A REVIEW OF RECENT LITERATURE ON THE "ASSOCIATION/CAUSAL LINK" BETWEEN BENZENE AND NON-HODGKIN'S LYMPHOMA

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Benzene is a sweet smelling, colorless liquid that is a common industrial solvent.[2] It is a precursor to chemicals used to make numerous products, including plastics, resins, dyes, drugs, and pesticides. Benzene ranks in the top 20 chemicals in the United States in production volume.[3] It is ubiquitous, resulting in exposures not only in occupational settings but also in the general population.[4] A natural constituent of petroleum, it is produced in combustion processes including automobile engines, fires, and cigarette smoke.[5]

The literature regarding benzene exposure and the development of hematopoietic malignancies has consistently shown that, other than specific subtypes of acute myelogenous leukemia (AML), there is no significant association between benzene exposure and the development of non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), or other forms of leukemia, such as chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML).[6] This author is unaware of any peer-reviewed literature linking benzene exposure to any increased risk of acute lymphocytic leukemia (ALL).

It is important that where an association with AML is consistent and significant, the threshold cumulative benzene exposure necessary for the development of AML, as supported by the relevant literature, is between 40-50 and 400-500 ppm-years, with some concluding that the best estimate is 200 ppm-years.[7] Quantifying and understanding exposures and thresholds are not only vital in arriving at specific causation, but such knowledge is critical to any epidemiologic analysis and the issue of general causation.

Non-Hodgkin's lymphoma (NHL) refers to cancers affecting the immune system, in particular the lymphocytes found within the lymph nodes and other lymphoid tissues. There are numerous types of NHL with a system of classification that has evolved over the years and continues to evolve.[8] The incidence rates for NHL have nearly doubled since the early 1970s, particularly for women. The average American's risk of developing NHL during his or her lifetime is now about 1 in 50, and in 2010, it was estimated that over 65,000 would be diagnosed with the disease.[9]

While the incidence of NHL has increased over the last several decades, its cause, and the reason for the increased incidence rate, remains unclear.[10] Given that benzene is identified as a carcinogen due to its consistent and significant causal association with AML, it is not surprising that it has also been investigated as a candidate cause of other cancers, including lymphatic cancers such as NHL. As the incidence rate has increased, not surprisingly so has litigation surrounding benzene exposure and NHL.

The scientific community continues to debate the existence of any association between benzene exposure and the development of certain hematopoietic malignancies, as evidenced by recent literature on the topic. For the status of this ongoing debate as it relates to NHL, an examination of recent review articles and/or meta-analyses by Steinmaus C, et al.[11], Kane EV, et al.[12],

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2 Agency for Toxic Substances and Disease Registry. ToxFAQs for benzene, 2007; accessed at http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=38&tid=14 on June 1, 2011.

3 Id.

4 Pyatt D. Benzene and hematopoietic malignancies. Clin Occup Environ Med 4 (2002):529-555, at 530-31.

5 Id.

6 Id. at 546.

7 Id. at 539. See also, Galbraith D, Gross SA, Paustenbach D. Benzene and human health: A historical review and appraisal of associations with various diseases. Crit Rev Toxicol 2010;40(S2):1-46, at 2.

8 American Cancer Society. Non-Hodgkin Lymphoma, 2010; accessed at http://www.cancer.org/acs/groups/cid/documents/webcontent/003126-pdf.pdf on June 1, 2011.

9 Id.

10 Galbraith D, Gross SA, Paustenbach D. Benzene and human health: A historical review and appraisal of associations with various diseases. Crit Rev Toxicol 2010;40(S2):1-46, at 18 (aging population, prevalence of HIV, autoimmune disorders and possible occupational exposures are suspected culprits.).

11 Steinmaus C, Smith AH, Jones RM, et al. Meta-analysis of benzene exposure and non-Hodgkin lymphoma: Biases could mask an important association. Occup Environ Med 2008;65:371-378.

12 Kane EV, Newton R. Benzene and the risk of non-Hodgkin lymphoma: A review and meta-analysis of the literature. Cancer Epidemiol 2010;34:7-12.

