

SOLVENTS AND LYMPHOMA

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INTRODUCTION: SOLVENTS AND LYMPHOMA

Everyone wants to be as healthy as possible. Whether you are a lymphoma survivor, a family member or friend of a lymphoma survivor, or someone concerned with cancer prevention, this report is dedicated to you.

What are solvents?

A solvent is a substance which dissolves things. Many solvents that we use today are strong chemicals that are not safe.

Examples of chemical solvents include acetone, alcohol (various alcohols, not just ethyl alcohol), toluene, xylene, turpentine, perchloroethylene, benzene, and others. All of these solvents are toxic to varying degrees, and when they enter your bloodstream and tissues, they have to be detoxified by your liver and kidneys. During this process, if the exposure is heavy, your kidneys and/or liver may suffer damage, and your individual cells, including lymphocytes, may be damaged as well.

What is benzene?

The chemical formula for benzene is C_6H_6 – six carbon atoms and six hydrogen atoms. The carbon atoms are arranged in a ring rather than in a straight line. This ring arrangement, which is also shared by some other compounds, including toluene, xylene, and others, is an important factor in benzene's ability to mix with or adhere to other substances, and is related to benzene's toxicity. Xylene and toluene are almost identical to benzene, except that they have other atoms or groups of atoms in place of some of the six hydrogen atoms. Commercially available xylene and toluene are likely to have benzene in them.

Benzene is a clear liquid with a strong smell. In general, the hydrocarbon compounds that have a ring structure have strong odors, and long ago these ring-shaped compounds were nicknamed "aromatic hydrocarbons", so that when a chemist hears the word "aromatic" she thinks of a ring-shaped, toxic compound. It's harmful to sniff any of these compounds.

Of the solvents commonly in use, benzene is the one most frequently found to be associated with lymphoma and is the most studied by scientists searching for a link.

Where is benzene found, and where might I be exposed to it?

Benzene is usually manufactured from petroleum. It is found in gasoline, cigarette smoke, paint thinners, and in many varnishes, paints, and sealers. It is thought that cigarette smoke, including “second-hand smoke” is a leading source of benzene exposure for most people.^{1,2} It is now believed that the benzene in cigarette smoke is an important factor in the cancer-causing effects of smoking. Benzene also occurs naturally when many other substances are burned.

Many people are exposed to benzene on the job. This is especially likely in jobs related to the petrochemical (gas, oil, refining, etc.) industries, in the manufacturing of plastics, and in making other substances such as pesticides and dyes etc.

Benzene is toxic to all living creatures. If you are a lymphoma survivor, you may want to take special care to avoid exposure to paints, paint thinners, gasoline and related products, strong-smelling solvents of all kinds, and cigarette smoke, including “second-hand smoke”.

How much benzene does it take to cause harm?

People often wonder how much exposure is dangerous. With highly toxic chemicals, it is always best to avoid them altogether whenever possible.

Benzene has been shown to be poisonous and carcinogenic at very low concentrations. In a study published by the journal *Science*, researchers reported that workers exposed to less than one part per million of benzene in their workplace air caused a significant decline in white cells, and impaired and reduced the activity of their blood-forming cells.³

The Environmental Protection Agency allows 0.005 milligrams per liter of benzene in drinking water. Please note that this doesn't mean this is a safe amount. EPA states that the safe level for benzene in drinking water is zero.⁴

For workplaces, OSHA (the U.S. Occupational Safety and Health Administration) allows only 10 parts per million of benzene in workplace air during a workday,⁵ though clearly, there are times in certain workplaces where considerably more benzene is present.

How can I tell whether benzene caused my lymphoma?

As scientists learn more about genetics, we are beginning to have access to information about exactly which genes are altered or damaged in a cell that then becomes cancerous. Since we don't all have the same genetic configuration, some people are more vulnerable than others to particular causes of cancer. But it is best to avoid toxic exposures and not take unnecessary chances.

There is a significant body of scientific research that shows a strong association between benzene exposures and lymphoma.

More studies on toxic chemical exposures and cancer are needed, but today scientists have sufficient information to conclude that many chemical solvents including benzene are linked to cancer.

Compiled by Susan Osburn

1. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
2. *Report On Carcinogens, Eleventh Edition - Substance Profiles - Benzene*. U. S. Department of Health and Human Services, Public Health Service, National Toxicology Program.
3. Qing Lan, Luiping Zhang, Guilan Li, Roel Vermeulen, Rona S. Weinberg, Mustafa Dosemeci, Stephen M. Rappaport, Min Shen, Blanche P. Alter, Yongii Wu, William Kopp, Suramya Waidyanatha, Charles Rabkin, Weihong Guo, Stephen Chanock, Richard B. Hayes, Martha Linet, Sungkyoon Kim, Songnian Yin, Nathaniel Rothman, and Martyn T. Smith. Hematotoxicity in workers exposed to low levels of benzene. *Science* 306: 5702, 3 Dec. 2004, 1774-1776.
4. *Consumer Factsheet on: Benzene*. U.S. Environmental Protection Agency (updated Feb. 14, 2005).
5. *Table Z-2, Occupational Safety and Health Standards: Toxic and Hazardous Substances*. U.S. Department of Labor, Occupational Safety and Health Administration.

SUMMARIES OF LITERATURE THAT CONSIDER A RELATIONSHIP BETWEEN BENZENE EXPOSURE AND NON-HODGKIN'S LYMPHOMA

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RESEARCH

Aksoy, M. Benzene: Leukemia and Malignant Lymphoma. In: *Topical Reviews in Haematology Volume 2*. Roath, S., ed. Bristol: Wright-PSG p.105-139 (1982).

In this book chapter, the author reports that there is sufficient information to support the conclusion that benzene, acting as a primary carcinogen, is capable of inducing hematological and lymphatic malignancies, including non-Hodgkin's lymphoma. The author feels that there is no safe level of exposure to benzene, because some individuals may be unusually susceptible to the effects of benzene, few studies have evaluated the effects of low exposures to benzene, and studies have found a wide variation in the duration of exposure to benzene that has been associated with malignant lymphoma and leukemia.

Tubitak Research Institute for the Basic Sciences, Turkey.

Aksoy, M. Malignancies Due to Occupational Exposure to Benzene. *American Journal of Industrial Medicine*. 7: 395-402 (1985).

This paper discusses 73 patients with cancers diagnosed between 1967 and 1974, all of who had had chronic exposure to benzene in their workplaces. Two patients had lymphocytic lymphoma and one patient had histolytic lymphoma. The other patients had been diagnosed with Hodgkin's disease, leukemia, multiple myeloma, and lung cancer. The levels of benzene exposure were not assessed.

Tubitak Research Institute for the Basic Sciences, Turkey

Aksoy, M. Chronic lymphoid leukemia and hairy cell leukemia due to chronic exposure to benzene: report of three cases. *British Journal of Haematology*. 66: 209-211 (1987).

This report describes three of 58 patients seen by the author between 1967 and 1985 with leukemia. The first case of chronic lymphatic leukemia occurred in a 43-year old male who sniffed a solution of 2.8% benzene in 95.3% toluene for control purposes in a printing shop for 2-3 hours per day for 2 years. The second case of chronic lymphatic leukemia was a 51-year old male who was not currently exposed to benzene, but had been intermittently exposed to a thinner containing 27.3% benzene between 1955 and 1965, when he owned a plastic plant. Hairy cell leukemia occurred in a 50-year old manager in a plastic plant who had been heavily exposed to benzene between 1957 and 1965. The author concludes that the short term, intermittent benzene exposures experienced in these cases may partly explain the different distributions of the types of leukemia seen with benzene toxicity.

Scientific Research Council of Turkey, Research Institute for Basic Sciences, Gebze-Kocaeli, Turkey.

Aksoy, M., Ozeris, S., Sabuncu, H., Inanici, Y., Yanardag, R. Exposure to benzene in Turkey between 1983 and 1985: a hematological study on 231 workers. *British Journal of Industrial Medicine*. 44: 785-787 (1987).

Between 1983 and 1985, 231 workers employed in 40 workplaces in Istanbul and Izmit were studied hematologically. The duration of exposure ranged from 1 month to 40 years, with a mean of 8.8 years. Air samples showed a mean benzene concentration of 0.73%, ranging from zero to 110ppm. The benzene concentrations measured in thinners, solvents, dyes, and lacquers, had decreased since the early 1970s. The authors found that 23.4% of the workers showed hematological abnormalities, and five cases of hematopoietic cancers were identified including, poorly differentiated lymphoma (1), Hodgkin's disease (1), acute lymphoblastic leukemia (1), and acute myeloblastic leukemia (2). All cases, except for the case of Hodgkin's disease, developed with five years or less of exposure to benzene or benzene containing solvents and thinners. Funded by the Scientific and Technical Research Council of Turkey. Scientific and Technical Research Council of Turkey; Istanbul University, Capa-Istanbul, Turkey.

Arnetz, B.B., Raymond, L.W., Nicholic, M.J., Vargo, L. Mortality among Petrochemical Science and Engineering Employees. *Archives of Environmental Health*. 46(4): 237-248 (1991).

The mortality rates of New Jersey based employees in two Exxon research and development companies who worked at least one day between 1964 and 1986, or were retired but alive during some part of this period, were studied. Industrial hygienists rated exposure by the average percentage of time a person was potentially exposed to chemical (not specifically benzene) and physical agents, and the job title with the highest potential for exposure. Potential exposures during college were considered, so that individuals with chemistry degrees were rated as having the highest potential for exposure. Compared to the US general population, there was a deficit of lymphosarcoma and reticulosarcoma mortality, but an excess of cancer of all other lymphopoietic tissues. Slightly increased mortality due to cancer of lymphopoietic tissues was seen among scientists and engineers when compared to the US general population, but when scientists and engineers were compared to managers and support staff, their mortality rate increased significantly. The differences in these comparisons indicate the healthy worker effect: the population of workers is generally healthier than the general population, which includes individuals who are unable to work.

Exxon Company, USA; Karolinska Institute, Sweden.

Arp, E.W., Wolf, P.H., Checkoway, H. Lymphocytic Leukemia and Exposure to Benzene and Other Solvents in the Rubber Industry. *Journal of Occupational Medicine.* 25(8): 598-602. (1983).

This study included a cohort of active and retired hourly rubber industry workers aged 40 to 84, who were alive on January 1, 1964. Mortality follow-up was conducted through 1973. Past solvent exposures were reconstructed according to process area using product specifications and standard operating procedures, and linked to an individual's work history. Exposure was defined as cumulative periods greater than 12 months, and exposed workers were compared to non-exposed workers. The odds ratio for lymphocytic leukemia and exposure to coal-based solvents was 6.67, and substantially higher than the value for exposure to petroleum-based solvents (OR=1.5). Of the coal-based solvents, benzene showed an OR of 3.0, compared to an OR of 5.5 for xylene. The authors speculate that the difference between the coal-based and petroleum-based solvents could be the presence of polycyclic aromatic hydrocarbon contaminants in the coal-based solvents. One limitation of this study is that the use of benzene was discontinued in the 1930s, and this study only included individuals who were still alive in 1964: During this 34-year interval, it is possible that additional workers died from benzene-induced cancers.

Funded by: United Rubber Workers Union, the Firestone Tire and Rubber Company, the General Tire and Rubber Company, the Goodyear Tire and Rubber Company, and Uniroyal, Inc. University of North Carolina.

Balarajan, R. Malignant Lymphomas in Road Transport Workers. *Journal of Epidemiology and Community Health.* 37: 279-280 (1983).

8222 men with cancers of the lymphoid tissue were matched in this study by age, sex, and region of residence to individuals with other cancers. Men employed as bus and coach drivers were more likely to have sarcomas and other neoplasms of the lymphoid tissue, with relative risks of 1.16 and 1.63, respectively. This means that individuals employed as bus and coach drivers were 16% more likely to have sarcoma, and 63% more likely to have other neoplasms than individuals who did not work in those occupations. Drivers of other road passenger vehicles also had an increased risk of dying from other neoplasms of the lymphoid tissue. The author concludes that environmental exposure factors common to vehicle drivers (possibly exhaust fumes) are a cause of lymphoma.

Southwest Regional Health Authority, London, and St. George's Hospital Medical School, London.

Baris, D., Garrity, T.J., Telles, J.L., Heineman, E.F., Olshan, A., Zahm, S.H. Cohort Mortality Study of Philadelphia Firefighters. *American Journal of Industrial Medicine*. 39: 463-476 (2001).

This study compared the mortality of 7789 firefighters employed by the City of Philadelphia between 1925 and 1986 to the United States population of white men. The authors evaluated station design and truck fuel to estimate exposure to diesel exhaust at each station. The standardized mortality ratio (SMR) for non-Hodgkin's lymphoma was 1.41, which means that they had 41% excess mortality from non-Hodgkin's lymphoma compared to white men in the general public. Risks of dying from non-Hodgkin's lymphoma increased with duration of employment as a firefighter, but not with the number of runs. Firefighters employed only in ladder companies (which initially work outside a structure, but may later enter burning structures) had the highest risks of dying from non-Hodgkin's lymphoma. The major drawbacks of this study include the lack of individual exposure data at fires and at the station houses, and the lack of information about smoking habits.

National Cancer Institute, the International Association of Fire Fighters, Delaware Valley Healthcare Council, Philadelphia, University of North Carolina.

Bernard, S.M., Cartwright, R.A., Bird, C.C., Richard, I.D.G., Lauder, I., Roberts, B.E.. Etiologic factors in lymphoid malignancies: A case-control epidemiological study. *Leukemia Research*. 8(4): 681-689 (1984).

This study was an investigation into the feasibility of a larger case-control study. Therefore, the study included only 158 adults diagnosed with non-Hodgkin's lymphoma in the Yorkshire Health Region between October 1979 and December 1981. These individuals were matched by age and sex with 158 controls from the in-patient population of the hospital. Men with non-Hodgkin's lymphoma had a relative risk of 4.21 of working in the petroleum industry, while men with lymphoid leukemia had a relative risk of 3.06 of having had exposure to benzene at work. Increased risks were also found among practitioners of the Jewish religion and among men with a history of basal cell sarcoma.

University of Leeds, Yorkshire Regional Cancer Organization, Leeds, Leeds General Infirmary.

Blair, A., Linos, A., Stewart, P.A., Burneister, L.F., Gibson, R., Everett, G., Schuman, L., Cantor, K.P. Comments on Occupational and Environmental Factors in the Origin of Non-Hodgkin's Lymphoma. *Cancer Research*. 52(Suppl.1): 5501s-5502s (1992).

In this study, 622 white men with non-Hodgkin's lymphoma who resided in Iowa and Minnesota were matched by age, state of residence, and vital status to 1245 individuals without non-Hodgkin's lymphoma. Subjects or next of kin were interviewed regarding occupation and potential risk factors. Men with non-Hodgkin's lymphoma had an odds ratio of 1.5 for having had exposure to higher intensities of benzene; which means that individuals with non-Hodgkin's lymphoma are 50% more likely to have been exposed to benzene than individuals without the disease. The odds ratio of benzene exposure and diffuse non-Hodgkin's lymphoma was 1.8, while the odds ratio was 1.9 for follicular non-Hodgkin's lymphoma. Men employed in the industries of special industrial machinery, real estate, and personal services (mostly dry cleaners) had elevated odds of having non-Hodgkin's lymphoma.

