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Benzene Related Hematological Disorders: Evidence for a Threshold in Animals and Humans

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Benzene Related Hematological Disorders: Evidence for a Threshold in Animals and

Humans

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
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Benzene Related Hematological Disorders: Evidence for a Threshold in Animals and Humans

James McCluskey

Abstract

Significant benzene exposure has historically been associated with the development of a host of hematological disorders in humans and animals. In particular, benzene is known to cause disturbances of the peripheral blood, aplastic anemia and cancer of the lymphohematopoietic system. In 1928, the first modern report of an association between cancer and benzene exposure was published. This case report was followed by additional reports from around the world. In most instances, ailments resulted from long term, high level exposure to benzene found in glues, and through accidental industrial spills. Throughout the 1960's and 1970's, case reports accumulated linking benzene exposure to hematological cancers, particularly among leather workers in Turkey and Italy. At the time, only qualitative measures of benzene exposure were often available and most exposure information was based upon short term grab samples and subjective symptoms. However, this situation changed drastically in the mid-1970s, when the first report was published on a little known industry that manufactured rubber hydrochloride, also known as Pliofilm. This clear film product was made from natural rubber latex and processing utilized benzene in multiple stages. It appeared from the outset that there were an unusually large number of acute leukemia cases in this cohort of workers. Since that time, multiple follow-up evaluations of the same cohort have attempted to refine the benzene exposure of these workers. Benzene has subsequently been classified as a human carcinogen by several regulatory bodies and the allowable 8 hour time-weighted average has been lowered to 1 ppm. In pursuing the goal of protecting workers, regulatory bodies utilize a linear extrapolation, or no threshold dose, approach to cancer causation. This methodology assumes that every exposure brings an incremental rise in risk. In this work, the linear extrapolation methodology is tested utilizing the criteria proposed by Sir Bradford Hill. The Hill Criteria are used to critically evaluate the weight of evidence for a threshold dose that can cause hematological cancer in humans following benzene exposure. This evaluation revealed that there is sufficient evidence for a threshold dose and that linear extrapolation is designed to protect, not predict disease.

Chapter One: Introduction

Most governmental organizations and regulatory bodies worldwide, including the U.S. Occupational Safety and Health Administration (OSHA), the U.S. Environmental Protection Agency (EPA) and the International Agency on Cancer Research (IARC), use a one-hit, linear model of cancer causation. Although this model is unproven, and in many cases is clearly incorrect, these bodies continue to assume that no threshold for carcinogenicity exists and each increase in exposure is accompanied by an incremental increase in risk of cancer. Further, the one-hit model assumes that a single, unique and irreversible event occurs in the genetic material of an organism and there is no repair of that injury. Yet, multiple DNA repair mechanisms are at work within all human cells and we repair and /or destroy damaged cells every minute of our respective lives.

Benzene is a very commonly used feedstock and industrial chemical throughout the world. In addition, low levels are found in ambient air throughout the world and in every human body. Common sources of benzene exposure include tobacco smoke, automobile emissions, products of combustion and drinking water. Historically, there has been a strong association between high benzene exposures, adverse health outcomes and cancer(s) of the blood-forming units. Although a no-threshold, linear extrapolation model is assumed by regulatory agencies, this is done with the express mission of protecting the health of the public. Inherent to this goal is the incorporation of multiple safety factors and the level propounded by a governmental body is not an absolute "red line" for disease. For instance, someone who is exposed to a substance at 1.01 part per million (ppm) for a working lifetime, versus the regulatory limit of 1.0 ppm, would not realistically have any excess risk above that of someone exposed to the regulatory level (Reference). And in fact, they may have no measurable risk at the regulatory limit. With that in mind, the stated purpose of this work is to thoroughly analyze both the human and animal data for evidence consistent with a threshold dose of benzene exposure at which no individual would be expected to develop a cancer of the hematopoietic system beyond the background rate of disease. It must be understood that "risk" is not "disease" – risk is a statistical measure that suggests a theoretical increase in probability of an adverse event, and is not an actual adverse event. Far too often, it is assumed that statistically significant "risk" is an absolute, and disease is simply a forgone conclusion.

In 1965, Sir Bradford Hill, an English statistician, elucidated a number of "criteria" that he felt should be considered when determining the validity of any causal association (Hill 1965). These criteria were in many ways a restatement of the scientific method – observe, hypothesize, empirically test, re-evaluate, consider all new knowledge and continuously eliminate or explain potential confounders as well as alternative explanations. The method is not necessarily a static process and solutions may change with acquisition of

new knowledge, or the dismissal of disproven hypotheses. Hill formulated the following criteria, and each is explained in terms of evaluating a threshold dose for benzene:

1. **Strength** – Does a certain dose cause a clearly elevated rate of cancer above that expected due to chance? Measurement of statistical significance is used to evaluate the likelihood of chance causation; however, it is not a measure of how large the effect is, or the "significance" of the finding. For instance, what does 0.1 deaths per million persons mean? Can this be assumed to mean that 1 person in 10,000,000 will die from this cause?

2. **Consistency** – Is there a dose at which no measurable increase in mortality occurs, no matter the investigator?

3. **Specificity** – Is there a dose at which the exposed person is at the same risk level as someone without any known exposure above the generally accepted background. Are there other causes of the disease that could explain the occurrence independent of the dose proposed?

4. **Temporality** – The disease must follow the exposure in a logical and explainable format. Is there an appropriate latency period?

5. **Biological Gradient** – Is there consistent dose response relationship?

6. **Plausibility** – This clearly depends upon the status of the knowledge base. Is there a dose at which the requisite sub-chronic effects are evident that will invariably lead to cancer?

7. **Coherence** – Is there suggestive animal evidence, or cell-based model evidence?

8. **Experiment** - If doses are reduced over time, is there a point at which the rate of cancer falls to an imperceptible rate above background?

9. **Analogy** – Are there other chemicals with similar mechanisms of action where a threshold is clearly evident?

Although not all of these criteria are relevant to this investigation, they serve as a guide for evaluating the existing literature on benzene-related hematopoietic cancer. This investigation was undertaken knowing that the majority of the medical literature searches for "statistical significance", yet this construct is frequently misinterpreted by medical and lay individuals. Over-analysis and dependence upon statistical measures of significance were addressed by Hill (Hill 1965), as follows:

> "…. there are innumerable situations in which they are totally unnecessary – because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance. What is worse the glitter of the *t* table diverts attention from the inadequacies of the fare."

If a "significant" finding is based upon an inadequate methodology, erroneous findings result. For instance, in order to ascertain whether there is a threshold dose for cancer causation by benzene from occupational exposure, a number of steps must logically follow: The dose must be accurately measured (exposure assessment), the disease of interest must be accurately and specifically identified in the exposed and unexposed populations, a

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matched comparison group must be evaluated and bias/confounding/modifying factors must be eliminated or controlled. In lieu of this methodology, laboratory investigations can be undertaken in a controlled environment in order to test the hypotheses. However, laboratory investigations can only offer so much information, particularly when attempting to extrapolate animal data to human beings. When using animal data to evaluate a scientific question the underlying question is always – What differences exist between an animal species and human being that may invalidate/modify the findings?

The vast majority of cases and cohorts detailing benzene and hematological cancer causation do not have quantitative measures of benzene exposure. Almost all of the early reports of an association had only qualitative metrics such as benzene content in products used by workers or subjective symptom reports. Although these reports are informative and important regarding uncontrolled exposure and the risk for adverse outcomes from benzene exposure, they are of minimal value for answering the question asked in this investigation. Since the recognition of the various disease processes related to excess benzene exposure, retrospective and prospective cohort investigations had been undertaken in several industries, particularly rubber hydrochloride (Pliofilm), various branches of petroleum companies, rubber products manufacturing, chemical synthesis, several manufacturing entities and rotogravure (printing). With that said, most do not have any way of estimating exposure beyond broad categories such as low, medium and high and therefore can offer little help determining whether a threshold dose exists, beyond qualitative information For practical purposes, the retrospective cohort and case-control study have been the most common methods used to study benzene exposure and health outcomes. Unfortunately, any retrospective occupational investigation examining exposures is subject to the limitations imposed by inadequate documentation, absent and inaccurate exposure measurements, as well as potential biases from multiple sources. Regarding benzene exposure, particularly related to the Pliofilm cohort, these limitations have provided ample fodder for publication, estimation and re-interpretation by a host of investigators. In addition to the Pliofilm cohort, several groups of exposed workers and cases have been studied in other industries where quantitative measures are available and the actual numbers and likelihood of disease can be compared to an estimated dose.

One of the primary challenges of studying benzene exposure and cancer causation in the current workforce is the welcome absence of cancer in presently exposed workers. In 1987, OSHA lowered the permissible exposure limit of benzene to 1 ppm over an 8 hour time weighted average. Some may argue that the lack of statistical significance between benzene exposure and cancer causation in current workers is *prima facie* evidence that a threshold exists and the current regulatory level is above that level; however, apparently self-evident hypotheses still need to be tested and proven, thus this investigation.

Question

Is there a threshold dose for benzene exposure where there is no theoretical risk for hematologic cancer?

Hypothesis of this Investigation

There is evidence to support a threshold dose for benzene where no theoretical risk for hematologic cancer would be expected.

Chapter Two: Methods

This investigation is a systematic, critical evaluation of the published literature detailing the relationship between benzene exposure and lymphohematopoietic cancer. Published literature is noted because some early investigations were undertaken by companies (particularly in the petroleum industry) and/or articles were only available in a foreign language. However, in the case of early internal company documents and studies, most have been written about in the publicly available literature by subsequent company investigators. For instance, every major petroleum company with operations in the United States (Exxon, Mobil, Shell, Texaco, Chevron and Union) has published mortality studies of their workforce(s) at various operations. Invariably, details of early company documents and studies have been included in the discussion section of the subsequent reports and information has been gleaned from these sources. Regarding the foreign literature, (French, Italian, Turkish, etc.) although many articles were obtained during the literature search portion of this investigation, only the abstract was typically available in English. With that said, most were case reports or case series and there were no instances found where benzene measurements were systematically compared with health outcomes. In the course of conducting this research, over 450 scientific articles and studies on benzene exposure, health effects, biomarkers and physiology were critically evaluated. Of these 450, approximately 50 articles were critical to understanding the issue of a possible threshold dose associated with benzene exposure.

As mentioned previously, most human studies to date have only looked at mortality and have not been capable of correlating a cumulative, peak or average benzene exposure in particular workers, with a health outcome. They have simply compared the rate of an outcome of interest with a population rate to ascertain if there is an increased risk of disease with the exposure. Alternatively, a large number of animal studies have been performed that look at not only outcomes, but also the associated dose. Yet, the exact metabolism of benzene is unknown in both humans and rodents, thus the question of human applicability always remains. From a purely practical standpoint, the lifespan of any rodent is years, versus the decade(s) of potential benzene exposure that are typically associated with human hematological cancers. In many cases, rodent data are only valuable for testing mechanisms versus health outcomes.

In addition to human cohort studies with no quantitative exposure estimates, there is a growing body of literature regarding human exposure that examines the sub-chronic effects of benzene exposure. This database includes studies on chromosomal aberrations, peripheral blood counts, metabolite production and biomarkers of exposure. Similar to the animal data, there are questions regarding the direct applicability of abnormalities in these measures and any relationship to eventual cancer causation. For instance, is benzene the only cause of

peripheral lymphocyte chromosomal aberrations, or is there a background rate of these in unexposed individuals that leads to no increased risk of developing a hematological cancer? In this investigation, the literature on the sub-chronic effects of benzene exposure was carefully and critically evaluated, particularly regarding any relationship to future cancer causation.

The primary information available that correlates exposure information with human cancer cases is limited to a relatively small number of studies. The most heavily studied group of workers in this cadre is the Pliofilm cohort, and in fact it is the only cohort judged to be adequate for risk assessment purposes by the U.S. Environmental Protection Agency (Infante, Rinsky et al. 1977; Infante 1978; Rinsky, Young et al. 1981; Rinsky, Smith et al. 1987; Paustenbach, Price et al. 1992; Crump 1994; Paxton, Chinchilli et al. 1994; Paxton, Chinchilli et al. 1994; Crump 1996; Schnatter, Nicolich et al. 1996; Rinsky, Hornung et al. 2002; Williams and Paustenbach 2003). This is primarily due to the limited exposures, except for benzene, that these workers could have possibly encountered while working at one of three rubber hydrochloride plants. In addition, there are two nested case-control mortality studies in the U.K. and Canadian petroleum industries, as well as, a nested case-control mortality and incidence study in the Australian petroleum industry (Schnatter, Armstrong et al. 1996; Rushton and Romaniuk 1997; Glass, Gray et al. 2003). Three series of studies in the American chemical industry also have estimates of exposure associated with disease outcomes (Ott, Townsend et al. 1978; Bond, McLaren et al. 1986; Wong 1987; Wong 1987; Ireland, Collins et al. 1997; Collins, Ireland et al. 2003; Bloemen, Youk et al. 2004). A cooperative study was started in the 1980s between the United States National Cancer Institute and the Chinese government agency responsible for worker health (Yin, Hayes et al. 1996; Yin, Hayes et al. 1996). This expansive study group attempted to incorporate *all* of the workers in industries with benzene and correlate their health outcomes with benzene exposure. In addition to the aforementioned studies, there are also three small studies that have examined hematopoietic cancer mortality and benzene exposure in caprolactam workers, shoe factory workers and gas/electricity utility workers. These studies are the total of human evidence available that directly links quantitatively measured benzene exposure with hematological cancer. For that reason, each study was critically evaluated, within the context of its underlying cohort studies (when applicable), and this evaluation is the primary work of this investigation. Although other studies can offer pieces of the puzzle, only these studies are "real-life" evaluations that measure actual cancer cases versus the calculated "risk" of cancer. As mentioned in the introduction section, the "risk" of disease is a mathematical consideration subject to re-interpretation, but only a case is an undeniable fact.

Critical evaluation of the literature has been mentioned throughout this section, yet, this deserves further explanation. Although the results of any study are potentially important, the results always depend upon the underlying question(s) asked, study design, methods of data collection, analysis method, comparison group(s), missing information and estimation procedures, study assumptions, biases, misclassification and confounders. In addition to surveying the literature results, each study has been carefully examined for any factor which detracts or limits the potential validity and implications of the findings. In many cases, the studies suffer from a lack of statistical power which could potentially be remedied by combining various cohorts. However, because of the divergent nature of the studies, it is

literally impossible to perform a meta-analysis of all studies. Only within industries utilizing similar methods can this hope to be accomplished. For this reason, a weight of evidence methodology based upon the criteria suggested by Hill has been used to draw conclusions in this investigation.

Interestingly, some of the most important reading that can be undertaken prior to examining the results of any study is found in the methods section and the last few paragraphs of the article. The methods section should tell you quite clearly if it is even possible to answer the questions posed in the investigation, as well as what is known about the factors that might impact upon the outcomes (confounder and modifying factors). Conversely, the last few paragraphs of most papers contain the limitations of the study, per the author(s). These are the two areas that this investigation primarily focused upon, in addition to the results.

In the following write-up of this investigation, the results section first details the seven groups of studies that have examined a correlation between quantitative benzene exposure and health outcomes, particularly hematologic cancer. In this portion of the results, a synopsis of the study description and study findings is presented. When multiple articles have been written by the author(s) about the same data, the articles have been presented together under the same heading. These grouped articles have only one description of the method and results. In most cases, each study, or group of related studies, is followed by the limitations of the respective study or studies, as determined by this investigator. However, in other instances there were no clear cut limitations that could be discerned from the information presented. With that said, there is no "perfect" study and an apparent lack of limitations may be the result of unstated limitations throughout the study series. For example, every study that draws conclusions about the Pliofilm Cohort includes the underlying uncertainty associated with the incomplete documentation of plant working conditions, equipment, personal protection use, as well as the inadequate industrial hygiene data available from the early years of Pliofilm production at both the St. Marys and Akron facilities. In addition, some primary research articles in the seven quantitative groups have been commented upon in editorials, as well as standalone articles have been written about the suspected deficiencies. These editorials and articles have been detailed immediately following the primary research article. In addition, any reply from the author(s) of the primary research study has been included, so as to capture their perspective on the editorial limitations.

The write-up detailing the quantitative study groups is followed by qualitative studies and finally the animal data for a threshold dose of benzene-related leukemogenesis. The qualitative studies are presented in table format, as this best lends itself to describing the vast number of studies and their associated findings. Alternatively, the animal data is broken into sub-chronic toxicity and carcinogenicity studies. The results are followed by a discussion section that consolidates and explains the data presented, as well as the limitations of the studies. The Hill criteria are then used to determine if adequate evidence exists to support a threshold dose for leukemogenesis following benzene exposure. Finally, the conclusions are stated, the limitations of this investigation are described and suggestions for future research are presented.

<center>**Chapter Three: Results**</center>

A. Evaluation of the Human Studies with Quantitative Exposure Measurements

1. The Pliofilm Cohort

Infante, P. F., R. A. Rinsky, et al. (1977). "Leukaemia in benzene workers." <u>Lancet</u> **2**(8028): 76-8. (Infante, Rinsky et al. 1977)

<center>-----AND-----</center>

Infante, P. F. (1978). "Leukemia among workers exposed to benzene." <u>Tex Rep Biol Med</u> **37**: 153-61. (Infante 1978)

<u>**Historical description, Cohort Description and Study Methods:**</u>

Natural rubber was masticated and then mixed with benzene in an agitating mixer. The solution was pumped to a blending tank and transferred in a reactor vessel where it was treated with hydrochloric acid to form rubber hydrochloride. Benzene was added to adjust the proportion of solids. This was then transferred to a neutralizing tank where scraps, soda ash, steam, plasticizers and more benzene were added. After filtration, the rubber hydrochloride was sent to a casting unit, benzene was evaporated and recovered, and finished film was taken onto a roll. The manufacturing process was essentially identical at both Ohio plants. In 1942, a management member recommended periodic air monitoring, complete blood counts for new employees and ventilation additions. Shortly thereafter, extensive ventilation equipment was installed in the Pliofilm department in one locality. In 1946, tests conducted by the Industrial Commission of Ohio in that department revealed that in most instances benzol concentrations ranged from zero to 10 or 15 parts per million. Between 1963-1974 benzene point source concentrations were measured by company personnel in 112 surveys. These indicated that benzene exposures were generally below the recommended limit in effect at the time of each survey. The allowable concentrations by time were as follows – 1941: 100 MAC, 1947: 50TWA, 1948: 35 TWA, 1957: 25 TWA, 1963: 25 Ceiling and 1969: 10 TWA.

Historical environmental data was missing for the second locality. Through the author's observations, discussions with company personnel, and meager environmental data it is suggested that the benzene exposure was generally well within the recommended limits.

Workers occupationally exposed to benzene in 1940-49 were followed for vital status up to 1975. Person-years of observation and causes of death were determined for the period

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Jan 1, 1950 to June 30, 1975. The cohort consisted of 748 workers, of which the vital status was confirmed for 75%. The missing workers were assumed to be alive for the purposes of the study. The data before 1950 was excluded because vital statistics on lymphatic and hematopoietic malignancies were not published before that date. Comparison was made between two control populations, the U.S. white male population standardized for age and time period, as well as, 1447 white men who had been employed in Ohio at a fibrous glass construction products factory during the same period.

Results:

There were a total of 140 deaths from all causes in the benzene-exposed workers which was below the expected number of 140. Compared to the two populations, there was a significant (p<0.002) excess of leukemia observed in the cohort. Seven deaths (four acute Myelogenous, 2 monocytic and 1 chronic Myelogenous) were recorded compared with an expected the number of 1.38 (p<0.002) for US white males and 1.48 (p<0.002) for the fibrous glass workers. The latency period from initial exposure to death was 2-21 years. There was a significant excess of hematopoietic deaths, with an SMR=506 (p<0.002) for all leukemias (ICD 204) and SMR=260 for malignancy of the lymphatic and hematopoietic systems (ICD 200-205) when compared to the US male population. The corresponding numbers for the fibrous glass workers was 474 and 176, respectively. When compared to the expected incidence for myeloid and monocytic and total leukemia form the Connecticut Tumor registry – 50.37% should be of this type. The expected deaths should be 0.6967 versus the 7 observed, resulting in an SMR of 1004. The authors concluded that there was a 10 fold risk of dying from myelogenous and/or monocytic leukemia in this cohort.

Limitations:
1. The vital information for the cohort was only 75% complete, thus cases may have been missed. This was rectified in a later analysis.
2. The exposures were considered to be same at each plant, although this was primarily due to a lack of measurements at the Akron facility.
3. The exposure assessment was a generalization indicating that exposures were mostly within the accepted regulatory limit at the time of exposure.
4. The authors studied only the "wet side" workers and assumed that the "dry side" workers had no benzene exposure.

Tabershaw, I. R. and S. H. Lamm (1977). "Benzene and leukaemia." Lancet **2**(8043): 867-9. (Tabershaw and Lamm 1977)

Comments about the Infante *et al.* (1977) Study:

In response to the above Infante article, two partial cohorts for plants 200 miles away where data was collected, analyzed separately and combined. They excluded workers from the "dry side" were benzene levels were still as high as 20 ppm up to 1974. This was based upon an environmental survey conducted by the Occupational Health Study Group at the

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University of North Carolina, School of Public Health (1974). They also excluded pipefitters, mechanics and maintenance workers and an unknown number of workers who left plant A prior to 1944. Workers at plant B worked only on Pliofilm, while those at plant A also worked in tire, hose, foams, rubber chemicals and metal products manufacture. They called into question the sensitivity and reliability of measurements in the range noted by Infante (10-15 ppm) at that time. A report by the Ohio Health Department at location A in the 1940's indicated a concentration up to 500 ppm. (Fluker, J.R. Division of Safety and Hygiene Report, Ohio State Department of Health, May 4, 1948.) In addition, measurements in the 1970s by the Occupational Health Study Group revealed levels as high as 355 ppm and means of 30 ppm (Environmental Survey, Occupational Health Study Group, University of North Carolina, School of Public Health, 1974.).

Case 1-5 came from location A (310 workers) and Cases 6-7 were from location B (436 workers), case 8 was at location B but was not part of the study cohort.   Plant A manufactured many products and workers moved from process to process, while workers at plant B tended to stay within the Pliofilm process.

The application of relative incidence of leukemia types to mortality is questionable because chronic leukemia lasts much longer. More appropriate calculations of age-specific mortality rate for specific types of leukemia by 5 year age groups for the USA from 1962-1967 can be calculated. The relative probability of specific leukemia type for a person dying of leukemia at a specific age can be calculated. Table II gives the expected distribution of leukemia by specific type for a group of 7 white males dying of leukemia at the same ages as in the reported cohort. "The differences between the observed and expected lies well within the realm of chance."

The vital status of 95% of the cohort has now been determined without any additional cases being identified.

Infante, P.F., Rinsky, R.A., Wagoner, J.K. and Young, R.J. Letter to the editor. Lancet ii: 868-869 (1977).

Response from the authors:

Men employed in Pliofilm operations but not on production jobs were never intended to be included. No details of the Environmental survey done by the University of North Carolina (sampling location, duration, analytical procedure or definition of department) was given to interpret the only data points (0.11,8 and 20 ppm) in that report. At least one pipefitter (not included in the study) had responsibilities in Pliofilm production and died of AML. An unknown number of workers in locality A left employment before 1944 and could not be included.

Job mobility, as judged by personnel records did not seem to be different at the two locations. The only common denominator of exposure at each locality was Pliofilm production.   The 500ppm noted by Tabershaw and Lamm was at the top of a tank. However, in some areas, high benzene concentrations existed where workers were present

intermittently. "There are conflicting reports of respirator use for workers entering those areas and it is impossible to determine exact exposure levels at which the cases of leukemia may have been induced."

In studies of long latency, calculations should be based upon age-specific person-years at risk. When reanalyzed the Lamm and Tabershaw age-specific leukemia mortality rates with age-specific person-years of observation, the results indicate 6 cases of AML and 1 monocytic leukemia observed versus 0.70 expected (SMR =857). This is a conservative estimate because acute leukemia rates include lymphatic leukemia and none where found in this cohort. With the new data up to July 22, 1977 the SMR is 560 (7 vs. 1.25). Thus the SMR increased.

Rinsky, R. A., R. J. Young, et al. (1981). "Leukemia in benzene workers." Am J Ind Med **2**(3): 217-45. (Rinsky, Young et al. 1981)

Cohort Description and Methods:

The cases were broken up into 2 groups: Group 1 consisted of 748 individuals who worked for at least 1 day between 01/01/41 and 12/31/1949. Group 2 consisted of 258 individuals who worked between 01/01/1950 and 12/31/1959. Vital status was ascertained for 98% of the entire cohort and the remaining 2% were considered to be alive as of the study end date 06/30/1975. Age and calendar year specific US white male death rates were used as referent rates to calculate the expected number of deaths for each temporal group. Mean duration of exposure to benzene was brief, and 437 (58%) of the cohort were exposed for less than 1 year. Location 1 (formerly location B in Infante study) operated from 1939 and completely ceased in April 1976. Location 2 (formerly location A in Infante study) had two plants that operated form 1937 – 1949 and 1949 to 1965, respectively. Almost all industrial hygiene data was generated from Location 1 (St. Mary's). At location 1, benzene concentrations prior to the installation of an exhaust system in 1946 are unavailable. The authors believe that benzene exposures at location 2 were similar to those at location 1.

Case Descriptions with abnormal notations
Case 2 – According to company records, it is alleged that on at least one occasion he entered a "quencher" in an attempt to break up some solidified soda ash. It is possible that exposure levels during this encounter were in excess of 1,000ppm.
Case 3 – Starting in 1944, he had other jobs in the plant but it is not known whether any of the other jobs involved exposure to benzene.
Case 4 – Starting in 1934 (up to 1959), he had other jobs in the plant but it is not known whether any of the other jobs involved exposure to benzene.
Case 5 – No environmental data exist prior to 1946, although concentrations of 100ppm were considered safe at the time. It is estimated that he had 40ppm 8-hour TWA from 1948-1959. At various times in his career at the plant he was involved in the manufacture of tires, where he probably had some exposure to solvents, although it is unknown if that included benzene.
Case 6 – He had worked at several jobs in the plant prior to starting in the rubber

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hydrochloride department which may have involved some contact with solvents. These solvents could not be determined.

Case 7 - He had worked at several jobs in the plant prior to starting in the rubber hydrochloride department which may have involved some contact with solvents. These solvents could not be determined.

Case 8 – Starting in 1952, he worked at several other jobs at the plant and it is not known if this involved potential benzene exposure. The benzene concentrations at the stripper rolls ranged from 66-680 ppm. These measurements represent peak exposure conditions, and the 8-hour time-weighted average exposures would have been considerably less.

Results:

A sharp increase in the SMR is seen among the group of workers exposed for longer than 5 years. Five leukemia deaths were seen whereas only 0.23 was expected (SMR =2100). When examined separately, location one had 2 cases of leukemia with only 0.58 expected (SMR =345). Location 2 had 5 cases with 0.67 expected, yielding an SMR of 746.

The case with the longest latency interval among the additional cases noted (did not fit in cohort) was in a worker whose mean benzene exposure was estimated to have been 16 ppm. There is no evidence to suggest that exposures between the two locations differed widely, either in type or in severity. Reliability of the instrumentation and methods used to measure these exposures were adequate for the levels being evaluated. The highest values observed were in areas not entered by workers or where they would have only occasional brief exposures. A tabular description of the cases is presented in the following pages.

Limitations:

1. The case descriptions are very informative and start to outline a persistent group of missing information that will never be accounted for, including: Lack of information regarding worker exposures prior to starting work at the Pliofilm plants, job mobility within the cohort (particularly to areas with exposures besides benzene) and inability to accurately estimate incident exposures such as peaks that are inherent to the worker and his practices versus the process related exposures. Although there are many estimations and assumptions regarding worker practices, personal protective equipment and potential for peak exposure the information is literally unverifiable.

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| Table 1 – Results for Group 1 Workers | | | | | | | | | |
| At least 1 day of Work in a Department with the Potential for Benzene Exposure between 1/1/40 and 12/31/49 – 748 individuals. | | | | | | | | | |
Case #	Age at Death	Year of Death	Cause of Death	Work Site	Work Type	Exposure Period	Benzene Exposure (years)	Latency (years)	Estimated Exposure (mean)
1	36	1958	Monocytic Leukemia (ICD 204)	Loc. 1	Casting Operator	12/30/40-03/20/42 04/13/42-07/14/42	1.5	17	Unknown prior to 1946
2	29	1950	Chronic Myelogenous Leukemia (ICD 204)	Loc. 1	Utility Operator*	08/23/48-09/30/48	1 month	2	35ppm*
3	60	1958	Acute Myelocytic Leukemia (ICD 204)	Loc. 2	Solution Neutralizer " "	08/21/45-10/03/45 07/18/45-08/21/45 03/10/47-06/13/49 09/23/49-06/24/53 08/11/53-11/26/58	11.5	13.5	35ppm
4	65	1960	Acute Myelocytic Leukemia (ICD 204)	Loc. 2	Casting Operator Cutting/Packing Film	01/19/49-09/19/49 05/17/50-02/26/58 09/19/49-05/17/50 02/26/58-03/31/58	8.5	10.5	40ppm
5	62	1961	Acute Myelocytic L:eukemia (ICD 204)	Loc. 2	Casting Operator Order preparation Rolling/inspecting film	05/11/39-11/13/40 03/30/48-12/08/59 12/08/59-12/21/59 12/21/59-04/10/61	13	22	Unknown prior to 1946 1948-1959 40ppm
6	57	1961	Acute Granulocytic Leukemia (ICD 204)	Loc. 2	Cement Mixer Casting Op Helper Casting Operator Supervisor	09/25/41-10/07/41 10/07/41-05/11/48 05/11/48-08/25/50 05/07/52-08/25/61 08/25/50-05/07/52	~20	~20	1947-1957 40ppm 1957-1961 25ppm
7	57	1957	Acute Monocytic Leukemia (204)	Loc. 2	Neutralizer Cameron machine operator Reactor operator Solution operator	06/15/42-08/27/47	~5	~15.5	<10ppm

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Table 2 – Results for Group 2 Workers									
At least 2 day of Work in a Department with the Potential for Benzene Exposure between 1/1/50 and 12/31/49 – 258 Individuals									
Case #	Age at Death	Year of Death	Cause of Death	Work Site	Work Type	Exposure Period	~Benzene Exposure (years)	Latency (years)	Estimated Exposure (mean)
8	28	1954	Myleogenous Leukemia (ICD 204)	Loc. 1	Utility Man Breakdown Mill Operator Casting Operator	5/31/50-7/20/05 7/20/50-9/27/50 3/10/51-1/23/52 9/27/50-3/10/51 1/31/52-2/17/52	1.5	3.5	Stripper rolls ranged from 66-680 ppm average less.

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Table 3-Additional Cases of Leukemia Deaths									
These workers were not included in either Groups 1 or 2 – Reason for Exclusion in Bold									
Case #	Age at Death	Year of Death	Cause of Death	Work Site	Work Type	Exposure Period	~Benzene Exposure (years)	Latency (years)	Estimated Exposure (mean)
9	67	1979**	Acute Myeloblastic Leukemia (ICD 204)	Loc. 2	Neutralizer operator	9/18/42-3/4/60	14	35	16ppm (Range 0-50ppm)
10	38	1955	Acute Myeloblastic Leukemia	Loc. 2	**Supervisor (salaried)**	1/16/48-6/30/49	~1.5	7.5	Unknown
11	58	1950	**Accidental Poisoning (ICD 961)** Leukemia Lymphocytic Aleukemia Phase	Loc. 2	Neutralizer Operator	10/07/37-4/28/41	3.5	~13	Unknown
1267	48	1958	**Benzol Poisoning (ICD 882)** Acute Myelocytic Leukemia	Loc. 2	Ass. Reactor Operator	7/10/50-1/09-52 8/13/52-5/21/54	~3 years	~6	Unknown

Infante, P.F. and M.C. White (1983). "Benzene: epidemiologic observations of leukemia by cell type and adverse health effects associated with low-level exposure." Environ Health Perspt **52**: 75-82.

Historical Context and Review:

Raised the fact that the previous evaluation by Rinsky et al. (Letter to the editor) that applied age specific death rates for acute and monocytic leukemia from the National Cancer Institute to the person-year distribution of the benzene exposed cohort was conservative. The expected number of deaths from acute and monocytic leukemia was calculated to be 0.70 with an SMR of 857. This SMR would be conservative because the rates included other types of cancer not seen such Acute lymphatic leukemia. A 29 year old with Chronic Myelogenous leukemia was not included because he died within 2 years of initial exposure to benzene. It is possible that he died of AML.

Commented about the Thorpe *et al.* paper and the methodological deficiencies: 1) The age breakdown of the entire population was unobtainable and had to be estimated from the age distribution of one company's work force. 2) The mortality rates used to generate the expected number of leukemia deaths reflect an average mortality experience of only some of the eight countries included. 3) Many companies had no mechanism which assured that the death of the worker or the cause of death would be reported to the company, and therefore an unknown number of deaths were missing from the analysis. 4) No verification of cause of death or of diagnosis of leukemia was available. 5) Infrequent monitoring and incomplete occupational histories made it difficult to distinguish persons exposed to benzene from those not exposed.

Brief *et al.* estimated that in petroleum refineries, the probability of benzene levels exceeding 1 ppm TWA is less than 5%, and in petrochemical plants, the probability of benzene levels exceeding 5 ppm TWA is less than 8%.

