

The following is a portion of the Declaration of Robert Jay Harrison's, M.D., M.P.H., Clinical Professor of Medicine at the University of California at San Francisco, regarding the relationship between benzene/organic-solvents and leukemia/non-Hodgkin's lymphoma. This Declaration was filed in a California State Court proceeding in November of 2007 in conjunction with a hearing on the defendant's motion challenging his qualifications and the basis for his opinions:

I. BENZENE AND BENZENE EXPOSURE

Benzene is the simplest aromatic hydrocarbon; it is 6 carbon atoms and 6 hydrogen atoms in a hexagonal (ring) structure. Benzene is a colorless liquid with a sweet odor; it evaporates into air very quickly and dissolves slightly in water. Benzene is highly flammable. Most people can begin to smell benzene in air at 1.5-4.7 parts of benzene per million parts of air (ppm) and smell benzene in water at 2 ppm. Most people can begin to taste benzene in water at 0.5-4.5 ppm. Benzene is found in air, water, and soil. Agency for Toxic Substances and Disease Registry, *Toxicological Profile of Benzene* (U.S. Dept. of Health and Human Services 1993) at p. 1.

Benzene occurs in the environment as a result of both human activities and natural processes. Benzene was first discovered and isolated from coal tar in the 1800s. Today, benzene is refined mostly from petroleum sources. Because of its wide use, benzene ranks in the top 20 in production volume for chemicals produced in the United States. Various industries use benzene to make other chemicals, such as styrene (for

Styrofoam® and other plastics), cumene (for various resins), and cyclohexane (for nylon and synthetic fibers). Benzene is also used for the manufacturing of some types of rubbers, lubricants, dyes, detergents, drugs, and pesticides. Benzene also occurs naturally, as a constituent of crude oil and cigarette smoke. Benzene is also used as an additive in gasoline to prevent vehicle engines from knocking.

Individuals employed in industries that make or use benzene may be exposed to the highest levels of benzene. More than 200,000 people may be occupationally exposed to benzene in the U.S. These industries include benzene production (petrochemicals, petroleum refining, and coke and coal chemical manufacturing), rubber tire manufacturing, and storage or transport of benzene and petroleum products containing benzene. Other workers who may be exposed to benzene because of their occupations include steel workers, printers, rubber workers, shoemakers, laboratory technicians, firefighters, and gas station employees.

A. Benzene Content of Organic Solvents

“The benzene content of crude oil ranges from below detectable limits to greater than 1 percent. Condensates produced from natural gas liquids present in both crude oil and natural gas have a higher percentage of benzene than crude ... ranging from approximately 0.2 to 1.0 percent by volume. The benzene in natural gas varies from 0 to about 4 percent.” OSHA, “Occupational Exposure to Benzene; Liquid Mixtures,” *Federal Register* 43(24);27962.

“Typical petroleum refining processes are many. Not all refineries have all of these processes since there is specialization, such as fuels, lubes or petrochemical operations, within refineries. At all refineries, however, additional benzene is generated during refining by catalytic cracker, reformer and coker operations.”

“Petroleum refined products are many and their benzene content varies according to the content of the crude taken into the refinery, the nature of the efficiency of the refining process, and the balance of the product demands on the refinery. Thus, the benzene content of product streams within a single company may vary from refinery to refinery or within a single refinery from year to year. The same product from different refineries or at different times from the same refinery consequently may have a different benzene content. Motor gasoline ranges from 1 to 3 percent benzene by volume. Aviation gasoline, specialty naphtha solvents and naphtha-based (type B) jet fuels may exceed 1 percent benzene concentrations. Heavier jet fuel (type A), light fuel oils and cutback asphalts may occasionally exceed 0.01 percent benzene. Petrochemical feedstock naphthas and certain aromatics, such as toluene, may contain up to 1 percent benzene. This petrochemical feedstock is used to produce ethyl benzene, styrene monomer, cumene, phenol, cyclohexane, and nitrobenzene.”

“Processed refined petroleum products ... have numerous uses, such as fuels, extractants, processing aids, and solvents in paints, surface coatings, adhesives and pesticides, inks, etc. The benzene content of these products varies from less than one-tenth to a few percent.”

The highest benzene concentration in solvents has been reported in hexane-based solvents. Shell Oil Company, *Benzene Content of Shell Hydrocarbon Solvents* (July 1977).

B. Benzene Content of Printing Solvents

In the printing industry organic compounds have long been used in printing inks and cleaning solvents used to clean printing presses. These solvents have contained substantial amounts of benzene, as is shown by historical documents which solvent and ink manufacturers and suppliers submitted to the U.S. Department of Labor regarding the Standard for Benzene in Liquid Mixtures promulgated by the Occupational Safety and Health Administration in 1978.