National Cancer Institute; University of Athens, Athens, Greece; University of Iowa, Iowa City, Iowa; University of Minnesota, Minneapolis, Minnesota; Orlando Regional Medical Center, Orlando, Florida.

Blair, A., Linos, A., Stewart, P.A., Burneister, L.F., Gibson, R., Everett, G., Schuman, L., Cantor, K.P. Evaluation of Risks for Non-Hodgkin's Lymphoma by Occupation and Industry Exposures From a Case Control Study. *American Journal of Industrial Medicine*. 23: 301-312 (1993).

This study included the same population studied by Blair *et al* in 1992, but excluded men employed solely as farmers and men living in major metropolitan areas. Comparisons between men with and without non-Hodgkin's lymphoma were made with regard to the occupation and industry in which they were employed. No association was found between non-Hodgkin's lymphoma and employment in a 2 or 3 digit Special Industrial Classification (SIC) code. An example of a two digit SIC code is "fabricated metal," which includes the three digit SIC codes "metalworking machinery," and "aircraft parts." The results of this study are similar to those in the previous paper. More men with non-Hodgkin's lymphoma were employed in the production of special industrial machinery (OR=9.6), real estate, and personal services (dry cleaning) than men without the disease. The likelihood of having non-Hodgkin's lymphoma and having been exposed to benzene increased with higher intensity benzene exposures. Men with diffuse lymphoma had higher odds of having been exposed to paints (OR=1.5), or employed in personal services or medical professions. Men with follicular lymphoma had higher odds of having had exposure to metals (OR=1.6), of having been employed as a cook/chef, or of having been employed in personal services. This study was limited by the small number of subjects in most of the industry or occupation categories.

National Cancer Institute; University of Athens, Athens, Greece; University of Iowa, Iowa City, Iowa; University of Minnesota, Minneapolis, Minnesota; Orlando Regional Medical Center, Orlando, Florida.

Bond, G.G., Mc Laren E.A., Baldwin, C.L., Cook, R.R. An Update of Mortality Among Chemical Workers Exposed to Benzene. *British Journal of Industrial Medicine.* 43:685-691 (1986).

Expanding on a previous study by Ott et al (1978), the mortality of 956 Dow employees in chlorobenzol, alkylbenzene, and ethyl cellulose operations between 1938 and 1978 were compared to the US white male population. Exposure to benzene was classified into four levels of intensity, and nearly 25% of the employees were employed in jobs classified as having a time-weighted average exposure of 30ppm benzene or greater. Two cases of reticulosarcoma or lymphosarcoma were observed, which was slightly more than expected. A variety of lymphatic and hematopoietic malignancies occurred among the employees, leading the authors to conclude that there is no evidence that benzene, or a single agent, is the cause of death. The authors, however, suggest that a co-factor may be present in the alkylbenzene plant that acts with benzene to cause cancer as more deaths due to myelogenous leukemia occurred in that plant than were expected.

Dow Chemical, Midland, Michigan

Burnett, C., Robinson, C., Walker, J. Cancer mortality in health and science technicians. *American Journal of Industrial Medicine.* 36(1): 155-158 (1999).

Using mortality data from death certificates collected from 28 states between 1984 and 1995 in the National Occupational Mortality Surveillance Database, the proportionate cancer mortality ratios (PCMR) were calculated for selected cancers among female health and science technicians aged 18 – 90 at time of death. Among clinical lab technologists and technicians, non-Hodgkin's lymphoma mortality was higher among women aged 18-64 than among women aged 65-90, but was slightly elevated throughout the cohort. Among science technicians, including biological and chemical technicians, the PCMR for non-Hodgkin's lymphoma was significantly elevated to 230 among women aged 18-64, but there was a deficit of mortality from the cancer among women who were over 65 years of age at the time of death. There was a slight deficit in mortality from leukemia among science technicians, with a PCMR of 93 among women aged 18-64. There was a deficit of non-Hodgkin's lymphoma among radiologic technicians. The authors conclude that the excess of lymphatic and hematopoietic cancers among the technicians could be related to chemical exposures in the workplace, though no exposure assessment was undertaken.

National Institute for Occupational Safety and Health, Cincinnati, Ohio

Checkoway, H., Wilcosky, T., Wolf, P., Tyroler, H. An Evaluation of the Associations of Leukemia and the Rubber Industry. *American Journal of Industrial Medicine.* 5:239-249 (1984).

This case-control analysis of lymphocytic leukemia extended a previous study among American rubber workers by Arp et al (1983). Benzene exposure was classified for each department in the rubber plant. The odds ratio of having lymphocytic leukemia and having worked in a department with benzene exposure was 2.5, though only four cases of lymphocytic leukemia had had exposure to benzene. Higher odds of lymphocytic leukemia were found in workers employed in departments with exposure to carbon tetrachloride (OR=14.8) and carbon disulfide (OR=8,7). The authors conclude that studies in the rubber industry need to increase their scope and consider multiple exposures as well as a wider variety of lymphopoietic malignancies. Funded by the United Rubber Workers Union, Firestone Tire and Rubber Company, General Tire and Rubber Company, Goodyear Tire and Rubber Company, and Uniroyal Inc. University of North Carolina, Chapel Hill.

Collingwood, K.W., Raabe, G.K., Wong, O. An Updated Cohort Mortality Study of Workers at a Northeastern United States Petroleum Refinery. *International Archives of Occupational and Environmental Health.* 68: 277-288 (1996).

This is an update of a study of 4855 employees who worked at a petroleum refinery in Palsbouro, New Jersey for at least one year between 1946 and 1987. The vital status of employees was determined at the end of 1987, and compared to expected mortality rates expected using data from the National Cancer Institute. Overall mortality among the refinery workers was lower than the United States population, which is typical as workers are thought to have better general health than the total population. Mortality due to lymphosarcoma and reticulosarcoma was also deficit. The cohort of workers experienced a SMR of 165 for other lymphatic tissue cancers. For all cell types of non-Hodgkin's lymphoma, the SMR was 135. Mortality from lymphosarcoma and reticulosarcoma did not increase with increasing duration of employment, but mortality due to other lymphatic tissue cancers did increase significantly such that the SMR was 208 among those employed for more than 30 years. Most of the individuals who died of other lymphatic tissue cancers had been first employed before 1950.

Funded by the Mobil Corporate Medical Department

Consonni, D., Pesatori, A.C., Tioni, A., Bernucci, I., Zoccheti, C., Bertazzi, P.A. Mortality Study of an Italian Oil Refinery: Extension of the Follow-Up. *American Journal of Industrial Medicine*. 35: 287-294 (1999).

This study extended the follow-up of a cohort of 1583 male oil refinery workers in Italy to May 31, 1991. These men had been employed for at least one day between 1949 and 1982, and were classified into one of six employment departments in the refinery based on the longest held job. The mortality experience of workers was compared to the population of the region in Italy where the refinery was located. The SMR for non-Hodgkin's lymphoma was 212, meaning that 2.12 times more refinery employees died of this cancer than were expected based on rates in the region. When a 10-year lag was applied, which results in the exclusion of individuals who worked less than 10 years, elevated mortality due to lymphoma correlated with increasing duration of employment. When lymphoma mortality was considered by time since first employment, the standardized mortality ratio was elevated among those employed for less than 19 years and those employed more than 30 years. No mortality from lymphoma was observed among refinery employees hired since 1962. When the job titles of individuals who died from lymphoma were evaluated, the mortality was not found to be specific to any one department. Istituti Clinici di Perfezionamento, Milano, Italy; University of Milan, Italy.

Constantini, A.S., Miligi, L., Kriebel, D., Ramazzotti, V., Rodella, S., Scarpi, E., Stagnaro, E., Tumino, R., Fontana, A., Masal, G., Vigano, C., Vindigni, D., Crosignani, P., Benvenuti, A., Vineis, P. A Multicenter Case-Control Study in Italy on Hematolymphopoietic Neoplasms and Occupation. *Epidemiology* 21(1): 78-87 (2001).

A case-control study of men newly diagnosed with hematolymphopoietic neoplasms between 1991 and 1993 in twelve areas of Italy was discussed in this paper. Occupations with elevated odds ratios for non-Hodgkin's lymphoma and chronic lymphocytic leukemia included managers or directive clerks, police, electrical workers, restaurant workers, and building caretakers or cleaners (odds ratios 1.2 to 2.8). The authors report that many differences were seen between genders, and suggest that the difference between genders may be partially an artifact of different employment patterns (i.e. there are not enough women managers to identify cases). The authors note, however, that there is gender inconsistency among teachers. Funded by the National Cancer Institute.

Dagg, T.G., Satin, K.P., Bailey, W.J., Wong, O., Harmon, L.L., Swencicki, R.E. An updated cause specific mortality study of petroleum refinery workers. *British Journal of Industrial Medicine.* 49: 203-212. (1992).

This study added six years of follow up to a cohort study of 14,074 employees at the Richmond and El Segundo refineries originally followed between 1950 and 1980. The update used the first and last job titles identified for each worker in the previous study, and compared mortality rates with the US death rates adjusted for age, race, sex, and calendar period. Among the men in the entire cohort, the standardized mortality ratios were slightly elevated for lymphosarcoma, reticulosarcoma, and other lymphatic tissue cancers, though there was a deficit in deaths due to all causes. At the Richmond refinery, mortality due to lymphosarcoma and reticulosarcoma were elevated among men employed for more than 15 years, and peaked among men 10-19 years since first hire. Mortality due to other lymphatic tissue cancers was elevated for all durations of employment at the Richmond refinery. The trends were less clear among workers at the El Segundo refinery due to the small number of cases, but excess mortality due to lymphosarcoma and reticulosarcoma was also observed among men 10-19 years since first hire. Using California as the reference population, there was no change in the standardized mortality ratios for lymphatic and hematopoietic system cancers.

Chevron Corporation Medical Staff, San Francisco; Applied Health Sciences, San Mateo, CA

Decoufle, P., Blattner, W.A., Blair, A. Mortality among Chemical Workers Exposed to Benzene and other Agents. *Environmental Research.* 30: 16-25 (1983).

The mortality experience of 259 men employed for at least one day between 1947 and 1960 at an alkylbenzene manufacturing facility was evaluated at the end of 1977, though the vital status of only 89% of the subjects was determined. 194 men in the cohort had been employed for at least one year at the facility. Four men died from hematopoietic neoplasms, producing a SMR of 377 when compared to the U.S. white male population. Two of these deaths were due to multiple myeloma, and one death was due to chronic lymphocytic leukemia; all three of these cancers were of B-cell lineage.

University of Arizona, Tuscon, AZ; National Cancer Institute

Delzell, E., Monson, R.R. Mortality Among Rubber Workers: V. Processing Workers. *Journal of Occupational Medicine.* 24(7): 539-545 (1982).

This study evaluated the mortality of 2666 white men employed for at least two years in the processing department of a rubber manufacturing plant in Akron, Ohio between 1940 and July 1971. The vital status of these men was determined in July of 1978 and compared to 10,904 non-processing workers at the same plant, and to the white males in the United States. Compared to the U.S. white male population, the SMR from lymphatic and hematopoietic tissue malignancies was 136, meaning the processing workers experienced a 36% excess mortality due to these causes. Most of that excess was due to leukemia among men who died more than 20 years after initial employment.

Harvard School of Public Health. Funded by B.F. Goodrich Co. and the United Rubber, Cork, Linoleum, and plastic Workers of America.

Divine, B.J., Barron, V. Texaco Mortality Study: II. Patterns of Mortality Among White Males by Specific Job Groups. *American Journal of Industrial Medicine.* 10: 371-381 (1986).

The Texaco mortality study was carried out using a cohort of refinery, petrochemical, and research workers who worked between 1947 and 1977 and were employed at least five years. The cohort members were followed through 1977, and job changes that occurred at least six months subsequent to the last job were coded. The mortality experience of four job groups presented in the paper (office, maintenance, operations, and laboratory) was compared to the U.S. population. Among white males employed as operators, there was a very slight excess in mortality from lymphosarcoma among those employed more than one year in the job, and a deficit in mortality among those employed for more than five years. Mortality due to cancers of other lymphatic tissues (ICD7 Codes 202, 203, 205) was elevated among operators and maintenance workers employed for more than one year and for more than five years. Among maintenance workers, however, a large deficit was seen in mortality to lymphosarcoma. No elevated mortality rates for lymphatic tissue cancers were seen among office or laboratory workers.

Texaco Inc., Houston, Texas

Fabbro-Perray, P., Daures, J-P., Rossie, J-F. 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).

This case-control study included all 455 cases of non-Hodgkin's lymphoma diagnosed between 1992 and 1995 in the Languedoc-Roussillon region of France. Unmatched controls were selected from electoral lists. 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, compared to those who did not self-report exposure. For those cumulatively exposed to benzene for more than 810 days, the odds ratio of having non-Hodgkin's lymphoma, compared to non-exposed individuals, was 5.7. The odds of non-Hodgkin's lymphoma were also elevated for those cumulatively exposed to benzene for less than or equal to 810 days. Exposure to benzene for a duration greater than 15 years, and exposure to benzene more than 10 years prior to diagnosis both had increased odds for the occurrence of non-Hodgkin's lymphoma. In the final multivariate model, the best fit with the data was found when exposure to benzene for more than 810 days was included with an odds ratio of non-Hodgkin's lymphoma of 4.6 (95% CI 1.1-19.2).

Hospital Gaston Doumerge, Nimes Cedex 4, France; Hospital Apeyroine, Montpellier, France.

Franceschi, S., Serraino, D., Bidoli, E., Talamini, R., Tirelli, U., Carbone, A., La Vecchia, C. The Epidemiology of Non-Hodgkin's Lymphoma in the Northeast of Italy: A Hospital-Based Case-Control Study. *Leukemia Research*. 13(6): 465-472 (1989).

208 individuals (110 men and 98 women) diagnosed with non-Hodgkin's lymphoma between June 1983 and March 1998 were compared with 410 controls selected from inpatients at the same hospitals with acute conditions. Chemical workers and petrochemical workers were over-represented in the cases, so that their relative risk of employment in these industries and having non-Hodgkin's lymphoma was 1.6 and 1.8, respectively. These risks were not substantially elevated among workers employed for more than 10 years in the chemical or petrochemical industries. Slightly more cases had exposure to benzene or solvents than controls. Conclusions in this study are limited by the few cases in occupations that have been identified in other studies as having elevated risks.

Funded by Italian Association for Cancer Research. Aviano Cancer Center, Aviano, Italy; Mario Negri Institute for Pharmacological Research, Milan, Italy' University of Lausanne, Lausanne, Switzerland.

Fritschi, L., Siemiatycki, J. Lymphoma, Myeloma, and Occupation: Results of a Case-Control Study. *International Journal of Cancer*. 67: 498-503 (1996).

This study included males aged 35-70 who lived in Montreal and had a new, histologically confirmed cancer. Of 258 eligible cases, 215 non-Hodgkin's lymphoma cases were interviewed. Individuals were asked to describe all of the jobs they had had in their working lifetimes. A team of chemists and industrial hygienists translated each job into a list of potential substance exposures and noted their degree of confidence that the exposure had occurred. Those with probable or definite exposure for more than five years at high frequency were defined as substantially exposed; those with some opportunity for exposure were defined as non-substantially exposed. The occurrence of non-Hodgkin's lymphoma was not associated with non-substantial or substantial exposure to benzene. There was no change in risk when only solvent exposures occurring in the two or five years prior to diagnosis were considered. High odds ratios for non-Hodgkin's lymphoma were seen with exposure to cotton dust and work in the textile industry. Funded by: Institut de recherche en sante et en securite du travail du Quebec, the Fonds de recherche en sante du Quebec, the National Health Research and Development Program, and the National Cancer Institute of Canada. Institut Armand-Frappier, Montreal, Canada.