Scottenfeld reported an excess of total leukemia but was not statistically significant (11 observed vs. 7.56 expected), but the excess in the incidence of specifically lymphocytic leukemia was significant (7 observed vs. 2.56 expected, p=0.03).

In 1965, Browning reviewed the literature and found 61 reported cases of leukemia among persons exposed to benzene: 6 acute myeloid, 1 subacute myeloid, 21 chronic myeloid, 7 lymphatic, 14 aleukemic and 12 erythroleukemic.

Vigliani and Forni remarked on 44 persons with chronic benzene exposure in Paris form 1950 to 1965, including 23 cases of acute leukemia, 13 chronic myeloid leukemia and 8 chronic lymphocytic leukemia.

Aksoy reported on 42 workers with chronic benzene exposure in Turkey, including 16 acute myeloblastic, 8 acute erythroleukemia, 7 preleukemia, 4 acute lymphoblastic leukemia, 3 acute monocytic leukemia, 2 chronic myeloid leukemia and 1 acute Promyelocytic and acute undifferentiated leukemia.

The epidemiological studies by Infante and Ott were of insufficient sample size and sensitivity to detect excesses in types of leukemia that may not demonstrate a risk as high as that for myelomonocytic leukemia. For example the statistical power of the Infante *et al.* study to detect a two-fold excess risk in types of leukemia other than acute or monocytic leukemia (at the 0.05 α level) was only 0.10.

The author commented upon threshold. Two studies conducted by Dow Chemical suggest that adverse health effects can be caused by exposure to benzene at average concentrations of less than 10 ppm. Ott suggested that all three workers had been exposed to benzene at TWA

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concentrations less than 10 ppm. A second study by Dow researchers demonstrated a significant increase in structural chromosome aberrations in workers whose average benzene exposures were below 10 ppm. Shown at OSHA docket. Data from cytogenetic studies shows that the percentage of workers who had cells with chromosome breaks was significantly greater for the benzene exposed group. Moreover, the percentage of workers who had both chromosome breaks and marker chromosomes was ten times higher among the benzene exposed workers. A later analysis showed chromosomal damage at exposures averaging below 2.5 ppm, as well as a dose-response relationship between chromosomal damage and benzene exposure level. Although there was a discrepancy between controls, who were much younger, and the exposed, large population studies have shown that cytogenetic breakage is not associated with age. An analysis of the distribution of benzene workers in this study with both chromosome breaks and markers showed no difference related to age. (Picianao, 1979)

For the Infante *et al*. (1977) study, the calculation of the risk assessment was based on the experience of cohort members with 5 years of work experience or more (5 observed versus 0.23 expected SMR =2100) They made two assumptions, 1) They were exposed for 5 years to estimates of average benzene exposure between 1937-53 and 30 years to average benzene exposure between 1937-75. Since dose response data were not available, the one-hit model was used to estimate the excess leukemia risk which could have result from a working lifetime exposure (assumed to be 45 years) at the current (10ppm) and proposed (1 ppm) PEL. The number of excess leukemia deaths at 10ppm for 45 years was 44-152 per 1000 exposed workers. The number of excess leukemia deaths at 1 ppm for 45 years was 5-16 per 1000 exposed workers.   In the Ott *et al.* study exposure to 10ppm for 45 years would result in an excess number of myelogenous leukemia deaths was estimated to be 48-136.3 per 1000 and 5 - 15 deaths at 1 ppm. "Because any risk assessment is attended by a great deal of uncertainty, these figures should be interpreted with caution."

The author concluded that epidemiological studies of workers exposed specifically to benzene have been too insensitive to determine the risk of death from cell types of leukemia that may have risk ratios of less than 5.0. Case series have indicated associations with chronic leukemia and lymphatic leukemia. Cytogenetic studies have indicated damage at levels below 10ppm.

Rinsky, R. A., A. B. Smith, et al. (1987). "Benzene and leukemia. An epidemiologic risk assessment." <u>N Engl J Med</u> **316**(17): 1044-50. (Rinsky, Smith et al. 1987)

Historical Context and Methods:

The three analyses completed by White *et al*, the EPA and IARC indicated that the amount of benzene exposure has been found to correlate positively with the risk of death from leukemia. All three, however, were based on estimates of group exposure rather than on estimates of the exposure of individual workers. The resultant risk estimates were therefore subject to wide variances.

This is an update of the original Pliofilm cohort with 6.5 more years of observation which updated the analysis to 1982. In addition the life-table analysis system of NIOSH were modified to allow incorporation of data on individual exposures, whereas previous analysis only the duration of employment could be used as a surrogate for exposure. The authors reiterated that "benzene was the only chemical in the rubber hydrochloride plants that could reasonably be associated with hematologic toxicity". The rubber hydrochloride plants were located within larger industrial facilities. Employees were likely during their working careers to have worked in areas of these facilities where materials other than rubber hydrochloride were produced."

Each unique rubber hydrochloride job title (described in a short narrative on the personnel record) was assigned a numerical code. Job codes and employment dates were then abstracted for each employee who had worked in a rubber hydrochloride department. Because of the large number of job codes, all workers were fitted to broader categories, referred to as "exposure classes," which could be associated with specific manufacturing areas. In general, exposure classes represented areas in which industrial hygiene measurements had been collected. In some instances, job titles did not readily fit into a single area; in such situations, hybrid exposure classes were developed.

A job-exposure matrix, which tabulated exposure-class codes by year, was constructed for each of the two locations. Cells for which no data where available were completed by interpolation between available previous and subsequent values. When interpolation could not be performed because no measured value existed for an exposure class in the first or last year of the study, the nearest measured value for that exposure class was projected forward or backward. "Processes and job assignments were essentially identical at both locations, so benzene exposure levels measured at Location 1 were assumed to be naturally occurring simulations of exposure levels in corresponding areas at Location 2, when actual exposure measurements did not exist."

A total of 1165 workers with at least 1 ppm-day of cumulative exposure through December 31, 1965 were included in the cohort. Vital status was ascertained for the cohort through December 31, 1981. Sixteen were lost to follow-up (1.4%).

Results:

There was a statistically significant increase in deaths from all lymphatic and hematopoietic neoplasms (15 observed vs. 6.6 expected, SMR 227 95% CI: 127 - 376. This was primarily due to the excess numbers of deaths from leukemia. With stratification according to levels of cumulative exposure, the SMR for leukemia increased from 109 to 322 (<40 ppm-years), 1186 (40-199 ppm-years) and 6637 (>400ppm-years). Even with halving and doubling of the respective cumulative benzene exposure categories (0 to 19, 20 to 99, 100 to 199 and >200 ppm-years, as well as, 0 to 79, 80 to 399 and >400 ppm –years) in both instances the SMR continued to show a strong trend of increasing risk with increasing exposure ($x\frac{1}{2}$ = 134, 277, 0 and 2338 and $x2$=141, 609 and 6833).

From the case-control analysis 10 controls were matched with each case (cases had a mean cumulative exposure of 254 vs. 50 ppm-years). Average duration of exposure was 8.7 years for the exposed and 2.6 years for the controls. The controls were chosen from among the cohort members still alive at the time of death of the corresponding case. They were

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matched by year of birth and the year first employed The case control study was intended to: 1) Evaluate the exposure terms that govern the relation between the risk of death from leukemia and exposure to benzene, 2) evaluate the effect of potential confounders and effect modifiers on this relation, and 3) identify the functional form of the exposure-response relation. .

After examining several models, the first examination looks at cumulative exposure, duration of exposure and average exposure rate. In the three separate models, cumulative exposure (ppm-years) was found to be the strongest single predictor of death from leukemia (ß=0.0126; 95% CI: 0.0028 to 0.0224; chi-square =6.4, P=0.011). "In this model, only cumulative exposure was found to contribute materially to the risk of death from leukemia, although it is not possible with only nine cases to establish cumulative exposure as the unqualified best expression."

To examine the shape of the exposure-response relation, a conditional logistic-regression analysis was performed, in which 10 controls were matched to each cohort member with leukemia. The exposure-response function was evaluated by logarithmic transformation (chi square=4.86; p=0.027) of cumulative exposures vs. untransformed cumulative exposures (chi-square=6.4) the untransformed fit the model best. A quadratic was added to form the odds ratio for leukemia in relation to cumulative exposure to benzene. OR = exp(0.0126 x ppm-years) From this equation, the average cumulative exposure of the cases and controls (69 ppm-years) was found to produce an odds ratio relative to the unexposed workers of 2.4 (95% CI 1.2 to 4.7). Upon re-examining the effect of cumulative exposure, the odds ratio increased slightly (ß = 0.0169), as did the statistical significance of the observation (chi-square=6.7; P=0.010).

The authors concluded that an average exposure level of 10 ppm for 40 years would have an increased risk of death from leukemia of 154.5 (95% CI: 3.1 – 77.85). At 1 ppm, the increase would be 1.7 (95% CI: 1.1 to 2.5) and at 0.1 ppm the increase would be virtually equivalent to the background risk (OR, 1.05 with CI: 1.01 to 1.09).

A tabular description of the Pliofilm cohort is detailed in the following pages.

Comments on Rinsky 1987 article:

Max Bader – No employee first exposed after 1954 had leukemia or myeloma, even though hiring continued for 11 years and even though 7 of the 13 cases had the onset of disease within 20 years of first exposure. Cases were followed through 1981, so there should have been some cases). In the study, two subjects died within 3.5 years of exposure. Looking at the year of initial exposure of the 13 cases, one can see that 9 had first exposures before the end of World War II. One wonders about the measuring instruments in that situation.

The authors responded that the most likely explanation for this finding is a reduction of cumulative exposure; relatively few workers were hired after 1954 and among those workers, total lifetime exposure was kept low by decreases in production and progressive diminution in exposure standards.

			Benzene Exposure Rinsky 1981 (years)	Benzene Exposure Rinsky 1987 (years)	Latency Rinsky 1981 (years)	Latency Rinsky 1987 (years)	Estimated Exposure Rinsky 1981 (mean)	Estimated Exposure Rinsky 1987 (ppm-years)
Table 4- A Comparison of Case Details Between the 1981 and 1987 Rinsky et al. Analyses								
Case #	Age at Death	Work Site	Benzene Exposure Rinsky 1981 (years)	Benzene Exposure Rinsky 1987 (years)	Latency Rinsky 1981 (years)	Latency Rinsky 1987 (years)	Estimated Exposure Rinsky 1981 (mean)	Estimated Exposure Rinsky 1987 (ppm-years)
1	36	Loc. 1	1.5	1.5	17	17	Unknown prior to 1946	49.99
2	29	Loc. 1	1 month	1 month	2	2	35ppm*	0.010
3	60	Loc. 2	11.5	11.5	13.5	13.5	35ppm	259.50
4	65	Loc. 2	**8.5**	**14**	**10.5**	**15.5**	40ppm	498.23
5	62	Loc. 2	13		22	22	Unknown prior to 1946 1948-1959 40ppm	478.45
6	57	Loc. 2	**~20**	**20**	**~20**	**20**	1947-1957 40ppm 1957-1961 25ppm	639.84
7	57	Loc. 2	~5	**5**	**~15.5**	**15**	<100 ppm	98.55
8	28	Loc. 1	1.5	1.5	3.5	3.5	Peak 66-680 average less	10.16
9	67	Loc. 2	14	14	35	37	16 ppm (Range 0-50)	252.66

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Case No.	Age at Death	Year of Death	Latency[*] (yr)	Cause of Death[†]	Corroborating Medical Reports	Plant Location: Duration of Employment	Cumulative Benzene Exposure (ppm-yr)
				Table 5 - Descriptions of Deaths from Leukemia and Multiple Myeloma in 13 Workers Exposed to Benzene			
1	36	1958	17	Monocytic Leukemia (204)	None available	Location 1: 1 ½ yr.	49.99
2	29	1950	2	Chronic Myelogenous Leukemia (204)	Hospital, autopsy, tissue slides	Location 1: 1 mo.	0.10
3	60	1958	13 ½	Acute Myelocytic Leukemia(204)	Hospital, hematologist	Location 2: 11 ½ yr.	259.50
4	65	1960	15 ½	Acute Myelogenous Leukemia (204)	Hematologist, hospital, tissue slides	Location 2: 14 yr.	498.23
5	62	1961	22	Di Guglielmo's Acute Myelocytic Leukemia (204)	Hospital, physician	Location 2: 13 yr.	478.45
6	57	1961	20	Acute Granulocytic Leukemia (204)	Hospital, tissue slides, autopsy	Location 2: 20 yr.	639.84
7	57	1957	15	Acute Monocytic Leukemia (204)	Tissue slides	Location 2: 5 yr.	98.55
8	28	1954	3 ½	Myelogenous Leukemia (204)	None available	Location 1: 1 ½ yr.	10.16
9	67	1979	37	Acute Myeloblastic Leukemia (204)	None available	Location 2: 14 yr.	252.66
10	69	1980	25 ½	Multiple Myeloma (203)	None available	Location 1: 1 ½ yr.	19.50
11	52	1963	22 ½	Multiple Myeloma (203)	Hospital	Location 1: 4 days	0.11
12	62	1968	24 ½	Plasma-cell Sarcoma (203)	Hospital	Location 1: 23 yr.	652.66
13	68	1981	26 ½	Multiple Myeloma (203)	None available	Location 1: 9 mo.	7.75

[*]Latency was defined as the length of time (in years) from the date of first exposure until death.
[†]In parentheses is the *International Classification of Diseases* code as determined by a nosologist from information on the death certificate.

R.A. Rinsky, A.B. Smith, R. Hornung, T.G. Filloon, R.J. Young, A.H. Okun and P.J. Landrigan. 1987. Benzene and Leukemia: An Epidemiologic Risk Assessment. *The New England Journal of Medicine* 14(2): 1044-1050.

Rinsky, R. A. (1989). "Benzene and leukemia: an epidemiologic risk assessment." <u>Environ Health Perspect</u> 82: 189-91. (Rinsky 1989)

This was very similar to the 1987 article by the same author. Subsequent to the previous analysis (Rinsky 1987) they learned of another leukemia death among the cohort. Ten additional controls were chosen and the case-control analysis was repeated. This resulted in slightly lower odds ratio but increased the statistical significance of the relationship. The data from this additional case serves as additional corroborating evidence.

(From Rinsky 1987 article) "It is of interest that the deaths from multiple myeloma occurred among the group with the lowest cumulative exposure to benzene (<40 ppm) and that all four required exceptionally long latency periods for hematologic malignancies (>20 years). This raises the possibility that low cumulative exposure to benzene may produce relatively well differentiated malignancy such as multiple myeloma, whereas higher exposures lead to leukemia." (From this article) "It is conceivable that the progressive reduction in benzene levels which has been achieved over the last several decades, may lead to a situation in which multiple myeloma will in the future become manifest in a large population of workers with relatively low cumulative exposures to benzene. The present observations must, however, be interpreted cautiously in absence of further corroborations."

Lamm, S. H., A. S. Walters, et al. (1989). "Consistencies and inconsistencies underlying the quantitative assessment of leukemia risk from benzene exposure." <u>Environ Health Perspect</u> **82**: 289-97. (Lamm, Walters et al. 1989)

Review of Methods and Comments:
This paper deals with the concept of consistency among the studies that generally support the concept of an association between benzene exposure and excess risk of leukemia within the studies critical to the quantitative assessment of that risk. In particular, the NIOSH study by Rinsky *et al*. is closely examined the consequences of the findings upon the possible dose response are determined.
The 2 primary classes of leukemia emanate from distinctly different cell lines, lymph tissue and marrow. These classes are further divided into acute and chronic subtypes. The particular type of leukemia most closely associated with benzene exposure, acute myelogenous leukemia, includes a number of further subtypes such as
myeloblastic, promyelocytic, myelomonocytic, monoblastic, erythroleukemic and megakaryoblastic. It contradicts our present understanding of cancer for a particular carcinogen to produce one type of leukemia in some people and another type in other individuals. Although it is possible, such a finding would suggest a different metabolic pathway and in the case of benzene there is no evidence to suggest that is the case.
Regarding the Ohio Pliofilm cohort, Plant 1 was established in 1939 and continued manufacturing Pliofilm until 1976. Plant 2A at Location 2 in Akron, Ohio commercially produced Pliofilm from 1936-1949 and Plant 2B produced Pliofilm from 1949-1965. The

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authors of the NIOSH study asserted that the benzene exposure for Pliofilm processed at each of these 3 plants was identical, although all of the benzene measurements came from plant 1. This has to be taken as a matter of faith.   All of the AML cases came from one location – Plant 2A – where no benzene-exposure data was available, while no cases of AML were diagnosed among workers at Plant 1 and 2B where some benzene exposure data are available. All the cases of AML occurred in workers hired at Plant 2A prior to 1945. None of the workers hired at Plant 2A from 1945 to 49 or at Plant 2B from 1949 to 65 has been reported to have any type of leukemia. None of the workers hired at the Plant 1 from 1939 to 1965 has been reported to have AML although the follow-up periods range from 16 to 42 years. The cohort of people from Plant 2A has incomplete personal records from that location. Records prior to 1945 were missing, except for records of people who continued to be employed after 1945, yet were hired prior to that point. Among the cohorts for whom employee rosters are complete, there is no known case of AML. This would suggest that exposures prior to 1945 were critical. See table 6 below for a breakdown of cases by location, diagnosis, year of hire, latency, year of death and cumulative benzene exposure.

Table 6 - Case List of Leukemias and Multiple Myelomas Ordered by Location and Year of Hire (11)					
Location	Diagnosis[a]	Year of Hire	Latency Years	Year of Death	Cumulative benzene Exposure, ppm-year
2	AML	1939	22	1961	478.5
2	AML	1941	20	1961	639.84
2	AMoL	1942	15	1957	98.55
2	AML	1942	37	1979	252.66
2	AML	1944	13.5	1958	259.5
2	AML	1944	15.5	1960	498.23
1	MM	1940	22.5	1963	0.11
1	MoL	1941	17	1958	49.99
1	PCS	1943	24.5	1968	652.66
1	CML	1948	2	1950	0.1
1	ML	1950	3.5	1954	10.16
1	MM	1954	25.5	1980	19.5
1	MM	1954	26.5	1981	7.75

[a]AML, Acute Myeloid Leukemia; AMoL, Acute Monoblastic Leukemia; MM, Multiple Myeloma; MoL, Monocytic Leukemia; PCS, Plasma Cell Sarcoma; CML, Chronic Myeloid Leukemia; ML, Myeloid Leukemia.

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S.H. Lamm, A.S. Walters, R. Wilson, D. Byrd and H. Grunwald. 1989. Consistencies and Inconsistencies Underlying the Quantitative Assessment of Leukemia Risk from Benzene Exposure. *Environmental Health Perspectives* 82: 289-297.

The AML cases in the study had latency periods ranging from 13.5 to 37 years, with a mean of 20.5 years. Typically, AML secondary to chemotherapeutic agents have a latency ranging from 0.5 to 10 years and a mean range of 2-5 years. In addition, the latencies reported by Rinsky are long when compared to other benzene exposed groups. Analysis of literature in the 1980's showed that 80% of benzene-associated leukemia deaths occurred no more than two years after the last benzene exposure.

Rinsky estimated that the AML cases at Location 2A have a cumulative benzene dosage 250 - 650 part per million years, yet all of the data that forms those measurements come from Location 1. In addition the workforces at the two plants differed in their potential for exposure to benzene and other chemicals in the non-Pliofilm job sites. Plants 2A and 2B were part of a large industrial tire building complex, while Location 1 a stand alone plant. In addition, exposure levels were considered to be the same when exposure data existed at one plant and this was also extrapolated when no exposure data existed. For instance, one job had measurement data for 1976 only, so it was assumed that this was the same level in 1945. Alternatively, Crump and Allen developed an exposure assumption in 1984 in which they estimated cumulative benzene exposure, as well as peak intensity exposure. To calculate or estimate exposure levels for jobs during time periods for which data existed, they calculated all exposure data for a particular job as a percentage of the allowable level at that time and then applied that percentage or proportion to each time period. Given the earlier example, with the extrapolation from 1976 to 1945, the Crump and Allen data would find a value of 150 ppm versus the 15 ppm determined by Rinsky.

Due to the different methods of extrapolating exposures, the Crump and Allen exposures are generally much higher than the Rinsky estimations. In addition, Rinsky limited the analysis to the "wet side", while Crump included these workers. It was reported that the odor of benzene was "perceptible" on the dry side of the process in the 1940s. The estimations of Crump and Allen are corroborated by the study performed by Kipen *et al*. which analyzed the available hematology data on the Pliofilm cohort. This analysis revealed a correlation coefficient for the white blood cell counts of 0.72 with the Crump and Allen data versus 0.03 for the Rinsky data when looking at the years 1940-1948. Unfortunately, by eliminating the dry side workers, Rinsky limited the inclusion and analysis of lower level exposures.

The authors noted that they found it "difficult to accept that the benzene exposure levels at Location 2, where all the AML cases occur, could have been the same as exposure levels at Location 1 where no AML cases occurred." They further noted that they would have reported the risk analyses separately for the two facilities. When comparing the two exposure estimates, there is a statistically significant excess of leukemia with the Rinsky measures at >40 ppm, while the Crump and Allen only achieves statistical significance with >250 ppm.

The Rinsky assumptions conclude that a statistically significant leukemia risk exists

with peak benzene exposure over 20 ppm and a work/life average exposure over 6 ppm. Alternatively, the Crump assumption, using the same model, included a statistically significant leukemia risk with peak exposure over 250 ppm and a work/life average exposure over 11 ppm. That would be 450 ppm-years divided by 40 years equals 11.25 ppm. The determination of risk is clearly dependent upon the methodological assumptions made in analyzing in the data. This data suggests a nonlinear dose-response relationship and threshold toxicity.

Byrd, D. M. and E. T. Barfield (1989). "Uncertainty in the estimation of benzene risks: application of an uncertainty taxonomy to risk assessments based on an epidemiology study of rubber hydrochloride workers." <u>Environ Health Perspect</u> **82**: 283-7. (Byrd and Barfield 1989)

  The impact of uncertainty about the structure of a risk model will vary with exposure level. For example, simple substitution of a quadratic term for cumulative exposure in the retrospective case-control formula results in a difference of two orders of magnitude in risk at 5 ppm-year instead of 500 ppm-year (0.0004 instead of (0.03), using the 1981 data. The 1987 data of Rinsky *et al*. improves the measurement uncertainty by about an order of magnitude, whereas the effect of a quadratic term on risk magnitude remains the same. Further, extrapolation to environmental levels of benzene (5-0.5 ppb) results in a five to six orders of magnitude difference in risk if a quadratic term is used.   Use of a quadratic term instead of a linear term constitutes a minimal change in methodological assumptions.

  Confounding factors such as sources of benzene exposure other than inhalation, systematic errors in exposure measurement, joint effects of other substances with benzene, indirect effects of benzene exposure through other effects on hematologic status, correlated exposure of benzene with other substances, skew in population age or chance occurrence could hypothetically explain the association seen among the cohort.

  "Disagreements about appropriate values for parameters derived from a study for a risk model (for example, the number of observed cases, population at risk, exposure levels, duration of exposure, latency of effect and/or appropriate control group for comparison) usually do not obtain much attention. This paper suggests that for benzene the preoccupation is justified. Methodological uncertainty constitutes the major source of uncertainty in benzene risk estimates."

  In animal studies, intermittent exposure to high concentrations of benzene also creates greater risk than continuous exposure. And current understanding of the effect of benzene on synchronization of hematopoietic cells does not suggest a linear dose-response relationship (Irons 1979).

Paustenbach, D. J., P. S. Price, et al. (1992). "Reevaluation of benzene exposure for the Pliofilm (rubber worker) cohort (1936-1976)." <u>J Toxicol Environ Health</u> **36**(3): 177-231. (Paustenbach, Price et al. 1992)

Results:

The results of this re-evaluation agreed far more with the estimates of Crump and Allen versus the Rinsky estimates. The estimates presented in this paper and Crump's were both ~5x greater with every job title when compared with the Rinsky data. However, there were two differences from the Crump data noted by the authors: 1) the average concentration of the two active facilities were higher than the estimate and 2) the wet side exposures, particularly the neutralizer, were higher than those for the dry side workers represented by the operator. The Paustenbach analysis incorporated new information into their model, including data about the accuracy of the measuring devices used to gather the existing industrial hygiene data, particularly from the early years of operation; evidence of extended work weeks beyond the 40 hours per week assumed by Rinsky *et al.*; the fact that the St. Marys facility was shut down during WWII; medical evidence of elevated exposure (Kipen, 1988) in the early years of operation; evidence of improved engineering controls over time (thus assumptions of the same exposure over time are incorrect); incorporation of dermal exposure into the model; changes in some exposure categories for certain jobs (based on new interview information)

The sensitivity analysis showed that no single factor produced a major change in the overall estimate exposure. For example, the assumption of higher workplace concentrations during the early years of production raised the estimates of exposure by 20%. The assumptions of an increased work week and use of personal protection devices changed the average estimate by less than 15%. During the 1940-1949 period, the assumption of increasing workplace concentration during the early years of production raised estimates of exposure by 30%. The role of erroneous analytical measure had only a minor impact on the estimates of exposure in either location.

The conclusion that Pliofilm manufacture was a relatively high exposure job was based on four factors.

1. Medical and clinical items of toxicity in Akron St. Mary's workers.
2. Evidence of significant engineering changes in St. Mary's in 1946 and at Akron
3. Industrial hygiene experience in other industries.
4. The higher TLVs that were in place in the 1940s and 50s

The lack of Pliofilm manufacture at St. Mary's from 1942-1945 raised a potential contradiction with the findings of Kipen *et al*, regarding the effects on blood. In the Kipen *et al* study, the workers blood count showed some indication of improving blood count in 1943; however, in 1946 when production resumed the blood counts did not fall. It is possible that this is related to how the records were kept.

For a number of reasons, some caution should be used in interpreting the data from the Pliofilm cohort. There may an effect that selected for tolerance, as there can be significant differences in inter-individual susceptibility to the effects of benzene. For instance, a susceptible person may have left the workforce due to forced removal following a decreased blood count. Second, some workers may have had additional, unaccounted for benzene exposure due to other workplace exposures.

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Crump, K. S. (1994). "Risk of benzene-induced leukemia: a sensitivity analysis of the Pliofilm cohort with additional follow-up and new exposure estimates." J Toxicol Environ Health **42**(2): 219-42. (Crump 1994)

Historical Description and Methods:

Three sets of exposure estimates have been proposed for the Pliofilm cohort, including Rinsky 1987, Crump and Allen 1984 and Paustenbach 1992. The primary differences between the evaluations have centered on the different methods used to estimate the exposures in the early years of production for very limited air monitoring data. The Paustenbach estimates are more consistent with the Crump and Allen versus the Rinsky data.

This paper updated the risk assessment of Crump and Allen up to 1987 and incorporated the exposure matrix of Paustenbach. A sensitivity analysis was performed to evaluate the effect of model assumptions on the risk estimates. Several dose response models were examined, including models that allow nonlinear dose response relationships. In addition, the fidelity of various models in describing the underlying data was studied.

Dose response modeling was conducted for AMML and total leukemia. Two of the leukemia cases were of an unidentified type. The background rates used in the life table analyses and dose response modeling were as follows: AMML - 1973 - 1977 US mortality date, U.S. white males, ICD code 205 acute granulocytic leukemia and 206, acute monocytic leukemia, all leukemia - 1975 U.S. white males, ICD codes 204 to 207, all lymphatic and hematologic cancer - 1975 U.S. white males. These periods were considered reasonable because the leukemia rates were stable over time during the follow-up period. For all leukemia, all lymphatic and hematopoietic cancer, the total mortality and the background mortality rates used were 1988 U.S. rates for all races and sexes.

Results:

Presented below in Table 7 is the life table analysis of the association of various categories of hematopoietic cancer with cumulative exposure based upon the Paustenbach exposure matrix. Three categories are considered – AMLL, all leukemia and total lymphatic/hematopoietic cancer. AMML had the strongest dose response and the other two are not significant if AMML is removed. None of the non-AMML leukemias were associated with exposures of <400 ppm, while five of the AMM cases were associated with exposures greater than 1,000 ppm-years. Thus, AMML was the only response clearly related to benzene exposure.

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Table 7 - Summary of Information on 21 Cases of Lymphatic and Hematopoietic Cancer Deaths in Males

Location[a]	Case[b] number	Year of: Death	Cumulative Exposure (ppm-yr) Crump and Allen	Paustenbach	Leukemia	AMML[c]
S	1	1958	381	127	X	Y
S	2	1950	3	3	X	
A	3	1958	251	1054	X	X
A	4	1960	1497	1242	X	X
A	5	1961	939	1122	X	X
A	6	1961	2155	1771	X	X
A	7	1957	307	670	X	Y
S	8	1954	23	54	X	
A	9	1979	325	1129	X	X
S	10	1980	31	51		
S	11	1963	0	0		
S	12	1968	1148	3075		
S	13	1981	16	12		
S	14	1973	54	651		
S	15	1978	175	138		
A	16	1984	65	338	X	
A	17	1985	18	598	X	X
S	18	1985	145	293	X	
S	19	1986	50	12	X	?
S	20	1987	6	8	X	?
A	22	1987	0	19		

[a]S, St. Marys; A, Akron.
[b]Case number 1-13 provided by Rinsky et al. (1987) and 14-22 by Paxton et al. (1994a). Case number 21 was a female and was excluded from the present analysis.
[c]Includes acute myelocytic (X) and acute monocytic leukemia (Y).

K.S. Crump. 1994. Risk of Benzene-Induced Leukemia: A Sensitivity Analysis of the Pliofilm Cohort with Additional Follow-up and New Exposure Estimates. *Journal of Toxicology and Environmental Health* 42: 219-242.

Table 8 - Observed and Expected Numbers of Cancer Deaths by Cumulative Exposure (Paustenbach et. al. Exposure Matrix) for Different Categories of Lymphatic and Hematopoietic Cancers

Cumulative exposure, ppm-yr range (mean)	Person-years	AMML			Leukemia			Total Lymphatic and Hematopoietic		
		OBS	EXP	RR	OBS	EXP	RR	OBS	EXP	RR
0-45 (11)	30,482	0-2[a]	0.82	0.0-2.4	3	2.41	1.2	6	6.16	1.0
45-400 (151)	16,320	1	0.51	2.0	4	1.50	2.7	6	3.83	1.6
400-1000 (602)	4867	2	0.22	9.1	2	0.65	3.1	3	1.65	1.8
>1000 (1341)	915	5	0.06	82.8	5	0.18	28.1	6	0.44	13.5
Total (132)	52,584	8-10	1.61	5.0-6.2	14	4.75	2.9	21	12.09	1.7

Note. AMML, combined acute myelogenous (AML) and acute monocytic leukemia (ICD codes 205.0 and 206.0). Leukemia, ICD codes 204-207. Total lymphatic and hematopoietic, ICD codes 200-209. OBS, number of observed cancer deaths. EXP, number of expected cancer deaths based on U.S. sex- and age-specific rates. RR, OBS/EXP.
[a]Two leukemias could not be identified as to type.

K.S. Crump. 1994. Risk of Benzene-Induced Leukemia: A Sensitivity Analysis of the Pliofilm Cohort with Additional Follow-up and New Exposure Estimates. *Journal of Toxicology and Environmental Health* 42: 219-242.

The two exposure matrixes (Paustenbach and Crump) lead to different conclusions concerning the shape of the dose response. With the Crump and Allen matrix the dose response is essentially linear and there was little evidence of intensity dependent nonlinearity. The dose responses derived using the Paustenbach exposure matrixes found that each of the three best fitting models were quadratic and departures from linearity with borderline significant in each case. The Paustenbach analysis was much more in-depth than the Crump and Allen analysis of exposure and likely provides a better representation of exposures in the cohort. Nevertheless, uncertainty still remains with regard to exposures during the earliest period of the plant. The Paxton study (1994) revealed that the average exposure predicted from the Paustenbach matrix was ~2x greater than the Crump and Allen exposure matrix and ~4x greater than the Rinsky exposure matrix.

Existence of nonlinearity in the dose responses derived from the Paustenbach exposure matrix provide some limited support for the Paustenbach matrix over the Crump and Allen matrix. "Random errors in classification of exposure will tend to obscure any nonlinearity that may be present in the dose response. Thus, if the true dose response is nonlinear, then a more accurate exposure characterization will tend to exhibit more nonlinearity. On the other hand, if a dose response is truly linear, then random errors in exposure characterization will tend to reduce the magnitude of the effect of exposure, but will not tend to make the dose response appear to be nonlinear."

The Rinsky exposure matrix did not conform to blood count data for this cohort as well as the Crump and Allen exposure matrix. Based on a study of over 17,000 peripheral blood counts collected from 459 workers at St. Mary's between 1940 and 1975, Kipen found that higher benzene exposure during the 1940s were consistent with the blood count data. An alternative hypothesis proposed by Hornung (1989) suggested that the temporal increase in blood counts was likely due to changing laboratory practices. However, this was not consist with a follow-up study which showed a decrease in white blood cell counts of approximately 1,000 cells/mm^3 during the first four months of employment in workers. This was not consistent with the Rinsky, but was best explained by the Crump and Allen exposure matrix.

Crump concluded that it was not possible to accurately determine the amount of nonlinearity present in the dose response curve based on the information now available from the cohort. Additional follow-up with the cohort should help to clarify the best response. It is possible that other measures of intensity dependent nonlinearity may be more appropriate, and if so, they might indicate nonlinearity more clearly.