On May 11, 1978, the Printing Industries of America, Inc., a Federation of National, Regional, State, and City Associations, submitted to the U.S. Department of Labor comments developed by the Environmental Conservation Board (ECB), to which the Printing Industries of America belonged. The transmittal letter noted that Printing Industries of America is the world's largest Graphic Arts trade association, whose more than 8,200 members produce nearly three-quarters of the nation's printed products.

The comments of the ECB stated, in relevant part, that "benzene is a pervasive substance, most frequently encountered as a contaminant which may be present in petroleum distillates and other petrochemical products supplied to the printer in several different commercial forms." (p. 2) "Benzene concentrations of hydrocarbon solvents is frequently cited as 0.1 percent maximum by the manufacturers, but limited random

sampling and analyses indicate that the upper limit sometimes is exceeded in commercial shipments. Similarly, benzene concentrations in liquid printing inks usually range between .05 and .09 percent but in isolated cases have been encountered as high as 0.4 percent of the solvent in the ink. Under these circumstances, it seems unlikely that the normal commercial supply sources can provide liquid products, the benzene content of which is assuredly less than 0.1 percent.” (p. 3)

The ECB comments further stated that benzene “is expected as a trace contaminant in all hydrocarbons with initial boiling points below 285°F. Hydrocarbon ink solvents which might be included in the formulation of the above types of inks involved: hexane, heptane, toluene, xylene, lactol spirits, all of which may contain the contaminant benzene.” (p. 5)

C. Benzene Exposure from Printing Solvents

On May 11, 1978, the National Association of Printing Ink Manufacturers, Inc. also submitted comments to OSHA. These comments noted that the “National Association of Printing Ink Manufacturers, Inc. (NAPIM) is an industry association representing large, medium, and small printing ink manufacturers throughout the United States and accounting for nearly 90 percent of the merchant sales of printing ink.” (p. 2) These comments further stated: “NAPIM does not know the level to which benzene might be reduced in the manufacturer of hydrocarbon solvents supplied to the ink industry. The level of benzene contamination depends upon the source of the feed stock and other variables in each individual supplier’s manufacturing operation for the various petroleum distillates products. NAPIM understands, however, that complete elimination

of benzene in petroleum distillates with initial boiling points below 285°F is either impossible or unlikely.”

NAPIM’s comments also addressed occupational exposure to benzene from printing solvents: “NAPIM has obtained monitoring data from certain of its member companies on workplace exposure to benzene in printing ink plants using solvents containing low levels of benzene. These data were obtained from 32 separate monitoring samples taken over a period of about seven months since September 14, 1977, in printing ink plants which use hydrocarbon solvents boiling below 285°F and which are known to contain trace amounts of 1% or less of benzene. These selected plants are believed to account for approximately 10% of all flexographic and gravure inks produced by merchant manufacturers of printing ink in the U.S. in 1977, plus a small percentage of total lithographic ink production. The results of this monitoring are summarized below:

<u>Samples</u>		<u>8-Hour TWA</u>
<u>Number</u>	<u>%</u>	<u>Benzene Concentration</u>
6	19.0%	less than 0.10 ppm
21	65.5%	0.10-0.20 ppm
5	15.5%	0.21-0.30 ppm
32	100%	less than 0.30 ppm (pp. 8-9)

While these exposure levels were considered to be safe at the time, epidemiologic studies published during the last decade show that occupational exposure to benzene at these levels significantly increase the risk of various hematolymphopoeitic malignancies.

D. Benzene’s Classification as a Human Carcinogen

Benzene is recognized as a human carcinogen by all organizations that evaluate the carcinogenicity of chemicals and governmental agencies that classify chemicals as carcinogens:

(a) The Environmental Protection Agency (EPA) classifies benzene as a “human carcinogen,” i.e., a chemical for which there is sufficient evidence from epidemiologic studies to support a casual association between exposure and cancer. National Center for Environmental Assessment, *Carcinogenic Effects of Benzene: An Update* (US EPA 1998).

(b) The International Agency for Research on Cancer (IARC) classifies benzene as “carcinogenic to humans.” IARC, “Benzene,” *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Industrial Chemicals and Dyestuffs* (Vol. 29, pp. 93-148, 1982).

(c) The National Institute for Occupational Safety and Health (NIOSH) lists benzene as a “potential occupational carcinogen,” i.e., “any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration.” This definition also includes any substance, “which is metabolized into one or more potential occupational carcinogens by mammals.” NIOSH *Pocket Guide to Chemical Hazards*.