Fu, H., Demers, P.A., Costantini, A.S., Winter, P., Colin, D., Kogevinas, M., Boffetta, P. Cancer Mortality Among Shoe Manufacturing Workers: An Analysis of Two Cohorts. *Occupational and Environmental Medicine*. 53: 394-398 (1996).

This study evaluated mortality of two cohorts of shoe manufacturers. The first cohort, from three English towns, included 4215 male shoe and boot manufacturers identified in the 1939 census records who were still alive in 1950. The vital status of these men was assessed in 1991. The discussion in this paper, however, focused on the second cohort, which included 2008 workers (1005 men, 1003 women) who had ever been employed after 1939 in a shoe manufacturing plant in Florence, Italy, and who worked between 1950 and 1984. Follow-up began in 1950 and was continued through 1990. Benzene was used in glues in Florence between 1950 and 1960, and contributed up to 70% of the glue by weight. After 1963, the amount of benzene was restricted to 2% of the total solvents in the glue. Exposure to benzene in England is likely to have been less than in Florence, since a different type of shoe manufacturing, which relied less on glues, was used. Among the Florence cohort, workers highly exposed to solvent experienced a 174% excess mortality due to non-Hodgkin's lymphoma. Among workers in Florence probably exposed to solvents, the SMR for non-Hodgkin's lymphoma was 244, 144% excess. Each of these exposure groups, however, included only two cases of non-Hodgkin's lymphoma so the risk estimates are uncertain.

Funded by the European Commission Directorate General V, and the European Commission BIOMED-1 Programme. International Agency for Cancer Research, Lyon, France.

Hardell, L., Eriksson, M., Degerman, A. Exposure to Phenoxyacetic acids, Chlorophenols, or Organic Solvents in Relation to Histopathology, Stage, and Anatomical Localization of Non-Hodgkin's Lymphoma. *Cancer Research*. 54: 2386-2389 (1994).

105 men between the ages of 25 and 85 admitted to the Department of Oncology at the University Hospital in Umea, Sweden were compared to 355 individuals from the National Population Registry matched by age, sex, place of residence, and vital status. It was found that significantly more individuals with non-Hodgkin's lymphoma had been exposed to benzene than individuals without the disease (OR 28). This risk estimate, however, was based on only three cases and one control. Development of non-Hodgkin's lymphoma was also significantly associated with exposure to all organic solvents (OR=2.4). Orebro Medical Center, Orebro, Sweden; University Hospital, Umea, Sweden.

Hayes, R.B., Yin, S.N., Domesmecci, M., Li, G.L., Wacholder, S., Chow, W.H., Rothman, N., Wang, Y.Z., Dai, T.R., Chao, X.J., Jian, Z.L., Ye, P.Z., Zhao, H.B., Kuo, Q.R., Zhang, W.Y., Meng, J.F., Zho, J.S., Lin, X.F., Ding, C.Y., Li, C.Y., Zhang, Z.N., Li, D.G., Travis, L.B., Blot, W.J., Linet, M.S. Mortality among Benzene-exposed Workers in China. *Environmental Health Perspectives* 104 (Suppl.6): 1349-1352 (1996).

This is a preliminary report of mortality data for a large cohort study of 74,828 benzene-exposed and 35,805 non-exposed workers in 672 factories in 12 cities in China. Approximately 2% of the study population died during the follow-up period, which concluded at the end of 1987. Deaths due to hematopoietic and lymphoproliferative malignancies showed a trend significantly correlated with cumulative exposure to benzene. Mortality due to hematopoietic and lymphoproliferative malignancies were elevated among benzene-exposed workers at all levels of cumulative exposure compared to non-exposed workers, with relative risks for cancer ranging from 2.1 to 3.2.

National Cancer Institute; Chinese Academy of Preventive Medicine

Hayes, R.B., Yin, S.N., Dosemeci, M., Li, G.L., Wacholder, S., Travis, L.B., Li, C.Y., Rothman, N., Hoover, R.N., Linet, M.S. Benzene and Dose-Related Incidence of Hematologic Neoplasms in China. *Journal of the National Cancer Institute*. 89(14): 1065-1071 (1997).

This study included 74,828 benzene-exposed workers and 35,805 workers not exposed to benzene, all of whom were employed in 672 factories in 12 Chinese cities between 1972 and 1987. The workers were followed through 1987, and the incidence of lymphatic and hematopoietic cancers evaluated. Individuals employed for less than six months and those employed before 1949 were excluded. Occupational exposures were determined for seven time periods for each job title, and a 1.5-year exposure time lag was applied, so that exposure in the most recent 1.5 years was not considered. Elevated risks for non-Hodgkin's lymphoma were seen among all occupations with exposure to benzene, including: coatings, rubber, chemical, shoe, and other/mixed industries. The highest relative risk was seen for employment in the chemical industry, where the relative risk for non-Hodgkin's lymphoma was 7.3. Among all workers occasionally exposed to benzene, the relative risk for non-Hodgkin's lymphoma was three times that of non-exposed workers. The risk for non-Hodgkin's lymphoma increased with the duration of exposure, but the relationship was less clear with other exposure measures such as cumulative exposure.

National Cancer Institute; Chinese Academy of Preventive Medicine.

Hayes, R.B., Yin, S.N., Rothman, N., Dosemeci, M., Li, G.L., Travis, L.T., Smith, M.T., Linet, M.S. Benzene and Lymphohematopoietic Malignancies in China. *Journal of Toxicology and Environmental Health Part A*. 61: 419-432 (2000).

This paper summarizes the findings reported by Hayes *et al.* in 1996 and 1997 and includes a discussion of the biomarker study by Smith and Rothman (2000). Biomarkers are biological indicators of exposure, and the authors report that urinary levels of phenol, muconic acid, hydroquinone, and catechol – all metabolites of benzene – correlate well with benzene air levels at the workplace. Additionally, among individuals with a history of benzene poisoning, there were increased odds that these individuals had increased enzyme (CYP2E1) activity and two copies of a gene mutation (NQO1 609C-T), two factors that influence the metabolism of benzene. National Cancer Institute; Chinese Academy of Preventive Medicine; University of California, Berkeley.

Huebner, W.W., Chem, V.W., Friedlander, B.R., Wu, X.C., Jorgensen, G., Bhojani, F.A., Friedman, C.H., Schmidt, B.A., Sales, E.A., Joy, J.A., Correa, C.N. Incidence of lymphohaematopoietic malignancies in a petrochemical industry cohort: 1983-1994 follow up. *Occupational and Environmental Medicine*. 57: 605-614 (2000).

This study pools two cohorts of 8942 employees at a Baton Rouge petrochemical facility. Exposure was classified by the start and stop dates of employment at the facility and the most common job held. The incidence of non-Hodgkin's lymphoma was only marginally elevated compared to rates in southern Louisiana: the standard incidence ratio (SIR) was 1.06, based on 25 cases. Of the non-Hodgkin's lymphoma subtypes, the rates of reticulosarcoma (SIR 1.12), other named variants of non-Hodgkin's lymphoma (SIR 1.95), and nodular or follicular non-Hodgkin's lymphomas (SIR 1.60) were elevated among employees at the facility. The standardized incidence ratio for non-Hodgkin's lymphoma was 1.44 among those employed before 1950. 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. Exxon Biomedical Sciences, Annandale, New Jersey; Exxon Corporation, Texas and New Jersey; Louisiana State University Medical Center, New Orleans, Louisiana.

Hunting, K.L., Longbottom, H., Kalavar, S.S., Stem, F., Schwartz, E., Wlech, L.S. Hematopoietic cancer mortality among vehicle mechanics. *Occupational and Environmental Medicine*. 52: 673-678 (1995).

This investigation began after three leukemia cases were reported among the fleet maintenance division of the Washington, D.C. Department of Public Works. The cohort included 338 men employed at least one year between 1977 and 1989. 80 jobs were classified as low, medium, and high exposure; where high exposure was defined as regular, but not necessarily frequent, contact with fuel and solvents and included 297 people. The expected mortality rates were calculated from the cause-specific death rates in Washington D.C. There was a pronounced healthy-worker effect, as the all-cancer mortality was lower than expected. There were three deaths due to hematological and lymphatic cancers resulting in an elevated SMR of 3.63. There was only one death from lymphoma (the individual was 69 years of age), producing an SMR of 2.57. George Washington University, Washington D.C.; District of Columbia Department of Human Services.

Infante, P.F., Rinsky, R.A., Wagoner, J.K., Young, R.J. Leukemia in Benzene Workers. *The Lancet*. July 9: 76-78 (1977).

This study reports the vital status as of 1975 of white male workers who had been exposed to benzene between 1940 and 1949 during the manufacture of Pliofilm. The authors were only able to follow up with 75% of the workers, which the authors expect to lead to the underestimation of risk. Deaths due to total lymphatic and hematopoietic cancers were elevated compared to the US white male population, and compared to an industrial population exposed to fibrous glass. Seven of the nine deaths due to these cancers were attributed to leukemia resulting in a five-fold excess of deaths. The other two cancers are not described. National Institute for Occupational Safety and Health, Cincinnati, Ohio

Jarvholm, B., Mellblom, B., Norrman, R., Nilsson, R., Nordlinder, R. Cancer incidence of workers in Swedish petroleum industry. *Occupational and Environmental Medicine*. 54: 686-691 (1997).

This study included 4128 male and 191 female employees who had at least one year of employment before 1991 with a job title indicating exposure to petroleum products, and who worked for one of 26 different companies with complete personnel registers. Follow-up began when a person had worked one year in an occupation and concluded in 1991. Occupations included in the study were refinery operators, distribution workers, manufacturing of lubricants, tank cleaners, handling of air fuel, and others. Exposure assessment was based on job titles. However, benzene exposure measurements performed in Scandinavia during the study period showed air concentrations ranging from 0.1mg/m³ to 18mg/m³, with short-term exposures up to 190mg/m³. A deficit in the incidence of lymphoma (ICD, 200-202) was observed in the cohort overall, and among all subgroups except male refinery operators exposed only after 1958 where the standardized incidence rate was 1.2, based on 2 cases. In this group, the incidence of leukemia was four times greater than expected, based on three cases. In the complete cohort, however, the incidence of leukemia was elevated to a SIR of 1.4, based on 6 cases.

Umea University, Sweden; Gotenburg University, Sweden; The Vocation Training and Working Environment Council of the Transport Trades, Sweden.

Kaplan, S.D. Update of a Mortality Study of Workers in Petroleum Refineries. *Journal of Occupational Medicine*. 28(7): 514-516 (1986).

This study updated through 1980 a study sponsored by the American Petroleum Institute (1972) which included 19,991 men employed in a sample of United States petroleum refineries. More than two-thirds of the cohort had been employed in the participating refineries for more than 20 years. 51.3% of the cohort was hired between 1940 and 1954, while 17.2% was hired before 1940. When compared to the United States population, matched by race, there was a significant deficit of mortality from all causes and from all malignant neoplasms in the cohort. 16 deaths due to lymphosarcoma and reticulum cell sarcoma were observed, compared to 17.78 expected, though there were more deaths due to cancer of other lymphatic tissues than expected, producing a SMR of 131. A slight excess mortality due to other primary malignant neoplasms of the lymphoid tissue (ICD8 202.2) was also seen. For the remainder of Code 202, no excess mortality was observed. Elevated standardized mortality ratios were seen for polycythemia vera and myelofibrosis.

Funded by the American Petroleum Institute. SRI International, Menlo Park, California

Lagorio, S., Forastiere, F., Iavarone, I, Rapitio, E., Vanacore, N., Perucci, C.A., Carere, A. Mortality of Filling Station Attendants. *Scandinavian Journal of Work, Environment, and Health.* 20: 331-8 (1994).

The mortality of 2665 service station managers (2308 men, 357 women) in the Latium region of Italy, who were employed between 1981 and July 1991, and in Rome, who were employed between 1981 and June 1992, was compared to the regional population. Exposure was estimated from duration of employment and a series of workload indicators such as station size and volume of fuel sold. In 1992, a study measured the 8-hour time weighted average exposure to benzene at service stations to be $0.55\text{mg}/\text{m}^3$. In the entire cohort, the standard mortality ratio was 155 for non-Hodgkin's lymphoma, based on three deaths. This mortality ratio did not vary between small stations with higher sales of super-premium fuel (the highest exposures) and large service stations. The small numbers of deaths due to non-Hodgkin's lymphoma limit the ability of this study to describe the risk of non-Hodgkin's lymphoma posed by employment as a service station manager. National Health Institute, Rome, Italy; Latium Regional Health Authority, Rome, Italy; "La Sapienza" University, Rome, Italy

LaVecchia, C., Negri, E., D'Avanzo, B., Franceschi, S. Occupation and Lymphoid Neoplasms. *British Journal of Cancer.* 60: 385-388 (1989).

This report evaluates the occupational histories of a series of cases of lymphoid cancer, including 153 cases of non-Hodgkin's lymphoma, identified in Milan between 1983 and 1988. Controls were not individually matched, but chosen from individuals admitted to the same hospitals for acute conditions. A slightly higher percentage of individuals with non-Hodgkin's lymphoma and multiple myeloma reported a history of exposure to chemicals, solvents/benzene, metals/metal dusts, and oil, than did the control population. Individuals with non-Hodgkin's lymphoma and multiple myeloma had a significantly increased relative risk of employment in agriculture. Mario Negri Institute for Pharmacological Research, Milan, Italy; Institute of Social and Preventive Medicine, Lausanne, Switzerland; Inter-University Consortium of Lombardy for automatic data processing, Milan; Italy; Aviano Cancer Institute, Aviano, Italy

Li, G-L., Linet, M.S., Hayes, R.B., Dosemeci, M., Wang, Y-Z., Chow, W-H., Jiang, Z-L., Wacholder, S., Zhang, W-U., Dai, T-R., Chao, X-J., Zhang, X-C., Ye, P-Z., Kuo, Q-R., Meng, HJ-F., Zho, J-S., Lin, X-F., Ding, C-Y., Wu., C., Blot, W.J. Gender Differences in Hematopoietic and Lymphoproliferative Disorders and Other Cancer Risks by Major Occupational Group Among Workers Exposed to Benzene in China. *Journal of Occupational Medicine*. 36(8): 875-881. (1994).

This study examined gender differences in risk for hematopoietic and lymphoproliferative cancers by occupational category for 74,828 benzene-exposed workers compared to 35,805 unexposed workers from 12 cities in China. There were no significant gender differences in total mortality observed, except for the occupational category of helpers, which was characterized by significantly higher relative risk among women than men. Gender differences in incidence risk from all hematopoietic and lymphoproliferative disorders were not significant, though both men and women had increased risks for these disorders in several occupational categories. With regards to non-Hodgkin's lymphoma, excess incidence was seen among male varnish and printing workers, and female chemical and non-production workers. The authors conclude that the gender differences were minor, and may reflect variation in exposure level and/or duration among occupational categories. The small numbers of malignancies limited this evaluation. Chinese Academy of Preventive Medicine, Beijing, China; National Cancer Institute, Bethesda, Maryland.