Paxton, M. B., V. M. Chinchilli, et al. (1994). "Leukemia risk associated with benzene exposure in the Pliofilm cohort. II. Risk estimates." Risk Anal **14**(2): 155-61. (Paxton, Chinchilli et al. 1994)

-----AND-----

Paxton, M. B. (1996). "Leukemia risk associated with benzene exposure in the Pliofilm cohort." Environ Health Perspect 104 Suppl 6: 1431-6.(Paxton 1996)

Study Description and Methods:

An absolute or at least a functional threshold seems possible for benzene induced by benzene; however, the conservative assumptions of regulatory agencies mandate the use of a linear dose mathematical model.

In this study a proportional hazards analysis was used to examine more than 4x as much information (35% v. 8%) as the conditional logistic regression previously used. Most importantly, it allows the incorporation of quantitative estimates of individual worker benzene exposure accumulated during the course of their employment. In contrast, the much more crude SMR technique considers only broad exposure categories. Proportional hazards analysis also reduces the possibility of arbitrary allocation of control by grouping controls with the cases in uniform strata. In the table below the additional number of leukemia deaths based upon the Rinsky and Crump & Allen exposure estimates are presented.

Table 9 - Previous Estimates[4] of Additional Leukemia Deaths[a] Derived Using the Conditional Logistic Model on the Pliofilm Cohort Updated

Exposure Estimates	Control Set	Cumulative Occupational Benzene Exposure[c] (ppm-years)	
		45	450
Rinsky[2]	Selected by Rinsky[3]	5.1 (0.8-12)	640 (16-990)
	Matched on plant, date of birth, start of Pliofilm job	4.2 (1.0-8.7)	450 (21-950)
Crump[6]	Selected by Rinsky[3]	0.5 (0.1-1.0)	8.3 (1.4-20)
	Matched on plant, date of birth, start of Pliofilm job	0.5 (0.1-1.0)	7.9 (1.1-20)

[a]Estimated mean number of leukemia deaths over the lifetime of 1000 exposed individuals in excess of an assumed background rate of 7.07[13] (95% confidence interval).
[b]All estimates based upon 10 controls matched to each of the original nine leukemia cases.
[c]Stated occupational exposure assumed to result from exposure to a concentration of 1 or 10 ppm for 8hr/day, 5 day/week, 50 week/year.

M.B. Paxton, V.M. Chinchilli, S.M. Brett and J.V. Rodricks. 1994. Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort. II. Risk Estimates. *Risk Analysis* 14(2): 155-161.

Paxton, M. B., V. M. Chinchilli, et al. (1994). "Leukemia risk associated with benzene exposure in the Pliofilm cohort: I. Mortality update and exposure distribution." Risk Anal **14**(2): 147-54. (Paxton, Chinchilli et al. 1994)

Study Description and Methods:

In the recent update of the Pliofilm cohort by NIOSH, only the wetside worker vital status data was updated, thus they are the only workers included in the SMR analysis. An additional 123 deaths were identified. In the update period 4,759 person years were accrued in addition to the 35,586 person years that had been recorded by the end of 1981. Loss to follow-up was minimal—2.6% through 1981 for the dryside workers and 0.9% for the wetside workers. All workers were retained and this resulted in a total cohort of 1,212 wetside workers. Estimates of cumulative exposure were derived from the three exposure matrices (Rinsky, Paustenbach and Crump). The table below revises the SMR calculations with the updated (1981 and 1987) information.

Table 10 - Summary of Changes in SMRs with Update[a]								
	Update of Status Through:							
	1981				1987			
	Observed	Expected	SMR	95%CI	Observed	Expected	SMR	95% CI
Death	358	352.22	1.02	0.91-1.13	481	468.22	1.03	0.94-1.12
Nonmalignant diseases of blood and blood-forming organs	4	0.86	4.65[*]	1.27-11.90	4	1.21	3.31	0.90-8.47
Cancer	72	70.88	1.02	0.79-1.28	111	102.57	1.08	0.89-1.30
Lymphatic and hematopoietic cancers	15 (9 leukemias, 4 multiple myelomas, 2 others)	6.93	2.16[*]	1.21-3.57	21 (14 leukemias, 4 multiple myelomas, 3 others)	9.51	2.21[*]	1.37-3.38

[a]N=1212 white male wetside workers; person-years start accumulating on 1/4/40.
[*]*p* Value <0.05 by two-sided Poisson test.

M.B. Paxton, V.M. Chinchilli, S.M. Brett, and J.V. Rodricks. 1994. Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: I. Mortality Update and Exposure Distribution. *Risk Analysis* 14(2): 147-154.

No new cases were reported in the update and the original statistically significant SMR of 4.65 decreased to a non-significant value of 3.31 for the nonmalignant diseases of the blood. For all types of cancer, the SMR remained non-significant. There were no new deaths from multiple myeloma in the 1987 update with the addition of 5 new deaths from leukemia and 1 from lymphoma left the SMR for all lymphatic and hematopoietic cancers

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literally the same. However, the SMR=2.21 and was still significant. The table below describes the SMRs for leukemia by update and location.

Table 11 - SMRs for Leukemia in Pliofilm Workers[a] by Update and Location						
Location	Update Through	Person-Years[b]	Observed	Expected	SMR[c]	95% Confidence Interval
All	1981	35,587	9	2.86	3.15[**]	1.44-5.98
	1987	40,345	14	3.89	3.60[**]	1.97-6.04
St. Marys	1981	19,945	3	1.26	2.38	0.49-6.95
	1987	22,807	6	1.79	3.36[*]	1.23-7.31
Akron	1981	15,642	6	1.60	3.76[*]	1.37-8.18
	1987	17,358	8	2.10	3.81[**]	1.64-7.51

[a]White male wetside workers.
[b]Accumulation of person-years started on 1/1/40 or at the start of the first Pliofilm job, whichever was later.
[c]p Values by two-sided Poisson test.
[*]$p < 0.05$
[**]$p < 0.01$.
M.B. Paxton, V.M. Chinchilli, S.M. Brett, and J.V. Rodricks. 1994. Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: I. Mortality Update and Exposure Distribution. *Risk Analysis* 14(2): 147-154.

With the 1987 update and 5 new leukemia cases the SMR increased form 3.15 to 3.60 with a narrower confidence interval. In addition, the addition of 3 cases at St. Mary's made the relationship statistically significant.

Table 12 - Distribution of Cumulative Exposures[a]					
	Exposure Estimates for Job Categories (% in cumulative exposure category)				
	Rinsky[2]		**Crump[5]**		**Paustenbach[6]**
Cumulative Exposure (ppm-years)	**St. Marys**	**Akron**	**St. Marys**	**Akron**	**St. Marys**	**Akron**
0	10.9	19.0	0.2	4.9	0.6	4.4
>0-5	52.6	32.0	44.3	34.4	31.0	15.5
>5-50	23.3	27.2	31.9	33.3	35.6	31.6
>50-500	12.3	20.6	20.9	22.4	25.2	34.3
>500	0.9	1.2	2.7	5.0	7.6	14.2
	100.0	100.0	100.0	100.0	100.0	100.0
	Estimates for this cohort[a] (ppm-years)				
	Rinsky[2]		**Crump[5]**		**Paustenbach[6]**
Descriptive Statistics	**St. Marys**	**Akron**	**St. Marys**	**St. Marys**	**Akron**	**St. Marys**
Median	1.0	4.7	7.2	10.9	14.8	46.0
Arithmetic mean	33.1	44.7	63.6	100.3	112.4	199.0
Maximum	728.0	815.2	1724.9	3185.5	3066.2	2321.6

[a]For white male wetside and dryside workers, $N=958$ at St. Marys and $N=759$ at Akron.

M.B. Paxton, V.M. Chinchilli, S.M. Brett, and J.V. Rodricks. 1994. Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: I. Mortality Update and Exposure Distribution. *Risk Analysis* 14(2): 147-154.

Interestingly, the exposure estimates for the two facilities is divergent: St. Mary's has an even spread and Akron has almost all of the leukemia cases clustered in the higher portion of the exposure distribution.

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Table 13 - Estimated Cumulative Exposures of Male Leukemia Cases[a]				
		Cumulative Exposure (ppm-years)		
Location	**Case no.[b]**	**Rinsky[2]**	**Crump[5]**	**Paustenbach[6]**
St. Marys	1	49.8	379.4	126.2
	2	0.1	2.8	2.6
	8	10.1	22.6	54.3
	18	61.7	144.4	286.1
	19	6.5	49.6	11.4
	20	0.7	6.5	8.5
	Average of male cases	21.5	100.9	81.5
	Average of male controls[c]	33.2	63.3	112.6
Akron	3	258.9	250.5	1051.2
	4	496.8	1492.6	1238.5
	5	474.3	937.2	1119.6
	6	638.8	2148.6	1765.8
	7	98.3	305.6	668.2
	9	252.1	323.9	1125.9
	16	90.3	64.6	337.4
	17	0.9	14.7	596.2
	Average of male cases	288.8	692.2	987.8
	Average of male controls[c]	43.1	94.0	190.6

[a]The female case (#21) had cumulative values by the three estimates of exposure of 0.0, 8.5 and 161.3 ppm-years, respectively.
[b]As in Table IV.
[c]For white male wetside and dryside controls, N=952 at St. Marys and N=751 at Akron.

M.B. Paxton, V.M. Chinchilli, S.M. Brett, and J.V. Rodricks. 1994. Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: I. Mortality Update and Exposure Distribution. *Risk Analysis* 14(2): 147-154.

For 5 of the 14 male leukemia cases of Crump is higher than the Paustenbach estimate. Overall, the Crump exposure estimates give a lower mean value for the controls versus the Paustenbach exposure estimates. At St. Mary's, however, the mean cumulative

exposure for the cases using the Crump exposure estimates is greater than that derived using the Paustenbach estimates, and the Paustenbach estimates actually give lower estimated average exposure for the cases than for the controls.

Table 14 - SMRs for Leukemia in Pliofilm Workers[a] by Cumulative Exposure at All Locations						
Exposure Estimates	**Cumulative Exposure (ppm-years)**	**Person-years**	**Observed**	**Expected**	**SMR[b]**	**95% Confidence Interval**
Rinsky[2]	0-5	18,178	3	1.52	1.97	0.41-5.76
	>5-50	13,456	3	1.31	2.29	0.47-6.69
	>50-500	8,383	7	1.01	6.93[**]	2.78-14.28
	>500	328	1	0.05	20.00	0.51-111.4
Crump[5]	0-5	12,974	1	1.14	0.88	0.02-4.89
	>5-50	13,951	4	1.23	3.25	0.88-8.33
	>50-500	11,448	6	1.23	4.87[*]	1.79-10.63
	>500	1,972	3	0.29	10.34[**]	2.13-30.21
Paustenbach[6]	0-5	9,645	1	0.75	1.33	0.03-7.43
	>5-50	12,882	2	1.12	1.79	0.22-6.45
	>50-500	14,095	4	1.43	2.80	0.76-7.16
	>500	3,723	7	0.59	11.86[**]	4.76-24.44

[a]White male wetside workers.
[b]*p* Value for two-sided Poisson test.
[c]*p* <0.05; [**]p<0.01

M.B. Paxton, V.M. Chinchilli, S.M. Brett, and J.V. Rodricks. 1994. Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: I. Mortality Update and Exposure Distribution. *Risk Analysis* 14(2): 147-154.

When evaluating the three sets of exposure estimates, there is a strong dose-response relationship, no matter the estimate. However, none of the estimates have a statistically significant increase in the SMRs for cumulative exposure < 50 ppm-years. This is consistent with the hypothesis that exposure in excess of some threshold value is necessary for leukemogenesis. The absence of any additional cases of multiple myeloma and the updates for 1987 weakens to non-significance the previous statistical association of this endpoint with benzene exposure. Tables 12, 13 and 14 present the information related to the three exposure matrices.

The 1987 update continues to be consistent with a threshold model of benzene leukemogenesis. All leukemia deaths in the cohort have occurred in individuals who began working prior to 1950, the period of time with the greatest likelihood of high exposures. The simplest explanation would be that industrial hygiene improved in both locations over the years and achieved a critical level of reduced benzene exposure in the early 1950s so that workers entering the workplace after that time were no longer at risk for developing leukemia. Alternatively, this phenomenon may be due to a lack of statistical power.

Utterback, D. F. and R. A. Rinsky (1995). "Benzene exposure assessment in rubber hydrochloride workers: a critical evaluation of previous estimates." <u>Am J Ind Med</u> **27**(5): 661-76. (Utterback and Rinsky 1995)

Methods:

This report critically examines the analysis of Paustenbach in 1992. Paustenbach based his upward adjustments on the following data:

1. Inaccuracy of benzene analytical methods employed for historical measurements.
2. Estimated length of the work week at two of the three plants.
3. Installation and use of exhaust ventilation controls.
4. Benzene absorption through the skin of workers in the cohort.
5. Selection and use of respirators by the workers.
6. Evidence of overexposure and available medical information for the plant.

Results:

Based upon the benzene predictions suggested by Paustenbach, there would likely have been an "epidemic" of deadly non-malignant blood disorders in these workers; however, this did not occur. Recent information from the WHO, indicates that a prolonged level of >100 ppm exposure who cause ~10% aplastic anemia. Yet, less than 2.3% of the Pliofilm workers developed this condition.

Only five lines of reasoning that are problematic are currently reviewed in this paper, including:

1. Review of the use of engineering controls rubber hydrochloride plants.
2. A search in the terminal exposure to benzene substantially added to the total body burden so that the estimates of exposure should be adjusted upward.
3. Series of arguments that actual measurement data reflect background "concentrations" instead of peak exposures.
4. Contention that the methods used to estimate exposure concentrations in the earlier years were biased low.

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5. The ramifications of the method developed by Crump and Allen made TLV based adjustments to more recent exposure estimates in order to estimate earlier exposure concentrations.

The 1942 Department of labor conference proceedings outline a great deal of information about the local exhaust ventilation in the plant. The plant physician stated, "At present, benzol is used in the manufacture of Pliofilm, but in an enclosed system." Control of benzene emissions from the spreaders was provided by "hooded ventilation with suction above and forced general ventilation in the room." Concentrations of benzene in the vicinity of the rubber hydrochloride spreader units was stated in the proceedings to be controlled to a level "in the neighborhood of 20 to 60 part per million". These were not noted by Paustenbach in his analysis.

In addition, the conference proceedings conflict with several statements about the general ventilation of the facilities. In 1946, the first engineering control measure was installed in the Pliofilm facility. A report in 1946, indicated that, "extensive exhaust equipment had recently been installed for the elimination of benzol vapors generated by presses", and that "tests were made with benzol detectors and the results indicate the concentrations have been reduced to a safe level, and in most instances range from 0 to 10 or 15 part per million". This was not mentioned in the Paustenbach exposure matrix. Samples collected several years later after engineering control showed levels of 19 to 50 ppm. The State of Ohio included that the filter press ventilation system was sufficient to maintain benzene concentrations below 100 part per million and typically below 35 part per million. In addition, the 1946 report stated that, "concentrations have been reduced to a safe level and in most instances range from 0 to 10 or 15 part per million". These values are consistent with the levels measured in 1974-1975 (6-10 ppm).

Another area of concern was dermal absorption, which Paustenbach estimated to be far greater than the Rinsky measurements. In addition, the rubber hydrochloride component would result in significant skin irritation if it was applied as often as indicated by Paustenbach. For this reason, the frequency and duration of contact selected by Paustenbach also appeared overestimated.

Regarding the representativeness of benzene samples, Paustenbach had questions regarding detector tube accuracy and believed that they underestimated the actual concentration of benzene in the air at the time of measurement. By his own admission, Hayes' results are inconsistent and unreliable, and therefore, do not support the adjustments made by Paustenbach.

Regarding a TLV ratio method related to Crump and Allen, their method of adjustment assumes that as the TLV becomes more restrictive benzene exposures in industries were lowered, presumably through work practice and engineering control measures. Therefore, Crump contends that exposure for historical periods may be reasonably estimated based on proportionate changes in the TLVs for benzene. Crump increased recent benzene exposure estimates for specific job titles by the ratio of the historical TLV to the TLV at the time of the measurements. This has been suggested elsewhere. When Paustenbach, et al applied this method to the rubber hydrochloride cohort, the Crump and

Allen estimates for many job titles exceeded 250 part per million annual average exposure concentration for many consecutive years. These estimates seem unrealistic high. In addition, the Crump estimates for the entire facility include annual average benzene exposure concentrations greater than the TLV eight-hour time weighted average for workers in seven out of eight job titles for the period of 1958 to 1965, and for six out of eight job titles for the period of 1949 to 1957. It is illogical on one hand to argue that the industry was sensitive to TLVs and would lower their exposure concentrations accordingly, while on the other hand showing the same industry in gross violation of those limits for the majority of the workers. In addition, there are other contradictions in the Paustenbach results when he used the Crump and Allen method of adjusting the exposure measures.

In conclusion, Paustenbach used select information to adjust the previously reported benzene exposure estimates for the rubber hydrochloride worker cohort. Multiple adjustments of early monitoring results by a number of factors were apparently based on worst case assumptions. Their factors are determined through extrapolation of the data collected under substantially different and frequently unknown conditions. In addition, some reconstructed measures have cohort members exposed to prolonged levels greater than 100-200ppm, levels that would result in epidemic blood disorders. There have been no reports of substantial engineering improvements after 1942 to limit benzene exposure to a large number of cohort members over the decades of operation at St. Mary's and Akron.

Wong, O. (1995). "Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene." <u>Occup Environ Med</u> **52**(6): 380-4. (Wong 1995)

Table 15 - Acute Myeloid Leukemia by Cumulative Exposure to Benzene			
	Deaths		
Cumulative Exposure (ppm-years)	**Obs**	**Exp**	**SMR (95% CI)**
<40	1	0.84	1.19 (0.03-6.63)
40-200	0	0.25	0 (0-14.75)
200-400	2	0.07	27.21[**] (3.29-98.24)
>400	3	0.03	98.37[**] (20.28-287.65)
Total	6	1.19	5.03[**] (1.84-10.97)

[**]P<0.01.

O. Wong. 1995. Risk of Acute Myeloid Leukaemia and Multiple Myeloma in Workers Exposed to Benzene. *Occup Environ Med* 52: 380-384.

Table 16 - Multiple Myeloma by Cumulative Exposure to Benzene			
	Deaths		
Cumulative Exposure (ppm-years)	**Obs**	**Exp**	**SMR (95% CI)**
<40	3	0.93	3.21 (0.66-9.39)
40-200	0	0.30	0 (0-12.29)
200-400	0	0.10	0 (0-36.89)
>400	1	0.04	25.17 (0.63-139.83)
Total	4	1.37	2.91 (0.79-7.45)

O. Wong. 1995. Risk of Acute Myeloid Leukaemia and Multiple Myeloma in Workers Exposed to Benzene. *Occup Environ Med* 52: 380-384.

This was a reanalysis of the Paxton *et al*. evaluation with the 1987 updated mortality. When analyzed by specific cell type, acute myeloid leukemia risk was only significant above 200ppm of cumulative exposure. In addition, Multiple myeloma was highly significant consistently at level greater than 400 ppm. This analysis reiterates the author's contention that leukemia risk should be analyzed by cell type. See the tables above for specific risk for AML and multiple myeloma related to cumulative exposure.

Schnatter, A. R., M. J. Nicolich, et al. (1996). "Determination of leukemogenic benzene exposure concentrations: refined analyses of the Pliofilm cohort." <u>Risk Anal</u> **16**(6): 833-40 (Schnatter, Nicolich et al. 1996)

Historical Context and Methods:
This study looked at exposure rates and the effect upon leukemogenesis. Effects of specific benzene exposure concentrations rather than the estimated cumulative exposure of benzene were analyzed. The exposure concentrations investigated included the work by Rinsky, Crump and Allen and Paustenbach. Analyses were performed on each set of exposure estimates, plus an estimate was derived by considering the median of the three sets of estimates. The median exposure estimate was calculated by simply selecting the rank middle estimate for each cell in the job/department/time exposure matrix. One advantage of this estimate is that it disregards extreme exposure estimates, which have been at the subject of previous criticism. Each worker's maximally exposed job/department combination and a long term average concentration with that job, was calculated for the median as well as each series of exposure estimates. This enabled enumeration of subgroups of workers and controls who were always exposed to specific concentrations of benzene. This method is useful for identifying empirical thresholds, i.e., critical concentrations which are not associated with any risk in the database.
It is clear that the estimates developed by Rinsky were on average lower than Crump and Allen, which was slightly lower then the estimates developed by Paustenbach. Total leukemia SMRs are not different among those workers always exposed to benzene

concentration < 20 ppm. However, for workers exposed to concentrations between 20 and 40 ppm, there is a non-statistically significant elevation of total leukemia for all estimates except Paustenbach. But, when analyzed for AMML the Crump estimates no increase in levels <20 ppm. Alternatively, the Rinsky estimates support the notion of a critical concentration below 20 ppm with an SMR=0 (95% CI: 0-4.53). The median exposure estimates in the Crump and Allen exposure estimates are also indicative of this critical concentration with exposures <50 ppm – SMR 0.86 (95% CI: 0.01-4.80. The Paustenbach exposure estimates do not show markedly excess risk until concentrations of 140 ppm are reached.

When the median exposure estimate is used, this critical concentration appears to be 50 to 60 part per million when AMML is the end point, and could be as low as 38 part per million for total leukemias. Risks for AMML are driving the risk for total leukemia.

Previous epidemiologic analyses have examined the importance of exposure concentration versus the more traditional cumulative exposure metric in the cohort. Rinsky reported that cumulative exposure was the strongest single predictor of death from leukemia. Crump investigated several metrics and reported that the risk of leukemias is explained better by concentration dependent upon linear exposure metrics for the Paustenbach but not the Crump and Allen exposure estimates. Both of these approaches inherently consider the full range of exposure concentrations represented in the data in one model. While these approaches are useful, they may miss the effects of exposure concentration if the exposure concentration has variable effects along the entire gradient. Thus the use of a continuous function could mask relevant versus irrelevant values.

The approach used in this paper did not depend on a model which simultaneously evaluates the entire exposure range for non linearities or rate effects. Instead, the approach is based on life table methodology and categorical exposure classification. The approach also lends itself to categorizing exposure data to directly examine the risk in relevant exposure categories, although this advantage is not unique to the life table approach. These analyses suggest that a critical concentration of benzene exposure must be reached in order for the risk of leukemia, more specifically AMML, to be expressed. When the median exposure estimate is used, the concentration appears to be between 50 and 60 part per million for both AMML and leukemia. The Rinsky exposure estimates critical concentrations were lower for both AMML and total leukemias, ranging between 20 and 25 part per million. While the duration of exposure is not explicitly accounted for in these analyses, the effects of exposure duration can be investigated. These results should not be taken to imply that instantaneous or short duration of exposures of 20 part per million can be leukemogenic. When AMML is considered no risk was evident for exposures below 200 ppm-years using the Rinsky estimates or 400 ppm-years using the Paustenbach.

In conclusion, this analysis suggests the following:

1. AMML risk is shown only above a critical concentration of benzene exposure measured as a long term average and experienced for years.
2. The critical concentration is between 50 to 60 part per million when using a median exposure estimate to derive three previous exposure estimates, and is between 20 and 25 part per million using the lowest exposure estimates.

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3. Risks for total leukemia are driven by risks for AMML suggesting that AMML is the sole type related to benzene exposure.

Rinsky, R. A., R. W. Hornung, et al. (2002). "Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment." Am J Ind Med **42**(6): 474-80. (Rinsky, Hornung et al. 2002)

Methods:

This study reported the updated mortality of the Pliofilm cohort through December 31, 1996 and additional 15 years from the last update. Every living cohort member has at least 20 years of follow-up. All 1,291 persons with at least 1 ppm day of exposure between January 1, 1940 and April 31, 1976 were included in the SMR analysis with no restrictions on race or gender. In addition, we modeled the exposure/disease relationship for all 1,845 non-salaried workers (1,291 exposed and 554 unexposed) who were alive as of January 1, 1950.

Person years were stratified by increasing levels of cumulative exposure. For historical consistency in the SMR analysis, we maintained the strata used in our previous report, 1 ppm day to 39.99 ppm-years, 40 to 199.99 ppm-years, 200 to 399.99 ppm-years, and 400 or more ppm-years. U.S. population death rates were used for comparison with death rates observed in the cohort. For leukemia, the non-actual cause of death rate file for 1940 to 1999, based on actual rates for 1940 to 1994 with rates for 1995 through 1999 duplicated from 1990 to 1994. For multiple myeloma and non-Hodgkin's lymphoma, cause specific rates of death are available only for 1960 onwards because prior to 1960 these causes were included in the category "Other lymphatic and hematopoietic malignancies." Therefore, for these outcomes we began observation in 1960 and used the natural cause of death file for 1960 to 1999 to obtain expected deaths.

To evaluate the effects of benzene on the risk of leukemia and multiple myelomas along potential confounders and effective modifiers, a generalized form of a proportional hazards regression model was used. All workers employed for at least 1 day in the rubber hydrochloride department after January 1, 1940 and alive as of January 1, 1950 were eligible for inclusion in the risk sets, regardless of exposure status.

Total benzene exposure was estimated by duration of exposure and by accumulative ppm-years. Benzene exposure was examined with dichotomous variables where workers with cumulative exposure of at least 1 ppm day were compared with other unexposed counterparts. Various lag periods were applied to allow for an induction period between exposure and death.

Results:

Nine hundred seventy-six (976) members of the 1,845 member cohort died between January 1, 1950 and December 31, 1996. For the 1,291 exposed workers, person years at risk of dying totaled 45,753. Ninety-seven percent (97%) of these person years at risk were contributed by males.

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Deaths from lymphatic and hematopoietic neoplasms were elevated with a combined SMR of 1.64 (95% CI: 1.06 to 2.44). The SMR for leukemia was 2.47 (95% CI: 1.38 - 4.07). For white male workers the SMR was 2.56 (95% CI:1.43 to 4.22). There were 17 leukemia deaths in the cohort; however, 2 deaths—1 male and 1 female—did not have a minimum 1 ppm day of cumulative exposure required by the SMR analysis. Therefore, the deaths were not counted among leukemia deaths nor did they contribute to any expectation of death.

The latency period for leukemia deaths varied widely with 6 or 15 deaths occurring ≥30 years after first exposure.   See the table below for complete updated information related to the Pliofilm cohort.

Table 17 - Deaths From Leukemia and Multiple Myeloma in the Rubber Hydrochloride Cohort						
Year of Death	**Age at Death**	**Latency (years since first exposed)**	**Cause of Death (ICD code for cause of death, using ICD revision in effect at time of death)**	**Plant location**	**Duration of Employment**	**Cumulative Benzene Exposure (ppm-yr)**
a. Descriptions of Deaths from Leukemia						
1950	29	2	Chronic Myelogenous Leukemia (204.1)	1	1 month	0.10
1954	28	3.5	Myelogenous Leukemia (204.1)	1	1.5 years	10.16
1957	57	15	Acute Monocytic Leukemia (204.2)	2	5 years	98.55
1958	36	17	Monocytic Leukemia (204.2)	1	1.5 years	49.99
1958	60	13.5	Acute Myelocytic Leukemia (204.3)	2	11.5 years	259.50
1960	65	15.5	Acute Myelogenous Leukemia (204.3)	2	14 years	498.23
1961	62	22	Di Guglielmo's Acute Myelocytic Leukemia (204.3)	2	13 years	478.45
1961	57	20	Acute Granulocytic Leukemia (204.3)	2	20 years	639.84
1974 (female)	82	Unexposed	Acute Myeloid Leukemia (205.0)	2	1.5 years	Unexposed
1979	67	37	Acute Myeloblastic Leukemia (205.0)	2	14 years	252.66
1984	67	17	Chronic Myeloid Leukemia (205.1)	2	7 years	10.27
1985	67	45	Acute Lymphoid Leukemia (204.0)	1	16 years	52.53
1985	67	27	Acute Myeloid Leukemia (205.0)	2	9.5 years	0.72
1986	80	Unexposed	Chronic Myeloid Leukemia (205.1)	2	3 days	Unexposed
1986	71	40	Leukemia – Unspecified (208.9)	1	3 months	259.98
1987	81	38	Leukemia – Unspecified (208.9)	1	4 months	0.79
1991	79	51	Myeloid Leukemia – Unspecified (205.9)	1	7 months	5.75
b. Descriptions of Deaths from Multiple Myeloma (ICD-203)						
1963	52	22.5		1	4 days	0.11
1968	62	24.5		1	23 years	652.66
1980	69	25.5		1	1.5 years	19.50
1981	68	26.5		1	9 months	7.75
1989	68	38		1	1 month	0.10
1991	66	Unexposed		1	0.5 months	Unexposed
1993	78	Unexposed		2	4.5 years	Unexposed
1996	79	Unexposed		1	30 years	Unexposed

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

Beginning observation in 1960 and using 1960 to 1999 rates for multiple myeloma yielded an SMR of 2.04 with a 95% confidence interval of 0.66 to 4.76 for men and women of all races, and an SMR of 2.12 with a 95% confidence interval of 0.69 to 4.96 for white males. Four cases of multiple myeloma have occurred in this cohort since the 1981 update, bringing the total to 8 cases. Three of the 4 new cases occurred in unexposed persons who are not included in the SMR calculations. With the 5 cases of multiple myeloma occurring in exposed workers in this cohort, 4 occurred in the lowest exposure category—1 ppm day to 30.99 ppm-years of exposure—with the fifth case in the highest exposure category of > 400 ppm-years.

This update suggests the relative risk has declined over time.

Williams, P. R. and D. J. Paustenbach (2003). "Reconstruction of benzene exposure for the Pliofilm cohort (1936-1976) using Monte Carlo techniques." J Toxicol Environ Health A **66**(8): 677-781 (Williams and Paustenbach 2003)

Methods:

Another evaluation of the Pliofilm cohort was undertaken in order to answer previous discrepancies and criticisms. This analysis used more complete information along with Monte Carlo techniques. This allowed the estimation of a distribution of benzene exposures for various job categories based on input parameters that take into consideration the likely range of plausible exposures. The Monte Carlo technique utilizes probability distributions rather than a single estimate to characterize the input values in the exposure assessment calculation. This is optimal for ensuring data transparency and can help to elucidate the strengths and weaknesses of the underlying data.

Results:

This analysis indicated that few workers would have likely had exposures that were >100ppm on a chronic basis. No job categories had estimated benzene exposure above this level at the 50th percentile and only a few job categories had estimated benzene exposures >100 ppm in the 95th percentile. But these levels were only observed for about 3 years with the exception of workers involved in the neutralization process of Akron plant 1 and 2.

The current analysis appears to yield results that are consistent with what one might expect in an enclosed facility that handled large quantities of benzene more than 50 years ago and that underwent improved ventilation starting in the mid-1940s. That is, estimated benzene exposures were greater for those job categories that involved frequent and close contact with benzene (that is, neutralizer and quencher) than for jobs that involve very little contact with benzene.

Airborne benzene concentrations were still predicted to be significantly higher during the early years (1930s to 1950s) versus those measured in the mid-1960s and 1970s. These findings are consistent with historical blood count data in which there was a clinically significant depression of white blood counts.

One of the purposes for conducting this reanalysis was to evaluate and qualitatively address, where appropriate, the comments offered by Utterback & Rinsky (1995). It was

suggested that a chronic level of 100-200 would result in an epidemic of fatal non-malignant blood disease which did not occur. However, the acceptable limit was 100 ppm in 1946 and it was generally thought that aplastic anemia was avoided at this concentration. In addition, some production workers transferred out of the same areas in Akron facilities either voluntarily or involuntarily as a result of single or repeated test results, indicating a significant depression in white blood cell counts. These findings suggest that benzene exposures for some jobs could have been in excess of 100 ppm for months or a few years. In addition, the workforce may have been composed of persons who were less susceptible to the adverse effects of benzene.

Utterback & Rinsky also suggested that engineering controls were installed in the plants in the early 1940s and that these were effective at controlling vapors in the workplace. They also note that benzene air concentrations reported by Fluker (1946) were consistent with airborne benzene concentrations measured in 1976 by NIOSH. However, the available information does not detail when the equipment was installed, or its effectiveness.

Regarding dermal contact, follow-up discussions with former employees indicate that some jobs, particularly on the dry side, probably had less skin surface area exposed than previously estimated. On the other hand, prior estimates of the rate of benzene exposure appear to be reasonable based on re-review of the literature. In addition, dermal contact, regardless of the level, was found to have only a modest effect on total dose.

Although we agree with Utterback & Rinsky that there is some degree of judgment in the approach we used to estimate benzene air concentration, we believe that this approach is more sound than relying solely on the results of detector tube samples.

Utterback & Rinsky state that the approach used by Paustenbach *et al.* (1992) for dealing with detector tube inaccuracies and the use of the combustible gas detectors was probably incorrect. That is, these researchers concluded that the additional correction factor of 1.5 to account for analytical limitations was probably too high. Given the lack of available documentation on these devices, it is not possible to better understand these issues today. However, as described in the method section an analytical adjustment factor was not applied to any of the air monitoring data in the current analysis.

Regarding the overtime hours worked, these were not considered by Utterback and Rinsky. This is a potentially important factor for characterizing benzene exposures and is a particular biological significant that may account for why some workers in this cohort developed leukemia while other employees exposed to similar benzene levels may not have developed this disease. There is growing evidence that peak blood levels or peak target tissue concentrations have a greater influence on the cancer risk for benzene than that from 8-hour time-weighted samples.