(d) The National Toxicology Program (NTP) classifies benzene as a “known carcinogen.” National Toxicology Program, “Benzene,” *11th Annual Report on Carcinogens* (U.S. Dept. of Health and Human Services, 2004).

(e) The Occupational Safety and Health Administration (OSHA) categorizes benzene as a carcinogen based on the classification of IARC and the NTP.

(f) The California Environmental Protection Agency classifies benzene as a chemical known to the State to cause cancer. 22 Code of California Regulations § 12000.

E. Benzene Exposure Limits

Several organizations and governmental agencies prepare regulations or recommendations limiting exposure to toxic chemicals. The regulations and recommendations for limiting benzene exposure are as follows:

(a) The Agency for Toxic Substances Disease Registry (ATSDR) has derived an Acute Inhalation Minimal Risk Level (MRL) of 0.05 ppm for benzene based on a Lowest Observed Adverse Effect Level (LOAEL) for immunological effects in mice. Agency for Toxic Substances and Disease Registry, *Toxicological Profile for Benzene* (U.S. Dept. of Health and Human Services 1997) at p. 325, citing Rozen, M.G., et al., “Depression in B- and T-lymphocyte Mogen-Induced Blastogenesis in Mice Exposed to low Concentrations of Benzene,” *Toxicology Letters* 20:343-394 (1984). The ATSDR has derived an Intermediate Inhalation MRL of 0.004 ppm for benzene based on a LOAEL for neurological effects in mice. Agency for Toxic Substances and Disease

Registry, *Toxicological Profile for Benzene* (U.S. Dept. of Health and Human Services 1997) at p. 325, citing Li, L., et al., “Effect of Low Benzene Exposure on Neurobehavioral Function, AChE in Blood and Brain and Bone Marrow Picture in Mice,” *Biomedical and Environmental Science* 5(4):349-354 (1992).

(b) The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a Threshold Limit Value (TLV) of 0.5 ppm (8 hour time-weighted average) and a Short-Term Exposure Limit (STEL) of 2.5 ppm (15 minute time-weighted average). These are recommendations for breathing zone concentrations which should not be exceeded in the workplace. As recommendations for industry, they do not have the force or effect of law. ACGIH, 2004 *TLVs and BEIs: Threshold Limit Values for Chemical Substances and Physical Agents* (2004).

(c) The California Environmental Protection Agency (Cal-EPA) has adopted a No Significant Risk Level (NSRL) of benzene of 7 ug/day. This represents the maximum amount of benzene that the State of California has determined a person may be exposed to daily that poses no significant risk of cancer. 22 California Code of Regulations § 12701.

(d) The Collegium Ramazzini has recommended a Threshold Limit Value (TLV) for benzene of 0.1 ppm. Letter from Collegium Ramazzini to the American Conference of Governmental Industrial Hygienists (Sept. 10, 1993). However, recently, the collegium Ramazzini issued a statement calling for reduction of benzene exposure to the lowest level possible. Eighth Collegium Ramazzini Statement: Call for a Reduction of Exposure to Benzene to the Lowest Possible Level (2004), available at <http://www.collegiumramazzini.org>.

(e) The National Institute for Occupational Safety and Health (NIOSH) has adopted a Recommended Exposure Limit for benzene of 0.1 ppm (8 hour time-weighted average) and a Short-Term Exposure Limit of 1 ppm (15 minutes). Table I: NIOSH Recommended Safety and Health Standards for Hazardous Agents in the Workplace (NIOSH 1992).

(f) Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit: 1 ppm (8 hour time-weighted average), Short-Term Exposure Limit (15 minute average) 5 ppm. These limits have the effect of law and represent maximal allowable exposures in the workplace.

F. Hematopoietic Toxicity of Benzene

Benzene is a hematopoietic toxin, i.e., benzene is toxic to the blood and blood-forming organs. The earliest reported toxic effects of benzene were frank blood disease which resulted from heavy occupational exposure to benzene. The diseases reported included leucopenia (decrease in white blood cell counts), anemia (decrease in red blood cell counts), thrombocytopenia (decrease in platelet counts), and pancytopenia (decrease in all blood counts) and aplastic anemia (anemia without blast, i.e., cancer, cells). The early cases reported in the literature were always fatal.

As the hematologic hazards of benzene exposure became recognized and industry began controlling exposures, workers continued to develop these diseases, but often not as rapidly. Upon cessation of exposure, some of these less exposed workers survived. However, as time passed, some of them developed various forms of leukemia and other

malignancies. As industry continued to devise controls to minimize exposure, frank blood diseases became less common, but even at low levels of exposure, workers continued to develop leukemias and other cancers years after their initial exposure to benzene.