Linet, M.S., Yin, S-N., Travis, L.B., Li, C-Y., Zhang, Z-N., Li, D-G., Rothman, N., Li, G-L., Chow, W-H., Donaldson, J., Dosemeci, M., Wacholder, S., Blot, W.J., Hayes, R.B. Clinical Features of Hematopoietic Malignancies and Related Disorders among Benzene-Exposed Workers in China. *Environmental Health Perspectives*. 104 (Suppl.6): 1353-64 (1996). .

This study evaluates the clinical features of hematopoietic and lymphoproliferative disease among a cohort of 74,828 benzene-exposed, and 35,805 non-exposed workers in China. Between 1972 and 1987, 17 cases of non-Hodgkin's lymphoma were diagnosed in the benzene-exposed population, and 3 cases in the non-exposed population. The authors were unable to update the non-Hodgkin's lymphoma diagnoses to reflect advances in disease classification, as many of the necessary tests had not been performed at the time of original diagnosis. A variety of types of non-Hodgkin's lymphoma were diagnosed among the exposed and non-exposed cases: No one type of lymphoma predominated among the workers. Overall, the survival of exposed individuals with hematopoietic and lymphoproliferative cancers was slightly shorter than the survival of the non-exposed individuals. The authors urge cautious interpretation of the last point due to the small number of cases and the many comparisons performed in their analysis. National Cancer Institute, Bethesda, Maryland; Chinese Academy of Preventive Medicine, Beijing, China; Mayo Clinic, Rochester, Minnesota; Chinese Academy of Medical Sciences, Beijing, China

Linnet, M.S., Malker, H.S.R., McLaughlin, J.K., Weiner, J.A., Blot, W.J., Ericsson, J.L.E., Fraumeni Jr., J.F. Non-Hodgkin's lymphoma and occupation in Sweden: a registry based analysis. *British Journal of Industrial Medicine.* 50: 79-84 (1993).

The Swedish Cancer-Environment Registry, which links the cancer incidence between 1961 and 1979 with the 1960 census, was used to correlate occupation with cancer incidence. 4496 Swedish men were diagnosed with non-Hodgkin's lymphoma and included in the Registry. When evaluated by 3-digit Standard Industrial Classification Code, elevated rates of non-Hodgkin's lymphoma were found in the occupations of shoe repair (SIR 1.8), research and scientific institutes (SIR 3.5, $p < 0.001$), mining engineer or technician (SIR 1.9), shoemaker (SIR 1.7), and lorry driver (SIR 1.4). The study could not evaluate different types of non-Hodgkin's lymphoma, because the diagnostic classification system has changed.

National Cancer Institute, Rockville, Maryland; National Board of Occupational Safety and Health, Solna, Sweden; National Board of Health and Welfare, Stockholm, Sweden.

Lynge, E., Anderson, A., Nilsson, R., Barlow, L., Pukkala, E., Nordlinder, R., Boffetta, P., Grandjean, P., Heikkila, P., Horte, L-G., Jakobsson, R., Lundberg, I., Moen, B., Partanen, T., Riise, T. Risk of Cancer and Exposure to Gasoline Vapors. *American Journal of Epidemiology.* 145(5): 449-457 (1997).

This study resulted from a meeting of scientists and petrochemical industry representatives in December 1993 at the International Agency for Research on Cancer in Lyon, France. The study included 16,524 men and 2,445 women identified as service station workers in the 1970 census in Denmark, Norway, Sweden, and Finland. They were followed for 15 to 20 years, depending on the country, for approximately 343,000 person-years. From a series of short-term and long-term samples collected at service stations in Europe during the study period, it was estimated that the average level of exposure to benzene was below $1\text{mg}/\text{m}^3$. No excess incidence of non-Hodgkin's lymphoma was seen in male or female service station workers. A slight excess of chronic lymphatic leukemia was seen among female workers, with two cases observed in Denmark for a standard incidence ratio of 5.9 in Denmark, and a SIR of 2.7 for the entire cohort. Among male service station workers, a slight excess in acute myeloid leukemia was observed, with 13 observed cases and 9.14 expected, producing an SIR of 1.4.

Funded by the Nordic Cancer Union.

McCraw, D.S., Joyner, R.E., Cole, P. Excess Leukemia in a Refinery Population. *Journal of Occupational Medicine* 27(3): 220-222.

This study evaluated the mortality of all 3,976 white men employed at Shell's Wood River Refinery between 1973 and 1982, or retired from that site but alive in 1973. Vital status was assessed as of 1983, and compared to the age-adjusted US white male death rates. A two-fold increase in leukemia deaths was observed and four-fold increases in acute myelogenous leukemia and acute lymphatic leukemia were seen. No cases of lymphosarcoma and reticulosarcoma were observed, though 2.8 were expected. A slight increase in cancer of other lymphatic tissues was seen. The authors note that while individual exposures were not assessed, it was determined that the subjects with acute myelogenous leukemia had not been assigned to jobs deemed to have the highest potential for exposure to benzene.

McMichael, A.J., Spirtas, R., Kupper, L.L. An Epidemiologic Study of Mortality within a Cohort of Rubber Workers, 1964-1972. *Journal of Occupational Medicine.* 16(7): 458-464 (1974).

This paper is the initial mortality study carried out within the research program negotiated between the United Rubber Workers, the six major U.S. rubber companies, and University of North Carolina, Chapel Hill. The study focused on 6678 hourly active and retired male employees, age 40-84 at January 1, 1964, from a tire-manufacturing plant in Akron, Ohio. Comparing these workers to the U.S. male population, the standardized mortality ratio for lymphosarcoma (ICD8 200) in the active age range of 40-64 was 251, but decreased slightly to 226 when the full age-range (40-84) was considered. Proportional mortality analysis carried out with populations from five other plants indicated elevated mortality risk due to lymphatic and hematopoietic system cancers, and that higher mortality risks were seen in the active age-range than in the full age-range of the cohort. The authors caution that as this is the report is only the first phase of the study: the cause-specific mortality excess may not yet be attributed to work-environment exposure in the rubber industry, as the cohort of workers may be a selected population with respect to some important etiologic factor.

University of North Carolina, Chapel Hill

McMichael, A.J., Spirtas, R., Kupper, L.L., Gamble, J.F. Solvent Exposure and Leukemia Among Rubber Workers: An Epidemiologic Study. *Journal of Occupational Medicine.* 17(4): 234-239 (1975).

The mortality of 6,678 male workers who had worked for one company at one of seven manufacturing plants was compared to the US male age-specific death rates. The men were active or retired workers aged 40 to 84 on January 1, 1964, with average employment duration of 25 years, and their vital status was followed for nine years. A nearly two-fold excess in mortality from lymphosarcoma (ICD 8th Rev 200) and a seven-fold excess in mortality from lymphatic leukemia were observed. In addition, a case-control study was performed, comparing the 88 deaths attributed to cancers of the lymphatic and hematopoietic systems to rubber workers who died of other causes during the same time period (1964-1973). It was found that lymphatic leukemia cases effectively spent about four years more in solvent-exposed workgroups than did the controls, and that six times as many cases worked in tire repair jobs than controls. The pattern among tire repair workers indicates that the exposure agent may still have been present in the workplace at the time of the study, if not first introduced in the period since 1945. The authors, however, provide no estimate of the level of exposures or the specific agents to which the rubber workers were exposed though benzene, xylene, toluene, and other organic solvents, have been used in rubber manufacturing.

University of North Carolina, Chapel Hill

Mallin, K., Rubin, M., Joo, E. Occupational Cancer Mortality in Illinois White and Black Males, 1979-1984, for Seven Cancer Sites. *American Journal of Industrial Medicine* 15: 699-717 (1989).

Subjects of this study were males aged 35 to 74, selected from Illinois deaths between 1979 and 1984. Controls were chosen by random sampling of non-cancer deaths among men aged 35 to 74. In the evaluation of deaths due to non-Hodgkin's lymphoma, 1248 white males and 102 black males were identified. Occupation and industry of the subjects were coded from the death certificates using the 1980 Census Bureau definitions and included 30 industry groups and 29 occupational groups. Industries with elevated odds ratios for non-Hodgkin's lymphoma mortality included: printing/publishing, manufacture of industrial/miscellaneous chemicals, chemicals and allied products, manufacture of farm equipment, public administration, and agriculture. Occupations with elevated odds ratios for non-Hodgkin's lymphoma mortality included: photoengravers/lithographers, inspectors, assemblers, fabricators, farmers, mechanics, and construction trades.

Illinois Cancer Council, Chicago, Illinois

Mao, Y., Hu, J., Ugnat, A-M., White, K. Non-Hodgkin's lymphoma and occupational exposure to chemicals in Canada. *Annals of Oncology*. 11(Suppl1): S69-S73 (2000).

This study used the National Enhanced Cancer Surveillance System in eight provinces of Canada to identify cases of non-Hodgkin's lymphoma diagnosed between 1994 and 1997. A total of 1469 individuals (764 men, 705 women) with non-Hodgkin's lymphoma (75%) responded to a survey and were compared with 5073 controls without cancer selected from the eight provinces. All histological types of non-Hodgkin's lymphoma were considered together. Benzene was not found to be associated with non-Hodgkin's lymphoma: The odds of having non-Hodgkin's lymphoma and having had benzene exposure was 1.2 among men and 0.6 among women. Slightly elevated risks for non-Hodgkin's lymphoma was found with exposures to coal tar, soot, pitch, creosote, or asphalt. Men with non-Hodgkin's lymphoma were found to have significantly elevated odds for exposure to benzidine (OR 1.9), and the risks of disease increased with the duration of exposure. This was not found to be true among women exposed to benzidine.

Laboratory Centre for Disease Control, Ottawa, Ontario, Canada

Marsh, G.M., Enterline, P.E., McCraw, D. Mortality Patterns Among Petroleum Refinery and Chemical Plant Workers. *American Journal of Industrial Medicine* 19:29-42 (1991).

6682 male hourly and salary employees at the Deer Park refinery and chemical plant who were employed for at least three months between 1948 and 1972 were assessed for their vital status at the end of 1983. Their mortality experience was compared to the death rates in Harris County, Texas where most of the cohort lived. There was a significant deficit among the cohort in mortality due to nonmalignant disease, possibly indicating a healthy worker effect. There was excess mortality due to lymphosarcoma and reticulosarcoma among the refinery workers (SMR=189), though fewer individuals employed in the chemical plant died of these cancers than expected. Among refinery workers, mortality due to all lymphopietic tissue malignancies and lymphosarcoma showed a significant upward trend associated with increased duration of employment: Though there was a deficit of deaths due to these malignancies among men employed for less than 20 years, there was excess mortality among those employed for more than twenty years. Mortality due to lymphosarcoma and reticulosarcoma among those employed 30+ years was elevated eight-fold (SMR=816, $p<0.01$). The authors did not find a clustering of work assignments or potential exposures among cases whose cancers showed positive mortality trends relative to duration of employment. The authors conclude that other lymphopietic malignancies were more associated with the chemical plant while lymphoreticulosarcoma was more associated with the refinery. The study found limited evidence for elevated rates of leukemia, a disease strongly associated with exposure to benzene.

Funded by Shell Oil Company, Houston, TX. University of Pittsburgh, Pittsburgh, PA,

Miligi, L., Constantini, A.S., Crosignani, P., Fontana, A., Masala, G., Nanni, O., Ramazzotti, V., Rodella, S., Stagnaro, E., Tumino, R., Vigano, C., Vindigni, D., Vineis, P. Occupational, environmental, and life-style factors associated with the risk of hematolymphopietic malignancies in women. *American Journal of Industrial Medicine* 36(1): 60-69 (1999).

This paper discusses a case-control study of women newly diagnosed with hematolymphopietic neoplasms between 1991 and 1993 in twelve areas of Italy. Occupations with elevated odds ratios of non-Hodgkin's lymphoma and chronic lymphocytic leukemia included restaurant workers, hairdressers, teachers, rubber and plastics makers, knitters, and textile product finishers (odds ratios 1.4-2.1). No risk was associated with hair dye use, but the odds ratio for non-Hodgkin's lymphoma and chronic lymphocytic leukemia was significantly elevated to 1.2 (95%CI 1.0-1.5) among smokers. Among women who never worked, the odds ratio for the cancers was 1.2. The authors do not address individual chemical exposures, but conclude that their study suggests some associations with hematolymphopietic malignancies.

Funded by the National Cancer Institute.

Nilsson, R.E., Nordlinder, R., Harte, L-G., Jarvholm, B. Leukemia, lymphoma, and multiple myeloma in seamen on tankers. *Occupational and Environmental Medicine* 58:1-5 (1998).

Swedish seamen with lymphatic and hematopoietic cancers were identified from the 1960 and 1970 Swedish Cancer-Environment Register, which links the Swedish National Cancer Registers of 1961-1979 and 1971-1987 to the National Census in 1960 and 1970, respectively. 46 cases and 159 referents were identified from 1960, and 46 cases and 132 referents were identified from 1970, though 11 cases were counted in both groups. Benzene-exposed seamen, identified from the Swedish Registry of Seamen, worked at least one month on chemical/product or crude oil tankers, and included six cases from 1960 and 14 cases from 1970. Elevated odds ratios for non-Hodgkin's lymphoma were seen among seamen on chemical/product tankers in the 1960 and 1970 census: OR 4.0 and OR 3.3, respectively. Among seamen on chemical/product tankers there was an odds ratio of 4.0 of leukemia incidence, and all of the leukemia cases on these ships were lymphocytic leukemia. On crude oil tankers, there were increased odds for non-Hodgkin's lymphoma from the 1960 census, but not the 1970 census. The authors estimate that the excess risk for lymphatic and hematopoietic malignancies from 1971-1987 due to cargo vapors on chemical/product tankers was 8.6 cases (14obs/5.4exp). This incidence is twice the rate of these malignancies in the general population, and represents an excess of 4 cases per 10,000 person years. This study is limited by the small number of cases among the exposed population. Funded by the Swedish Work Environment Fund. Sahlgrenska University Hospital, Goteborg, Sweden; University of Uppsala, Uppsala, Sweden.

Norseth, T., Anderson, A., Giltvedt, J. Cancer Incidence in the Rubber Industry in Norway. *Scandinavian Journal of Work, Environment, and Health* 9(Suppl.2): 69-71 (1983).

The cancer incidence among a cohort of 2448 men employed at a footwear and tire plant for at least 18 months after 1940, and still alive at the beginning 1953, was determined in 1978 from the Norwegian Cancer Registry and compared to age-specific incidence rates. Eight cases of lymphoma were observed (5.64 expected), five of which occurred in the footwear department (2.26 expected). Of these cases, one was reticulosarcoma, one was giant follicular cell lymphoma, and two were unclassified. The incidence of leukemia was also elevated in this plant, and cases were found in almost every department. Benzene glue was used in the footwear department until 1940. From 1940-1978 a benzene-based glue with up to 4% aromatics, probably predominately benzene, was used. Six of the eight lymphoma cases and six of nine leukemia cases had documented benzene exposure, and only three of these workers were employed before 1940. The exposures experienced by non-cases are unknown. Institute of Occupational Health, Oslo, Norway; Norwegian Cancer Registry, Montebello, Norway; Viking-Askim AIS, Askim, Norway

Olin, G.R. The hazards of a chemical laboratory environment – a study of the mortality in two cohorts of Swedish chemists. *American Industrial Hygiene Association Journal* 39: 557-562 (1978).