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Alexander DD, et al.[13], Weed DL, et al.[14], Galbraith D, et al.[15] and Wong O, et al.[16] is necessary.[17]

Interest in the possible link between benzene and NHL began in earnest in 1979, following a publication in the prominent journal Lancet claiming a positive association between the two.[18] Subsequent animal studies have bolstered this hypothesis. For example, thymic and nonthymic lymphomas have been observed in mice following exposure to relatively high chronic airborne concentrations of benzene (300 ppm six hours/day, six days/week, over the lifetime of the animals). In addition, exposures in mice to levels of 100 and 200 ppm (but not lower) have lead to dramatic decreases in the number of splenic, thymic, and femoral lymphocytes.[19]

Despite these suggestive results, studies in humans have failed to establish a causal role for benzene in the onset of NHL. To begin with, the initial Lancet report was shown to be seriously flawed. For example, benzene exposure was estimated based on occupational subtype rather than actually measured results. Moreover, the claimed effects of benzene were confounded by the presence of a wide variety of other known carcinogens, and, as was pointed out in a later letter to the editor, there were even inconsistencies in the reported calculations.[20] Scientists sought to correct these methodological flaws through future studies, which has lead to a collection of an impressive body of work . In the past decade, there have been at least 16 reviews and 3 meta-analyses examining whether benzene causes NHL.[21] Although a few authors have suggested that benzene might be associated with NHL, a consensus has emerged that there is currently insufficient evidence to support the claim that benzene causes NHL.[22]

A fairly recent meta-analysis by Steinmaus, et al., which not only purported to find an association but also a causal link, analyzed 22 studies of benzene exposure and NHL, consisting of 16 case studies and 6 cohort studies. It also analyzed 21 cohort studies dealing with refinery workers and NHL. According to the authors, this meta-analysis differed from prior analyses that found no association or causal link in that this analysis attempted to "objectively evaluate the impact of the healthy worker effect and exposure misclassification (in particular, the inclusion of unexposed or lesser exposed workers in 'exposed' cohorts) and incorporate the results of these evaluations directly into [the author's] overall summary relative risk estimates."[23]

The result of this analysis is an increased summary relative risk for the development of NHL in individuals exposed to benzene and individuals involved in refinery work to the point that the authors conclude benzene causes NHL. The authors' analyses considered the healthy worker effect (HWE), focused only on highly exposed individuals, and excluded all self-reported exposures to, in their opinion, properly account for exposure misclassification and the inclusion of low or unexposed workers in "exposed" cohorts, which might bias or dilute relative risk estimates.[24]

This meta-analysis has not gone unnoticed by others in the scientific community. Its conclusions are addressed at least to some extent in most of the recent referenced articles. Some criticisms are: (1) the only subgroups selected were the ones with the highest exposures; (2) the cohort studies were adjusted for the HWE; (3) outdated cohort studies were used instead of updates; and (4) the authors' inconsistently applied their own selection criteria.[25]

Kane, et al. also conducted a meta-analysis based on their review of 6 cohort studies, 16 case-control studies,

13 Alexander DD, Wagner ME. Benzene exposure and non-Hodgkin lymphoma: A meta-analysis of epidemiologic studies. J Occup Environ Med 2010;52(2):169-189.

14 Weed DL. Meta-analysis and causal inference: A case study of benzene and non-Hodgkin lymphoma. Ann Epidemiol 2010;20:347-355.

15 Galbraith D, Gross SA, Paustenbach D. Benzene and human health: A historical review and appraisal of associations with various diseases. Crit Rev Toxicol 2010;40(S2):1-46.

16 Wong O, Harris F, Armstrong TW, et al. A hospital-based case-control study of non-Hodgkin lymphoid neoplasms in Shanghai: Analysis of environmental and occupational risk factors by subtypes of the WHO classification. Chem-Biol Interact 2010;184:129-146.

17 Additional recent articles and meta-analysis exist on this topic but were outside the scope of this article.

18 Vianna NJ, Polan A. Lynmphomas and occupational benzene exposure. Lancet 1979;1(June(8131)):139-1395. *Cited in* Kane EV, Newton R. Benzene and the risk of non-Hodgkin lymphoma: A review and meta-analysis of the literature. Cancer Epidemiol 2010;34:7-12, at 7.