II. HEMATOLYMPHOPOIETIC MALIGNANCIES

Human blood performs many functions, e.g., transporting oxygen to the tissues, clotting, and combating infection. The organ system which makes blood cells is the hematopoietic system and consists of the blood-forming organs, i.e., the bone marrow and blood cells of all types. A related organ system is the lymphatic system, a complex network of cells and channels throughout the body which transports lymph, a liquid essential to immune function, to the blood. The lymphatic system includes the lymphatic vessels and clusters of lymphatic cells such as the lymph nodes.

Hematopoietic cancers are cancers which develop in the hematopoietic system, i.e., the bone marrow and the blood cells. Lymphatic cancers are those that develop in the lymphatic system. Sometimes cancers which develop in these related organ systems are collectively referred to as hematolymphopoietic cancers or lymphohematopoietic cancers.

Hematopoietic cancers are liquid tumors and are commonly referred to as leukemias. Lymphatic cancers can either occur in clusters in lymph nodes as solid tumors, or can be diffusely distributed throughout the lymphatic system as liquid tumors. Lymphatic cancers are generically referred to as lymphomas.

Generally, leukemias are those cancers which occur predominantly in the bone marrow and the peripheral blood, whereas lymphomas are those cancers which occur predominantly in extramedullary sites, i.e., sites other than the bone marrow and the peripheral blood. The blood cells found in the lymph are called lymphocytes.

Lymphomas may be found wherever normal lymphocytes go; they may occur in an isolated lymph node or a group of lymph nodes, in organs such as the stomach or intestine, the sinuses, bone, or any combination of these sites. Leukemias may be of lymphocytes or myelocytes, a type of blood cell that is not found in the lymphatic system.

With advances in molecular biology, histochemistry, immunophenotypic analysis, and cytogenetics, researchers came to appreciate that classifying hematolymphopoietic malignancies by site of manifestation was inappropriate, because malignancies that were morphologically, histochemically, immunologically and cytogenetically identical were assigned different nomenclature simply because they happened to be observed at different sites. For example, the cancer known as diffuse small cell lymphoma, on a molecular basis, is the same cancer as chronic lymphocytic leukemia, the only difference being the predominant site of occurrence.

From an etiologic standpoint, it would make sense to group cancers in epidemiologic studies based on molecular biology rather than site of occurrence, because cancers shown to be identical by molecular biology should have an identical pathogenesis and etiology. However, epidemiologic studies have generally not yet been conducted using cancer classifications based upon molecular biology, although such a classification would be most pertinent to etiology.

Epidemiologic studies of hematolymphopoietic cancers have historically been conducted based upon classifications of these cancers in use at the time the studies were done. For example, many epidemiologic studies have evaluated causative factors for all lymphomas. In these studies diffuse small cell lymphoma and chronic lymphocytic leukemia are evaluated as different diseases, although they are the same cancer. This is

unfortunate, because most epidemiologic studies of hematolymphopoietic malignancies have insufficient statistical power to generate scientifically valid results for subtypes of lymphomas and subtypes of leukemias. By reanalyzing data in such studies by combining the cases of chronic lymphocytic leukemia with cases of diffuse small cell lymphoma, a larger number of cases in a discrete category of etiologic relevance could be derived, which could increase the power to detect statistically significant effects. However, most of the published epidemiologic studies of lymphomas do not provide sufficient pathological descriptions of the subject cases to determine which lymphomas are diffuse small cell lymphomas, so as to permit regrouping them with chronic lymphocytic leukemias and reanalysis of the data.

Given the shortcomings of disease classification in epidemiologic studies of hematolymphopoietic malignancies conducted during the last few decades and the usual lack of statistical power of such studies, the best and, in many cases, the only scientifically valid use of such epidemiologic studies, is to evaluate broad categories of hematolymphopoietic malignancies.

A. **Lymphomas**

While there are many classification systems for lymphomas, most recognize two broad categories of lymphomas: Hodgkin's lymphomas (often called Hodgkin's disease) and non-Hodgkin's lymphoma. Hodgkin's disease is characterized by a specific type of cell known as the Reed-Sternberg cell. Non-Hodgkin's lymphomas comprise all lymphomas that are not characterized by these cells.

There can be many different presentations of leukemias and lymphomas. However, the leukemias and lymphomas are all cancers of the hematolymphopoietic system and are therefore closely related. Indeed, some researchers have referred to the diagnostic distinction between some forms of leukemia and lymphoma as an artifact of medical history. While the diverse pathological appearances of these diseases under the microscope is of great interest to pathologists, due to the substantial similarities of these cancers and their common clonal origin (which is thought to indicate common etiologic factors), they are often grouped together in epidemiologic studies.