The re-evaluation of the data did not have a dramatic impact on estimated benzene exposure levels for many jobs or time periods. Specifically, estimates of benzene exposure were found to be too high in the 1992 analysis for some job categories and years. However, most predictions of benzene exposure were within the current 50th and 95th percentile estimates. The conclusions of this study remain the same as the previous study.

There are some limitations to the current analysis, including: the lack of information on how or why detector tube samples were collected makes it difficult to assess whether the benzene air sampling data represent background or peak exposure levels and the use of a

uniform probability distributions to characterize the benzene air concentration data and most other exposure parameters which are not particularly useful when addressing skewed data sets. The substitution of log normal or triangular distributions for uniform distributions when evaluating benzene air concentration was found to have a modest to moderate impact on the estimated exposure levels for the same job categories and time periods suggesting that these results are somewhat sensitive to the choice of probability distribution.

2. The Chinese (NCI-CAPM) Cohort

Yin, S. N., G. L. Li, et al. (1987). "Leukaemia in benzene workers: a retrospective cohort study." <u>Br J Ind Med</u> 44(2): 124-8. (Yin, Li et al. 1987)

Cohort Description and Study Methods:

The cohort consisted of 28,460 benzene exposed workers (178,556 person-years in 1972-81) and 28,257 control workers (199,201 person-years).

A retrospective cohort study was conducted (1982-1983) in 233 benzene factories and 83 control factories in 12 cities in China. This included workplaces involved in the painting, shoe-making, rubber synthesis, adhesive synthesis and organic synthesis industries. The exposed group worked in a factory for at least .5 year between January 1, 1972 and December 31, 1981. The control cohort consisted of workers from machine production, textile and cloth factories with no known exposures to benzene or other occupational carcinogens. The drop out rate was 0.8% in the benzene cohort and 1.3% in the control cohort.

Items investigated through the use of factory records included the occupational history of the individuals, a history of benzene poisoning and other specific diseases, working conditions, and atmospheric benzene concentrations in the workplace.

Benzene concentrations were determined by means of grab samples with gas chromatographic analysis.

Cases of leukemia, aplastic anemia and benzene poisoning were obtained from hospital records. Benzene poisoning was diagnosed based upon occupational history, a peripheral leukocyte count of less than 4000 cells/mm^3, and symptoms or signs in the central nervous system.

Results:

Thirty cases of leukemia (25 dead and 5 alive) were detected in the exposed group and four cases of leukemia (all dead) in the control group. Of the 25 cases of leukemia in the exposed group, seven had a history of chronic benzene poisoning before the leukemia developed. In the benzene exposed cohort, 196 cases of benzene poisoning and aplastic anemia were found. The leukemia mortality among benzene poisoning cases was 700.70/100,000 person years, which was 49 times higher than the benzene exposed workers.

The acute leukemias (76.6%) included 13 myelogenous, four monocytic, two myelocytic/monocytic, one erythromyelocytic and three lymphocytic leukemia cases. The chronic leukemias (23.3%) included five myelogenous, one lymphosarcomatous and one unidentified case. The leukemia mortality rate was 14/100,000 person-years in the benzene cohort and 2/100,000 person-years in the control cohort. The relative risk for leukemia in benzene workers was 6.97. The SMR for all deceased cases (excludes five living leukemia cases) was 5.74 (p > 0.01) - 5.01 (men) and 8.30 (women). The average latency of benzene leukemia in the exposed cohort was 11.4 (0.8 - 49.5) years. The mortality due to benzene

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leukemia was highest in organic synthesis plants followed by painting and rubber synthesis industries.

The concentration of benzene to which exposed workers with leukemia ranged from 10 - 1000 mg/m^3 (3.1321 - 313.21 ppm). However, the authors asserted that most measurements ranged from 50 - 500 mg/m^3 (15.661 - 156.61 ppm). Three cases of leukemia in the exposed group were associated with concentrations (grab samples) of 10 mg/m^3 (3.1321 ppm).

Limitations:
1. No personal, time-weighted industrial hygiene measurements.
2. Exposure history was based upon standard company records, not individualized data, including work practices, personal protective equipment use, etc.
3. Exposed workers were potentially working with innumerable chemicals, including benzene.
4. Control workers additional exposures except for "benzene and other occupational carcinogens" not detailed.
5. No control for potential confounders and modifying factors, such as smoking.
6. The ascertainment of cases from hospital records could potentially lead to under-attainment and misclassification.

Yin, S. N., Q. Li, et al. (1987). "Occupational exposure to benzene in China." Br J Ind Med **44**(3): 192-5. (Yin, Li et al. 1987)

Cohort Description and Study Methods:
508,818 Chinese workers exposed to benzene or benzene mixtures out of a total of 528,729 workers (92.6%). 26,319 4.98%) exposed to benzene and 502,410 (95.02%) exposed to mixtures typically containing benzene, toluene and xylene in various concentrations. The primary source of benzene was petroleum. The percentages of workers were as follows: painting (63.6), organic synthesis (10.9), insulation varnish (5.4), shoemaking (4.2), printing (<3.5), rubber (<3.5) and refinery (<3.5). There were 27,808 factories using benzene and data were obtained from 19,969.

In the 1950's, 3,917 factory workers with benzene exposure were examined and 481 cases of chronic benzene poisoning were discovered (10.1%). In the 1970s, 33,312 benzene workers were examined and 366 cases of chronic benzene poisoning were found, a prevalence rate of 1.1%. This study was conducted from 1979 – 1981.

Atmospheric benzene concentrations were determined by gas chromatographic or colorimetric testing. These were short term samples.

Results:
Nine cases of benzene leukemia (6 men and 3 women) were found and exposure time ranged from 2-25 years. Jobs included painting (4), shoemaking (1), insecticide packing (1), cleaning (1) and analytical technician (2). There were six case of acute myelocytic, one case

of acute erythroleukemia, one case of acute monocytic leukemia and one case of acute lymphocytic leukemia, respectively. Six had had a preceding leukopenia or pancytopenia.

Twenty-four cases of aplastic anemia were identified and complete records were available in 17 (7 men, 10 women). Exposure ranged from 3.5-19 months. Most cases came from shoemaking and paint production. Benzene measurements ranged from 93 - 1,156 mg/m^3 (29.129 - 362.08 ppm). In one shoemaking factory using glue with a 1:3 mixture of chlorobutadiene and benzene, four workers with aplastic anemia worked an average of 118.5 days at an estimated daily concentration of 1035.6 mg/m^3 (324.37 ppm).

2,676 cases of benzene poisoning were found, a prevalence of 0.15%. The prevalence rate of benzene poisoning was 0.94% in workers exposed to benzene and 0.44% in workers exposed to benzene mixtures. The difference was statistically significant. There was a positive correlation (0.42, p<0.05) between the prevalence of benzene poisoning (white blood cell count <4000/mm^3 blood) and the concentration in shoemaking factories. The prevalence of benzene poisoning in shoemakers was ~5.8 times that of the general population, or 1.25% of workers. See the table below for additional information on leukopenia in various industries.

Table 18 - Comparison of Prevalence of Leucopaenia in Different Industries Using Benzene			
Industries	**Workers**	**Cases**	**%**
Shoemaking	19213	240	1.25
Paint Producing	12359	67	0.54
Painting	101379	415	0.41
Spray Painting	175313	682	0.39
Benzene Refining	6452	11	0.17
Chemical Synthesis	42766	190	0.44
Pharmaceuticals	6576	41	0.62
Rubber	13877	56	0.40
Insulation Varnish	24378	101	0.41
Printing	15453	46	0.30
Loading Workers	870	7	0.80
Others	35906	142	0.40
Total	454542	1998	

S.N. Yin, Q. Li Q, Y. Liu, F. Tian, C. Du, C. Jin. 1987. Occupational Exposure to Benzene in China. *British Journal of Industrial Medicine* 44: 192-195.

Benzene concentration was higher than 25 mg/m^3 (7.8304 ppm) in 86% of the shoemaking factories and 10 mg/m^3 (3.1321 ppm) in only a few factories.

The geometric mean concentration of benzene in 50,255 workplaces was 18.1 mg/m^3 (5.7005 ppm) with a 95% range of 0.06 to 844.74 mg/m^3 (0.018793 - 264.59 ppm). Sixty four percent of workplaces had a benzene value of less than 40 mg/m^3 (12.529 ppm). 1.3% of

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workplaces had benzene concentrations in excess of 1,000 mg/m^3 (313.21 ppm).

Limitations:
1. No personal, time-weighted industrial hygiene measurements.
2. Exposure history was based upon standard company records, not individualized data, including work practices, personal protective equipment use, etc.
3. Exposed workers were potentially working with innumerable chemicals, including benzene.
4. No control for potential confounders and modifying factors, such as smoking.

Yin, S. N., G. L. Li, et al. (1989). "A retrospective cohort study of leukemia and other cancers in benzene workers." Environ Health Perspect **82**: 207-13. (Yin, Li et al. 1989)

Cohort Description and Study Methods:
A retrospective cohort study was carried out in 1982-1983 among 28,460 benzene-exposed workers (15,643 males, 12,817 females) from 233 factories and 28,257 control workers (16,621 males, 12,366 females) from 83 factories in 12 large cities in China. There were 178,556 person years of follow-up in the exposed group and 199,201 in the unexposed group.

Exposed and unexposed workers were followed from January 1, 1972 – December 31, 1981. Factory and hospital list were used to ascertain information about vital status, job status and history of benzene poisoning, aplastic anemia, leukemia and other malignancies. Additional history, such as smoking history, was obtained from subjects and next of kin (deceased). Detailed information was ascertained for all subjects with leukemia, aplastic anemia and other hematopoietic and lymphatic neoplasms. Information about products manufactured, raw materials used, production processes and occupational history of subjects came from factory records and supervisors. Participation was 99.2% of factories with benzene exposure and 98.7% among non-exposed factories.

Benzene levels were determined from factory records of benzene air measurements, benzene concentration in materials and products, as well as, factory information about environmental measures (ventilation, etc.) and personal protective equipment.

Results:
Age-adjusted, all cause mortality was significantly higher among all workers with benzene exposure (265.46/100,000 person-years vs. 139.06/100,000 person-years in controls). Mortality from all malignant neoplasms had a similar pattern, 123.21/100,000 person years vs. 54.7/100,000 person years, respectively. In benzene exposed males, the total mortality rate was 393.90/100,000 person years and 194.61/100,000 person years in the unexposed. Conversely in the female group, the mortality rate was 101.87 and 52.61 per 100,000 person years, respectively.

The SMR for leukemia in exposed workers was 5.74. Relative risk of leukemia increased with duration of benzene exposure up to 15 years and declined with additional years of exposure. No effect was found for smoking on leukemia mortality.

Exposures for the 30 benzene-exposed leukemia cases average accumulation of lifetime levels of exposure where estimated using all available measurements. The average exposures ranged from 6.5 – 487.0 mg/m^3 (2.0359 - 152.54 ppm), while the cumulative exposures ranged from 33.2 – 16359.0 mg/m^3 years (10.399 - 5123.9 ppm-years). See the table below for complete information on the 30 cases of leukemia.

Table 19 - Description of Leukemia Cases by Sex, Age, Duration of Exposure and Type of Leukemia Among Benzene-Exposed and Control Workers from 12 Cities in China, 1972-1981			
Leukemia Cases Identified	**Age**	**Duration of Benzene Exposure, Years**	**Type of Leukemia**
1	35	11	Acute Myelomonocytic
2	25	4	Acute Monocytic
3	37	6	Acute Monocytic
4	61	20	Acute Monocytic
5	62	49	Lymphosarcomatous
6	32	18	Acute Promyelocytic
7	46	20	Acute Myelocytic
8	60	6	Acute Myelocytic
9	30	1	Chronic Myelocytic
10	61	48	Acute Myelocytic
11	31	12	Acute Myelocytic
12	25	7	Acute Lymphocytic
13	47	17	Chronic Myelocytic
14	23	5	Acute Myelocytic
15	53	8	Chronic Myelocytic
16	36	7	Acute Myelocytic
17	37	14	Acute Myelocytic
18	57	3	Acute Myelomonocytic
19	36	13	Chronic Myelocytic
20	41	19	Acute Myelocytic
21	47	18	Acute Unspecified
22	24	8	Acute Myelocytic
23	45	16	Acute Erythromyelocytic
24	57	19	Chronic Myelocytic
25	41	16	Acute Myelocytic
26	47	1	Acute Monomyelocytic
27	40	4	Acute Myelocytic
28	42	19	Acute Lymphocytic
29	25	6	Acute Myelocytic
30	41	18	Lymphocytoid
Control Workers			
1	36	22	Chronic Myelocytic
2	34	12.5	Acute Myeloblastic
3	72	30	Chronic Myelocytic
4	54	22	Leukemia Unspecified

S.-N. Yin, G.-L. Li, F.-D. Tain, Z.-I. Fu, C. Jin, Y.-J. Chen, S.-J Luo, P.-Z. Ye, J.-Z. Zhang, G.-C. Wang, X.-C. Zhang, H.-N. Wu and Q.-C. Zhong. 1989. A Retrospective Cohort Study of Leukemia and Other Cancers in Benzene Workers. *Environmental Health Perspectives* 82:207-213.

66.6% of the exposed cases had a variant of acute non-lymphocytic leukemia compared with 50.1% of leukemia cases from the general population. Only 10% of the cases among the exposed group had acute lymphocytic leukemia compared with 23.5 in the general population.

Limitations:
1. There was no detailed description of exposure measurements, including purpose (peak, spill, personal, area, etc.), time period of samples (grab, short term, TWA, etc.), testing methodology and instrumentation and/or analysis methodology.
2. The authors noted that there findings of leukemia following relatively low cumulative exposures must be interpreted cautiously because the estimated average and cumulative lifetime benzene exposure levels were based on relatively few measurements.
3. Information about living and deceased subjects was ascertained from a variety of potentially non-consistent sources, including subject interviews, next of kin, hospital death certificates and local police stations.
4. Information about the factories, production, benzene use and personal protection was ascertained from a variety of potentially non-consistent sources, particularly factory records and supervisors.

Yin, S. N., M. S. Linet, et al. (1994). "Cohort study among workers exposed to benzene in China: I. General methods and resources." Am J Ind Med **26**(3): 383-400. (Yin, Linet et al. 1994)

Description of the Study and Study Methods:
This was an expansion (more exposed and unexposed workers) of the retrospective cohort mortality study completed by Yin *et al.* in 1987. However, this study (CAPM-NCI) was designed independently of the earlier CAPM study. Six more years of follow-up were included. In addition, a detailed exposure evaluation was undertaken for the years 1949 – 1987. There were two major components, including a cohort and nested case-control study. Major objectives, included:
1. Compare incident rates for leukemia and its subtypes, other hematopoietic and lymphoproliferative neoplasms and related non-malignant hematologic disorders among benzene exposed and unexposed workers and among workers with benzene poisoning;
2. To classify risk of leukemia, other HLP disorders and other cancers by industry, occupation, job title, age and year of first exposure, level and duration of exposure;
3. To examine the role of other risk factors including cigarette use, lifetime job related and environmental exposures, medical and family history and the benzene/leukemia relationship;

4. To determine the rates of mortality for cancers other than leukemia and other HLP malignancies among benzene exposed and unexposed workers by job and exposure characteristics

The cohort study included workers from 672 factories with benzene use and 40 unexposed factories. Workers were identified from work units, the key administrative entity found in Chinese industrial settings. A work unit typically consists of one or more rooms with workers performing closely related production tasks. All workers employed for any length of time in the 1472 exposed work units was eligible for study inclusion. Eligible workers were identified from a systematic review of factory records and their entire job history was also abstracted from the factory records.

The nested-case control component of the study was intended to evaluate dose-response relationships. For each case of leukemia and hematolymphoproliferative (HLP – includes both malignant and nonmalignant) disorders, four controls were randomly selected from the pool of exposed and unexposed workers. They were matched by sex, city and time period of employment (pre-1962, 1962-1971, 1972-1981 and 1982-1987). Each control must have entered the cohort at an age that was younger than the case's age at diagnosis and must have remained in the cohort without developing a blood malignancy or related disorder up to an age that was older than the case's age at diagnosis.

Cause of death was obtained from medical records, other factory records or death certificates. Next of kin were contacted as a last resort. Medical records and available samples (pathology – blood smears) were sought for validation of all leukemia and HLP diagnoses. A diagnosis and a corresponding level of certainty were assigned to each case. In addition, all available records preceding the diagnosis of each case were sought.

Standardized mortality ratios were calculated; however, national and city-specific mortality rates were only available for 1973 - 1975. Accurate cancer incidence data have been routinely collected in only one city back to the 1970's and this limited the utility of external comparisons. Internal comparison using Poisson regression models were used to estimate risk. Each cohort member contributed to person-year tables with partitioning across levels of demographic and exposure variables, with consideration of time dependency. Exposure was treated as a time dependent variable in all analyses. Analysis of the nested-case control data was completed using standard statistical methods, including conditional logistic regression.

Results:

The cohort study population included the 74,828 (38,832 males and 35,996 females) exposed workers and a control population of 35,905 (20,795 males and 15,010 females) non-exposed workers. Workers came from 712 factories: 603 with exposed work units, 40 with unexposed only and 69 with both exposed and unexposed. Approximately 60% of the person years were from workers hired between 1959 – 1978, while <20% came from workers hired after 1980. Salary lists were used to identify 84% of exposed and unexposed workers; however, slightly more exposed workers were identified by this method. At the end of the study period, there were 1,967 (1,369 exposed/598 unexposed) deaths (1.8%) and 237 (147

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exposed/90 unexposed) had an unknown vital status (0.2). There were 712 (1%) cases of benzene poisoning in exposed workers and 680 (95.5%) were still alive.

Regarding verification of the 95 cases of leukemia and HLP included in the case-control study, 85 (89.5%) were verified with medical records, 7 (7.4%) were verified with other written records and 3 (3.1%) were only verified with oral information. Of the leukemia cases (n=51), 11 (21.6%) were confirmed by histopathology, 36 (70.6%) by cytology, 2 (3.9%) by clinical evidence only and 2 (3.9%) were unknown. In addition to leukemia, there were 7 persons with myelodysplasia, 23 with non-Hodgkin's lymphoma or other neoplasms of lymphoid and histiocytic tissue, 2 with multiple myeloma, 9 with aplastic anemia, 2 with granulocytosis and one with another HLP disorder.

Among the cases, 83(87%) were deceased and the interviews were completed by next of kin or others. Only 6.8% of controls were deceased. Interviewers included a detailed lifetime job history, residential exposure to benzene, xylene, toluene or paint. Past medical history including cancer, benzene poisoning or aplastic anemia, use of specific medications, history of diagnostic x-rays and radiation therapy, cigarette smoking history, use of hair dyes and family cancer histories.

Quality control checks on 600 workers found discrepancies in demographic factors and vital status ranged from 0.5-0.8%, for job title or work unit from 0.7 to 3%, for duration of employment differences of 2-10 years 0.8 to 1.5% and for differences of <2 years from 3.9 to 5.5%. There were no discrepancies in determination of cancer as a cause of death.

Review of the medical record data shows the level of information was quite detailed and generally complete for cases diagnosed in the 1980's and varied in completeness for cases diagnosed in the 1970s. Medical record information was located for 62% of the 95 cases, less detailed or sketchy records for 27% of the cases and 11% of cases had no medical records. Pathology slides and/or peripheral blood smears were obtained for 23 (24%) of cases.

According to the authors, the study has five unique strengths:
1. Detailed characterization of exposure on the job title level within a given work unit time period for the cohort component and on the individual worker level for the case control component.
2. A large number of benzene-exposed and unexposed workers including the largest cohort of female benzene exposed workers ever evaluated.
3. A comprehensive assessment of lifestyle exposure to benzene and other factors that may confound the benzene/leukemia relationship for persons in the nested case control study.
4. A substantially larger number of leukemia and other HLP cases.
5. Detailed clinicopathologic characterization of these cases.

Limitations:
1. The authors noted the difficulty in coordinating >400 staff members, assuring consistency in the results and dealing with the differing resources among the various study centers, however, they noted the numerous quality checks performed throughout.
2. 87% of cases were deceased, thus limiting and potentially distorting the data

gathered, as it was secondhand data. Conversely, only 6.8% of the unexposed were deceased.

3. Thirty-eight percent of cases had only limited or no medical information, yet 89.5% of all diagnoses came from medical records, 7.4% from other written records and 3.1% from oral information.

4. Four of 51 leukemia cases (12.75%) were diagnosed by clinical evidence (2) and unknown (2).

Dosemeci, M., G. L. Li, et al. (1994). "Cohort study among workers exposed to benzene in China: II. Exposure assessment." Am J Ind Med **26**(3): 401-11. (Dosemeci, Li et al. 1994)

Historical Context and Study Methods:

Until the early 1970s, pure benzene was commonly used as a solvent in various paints, varnishes, glues, coatings and other products. Monitoring was first undertaken in factories during the 1960's, with colorimetric measures. In 1972, gas chromatographic techniques became available. During this same period (1972-1975), ventilation was improved and alternative solvents (xylene and toluene) were substituted for benzene.

Historical estimates of benzene exposures since 1949 were generated for 75,008 workers employed for at least one day during 1972 -1987. In total, estimates were made for 18,435 factory/work unit/job titles/calendar year time period combinations.

A standardized job title dictionary was developed that classified 60 benzene exposures into 70 job title categories and 11 major activity groups. An exposure factory form was used to collect factory level exposure information including industrial classification, major production activities, the types of amounts of historical changes in benzene containing raw materials and final products, engineering controls and use of personal protective equipment. In addition, all historical benzene and organic solvent measurements were identified by factory, work unit and job title. Information on air monitoring data also included the sampling date and sampling location, the associated work unit and job title and the type of analytical method used. There were a total of 8,477 benzene measurements available since the 1950s.

Historical exposure information at each factory was abstracted for seven time periods at the job title level, including:

1. Information on the monitoring data for benzene and other organic solvents,
2. Amount of benzene-containing materials use,
3. Percent benzene of raw materials (1-29%, 30-59% and 65-100%),
4. Average daily frequency of benzene exposure,
5. Historical changes in engineering controls
6. Change in the process for new locations,
7. Use of personal protective equipment,
8. Occurrence or change in other control measures

All estimates of benzene exposure were completed by local industrial hygienists and other occupational health personnel for each work unit job title. They categorized exposures

in six ranges: <1 ppm, 1-5 ppm, 6-10 ppm, 11-25 ppm, 26-50 ppm and >50 ppm over seven different calendar periods: 1949-1959, 1960-1964, 1965-1969, 1970-1974, 1975-1979, 1980-1984 and ≥1985. If the information listed above was limited, field center staff used all available exposure information and their professional judgment to estimate exposures.

Subject work histories were abstracted from written factory records, including the name of the site, factory work unit, and job titles held by the subject with starting and ending dates of each job. Job title codes were assigned for each individual job based upon the job title dictionaries. Average exposure (by time period and job held) and cumulative exposure was developed for each study subject.

There were a total of 18,435 benzene exposure estimates, 38% were based on monitoring data primarily collected after 1972. Over the 7 time periods the estimated benzene exposure level was 16.7 parts per million, ranging from 20.4 parts per million in the first period to 11.5 parts per million in the last period. Percentage of estimates made with high confidence increased over time from 2% to 42% for the first and last periods, respectively. See table below for further information related to confidence level of measurements by period.

The highest benzene exposure was observed among rubber workers, especially among rubber workers with an average exposure level estimate of 52.6 ppm. Painters, paint manufacture workers, shoe glue applicators and chemical manufacturing workers were also highly exposed, with an average level of >20 ppm.

Table 20 - Cohort Study of Benzene Workers in China 1972-1987: Distribution of Exposure Variables and Estimates Over Seven Calendar-Year Periods							
Exposure Parameters	**1949-1959**	**1960-1964**	**1965-1969**	**1970-1974**	**1975-1979**	**1980-1984**	**85+**	**All Years**
No. of estimates made	1,522	2,041	2,581	2,914	3,095	3,159	3,123	18,435
No. of measurements done	44	256	386	457	1,766	2,551	2,950	8,477
No. of estimates based on meas.	52	217	326	591	1,643	1,956	2,111	6,896
% estimates based on measurements	3.4	10.6	12.6	20.3	53.1	61.9	67.6	37.4
Mean of measurements (ppm)	25	33	33	27	15	11	8	13
% benzene in materials	40	41	40	36	32	30	28	34
Duration of exposure/day (hours)	4.3	4.3	3.8	4.1	4.3	4.3	4.3	4.2
% jobs having general ventilation	63	68	75	77	81	85	86	78
% jobs having local ventilation	39	44	52	58	64	77	81	62
% jobs having closed system	2	2	4	5	7	11	13	7
% jobs having process change	2	4	7	10	18	36	46	20
% jobs having glove	87	92	93	94	96	98	98	95
% jobs having cloth mask	87	91	92	93	95	97	97	94
% jobs having cartridge mask	5	11	12	16	24	30	31	20
% jobs having work clothing	83	86	87	89	92	93	93	90
% jobs having monitoring	7	22	27	40	81	94	98	59
% jobs having safety education	37	47	52	61	77	91	93	69
% jobs having physical exam	15	25	27	44	83	98	99	62
Mean of estimates (ppm)	20.4	19.6	17.5	17.2	16.8	13.9	11.5	16.7
% estimate with high confidence	2	6	6	11	31	38	42	22

M. Dosemeci, G.-L. Li, R.B. Hayes, S.-N. Yin, M. Linet, W.-H. Chow, Y.-Z. Wang, Z.-L. Jiang, T.-R. Dai, W.-U. Zhang, X.-J. Chao, P.-Z. Ye, Q.-R. Kou, Y.-H. Fan, X.-C. Zhang, X-F. Lin, J.-F. Meng, J.-S. Zho, S. Wacholder, R. Kneller, and W.J. Blot. 1994. Cohort Study Among Workers Exposed to Benzene in China: II. Exposure Assessment. *American Journal of Industrial Medicine* 26: 401-411.

Limitations:

1. The authors noted that there was no central team of industrial hygienists to walk through all factories. All estimates, whether based upon historical data or extrapolations with little information were done by local industrial hygienists. Because of these limitations and historical nature of the retrospective exposure assessment, the exposure ranges were used rather than quantitative point estimates.

2. Virtually all of the benzene measurements were based on short term area samples which may, or may not be indicative of personal exposure. The area measurements are most likely a significant underestimation of personal exposure as these industries are task based and require the active participation of workers in the application of glues, etc. For area samples to be equivalent to personal sampling, one must assume complete mixing of the workplace air which is unlikely.

3. The authors assigned confidence scores to their exposure estimates and during the earliest period, they had only 2% high confidence, i.e. – they did not have confidence in 98% of these measurements. This continued for much of the study and only reached a level of 42% high confidence for the measurements after 1985. Given that the researchers did not consider the measurements to be highly accurate, it is difficult to except their conclusions regarding the dose-response curve and the level at which the workers supposedly had an elevated leukemia risk.

Travis, L. B., C. Y. Li, et al. (1994). "Hematopoietic malignancies and related disorders among benzene-exposed workers in China." <u>Leuk Lymphoma</u> **14**(1-2): 91-102. (Travis, Li et al. 1994)

Cohort and Nested-Case Control Description:

      The retrospective cohort study of incident cases was conducted among 74,828 benzene-exposed workers employed between January 1, 1972 and December 31, 1987, in 672 factories in twelve Chinese cities. A comparison group consisted of 35,805 unexposed workers employed during the same period in 109 factories in the same cities.

Study Methods:

See Yin *et al.* 1994 – General Methods and Resources

Results:

      Eighty-two hematopoietic malignancies and HLP cases were identified in exposed workers and 13 in unexposed workers. Diagnoses confirmed by pathology reports and medical records for 51 benzene-exposed subjects included acute leukemia - 17 patients, myelodsyplastic syndrome (MDS) - 2 patients, chronic granulocytic leukemia (CGL) - 5 patients, malignant lymphoma-related malignancies (ML) -16 patients, aplastic anemia (AA) - 8 patients and 3 other disorders. For the remaining 31 exposed cases, diagnosis was based on evaluation of histopathological material, including 9 cases of acute non-lymphocytic

leukemia (ANLL), 5 acute leukemias which could not be classified further, 5 MDS, 4 CGL, 4 ML, 1 acute lymphoblastic leukemia (ALL) and 1 AA.

Analysis indicate that the age and sex adjusted relative risk for all confirmed lymphohematopoetic disorders in exposed versus unexposed workers was 3.4, 95% CI (1.9-6.1).

Important findings of this study include the observation that the hematopathological features of ANLL associated with benzene exposure resemble those following chemotherapy and radiotherapy. There was a far greater diversity of hematologic malignancies than has typically been ascribed to benzene exposure. In previous investigations only AML and aplastic anemia appeared to be consistently increased.

Limitations:
1. There was no breakdown and calculation of relative risk by particular cell and disease types, particularly leukemia subtypes.

Yin, S. N., R. B. Hayes, et al. (1996). "A cohort study of cancer among benzene-exposed workers in China: overall results." Am J Ind Med **29**(3): 227-35. (Yin, Hayes et al. 1996)
-----AND-----
Hayes, R. B., S. N. Yin, et al. (1996). "Mortality among benzene-exposed workers in China." Environ Health Perspect **104 Suppl 6**: 1349-52. (Hayes, Yin et al. 1996)
-----AND-----
Yin, S. N., R. B. Hayes, et al. (1996). "An expanded cohort study of cancer among benzene-exposed workers in China. Benzene Study Group." Environ Health Perspect **104 Suppl 6**: 1339-41. (Yin, Hayes et al. 1996)
-----AND-----
Linet, M. S., S. N. Yin, et al. (1996). "Clinical features of hematopoietic malignancies and related disorders among benzene-exposed workers in China. Benzene Study Group." Environ Health Perspect **104 Suppl 6**: 1353-64. (Linet, Yin et al. 1996)

Cohort and Case-Control Description:
See Yin *et al.* 1994

Study Methods:
See Yin *et al.* 1994

Combined Results:
Benzene-exposed subjects were followed for an average of 10.5 years, while unexposed subjects were followed for 11.7. Women contributed 47% of the person years in the benzene-exposed group and 40% in the unexposed group. In the initial external analysis, which compared the population mortality rate (1973-1975), the all cause SMR was 0.5 (95% CI: 0.4 -0.5) and 0.4 (95% CI: 0.4 - 0.5 for the benzene-exposed and unexposed study groups, respectively. Analysis by specific cause of death revealed an excess of leukemia

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deaths (38) versus the population rate – SMR 1.5 (95% CI: 1.1 – 2.1) – as well as lymphoma deaths (17) – SMR 1.2 (95% CI: 0.7 – 2.0). Further analysis was limited to consideration of disease occurrence due to the large differences between the external population mortality rates and the study population. Significant excesses of mortality were noted for leukemia (RR=2.3) and lymphoma (RR=4.5) in exposed workers, with similar excesses for men and women. There were no deaths due to multiple myeloma.

There were 81 total cases of hematopoietic disorders among exposed workers, including 63 malignancies and 18 "other" disorders. Thirteen lymphohematopoietic malignancies and no "other" hematological disorders were found in the unexposed group. Of 9 ANLL with sufficient information to classify by the FAB subtype, 3 cases were M2, 4 cases were M3, 1 case was M2 or M4, one case was M4 or 5. The relative risk of all lymphohematopoietic malignancies in the exposed group was 2.6 (95% CI: 1.5 -5.0). For all leukemia, there was a relative risk of 2.6 (95% CI: 1.3 – 5.7), myeloid leukemia was 3.0 (95% CI: 1.3 – 7.9) and acute myelogenous leukemia was 3.1 (95% CI: 1.2 – 10.7). There were non-significant excesses of chronic myelogenous leukemia and lymphocytic leukemia. Since table below of incidence data of types of cancer.

Table 21 - Incidence of Lymphohematopoietic Malignancies and Other Hematologic Disorders Among Benzene-Exposed and Unexposed Workers, China, 1972-1987				
Diagnosis	**Exposed Workers**	**Unexposed Workers**	**RR[a]**	**95% CI[b]**
Lymphohematopoietic Malignancies	63	13	2.6	1.5-5.0
Malignant Lymphoma	20	3	3.5	1.2-14.9
Non-Hodgkin's Lymphoma	17	3	3.0	1.0-13.0
Multiple Myeloma	1	1	0.4	0.0-10.7
All Leukemia	42	9	2.6	1.3-5.7
Myeloid Leukemia	32	6	3.0	1.3-7.9
Acute Myelogenous Leukemia	23	4	3.1	1.2-10.7
Chronic Myelogenous Leukemia	9	2	2.6	0.7-16.9
Lymphocytic Leukemia	5	1	2.8	0.5-54.5
Acute Lymphocytic Leukemia	5	1	2.8	0.5-54.5
Other NOS[c]	5	2	1.3	0.3-9.2
Other Hematologic Disorders	18	0	∞	4.8-∞
Agranulocytosis	2	0	∞	0.3-∞
Aplastic Anemia	9	0	∞	2.2-∞
Myelodysplastic Syndrome	7	0	∞	1.7-∞
Total	81	13	3.4	1.9-6.3

[a]RR: relative risk, compared with nonexposed workers, adjusted for age and sex.
[b]CI: confidence interval.
[c]NOS= not otherwise specified.