The mortality experience of 857 Swedish chemists who graduated from the School of Chemical Engineering at the Royal Institute of Technology and from the School of Chemical Engineering at the Chalmers Institute of Technology between 1930 and 1950 was compared to the mortality rates of the Swedish population between 1961 and 1970. Among the graduates, 8 cases of lymphatic and hematopoietic cancers were observed, though only 2.6 deaths were expected based on rates in the general population. Among these 8 cases, three individuals had been diagnosed with lymphosarcoma and three with Hodgkin's disease. The authors conclude that it is probable that employment in chemical laboratories is associated to some extent with increased rates of leukemia, urogenital tumors, brain tumors, and malignant lymphoma.

Royal Institute of Technology, Stockholm, Sweden

Olin, G.R., Ahlbom, A. The Cancer Mortality among Swedish Chemists Graduated during Three Decades: A Comparison with the General Population and with a Cohort of Architects. *Environmental Research*. 22: 154-161 (1980).

The chemists included in this study were 820 men who graduated from the School of Chemical Engineering at the Royal Institute of Technology, Stockholm, between 1930 and 1959. The mortality experience of the chemists was compared, using relative risk estimates, to a cohort of 657 architects who graduated from the School of Architecture at the same institution during the same time period. The standard mortality ratios for each cohort were calculated based on death rates in the general population between 1960 and 1969. Compared to the general population, chemists experienced excess cancer mortality while architects experienced less cancer mortality than expected. The relative risk of being a chemist and dying from cancer was 254, when compared with architects. Compared to the general population, chemists experienced elevated mortality due to lymphatic and hematopoietic cancers (7 observed, compared to 3.2 expected). No cancers of these types occurred among architects. Among chemists, one case of lymphosarcoma and one case of reticulum cell sarcoma were observed. The author reports that benzene was widely used in Swedish chemical laboratories until recently, but notes that there are many other substances in chemical labs that may be carcinogenic.

Royal Institute of Technology, Stockholm, Sweden; Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden

Olsson, H., Brandt, L. Supradiaphragmatic Presentation of Non-Hodgkin's Lymphoma in Men Occupationally Exposed to Organic Solvents. *Acta Medica Scandinica* 210: 415-418 (1981).

This study evaluated the occupational exposures to organic solvents among 61 consecutive male patients with NHL referred to the University Hospital in Lund, Sweden between October 1978 and September 1980 for diagnosis and clinical staging. A personal interview prior to classification and staging was conducted to assess exposures. 38% (23) of patients reported handling organic solvents every working day for at least one year, and were classified as exposed, though only one patient reported handling benzene. There was no predominant type of non-Hodgkin's lymphoma among the exposed compared to the non-exposed. 80% (12 of 15) of patients with Stage I-II located above the diaphragm had been exposed, while only 1 of 9 patients with Stage I-II non-Hodgkin's lymphoma located below the diaphragm had been exposed. Among patients with Stage III-IV non-Hodgkin's lymphoma, in which the primary location of the cancer is uncertain, 10 of 37 patients had been exposed to organic solvents. Each group had similar mean ages. The authors hypothesize that as many organic solvents are volatile, they are inhaled and high exposures are experienced in the mucous membranes of the upper and lower respiratory tracts. The authors suggest that this would lead to an increase in the presentation of non-Hodgkin's lymphoma above the diaphragm.

University Hospital, Lund, Sweden

Olsson, H., Brandt, L. Risk of Non-Hodgkin's Lymphoma among Men Occupationally Exposed to Organic Solvents. *Scandinavian Journal of Work, Environment, and Health* 14: 246-251 (1988).

A consecutive series of 167 adult men with non-Hodgkin's lymphoma admitted to the University Hospital in Lund, Sweden between 1978 and 1981, representing 70% of the patients in the health region, were compared to 50 men from the same geographic area and to 90 men from different parts of Sweden. Patients and referents were interviewed, but the interviewers were not blinded to the case or referent status of the study participants. 38% of patients and 14% of referents reported handling organic solvents daily for at least one year, and were considered exposed to organic solvents. The authors do not discuss benzene exposure in particular, but there is not likely to have been much exposure to benzene as it was declared a poison in Sweden in 1972. Risk of non-Hodgkin's lymphoma was found to increase with duration of exposure to organic solvents, and the exposure duration among the study population ranged from 1 to 47 years, with median duration of 10 years. The latency from the start of exposure to diagnosis ranged from 2 to 60 years, with a median of 21 years. In a logistic model adjusted for age and other risk factors, solvent exposure was found to be an independent risk factor with an odds ratio of 2.0 (95% CI 1.5-2.6). In another adjusted logistic model, solvent exposure increased the odds of lymphoma presentation above the diaphragm to 3.4 (95% CI 2.3-5.2).

Funded by the Swedish Cancer Society. University Hospital, Lund, Sweden;

Ott, M.G., Townsend, J.C., Fishbeck, W.A., Langner, R.A. Mortality among Individuals Occupationally Exposed to Benzene. *Archives of Environmental Health*. January/February: 3-10 (1978).

594 men employed on or after January 1, 1940 in the Michigan Division of Dow Chemical Company with potential exposure to benzene were followed until 1973. There were three work areas with potential exposure to benzene: (I) The chlorobenzol plant which used benzene as a raw material and operated from 1920 to the present; (II) The alkyl benzene plant which also used benzene as a raw material and operated from 1935 to the present; (III) The ethyl cellulose plant which used benzene as a solvent and operated from 1936 to the present. Exposures were classified into four levels based on industrial hygiene surveys, which were highly variable. 108 employees had 20+ years of work in areas of benzene exposure; 175 had potential exposures of >25ppm TWA for at least one month. Expected deaths were estimated from the US white male mortality. 102 deaths occurred among the cohort. Two deaths were attributed to lymphatic/hematopoietic cancers (except leukemia), when 1.5 deaths were expected. These were due to aplastic anemia and pernicious leukemia. No deaths were attributed to non-Hodgkin's lymphoma.

Dow Chemical Company, Midland, Michigan

Ott, M.G., Teta, J., Greenberg, H.L. Lymphatic and Hematopoietic Tissue Cancer in a Chemical Manufacturing Environment. *American Journal of Industrial Medicine* 16: 631-643 (1989).

This report is a case-control study nested in a cohort study of chemical manufacturing workers previously described by Rinsky *et al.*, 1988. 52 cases of NHL and 20 cases of multiple myeloma were included, having been identified from review of underlying and contributory causes of death among males employed between 1940 and 1978 and included in the cohort. Controls were selected from the total employee cohort. When exposure to benzene was classified as ever exposed or never exposed, there was no excess mortality from non-Hodgkin's lymphoma, but there was a slight excess of mortality due to lymphocytic leukemia. When exposure was defined as ever or never having been employed in work areas with exposure to suspect chemicals, foremen and others in the maintenance and construction group had elevated odds of mortality due to non-Hodgkin's lymphoma and lymphocytic leukemia; while instrument men in the maintenance and construction group, and those employed on the ethanol unit experienced excess mortality due to non-Hodgkin's lymphoma. The foremen and others group was very heterogeneous, but generally included men who had worked at the company for a long time and were promoted to foreman. When evaluated by groups of chemicals, increased odds ratios for non-Hodgkin's lymphoma was seen with alkenes and fused cyclics: OR 1.7 and OR 2.1, respectively. The authors concluded that there was a weak association between benzene and multiple myeloma and lymphocytic leukemia.

Union Carbide Corporation, Danbury, Connecticut; Arthur D. Little Inc, Cambridge, Massachusetts; ARCO, Los Angeles, California

Persson, B., Frderickson, M. Some Risk Factors for Non-Hodgkin's Lymphoma. *International Journal of Occupational Medicine and Environmental Health*12(2): 135-142 (1999).

This study reports a pooled analysis of two previously reported case-control studies. The first study (Persson *et al.* 1989) included 106 cases of non-Hodgkin's lymphoma of B-cell origin diagnosed between 1964 and 1986 at Orebro Medical Center Hospital, Sweden. The second study (Persson *et al.* 1993) included 93 cases of non-Hodgkin's lymphoma included in the Regional Cancer Registry at the University Hospital in Linkoping between 1975 and 1984. It is unclear whether cases of non-Hodgkin's lymphoma included in the latter study were restricted to those of B-cell origin. Exposure assessment was conducted through a 9-page questionnaire. The minimum exposure time was one year, and latency was applied such that only exposures occurring 5-45 years prior to diagnosis were included. Exposure intensity was qualitatively assigned to two levels by the researchers. Exposure to benzene was not found to increase the odds of non-Hodgkin's lymphoma, though the odds of non-Hodgkin's lymphoma increased with exposure to solvents, gasoline, aviation gasoline, creosote, plastic or rubber chemicals, engine exhausts, and welding.

Centre for Public Health Sciences, Linkoping, Sweden.

Peters, J.M., Monson, R.R., Burgess, W.A., Fine, L.J. Occupational Disease in the Rubber Industry. *Environmental Health Perspectives* 17: 31-34 (1976).

The mortality experience between 1940 and 1974 of 13,571 male employees at a single rubber plant was compared to the U.S. death rates, with consideration for race, sex, age, and time. Though overall mortality among the workers was less than expected, excess mortality due to gastrointestinal cancer, lung cancer, bladder cancer, lymphatic cancer and myeloma were seen in some work areas, while an excess of mortality due to leukemia was found in all work areas. In the tire building work area, 11 deaths due to lymphatic cancer and myeloma were observed, though only 7.1 were expected. The authors note that no excess mortality due to lymphatic cancer and myeloma was seen among men who started working before age 25, or among men who started working after 1934.

Harvard School of Public Health, Boston, Massachusetts; B.F. Goodrich Co., Armstrong Rubber Co., Mansfield Tire and Rubber Co., United Rubber, Cork, Linoleum and Plastic Workers of America.

Raabe, G.K., Collingwood, K.W., Wong, O. An Updated Mortality Study of Workers at Petroleum Refinery in Beaumont, Texas. *American Journal of Industrial Medicine* 33: 61-81 (1988).

This study evaluated the mortality experience as of 1987 of 7,119 workers who had been employed at a Beaumont, Texas, refinery as operators and maintenance craftworkers for at least one year between 1945 and 1987. Overall, there was a significant deficit of 18% in overall mortality, though there was a significant 58% excess in mortality due to other lymphatic tissue cancers. Among all male employees, mortality due to lymphosarcoma and reticulosarcoma peaked at an SMR of 142 among men whose length of employment was 10-29 years, and was deficit among men employed 30+ years. Mortality due to other lymphatic tissue cancers, however, was highest among men employed for less than ten years: two-fold excess mortality was seen, and decreased with duration of employment while remaining elevated compared to the US general population. The same trend was seen for non-Hodgkin's lymphoma among maintenance craftworkers. Mortality due to other lymphatic tissue cancers was significantly elevated to an SMR of 233, and the mortality risks were higher among men employed in 1950 or later than among men employed before 1950.

Mobile Business Resources Corporation, Global Medical Services, New Hope, Pennsylvania;
Applied Health Sciences, Inc., San Mateo, California

Rinsky, R.A., Young, R.J., Smith, A.B. Leukemia in Benzene Workers. *American Journal of Industrial Medicine* 2: 217-245 (1981).

This study retrospectively evaluated the mortality of workers who had been exposed to benzene in the manufacture of rubber hydrochloride at two locations in Ohio. Information on the level of benzene exposures was available from a variety of sources, and ranged from zero to 167ppm in 1977 in the two locations. The level of exposure was not included in the mortality analysis. Among the cohort who worked at least one day in a benzene-exposed department between 1940 and 1949, there were more deaths than expected from all causes. The SMR for leukemia was 560, and for other malignant neoplasms of the lymphatic and hematopoietic tissue (ICD 7th revision codes 200-203, 205) the SMR was 169. The remainder of the paper focuses on leukemia mortality, and no information on the relationship of lymphoma duration of exposure or latency is provided.

National Institute for Occupational Safety and Health, Centers for Disease Control, Cincinnati, Ohio

Rinsky, R.A., Hornung, R.W., Silver, S.R., Tseng, C.Y. Benzene Exposure and Hematopoietic Mortality: A Long-Term Epidemiologic Risk Assessment. *American Journal of Industrial Medicine* 42: 474-480 (2002).

This is an update of a cohort of employees at three rubber hydrochloride plants in Ohio, first described by Infante *et al.* (1977) and Rinsky *et al.* (1981). The cohort included all 1,291 persons with at least 1ppm-day of exposure to benzene between 1940 and April 1976, when operations had ceased in all plants. Observation began in 1950 for all workers employed in an exposed area for at least one day after 1940, except for cases of multiple myeloma and non-Hodgkin's lymphoma for which observation began in 1960. This means that there was up to a 20-year lag between exposure to benzene and evaluation of the outcomes of non-Hodgkin's lymphoma and multiple myeloma. No elevated mortality due to non-Hodgkin's lymphoma was observed in the complete cohort nor among white males. The excess mortality due to multiple myeloma was twofold higher than expected, while a six-fold excess in leukemia was seen among the entire cohort.

National Institute for Occupational Safety and Health, Cincinnati, Ohio

Rushton, L., Alderson, M.R. An epidemiological survey of eight oil refineries in Britain. *British Journal of Industrial Medicine*. 38: 225- 234 (1981).

To generate hypotheses for further investigation, the mortality of all men who worked at least one year continuously between 1950 and 1975 at eight refineries in Britain was compared to the population of the geopolitical area of the refinery using weighted means. Exposures were broadly classified based on last job title, which could lead to misclassification as many senior workers move to less taxing or supervisory roles with less chemical exposures. In total there were 575,982 person-years, and the mean follow-up time was 16.6 years per person. Among all workers there was no significant excess of any lymphatic and hematopoietic tissue malignancies, though mortality due to lymphosarcoma was slightly elevated. At one refinery there were four deaths from lymphosarcoma, when only 1.23 deaths were expected ($p < 0.05$). Among operators at the same refinery, seven deaths were observed due to all lymphatic and hematopoietic tissue malignancies though only 2.97 were expected ($p < 0.05$).

Institute of Cancer Research, Sutton, Surrey, United Kingdom

Scherr, P.A., Hutchison, G.B., Neiman, R.S. Non-Hodgkin's Lymphoma and Occupational Exposures. *Cancer Research* 52(suppl): 5503s-5009s (1992).

303 patients diagnosed with non-Hodgkin's lymphoma between 1980 and May 1982 in the Boston Standard Metropolitan Statistical Area (9 hospitals) were matched with controls by age, sex, town, and precinct of residence. 99% of the cases and 98% of the controls were interviewed at home about occupational exposures. No increased risk of non-Hodgkin's lymphoma was seen with exposure to benzene or gasoline/kerosene. Employment in the leather industry, agriculture, construction, and the paper or wood industries was associated with increased risk of non-Hodgkin's lymphoma.

Harvard School of Public Health, Boston, Massachusetts; Boston University, Boston, Massachusetts

Schnatter, A.R., Theriault, G., Katz, A.M., Thompson, F.S., Donaleski, D., Murray, N. A Retrospective Mortality Study Within Operating Segments of a Petroleum Company. *American Journal of Industrial Medicine* 22: 209-229 (1992).