B. Classification of Lymphomas

Various classification systems have been devised for categorizing the different human blood cells and malignancies developing in them. Historically, leukemias have been classified according to four major types, based upon cell of origin and manifestation of disease: Acute Myelogenous Leukemia (AML), Chronic Myelogenous Leukemia (CML), Acute Lymphocytic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL). Historically, lymphomas have been classified according to two basic types: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Hodgkin's lymphoma (also known as Hodgkin's disease) is a common type of lymphoma that was first described by Thomas Hodgkin in 1832 and is characterized by pathognomic giant cells which were first identified by Reed and Sternberg (so-called "Reed-Sternberg" cells). All other malignancies manifesting in lymphatic tissue have, by default, been classified as non-Hodgkin's lymphomas. A subtype of non-Hodgkin's lymphoma has been recognized for

those malignancies manifesting at extramedullary sites in plasma cells – the disease commonly called multiple myeloma.

III. THE SCIENTIFIC LINK BETWEEN BENZENE EXPOSURE AND DEVELOPMENT OF NON-HODGKIN'S LYMPHOMA

Utilizing Sir Austin Bradford Hill's "cause and effect" viewpoints as a framework to determine the issue of general causation, i.e., whether occupational exposure to organic solvents generally is a cause of non-Hodgkin's lymphoma and whether occupational exposure to benzene specifically is a cause of this disease, it becomes apparent such a link exists.

A. Consistency of the Association

The first factor specified by Sir Hill is consistency of the observed association. As previously mentioned, a pattern of elevated risks observed across several independent studies supports and strengthens an inference of causality, and reproducibility of findings constitutes one of the strongest arguments for causality.

As is shown by the many case-control studies of persons diagnosed with non-Hodgkin's lymphoma or who died from this disease, an association between organic solvents and non-Hodgkin's lymphoma is consistently found among the studies.

In his 1998 review of this literature, Rego summarized 45 epidemiologic studies that directly or indirectly evaluated a relationship between organic solvents and non-Hodgkin's lymphoma and found 18 studies that defined exposure well, of which 13 (72%)

indicated that organic solvent exposure was a risk for non-Hodgkin's lymphoma and more often than not had statistically significant findings. He also observed that 25 of the 45 studies (56%) reported a total of 54 significant associations between non-Hodgkin's lymphoma and organic solvent exposure and related occupations or industries, including those involving benzene. Rego, M.A.V., "Non-Hodgkin's Lymphoma Risk Derived from Exposure to Organic Solvents: A Review of Epidemiologic Studies," *Cadernos de Saude Publica* 14(Suppl.3):41-66 (1998).

Those case-control studies which post-date Rego's review, which are generally superior in their dose characterization and methodology, uniformly describe significant positive associations among non-Hodgkin's lymphoma patients for non-Hodgkin's lymphoma. A total of 11 case-control studies were found which post-date Rego's review, including one by Rego himself. All of these studies found positive associations between organic solvent exposure and non-Hodgkin's lymphoma, most of which were statistically significant. In addition, a few of the studies which were well-designed, well-conducted, had adequate statistical power, and stratified the data, reported significant associations specifically for benzene and non-Hodgkin's lymphoma. See, Fabbro-Perry, P., et al., "Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France," *Cancer Causes and Control* 12:201-212 (2001) [among individuals self-reporting exposure to benzene for at least one year, the odds ratio of having non-Hodgkin's lymphoma was significantly increased to 2.0 (95% CI = 1.1 – 3.9), compared to those who did not self-report exposure]; Xu, A., et al., ["A case-control study for assessing the relation between the incidence of malignant lymphomas and environmental factors in Sichuan province"], *Zhonghua Liu Xing Bing*

Xue Za Zhi. 24(10):875-858 (2003) [highly significant excess of malignant lymphoma found for exposure to benzene (AOR = 2.78; $p = 0.001$)]. See, also, Dryver, E., et al., “Occupational Exposures and Non-Hodgkin’s Lymphoma in Southern Sweden,” *International Journal of Occupational and Environmental Health* 10:13-21 (2004) [risk significantly increased for exposure aromatic solvents (OR = 1.45, 95% CI = 1.13 – 1.86)].

The epidemiologic studies of workers exposed to organic solvents are also quite consistent in reporting excesses of non-Hodgkin’s lymphoma, and a few of these report increased risks of non-Hodgkin’s lymphoma specific for benzene, either because the workers only used benzene as a solvent, or by using logistic regression analysis to isolate the effect of benzene.

