electronic workers. Again, however, confidence intervals invariably included 1.0, with the exception of sales workers, where the OR was 3.2, and the 95 percent confidence interval was 1.3–7.7. The authors noted that the grouping of employees by certain sectors, such as chemicals, chemical products and manmade fibers, tended to “conglomerate” different work places and different factual exposures, which naturally affected the overall risks reported.

A notable follow-up was written by Dr. Blair of the National Cancer Institute, “Occupational Exposures and Non-Hodgkin’s Lymphoma: Where Do We Stand,” 63 *Occupational and Environmental Medicine* 1 (2006). Dr. Blair noted that Mester’s article found elevated risks for NHL associated with several occupations and industries, some of which have been linked with NHL in prior studies. Nevertheless, Dr. Blair stated, “despite many leads from this and other studies, the literature on occupational exposures and risk of NHL is inconsistent. No workplace exposures have been conclusively identified as causal factors.” Dr. Blair noted that future investigations of risk factors for NHL



required first investigating the risks among the diagnostic subentities of NHL, which was included in Mester's study and in Seidler's 2007 follow-up study. Echoing the WHO, the need to investigate the subcategories of NHL is "critical because there is growing evidence that the different subtypes of NHL have different etiologies."

The second area for future investigation

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of NHL, according to Dr. Blair, is summarized as follows:

Although studies like the one [Mester's article] help to identify promising areas for future research and should be encouraged, we are unlikely to make major headway in the identification of new chemical risk factors for NHL unless we substantially improve the quality of occupational and environmental exposure assessments.

Mandel, et al., "Occupational Trichloroethylene Exposure and Non-Hodgkin's Lymphoma: A Review and Meta-Analysis," 63 OCCUPATIONAL AND ENVIRONMENTAL MEDICINE 597 (2006)

Given the findings by Seidler regarding chlorinated hydrocarbons, generally, and trichloroethylene, in particular, this article is a useful counterpoint to Seidler, although it predates Seidler by one year. The authors conducted a meta-analysis and review of 14 occupational cohort and four case control studies of workers exposed to trichloroethylene, to investigate the relationship between trichloroethylene and NHL. The cohort studies were divided into two groups. Group I included those studies that had (1) sufficient workforce enumeration; (2) a sub-cohort identifiable

within the larger cohort that was more likely to have had trichloroethylene exposure; (3) cases identifiable as having NHL, as opposed to less specific classifications, such as "lymphoma," which the authors noted would include both Hodgkin's disease and NHL, problematic in both the Mester and Seidler studies, or the designation of hematopoietic cancer, which obviously broadens the list to include not only Hodgkin's disease and NHL, but also leukemias. Group II studies mentioned or identified trichloroethylene exposure and NHL, but lacked data to verify actual exposure and were unable to identify a specific sub-cohort exposed to trichloroethylene. The individual studies reviewed by the authors are discussed in the article and will not be discussed here.

The authors concluded that the studies did not consistently establish a causal relationship between NHL and trichloroethylene exposure. Although some of the individual studies did find increased risks above 1.0, significantly, the authors found that no dose-response trend could be identified from the studies. The authors also found supportive information lacking from the toxicological and mechanistic data, and the absence of consistent findings in the various epidemiological studies, both of which did not support a causal link between trichloroethylene and NHL.

Miligi, et al., "Occupational Exposure to Solvents and the Risk of Lymphomas," 17 EPIDEMIOLOGY 552 (2006)

The authors of this Italian study evaluated the association between exposure to solvents and lymphomas, including both Hodgkin's disease and NHL in a population-based case control study covering 11 areas of Italy. All newly diagnosed cases of NHL and chronic lymphocytic leukemia among men and women ages 20-74 between 1991 and 1993 were included. However, the authors did not use the WHO classification system. Instead, the authors elected to rely on a 1992 classification system published by the National Cancer Institute. The authors established a general category of "solvents" and divided them categorically as aromatic hydrocarbons, chlorinated hydrocarbons, aliphatic hydrocarbons, technical hydrocarbons and oxygenated derivative hydrocarbons. When

information was available to assess individual solvents, exposure judgments were made regarding benzene, styrene, xylene and toluene for aromatic hydrocarbons, dichloromethane, tetrachloroethylene, trichloroethylene, 1,1,1 trichloroethane, and chloroform among chlorinated hydrocarbons, and 1,4 dioxane among oxygenated derivative hydrocarbons. Four exposure level classifications were established: very low, low, medium and high.