S.-N. Yin, R.B. Hayes, M.S. Linet, G.-L. Li, M. Dosemeci, L.B. Travis, C.-Y. Li, Z.-N. Zhang, D.-G. Li, W.-H. Chow, S. Wacholder, Y.-Z. Wang, Z.-L. Jiang, T.-R. Dai, W.-Y. Zhang, X.-J. Chao, P.-Z. Ye, Q.-R. Kou, X.-C. Zhang, X.-F. Lin, J.-F. Meng, C.-Y. Ding, J.-S. Zho, and W. Blot. 1996. A Cohort Study of Cancer Among Benzene-Exposed Workers in China: Overall Results. *American Journal of Industrial Medicine* 29:227-235.

Significant excess risks were noted for all nonmalignant hematopoietic disorders, including agranulocytosis, aplastic anemia and myelodysplastic syndrome. In addition to the findings related to the hematopoietic malignancies, there was a moderately significant excess of lung cancer primarily due to an increase in men. It is noteworthy that tobacco use is frequent among Chinese men but not among women. However, tobacco information was not available for the lung cancer cases.

Tests for trend of increasing risk with increasing exposure were undertaken and all cause mortality was slightly increased among workers with greater cumulative exposure to benzene (p value for trend < 0.01); however, this excess was largely due to cancer deaths (p value for trend < 0.002). Deaths due to all hematopoietic malignancies (p value for trend = 0.01), which includes leukemia, were increased with greater cumulative exposure. The relative risks for cumulative exposure (ppm-years) were as follows: <10ppm – 2.5, 10-39ppm – 2.1, 40-99ppm – 2.9, 100-400ppm – 3.0 and 400 + ppm – 2.0.

Limitations:
1. The authors noted that their previous estimates utilizing limited, general Chinese population comparisons may be unreliable. With that said, they noted that the all cause mortality and deaths due to major disease groups were similar between the exposed and unexposed cohorts, which suggests that internal comparisons may be appropriate.
2. The authors also noted that "exposure assessment relied upon limited measurement data, particularly for the early years of the study".

Dosemeci, M., S. N. Yin, et al. (1996). "Indirect validation of benzene exposure assessment by association with benzene poisoning." Environ Health Perspect **104 Suppl 6**: 1343-7. (Dosemeci, Yin et al. 1996)

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Dosemeci, M., N. Rothman, et al. (1997). "Validation of benzene exposure assessment." Ann N Y Acad Sci **837**: 114-21. (Dosemeci, Rothman et al. 1997)

Description of the Study and Study Methods:
This was a "validation" exercise of the exposure estimates generated for workers exposed to benzene in Chinese industry. Typically, validation of an assessment method is accomplished by comparing estimated results to actual monitoring data. However, in this study there was a lack of historical monitoring data. Alternatively, estimation of current levels based upon the methodology utilized to estimate previous unknown levels can be compared with current measured levels to indirectly validate past exposures. Another alternative is to use a well established association between an exposure and effect to validate the exposure assessment method used in the study.

In this study, the association between a clinical diagnosis of chronic benzene poisoning and estimated historical benzene exposures was used to evaluate the accuracy of the estimates developed from the assessment method. Duration of exposure, intensity of

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exposure and cumulative exposure to benzene were the exposure variables and the diagnosis of benzene poisoning was the outcome variable.

Cases of benzene poisoning were identified from factory records. Benzene poisoning was defined by Chinese government standards, including: White blood cell (WBC) <4,000 mm^3 blood or WBC between 4,000 and 5,000 mm^3 blood and platelet count < 80,000/mm^3 blood. These values must be documented on multiple occasions over several months, there must be documented benzene exposure for >6 months and other causes must be ruled out.

Subjects from one of 12 cities were excluded from the analysis due to difficulties categorizing benzene poisoned workers.

Results:

There were 412 benzene poisoning cases among 62,234 exposed subjects with 614,509 person years in 11 cities. When determining the relative risk of benzene poisoning by intensity of exposure at 1.5 years prior to the diagnosis of benzene poisoning, compared to subjects who had <5 ppm exposure at that time, they obtained relative risks of 2.2, 4.7, and 7.2 for intensities ranging from 5 to 19 ppm, 20 to 39 ppm, and > 40 ppm, respectively. Relative risk of benzene poisoning by cumulative exposure to benzene are 1.7, 2.0 and 2.4 for cumulative exposures of 40 - 99 ppm-years, 100 - 399 ppm-years and >400 ppm-years, respectively. This was compared to subjects with cumulative exposure of >40 ppm-years. Higher relative risks were seen with recent intensity, suggesting that recent exposure level has a greater effect on benzene poisoning than duration of exposure or cumulative exposure. See table below for information on benzene poisoning cases.

Table 22 - Relative Risks of Benzene Poisoning by Duration of Exposure, Intensity of Exposure and Cumulative Exposure				
Duration of Exposure	**<5 years**	**5-9 years**	**10-19 years**	**20+ years**
Relative risk [n] (95% CI)	1.0 [92] -	1.3 [91] (1.0-1.8)	1.6 [148] (1.2-2.1)	2.7 [80] (1.9-3.9)
Intensity of Exposure[a]	**<5 ppm**	**5-18 ppm**	**20-39 ppm**	**40+ ppm**
Relative risk [n] (95% CI)	1.0 [109] -	2.2 [140] (1.7-2.9)	4.7 [58] (3.4-6.5)	7.2 [64] (5.3-9.8)
Cumulative Exposure	**<40 ppm-years**	**40-99 ppm-years**	**100-399 ppm-years**	**400+ ppm-years**
Relative risk [n] (95% CI)	1.0 [109]	1.7 [74] (1.3-2.3)	2.0 [128] (1.5-2.6)	2.4 [100] (1.8-3.2)

[a]Recent intensity of exposure (ppm) at 1.5 years prior to the diagnosis..

M. Dosemeci, N. Rothman, S.-N. Yin, Li G-L, M. Linet, S. Wacholder, W.-H. Chow, and R. Hayes. 1997. Validation of Benzene Exposure Assessment. *Annals New York Academy of Sciences* 837: 114-121.

The authors determined that there was a strong relationship between benzene and benzene poisoning utilizing the assessment method in the cohort mortality study. They concluded that their results suggested that the estimated exposure values were valid enough to detect the association between benzene exposure and hematotoxicity and therefore, are reasonable measures to use in the evaluation of the relationship between benzene exposure and cancer risk.

Limitations:
1. There is no reason to associate the intensity of exposure 1.5 years prior to the diagnosis of benzene poisoning with relative risk for a person having <5 ppm total exposure or any level of cumulative exposure. As stated in the study, recent exposure level has the greatest effect on benzene poisoning. The reason for this lag was not explained in the study and potentially invalidates the "findings" of this validation exercise. It was most likely a carryover of the 1997 case-control results which associated hematopoietic malignancy with values 1.5 years prior due to the lack of association between recent exposure and malignancy, unlike that seen in benzene poisoning.
2. The authors noted the previous limitations, including: Lack of a walk through survey by a single industrial hygiene coordinator, lack of personal sampling and dependence on short term area sampling data.

Hayes, R. B., S. N. Yin, et al. (1997). "Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group." <u>J Natl Cancer Inst</u> **89**(14): 1065-71. (Hayes, Yin et al. 1997)

Description of the Study and Study Methods:
This study reported the case-control results from the previously described cohort study results (Yin *et al*. 1996a, Yin *et al*. 1996b and Hayes *et al.* 1996). For general methods, see Yin *et al.* 1994. Because myelodysplastic syndromes (MDS) may be a precursor of acute non-lymphatic leukemia (ANLL), these values were combined in several analyses. Subjects employed <6months, or hired prior to the exposure assessment period (1949) were excluded from analysis. This eliminated 1.4% of potentially exposed individuals and 0.8% of unexposed individuals. In order to derive stable risk estimates, fairly broad groups were defined for duration of exposure (<5, 5-9, and ≤10 years), average exposure (<10 ppm, 10-24 ppm and ≥25 ppm), and cumulative exposure (<40 ppm-years, 40-100 ppm-years and >100 ppm). Person years and disease events were assigned to benzene exposure levels with a 1.5 year lag, according to the level 1.5 years previously. A lag period of 1.5 years was used in making these calculations because more recent exposures are unlikely to be biologically linked to the development of cancers.

Tests for linear trend (two sided) of increasing risk with increasing amounts of benzene exposure were based on the mean of years in duration exposure categories, the log

of the mean of ppm in average exposure categories and the log of the mean of ppm in cumulative exposure categories.

Results:

In workers higher before 1972, there was an increased risk – RR= 2.9 (95% CI: 1.5-5.4) for all hematological neoplasms. The cancer risk assessment period began in 1972. From that point forward the relative risk fell to 2.5 (95% CI: 1.1-5.4). Fifteen of the 16 exposed cases of non-Hodgkin's lymphoma occurred among workers hired before 1972, which was a RR=4.1 (95% CI: 1.2-14.4). For ANLL (including AML), significantly increased risk was found for workers hired after 1972 with a RR=5.1 ((95% CI: 1.5-17.2). For ANLL/MDS the RR=4.0 (95% CI: 1.3-11.9) for hires before 1972 and RR=5.1 (95% CI: 1.5-17.2) for those hired after 1972.

				Relative Risk (no. of cases)					
Study Group	Person-Years, x10³	Mean Exposure, ppm[*], [†]	Mean Exposure, y[*]	All Hematologic Neoplasms[‡]	NHL	Leukemia	ANLL	ANLL/MDS	Other Leukemias
All exposed subjects	698	22.5	9.3	2.6 (58) 95% CI§ = 1.4-4.7	3.0 (16) 95% CI§ =0.9-10.5	2.5 (38) 95% CI§ = 1.2-5.1	3.0 (21) 95% CI§ = 1.0-8.9	4.1 (28) 95% CI§ = 1.4-11.6	2.0 (17) 95% CI§ = 0.7-5.4
Exposed subjects: y of hire									
<1972	404	24.9	13.2	2.9 (44)	4.1 (15)	2.4 (25)	2.6 (12)	4.0 (19)	2.2 (13)
≥1972	294	19.2	4.0	2.5 (14)	0.5 (1)	3.4 (13)	5.1 (9)	5.1 (9)	2.0 (4)
Exposed subjects: Occupation									
Coatings‖	350	21.5	9.4	2.1 (23)	1.6 (4)	2.2 (17)	2.9 (10)	4.2 (14)	1.7 (7)
Rubber	34	53.5	11.1	1.8 (2)	4.0 (1)	1.3 (1)	3.0 (1)	6.1 (2)	- (0)
Chemical	88	24.8	8.5	5.0 (14)	7.8 (5)	3.6 (7)	4.5 (4)	4.5 (4)	2.8 (3)
Shoe	68	21.8	7.9	1.9 (5)	1.6 (1)	2.5 (4)	1.5 (1)	1.3 (1)	3.2 (3)
Other/mixed	158	17.4	9.8	2.7 (14)	4.1 (5)	2.5 (9)	3.1 (5)	4.4 (7)	2.0 (4)
All Unexposed Subjects (referent) ¶	405	0	0	1.0 (13)	1.0 (3)	1.0 (9)	1.0 (4)	1.0 (4)	1.0 (5)

[*]Time-Weighted Average, Lag 1.5 y.

[†]ppm = part(s) per million.

[‡]Hematologic neoplasms (International Classification of Diseases [ICD]9: 200-208); NHL = non-Hodgkin's lymphoma (ICD9: 200, 202); leukemia (ICD9: 204-208); ANLL = acute non-lymphocytic leukemia (ICD9: 205.0, 206.0, 207.0); MDS = myelodysplastic syndromes (ICD-02: 9980-9989); other leukemias: includes leukemias other than ANLL and leukemias not otherwise specified (ICD9: 204, 205.1-205.9, 206.1-206.9, 207.1-207.9, 208). See (34) for ICD9 and (35) for ICD-02.

§CI = confidence interval

‖Coatings: painters and other coating application workers.

¶Referent: relative risk = 1.0 for unexposed workers, with all risks adjusted for age and sex.

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

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Exposed subjects had significantly increased risks for hematologic neoplasms at average exposures of <10 ppm (RR=2.2; 95% CI = 1.1-4.2) and cumulative exposures of <40 ppm-years (RR=2.2; 95% CI = 1.1-4.5).

ANLL and ANLL/MDS both showed patterns of increasing risk with increasing average exposure to benzene. These results were more consistent for the category ANLL/MDS versus ANLL alone. The link of ANLL/MDS with average exposure was strongest when restricted to subjects with constant levels of exposure: <10 ppm = 3.2 and ≥25 ppm=7.1. Risks for ANLL/MDS did not increase with duration of exposure to benzene. (Relative risk with <5 years = 11.7, 5.5 – 9 years = 5.2 and ≥10 years = 2.8) Relative risk for ANLL/MDS increased with cumulative exposure, but the highest risk wasn't seen in the highest category - RR at 40-99ppm-years = 6.0 and at ≥100 ppm = 4.4. Clear patterns of risk were not seen for leukemias other than ANLL. Risk of ANLL/MDS was strongly associated with increasing recent exposures (P for trend = .003) versus distant (P for trend=.51).

The authors concluded that the results provided evidence that benzene may cause hematological neoplasms at average exposures of <10 ppm and cumulative exposures of <40 ppm-years. However, they noted the "relatively modest dose-response effect, with proportionally small increases in risk at increasing levels of exposure. The dose-response curve can only be "estimated with caution".

Limitations:
1. The authors noted that workers were likely exposed to a number of chemicals besides benzene. However, because the subjects were employed in a number of different industries, and hematological disease was widespread, it suggests that the effects were most likely due to benzene.
2. The underlying weakness in the exposure assessment methodology, particularly in workers from 1949 – 1970, severely limit the trust that can be placed in the levels estimated for both exposure and effect level.

Wong, O. (1998). "Re: Benzene and the dose-related incidence of hematologic neoplasms in China." J Natl Cancer Inst **90**(6): 469-71. (Wong 1998)
-----AND----
Wong, O. (1999). "A critique of the exposure assessment in the epidemiologic study of benzene-exposed workers in China conducted by the Chinese Academy of Preventive Medicine and the US National Cancer Institute." Regul Toxicol Pharmacol **30**(3): 259-67. (Wong 1999)
-----AND-----
Budinsky, R. A., R. P. DeMott, et al. (1999). "An evaluation of modeled benzene exposure and dose estimates published in the Chinese-National Cancer Institute collaborative epidemiology studies." Regul Toxicol Pharmacol **30**(3): 244-58. (Budinsky, DeMott et al. 1999)

Comments:

1. Although the Chinese benzene study was one of the largest studies in terms of the number of exposed workers, many results driving the study were extremely unstable due to the small numbers of cases in the comparison group. This was particularly true for hematologic malignancies because mortality or incident rates of these diseases are much lower among the Chinese than among Caucasians. Study size should be judged not only by the number of deaths in the exposed group, but also by the number of deaths in the unexposed group. For example, there were only four ANLL cases among unexposed workers. Misclassification of even one case would change the results drastically.

2. There are a number of potential biases, including selection and cohort identification biases. For instance, the prior national survey in 1987 and this could have influenced the choice of facilities in the current study. Some of the records used to identify exposed workers could have introduced bias in the cohort selection.

3. The vast majority of workers (95%) by one estimate were exposed to multiple chemicals besides benzene. It is not appropriate to attribute any or all of the health outcomes in the exposed group without examining these additional exposures.

4. The exposure estimates developed by the NCI were the most serious limitation of the overall study. The exposure categories were inadequate and many of the values conflicted with NCI's own prior estimates, as well as those from prior literature. See tables below for specific discrepancies.

5. This was not a study of all workers exposed to benzene, it was primarily a study of painters (64%). Of the 30 deaths in the original (1987) cohort, 18 were painters and 2 were paint production workers. In the updated expanded study, no information on cohort composition by industry or occupation was provided.

6. Regarding the unexposed workers and the original cohort which stated that there was no known exposure to benzene or other occupational carcinogens, thus, according to the authors, the benzene controls were exposed to neither benzene nor any other occupational carcinogen. Whereas, the exposed workers were exposed to not only benzene but also possibly to other occupational carcinogens. Thus by design, a comparison between the benzene exposed workers and control workers would not be limited to effects of benzene, but would also reflect the effects of other occupational carcinogens. Therefore, this study was not designed properly to address the affects of benzene only.

7. Regarding the assumptions in the exposure estimates, it appears that Dosemeci consistently underestimated benzene content in solvents used, resulting in lower exposure estimates. In addition, the duration of exposure per day was remarkably constant at 3.8 to 4.3 hours throughout the entire exposure assessment period of some 40 years. If assumed for all industries, this would introduce substantial misclassification. They also did not take into account that until ~1995, most Chinese workers worked 6 days per week. Although it was stated that significant ventilation improvements were made in the early 1970's, this was not apparent from the estimated ventilation rate. These historical changes were not reflected in the assumptions used by the estimates developed in subsequent paper.

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8. A number of average measurements calculated with the exposure methodology were not consistent with case reports in the literature, as well as, prior reports from members of the same research group. By all indications, the estimates developed by the Dosemeci, *et al.* were not consistent with exposure levels provided by the investigators prior to the involvement of NCI in the study. They were substantially lower than previously report data.

9. The indirect validation did not actually validate the exposure measurements. (1) It simply indicated that if indeed, benzene poisoning was related to duration of exposure, then the duration of exposure used in the analysis was relatively valid. (2) Cumulative exposure is defined as the product of duration and level of exposure. Cumulative exposure is not independent of duration of exposure. (3) The relationship between recent intensity of exposure 1.5 years prior to diagnosis was not a validation for exposure estimates throughout the entire exposure assessment.

10. A variety of benzene exposure variables were extremely wide. For example, the benzene content in one of the categories was 60% to 100%. Since pure benzene was commonly used until the early 1970's, this category of 60% to 100% would substantially underestimate the benzene content in solvents used prior to 1970. Similarly, the highest category for benzene exposure estimates was greater than 50 parts per million. There is substantial evidence that workers were exposed to very high levels of benzene, up to several hundred or even a thousand parts per million. Grouping these workers in the same category with those exposed to 50 or 60 part per million, would introduce substantial misclassification.

11. Regarding NCI's own level of confidence in its exposure estimates, they were fully aware of the inadequacies of the exposure estimate. They placed little confidence in their own exposure estimates for the entire study period. Only 22% of the estimates were rated in high confidence category. For 1949 to 1959, only 2% of the estimates were rated with high confidence. This was not surprising, since only 3.4% of the estimates were based on benzene measurements which as indicate above, were inadequate in themselves. This must be kept in mind when interpreting any exposure response analysis. Inexplicably, NCI's lack of confidence in its own exposure measurements was not mentioned at all in subsequent analysis.

Table 24 - The Yin *et al.* (1987a) Painter Exposures Compared to Modeled Benzene Exposures for Painters			
Case No.	**Type of Leukemia**[a]	**Average Exposure Reported (ppm)**	**Range of Exposures Reported (ppm)**
3	Acute Monocytic	15.7	0-69
5	Lymphosarcomatous	59.7	1.6-376.2
6	Acute Promyelocytic	8.3	0-78.4
7	Acute Myelocytic	4.9	0.9-12.3
8	Acute Myelocytic	4.7	3.1-6.3
9	Chronic Myelocytic	63.7	7.8-156.7
10	Acute Myelocytic	75.0	0-1484.6
11	Acute Myelocytic	9.5	0-107
14	Acute Myelocytic	346.3	1.1-1199.3
17	Acute Myelocytic	76.4	0-193.7
19	Chronic Myelocytic	59.8	13.2-142
20	Acute Myelocytic	146.7	4.3-1726.5
21	Acute Unspecified	94.4	78.4-110.3
22	Acute Myelocytic	37.3	9.8-64.7
23	Acute Erythromyelocytic	180.3	0.7-1912.7
25	Acute Myelocytic	30.3	Single Measurement
26	Acute Monomyelocytic	21.4	17.1-43.5
28	Acute Lymphocytic	11.6	0.7-29.5

[a]Based on the type of leukemia reported in Yin *et al.* (1989) and the assumption that the case numbers assigned to leukemia cases in the 1987a paper are identical to those reported in 1989.

R.A. Budinsky, R.P. DeMott, M.J. Wernke and J.D. Schell. 1999. An Evaluation of Modeled Benzene Exposure and Dose Estimates Published in the Chinese-National Cancer Institute Collaborative Epidemiology Studies. *Regulatory Toxicology and Pharmacology* 30: 224-258.

Table 25 - Apparent Discrepancies Between Exposure Data Reported Between the Two Yin *et al.* Studies

Case No.	Leukemia Type	Yin *et al.* (1987a)		Yin *et al.* (1989)	
		Ave (ppm)	Range (ppm)	Ave (ppm)	Range (ppm)
3	Acute Monocytic	15.7	0-69	15	15-404
5	Lymphosarcomatous	59.7	1.6-376.2	57	3.0-129.3
6	Acute Promyelocytic	8.3	0-78.4	17	1.2-28.7
7	Acute Myelocytic	4.9	0.9-12.3	4.9	Single Measurement
8	Acute Myelocytic	4.7	3.1-6.3	4.7	Single Measurement
9	Chronic Myelocytic	63.7	7.8-156.7	12	11.8-108.7
10	Acute Myelocytic	75.0	0-1484.6	36	2.9-70.5
11	Acute Myelocytic	9.5	0-107	3	2.9-17
14	Acute Myelocytic	346.3	1.1-1199.3	88	Single Measurement
17	Acute Myelocytic	76.4	0-193.7	47	46.7-120.8
19	Chronic Myelocytic	59.8	13.2-142	54	17.9-54.3
20	Acute Myelocytic	146.7	4.3-1726.5	14	14.1-229.6
21	Acute Unspecified	94.4	78.4-110.3	94	Single Measurement
22	Acute Myelocytic	37.3	9.8-64.7	65	9.8-64.7
23	Acute Erythromyelocytic	180.3	0.7-1912.7	153	31.9-152.7
25	Acute Myelocytic	30.3	Single Measurement	30.3	17.1-43.5
26	Acute Monomyelocytic	21.4	17.1-43.5	30	Single Measurement
28	Acute Lymphocytic	11.6	0.7-29.5	27	2.8-27.0

R.A. Budinsky, R.P. DeMott, M.J. Wernke and J.D. Schell. 1999. An Evaluation of Modeled Benzene Exposure and Dose Estimates Published in the Chinese-National Cancer Institute Collaborative Epidemiology Studies. *Regulatory Toxicology and Pharmacology* 30: 224-258.

Hayes, R. B., S. Yin, et al. (2000). "Benzene and lymphohematopoietic malignancies in China." <u>J Toxicol Environ Health A</u> **61**(5-6): 419-32. (Hayes, Yin et al. 2000)

Description of the Study and Study Methods:

See Yin *et al*. (1994) for a description of basic details.

Results:

Previously reported in 1996 – this is a restatement of the previous results.

Limitations:

1. The authors noted the samples collected were not intended for epidemiologic purpose and often do not represent the usual exposure condition. Thus the historical exposure levels estimated for workers in our study can differ from the benzene exposure measures recorded in a given work unit.

Hayes, R. B., Y. Songnian, et al. (2001). "Benzene and lymphohematopoietic malignancies in humans." <u>Am J Ind Med</u> **40**(2): 117-26. (Hayes, Songnian et al. 2001)

Response to Wong and Budinsky *et al.* (1999)

1. Regarding methods of an NCI/CAPM study, it was argued that the exposure assessment procedures used in this study misclassified large numbers of highly exposed workers as having lower levels of exposure. Although the historical benzene exposure measurements were short-term "grab" samples and served only as one component of the data used for exposure assessments.
2. The conclusion that this summary data was used to estimate factory work-unit calendar-specific exposures is incorrect. Consequently, the conclusion that this led to systematically underestimated historical exposures was also incorrect. By our estimates, 20% of the person-years in the NCI/CAPM study were contributed by workers with average exposures of 25 ppm or greater and about 40% of the person-years were accumulated among subjects with cumulative exposures of 100 ppm or greater.
3. It has been argued that the exposure assessments are in substantial disagreement with the truer values based on other published data from studies carried out in China. It is completely without basis to conclude that the exposures in these specially chosen small number of workplaces would be in any sense reflective of those found in the 672 factories in our study.
4. Budinsky and Wong also compared exposure data reported for the NCI/CAPM study with benzene exposure measurements reported for workplaces in which leukemia occurred in the earlier CAMP study (Yin, 1987). The CAMP study exposures were taken at a single point in time. In addition, they may have been collected for any number of reasons.

5. Budinsky and Wong were concerned about the substantial shift of highly exposed workers in the CAMP study to assignment at lower-level categories in the NCI/CAMP study. There are two more cases at the highest level of average exposure in the CAMP study than in the NCI/CAMP study and no greater number of subjects in the highest category of cumulative exposure. These differences demonstrate no evidence of systematic bias toward lower-exposure classification to the NCI/CAMP study.

6. Budinsky and Wong also were concerned about potential confounding in the NCI/CAMP study. Lifestyle factors could confound an occupational association with disease if the confounding factor was causally associated with the disease correlated with the study exposure. The exposed and unexposed groups in our study derive from similar occupational backgrounds. There is no evidence that differential lifestyle factors such as tobacco use could account for benzene-associated risk differences. The workers in this investigation may have been exposed to chemicals other than benzene in principal. The observed excesses for ANLL could be due to these alternative chemical exposures, however risk for ANLL/MDS were systemically increased across the spectrum of industries studied, arguing that these associations were due to the common exposure to benzene and not to other industry-specific exposures.

7. For the observed dose-response, it has been suggested that exposure estimates for benzene were incorrectly assigned; however, these assignments of incorrect levels would have to have been carried out with a similar degree and in each of the 12 cities.

Wong, O. (2002). "Investigations of benzene exposure, benzene poisoning, and malignancies in China." Regul Toxicol Pharmacol **35**(1): 126-35. (Wong 2002)

Response to Hayes (2001)

Previous comments and questions have been raised about several aspects of the NCI-CAMP study on a number of occasions. The remainder of the comments can be summarized as follows:

1. Unstable comparison rates: The study relied on relatively small ad hoc unexposed groups. For example, among the four cases of ANLL and the unexposed group, the diagnoses of only one case was confirmed.

2. Selection bias: Some of the secondary documents physical examination forms and hazardous work compensation registries were potentially related to the workers' health status in using them to identify cohort members would introduce bias in the selection of the cohort.

3. Bias and mortality or case ascertainment: The vital or disease status of employed or retired workers was determined from records maintained in the factories. Deceased and departed workers were followed-up with their new place of employment,

contacting next of kin, contacting their doctor or contacting a local police stations. Thus the quality of follow-up could vary markedly from location to location, industry to industry and factory to factory. As a result of the high awareness of the health hazards, particularly lymphohematopoietic disorders, associated with benzene exposure, workers with benzene exposure could have more complete records versus the unexposed workers.

4. Low diagnostic confirmation: Yin *et al*. (1994), reported that 85% to 95% or 89.5% of the diagnoses of HLP disorders were verified with medical records. This was misleading since the verification was not based on specific categories. Confirmation of diagnosis accuracy should be in terms of specific disease categories since the latter were used in the analysis. According to Travis *et al*. (1994), only 9 cases of ANLL among the exposed workers and 1 case of ANLL among the unexposed workers, were actually confirmed according to the criteria set forth in the chapter. According to Yin *et al*. (1996), the numbers of ANLL cases among the exposed and unexposed workers were 23 and 4, respectively. The corresponding diagnostic confirmation rates for ANLL were therefore, 39% for the exposed workers and 25% in the unexposed workers respectively.

5. Confounding exposures of benzene exposed cohort: By design, a comparison between the benzene exposed workers and control workers would not have been limited to the effects of benzene, but would also reflect the effects of other occupational carcinogens such as insecticides. Therefore, this study was not designed properly to address the effects of benzene only.

6. Confounding Factors: Hayes *et al*. dismissed all of the potential confounding factors completely. Regarding smoking, it has been found to be a risk factor for leukemia, particularly ANLL. The fact that lung cancer risk was significantly elevated among the exposed male workers in the Chinese benzene cohort suggested that there might be a disproportionately large number of smokers in the exposed cohort. Smoking information was collected and analyzed in the CAPM study, but not in the CAPM-NCI study. The possibility of confounding due to other exposures, particularly other chemical exposures was categorically dismissed with - only radiation and benzene have been linked with leukemia.

7. Exposure Estimates Discrepancies: He dismissed the discrepancies by making a blanket statement that the 1,477 actual measurements taken by Chinese scientists and government health agencies since 1950 were short term grab samples. In other words, Hayes *et al*. claimed that for the last 50 years, Chinese scientists and government health agencies, in an effort to monitor the exposures of Chinese workers, had virtually never taken any time weighted personnel samples. This claim is obviously not true. In addition, he never offered any proof that the estimates were indeed accurate or representative of actual exposures over time.

In summary, Hayes *et al.* did not respond to several important mythological issues raised in the previous critique. Large question still remain about potential confounding and the lack of any evidence validating the estimates made by Dosemeci e*t al*. (1994).

3. The Chemical Worker Studies

<u>**Dow Chemical Studies – Three Successive Retrospective Mortality Studies**</u>

Ott, M. G., J. C. Townsend, et al. (1978). "Mortality among individuals occupationally exposed to benzene." <u>Arch Environ Health</u> **33**(1): 3-10. (Ott, Townsend et al. 1978)

<u>**Cohort Description and Methods:**</u>

The present retrospective cohort study examines the long-term mortality experience of 594 workmen exposed to benzene at the Michigan Division of Dow Chemical. Three production areas used benzene on a continuous basis: Chlorobenzol (1920 – present), alkylbenzene (1935 – present) and ethyl cellulose (1936 to present). In the first two production areas, benzene is a raw material consumed in the process, whereas in the ethylcellulose department, benzene is employed as a solvent. Benzene concentrations in the work areas were estimated from industrial hygiene surveys and discussed with plant operating personnel. Other compounds were present in the occupational environment and throughout the manufacturing complex. Therefore, none of the employees in the study experienced exposure to benzene alone. Many long-term workers may have been exposed to a wide range of chemicals as a result of transfers to and from non-benzene production areas. A description of the environment in each benzene area is presented. Analysis covered the years 1940 to 1973.

Benzene concentrations in the work areas were estimated from industrial hygiene surveys and discussed with plant operating personnel. Additional chemicals were present throughout the complex, and no employee was exposed to only benzene. Many long term workers had exposure to a wide range of chemicals due to movement within departments of the facility.

The following categorization rules were adopted for jobs in the chlorobenzol production area: very low exposure - <2 ppm TWA and low exposure - 2-9 ppm TWA. Prior to 1960 there was limited sampling and the categorization scheme may be conservative for the exposures during that period. In the ethylbenzene production area, exposures were categorized as follows: very low exposure - <2 ppm TWA, low exposure – 2-9 ppm TWA, moderate exposure – 10-24 ppm TWA and high exposures - 25+ ppm TWA. The ethylbenzene production area also had the potential for exposure to other toxicologically important chemicals, including ethylbenzene, divinylbenzene, toluene, xylene, isopropylbenzene, styrene, isopropylbenzene, and alpha-methylstyrene. Categorization of exposures in the ethyl cellulose production department was similar to the two previous areas. Additional toxic materials in the production area were methylchloride, ethyl ether, and ethyl alcohol.

In the ethylcellulose production area, high exposures occurred in the sheeting operation where operators entered closed areas to make adjustments to the casting equipment. High levels were documented in 1953 and engineering changes were made including increased localized ventilation. In 1963-1964, concentrations were once again found to be high due to process changes and the deteriorating condition of the equipment. At

that time, detailed medical examinations were given to employees. A continuous monitor was installed and improvements were made to lower exposure levels. A review of the medical records of the 10 workmen has shown no subsequent hematopoietic abnormality.

Fifty-three workers had prior exposure to arsenicals, vinylchloride, or asbestos which are all associated with excess malignancies. These employees were excluded from analyses dealing with mortality related to benzene exposure.

All job assignments for one or more months were categorized. The analysis of cumulative dose which was calculated by multiplying the time-weighted average value for each category of intensity by the number of months spent exposed to each level The mean time-weighted value of 1 ppm was used for the very low level, 5 ppm for low level, 17 ppm for moderate level, and 30 ppm for high level. The mortality data were analyzed by production area according to cumulative dosage and interval since first exposure. Expected deaths were calculated from U.S. white male mortality for the years 1942, 1947, 1952, 1957, 1962, 1967, and 1971. Age and cause-specific standardized mortality ratios were utilized in the comparison.

Five hundred ninety individuals were included in the cohort. Through company record searches 255 were found to still be working for the company, 87 individuals were retired and 71 former employees were deceased. Of the remaining 181 former employees, 31 were identified as dead from social security records. Sixty- four had worked for less than 1 year in benzene areas and 165 had worked for less than 10 years in benzene areas. Copies of death certificates were not obtained for 3 decedents traced through Social Security, all of whom were exposed to benzene doses estimated to be less than 1,000 ppm x months of exposure or ppm months.

Results:

No statistically significant increases were found in any cause of death category in the population, excluding employees with arsenicals, asbestos, or high monochloride exposure. No association with intensity of benzene exposure or cumulative dose was found with respect to these individuals.   Analysis by production area revealed no statistically significant differences in mortality: Chlorobenzol, SMR = 89; Alkyl benzene, SMR = 90 and ethylcellulose, SMR=72.

A detailed review of medical and occupational records was undertaken for 5 decedents whose medical findings were consistent with benzene toxicity. Two died of anemia – one was pernicious anemia, while the other was aplastic anemia. The third death was a case of myeloblastic leukemia. Two deaths from leukemia were observed, compared with one expected, to the end of 1973. One case was simply labeled leukemia, while the other was acute myelogenous leukemia. After excluding cohort members with other hazardous exposure, they observed one death from leukemia versus 0.9 expected. See table below for specific information on various causes of death.