The epidemiologic studies of American refinery workers are quite consistent in reporting excesses of non-Hodgkin’s lymphoma among those refinery workers whose jobs actually involve substantial exposure to petroleum hydrocarbons (including benzene), especially those workers with long durations of employment. Excesses of non-Hodgkin’s lymphoma (most of which were statistically significant) were found at Chevron, Exxon, Mobil, Shell, and Unocal refineries, which comprise most of the major petroleum refineries in the United States.

The largest and most robust epidemiologic studies of chemical workers are those of American chemical workers sponsored by the Chemical Manufacturers Association and Chinese chemical workers sponsored by the National Cancer Institute. These studies are consistent in finding significant associations among benzene-exposed workers from non-Hodgkin’s lymphoma.

Of the many epidemiologic studies of benzene-exposed workers, the best designed and conducted studies are the nested case-control studies of American refinery workers and the studies of American chemical workers sponsored by the CMA and Chinese workers sponsored by the NCI. Taken together, along with the well-conducted case-control studies, the epidemiologic literature is consistent in reporting significantly increased risks of non-Hodgkin's lymphoma among benzene-exposed workers.

B. Strength of the Association

As earlier mentioned, the finding of large, precise risks increases confidence that an association is not likely due to chance, bias, or confounding factors, although a modest risk does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease (for example, when there is a relatively high incidence rate of a disease in the general population, it is more difficult to reach a doubling of that incidence rate).

Most of the case-control studies lack sufficient statistical power and adequate characterization of exposure to detect substantial increased risks that are statistically significant. However, some of the studies do report substantial increased risks for non-Hodgkin's lymphoma. The study by Hours (1995) found an almost 15-fold increased risk of non-Hodgkin's lymphoma among patients exposed to "mineral oils," a category of aromatic/aliphatic hydrocarbons containing more than 5% benzene (OR = 14.86, 95% CI – 2.76 – 80.0). A 28-fold increased risk of non-Hodgkin's lymphoma was found in the study by Hardell (1994) among the non-Hodgkin's lymphoma patients exposed to benzene (OR = 28; 95% CI = 1.8 – 730). In the study by Fabbro-Perray (2001) a greater

than four-fold increased risk of non-Hodgkin's lymphoma was found for exposure to benzene for more than 810 days (OR = 4.6; 95% CI = 1.1 – 19.2). Finally, the study by Xu (2003) found an almost three-fold increased risk of non-Hodgkin's lymphoma specifically for benzene, which was highly significant (OR = 2.78; $p = 0.001$). Thus, despite the difficulty of evaluating benzene separately from organic solvents in studies using a case-control design, the well-designed and well-conducted studies show increased risk of non-Hodgkin's lymphoma for benzene ranging from about 3 – to 28-fold. These are relatively high odds ratios, indicative of a causal association of substantial strength.

The studies of American refinery workers have generally reported increased, but lower odds ratios than those reported in the case-control studies. Increases in standardized mortality ratios for non-Hodgkin's lymphoma ranging from a low of 127 to a high of 357 were reported among Chevron's refinery workers in California. Excess deaths from lymphosarcoma/reticulosarcoma were found at three Exxon refineries and chemical plants, the largest excess occurring at Exxon's Baton Rouge facility (SMR = 156). In the earliest study of Mobil Oil refinery workers, the risk of death from non-Hodgkin's lymphoma was almost doubled with a latency of 40 years or more (SMR = 189.9, $p < 0.05$). At the Shell Wood River refinery, a significant 8-fold increased risk of death from lympho-reticulosarcoma was found among male workers employed for 30 or more years, compared to the Harris County population (SMR = 815.8, $p < 0.01$). Finally, in the Unocal refinery cohort, a significant nearly 5-fold increased risk of non-Hodgkin's lymphoma was found when oil and gas division workers were compared to subjects never employed in this division (RR = 4.8, 95% CI = 2.0 – 11). Thus, the refinery worker studies report increased risks for non-Hodgkin's lymphoma among the exposed workers

ranging from a 2-fold to an 8-fold increase among workers with lengthy duration of employment. The study by Consonni of Italian refinery workers is consistent with the American refinery worker studies, showing a duration response relationship and a 4-fold increased risk of non-Hodgkin's lymphoma among refinery workers employed more than 30 years.