In accordance with a dose-response model, the authors found no evidence for increased NHL risk at the very low/low exposure level for any class of solvent or specific solvent. The authors, however, did find a "slightly increased risk" for those with moderate/high intensity exposure to chlorinated hydrocarbons and aromatic hydrocarbons. In a separate analysis of medium/high exposure levels to aromatic hydrocarbons exposure, the authors found a greater increase in risk for NHL for those exposed to high levels. For specific aromatic hydrocarbons, increased risks at the medium/high exposure level were found for benzene, styrene, xylene, and toluene. For chlorinated hydrocarbons, in the medium or high exposure level category, elevated risks were reported for dichloromethane, tetrachloroethylene, and trichloroethylene. Again, because 1.0 is either the starting point for the confidence interval, or included within the confidence interval range for all of the specific solvents except for toluene, one must question whether these are statistically significant.

When duration of exposure was substituted for exposure intensity classifications, only aromatic hydrocarbons reported a slightly increased risk. In fact, with any solvent, which would include aromatic hydrocarbons, chlorinated hydrocarbons, technical hydrocarbons, aliphatic hydrocarbons, and oxygenated derivative hydrocarbons, the OR was exactly 1.0, with a 95 percent confidence interval of 0.7-1.4, for exposures of greater than 15 years. For specific solvents, increased risks above 2.0 were reported for benzene, xylene, and toluene.

In this author's view, the overall data for *duration of exposure* is confusing and contradictory. Among subjects in the medium or high intensity exposure level categories, separate analyses were performed for

chronic lymphocytic leukemia and small lymphocytic lymphoma, follicular NHL, and diffuse NHL. Without discussing each data point, the highlights for this particular analysis, focusing on specific NHL subentities, found elevated risks above 2.0 for diffuse NHL and benzene, xylene, and toluene; follicular NHL, for xylene and toluene; and chronic lymphocytic leukemia and small lymphocytic lymphoma, toluene and dichloromethane. The confidence intervals for small lymphocytic NHL and dichloromethane and toluene, and follicular NHL and xylene and toluene, all included 1.0. The study authors concluded that increased risks for diffuse large cell and chronic lymphocytic leukemia and small lymphocytic lymphoma is suggested "among subjects exposed to aromatic and chlorinated hydrocarbons."

An interesting follow-up study to Miligi, using the same data, is Vineis, *et al.*, "Exposure to Solvents and Risk of Non-Hodgkin's Lymphoma: Clues on Putative Mechanisms," 16 *Cancer Epidemiology Biomarkers* 381 (2007). Taking the same data, the authors examined "hypotheses regarding the putative mechanisms of action of solvents in lymphoma genesis." They found an increased risk of NHL, which they termed "not statistically significant," in those persons exposed to benzene with a history of autoimmune disease, and they also found an elevated risk in those persons with "high level exposure to benzene" with a positive family history of hematologic neoplasms.

Dryver, *et al.*, "Occupational Exposures and Non-Hodgkin's Lymphoma in Southern Sweden," 10 *INTERNATIONAL JOURNAL OF OCCUPATIONAL AND ENVIRONMENTAL HEALTH* 13 (2004)

In this study, 859 NHL cases, which were reported between 1990 and 1998, were identified through Sweden's Tumor Registry. The authors collected the appropriate demographic, occupational and exposure information and reported their results.

The authors used three different methods to determine exposure, which makes this a unique study. The three methods were self-reporting exposure, job/matrix derived exposures and occupational history. In the self-reporting exposure category, solvent exposure of greater than five years had an OR of 1.59 with a 95 per-

cent confidence interval of 1.11–2.28. However, as the authors noted, self-reported exposures "may suffer from recall bias or ignorance of the fact that the exposure occurred. Cases may also report exposures more completely than controls, resulting in differential mis-classifications of exposures. Self-reporting of occupational histories is unlikely to be significantly affected by recall bias, but occupations do not consistently determine exposures." Nevertheless, the authors concluded that each of the three methods of determining exposure showed an association between exposures to solvents and an increased risk of NHL.

Some of the data, particularly data derived from a job/exposure matrix failed to delineate a dose-response relationship, and as such, is interesting. In the job/exposure matrix to determine exposure, a dose-response relationship was delineated for low exposure, medium exposure and high exposure in the category of aromatic hydrocarbon solvents. However, no such relationship was delineated for chlorinated hydrocarbon solvents, other categories of chlorinated hydrocarbon solvents and other organic solvents. For chlorinated hydrocarbons, those persons in the low exposure category had an OR of 1.7, but the medium exposure category had an OR of .4. With solvents categorized as other organic solvents, those persons with low exposure had an OR of 7.58, while those persons with medium exposure had an OR of 1.77, and those persons with high exposure had an OR of .67. The job/exposure matrix for polycyclic aromatic hydrocarbons did show a dose-response relationship, in contrast to the case of aromatic hydrocarbons. Aliphatic hydrocarbons also showed a dose-response relationship at the high exposure level; the OR was 15.66 with an extremely wide confidence interval.