Table 26 - Observed and Expected Deaths by Cause Including and Excluding Employees with Arsenicals, Asbestos, or High Vinyl Chloride Exposure, 1940-1973				
	Total Population		**Population Less Exclusions**	
Cause of Death Category	**Obs/Exp**	**SMR**	**Obs/Exp**	**SMR**
All Causes	102/128.2	80	91/114.1	80
Total Malignancies	30/22.8	132	24/20.3	108
Lymphatic & Hematopoietic Tissue (except Leukemia)	2/1.5	*	2/1.3	*
Leukemia	2/1.0	*	1/.9	*
All Other	3/2.6	*	3/2.4	*
Anemias	2/.2	*	1/.1	*

[*]Less than five observed deaths.

M. G. Ott, J.C. Townsend, W.A. Fishbeck and R.A. Langner. 1978. Mortality Among Individuals Occupationally Exposed to Benzene. *Archives of Environmental Health* 3-10.

Limitations:
1. No personal, time-weighted industrial hygiene measurements.
2. Exposure history was based upon estimated ranges from area sampling, not individualized data, including work practices, personal protective equipment use, etc.
3. Exposed workers most likely had innumerable chemical exposures, including benzene.
4. Use of general population data for the control introduces the possibility of the "healthy worker" effect, which tends to lower standardized mortality ratios artificially and may obscure any significant findings.
5. No control for potential confounders and modifying factors, such as smoking.
6. There was incomplete follow-up of the cohort members and data was very likely missing and possibly skewed due to non-differential effects.

Bond, G. G., E. A. McLaren, et al. (1986). "An update of mortality among chemical workers exposed to benzene." Br J Ind Med **43**(10): 685-91. (Bond, McLaren et al. 1986)

Cohort Description and Methods:
This study updates the mortality experience of the Dow Michigan division previously studied with an additional nine years of follow-up to the end of 1982. During the follow-up period, 364 additional employees were added to the cohort. This study presents the mortality among 956 total employees.

Similar methods to the first study were followed with little deviation. Company census lists were consulted for all workers with >1 month work experience in the three production areas between 1938 – 1970. All job assignments involving potential exposure to benzene up to the end of 1978 were coded and considered for exposure classification. Each job entry was assigned one of four exposure intensity level: very low, low, moderate, and high - based on available industrial hygiene monitoring. All jobs held after 1972 were classified as either low or very low exposure. Allowance was made for a possible latency period by lagging exposures 15 years.

As in the first study, employees were identified with prior exposure to arsenic, vinylchloride and asbestos. Analyses were performed both with and without these employees.

Death certificates were obtained for all but 1 (0.4%) of the decedents. This death of unknown cause was included in the totals for analysis but was not allocated to any specific category. The main duration of exposure was 7.0 years with a median of 2.6. The 956 employees contributed a total of 24,571 person years with an average follow-up of 25.7 years. The average age at entry into follow-up was 31 years.

Nearly a quarter (229 subjects) of the cohort were exposed to jobs categorized as 30 ppm TWA benzene exposure, and nearly a third (311) were exposed in jobs categorized as 17 ppm TWA.

Results:

All cause mortality had an SMR=84, or 83 if the arsenic, asbestos, and vinylchloride exposed subjects were excluded. This represented a significant deficit, but was consistent with the general pattern of a healthy worker effect. Four deaths were observed from leukemia, which was a non-significant excess. However, there was a significant excess of myelogenous leukemia, four observed versus 0.9 expected (p=0.011). There was also a case of myeloblastic leukemia previously identified in the first cohort study, but the cause of death was walking pneumonia. See table below specific causes of death in the cohort.

Estimated exposures for the five leukemia deaths were as follows: 1) 545 ppm months (45.4167 ppm-years), 2) 18 ppm months (1.5 ppm-years), 3) 305 ppm months (25.4167 ppm-years), 4) 421 ppm months (35.0833 ppm-years), and 5) 343 ppm months (28.5833 ppm-years). Both new leukemias had the potential for unquantified brief, but potentially relatively high, exposure to benzene. In the alkylbenzene area, benzene levels were measured as high as 283 ppm in some samples and in ethylcellulose as high as 937 ppm. Therefore, caution must be exercised when interpreting the cumulative dose in the cases. An additional case (besides the two cases of anemia originally found by Ott) of a nonmalignant blood disease, specifically identified as myelofibrosis, was identified in an 80 year old former worker with an estimated cumulative exposure of 6,027 ppm month (502.25 ppm-years).

When the analysis for mortality in the total cohort was carried out with a 15-year minimal latency period, the mortality patterns were not significantly altered, although some of the cause specific SMR were increased slightly. The 15 year lag effectively removed those cohort members first exposed after 1967 from the analysis.

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Analysis by work area, duration of exposure and cumulative dose index did not show a pattern suggested of a causal association between exposure to benzene and any particular category of death. Three of the four patients with leukemia, one with multiple myeloma and one with myelofibrosis, worked in the alkyl benzene department. This may indicate some additional co-factor that is important in the etiology of these deaths.

Table 27 - Observed and Expected Deaths by Cause, SMRs and 95% confidence limits.[*] Mortality Among Benzene Cohort, 1940-82								
	Total Cohort				Cohort Less Exclusions[†]			
Cause of Death (ICD-8th)	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All Causes (including 1 unknown)	225	286.6	84	73-95	200	242.3	83	72-95
All Malignant Neoplasms (140-209)	59	54.7	108	82-139	49	49.2	100	74-132
Lymphosarcoma and Reticulosarcoma (200)	2	1.1	180	22-657	2	1.0	199	24-722
Hodgkin's Disease (201)	0	0.7	-	0-527	0	0.6	-	0-615
Leukaemia and Aleukaemia (204-207)	4	2.1	194	52-488	3	1.9	162	33-461
Other Lymphatic Tissue (208)	1	1.3	76	2-429	1	1.2	84	2-464
Other and Unspecified Sites (199)	7	3.8	184	74-380	7	3.4	205	83-424
Diseases Blood and Blood-forming Organs (280-289)	3	0.7	444	88-1252	1	0.6	164	4-929

[*]Fisher's exact limits when observed less than 20 approximate limits otherwise.
[†]Less those exposed to arsenic, asbestos, or high levels of vinyl chloride.

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

Table 28 - Mortality Summary by Estimated Cumulative Dose of Benzene Exposure, Excluding Employees with Competing Exposures[†]

	Exposure Lagged By					
	0 years			15 years		
Cause of Death and Cumulative Dose Level	Obs	Exp	SMR	Obs	Exp	SMR
All Causes (001-999)						
0-499 ppm months	115	151.4	76	105	117.8	89
500-999 ppm months	43	35.2	122	33	25.7	129
≥1000 ppm months	42	55.6	76	27	37.4	72
Total	200	242.3	83[*]	165	180.5	91
All Cancer (140-209)						
0-499	27	30.0	90	27	25.0	108
500-999	11	7.3	150	9	5.7	159
≥1000	11	11.9	92	7	8.4	84
Total	49	49.2	100	43	39.1	110
Lymphopoietic Cancer (200-209)						
0-499	4	3.0	133	3	2.3	132
500-999	0	0.7	-	0	0.5	-
≥1000	2	1.1	183	2	0.7	274
Total	6	4.8	125	5	3.5	142
Leukaemia (204-209)						
0-499	2	1.2	167	2	0.9	222
500-999	0	0.3	-	0	0.2	-
≥1000	1	0.4	250	1	0.3	333
Total	3	1.9	158	3	1.4	214

[*]Significant at α = 0.05.
[†]Less those exposed to arsenic, asbestos, or high levels of vinyl chloride.

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

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Limitations:

1. No personal, time-weighted industrial hygiene measurements.
2. Exposure history was based upon estimated ranges from area sampling, not individualized data, including work practices, personal protective equipment use, etc.
3. They were unable to account for peak exposures that may have added significant exposure to the cumulative dose of effected workers.
4. Exposed workers most likely had innumerable chemical exposures, including benzene.
5. Use of general population data for the control introduces the possibility of the "healthy worker" effect, which tends to lower standardized mortality ratios artificially and may obscure any significant findings.
6. No control for potential confounders and modifying factors, such as smoking.
7. There was incomplete follow-up of the cohort members and data was very likely missing and possibly skewed due to non-differential effects.

Bloemen, L. J., A. Youk, et al. (2004). "Lymphohaematopoietic cancer risk among chemical workers exposed to benzene." Occup Environ Med **61**(3): 270-274. (Bloemen, Youk et al. 2004)

Cohort Description and Methods:

This is an update on the previous studies undertaken by Ott *et al.* and Bond *et al.* The observation period is extended by 14 years and includes new data from previously unevaluated areas of low benzene exposure. The expanded cohort included 2,266 who with more than one month of work in one of three benzene-exposed departments in the Dow Michigan operations. The three departments were chlorobenzol, alkyl benzene and etylcellulose production. Use of benzene in all three departments ceased completely by 1978. There were a total of 82,411 person years of observation encompassing the mortality experience from 1940-1996. Approximately two-thirds (68%) worked for at least 30 years. The cohort is predominantly white (99.5%) and mostly male (94%). Nearly half (47%) were hired in the decade following 1950. A large portion was short-term workers: 42% worked less than a year and only 26% worked 5 or more years. Fifty-nine percent (59%) of the cohort worked in ethyl cellulose. The average duration of exposure to benzene was 4.8 years, with a range of 3 months to 45 years. Average cumulative exposure was 39.7 ppm-years (range: 0.05 to 852 ppm-years) and average intensity of exposure was 9.6 ppm (range: 0.5 to 35 ppm).

This update has the advantage of improvements made in the Dow Epidemiology department. Starting with 1940, the complete work history of all United States workers was placed in a database. The original inclusion criteria were continued in this update. Persons employed in the chlorobenzol area with jobs in the lowest exposure category are now included in the cohort. For each employee, persons at risk for mortality were accumulated until date of death, date lost of follow-up, or the end of the study period, December 31, 1996, whichever occurred first.

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A certified industrial hygienist with knowledge of the three production areas reevaluated all jobs for exposures. The same categorization scheme was used; however, the very low category was changed to <1ppm, versus <2 ppm. There were no noted changes in individual exposure estimates when compared to the previous study.

Three exposure measures were used to evaluate risk: duration of exposure, cumulative exposure and average intensity. Each exposure measure was broken down into three levels in order to include 1/3 of cumulative cases in each level.

A 15 year lag period was analyzed in order to evaluate risks associated with cumulative exposure.

Results:

A total of 1,054 (46%) deaths were noted in the cohort by the end of the evaluation period. Out of the total cohort of 2,266 workers, only 13(0.6%) had an unknown vital status. Overall, mortality was significantly below (10%) the U.S. comparison values. Comparisons with the local county data yielded similar results. Non-malignant diseases of the blood and blood-forming organs had an SMR = 2.17 (95% CI: 0.87 – 4.48). The number of deaths due to malignancies was in line with expectations (SMR = 0.97). The category of multiple myeloma had 3 observed deaths with 4.2 expected. Chronic lymphatic leukemia also had a deficit with 1 observed and 2.4 expected. Estimates for Non-Hodgkin's leukemia, leukemia, acute non-lymphatic leukemia were slightly increased (1.06, 1.14 and 1.11), although none were significant. See table below for SMR related to specific causes of death.

The analysis by duration of exposure, cumulative exposure and average intensity revealed some difficult to interpret findings. Non-malignant diseases of the blood risk increase with increasing duration of exposure; however, this did not hold true for cumulative exposure or average intensity. Both leukemia and ANLL risk appeared to increase with cumulative exposure, but this pattern was not repeated when evaluating duration or average intensity. With that said, ANLL had very low numbers of deaths, thus limiting any findings. The authors concluded that even with the limited number of ANLL cases the data suggests a weak trend of leukemia and possibly ANLL at lower levels of cumulative exposure which approach the low estimated exposures seen in the Pliofilm cohort.

Table 29 - Observed Deaths and SMRs for Selected Causes of Death Among Benzene Exposed Chemical Workers, Compared to the US Population[†]

Cause of Death (9th revision)	Deaths	SMR	95% CI
All Causes of Death (001-999)	972	0.90[**]	0.85 to 0.96
All Lymphatic and Haematopoietic Tissue (200-208)	27	1.01	0.66 to 1.46
Non-Hodgkin's Lymphoma (200.0-200.8, 202.0, 202.8)	10	1.06	0.51 to 1.95
Hodgkin's Disease (201)	2	1.01	0.12 to 3.63
Multiple Myeloma (203)	3	0.72	0.15 to 2.10
Leukaemia and Aleukaemia (204.1)	12	1.14	0.59 to 1.99
Chronic Lymphatic Leukaemia (204.1)	1	0.42	0.01 to 2.36
Acute Non-Lymphocytic Leukaemia (205.0, 206.0, 207.0)	4	1.11	0.30 to 2.83
Diseases of Blood and Blood Forming Organs (280-289)	7	2.17	0.87 to 4.48

[†]Non-malignant causes: 1960-96, 2171 workers, 60 506 person-years at risk. Malignant causes: 1940-96, 2266 workers 82 411 person years at risk.
[*]$p < 0.05$, [**]$p < 0.01$.

L.J. Bloemen, A. Youk, T.D. Bradley, K.M. Bodner and G. Marsh. 2004. Lymphohaematopoietic Cancer Risk Among Chemical Workers Exposed to Benzene. *Occup. Environ. Med.* 61: 270-274.

Table 30 - Observed Deaths and SMRs by Benzene Exposure Measures for Selected Causes of Death, Benzene Exposed Chemical Workers, US Comparisons

Exposure Measure		0 year lag			15 year lag		
		Obs	SMR	95% CI	Obs	SMR	95% CI
Leukaemia and Aleukaemia							
Duration (y)	<5	5	0.70	0.23 to 1.63	6	0.78	0.29 to 1.70
	5-9	4	3.09	0.84 to 7.90	3	2.51	0.53 to 7.34
	10+	3	1.44	0.30 to 4.20	3	1.84	0.38 to 5.38
Cumulative Exposure	<340	4	0.60	0.16 to 1.54	5	0.69	0.23 to 1.62
(ppm-years)	28.3-79.1	4	2.00	0.54 to 5.11	3	1.71	0.35 to 5.00
	79.1+	4	2.16	0.59 to 5.53	4	2.55	0.70 to 6.54
Average Intensity (ppm)	<5	3	0.75	0.16 to 2.20	9	0.95	0.44 to 1.81
	5-14	5	1.57	0.51 to 3.66	3	2.96	0.61 to 8.64
	15+	4	1.19	0.32 to 3.05	0	0.00	0.00 to 60.93
Acute Non-Lymphocytic Leukaemia							
Duration (y)	<5	2	0.82	0.10 to 2.97	3	1.18	0.24 to 3.46
	5-9	1	2.20	0.06 to 12.23	0	0.00	0.00 to 8.33
	10+	1	1.37	0.03 to 7.66	1	1.58	0.04 to 8.79
Cumulative Exposure	<28.3	2	0.87	0.11 to 3.13	3	1.26	0.26 to 3.69
(ppm-years)	28.3-79.1	1	1.47	0.04 to 8.17	0	0.00	0.00 to 5.65
	79.1+	1	1.61	0.04 to 8.95	1	1.71	0.04 to 9.51
Average Intensity (ppm)	<5	0	0.00	0.00 to 2.64	3	0.93	0.19 to 2.73
	5-14	3	2.66	0.55 to 7.76	1	2.65	0.07 to 14.74
	15+	1	0.92	0.02 to 5.13	0	0.00	0.00 to 146.28

L.J. Bloemen, A. Youk, T.D. Bradley, K.M. Bodner and G. Marsh. 2004. Lymphohaematopoietic Cancer Risk Among Chemical Workers Exposed to Benzene. *Occup. Environ. Med.* 61: 270-274.

Limitations:

1. None of the risk estimates were significant. All CI included the value 1.
2. No personal, time-weighted industrial hygiene measurements.
3. Exposure history was based upon estimated ranges from area sampling, not individualized data, including work practices, personal protective equipment use, etc.
4. They were unable to account for peak exposures that may have added significant exposure to the cumulative dose of effected workers.
5. Exposed workers most likely had innumerable chemical exposures, including benzene that they were unable to account for in the analysis.
6. Use of general population data for the control introduces the possibility of the "healthy worker" effect, which tends to lower standardized mortality ratios artificially and may obscure any significant findings.
7. No control for potential confounders and modifying factors, such as smoking.

Monsanto/Salutia Chemical Plant Studies – Two Successive Retrospective Cohort Studies

Ireland, B., J. J. Collins, et al. (1997). "Cancer mortality among workers with benzene exposure." Epidemiology **8**(3): 318-20._ (Ireland, Collins et al. 1997)_____

Cohort Description and Methods:

This is an update of a cohort of employees from the Monsanto company plant in Sauget, Illinois. The previous evaluation of the plant was part of an industry wide benzene study performed by Wong (1987). The updated cohort includes all hourly workers who worked at the plant from 1940 -1991. Person-time accumulation began on the date of hire and ended on December 31, 1991, or earlier if the employee left for any reason. A total of 4,172 men were identified through company records and reports to the IRS. Follow-up was completed for 4,091 (98%) of the eligible employees. Eighty-one (2%) were lost to follow-up. Death certificates were ascertained for all but 20 (1%) members. Workers without a death certificate were included in all cause mortality analyses.

Exposure assessment was completed for multiple departments, including: nitrobenzene, phenol, chlorobenzene, muriatic acid and alkylbenzene production. Data collection began in 1980 and at that time only the chlorobenzene and muriatic acid departments were still operational. Most exposures had to be estimated. Information regarding process changes and the input of an industrial hygienist were used to estimate historical exposures. Continuous exposures were categorized into the following 8-hr TWAs: <1, 1-10 and 11-50 ppm. This process was not completed for maintenance jobs. In order quantify peak exposures, the number of days with a 15-minute exposure excursion above 100 ppm were estimated for all jobs. Cumulative daily exposures were categorized as follows: <12, 12-72 and >72 ppm-months. The number of days with peaks >100 ppm were categorized as follows: 0, <7, 7-40 days and >40 days. The number of days with peak exposures greater than 100 ppm range from 1 to 2,590 with a median of 22 days.

Cohort member death rates were compared with death rates for the State of Illinois.

Results:

The total mortality rates for unexposed workers was higher than the rate for Illinois with an SMR = 1.1 (95% CI: 1- 1.2).   This was largely due to heart disease and lung cancer. The exposed workers had a mortality rate similar to the Illinois population, SMR=1.0 (95% CI: 0.9-1.1). Maintenance workers had a slight deficit, SMR=0.9 (95% CI: 0.8 - 1.0). No death from Hodgkin's lymphoma or diseases of the blood or blood-forming organs occurred among exposed workers. For all leukemia, the SMR= 1.1 (95% CI: 0.4 - 2.6) in the non-exposed group and an SMR=2.5 (95% CI:0.3 - 8.9) in <12 ppm-months (1 ppm-years) category, SMR=0.0 (95% CI: 0.0 -5.4) in the 12 -72 ppm-months (1 – 6 ppm-years) category and SMR=4.6 (95% CI: 0.9 to 13.4) in the ≥72 ppm-months (≥6 ppm-years) category. For ANNL and CLL, the SMRs were also elevated in the lowest and highest continuously exposed groups; however, this is based on only one case of each type of leukemia in the respective cumulative benzene exposure categories.   The findings were similar when examined by peak exposure category.

The SMR for leukemia by year of hire was 2.9 (95% CI: 0.8-7.4) for years 1940-1949, 1.6 (95% CI: 0.0 – 8.7) for years 1950-1959 and 0.0 (95% CI: 0.0-21.7 for years 1960-1977. The SMR for the interval from onset of exposure to death was 0.0 (95% CI:0.0 - 20.4) for <10 years, 2.9 (95% CI: 0.1-16.4) for 10-19 years, 0.0 (95% CI:0.0 – 7.0) for 20-29 years and 3.5 (95% CI: 0.9 - 8.9) for <30 years. See table below for specific information.

The authors noted that they found elevated, but imprecise rates of leukemia and MM for workers ≥20 years from date of hire.

Cause of Death (ICD-9[*] Code)	Production Workers OBS/EXP and SMR (95% CI)								Maintenance Workers OBS/EXP and SMR (95% CI)	
	Non-Exposed		<12 ppm-month		12-72 ppm-month		≥72 ppm-month			
All Cancers (140-209)	157/135.8	1.2 (1.0-1.4)	21/25.0	0.8 (0.5-1.3)	15/20.5	0.7 (0.4-1.2)	28/19.1	1.5 (1.0-2.1)	242/226.54	1.1 (0.9-1.2)
Hodgkin's Disease (201)	0/1.11	0.0 (0.0-3.3)	0/0.22	0.0 (0.0-16.8)	0/0.17	0.0 (0.0-21.4)	0/0.13	0.0 (0.0-27.4)	2/172	1.2 (0.1-4.3)
Multiple Myeloma (203)	1/1.97	0.5 (0.0-2.8)	0/0.37	0.0 (0.0-10.1)	2/0.29	6.8 (0.8-2.5)	1/0.27	3.7 (0.1-20.1)	4/3.48	1.2 (0.3-2.9)
Leukemia (204-207)	5/4.51	1.1 (0.4-2.6)	2/0.81	2.5 (0.3-8.9)	0/0.69	0.0 (0.0-5.4)	3/0.65	4.6 (0.9-13.4)	9/7.16	1.3 (0.6-2.4)
Chronic Lymphatic (204.1)	1/1.01	1.0 (0.0-5.5)	1/0.17	5.9 (0.1-32.6)	0/0.15	0.0 (0.0-24.7)	1/0.15	6.7 (0.2-37.7)	1/1.56	0.6 (0.0-3.6)
Acute Non-lymphatic (205.0, 206.0)	2/1.46	1.4 (0.2-5.0)	1/0.27	3.7 (0.1-20.6)	0/0.23	0.0 (0.0-44.1)	1/0.22	4.5 (0.1-25.3)	2/2.27	0.9 (0.1-3.2)

Table 31 - Observed Deaths (OBS), Expected Deaths (EXP), SMRs and 95% CIs for Selected Causes of Death by Cumulative Benzene Exposure Category

[*]ICD-8 = International Classification of Diseases, 8th revision.

B. Ireland, J.J. Collins, C.F. Buckley and S.G. Riordan. 1997. Cancer Mortality Among Workers with Benzene Exposure. *Epidemiology* 8(3): 318-320.

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Limitations:

1. None of the risk estimates were significant, with the exception of all cancers at ≥72 ppm month (6 ppm-years). All CI included the value 1. In addition, the SMR approached significance for all leukemias at ≥72 ppm month (6 ppm-years).

2. The authors noted that exposure estimates were "difficult" for the 1940's and 1950's because of the lack of information. However, they assigned the highest exposure category to jobs during those periods. Nevertheless, they admitted that exposures could have been much higher. Four of the five leukemia cases occurred in workers who started working before 1950. The SMR for leukemia by year of hire was 2.9 (95% CI: 0.8-7.4) for years 1940-1949, which approached significance.

3. No personal, time-weighted industrial hygiene measurements.

4. Exposure history was based upon estimated ranges from area sampling (in many cases incomplete), not individualized data, including work practices, personal protective equipment use, etc.

5. Although an attempt was made to account for peak exposures, this categorization technique did not consider individual workers experience, they were simply the estimates made by the industrial hygienist.

6. Confounding variables such as cigarette smoking were not accounted for, yet there was a clear excess of lung cancer deaths in the unexposed cohort of workers, SMR=1.3 (95% CL: 1.0-1.7) and in maintenance workers, SMR=1.4 (95% CI: 1.1-1.7). There was no significant excess of lung cancer in any category of cumulative exposure in exposed workers.

7. All leukemia diagnoses were from death certificates, without verification of diagnosis, much less the particular cell type of the disorder. Misclassification of even one case with the various categories of leukemia could drastically change the outcomes. In addition, if a person died of another primary cause, it is possible that underlying leukemia would not be listed and would thus be underreported.

8. There were 2 cases of ANLL in the unexposed category and 3 in the exposed category – such limited numbers in both the unexposed and exposed categories lead to very unstable estimates of risk and severely limit any conclusions being drawn from this study.

9. Coal tar derived leukemia was used in the plant prior to 1950. It has been suggested that PAHs from coal tar are linked to lymphocytic leukemia. Both of the workers with lymphocytic leukemia started working before 1950.

Collins, J. J., B. Ireland, et al. (2003). "Lymphohaematopoietic cancer mortality among workers with benzene exposure." Occup Environ Med **60**(9): 676-9. (Collins, Ireland et al. 2003)

Cohort Description and Methods:

This is a follow-up study to the Ireland *et al.* (1997) study that examined mortality at the Solutia (formerly Monsanto) plant in Sauget, Illinois. A particular interest of this study

was to examine the lymphohematopoietic effects of low cumulative benzene exposure from short term exposure peaks.

All hourly workers employed between 1940-1970 were included in the cohort. Vital status follow-up was complete for 4,352 (99%) and 2,431(56%) were deceased. Death certificates were obtained for all but 27 (1%) of decedents. Deceased workers with no death certificate were included in all cause mortality analysis.

In order to ascertain exposures for individuals, the history of process changes, area sampling levels, individual exposures (1,090 personal TWA 8-hour benzene exposures and 247 personal short-term exposure levels) were available. Personal exposure sampling began in 1980. Some area sampling was available for all departments. In addition, the plant industrial hygienist's judgment was used to estimate exposures. Most exposures stratified by time, department and job had to be estimated without relevant personal exposure data. The exposure categories for cumulative exposure and number of days with peaks >100 ppm were carried over from the previous study. Most job types had no potential for peaks over 100 ppm. The culminated individual daily exposure and divided the exposure categories into three groups used in the previous study. Cumulative exposures ranged from 0.1 ppm-years to 632 ppm-years with a median of 3 ppm-years. Similarly when we culminated the number of days with peaks into categories used in the previous study, those job types in the plant had no potential or peak exposures over 100 ppm.

We compared worker death rates with rates of the population of Illinois and calculated standardized mortality ratios in 95% confidence levels.

Results:

Cumulative exposures ranged from 0.1 ppm-years to 632 ppm-years with a median of 3 ppm-years.

The category of all leukemia had the following SMRs: 1.0 (95% CI: 0.5 - 1.8) for no exposure; 0.7 (95% CI: 0.1 - 2.5) for >1 ppm; 1.4 (95% CI:0.4 - 3.6) for 1-6 ppm-years and 1.7 (95% CI:0.6 -3.8) for >6 ppm-years. The SMRs for ANLL were as follows: 0.8 (95% CI: 0.1 – 2.8) for no exposure; 1.4 (95% CI: 0.1 – 5.1) for >1 ppm; 2.7 (95% CI:0.3 – 9.9) for 1-6 ppm-years and 2.2 (95% CI:0.3 – 8.1) for >6 ppm-years. The SMRs for multiple myeloma also increased with progressive cumulative exposure category. Both Hodgkin's disease and non-Hodgkin's lymphoma SMRs did not increase consistently with increasing exposure.

When analyzed by frequency of peak exposures over 100 ppm, both multiple myeloma and ANLL showed an increased SMR at >40 days with a peak exposure. Twelve of the cases had cumulative exposure, while 4 had both cumulative and peak exposure and 3 had only peak exposure. Ten out of 13 cases of multiple myeloma occurred in workers with benzene exposure and all 10 deaths occurred 20+ from first exposure. Six of the cases had cumulative exposure, 2 had cumulative and peak exposure and 2 had only peak exposure. All 10 deaths from multiple myeloma occurred 20 or more years after first exposure. No deaths from anemia were found among benzene-exposed workers. In the 22 leukemia deaths, 15 occurred in workers with benzene exposure.

SMRs for leukemia by year of hire for all benzene exposed workers were 0.9 (95% CI: 0.4 – 1.7) if hired from 1940-1949, 1.6 (95% CI: 0.4 - 4.1 if hired from 1950-1959 and

3.2 (95% CI:0.7 − 9.4) if hired from 1960-1977. The SMRs for interval from onset of exposure in exposed workers were as follows: 1.3 (95% CI: 0.0 - 7.0) for <10 years; 2.2 (95% CI: 0.5 - 6.5) for 10 - 19 years and 1.1 (95% CI: 0.6 - 1.9) for 20+ years.

Unlike the Pliofilm workers there was little evidence for increasing leukemia or AML risk with increasing cumulative exposure to benzene. However, there were more leukemias (5 observed, 1.8 expected) and more AML (2 observed, 0.5 expected) when there were >40 days of peak exposures over 100 ppm. There was little to no risk with lower numbers of peak exposures in any category. See table below for more details.

Table 32 - SMRs, 95% CI, Observed Deaths (OBS), and Expected Deaths (EXP) for Selected Causes of Death by Peak Benzene Exposure Category

| | Number of Days with Peak Exposure over 100 ppm | | | | | | | |
| | None | | <7 | | 7-40 | | >40 | |
Cause of Death (ICD8 Code)	SMR (95% CI)	OBS/EXP	SMR (95% CI)	OBS/EXP	SMR (95% CI)	OBS/EXP	SMR (95% CI)	OBS/EXP
All Deaths (000-999)	1.0 (1.0 to 1.0)	1951/1943.7	1.2 (1.0 to 1.4)	117/98.5	1.0 (0.9 to 1.2)	161/160.6	1.0 (0.9 to 1.1)	202/202.1
All Cancer (140-209)	1.1 (1.0 to 1.2)	508/465.7	1.3 (0.9 to 1.8)	30/23.8	1.1 (0.8 to 1.5)	46/39.8	1.2 (0.9 to 1.5)	61/51.2
Hodgkin's Disease (201)	0.7 (0.1 to 2.4)	2/3.0	0.0 (0.0 to 22.8)	0/0.2	0.0 (0.0 to 14.5)	0/0.3	0.0 (0.0 to 13.1)	0/0.3
Non-Hodgkin's Lymphoma (200, 202)	1.4 (0.9 to 2.2)	20/14.3	1.3 (0.0 to 7.4)	1/0.8	0.7 (0.0 to 4.2)	1/1.3	1.8 (0.4 to 5.1)	3/1.7
Multiple Myeloma (203)	1.2 (0.6 to 2.4)	9/7.2	0.0 (0.0 to 10.2)	0/0.4	1.7 (0.0 to 9.4)	1/0.6	4.0 (0.8 to 11.7)	3/0.8
Leukaemia (204-207)	1.0 (0.5 to 1.6)	15/15.6	1.2 (0.0 to 6.8)	1/0.8	0.7 (0.0 to 4.0)	1/1.4	2.7 (0.8 to 6.4)	5/1.8
Chronic Lymphatic (204.1)	0.9 (0.2 to 2.5)	3/3.5	0.0 (0.0 to 20.6)	0/0.2	0.0 (0.0 to 12.2)	0/0.3	2.5 (0.0 to 13.8)	1/0.3
Acute Non-lymphatic (205.0-206.0)	1.3 (0.4 to 3.0)	5/3.9	0.0 (0.0 to 10.2)	0/0.2	0.0 (0.0 to 10.4)	0/0.4	4.1 (0.5 to 14.9)	2/0.5
Persons at Risk	4417		898		690		339	
Person-years	129000		6991		11593		11448	

J.J. Collins, B. Ireland, C.F. Buckley and D. Shepperly. 2003. Lymphohaematopoietic Cancer Mortality Among Workers With Benzene Exposure. *Occup. Environ. Med.* 20: 676-679.

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Table 33 - SMRs, 95% CI, Observed Deaths (OBS), and Expected Deaths (EXP) for Selected Causes of Death by Cumulative Benzene Exposure Category

| | Cumulative Exposure (ppm-years) | | | | | | | |
| | No Exposure | | <1 | | 1-6 | | >6 | |
Cause of Death (ICD8 Code)	SMR (95% CI)	OBS/EXP	SMR (95% CI)	OBS/EXP	SMR (95% CI)	OBS/EXP	SMR (95% CI)	OBS/EXP
All Deaths (000-999)	1.0 (1.0 to 1.1)	1300/1290.7	0.9 (0.8 to 1.1)	342/361.7	1.1 (1.0 to 1.2)	365/345.8	1.0 (0.9 to 1.1)	424/406.8
All Cancer (140-209)	1.1 (1.0 to 1.2)	336/305.2	0.9 (0.8 to 1.2)	84/88.7	1.1 (0.9 to 1.4)	97/85.5	1.3 (1.1 to 1.5)	128/101.2
Hodgkin's Disease (201)	0.5 (0.0 to 2.8)	1/2.0	1.7 (0.0 to 9.7)	1/0.6	0.0 (0.0 to 6.7)	0/0.6	0.0 (0.0 to 6.6)	0/0.6
Non-Hodgkin's Lymphoma (200, 202)	1.5 (0.8 to 2.5)	14/9.6	1.1 (0.2 to 3.4)	3/2.6	1.5 (0.4 to 3.8)	4/2.7	1.2 (0.3 to 3.2)	4/3.2
Multiple Myeloma (203)	1.1 (0.3 to 2.5)	5/4.7	1.4 (0.2 to 5.1)	2/1.4	1.5 (0.2 to 5.4)	2/1.3	2.6 (0.7 to 6.7)	4/1.5
Leukaemia (204-207)	1.0 (0.5 to 1.8)	10/10.4	0.7 (0.1 to 2.5)	2/2.9	1.4 (0.4 to 3.6)	4/2.9	1.7 (0.6 to 3.8)	6/3.5
Chronic Lymphatic (204.1)	0.9 (0.1 to 3.1)	2/2.3	1.6 (0.0 to 8.9)	1/0.6	0.0 (0.0 to 5.9)	0/0.6	1.3 (0.0 to 7.2)	1/0.8
Acute Non-lymphatic (205.0-206.0)	0.8 (0.1 to 2.8)	2/2.6	1.4 (0.1 to 5.1)	1/0.7	2.7 (0.3 to 9.9)	2/0.7	2.2 (0.3 to 8.1)	2/0.9
Persons at Risk	4063		2037		1343		683	
Person-years	86268		25798		24106		22859	

J.J. Collins, B. Ireland, C.F. Buckley and D. Shepperly. 2003. Lymphohaematopoietic Cancer Mortality Among Workers With Benzene Exposure. *Occup. Environ. Med.* 20: 676-679.