In the CMA study, the relative risk for non-Hodgkin's lymphoma among benzene-exposed workers compared to unexposed workers was significantly increased at 8.60 ($p = 0.02$). When only the continuously exposed workers were compared to the unexposed workers, the risk was significantly increased further to 9.6 ($p = 0.01$). Wong, O., "An Industry-Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene: I. General Results," *British Journal of Industrial Medicine* 44:365-381 (1987). When all types of non-Hodgkin's lymphoma were grouped together, there was a trend of increasing excess mortality associated with cumulative exposure level, compared to the general population. Compared with non-exposed employees at the chemical plants, cumulative exposure to benzene increased the relative risk of all non-Hodgkin's lymphopoetic cancers (ICD 8th revision 200, 202-2007) by 2-4-fold. Relative risks ranged from 2.7 for the lowest cumulative exposure level to 4.12 for the highest cumulative exposure level. Wong, O., "An Industry-Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene: II. Dose Response Analyses," *British Journal of Industrial Medicine* 44:382-395 (1987).

In the NCI study, elevated risks for non-Hodgkin's lymphoma were seen among all occupations with exposure to benzene, including coatings (RR = 1.6), rubber (RR = 4.0), chemical (RR = 7.8), shoe (RR = 1.6), and other/mixed industries (RR = 4.1).

Significant dose-response trends were found for non-Hodgkin's lymphoma for all dose metrics except constant exposure. For workers exposed to benzene for 10 years or more, a significantly increased 4-fold risk of non-Hodgkin's lymphoma was observed (RR = 4.2; 95% CI = 1.1 – 15.9) (p for trend = 0.01).

Taken together, all these epidemiology studies show increased risks of non-Hodgkin's lymphoma among benzene-exposed workers ranging from approximately doubling to a 28-fold increase.

C. Specificity of the Association

As previously mentioned, as originally described by Hill, this refers to a single cause associated with a single effect. However, it is now generally recognized that many agents cause cancer at multiple sites, and many cancers have multiple causes. Therefore, while the presence of specificity supports causality, an absence of specificity hardly excludes causality.

The concept of specificity of the association does not apply to either benzene or non-Hodgkin's lymphoma. First, benzene has been reported to cause many hematologic and other diseases, including different cancers. See, Mehlman, Myron A., "Benzene: A Haematopoietic and Multi-Organ Carcinogen at Any Level Above Zero," *European Journal of Oncology* 9(1):15-36 (2004). Second, non-Hodgkin's lymphoma is generally recognized as having several different causes or risk factors, including pesticides, organic solvents, certain viruses (especially Human Immunodeficiency Virus), and immunosuppressive and certain other medications. For these reasons, specificity of the association is a concept that is not applicable to the present inquiry.

D. Temporality of the Association

There are two major aspects to temporality: precedence and latency. As previously mentioned, a causal interpretation is strengthened when exposure is known to precede development of the disease. Likewise, because some cancers first manifest 20 or more years after exposure, the latent period of a disease must be taken into consideration. For this reason, in evaluating epidemiologic studies, it is important to ascertain whether the studies have sufficient follow-up time after exposure to allow for manifestation of disease in the exposed individuals.

The epidemiologic studies generally satisfy the first aspect of temporality, because the studies all report non-Hodgkin's lymphoma following exposure to organic solvents including benzene. Among cancers, non-Hodgkin's lymphomas are generally thought to have a medium to lengthy latency period, i.e., from 10 years or less to more than 30 years.

The latency period for the development of non-Hodgkin's lymphoma secondary to chemotherapy is generally much longer than that of acute myelogenous leukemia. While an increased risk of lymphoma has been reported within a few years after chemotherapy (as has been reported for AML), the risk of these patients developing non-Hodgkin's lymphoma increases over time, especially after the peak period for development of secondary leukemias has past. Notably, as patients administered chemotherapy for primary cancers are followed up to detect the development of secondary cancers, substantial excesses of non-Hodgkin's lymphoma are ascertained in the second and third decades after administration of chemotherapy – long after these

patients have ceased developing leukemia at an excess rate. Indeed, when these patients are following for two or more decades, non-Hodgkin's lymphoma displaces AML as the most common secondary malignancy in a number of these studies. Tucker, M.A., et al., "Risk of Second Cancers After Treatment for Hodgkin's Disease," *New England Journal of Medicine* 318:76-81 (1988).

Likewise, the latency period for non-Hodgkin's lymphoma from exposure to phenoxyherbicides and dioxin is longer than pesticide-induced acute myelogenous leukemia. "The available evidence suggests that the effect of herbicide exposure on the risk of non-Hodgkin's lymphoma lasts for more than 20 years." Institute of Medicine, "Latency and Cancer Risk," *Veterans and Agent Orange: Update 1998*, pp. 407-433 at p. 430 (National Academy Press, 1999).