This study evaluated the mortality of 34,597 oil industry workers in diverse operating segments who were active employees or living retirees in 1964, or new regular employees hired between 1964 and 1983 who worked for one year. 60% of the employees entered after 1964, indicating that the cohort was relatively young. Expected deaths were calculated from the Canadian population mortality rates, specified by 5-year age ranges, gender, and calendar period. The all cause mortality had a standardized mortality ratio of 0.85, indicating a deficit in mortality in the cohort. In the total cohort, there was excess mortality due to reticulum-cell sarcoma (SMR=1.45), but mortality due to non-Hodgkin's lymphomas was only marginally elevated. Non-Hodgkin's lymphoma mortality patterns did not linearly increase with duration of employment among male workers, but SMRs were elevated among those employed 0-4, 5-14, and 25-34 years. There were, however, few deaths among workers employed for less than 24 years. The SMR for reticulum-cell sarcoma among petroleum company workers was 2.44, based on 6 cases, and the SMR for all non-Hodgkin's lymphomas was 1.27, based on 14 cases. Exxon Biomedical Sciences, Inc., East Millstone, New Jersey; McGill University, Montreal, Canada; Imperial Oil, Limited, Toronto, Canada

Schnatter, A.R., Armstrong, T.W., Nicolich, M.J., Thompson, F.S., Katz, A.M., Huebner, W.W., Pearlman, E.D. Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occupational and Environmental Medicine* 53: 773-781 (1996).

29 individuals with lymphohaematopoietic malignancies, including 8 with non-Hodgkin's lymphoma, who died between 1964 and 1983 and ever worked in marketing or distribution, marine or pipeline segments were matched to 115 controls from the same cohort of Canadian petroleum workers who were still living at the time of the petroleum workers' deaths. Industrial hygienists estimated the levels of exposure to benzene and total hydrocarbons for each job in each area, and noted the potential for dermal exposures in each job. Individuals with non-Hodgkin's lymphoma were exposed for an average duration of 21.8 years, 3.3 years less than controls. Elevated odds of non-Hodgkin's lymphoma were found among workers exposed to benzene in the concentration of 0.5-1ppm at some point in their career, but there were too few cases to accurately characterize risk, particularly as there was only one case of non-Hodgkin's lymphoma that had experienced exposure to benzene in excess of 1ppm at some point during his career. Exposure to benzene was found in a conditional logistic regression model to increase the odds of leukemia by 6% per year exposed. Exxon Biomedical Sciences, Millstone, New Jersey; Imperial Oil, Toronto, Canada

Schumacher, M.C., Delzell, E. A Death Certificate Case-Control Study of Non-Hodgkin's Lymphoma and Occupation in Men in North Carolina. *American Journal of Industrial Medicine* 13: 317-330 (1988).

This study included 501 randomly selected men who died between 1968-70, 1975-77, and 1980-82 when they were between the ages of 35 and 75 and had non-Hodgkin's lymphoma mentioned on their death certificate as an underlying or contributing cause of death. 569 controls were selected from all other deaths not due to neoplastic diseases in the same time periods, and were matched to the cases by year of diagnosis, age, and race (matched 2:1 for blacks, and 1:1 for whites). Occupational title and industry were coded from the death certificate. Exposure to benzene did not increase the odds for non-Hodgkin's lymphoma among blacks or whites. Increased odds of non-Hodgkin's lymphoma were seen among blacks working in the textile industry (OR=2.4), but there was not enough information on specific activities to evaluate the risk by job. Elevated risks were also seen among white professional/technical/managerial workers (OR=2.7), and among blacks employed in the machine trades (OR=3.6).

Funded by National Institute of Environmental Health Sciences. University of Utah School of Medicine, Salt Lake City, Utah; School of Public Health University of Birmingham, Birmingham, Alabama

Schwartz, E. Proportionate Mortality Ratio Analysis of Automobile Mechanics and Gasoline Service Station Workers in New Hampshire. *American Journal of Industrial Medicine* 12: 91-99 (1987).

In this study, cases were defined as automobile mechanics (435 white males) and gas service station employees (134 white males) who died between 1975 and 1985 in New Hampshire. The expected death rates were calculated from the United States population, and the proportionate mortality rates were standardized on age, sex, race, and year of death. Among mechanics there was a 78% excess (PMR=178) mortality due to leukemia (ICD 8th Revision codes 204-207) and a 100% excess (PMR=200) mortality due to malignancies of other lymph tissues (ICD 8th Revision codes 202, 203, 208, 209). Among employees in the gas service station industry, the PMR for leukemia was 328, while there was only a slight excess of mortality due to malignancies of other lymph tissues. This study was limited by the few cases of lymphopoietic malignancies observed. New Hampshire Department of Health and Human Services, Concord, New Hampshire

Shallenberger, L.G., Acquavella, J.F., Donaleski, D. An updated mortality study of workers in three major United States refineries and chemical plants. *British Journal of Industrial Medicine* 49: 345-354 (1992).

A cohort of workers originally observed from 1970 to 1977 was updated to the end of 1982. The cohort included 25,321 employees who worked for at least one month between 1970 and 1982 at the Exxon refineries and chemical plants in Baton Rouge, LA; Baytown, TX; and Bayway/Bayonne, NJ. Retired employees who were still alive in 1970 were included. Standard mortality ratios were calculated by comparing observed deaths with expected deaths estimated from the states in which each refinery was located, specific for age, sex, race, and calendar period. Each employee was described as blue-collar or white-collar based on where she/he spent the largest proportion of time. In 1982, 94% of the cohort was less than 40-years old, and 72% had worked less than five years. Employees at the Baton Rouge facility had the largest excess of mortality due to lympho/reticulosarcoma of all facilities (SMR=156), and the total cohort had a standardized mortality ratio of 129 for these malignancies. Smokers showed larger risks for all types of hematopoietic and lymphatic malignancies than non-smokers, though smoking habits were unknown for 40% of the cohort.

Exxon Company USA, Houston, Texas; Monsanto Company, Saint Louis, Missouri; Exxon Biochemical Sciences, Inc, East Millstone, New Jersey

Thomas, T.L., Waxweiler, R.J., Moure-Eraso, R., Itaya, S., Fraumeni, Jr., J.F. Mortality Patterns Among Workers in Three Texas Oil Refineries. *Journal of Occupational Medicine* 24(2): 135-141 (1982).

This study focuses on 2,509 deceased active and retired members of the Oil, Chemical, and Atomic Workers International Union (OCAW) employed at refineries A, B, and C in the Beaumont/Port Arthur area of Texas. The proportionate mortality ratio (PMR) was calculated from the ratio of observed to expected deaths, predicted from cause-specific proportions of deaths among U.S. males. When the PMR was significantly elevated, the expected deaths were re-calculated using site-age-time-race-specific relative frequencies among cancer deaths in the U.S. population. The mortality of OCAW members was elevated for the causes of non-Hodgkin's lymphoma (8th ICD 200, 202, 208), multiple myeloma, and leukemia with PMR of 1.32, 1.96, and 1.83, respectively. Elevated mortality due to non-Hodgkin's lymphoma was seen in both the active and retired members of OCAW. The PMR for non-Hodgkin's lymphoma, however, was elevated only among employees at Refinery A, while the number of observed deaths due to non-Hodgkin's lymphoma was similar to the expected deaths at Refineries B and C. The authors describe the three refineries as utilizing similar technologies and processes. National Cancer Institute, Bethesda, Maryland; National Institute for Occupational Safety and Health, Cincinnati, Ohio; Oil, Chemical and Atomic Workers International Union, Denver, Colorado

Tsai, S.P., Wen, C.P., Weiss, N.S., Wong, O., McClellan, W.A., Gibson, R.L. Retrospective Mortality and medical Surveillance Studies of Workers in Benzene Areas of Refineries. *Journal of Occupational Medicine* 25(9): 685-692 (1983).

This paper describes a retrospective mortality study of benzene workers at a Texas refinery, and the outcome of a medical surveillance program for benzene workers. The mortality study included 454 men who ever worked directly on any of the four primary units in the refinery between September 1952 and 1978. Exposure levels were determined from industrial hygiene monitoring between 1973 and 1982. Benzene exposure concentrations on the units ranged from 0.04ppm to 1.37ppm (geometric mean). Fewer benzene-exposed workers than predicted from the general population died from all causes and from all cancers, demonstrating a healthy worker effect. No deaths due to lymphopoietic cancer occurred, though 1.12 deaths were expected. The medical surveillance program at the refinery began operation in 1959 and included blood tests performed on each benzene worker up to four times a year. As of 1979, no significant changes in hematology or blood chemistry were observed, though one case of multiple myeloma was diagnosed through the surveillance program.

Gulf Oil Corporation, Houston, Texas; Environmental Health Associates, Berkeley, California

Tsai, S.P., Daud, C.M., Cowles, S.R., Ross, C.E. Morbidity Patterns among employees at a Petroleum Refinery. *Journal of Occupational Medicine* 33(10): 1076-1080 (1994).

Routinely collected health surveillance data at Shell's Wood River refinery and chemical plant was used to identify elevated morbidity among full-time male employees. The cohort included 2132 men who were employed at some time between 1981 and 1988. Production workers contributed 8144 person-years, while staff employees contributed 4548 person-years. Morbidity was determined from absences of more than 5 days, and morbidity at Wood River was compared to employees at 14 of Shell's manufacturing facilities, including Wood River, which comprised 11% of the comparison group. Among production workers the standardized morbidity ratio (SMR) for lymphatic and hematopoietic tissue neoplasms was 125, based on 2 cases of lymphoma and 1 case of multiple myeloma. Among staff employees, one case was observed compared to the 1.1 cases expected, so the SMR for lymphatic and hematopoietic tissue neoplasms was not elevated, compared to other Shell facilities.

Shell Oil Company Corporate Medical Department, Houston, Texas

Tsai, S.P., Daud, C.M., Cowles, S.R., Ross, C.E. A prospective study of morbidity patterns in a petroleum refinery and chemical plant. *British Journal of Industrial Medicine* 49: 516-522 (1992).

Routinely collected health surveillance data at Shell's Deer Park refinery and chemical plant was used to identify morbidity patterns among full-time male employees. The cohort included 3422 men who were employed at some time between 1981 and 1988. Production workers contributed 12162 person-years, while the staff contributed 8028 person-years. Morbidity was determined from absences of more than 5 days with a diagnosis and compared to employees at 14 of Shell's manufacturing facilities, including Deer Park, which comprised 27% of the comparison group. Among production workers, the standard morbidity ratio (SMR) for lymphatic and hematopoietic tissue neoplasms was 124 based on 4 observed and 3.2 expected cases. Production workers experienced one case of lymphoma, one case of Hodgkin's disease, one case of myeloid leukemia, and one case of leukemia of unspecified cell type. Among staff employees, two cases of lymphatic and hematopoietic tissue neoplasms of unspecified type were observed, producing an SMR of 91. Shell Oil Company Corporate Medical Department, Houston, Texas

Tsai, S.P., Gilstrap, E.L., Cowles, S.R., Snyder, P.J., Ross, C.E. A Cohort Mortality Study of Two California Refinery and Petrochemical Plants. *Journal of Occupational Medicine* 35(3): 415-421 (1993).

The 1973-1989 mortality experience of 4,585 employees at Shell's manufacturing complexes in Martinez and Willmington, California was compared to the population of California. Vital status was assessed at the end of 1989 for employees who had worked more than six months, and who were actively employed or living pensioners as of 1973. At Martinez, there were excess deaths due to lymphosarcoma and reticulosarcoma, and due to other lymphatic tissue cancers (8th ICD 202, 203, 208, 209). In the combined cohort, the excess due to lymphosarcoma and reticulosarcoma disappeared, but the standardized mortality ratio for other lymphatic tissue cancers remained elevated to 1.22. In a subgroup of employees who worked at least ten years, the mortality ratio for non-Hodgkin's lymphomas was not elevated. The authors discuss the impact of the healthy worker effect on this population because the SMR for all causes of death (SMR=0.89) was somewhat higher in this study than is usually observed in oil refinery and petrochemical cohort studies (SMR=0.80). They note that when the pre-1973 retirees are excluded from the study (n=1,257), the SMR for all causes decreased to 0.71. The impact of excluding these retirees on the SMR for all cancer deaths, however, is small, decreasing from 0.80 to 0.77.

Shell Oil Company Corporate Medical Department, Houston, Texas

Tyroler, H.A., Andjelkovic, D., Harris, R., Lednar, W., McMichael, A., Symons, M. Chronic Diseases in the Rubber Industry. *Environmental Health Perspectives* 17: 13-20 (1976).

This paper presents an overview of studies performed by researchers at the University of North Carolina in conjunction with the United Rubber Workers Union and the major rubber and tire manufacturers in the United States. Mortality studies of two cohorts of male rubber workers in Akron, Ohio, showed consistent excesses of mortality due to lymphosarcoma and leukemia in all age groups, though lymphosarcoma risks were higher among workers aged 40-64. In a case control study of lymphocytic leukemia, cases were more likely than controls to have work histories of jobs with solvent exposure potential: the estimated relative risk of lymphocytic leukemia deaths for workers with a history of exposure was 3.25. The authors also discuss ongoing morbidity studies, which focus on the burden of chronic respiratory disease, rather than lymphopoietic cancers.

University of North Carolina, Chapel Hill, North Carolina.

Vianna, N.J., Polan, A. Lymphomas and Occupational Benzene Exposure. *The Lancet*. June 30, 1979: 1395 – 1395 (1979).

The hypothesis of this study was that certain occupational groups with established exposure to benzene and/or coal tar fractions, which can contain high amounts of benzene, might be at increased risk for the major types of malignant lymphomas. The book *Work is Dangerous to Your Health*, (Stellman & Daum, 1973) was used to identify 14 occupations with established exposures to benzene or coal tar fractions. White male workers who died between 1950 and 1969 in New York State (excluding New York City) of reticulum cell sarcoma, lymphosarcoma, and Hodgkin's Disease and whose death certificate indicated employment in the 14 occupations of interest were included in the study. The non-exposed comparison population included residents of New York State (excluding New York City) and men employed in the 14 occupational groups of interest, as identified in the 1960 census. From the crude death rates, the relative risk for reticulum-cell sarcoma associated with employment in the 14 occupations was 1.6, while the relative risk was 2.1 for lymphosarcoma. When evaluated by age, the observed deaths were significantly different from the expected deaths for men 45 years and older: 1.7 times the expected deaths from reticulum cell sarcoma were observed among those employed in the 14 occupations, and deaths from lymphosarcoma were 2.1 times more than expected. The authors indicated that they crosschecked the occupational groups to identify any agents other than benzene and coal tar fractions to which there were common exposures; however, the results and methods of this investigation were not reported.

New York State Department of Health, Albany, New York

Wilcosky, T.C., Checkoway, H., Marshall, E.G., Tyroler, H.A. Cancer Mortality and Solvent Exposures in the Rubber Industry. *American Industrial Hygiene Association Journal* 45(12): 809- 811 (1984).

This case-control study was nested in a cohort of 6678 active or retired male rubber workers who were aged 40-84 and followed for 10 years beginning in 1964. Product specifications and operating procedures were reviewed to generate a history of authorized solvent use, though not all 25 authorized solvents may have been used in the plant. Work history records (job title) were linked to the solvent data to identify workers present for at least one cumulative year in areas where an authorized solvent was used. The odds ratio for exposure to benzene among those with lymphosarcoma or reticulosarcoma was 3.0, based on 6 cases. Benzene had been withdrawn from the plant before the follow up period, and the authors note that all leukemia deaths in the cohort died before 1964, and had been exposed between 1940 and 1949. Carbon tetrachloride and carbon disulfide were strongly associated with lymphatic leukemia (odds ratios 15.3 and 8.9, respectively). As neither of these chemicals has been linked with lymphoma or leukemia previously, the authors suggest that there may be another exposure or agent correlated with exposures to these chemicals.