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Limitations:

1. None of the risk estimates were significant, with the exception of all cancers at ≥72 ppm month (6 ppm-years). All other CI were wide and included the value 1.
2. The authors noted that exposure estimates were "difficult" for the 1940's and 1950's because of the lack of information. However, they assigned the highest exposure category to jobs during those periods. Nevertheless, they admitted that exposures could have been much higher. Four of the five leukemia cases occurred in workers who started working before 1950.
3. No personal, time-weighted industrial hygiene measurements.
4. Exposure history was based upon estimated ranges from area sampling (in many cases incomplete), not individualized data, including work practices, personal protective equipment use, etc.
5. Although an attempt was made to account for peak exposures, this categorization technique did not consider individual workers experience, they were simply the estimates made by the industrial hygienist.
6. Confounding variables such as cigarette smoking were not accounted for, yet there was a clear excess of lung cancer deaths in the unexposed cohort of workers, SMR=1.3 (95% CL: 1.0-1.7) and in maintenance workers, SMR=1.4 (95% CI: 1.1-1.7). There was no significant excess of lung cancer in any category of cumulative exposure in exposed workers.
7. All leukemia diagnoses were from death certificates, without verification of diagnosis, much less the particular cell type of the disorder. Misclassification of even one case with the various categories of leukemia could drastically change the outcomes. In addition, if a person died of another primary cause, it is possible that underlying leukemia would not be listed and would thus be underreported.
8. There were 2 cases of ANLL in the unexposed category and 5 in the exposed category – such limited numbers in both the unexposed and exposed categories lead to very unstable estimates of risk and severely limit any conclusions being drawn from this study.
9. Coal tar derived leukemia was used in the plant prior to 1950. It has been suggested that PAHs from coal tar are linked to lymphocytic leukemia. Both of the workers with lymphocytic leukemia started working before 1950.

Wong, O. (1987). "An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results." Br J Ind Med **44**(6): 365-81. (Wong 1987)

Cohort Description and Methods:

This study examined the mortality of a cohort of 7676 male chemical workers from seven plants from January 1, 1946-December 31, 1977. Women were not included due to small numbers. All of the workers had been exposed to benzene in a continuous or intermittent fashion for at least six months. The continuous category consisted of jobs in which work was assigned to a discrete area in which benzene was produced, separated,

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recovered, processed, loaded/unloaded, and potential exposure to benzene occurred on at least 3 days a week. The intermittent category included a pattern which could not be characterized as continuous. There were a total of 130,967.9 person years of observation. For most plants, the comparison group consisted of all occupationally non-exposed workers at the same plant, although this was modified for two plants due to size considerations. The U.S. rates (5 year periods) were applied to person years of observation to obtain the expected number of deaths when the groups were matched for person years, race and age by calendar year. Race was not available for 604 (7.87%) of the cohort and these persons were considered to be white which may overestimate risk due to the higher death rate for leukemia among the U.S. white male population compared to the non-white population.

The beginning date of the cohort at each plant was set by the introduction of benzene and the earliest date with complete employment records. The closing date of cohort boundary was generally 1975, except that it was extended to 1976 and 1977 in two plants. Originally, a cohort of 14,000 from nine plants and seven companies was assembled; however, one company with two plants withdrew from the study (-4,000 cohort members) and another company had incomplete records prior to 1957. The cohort definition was restated for these two plants and moved from 1946 to 1957.

Data were collected from the companies in a variety of ways, including abstracting from existing company studies and employment of an outside company to gather data. Nevertheless, each group used a uniform cohort definition and a common protocol. Demographic and complete work histories came from the companies and death certificates were requested and coded in a uniform fashion. Of the 1,036 individuals who died during the study period, death certificates were obtained for 1,013 (97.8%). The unexposed group had 4.29% of death certificates missing, while the exposed group was missing (1.12% and 1.32%). At the end of the study period, the vital status of 177 terminated employees (2.31%) remained unknown, which was comparable across the two groups.

All data was verified by the research team, although this procedure was infeasible for one plant because of inadequate work histories and the fact that exposed workers had been identified by supervisors. The number of individuals correctly included or excluded compared to the number of records examined was 99.2%. In addition, 10% of records were checked for coding errors and a 2.6% rate was found.

Exposures were categorized as unexposed, intermittently exposed and continuous exposure. Three-thousand seventy four were unexposed, while 1,066 were intermittently exposed and 3,536 were exposed continuously. If a person had continuous intermittent exposure, they were categorized in the continuous category. The average duration of employment was 15.82 years for the total cohort, 13.00 years for the comparison group, 15.63 years for the intermittent exposure group, and 18.32 years for the continuous exposure group.

Because SMR may not be optimal for data based on small control comparison groups, relative risk (derived through Mantel-Haenszel chi-square procedures) may be computed to compare the exposed to unexposed population.

Results:

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The total number of observed deaths was 1,036, versus 1,253.06 expected. This resulted in an SMR=82.7, which was statistically significant at the 0.01 level. In addition, mortality from all cancers was also less than expected; however, the SMR was not significant. There were 7 deaths due to cancer of the lymphatic tissue (5.5 expected), which was not significant. Hematopoietic and lymphopoietic combined mortality was less than expected with an SMR=90.3.

Standardized mortality ratios (SMRs) from all lymphatic and haematopoietic (lymphopoietic) cancer combined, leukemia, non-Hodgkin's lymphoma (lymphosarcoma, reticulosarcoma, and other lymphoma), and non-Hodgkin's lymphopoietic cancer (non-Hodgkin's lymphoma and leukaemia) for the exposed group were slightly, but not significantly, raised above the national norm. However, these SMRs were considerably higher than those in the comparison group. When the group with no occupational exposure was used for direct comparison, the continuously exposed group experienced a relative risk from lymphopoietic cancer of 3.20 (p< 0.05). In addition, the Mantel-Haenszel chi-square showed that the association between continuous exposure to benzene and leukemia was statistically significant (p< 0.05). See table below for specific results related to cause of death and benzene exposure.

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Cause of Death (8th ICDA)	Observed Deaths	Expected Deaths	SMR	Lower Limit	Upper Limit
All Cohort Members					
All Causes	1036	1253.06	82.7[†]	77.7	87.9
All Cancers (140-209)	214	239.85	89.2	77.7	102.0
Lymphatic and haematopoietic cancer (200-209)	22	24.36	90.3	56.6	136.7
Lymphosarcoma and reticulosarcoma (200)	5	5.52	90.6	29.2	211.4
Hodgkin's disease (201)	3	3.71	80.9	16.3	236.3
Leukaemia and aleukaemia (204-207)	7	9.36	74.8	30.0	154.1
Other lymphatic tissue cancer (22, 203, 208)	7	5.55	126.1	50.5	259.9
Cohort Members Continuously Exposed to Benzene					
All Causes	531	613.12	86.6[†]	79.4	94.3
All Cancers (140-209)	123	117.71	104.5	86.8	124.8
Lymphatic and haematopoietic cancer (200-209)	15	11.74	127.8	71.4	210.9
Lymphosarcoma and reticulosarcoma (200)	3	2.65	113.0	23.3	330.6
Hodgkin's disease (201)	2	1.78	112.2	13.6	405.1
Leukaemia and aleukaemia (204-207)	6	4.43	135.4	49.6	294.9
Other lymphatic tissue cancer (22, 203, 208)	4	2.77	144.7	39.4	370.0
Cohort Members Intermittently Exposed to Benzene					
All Causes	179	200.88	89.1	76.5	103.2
All Cancers (140-209)	38	38.93	97.6	68.9	134.1
Lymphatic and haematopoietic cancer (200-209)	4	3.85	104.0	28.3	265.9
Lymphosarcoma and reticulosarcoma (200)	1	0.87	114.6	2.9	636.5
Hodgkin's disease (201)	0	0.56	0	-	-
Leukaemia and aleukaemia (204-207)	1	1.49	67.0	1.7	372.2
Other lymphatic tissue cancer (22, 203, 208)	2	0.88	226.0	27.4	816.1
Cohort Members Intermittently or Continuously Exposed to Benzene					
All Causes	710	819.49	86.6[†]	80.4	93.2
All Cancers (140-209)	161	157.36	102.3	87.1	119.3
Lymphatic and haematopoietic cancer (200-209)	19	15.68	121.1	73.0	189.3
Lymphosarcoma and reticulosarcoma (200)	4	3.55	112.8	30.7	288.4
Hodgkin's disease (201)	2	2.37	84.4	10.2	304.6
Leukaemia and aleukaemia (204-207)	7	5.96	117.4	47.1	242.0
Other lymphatic tissue cancer (22, 203, 208)	6	3.66	163.8	60.0	356.8

[†]Significant at 0.01

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. I General Results. *British Journal of Industrial Medicine.* 44: 365-381.

		Observed Deaths:				
Table 35 - Mantel-Haenszel Relative Risk and Chi-Squares for Leukaemia Between Chemical Workers Occupationally Exposed and Not Exposed to benzene, Adjusted for Age and Race						
Exposure Groups Compared	**Race**	**Exposed**	**Non-Exposed**	**Relative Risk**	**Mantel-Haenszel Chi-Square**	**p Value**
Total exposed (continuous and intermittent) *v* comparison	White	6	0	Undefined	3.58	0.06
	Non-white	1	0	Undefined	0.18	0.67
	Both	7	0	Undefined	3.73	0.05
Continuously Exposed *v* comparison	White	5	0	Undefined	4.26[*]	0.04
	Non-white	1	0	Undefined	0.23	0.63
	Both	6	0	Undefined	4.42[*]	0.04

[*]Statistically significant at the 0.05 level.

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. I General Results. *British Journal of Industrial Medicine.* 44: 365-381.

Table 36 - Mantel-Haenszel Relative Risk and Chi-Squares for non-Hodgkin's Lymphopoietic Cancer (non-Hodgkin's lymphoma and leukaemia) Between Chemical Workers Occupationally Exposed and Not Exposed to benzene, Adjusted for Age and Race

Exposure Groups Compared	Race	Observed Deaths: Exposed	Non-Exposed	Relative Risk	Mantel-Haenszel Chi-Square	p Value
Total exposed (continuous and intermittent) *v* comparison	White	14	1	8.60	5.84[*]	0.02
	Non-white	3	1	0.48	0.48	0.49
	Both	17	2	3.71	4.14[*]	0.04
Continuously Exposed *v* comparison	White	11	1	9.60	6.33[*]	0.01
	Non-white	2	1	0.43	0.60	0.44
	Both	13	2	3.77	4.34[*]	0.04

[*]Statistically significant at the 0.05 level.

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. I General Results. *British Journal of Industrial Medicine.* 44: 365-381.

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Limitations:

1. The use of a relatively small internal comparison group can introduce statistical instability and lead to the appearance of significance where this is not true. There were only seven cases of leukemia, 6 in the continuously exposed and 1 in the intermittent grouping. There was a deficit of leukemia in the comparison group (0 observed vs. 3.4 expected) which magnifies the relative risk of the exposed.

2. The types of leukemia were not broken down by cell type, thus limiting the analysis. For instance, if most or all were of one type not associated with benzene exposure this would completely change the analysis.

3. The diagnoses were ascertained from death certificates, which may have limited information, or even incorrect information, particularly regarding cell type of lymphohematopoietic cancer. This may have led to misclassification and significant changes in the outcomes primarily due to the very small numbers of individual types of lymphohematopoietic cancer cases in the exposed and unexposed groups. There was no way of verifying the diagnosis stated on the certificate. In addition, if a person died of an alternative cause, besides a lymphohematopoietic disorder, this may have been excluded from the death certificate if it was not the "cause" of death. For instance, if a person was in the early stages of lymphohematopoietic disorder without clinical signs, this may have simply been missed without an autopsy.

4. In addition of lymphohematopoietic cancer, the exposed versus unexposed group had higher SMRs for: all cancer, stomach cancer, lung cancer, kidney cancer, brain cancer, benign neoplasms, diabetes and emphysema. This raises the question of whether there was an additional factor, besides benzene, that was particular to the exposed group versus the unexposed group. This is particularly true regarding smoking, which was not controlled for in the analyses, yet two diseases which are closely associated with smoking, lung cancer and emphysema, were higher in the exposed group.

5. There was a variety of missing information that resulted in the exclusion of some data in the analyses: (1) Two of the 7 plants did not include 1946-1957 – years which have historically been associated with higher exposures in other studies. (2) The unexposed group was missing 14 death certificates (4.29% vs. 1.12% and 1.32%) versus the two groupings (Based upon different exposure groups, thus the two percentages) of exposed workers who combined were missing nine. This could have potentially affected analysis, particularly given the small numbers in each disease category.

Wong, O. (1987). "An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses." Br J Ind Med **44**(6): 382-95. (Wong 1987)

Cohort Description and Methods:

See above for general methods. In the jobs categorized as "continuous" benzene exposure, categories were further delineated into 8 hr TWA and peak exposure (no control

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for respirator use) as follows: 8 hr TWA low <1 ppm, medium = 1-10 ppm, high = 11-50 ppm and very high > 50 ppm. Peak exposure was categorized as follows: low < 25 ppm, medium = 25-100 ppm and high >100 ppm. In the jobs categorized as "intermittent" benzene exposure categories were further delineated as follows (no control for respirator use): low <25 ppm, medium 25-100 ppm and high > 100 ppm.

Classification of each job by exposure was based on a uniform task approach and these were completed by a group of industrial hygienists from the participating companies who were familiar with the plant operations. There were 34 uniform tasks.   In addition, they considered available industrial hygiene measurements, current and past changes in production and process modification to determine a concentration level of benzene exposure for each task. An 8-hour time-weighted average for each job was obtained by summing the products of the proportion of the time at each uniform task and a corresponding benzene concentration.

The industrial hygiene data for some plants were limited before 1970. Two plants did not use the uniform task approach to estimate exposure levels due to lack of specific employment histories. At one plant, supervisors and co-workers from exposed departments with cohort members estimated the exposures. At the other plant, exposure levels were estimated by a long term industrial hygienist who primarily used are measurements.

Cohort members were classified into three categories according to their occupational benzene exposure history.   See table below for specific categories of exposure and frequency/percent of the cohort.

Table 37 - Distribution by Cumulative Exposure (ppm-months) of Cohort Members in the Continuous Exposure Group		
Cumulative Exposure (ppm-months)	Frequency	%
<180	1809	51.16
180-719	1047	29.61
≥720	680	19.23
Total	3536	100.00

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. II Dose Response Analyses. *British Journal of Industrial Medicine* 44: 382-395.

The first level, 180 ppm months (15 ppm-years), is equivalent to a long-term exposure of 0.5 ppm for 30 years or 1 ppm for 15 years and so on. This classification system did not distinguish between concentration and duration of exposure. Approximately 50% of the continuously exposed workers were exposed to < 180 ppm months, 30% to 180-719 ppm months and 20% to > 720 ppm months. Because of the nature of the estimated historical industrial hygiene exposure, these exposure groups should be viewed on a relative vs. absolute basis.

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Peak vs. cumulative exposure was also analyzed. Each job and cohort member was categorized by maximum peak exposure throughout the person's whole work history. More than half of those exposed were exposed to a ceiling level of more than 100 ppm at some time during their employment. See table below for peak exposure information.

Table 38 - Distribution by Maximum Peak Occupational Exposure to Benzene and Exposure Group						
	Intermittent Exposure		**Continuous Exposure**		**Total**	
Maximum Peak	**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**
<25 ppm	336	31.52	413	11.68	749	16.28
25-100 ppm	114	10.69	1272	35.97	1386	30.12
>100 ppm	616	57.79	1851	52.35	2467	53.61
Total	1066	100.00	3536	100.00	4602	100.00

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. II Dose Response Analyses. *British Journal of Industrial Medicine* 44: 382-395.

The average range of exposure was 10 years. Slightly more than half (56.66%) were exposed for the first time before 1955. Thus with regard to exposure to benzene, more than half the exposed cohort could have a latent period of at least 22 years. There was a mildly increasing trend of latency detected for all cancers, lung cancer, brain cancer, leukemia, and arteriosclerotic heart disease.   See table below for observed deaths by cause and exposure category.

Table 39 - Observed Deaths by Cause and SMRs for:
1) **All Cohort Members Exposed to Benzene (Intermittent and Continuous Exposure) by Latency Since First Exposure and**
2) **Continuously Exposed Cohort Members by Latency Since First Occupational Exposure**

	Duration of Exposure					
	<10 years		10-19 years		≥20 years	
Cause of Death (8th ICDA)	Obs	SMR	Obs	SMR	Obs	SMR
All Cohort Members Exposed to Benzene (Intermittent and Continuous Exposure) by Latency Since First Exposure						
All Causes	90	68.0[†]	201	87.2	419	91.8
All Cancers (140-209)	16	82.8	41	101.1	104	106.7
Lymphatic & Haematopoietic Cancer (200-209)	3	102.3	8	175.9	8	97.6
Lymphosarcoma and Reticulosarcoma (200)	1	161.3	1	89.4	2	110.5
Hodgkin's Disease (201)	1	130.5	1	121.1	0	0
Leukaemia & aleukaemia (204-207)	1	87.5	2	116.9	4	128.6
Other Lymphatic Tissue Cancer (202, 203, 208)	0	0	4	455.6[*]	2	83.7
Benign Neoplasms (210-239)	0	0	2	268.7	1	91.7
Diseases of the Blood (280-289)	0	0	0	0	1	108.7
Continuously Exposed Cohort Members by Latency Since First Occupational Exposure						
All Causes	76	68.6	170	93.1	285	89.1
All Cancers (140-209)	14	86.2	41	126.5	68	98.5
Lymphatic & Haematopoietic Cancer (200-209)	2	84.8	7	198.2	6	102.7
Lymphosarcoma and Reticulosarcoma (200)	1	199.7	1	115.8	1	77.5
Hodgkin's Disease (201)	1	166.6	1	159.8	0	0
Leukaemia & aleukaemia (204-207)	0	0	2	151.3	4	181.8
Other Lymphatic Tissue Cancer (202, 203, 208)	0	0	3	423.3	1	58.5
Benign Neoplasms (210-239)	0	0	2	347.1	1	129.9
Diseases of the Blood (280-289)	0	0	0	0	1	156.3

[*]Significant at 0.05.

[†]Significant at 0.01.

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. II Dose Response Analyses. *British Journal of Industrial Medicine* 44: 382-395.

There was monotonic increasing trend of lymphohematopoietic cancer SMR by cumulative exposure. The SMRs in increasing cumulative exposure order were 34.6, 91.3, 146.8, and 175.2. The increase did not appear to be linear but rose more steeply in the lower exposure range and became flatter at the high exposure levels. The response relationship for leukemia was not strictly monotonic. The SMR rose from 0 to 96.8, dropped slightly to 78.2, and rose back to 275.8. The number of deaths from leukemia in each of the cumulative exposure groups was small and the associated statistical variability was large.

For non-Hodgkin's lymphoma, lymphosarcoma, reticulosarcoma, and other lymphatic tissue cancer, the SMRs rose from 50.8 in the comparison group through 116.7 in the > 180 ppm-months group, to 186.3 in the 180-719 ppm-months group, and dropped to 74.6 in the > 720 ppm months group. See table below for specific information regarding observed deaths by diagnosis and exposure category.

Table 40 - Observed Deaths, Expected Deaths, SMRs and 95% Confidence Intervals for Lymphatic and Haematopoietic Cancer, Leukaemia, non-Hodgkin's Lymphopoietic Cancer by Cumulative Occupational Exposure

Cause of Death (8th ICD)	Variable	Non-Exposed	<180 ppm-months	180-719 ppm-months	≥720 ppm-months
Lymphatic and Haematopoietic Cancer (200-209)	Obs	3	5	5	5
	Exp	8.68	5.48	3.41	2.85
	SMR	34.6	91.3	146.8	175.2
	95% CI	7.1-101.1	29.5-213.3	47.5-343.0	56.7-409.3
Leukaemia and Aleukaemia (204-207)	Obs	0	2	1	3
	Exp	3.40	2.07	1.28	1.09
	SMR	0	96.8	78.2	275.8
	95% CI	-	11.7-349.4	2.0-434.4	56.9-806.4
Non-Hodgkin's Lymphoma (200, 202, 203)	Obs	2	3	3	1
	Exp	3.94	2.57	1.61	1.34
	SMR	50.8	116.7	186.3	74.6
	95% CI	6.2-183.4	24.1-341.2	38.4-544.7	1.9-414.4
Non-Hodgkin's Lymphopoietic Cancer (200, 202-207)	Obs	2	5	4	4
	Exp	7.34	4.64	2.89	2.23
	SMR	27.2*	107.8	138.4	164.6
	95% CI	3.3-79.5	34.9-251.9	37.7-354.0	44.8-421.0

[*]Statistically significant at the 0.05 level.
(Lymphatic and haematopoietic cancer includes non-Hodgkin's lymphoma, Hodgkin's disease and leukaemia.)

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. I General Results. *British Journal of Industrial Medicine.* 44: 365-381.

When examining the Mantel-Haenszel relative risk and corresponding extension chi-squares for all lymphatic and hematopoietic cancer, leukemia, non-Hodgkin's lymphoma, and non-Hodgkin's lymphohematopoietic cancer by cumulative exposure to benzene adjusted for age and race, the following was found: For all lymphatic and hematopoietic cancer, the relative risk rose steadily from 1 in the comparison group to 3.93 in the > 720 ppm month group. The corresponding Mantel-Haenszel extension chi-square which measured the significance of the upward trend was 5.42 (p value = 0.02). The Mantel-Haenszel extension chi-square for leukemia was 6.46 (p value = 0.011).

A number of other analyses were done and are graphically depicted in the tables on the following pages.

Table 41 - Mantel-Haenszel Relative Risk and Extension Chi-Squares for Lymphatic and Haematopoietic Cancer, Leukaemia, non-Hodgkin's Lymphoma and non-Hodgkin's Lymphopoietic Cancer by Cumulative Occupational Exposure to Benzene

Cause of Death (8th ICD)	Cumulative Exposure (ppm-months)	Observed Deaths	Relative Risk	Chi-Square for Trend	P Value
Lymphatic and Haematopoietic Cancer (200-209)	Non-exposed	3	1.00		
	<180	5	2.10		
	180-719	5	2.95	5.42[*]	0.02
	≥720	5	3.93		
Leukaemia and Aleukaemia (204-207)	Non-exposed	0			
	<180	2			
	180-719	1	Undefined	6.46[*]	0.01
	≥720	3			
Non-Hodgkin's Lymphoma (200, 202, 203)	Non-exposed	2	1.00		
	<180	3	1.40		
	180-719	3	2.23	0.14	0.71
	≥720	1	1.07		
Non-Hodgkin's Lymphopoietic Cancer (200, 202-207)	Non-exposed	2	1.00		
	<180	5	2.71		
	180-719	4	2.96	3.64	0.06
	≥720	4	4.12		

[*]Statistically significant at the 0.05 level.
(Lymphatic and haematopoietic cancer includes non-Hodgkin's lymphoma, Hodgkin's disease and leukaemia.)

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. I General Results. *British Journal of Industrial Medicine.* 44: 365-381.

Table 42- Observed Deaths by Cause and SMRs for All Cohort Members Continuously Exposed to Benzene by Cumulative Exposure

Cause of Death (8th ICDA)	Cumulative Exposure (ppm-months)					
	<180		180-719		≥720	
	Obs	SMR	Obs	SMR	Obs	SMR
All Causes	259	90.5	181	98.6	91	63.5[†]
All Cancers (140-209)	56	102.5	45	129.4	22	77.8
Lymphatic & Haematopoietic Cancer (200-209)	5	91.3	5	146.8	5	175.2
Lymphosarcoma and Reticulosarcoma (200)	1	81.2	1	131.6	1	151.0
Hodgkin's Disease (201)	0	0	1	191.6	1	240.5
Leukaemia & aleukaemia (204-207)	2	96.8	1	78.2	3	275.8
Other Lymphatic Tissue Cancer (202, 203, 208)	2	155.4	2	244.9	0	0
Benign Neoplasms (210-239)	2	239.1	1	188.9	0	0
Diseases of the Blood (280-289)	1	156.4	0	0	0	0

[*]Significant at 0.05.
[†]Significant at 0.01.

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. II Dose Response Analyses. *British Journal of Industrial Medicine* 44: 382-395.

Table 43 - Observed Deaths by Cause and SMRs for all Cohort Members Exposed to Benzene by Duration of Occupational Exposure to Benzene

	Duration of Exposure					
	<5 years		5-14 years		≥15 years	
Cause of Death (8th ICDA)	**Obs**	**SMR**	**Obs**	**SMR**	**Obs**	**SMR**
All Causes	263	88.6[*]	215	83.2[†]	232	87.8[*]
All Cancers (140-209)	49	91.4	53	108.8	59	107.2
Lymphatic & Haematopoietic Cancer (200-209)	7	118.0	8	163.1	4	82.6
Lymphosarcoma and Reticulosarcoma (200)	1	76.3	1	89.2	2	179.5
Hodgkin's Disease (201)	1	92.6	1	130.1	0	0
Leukaemia & aleukaemia (204-207)	2	88.5	4	215.8	1	54.0
Other Lymphatic Tissue Cancer (202, 203, 208)	3	241.9	2	177.8	1	76.9
Benign Neoplasms (210-239)	1	108.7	2	258.3	0	0
Diseases of the Blood (280-289)	1	144.9	0	0	0	0

[*]Significant at 0.05.
[†]Significant at 0.01.

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. II Dose Response Analyses. *British Journal of Industrial Medicine* 44: 382-395.

Table 44 - Observed Deaths by Cause and SMRs for all Cohort Members Exposed to Benzene by Maximum Peak Occupational Exposure						
	Maximum Peak Exposure					
	<25 ppm		**25-100 ppm**		**>100 ppm**	
Cause of Death (8th ICDA)	**Obs**	**SMR**	**Obs**	**SMR**	**Obs**	**SMR**
All Causes	135	91.7	280	94.5	295	78.4[†]
All Cancers (140-209)	35	125.5	63	113.3	63	85.3
Lymphatic & Haematopoietic Cancer (200-209)	4	141.5	7	140.8	8	101.5
Lymphosarcoma and Reticulosarcoma (200)	1	154.2	2	188.2	1	54.5
Hodgkin's Disease (201)	0	0	1	143.3	1	80.0
Leukaemia & aleukaemia (204-207)	1	89.9	2	108.5	4	132.9
Other Lymphatic Tissue Cancer (202, 203, 208)	2	322.8	2	150.7	2	116.5
Benign Neoplasms (210-239)	0	0	1	120.6	2	178.4
Diseases of the Blood (280-289)	1	299.5	0	0	0	0

[†]Significant at 0.01.

O. Wong. 1987. An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. II Dose Response Analyses. *British Journal of Industrial Medicine* 44: 382-395.

Case	Exp	COD	Age	Yrs Exp	Yrs Cont Exp	ppm-months	Max TWA	Max Peak	Yrs Latency
1	C	202.2- Giant follicular lymphoma	55.0	7.2	7.2	43	L	L	13.4
2	C	201.X- Hodgkin's disease	36.2	1.8	1.6	192	H	M	11.0
3	C	200.0- Reticulum cell sarcoma	54.2	0.9	0.2	14	M	M	2.5
4	C	204.1- Chronic lymphatic leukemia	48.7	9.9	9.9	524	H	H	14.3
5	C	204.9 Unspecified lymphatic leukemia	59.9	14.9	14.6	1361	H	H	28.6
6	C	**205.1- Chronic myeloid leukemia**	64.2	5.8	1.9	120	H	M	28.9
7	C	202.2- Giant follicular lymphoma	55.8	1.3	1.3	334	H	M	10.6
8	C	203.X- Multiple myeloma	57.0	2.3	2.3	14	L	L	11.3
9	C	204.0- Acute lymphatic leukemia	70.2	12.2	12.2	731	M	M	49.4
10	C	200.0- Reticulum cell sarcoma	74.5	26.8	26.8	1512	M	M	41.4
11	C	**205.1-Chronic myeloid leukemia**	61.8	1.2	1.2	7	L	L	18.9
12	C	**207.0-Acute leukemia**	49.6	29.2	29.2	851	M	H	29.7
13	C	202.2- Giant follicular lymphoma	44.4	1.7	1.7	601	H	H	21.9
14	C	201.X- Hodgkin's disease	65.4	7.0	7.0	2522	H	H	8.7
15	C	200.1- Lymphosarcoma	50.1	8.9	8.9	533	M	H	17.4
16	I	204.1- Chronic lymphatic leukemia	47.6	1.4				H	6.0
17	I	200.0- Reticulum cell sarcoma	67.3	35.4				L	38.2
18	I	203.X- Multiple myeloma	64.0	6.6				M	17.8
19	I	203.X- Multiple myeloma	56.4	20.4				H	21.1
20	U	201.X- Hodgkin's disease	64.1						
21	U	200.1- Lymphosarcoma	68.7						
22	U	202.2- Giant follicular lymphoma	71.4						

Table 45 - Characteristics of 22 Deaths from Lymphatic and Haematopoietic Cancer

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Key:

Exposure	Race	Peak Exposure	Eight hour TWA
C=Continuous	W=White	L= Low (<25 ppm)	L=Low (<1 ppm)
I=Intermittent	N=Non-white	M=Medium (25-100 ppm)	M=Medium (1-10 ppm)
U=Unexposed		H=High (>100 ppm)	H=High (11-50 ppm)
			VH=Very High (>50 ppm)

The analyses indicated the duration of exposure was not a particularly sensitive parameter for quantification of either leukemia or the lymphopoietic cancer mortality risk. When analyzed by cumulative exposure (ppm-months) there was a statistically significant dose response for leukemia. When the data were analyzed by maximum benzene peak, no significant dose response relation was apparent. In summary, the study suggests that cumulative exposure, not peak exposure, was the major determinant of mortality from lymphopoietic cancer. With that said, this must be viewed with great caution because of the inability to take frequency of exposure into account.

Unlike previous studies, this did not reveal a preponderance of acute myeloid leukemia.

Limitations: (From the Authors)
1. The percentage lost to follow-up and the proportion of outstanding death certificates was low at 2.3 and 2.2%, thus it is possible that some deaths from lymphopoietic cancer might have been missed.
2. The results of cohort verification indicate an error rate of 0.8. Although this error rate was extremely small, the small number of individuals inadvertently excluded could subsequently have died from lymphopoietic cancer.
3. Based on a 10% random sample of the cohort, coding accuracy was estimated at 97.4%.
4. Historical exposure levels for the early part of the study were limited for some of the plants. The problem was personally dealt with by the uniform task approach. This required the breakdown of exposed jobs into specific uniform tasks for which benzene exposure levels could be estimated more readily.
5. It is assumed that benzene exposed workers were also exposed to other chemicals.
6. The cohort size was small for several specific analyses.
7. There was no practical means of checking the comparability of the exposed and comparison groups with regard to some non-occupational risk factors.
8. There are problems associated with ascertainment of specific causes of mortality for death certificates and a lack of in-depth clinical information.

4. The Australian Petroleum Industry Studies

Glass, D. C., C. N. Gray, et al. (2003). "Leukemia risk associated with low-level benzene exposure." Epidemiology **14**(5): 569- 77. (Glass, Gray et al. 2003)

Cohort Description and Methods:

This is a nested-case control study of all cause mortality and cancer incidence in the Australian petroleum industry. There is a nationally funded program, Health Watch, that oversees the operation of this study. The cohort members included all employees except head office staff and those employed at Australian sites with <10 employees. Approximately 95% of eligible employees in the industry participated in Health Watch surveys. Members are recruited after 5 years employment in the petroleum industry, and remain in the cohort for life. Copies of death certificates were obtained, and cancer incidence was validated through state cancer registries and the treating doctor. Cancer registration in Australia is a legal requirement of pathology laboratories and hospitals.

In 1998, the cohort consisted of 15,732 men and 1,178 women. In the past evaluations, men have been shown to have standardized incident ratios (SIRs) = 2.0 for leukemia (95% CI: 1.3 - 2.9) and for multiple myeloma at1.9 (95% CI: 1 to 3.3).

The occupational exposure to benzene for both cases and controls was based upon their entire work history correlated with a task based algorithm. Diagnosis was confirmed by pathology report, cancer registration, letter from a medical practitioner, or death certificate.

Seventy-nine (79) cohort members met the definition of a lymphohematopoietic cancer case. One case was found in the cancer registry, but was excluded due to the terms of the cohort. All documentation of the cases was reviewed by the investigators, and cases were assigned to international classification of disease groupings.

Nine cases had uncertain histology and the documentation was reviewed by hematologists using the French-American-British system. Five male control subjects were chosen for each case. Control subjects were selected randomly from a list of all cohort members who were eligible at the time of diagnosis and matched by year of birth. As a result of random selection, 5 workers were used as control subjects for more than one case. Four of them were used in two case control sets, and 1 in three. Thus, the total number of control subjects was 395. One worker selected as a control subject subsequently became a case. The subject was retained as a control subject because he was not diagnosed at the time of selection.