Consistent with a medium to long latency period for the development of non-Hodgkin's lymphoma, the studies of organic solvent and benzene-induced non-Hodgkin's lymphoma indicate a latency period ranging from about 10 years or less to more than 30 years.

Several case-control studies regarding organic solvents and non-Hodgkin's lymphoma evaluated latency. Fonte (1985) reported a latency period from commencement of exposure to onset of disease of 23.2 years. Olsson (1988) reported a latency period from start of exposure to diagnosis ranging from 2 to 60 years, with a median of 21 years. Fabbro-Perray (2001) found increased risks for latency of more than 10 years (OR = 2.1, 95% CI = 1.1 – 4.1)

Similar latency periods have been reported in the refinery cohort studies. In the original Chevron refinery cohort study, lymphoma risk was increased with a latency of

10-19 years (lymphosarcoma and reticulosarcoma SMR = 180.7; other lymphatic tissue cancer SMR = 263.3), and greater than 20 years (lymphosarcoma and reticulosarcoma SMR = 128.7; other lymphatic tissue cancer SMR = 121.9). In the incidence study of lymphohematopoietic malignancies of the Exxon Baton Rouge facility (Heubner 2000), most cases of non-Hodgkin's lymphoma were seen among those employed at the facility for 20-39 years, and no cases occurred among those employed for less than 20 years. In the Mobil refiner cohort, an increasing trend in mortality was detected for lymphatic and hematopoietic cancer by latency. The SMR for those with 40+ years of latency (SMR = 189.9, $p < 0.05$) was more than 2.5 times that for those with less than 20 years of latency.

In the study by Hagmar (1986) of Swedish chemical workers, mortality from non-Hodgkin's lymphoma was increased among those workers who were employed for at least six months and who had an induction-latency time of at least 10 years (SMR = 479; $p = 0.03$), and morbidity was likewise increased among workers employed for at least six months and who had an induction-latency time of at least 10 years (SMR = 462, $p = 0.01$).

In conclusion, the case-control studies regarding organic solvent exposure and the cohort studies of refinery and chemical workers exposed to benzene generally report latency periods ranging from about 10 years to more than 30 years for the development of non-Hodgkin's lymphoma, consistent with the latency period for chemically-induced non-Hodgkin's lymphoma as ascertained from studies regarding chemotherapy and herbicide-induced non-Hodgkin's lymphoma.

E. Biological Gradient (Exposure-Response Relationship)

A clear exposure-response relationship (that is, increasing effects associated with increasing exposure) strongly suggests cause and effect, especially when such relationships are observed for both level and duration of exposure. Because an epidemiological study may fail to detect an exposure-response relationship for several reasons (for example, a small range of observed exposure levels or exposure misclassification), the absence of an exposure-response relationship does not exclude a causal relationship.

Those few case-control studies of superior design and execution provide evidence of a dose-response relationship for exposure to organic solvents and the development of non-Hodgkin's lymphoma. Tatham (1997) found a duration of exposure-response trend for small cell diffuse lymphoma in men occupationally exposed to solvents: 9 years of exposure (OR = 1.50, 95% CI = 0.99 – 2.20), > 9 years of exposure (OR = 1.70, 95% CI = 1.10 – 2.60). Fabbro-Perray (2001) reported a dose-response relationship for duration of exposure: for those never exposed to benzene the risk of non-Hodgkin's lymphoma was 1.0; for those exposed 15 years or less, the risk was increased to 1.7 (95% CI = 0.7 – 4.3); for those exposed more than 15 years, the risk was increased to 2.4 (95% CI = 0.9 – 5.9). A dose-response relationship was also apparent for cumulative exposure: for those never or only erratically exposed, the risk was 1.0; for those exposed 810 days or less, the risk was increased to 1.7 (95% CI = 0.4 – 6.8); for those exposed more than 810 days, the risk was significantly increased to 5.7 (95% CI = 1.4 – 23.2). In a multivariable logistic regression analysis, Dryver (2004) found a dose-response relationship for exposure to aliphatic or alicyclic hydrocarbon solvents: no exposure (OR = 1.00) medium exposure (OR = 1.42, 95% CI = .077 – 2.60), high exposure (OR = 15.66, 95% CI = 1.98 – 123.67);

a dose response relationship was also evidence for exposure to aromatic hydrocarbon solvents: no exposure (OR = 1.00), low exposure (OR = 1.35, 95% CI = 1.02 – 1.79), medium exposure (OR = 1.72, 95% CI = 0.91 – 3.25), high exposure (OR = 1.95, 95% CI = 0.90 – 4.21).