The wide confidence intervals, and the fact that many of the confidence intervals included 1.0, raise substantial questions regarding whether the findings are statistically significant. In fact, if one examines just the confidence intervals, the dose-response relationship for aromatic hydrocarbons and polycyclic aromatic hydrocarbons in this study is, in fact, reversed, with tighter confidence intervals at the low exposure categories, and wider confidence intervals at the higher exposure categories.

Fritschi, *et al.*, "Risk of Non-Hodgkin's Lymphoma Associated with Occupational Exposure to Solvents, Metals, Organic Dust and PCB's" (Australia), 16 *CANCER CAUSES AND CONTROL* 599 (2005)

In this study, 694 cases and 694 matched controls were analyzed for NHL risk. This involved taking a detailed history of all jobs over the subject's lifetime, with follow-up questions about various tasks within certain jobs that may have involved "high exposures to specific chemicals." An occupational exposure expert reviewed the answers.

Despite the authors' assurance that this study used a "more accurate means" to assess exposures, an analysis of the data reveals substantial subjectivity, particularly in the attempt to establish a dose-response relationship. The two categories for exposure utilized to establish the dose-response relationship were "non-substantial" and "substantial." How these terms and the corresponding parameters for each were developed is confusing. The occupational hygienist reviewing the information allocated levels of exposure based on internationally recognized threshold limit values (TLV), with levels higher than the specific TLVs considered high, those less than or equal to one-tenth of the relevant TLVs considered low, and those in-between considered medium. Lifetime dose was then calculated based on these parameters, with the "substantial category falling into those who worked at the medium or high levels for more than 5 days (8 hour per day), for a combined total of more than 5 years, and with all other exposures falling into the category of non-substantial." Based on the assumptions that defined "substantial" versus "non-substantial," the authors found ORs for aromatic hydrocarbons, excluding benzene, of 1.24 for those in the non-substantial exposure category, and an OR of 1.55 for the substantial exposure category. Aliphatic hydrocarbons had an OR of 1.16 for non-substantial exposures, and an OR of 1.59 for the substantial exposure category. Chlorinated hydrocarbons demonstrated an OR of 1.03 for non-substantial category, and an OR of 1.81 for the substantial category. Under the general category of "any solvents," an OR of 1.25 was reported for the persons in the non-substantial exposure category, and an OR



of 1.45 for those persons in the substantial exposure category.

The authors determined the dose-response relationship for the “any solvents” category and aliphatic solvents category was significant. For the aromatic solvents category, the authors stated that the dose-response relationship “just failed to reach statistical significance.” Notably, when the authors separated data into the exposure categories of low, medium and high, an inverse dose-response relationship was reported, with the medium exposure category for any solvents having an OR of 1.54, while the high exposure category for any solvents had an OR of .92. Thus, while the authors relied on one table to establish a dose-response relationship, another table seems to detract from that claim. Indeed, in that same table, the authors noted that the only significant dose-response relationship

shown was under the category of frequency of exposure—with those persons exposed to any solvents more than four days per year having a higher OR than those who claimed exposure to any solvents at four or less days per year.

The authors specifically found no increased risk reported for benzene in their data, stating that “whether benzene exposure causes NHL has been controversial.” In conclusion, the authors believed that their data showed an increased risk of NHL, by about 30 percent, for exposures to aromatic (other than benzene) or aliphatic solvents, but also qualified their conclusion by adding, “although the effect was not always statistically significant.”

Conclusion

The most important point for the defense practitioner to remember is that the cause

of NHL in the vast majority of cases remains “unexplained.” Important advances have been made in the study of NHL by using the 2001 WHO classification system, and many of the more recent epidemiological studies are now taking into account that classification system. However, the bulk of the literature predates the WHO classification system, which confounds and confuses analysis of the NHL epidemiology literature. The best advice that this author can give the practitioner is to pay close attention to the WHO classification system and the dose-response relationship in your particular case, and to work very closely with your epidemiology witness to thoroughly review the entire body of available but widely variable NHL epidemiological literature. 