School of Public Health University of North Carolina, Chapel Hill, North Carolina.

Wong, O., Morgan, R.W., Bailey, W.J., Swencicki, R.E., Claxton, K., Kheifets, L. An epidemiological study of petroleum refinery employees. *British Journal of Industrial Medicine* 43: 6-17 (1986).

14170 employees (13501 men and 678 women) at Chevron's Richmond and El Segundo refineries who had worked at least one year before the end of 1980, and who worked at least one day between 1950 and 1980 were included in this study cohort. The mortality of these workers was compared to the United States national mortality rates. There was a significant deficit in total mortality, indicating that these workers are healthier than the general public. In the total cohort, mortality due to lymphosarcoma, reticulosarcoma, and other lymphatic tissue cancers was increased by 27% and 42%, respectively (SMR of 126.6 and 141.6). Employees in the laboratory, maintenance, and operating all experienced elevated standard mortality ratios for lymphosarcoma, reticulosarcoma, and other lymphatic tissue cancers. The highest rates of lymphosarcoma and reticulosarcoma mortality were seen after a 10-19 year latency between the start of exposure and death, with a SMR of 180.7. Mortality due to lymphosarcoma and reticulosarcoma increased with duration of employment: there were no deaths among those employed for less than five years, and the highest rates were seen among those employed for more than 15 years. Most deaths due to these cancers occurred in individuals first employed in 1948 or earlier, and all leukemia deaths occurred among those employed during this time. The authors report that there was no job clustering among Richmond refinery employees who died from non-Hodgkin's lymphoma. The authors report that the study could exclude with 80% confidence the possibility that a standardized mortality ratio for non-Hodgkin's lymphoma among the entire cohort greater than 150 was not likely due to chance, but this level of risk was not observed. Environmental Health Associates, Oakland, California; Chevron Corporation Medical Staff, San Francisco, California.

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).

This study evaluates the mortality experience of 7676 men employed for at least six months between 1946 and 1975 in one of seven chemical plants. 3074 of the cohort were not occupationally exposed to benzene, while 1066 were intermittently exposed and 3536 were continuously exposed (exposure for at least three days per week) for some portion of their employment. When the entire cohort was compared to the United States male population, fewer deaths than expected were attributed to lymphosarcoma and reticulosarcoma, though there was a small excess mortality due to other lymphatic tissue cancers (SMR=112.7). Among benzene-exposed workers, when compared to the US male population the standardized mortality ratios were elevated for all categories of lymphatic and hematopoietic cancers except Hodgkin's disease. The relative risk for non-Hodgkin's lymphoma among benzene-exposed workers was 8.6, compared to unexposed workers. The risk increased to 9.6 when only the continuously exposed workers were compared to the unexposed workers.

Funded by the Chemical Manufacturers Association Benzene Panel. Environmental Health Associates, Inc., Oakland, California.

Wong, O. An industry wide mortality study of chemical workers occupationally exposed to benzene II. Dose response analysis. *British Journal of Industrial Medicine* 44: 382- 395 (1987).

This paper describes the mortality experience of 3556 workers continuously exposed to benzene and 1006 workers intermittently exposed to benzene while employed for at least six months between 1946 and 1975 in one of seven chemical plants. It is an extension of the analysis presented by Wong in 1987 (above). These workers were compared to 3074 workers at the same plants during the same time period that had no exposure to benzene, and to the United States population. Jobs in which exposure to benzene occurred at least three days per week were classified as having continuous exposure and included maintenance and lab personnel assigned to the benzene unit. Those with intermittent exposure to benzene had periodic entry into benzene areas and included maintenance and lab personnel assigned to the whole plant. 34 tasks were assigned an 8-hour time weighted average and maximum peak exposure levels by an industrial hygienist. Vital status was assessed at the end of 1977. Among workers with continuous exposure to benzene, increasing mortality due to lymphosarcoma and reticulosarcoma correlated with the duration of exposure, but the number of cases was small. When all types of non-Hodgkin's lymphoma (ICD 8th revision 200, 202, 203) were grouped, there was a trend of increasing excess mortality associated with cumulative exposure level when compared to the general population. Compared with non-exposed employees at the chemical plants, cumulative exposure to benzene increased the relative risk of non-Hodgkin's lymphopoietic cancers (ICD 8th revision 200, 202-207) 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.

Funded by the Chemical Manufacturing Association Benzene Panel. Environmental Health Associates, Oakland, California.

Wong, O., Raabe, G.K. Critical Review of Cancer Epidemiology in Petroleum Industry Employees, With a Quantitative Meta-Analysis by Cancer Site. *American Journal of Industrial Medicine* 15: 283-310 (1989).

The authors reviewed nearly 100 articles and reports from the United States, the United Kingdom, Canada, Europe, Australia, and Japan, though studies that used proportional mortality ratios (three studies), and methodological or data deficiencies (two studies), and population-based case-control studies (six studies) were excluded. The observed and expected deaths for each cancer site from all eligible studies were summed, and the summary standardized mortality ratio (meta-SMR) was calculated. For all lymphatic and hematopoietic cancers, the meta-SMR was 1.03, based on 460 deaths. Many of the studies that looked at lymphosarcoma and reticulosarcoma mortality reported few deaths, and the meta-SMR was 0.87. The authors also found only slight excess in leukemia mortality, with a meta-SMR of 1.10. This result is unusual since the link between benzene exposure and leukemia is very strong, so the authors provide four reasons that the data many have underestimated the leukemia risk: poor exposure assessment, misclassification, diagnosis, and disease classification in the studies. All of these considerations should apply equally to other cancer site-specific outcomes, particularly cancers of the lymphatic tissue.

ENSR Health Sciences, Alameda, California; Mobile Corporation Medical Department, New York.

Wong, O., Harris, F., Smith, T.J. Health Effects of Gasoline Exposure. II. Mortality Patterns of Distribution Workers in the United States. *Environmental Health Perspectives Supplements* 101(Suppl. 6): 63-76. (1993).

This study included 9026 land-based and 9109 marine distribution employees with potential exposure to gasoline for at least one year between 1946 and 1985 at one or more of the selected locations or vessels. All job titles were assigned a time-weighted average for four time periods based on measurements of the concentration of total hydrocarbons. Peak exposure and length of exposure were also evaluated. The overall mortality of the cohort was only half of that expected; the authors attribute this to health screening during employment. Interestingly, the authors found a three-fold excess mortality among individuals who were employed for less than one year. Mortality risk for all lymphopoietic cancers was not increased in either the land-based or marine based cohort members. Mortality due to cancer of other lymphatic tissue (ICD8 202,203, 208) was increased among land-based employees with exposure durations of 10-19 and 20-29 years, and among marine employees in the later category. Among land-based employees risk for cancer of other lymphatic tissues was not clearly associated with cumulative exposure to hydrocarbon vapors or with frequency of peak exposures, and no similar data were presented regarding marine employees.

Funded by the American Petroleum Institute. Applied Health Sciences, Inc, San Mateo, CA; ENSR Health Sciences, Alameda, CA; University of Massachusetts Medical Center, Worcester, MA.

Wong, O., Rabbe, G.K. Non-Hodgkin's Lymphoma and Exposure to Benzene in a Multinational Cohort of More than 308,000 Petroleum Workers. *Journal of Occupational and Environmental Medicine* 42(5): 544- 568 (2000).

The results for cohort studies of petroleum workers in the United States, Australia, Canada, the United Kingdom, Finland, and Italy were pooled. Among refinery division employees, 19 cohorts were pooled to yield a standardized mortality ratio for non-Hodgkin's lymphoma of 0.99 based on 408 deaths and 412.2 expected deaths. In a pooled analysis of all the United States refinery division worker cohorts, the SMR was 0.96, compared to 1.12 for all non-United States cohorts. There was no significant difference in mortality between those employed before 1950 and those hired in 1950 or later among US petroleum workers, or in the global pooled cohort. In the distribution division, the global pooled SMR was 0.64. One problem with this meta-analysis was also a problem with the individual cohort analyses: comparisons were made to the mortality of the general population, and there is likely to be a significant healthy worker effect. A complicating factor is that the cohorts used different classification systems to describe non-Hodgkin's lymphomas. In this meta-analysis there was 80% power to detect a SMR greater than 1.11 if the risk is not likely due to chance.

Funded by the American Petroleum Institute. Applied Health Sciences, San Mateo, California; Tulane University Medical Center, New Orleans, Louisiana; Exxon Mobile Corporation, New Hope, Pennsylvania

Wongsrichanalai, C., Delzell, E., Cole, P. Mortality from Leukemia and Other Diseases among Workers at a Petroleum Refinery. *Journal of Occupational Medicine* 31(2): 106-111 (1989).

This study evaluated the mortality experience of 9484 white men employed at a petroleum refinery for at least six months between 1940 and 1984. Compared to U.S. white men, the refinery workers experienced a 20% deficit in overall mortality. Among hourly employees, mortality due to lymphosarcoma and other lymphatic and hematopoietic tissue cancers was in slight excess, though mortality due to these causes was deficit by 50% among salaried employees. Lymphocytic leukemia mortality was not related to period of hire, but there was a five-fold excess mortality in the 1950s, which decreased over time so that there was only 20% and 30% excess observed for chronic and acute lymphocytic leukemia, respectively, after 1970. The authors conclude that the different lymphocytic and myelocytic leukemia mortality rates among men hired before 1940 suggests that benzene was not entirely responsible for the excess of lymphocytic leukemia. However, no exposure assessment was performed.

Funded by Shell Oil Company. University of Alabama, Birmingham, AL.

Yin, S-N., Li, G-L., Tain, F-D., Fu, Z-I., Jin, C., Chen, Y-J., Luo, S-J., Ye, P-Z., Zhang, J-Z., Wang, G-C., Zhang X-C., Wu, H-N., Zhong, Q-C. A retrospective cohort study of leukemia and other cancers in benzene workers. *Environmental Health Perspectives* 82: 207-213 (1989).

The mortality among 28,460 workers in 233 factories in 12 cities in China who worked in operations with benzene exposure for at least six months between 1972 and 1981 was determined at the end of 1981. Their mortality experience was compared to that of individuals employed at 83 factories for at least six months during the same time period who had no exposure to benzene or other known occupational carcinogens. Exposure levels were determined from air measurements, the concentration of benzene in production materials, and records of devices used to reduce exposure. Most of the analysis in the paper was focused on leukemia, though more deaths due to lymphosarcoma occurred among men and women exposed to benzene than among the unexposed workers.

Funded by the Ministry of Public Health of the Government of China. Chinese Academy of Preventive Medicine, Beijing, China; Stations for Health and Prevention of Infection, China; China Institute for Prevention and Treatment of Occupational Disease, China

Yin, S.N., Hayes, R.B., Linet, M.S., Li, C.L., Dosemeci, M., Travis, L.B., Li, C.Y., Zhang, Z.N., Li, D.C., Chow, W.H., Wacholder, S., Wang, Y.Z., Jiang, Z.L., Dai, T.R., Zhang, W.Y., Chao, X.J., Ye, P.Z., Kuo, Q.R., Zhang, X.C., Lin, X.F., Meng, J.F., Ding, C.Y., Zho, J.S., Blot, W.J. A cohort study of cancer among benzene-exposed workers in China: Overall Results. *American Journal of Industrial Medicine* 29: 227-235 (1996).

The cohort included 74,828 individuals employed between 1972 and 1987 in 1427 benzene-exposed work units in 672 factories in 12 Chinese cities. Tasks performed by the exposed individuals included painting, printing, and manufacture of footwear, paint, and other chemicals. 35,805 controls were selected from unexposed work groups in 69 of these and 40 additional factories. Vital status was followed through 1987. Compared to the Chinese population of 10 cities in 1973-1975, there was a substantial mortality deficit, but mortality due to lymphoma was slightly elevated (SMR=1.2). Workers exposed to benzene had a 4.5-fold elevated relative risk for malignant lymphoma compared to unexposed workers. A relative risk of 3.0 for non-Hodgkin's lymphoma was seen among benzene-exposed workers, compared to unexposed workers. There was no increased risk for extranodal non-Hodgkin's lymphoma among benzene-exposed workers seen, but the relative risk for nodal non-Hodgkin's lymphoma and benzene exposure was 4.0. This study is limited by the short followup time and the limited ability of the researchers to verify all diagnoses of non-Hodgkin's lymphoma, as not all of the necessary tests had been performed.

National Cancer Institute, Bethesda, Maryland; Chinese Academy of Preventive Medicine, Beijing, China; Mayo Clinic, Rochester, Minnesota; Stations for Health and Prevention of Infection, Shanghai and Chonqing, China; Institutes of Labor Health and Occupational Disease, China

Zoloth, S.R., Michaels, D.M., Villalbi, J.R., Lacher, M. Patterns of Mortality Among Commercial Pressmen. *Journal of National Cancer Institute* 76: 1047-1051 (1986).

This study was requested by the union in response to a cluster of bladder cancers among commercial pressmen. A proportionate mortality ratio (PMR) analysis was undertaken among the union local members, which included journeyman commercial printers who have had at least a 5-year apprenticeship. Between 1958 and 1981, the death certificates of 1401 white male pressmen were identified from the union, which pays out benefits to the families of deceased members. Mortality was compared to the United States population. The PMR for all lymphatic and hematopoietic cancers was 122, based on 27 observed deaths. For other lymphatic cancers (ICD8 202 and 203) the PMR was 209. Seven cases of these other non-Hodgkin's lymphomas occurred among men less than 65 years of age, for a PMR of 388. There was a deficit in mortality due to leukemia. The actual exposures experienced by the pressmen were undefined. Historically, there has been widespread use of benzene as a solvent in the printing industry, but carbon disulfide and carbon tetrachloride may also have been used and have been associated with lymphomas. Hunter College of Health Sciences, New York, New York; Albert Einstein College of Medicine, Bronx, New York; Institut Catala de la Salut, Barcelona, Spain; Local 51 Graphics Communication International Union

REVIEWS, COMMENTS & LETTERS

Enterline, P.E. Letter: Lymphomas and Benzene. *The Lancet*. November 10: 1021 (1979).

This letter critiques the methods employed by Vianna and Polan. Vianna and Polan used death certificates and the U.S. Census to establish cause of death and occupation. The author notes, however, that while the U.S. Census reports the current or last occupation, the death certificate reports the usual occupation. This means that the occupations may not correlate, particularly when an individual is retired. The author suggests that the results of Vianna and Polan are artifacts and suggests that they use Milham's method to calculate proportionate mortality ratios. University of Pittsburgh, Pittsburgh, Pennsylvania

Goldstein, B.D., Shalat, S. Letter to the Editor: Non-Hodgkin's Lymphoma and Exposure to Benzene in Petroleum Workers. *Journal of Occupational and Environmental Medicine* 42(12): 1133-1134 (2000).