19 Galbraith D, et al. at 20.

20 Id. at 20-21.

21 Weed DL, at 348.

22 Id. at 349.

23 Steinmaus, et al. at 371.

24 Id. at 374.

25 Swaen GMH, Tsai SP, Burns C. Letters to the Editor: Occup Environ Med 2010;67:286-287.

and 1 study each of cancer registrations and death certificates. They also relied upon the latest publications on populations where possible.[26] Concluding that there is little evidence of an association between NHL and occupational exposure to benzene, Kane, et al. was critical of the conclusions reached by Steinmaus, et al., mainly due to their pooling of "risks associated with different metrics and levels of exposure" and a failure to examine dose-response relationships.[27]

Alexander, et al. conducted a meta-analysis and again found no association between benzene exposure and NHL. While this analysis did find some positive association among a subgroup with "long" exposure duration, that association was limited to 3 cohort and 2case-control studies with a broad range of exposure years, making it difficult, in the authors' opinion, to evaluate dose-response relationship.[28] Cumulative exposure is the most commonly used summary measure for chronic disease, and, in this instance, did not corroborate the significance of the "long" duration of exposure findings. Alexander also took issue with the evaluation by Steinmaus, et al. of only high exposure subgroups and the failure to consider dose-response, the study selection, and the use of the HWE.[29] Despite their findings, or lack thereof, Alexander, et al. acknowledges that, due to the numerous subtypes of NHL, additional research is needed in order to understand any potential association.[30]

Weed DL is especially critical of the conclusions and methodology followed by Steinmaus, et al. Prior to Steinmaus, a consensus existed that there was no causal link between benzene and NHL, and legitimate debate existed as to even an association.[31] In addition to use of the HWE and analysis of only "high" exposures, Weed DL points out that Steinmaus selected studies with no consistency, excluded the results of the Pliofilm cohort (frequently cited as possibly the best cohort for evaluating dose-response relationships for benzene), and in essence attempted to jump to causation while the rest of the scientific community was not convinced of any association.[32] Weed DL is particularly critical of the attempt made to establish causation without engaging in a full analysis of the general causation criteria used in the scientific community, by ignoring the results of what analysis was done, and by not even mentioning a majority of the criteria.[33]

Wong, et al. conducted a case-control study of 649 newly diagnosed non-Hodgkin lymphoid neoplasm (NHLN) cases and 1298 patient controls at 25 hospitals in Shanghai. NHL is the largest subgroup of NHLN.[34] In this case-control study, the authors discuss briefly the potential shortcomings of prior epidemiologic studies - namely that NHL was treated as a single diagnostic category and that research related to NHL has been hampered "by the complexity and the confusion of historical changes in NHL subtype classification."[35] Recognizing the need for recent studies based upon the 2001WHO classification of lymphoid neoplasms, this study attempts to do just that by investigating the potential environmental and occupational risk factors of NHLN, and by exploring any relationships between risk factors and specific NHLN subtypes.[36] The important results from this study are that there was no significant odds ratio (OR) and no pattern with respect to any exposure variables as to exposure to benzene and NHLN as a whole.[37] There was, however, an overall increase in follicular lymphoma (FL) for those exposed to benzene, but no such increase at higher exposure levels.[38] Similarly, exposure to petroleum fuels reflected an increased risk for FL, but no overall increase as to NHLN as a whole.[39] In addition, exposure to solvents was not related to total NHLN, but was related to the subtype precursor B-cell neoplasms.[40]

Wong O, et al. noted that these findings should be interpreted with caution and confirmed in future studies. Nonetheless, this study does seem to indicate a potential significant association between benzene and certain NHL subtypes.

The debate continues, as does the research on this issue. It is safe to say that there is still no consensus on any causal connection, or even any agreed-upon signification consistent association, between benzene and NHL. Future studies will undoubtedly focus on examining NHL subtypes to explore any potential increase in risks from exposure to benzene and solvents. ⚖

26 Kane, et al. at 7-9.
27 Id. at 11.
28 Alexander, et al. at 186.
29 Id. at 187.
30 Id. at 188.
31 Weed DL at 348.
32 Id. at 348, 350 and 351.
33 Id. at 353.
34 Wong O, et al. at 129.
35 Id. at 130.
36 Id.
37 Id. at 141.
38 Id. at 141.
39 Id. at 143.
40 Id.