This letter includes three critiques of the meta-analysis by Wong and Raabe (2000). First, the authors believe that the meta-analysis is invalid because it does not show increased mortality due to acute myeloid leukemia, a cancer caused by benzene. Second, the authors feel that Wong and Raabe cannot justify the claim that there is no healthy worker effect occurring in the populations studied, particularly as previous studies by Wong have shown that the generally good health of workers can hide excess mortality due to non-Hodgkin's lymphoma. The third criticism is that the level of exposure to benzene (the dose) was not included in the meta-analysis. Environmental and Occupational Health Sciences Institute, Piscataway, New Jersey

Hayes, R.B., Linet, M., Dosemeci, M., Yin, S-N. Response to a letter by Wong, 1998. *Journal of the National Cancer Institute* 90(6): 469-71 (1998).

The authors agree with Wong (1998) that the earlier literature did not demonstrate an elevation in non-Hodgkin's lymphoma risk, but argue that this information is limited. Petroleum workers, for example, have relatively low exposures to benzene. Among the earlier studies of workers with substantial exposure, however, there were more cases of non-Hodgkin's lymphoma than expected. The authors conclude that their large study (Hayes *et al.* 1997) in China of workers with well-characterized exposure to benzene provides new data concerning the possible association of benzene with non-Hodgkin's lymphoma.

National Cancer Institute, Bethesda, Maryland; Chinese Academy of Preventive Medicine, Beijing, China.

Hayes, R.B., Songnian, Y., Dosemeci, M., Linet, M. Benzene and lymphohaematopoietic Malignancies in Humans. *American Journal of Industrial Medicine* 40: 117-126 (2001).

The authors review evidence implicating benzene in the etiology of an array of hematopoietic disorders, including lymphomas, and respond to the criticisms of the NCI/CAPM study of benzene-exposed workers in China by Budinsky *et al.* (1999) and Wong (1998, 1999). With regards to lymphomas, the authors note that lymphocytes in peripheral blood have been found to be the most sensitive hematological cell type to benzene exposure. Additionally, they note that several case control studies, cohorts of rubber workers, and their own study (Hayes *et al.*, 1997) have suggested a relationship between benzene and non-Hodgkin's lymphoma. The discussion of methodology in the NCI/CAPM study focuses on the exposure assessment, and clarifies the differences between the methodology in the NCI/CAPM and the CAPM study by Yin *et al.*

(1987, 1989). The authors reiterate their clear dose-response for benzene poisoning as an indirect validation of the exposure assessment in the NCI/CAPM study. The authors conclude that like all retrospective studies, the NCI/CAPM study has limitations, but that it has extended quantitative estimates of risk to levels of exposure below 10ppm, which heretofore had been lacking.

National Cancer Institute, Bethesda, Maryland; Chinese Academy of Preventive Medicine, Beijing, China.

Hotz, P., Lauwerys, R.R. Hematopoietic and Lymphatic Malignancies in Vehicle Mechanics. *Critical Reviews in Toxicology* 27(5): 443-494. (1997).

The authors critically examine studies that look at hematopoietic and lymphatic malignancies in vehicle mechanics. The percentage of benzene in gasoline is generally less than 5%, and measurements in garages during different operations showed that benzene exposure varies considerably according to the type of job, ranging up to 15ppm during 5 minutes. However, the 8-hour time weighted average is often below 1ppm. Vehicle mechanics may also have substantial skin exposure, and ingestion of benzene is possible during siphoning of gasoline by mouth. The authors did not find any convincing arguments to support a causal association between work as a vehicle mechanic and non-Hodgkin's lymphoma: The most powerful and well-designed studies did not find any evidence of an association, and the poorer methodology and power of the other studies did not explain the lack of association. The authors conclude that at best, there are indirect or weak arguments supporting an association between lymphatic or hematopoietic malignancies and work as a vehicle mechanic.
Catholic University of Louvain, Brussels, Belgium.

Infante, P.F., White, M.C. Benzene: Epidemiologic Observations of Leukemia by Cell Type and Adverse Health Effects Associated with Low-Level Exposure. *Environmental Health Perspectives* 52: 75-82 (1983).

The authors revisit and address critiques of the study of Pliofilm workers by Infante *et al.* (1977) and discuss cell types of leukemia associated with benzene. The authors note that several studies have reported increased risks for lymphocytic leukemia, and suggest that in other studies increased risks of lymphocytic leukemia were not detected because no cell-specific mortality analysis was undertaken. The authors conclude that epidemiologic studies have not been sensitive enough to determine the risk of death from cell types of leukemia that may have risk ratios of less than 5.0, though case series suggest an association between lymphatic leukemia and benzene.
Occupational Safety and Health Administration, Washington DC.

Infante, P.F. State of the Science on the Carcinogenicity of Gasoline with Particular Reference to Cohort Mortality Study Results. *Environmental Health Perspectives Supplements* 101(Suppl. 6): 105-109 (1993).

This manuscript was presented at the International Symposium on the Health Effects of Gasoline held in November 1991 in Miami, Florida. In the paper, Infante reviews the plausibility that benzene, as a contaminant in gasoline, can cause cancer at multiple sites, including kidney cancer, multiple myeloma, leukemia, and malignant melanoma. Infante notes that the rarity of multiple myeloma and its inclusion with other forms of lymphoma make the association between benzene and the cancer difficult to identify, but refers to studies of petroleum refinery workers and petroleum distribution workers which showed elevated risks for multiple myeloma. The biological plausibility is also discussed, and is based primarily on the fact that the bone marrow and cells of the B-lymphocyte lineage are targets of benzene. Multiple myeloma is a tumor of plasma cells within the bone marrow, which are derived from lymphocytes. The author concludes with a challenge to the American Petroleum Institute to develop a program to prevent the misuse of gasoline.

Occupational Safety and Health Administration, Washington DC.

McMichael, A.J. Carcinogenicity of Benzene, Toluene, and Xylene: Epidemiological and Experimental Evidence. In: *Environmental Carcinogens Methods of Analysis and Exposure Measurement Volume 10 – Benzene and Alkylated Benzenes*. Eds. L. Fishbein, and I.K. O'Neil. Lyon: IARC. p. 3-18 (1988).

In this chapter, the author reviews the evidence of benzene carcinogenicity in humans, evaluating the epidemiologic evidence, mutagenicity and chromosomal effects in humans, and experimental evidence in animals. The author concludes that while the epidemiological evidence is strongest for acute myelocytic leukemia, there is some evidence of increased risks for chronic myeloid and chronic lymphocytic leukemia, and that there is indication of a dose-related increased for total lymphatic and hematopoietic neoplasms. To illustrate the generalized effects on the lymphatic and hematopoietic tissues, he refers to experimental studies showing that benzene exposure depresses all lymphohematopoietic cell lines.

University of Adelaide, Adelaide, South Australia.

Niazi, G.A., Fleming, A.F. [Letter] Re: Benzene and the Dose Related Incidence of Hematologic Neoplasms in China. *Journal of the National Cancer Institute* 89(22): 1728-1729 (1997).

In response to Hayes *et al.* (1997), the authors convey a summary of their findings in a study of unofficial vendors of gasoline and motor mechanics of Nigeria, who sucked gasoline by mouth and smelled of oil and gasoline, and/or used gasoline products as skin cleansers. The authors report finding significant degrees of anemia, neutropenia, and thrombocytopenia in the roadside vendors compared with adolescent and adult control subjects. Motor mechanics also were at risk of anemia, while attendants at modern filling stations showed no significant differences from the control group. The authors note that the blood dyscrasias among roadside vendors and motor mechanics were certainly premalignant, so that some subjects will eventually develop aplastic anemia, acute myeloid leukemia, or non-Hodgkin's lymphoma.

Yale University School of Medicine, New Haven, Connecticut; University Teaching Hospital, Lusaka, Zambia

O'Conner, S.R., Farmer, P.B., Lauder, I. Benzene and Non-Hodgkin's Lymphoma. *Journal of Pathology* 189:448-453 (1999).

This paper is a succinct review of the mechanisms of benzene's toxicity and the chromosomal abnormalities associated with benzene exposure. The authors discuss exposure to benzene in the environment, including in the home, noting the difficulty of extrapolating the data obtained in the industrial setting to the possible risks of environmental benzene exposure. An additional consideration of the risks of environmental exposure to benzene is that vehicle exhaust, which contributes 70% of benzene in the environment, is a complex mixture of chemicals and particulate matter, many of which are highly toxic. The rise in environmental levels of benzene and related toxic compounds produced by increasing numbers of motor vehicles parallels the increased incidence of non-Hodgkin's lymphoma since the Second World War. The authors conclude that there is compelling evidence to suggest a role for several atmospheric pollutants, benzene being the most important, in the genesis of non-Hodgkin's lymphoma.

University of Leicester, Leicester, U.K; Leicester Royal Infirmary NHS Trust, Leicester, UK.

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).

The author impartially describes and summarizes the results of 45 epidemiologic studies that directly or indirectly looked for a relationship between organic solvents and non-Hodgkin's lymphoma. The author noted that of the 18 studies that defined exposure more accurately, 13 (72%) suggested organic solvent exposure as a risk for non-Hodgkin's lymphoma and often had statistically significant findings. 25 of the 45 studies (56%) reported a total of 54 statistically significant associations between non-Hodgkin's lymphoma and exposure to organic solvents, including benzene, and related occupations or industries.

Funded by Centro de Aperfeçoamento de Pessoal de Nivel Superior, Brazil

Savitz, D.A., Andrews, K.W. Review of Epidemiologic Evidence on Benzene and Lymphatic and Hematopoietic Cancers. *American Journal of Industrial Medicine* 31: 287-295 (1997).

The authors concisely review published studies that estimate exposure to benzene explicitly, generate risk estimates relating benzene exposure to lymphatic and hematopoietic cancers, and compare the risk for persons thought to be exposed to benzene to those not thought to be exposed. Of the eleven studies reporting on benzene and non-Hodgkin's lymphoma, only three studies provided support for the association. The other eight studies found relative risks in the range of 0.7 to 1.2, and included several of what the authors call large, well-designed studies. Both of the studies that examined lymphocytic leukemia and two of three studies addressing chronic lymphocytic leukemia generated relative risks of 1.5 or more. The authors conclude that the data is supportive of a rather broad effect of benzene on lymphatic and hematopoietic cancer or leukemia in general. The authors feel that the perception that the association between benzene and acute myelogenous leukemia dominates the overall pattern of association with leukemia is not supported by their review of the epidemiologic studies.

Funded by: The National Institute of Environmental Health Sciences. University of North Carolina, Chapel Hill.

Smith, P.R., Norelle Lickiss, J. [Letter] Benzene and Lymphomas. *The Lancet*. March 29: 719 (1980).

The authors attempt to confirm the findings of Vianna and Polan (1979) with data from their study in Tasmania. Using the census years 1971, representing a period just before diagnosis, and 1961, approximately 11-16 years before diagnosis, the proportion of workers in occupations listed by Vianna and Polan were determined, and the expected number of patients within five-year age groups calculated. These expected numbers of patients were compared to the employment history of male patients with Hodgkin's disease, non-Hodgkin's lymphoma, and acute leukemia participating in the Tasmania study. The authors did not find the observed number of patients with Hodgkin's disease and non-Hodgkin's lymphoma to be larger than expected. However, more patients were observed to have acute leukemia than expected, and the association with occupations identified by Vianna and Polan was greater in 1961 than in 1971, reflecting the suspected 10-year latency period in carcinogen exposure situations.

University of Tasmania, Australia

Wong, O., Bailey, W.J. [Letter] Epidemiologic Studies of Petrochemical Workers in California. *Journal of Occupational Medicine.* 36(1): 9-11 (1994).

This letter is a response to a discussion of occupational and environmental epidemiologic studies in Contra Costa County, California by Tsai *et al.* (1993). The authors argue that of the conflicting studies, the one by Austin *et al.* (1984), which did not find an association between industrial emissions and cancer in Contra Costa County, was methodologically superior to the study by Kaldor *et al.* (1984). The authors summarized the mortality experience of white male employees at three Chevron facilities in Contra Costa County, where slightly elevated mortality due to lymphosarcoma and other lymphatic tissue cancers were seen. None of the cause-specific standardized mortality ratios were significantly elevated, though the deficit in mortality due to all causes and all cancers suggest a significant healthy worker effect. The authors conclude that since there is substantial evidence that petrochemical employees in the county are not at increased risk of cancer or other disease, these facilities should pose no significant risk to residents in the surrounding communities. Additionally, when cancer incidence in census tracts downwind from the Chevron Richmond refinery were compared to three census tracts in West Oakland, where the author reports there are no major sources of industrial emission, the cancer incidence in the North Richmond census tracts was lower than in West Oakland.

Wong, O., [Letter] Re: Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China. *Journal of the National Cancer Institute* 90(6): 469-471 (1998).

This letter is a response to Hayes *et al.* (1997) in which Wong reports non-Hodgkin's lymphoma results that had not been published in his previous studies. Among 4062 workers exposed to benzene at seven U.S. chemical plants (Wong 1987, 1987, 1995), Wong reports that there were seven non-Hodgkin's lymphoma deaths, compared with 5.12 expected from the U.S. general population. The standardized mortality ratio (SMR) was 1.37. In a second study of 1165 men exposed to benzene at rubber hydrochloride plants and updated through 1987 (Wong 1995), three non-Hodgkin's lymphoma deaths were observed compared to 3.28 expected. Wong reports that in a study of 18,135 gasoline distribution workers (Wong *et al.*, 1993), no increased risk for non-Hodgkin's lymphoma was observed (SMR=0.42), based on 19 deaths. Wong also refers to eight case-control studies of non-Hodgkin's lymphoma and benzene published by other authors in which risk ratios ranged from 0.49 to 1.2.

Applied Health Sciences, San Mateo, California

Wong, O. Recent Findings and New Initiatives for Epidemiologic Research on Benzene. *Journal of Toxicology and Environmental Health, Part A.* 61: 457-466 (2000).

This paper is a critique of the methods employed in the NCI/CAPM study of benzene-exposed workers in China. The author feels that the increased mortality risk for all cancers, many of which have never previously been associated with benzene, raises concerns regarding the comparability of the unexposed workers to the exposed workers, the potential underascertainment of cancer among unexposed workers, and confounding exposures or other risk factors in the exposed group. The author also critiques the exposure estimates reported by Dosemeci et al. (1994), which he states were consistently lower than the actual exposure data reported by Dosemeci et al. (1994) and others. The author concludes that future benzene epidemiologic research should consider more thoroughly: exposure assessment, concomitant exposures, nonoccupational risk factors, specific characterization of hematologic malignancies, and the incorporation of biomarkers.

Applied Health Sciences Inc., San Mateo, California; Tulane University Medical Center, New Orleans, Louisiana.

Young, N. Editorial: Benzene and Lymphoma. *American Journal of Industrial Medicine* 15: 495-498 (1989).

This editorial discusses the relationship of benzene to the pathogenesis of lymphoma, and suggests three mechanisms. The first proposed mechanism is that benzene or a metabolite of benzene functions as a chronic hapten in inducing a lymphocytic response to bone marrow cells. The second mechanism proposed is that the DNA binding activity of benzene activates latent viruses. The third mechanism is based on the observations of chromosomal translocations involving the c-myc locus in some human lymphomas, implicating dysregulated oncogene expression in at least one stage of transformation. This means that benzene's reactivity with DNA, RNA, or proteins may affect the expression of genes that regulate cell proliferation.

National Heart, Lung, and Blood Institute, Bethesda, Maryland