The job histories were cross-checked with company personnel records. When discrepancies were found, the most specific history was used. Cases were not interviewed about their tasks because this information might have been subject to recall bias. Instead, contemporary co-workers were interviewed. They provided information on the tasks performed, technology in use and the products worked with during the period they worked together. The interviewers had no knowledge of the names and health status of the subjects.

The benzene exposure of each case and control was calculated using a task based algorithm that incorporated the subject's occupational history, previously measured exposures for a particular task, and the Australian petroleum industry and task site and period

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specific data. We used the following additional exposure metrics to test the association with the risk of leukemia: (1) Start date: Subjects were divided into three groups by their start date in the industry: pre-1965, 1965 to 1975, and post-1975. (2) Duration of employment: The calculated quintiles of duration with cut points approximately every 7 years. (3) Whether most of the career was spent as an office worker or as a blue collar worker. (4) Site of longest job held and highest exposed job. Each site where a subject worked was allocated to a job type. (5) Intensity of exposure: the average exposure intensity, cumulative benzene exposure estimate divided by duration of employment and ppm for each job. (6) Subjects with exposure to benzene concentrate: We identified those subjects who had handled benzene concentrate, which is 100% benzene, or BTX (benzene-toluene-xylene) which is principally an aromatic mixture that contains ~70% benzene. All odds ratios and 95% confidence intervals are for matched analyses.

Results:

The risk of leukemia was not associated with smoking. On average, cases had a higher lifetime cumulative exposure and a greater proportion of the cases were in higher exposure categories. No increase in risk for non-Hodgkin's lymphoma or multiple myeloma was found with increasing exposure to benzene. The highest exposure group (> 16 ppm-years) contained 7 of 33 leukemia cases, but only 3 of their 165 matched control subjects. For the two highest exposure categories combined, 13 case sets with > 8 ppm cumulative exposure the odds ratio was 11.3 (95% CI:2.8 to 45.1).

In a comparable study in the U.K. petroleum industry, a cut-point of 4.79 ppm-years was used in the analysis. For comparison purposes, we analyzed our data using the same cut-point and obtained an odds ratio of 2.51 (95% CI: 1.1 to 5.7). The odds ratio associated with cumulative exposure as a continuous measure was 1.65 (95% CI: 1.25 - 2.17). This was consistent with an increase of 65% for each doubling of mean cumulative exposure.

Blue collar workers had a three-fold risk of leukemia compared with office workers, but this risk disappeared when adjustment was made for cumulative benzene exposure. Subjects who had worked longest in an airport had nearly four times the risk of leukemia compared with terminal workers, but this result was based on small numbers. This finding did not change after adjustment for cumulative benzene exposure. There was a strong association between leukemia risk and exposure to benzene concentrate that was somewhat reduced when cumulative exposure was controlled. Exposures to benzene concentrate resulted in a higher risk of leukemia than exposure to the same amount of benzene encountered in a more dilute form such as gasoline.

Exposure intensity in the highest exposed job was strongly related to leukemia risk with the increase starting around 0.8 - 1.6 ppm. Cohort members in the highest exposure category were ~20 times more likely to develop leukemia than those who were not exposed to benzene. Adjusting for cumulative exposure removed the association between high intensity exposure and leukemia. Goodness of fit statistics and step-wise conditional logistic regression; however, did not provide unequivocal evidence that would distinguish between the relative contribution of the cumulative exposure and exposure to intensity of leukemia risk.

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Odds ratios were also calculated for the leukemia subtypes: acute non-lymphocytic leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia. It was not possible to calculate the odd ratio for acute lymphocytic leukemia because there were only 2 cases. Because there were relatively few cases of leukemia, sometimes it was necessary to combine the three lowest exposure groups and the two highest exposure groups. The odds ratios in the combined higher exposure group were raised relative to the combined lower exposure group for both chronic lymphocytic leukemia and acute non-lymphocytic leukemia.

In conclusion, these data provide strong evidence for an association between benzene exposure in the Australian petroleum industry and increased risk of leukemia. H. The estimated cumulative exposures were generally similar to those reported for other petroleum industry studies except the most highly exposed subjects in our study had cumulative exposures of < 60 ppm-years whereas those in other studies were as high as 220 ppm-years. Combining the two highest cumulative exposure groups resulted in an odds ratio of 11.3 (95% CI: 2.8 - 45.1). These results differ greatly from the previous values found in the UK cohort of petroleum workers.

Limitations:

1. There were a relatively small number of hematological cancer cases and only 33 leukemia cases. Of the leukemia cases, only 11 were acute non-lymphocytic leukemia, while another 11 were chronic lymphocytic leukemia. These small numbers limit the power to detect excess risk, particularly in individual leukemia subtypes. In addition, misclassification of just a few cases from the lowest groups to a higher group would markedly change the dose response curve.

2. In formulating the base estimates for each job task, the research team calculated the arithmetic mean for each task.

3. These results are inconsistent with the results of similar studies performed in the UK and Canada. In both of those studies, the exposures were greater, yet the estimated risks are far less.

4. The exposure estimates were derived from monitoring data that was collected after 1975. In addition, there was far more information available regarding lower exposed jobs versus the highly exposed jobs.

5. The researchers collected the work history from co-workers versus the cases which controls for recall bias; however, it also limits the amount of personally relevant information about the case, their work habits and uncontrolled exposures. If they were describing how a job/task would be optimally carried out, without consideration of these factors, it would have the effect of smoothing the peaks and potentially lowering the estimates for each case. The work histories were collected through interview by Health Watch from 1980 onward (from co-workers) and were based on recall before that date.

6. The base estimates which are the beginning of all exposure estimation in this study were questionable even by the author's estimation. When they were compared to relevant exposure data in the literature: 12 were not available, 19 were validated, 4 were adjusted and 14 were not confirmed by the literature. However, the 14 not confirmed were judged to be inadequate and were ignored.

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7. The exposure level categories were very tight and small errors in exposure estimation could markedly affect the placement of cases into different exposure levels.
8. The authors subsequently re-analyzed the data in a 2006 update (Glass, Gray et al. 2006) and attempted to take into account high exposure events (HEEs) the resulted form spillage and poor work practices. These estimates were added to the previously calculated cumulative exposures for cases and controls. The odds ratios were recalculated and this increased the exposure for 25% of subjects. For most individuals the increase was <5%. With the added HEEs the odds ratio for leukemia with matched analyses went from 1.10 (95% CI: 1.04-1.16) to 1.03 (95% CI: 1.01 – 1.05). When treated as a categorical variable the odds ratio in the 7 cases of leukemia with >16 ppm-years was 98 (8.8 -1090), when compared to individuals with <0.5 ppm-years cumulative exposure. When the two lowest groups of exposure <1 ppm-years were compared with the highest exposure group the odds ratio was 51.9 (5.6 – 477) without HEEs and 7.79 (2.34 – 25.89) with HEEs. It was thought that the odds ratio fell because leukemia is associated with higher exposures and thus the risk per ppm year is reduced.

5. The United Kingdom Petroleum Industry Studies

Rushton, L. and H. Romaniuk (1997). "A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom." Occup Environ Med **54**(3): 152-66. (Rushton and Romaniuk 1997)

<u>Cohort Description and Methods</u>:

In this study, the cases were recruited from the existing cohort database and were included if the following criteria were met:

1. Died before January 1, 1993 with a mention of leukemia on the death certificate; or
2. Had a cancer registration of leukemia.

A total of 91 cases were identified and 88 came from death certificates with or without cancer registration, and 3 came from cancer registration alone. In 11 cases there was a discrepancy between the diagnoses and the cancer registration. In each case the more specific diagnosis was chosen.

Four controls per case were randomly selected from all men in the same oil company with a year of birth within three years either side of the date of birth of the case. The controls were selected from people alive and under follow-up at the time of case occurrences. Two controls were erroneously selected who were not under follow up on the relevant date. These have been excluded from the study. At a later time, it was found that eight of the controls from one company had been incorrectly matched for age. These controls have also been excluded from the analysis. This also resulted in the exclusion of one case of acute myeloid leukemia.

Six variables were identified that were necessary to establish quantitative exposure estimates, including: 1. Work history, 2. Job descriptions, 3. Terminal histories, 4. Fuel compositions, 5. Occupation hygiene measurements, and 6. Possible confounding variables such as smoking.

For any members who had incomplete information in their personnel record, the missing information was obtained from a variety of sources including pension records, medical records, and interviews with retired or long service staff. When a work history was largely unavailable, a typical work history was used. When assumptions were made, these were flagged in the database. As a measure of quality of the work history, each study participant was assigned a job confidence code of 1, 2, or 3. A code 1 indicates a complete work history or one for which the last job only was known, but the duration of employment was less than ten years. Code 2 indicates a partially complete work history for which an assumption has been made. And code 3 indicates a poor work history and was assigned when only the last job title was known. This was a supervisor or managerial post, and the duration of employment was over ten years. None of the cases, and only 8 (2%) of the controls had a job confidence score of 3, the poor category. Twenty one percent of the work histories were assigned to the partially complete category. This included 26% of the cases and 19% of the

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controls.

315 petroleum terminals were identified from work histories and over 95% were closed by the time of data collection. All remaining terminals were visited and retired/long service employees were interviewed about closed sites. Other sources of information included site plans, booklets, photographs, company magazines, and other materials available from company libraries and property engineering documents. Data collection for fuel compositions, occupational hygiene measurements and the methods of developing quantitative exposure estimates related to work histories of each study member was detailed. The method used for this study was an extension of that developed for the Canadian case control study. Similar to the Canadian study, six adjustment factors were added to the base estimates, including job activity, number of loads handled per day, loading technology, percent of benzene in the fuel product mix, and air temperature. For some terminals, the data on individual employees were sufficient to indicate whether drivers were assigned to road tankers carrying black oil or white oil. This is relevant since black oils do not contain benzene. Workplace estimates were derived for each line of a work history. The base estimate was multiplied by the six modifying factors. This was then multiplied by the time spent for that job and these were then summed over each study members' complete work history to give a cumulative exposure in ppm-years.

Exposures were further classified into twelve categories according to whether they were likely to have occurred in intermittent peaks defined by a frequency of intensity: 1 to 3 parts per million or greater than 3 part per million, and duration: 1 to 15 minutes and 15 to 60 minutes. The potential for skin exposure was estimated as none, low, medium or high. Cumulative exposure was categorized as a continuous variable, mean intensity and cumulative exposure divided by duration of employment. Maximum intensity, highest intensity for any job in the work history, and years of employment were also analyzed. Cumulative exposure was analyzed in quintiles, primarily to check linearity and in four categories: <0.45 ppm-years, 0.45 – 4.49 ppm-years, 4.5 – 44.49 ppm-years and >45.0 ppm-years. The cumulative exposure quintiles for all leukemias of less than 0.26, 0.26 to 0.59, 0.60 to 1.64, and 1.65 to 4.78, and greater than equal to 4.79 ppm for all analysis. Categorizations per maximum mean intensity of exposure and duration of employment were chosen by examining the distribution of these variables for the whole study sample before separating them into cases and controls. Lag exposures of five to ten years were also analyzed. Potential confounding or effect modifying variables including smoking, employment status at end date, socioeconomic status based on job title, longest duration, age, date started working, ever had a previous job, never had a previous job as a driver were all considered. The highest potential skin contact in the work history was used to characterize dermal exposure. Two variables which categorized peak exposure were derived - the number of years exposed to the peak, and ever experiencing the peak for more than one year. Although these derived variables attempt to characterize the nature of peak exposures, the results of these variables proved difficult to interpret and should be treated with caution.

Separate analyses were carried out for all leukemias and for four leukemia groups, acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid and acute monocytic leukemia and chronic myeloid leukemia. See table below for a description of the cohort characteristics.

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Table 46 - Characteristics of the Study Sample			
Variable	Cases n (%)	Controls n (%)	Total n (%)
Cumulative Exposure (ppm-y)			
<1	44 (49)	183 (52)	227 (51)
1-4	27 (30)	105 (30)	132 (29)
5-9	11 (12)	40 (11)	51 (12)
≥10	8 (9)	26 (7)	34 (8)
Mean Cumulative Exposure	5.6	4.4	4.6
Mean Intensity (ppm)			
<0.02	32 (36)	114 (32)	146 (33)
0.02-0.19	33 (37)	163 (46)	196 (44)
0.2-0.39	19 (21)	45 (13)	64 (14)
≥0.4	6 (7)	32 (9)	38 (9)
Mean of Mean Intensity (ppm)	0.20	0.22	0.21
Maximum Intensity (ppm)	31 (35)	104 (29)	135 (30)
<0.02	30 (33)	131 (37)	161 (36)
0.02-0.19	9 (10)	43 (12)	52 (12)
0.2-0.39	20 (22)	76 (22)	96 (22)
≥0.4	0.39	0.41	0.40

L. Rushton and H. Romaniuk. 1997. A Case-Control Study to Investigate the Risk of Leukaemia Associated with Exposure to Benzene in Petroleum Marketing and Distribution Workers in the United Kingdom. *Occupational and Environmental Medicine* 54: 152-166.

Emphasis has been placed on exploration of patterns and magnitude of risk with sensitivity analysis were appropriate.

Results:

Cumulative exposures range from close to 0 to greater than 200 parts per million years, although 81% of exposures were less than 5 parts per million years. The upper tail of the distribution was distorted by 15 subjects who were known to have worked previously for a company which had marketed benzene enriched products. Only one of these was a case. There was a larger proportion of cases and controls with a mean intensity of exposure between 0.2 and 0.4 part per million. The distribution of smokers and nonsmokers was the same in case and controls but information on smoking was unobtainable for nearly 90% of the study members. For all leukemias, cumulative exposure tended to be highly correlated with both mean intensity of exposure (R=.084) and maximum intensity of exposure (R=0.82), but not with duration of employment (R=0.15). See table below for a listing of

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leukemia by subtype.

Table 47 - Number of Leukaemias by Subtype	
Lymphoid	
Acute	7
Chronic	31
Other	1
Total	39
Myeloid	
Acute	31
Chronic	11
Other	2
Total	44
Monocytic	
Acute	1
Chronic	1
Other	1
Total	3
Other	
Acute	3
Other	2
Total	5
Total Leukaemia	91

L. Rushton and H. Romaniuk. 1997. A Case-Control Study to Investigate the Risk of Leukaemia Associated with Exposure to Benzene in Petroleum Marketing and Distribution Workers in the United Kingdom. *Occupational and Environmental Medicine* 54: 152-166.

There was little evidence of an increasing risk of all leukemias with increased cumulative exposure. There were seven cases of acute lymphoblastic leukemia, including the only case who was previously employed by a company marketing benzene enriched products. The mean cumulative exposure for all seven cases was 29.6 ppm-years, compared with 2.06 ppm-years for controls. There were 31 cases of chronic lymphocytic leukemia. The cases had a lower mean cumulative exposure of 2.6 ppm-years versus the controls at 3.6 ppm-years. Nearly a third of the cases were white collar men compared with only 14% of the controls.

There were 31 cases of acute myeloid and monocytic leukemia included in the analysis, all but one being myeloid. One further case was excluded, as all four controls were erroneously matched. Most of the cases, 94%, were blue collar workers, compared with 89% of the controls. The cases and controls had similar mean cumulative exposures with cases at 3.7 ppm-years and controls with 3.8 ppm-years, The range for the controls was much greater (up to 103.8 ppm-years) than for the cases (up to 22.3 ppm-years). Cases had slightly more

exposure to peaks than controls with 75% of cases versus 66% of controls, and slightly more medium or high skin contact (cases 71% vs. controls 65%).

Acute myeloid leukemia has been most frequently associated with exposure to benzene and in contrast with chronic lymphocytic leukemia, 94% of cases occurred in blue collar workers. Risk was highest in men with cumulative exposures of 4.5 to 45 ppm-years. There was no association with cumulative exposure when analyzed as a continuous variable. The excess of cases with cumulative exposures of 4.5 to 45 ppm-years occurred particularly in men with daily or weekly peak exposure. Risks also increased to greater than 2 for a mean intensity of 0.2 to 0.4 part per million compared with less than 0.02 part per million. See table below for risk of acute myeloid and monocytic leukemia in the cohort members.

It was not possible to assess the risk of smoking and the risk of acute myeloid and monocytic leukemia in the study due to the lack of data.

The authors concluded "in view of the limitations, doubt remains to whether the risk for acute myeloid and monocytic leukemia is increased by cumulative exposures of less than 45 part per million years".

Table 48 - Odds Ratios (95% CIs) for Acute Myeloid and Monocytic Leukaemia						
					OR	
Variable	Cases n	Controls n	OR ((95% CI)	Goodness of Fit (p value)	White Oil[*]	Black Oil[†]
Cumulative Exposure (continuous)	-	-	1.00 (0.96 to 1.04)	0.95	1.00	1.00
Cumulative Exposure Quintiles (ppm)						
<0.26	6	35	(1)	0.75	(1)	(1)
0.26-0.59	5	17	1.88 (0.49 to 7.16)	-	2.57	1.67
0.60-1.64	6	23	1.68 (0.46 to 6.11)	-	1.60	1.47
1.65-4.78	6	24	1.60 (0.44 to 5.79)	-	2.16	1.78
≥4.79	8	22	2.38 (0.65 to 8.73)	-	3.21	2.16
Cumulative Exposure Working Lifetime (ppm-y)						
<0.45	7	46	(1)	0.18	(1)	(1)
0.45-4.49	15	51	2.17 (0.77 to 6.09)	-	1.95	1.61
4.5-44.9	9	23	2.82 (0.82 to 9.38)	-	2.78	2.28
≥45	0	1	0	-	0	0
Duration of Employment (continuous)	-	-	1.03 (0.99 to 1.07)	0.19	-	-
Years of Employment						
<10	7	48	(1)	0.38	-	-
10-19	10	29	2.65 (0.88 to 7.93)	-	-	-
20-29	8	23	2.76 (0.79 to 9.58)	-	-	-
30-39	5	16	2.86 (0.66 to 12.29)	-	-	-

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≥40	1	5	1.86 (0.12 to 29.52)	-	-	-
Maximum Intensity (continuous)	-	-	0.66 (0.28 to 1.52)	0.22	0.68	0.69
Maximum Intensity (ppm)						
<0.02	6	32	(1)	0.86	(1)	(1)
0.02-0.19	13	47	1.45 (0.51 to 4.10)	-	1.35	1.62
0.2-0.39	5	14	1.69 (0.46 to 6.17)	-	1.70	2.27
≥0.4	7	28	1.34 (0.37 to 4.86)	-	1.53	1.56
Mean Intensity (continuous)	-	-	0.68 (0.17 to 2.82)	0.57	0.77	0.72
Mean Intensity (ppm)						
<0.02	6	34	(1)	0.13	(1)	(1)
0.02-0.19	14	56	1.34 (0.48 to 3.74)	-	1.20	1.31
0.2-0.39	10	18	2.76 (0.90 to 8.48)	-	2.89	2.84
≥0.4	1	13	0.43 (0.05 to 4.05)	-	0.43	0.46
Highest Potential Skin Exposure						
None	6	30	(1)	0.84	Does not converge	(1)
Low	3	12	1.19 (0.26 to 5.42)	-		1.70
Medium	16	51	1.54 (0.54 to 4.39)	-		1.56
High	6	28	1.11 (0.32 to 3.87)	-		1.35
Date of Hire						
Before 1950	15	63	(1) (0.46 to 3.17)	0.69	-	-
After 1950	16	58	1.21 -	-	-	-
Ever Employed as Previous Driver	4	4	1.71 (0.49 to 6.03)	0.41	-	-
Employment Status at Study End Date	11	26	2.97 (0.95 to 9.27)	0.06	-	-
Socioeconomic Status						
Blue Collar	29	108	(1) (0.12 to 2.53)	0.42	-	-
White Collar	2	13	0.56	-	-	-
Age Started Work (continuous)	-	-	1.01 (0.96 to 1.05)	0.75	-	-
Age Started Work:						
<25	14	49	(1)	0.90	-	-
25-34	12	50	0.84 (0.36 to 1.93)	-	-	-
≥35	5	22	0.81 (0.25 to 2.62)	-	-	-

[*]Assumes exposure to white oil products which contain benzene.
[†]Assumes exposure to black oil products which do not contain benzene.

L. Rushton and H. Romaniuk. 1997. A Case-Control Study to Investigate the Risk of Leukaemia Associated with Exposure to Benzene in Petroleum Marketing and Distribution Workers in the United Kingdom. *Occupational and Environmental Medicine* 54: 152-166.

Limitations:
1. The work history was incomplete in many cases and controls. This information was extrapolated in most instances from existing records.
2. According to the authors, some bias may have been possible because information was more readily available for surviving controls.
3. In the data sets which included only work histories taken mainly from personnel records which still exist, the patterns were similar for three of the leukemia subtypes, but different for acute myeloid and monocytic leukemia.
4. Workers who were employed prior to 1950, yet left before that date were excluded from the cohort. This precludes any estimation of risk for that period.

Wong, O. and G. K. Raabe (1998). "Acute myeloid and monocytic leukaemia and benzene exposure in petroleum distribution workers in the United Kingdom." Occup Environ Med **55**(5): 360-1. (Wong and Raabe 1998)

Comments on the Study:

Employment histories of only 48 cases (53%) based on personnel records. The employment histories of the remaining 47% of the cases were reconstructed or synthesized from sources such as recall interviews, entries in medical records, etc. Similarly, the work histories of only 55%, or 193 of 354 controls were based on complete personnel records. Furthermore, although these percentages for the cases and controls in the entire study seem comparable, this was not true for some important subcohort analyses. Based on the analysis of all subjects regardless of quality of employment histories, the authors assigned an increased odds ratio of 2.82, which was not significant at 0.05 level, for cumulative exposures of 4.5 to 44.9 part per million. However, of the 9 cases assumed to have 4.5 - 44.9 ppm-years exposure, the employment histories of only 2, or 22%, were based on personnel records. Furthermore, there was a strong possibility of differential bias between the cases and controls in this exposure category, as the employment histories of 65%, or 15 of 23 controls, were based on personnel records. If the analysis were restricted to workers with complete employment histories from personnel records, the odds ratio for the greater than equal to 4.5 ppm year group was 0.33. Clearly, the excess based on all subjects came from those workers with employment histories of poorer quality.

The authors seem to downplay the sensitivity analysis for AMML. The finding of AMML of an increased odds ratio of 2.82 for the 4.5 to 44.9 part per million year cumulative exposure group was further weakened by the lack of internal consistency. For example, the model treating cumulative exposures as a continuous variable did not find any increased risk, odds ratio of 1.0 with a 95% competence interval of 0.96 to 1.04. In general, a model based on continuous variables is more informative and less vulnerable to artifacts created by categorization. Analysis based on group data can be influenced heavily by the grouping itself. Furthermore, in many of the 50 models on AMML presented in an earlier report dated April, 1995, no increased risk was found for cumulative exposure of greater than 4.5 ppm-years.

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Unfortunately, all the uncertainty in employment histories and exposure assessment seemed to have been lost in the statistical manipulation of the data. We doubt very much that the quality of the employment and exposure data in the study warranted such a fine distinction as when the authors attempted several analysis to discriminate the potential difference in risk resulting from exposure to 0.2, 0.3, or 0.4 part per million. In fact, we question whether measurements in early present study period, even if such data were available or that precise. The level of analysis was inappropriate given the uncertainties of the original data.

Another problem with the paper is the multiple comparison issue. An extremely large number of risk estimates were calculated. With this many odds ratios calculated several would be significant due to chance alone. The authors themselves recognize the multiple comparison problem and labeled the entire investigation as hypothesis generating in the early reports.

In summary, an interpretation by the authors that exposure to low concentrations of benzene in the range of 4.5 to 45 part per million could increase the risk of developing AMML was not justified.

In response, the authors replied.

As well as the deficiencies noted by Wong and Raabe, there were other limitation including quality of information on distribution terminals and inconsistencies in some of the analyses. However, hey seem to be confusing the quality of information compared with the source of information. As we point out in our discussion, use of work histories from only existing personnel records excluded much good quality and reliable information from other sources.

In response to there comments on Dr. Peto's observations, Dr. Peto also commented, "The study seemed to be very well conducted and analyzed. There is no evidence in this study of an association between exposure to benzene and lymphoid leukemia, either acute or chronic… however, in view of the limitations of this study, doubt remains as to whether the risk of acute myeloid and monocytic leukemias increase with an exposure of less than 45 ppm-years."

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6. The Canadian Petroleum Industry Studies

Schnatter, A. R., T. W. Armstrong, et al. (1996). "The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers." <u>Environ Health Perspect</u> 104 Suppl 6: 1375-9. (Schnatter, Armstrong et al. 1996)

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Schnatter, A. R., T. W. Armstrong, et al. (1996). "Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers." <u>Occup Environ Med</u> **53**(11): 773-81. (Schnatter, Armstrong et al. 1996)

<u>Description of the Underlying Cohort, the Case Control Study and Methods:</u>

Petroleum distribution workers are potentially exposed to benzene in white (gasoline) and black (heating oil) petroleum products while transferring the product into and out of containers/trucks. Generally, the exposure is <1 ppm 8 hr TWA. This case control study examines mortality in a group of workers previously examined in a retrospective cohort study (Schnatter, 1993). Cases for this study were identified using the following criteria:

1. Died with an underlying cause of death of leukemia (ICD-8 204-207), multiple myeloma (ICD-8 203) or non-Hodgkin's lymphoma (ICD-8 200, 202.0, 202.1, 202.2, and 202.9).
1. Ever worked in either the marking/distribution marine or pipeline segments.
2. Died between 1964 and 1983

From the above criteria 16 leukemia cases, 7 multiple myeloma and 8 non-Hodgkin's lymphoma cases were identified. Leukemia cell types were not available. Four controls were selected from the same cohort of male workers and were matched by decade of birth. In addition, the controls were required to be alive at the time of the case's death. After examining information on work histories, two leukemia cases were eliminated from further analysis due to inadequate job information. This left 14 cases of leukemia matched with 115 controls.

Of the 155 workers, 30 (19%) had some missing work history and 10 (6%) were missing more than half of their work history. Missing job histories were interpolated from the other jobs held. The exposure assessment process was a lengthy process which involved exposure estimation by industrial hygienists for benzene and total hydrocarbons for every job, location and era combination. The process began with site characterization for the 89 study locations. This included the following information: loading/unloading frequency, technology in use at the sites, types of materials handled, typical tasks performed by workers and typical environmental conditions such as average temperature. Surveys were not available for all locations; however, the information was drawn from data on similar operations from outside the company. This information was used to derive "base exposure estimates" for job/location/area scenarios in each work history. Adjustment factor(s) were then added to the base estimate by the industrial hygienists in order to take into account

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differences in environmental, operational, task and worksite conditions. The values for the adjustment factors were always estimated through physical/chemical or empirical data preferably.

In order to test the validity of the estimated exposures, exposure estimates were compared with actual industrial hygiene surveys taken during the relevant time period. On average, estimates were within 22% of the measured data. This was considered reasonable agreement.

8 hr TWA exposure intensity estimates were assigned to each worker's job/location history. Absentee information was taken into account. Intensity estimates were then estimated by the length of time in every particular job category. We subtracted absentee information from time at work and then multiplied the intensity estimates by length of time at a job. Dermal absorption was estimated by the industrial hygienists based upon presumed exposures ranked as low, medium and high for potential exposure.

Potential confounders were extracted from company medical records, including smoking status, hobby, previous exposures previous occupations, diagnostic radiation exposure and family history of cancer. Additional exposure metrics, such as dermal exposure and average intensity during the entire working career were also analyzed.

Cumulative exposure was categorized in a number of ways to minimize cut point effect. Schemes using the distribution of exposure in the controls were also examined, including:

- quartile distribution
- tertile distribution
- four categories split at the median, 75th and 90th percentile,
- ppm-years split at 0.45, 4.5 and 45 part per million years. The category boundaries corresponding to 0.01, 0.1 and 1 ppm for 45 years.
- ppm-years split at 0.9, at 9.9 and 99 part per million years. The category midpoints corresponding to 0.01, 0.1, and 1.0 ppm for 45 years.

Results:

Average daily benzene ranged for 0.01 to 6.2 ppm for all jobs.

The two strongest risk factors for the leukemia cases were family history of cancer (OR-=2.51) and smoking (OR=∞). Both had wide and/or non calculable confidence intervals. The highest risk of leukemia was found in managerial and professional job designations. For the category managerial/professional the OR=0.0, for clerk/technician the OR=.34 (95% CI: 0.03-3.10) and for operator/driver the OR=.41 (95% CI: 0.07-2.33).

With an alternative categorization by cumulative exposure, there was a monotonic trend for leukemia; however, there were a small number of cases and controls in each category. The highest risk with cumulative exposure was found in the second quartile (OR=5.06) and middle tertile (OR=4.37). The odds ratio decreased in the higher quartiles and tertile. All five of the categorizations suggest risk consistent with a unity. See table below for an estimation of risk by cumulative exposure to benzene.

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Table 49 - Leukemia Risk by Cumulative Exposure to Benzene

Benzene Exposure, ppm-years	No. Exposed Cases	Odds Ratio	95% CI
0-0.17[a]	2	1.00	-
0.18-0.49	8	5.06	0.34-295
0.50-7.9	1	0.88	0.01-18.2
8.0-219.8	3	2.11	0.10-138
0-0.22[b]	3	1.00	-
0.23-5.49	8	4.37	0.72-48.6
5.50-219.8	3	0.92	0.10-11.2
0-0.49[c]	10	1.00	-
0.50-7.99	1	0.22	0-1.82
8.0-19.99	1	0.42	0.01-3.95
20.0-219.8	2	0.96	0.09-6.81
0-0.45[d]	10	1.00	-
>0.45-4.5	1	0.43	0.01-4.05
>4.5-45	1	0.16	0-1.32
>45	2	1.47	0.16-13.1
0-0.90[d]	10	1.00	-
>0.90-9.9	2	0.43	0.04-2.36
>9.9-99.9	1	0.48	0.01-4.55
>99.9	1	1.03	0.02-20.3

[a]Categorized according to quartiles.
[b]Categorized according to tertiles.
[c]Categorized according to median, 75th and 90th percentiles.
[d]Categorized according to regulatory considerations.

A.R. Schnatter, T.W. Armstrong, L.S. Thompson, M.J. Nicolich, A.M. Katz, W.W. Huebner and E.D. Pearlman. 1996. The Relationship Between Low-Level Benzene Exposure and Leukemia in Canadian Petroleum Distribution Workers. *Environmental Health Perspectives*. 104: 1375-1379.

Cumulative benzene exposure did not show a strong relationship with leukemia when regressed separately. This model did not fit the data well. For these data, measurement of exposure duration was most closely associated with leukemia. Alternatively, benzene exposure and mean intensity did not explain leukemia risk.

The authors also examined whether exposure above a certain level was related to leukemia risk by using the number of years worked above either 0.5 or 1 ppm as independent variables. Neither of these variables explained leukemia risk, or fit the data well. See table below for an examination of risk by alternative exposure metrics.

For leukaemia, the logistic regression model predicted an OR of 1.002 (P < 0.77) for each ppm-year of exposure to benzene.

Table 50 - Leukemia Risk by Alternate Benzene Exposure Metrics			
	No. Exposed Cases	Odds Ratio	95% CI
Benzene Intensity, mean ppm			
0-0.01	9	1.00	-
>0.01-0.19	2	0.88	0.08-6.47
0.20-0.49	1	0.19	0-1.55
0.50-6.16	2	0.96	0.09-6.81
Maximum Benzene Intensity, ppm			
<0.5	10	1.00	-
0.5-0.99	0	0	0-7.57
1.0+	4	1.02	0.21-4.26
Maximum Probability of Dermal Exposure			
Low	8	1.00	-
Medium	4	0.61	0.12-2.51
High	2	0.47	0.04-2.86

A.R. Schnatter, T.W. Armstrong, L.S. Thompson, M.J. Nicolich, A.M. Katz, W.W. Huebner and E.D. Pearlman. 1996. The Relationship Between Low-Level Benzene Exposure and Leukemia in Canadian Petroleum Distribution Workers. *Environmental Health Perspectives.* 104: 1375-1379.

The Mantel-Haenszl analysis showed that leukemia risk did not increase with increasing categories of cumulative exposure, therefore, they constructed models with square terms for duration and intensity of exposure. This allows for non exponential increases in risk per unit exposure. For all combinations of duration and intensity of exposure in the squares of these variables a model with only duration of exposure squared fit the data best with a p value = 0.05. The odds ratio for this model was not quite statistically significant.

The authors concluded that they did not find evidence that low level exposure increased the risk of leukemia, multiple myeloma or non-Hodgkin's lymphoma. The fact that duration of exposure was most strongly related to leukemia occurrence versus exposure intensity or cumulative exposure might have indicated that long term exposure regardless of the concentration can result in leukemia. However, this interpretation would suggest that there was severe misclassification even between the highest and lowest intensity designations. This was judged to be unlikely given the validation exercise.

Limitations:
1. The size of the study was small and this limited any findings. For instance, if benzene exposure caused a two fold increase in risk for >45 ppm year category, the study would have only a 16% chance of discovering the relationship at a 20% exposure rate and a 5% significance level. In order to attain 80% power, 90 cases would have been needed.
2. None of the OR for cumulative exposure were significant at the p=0.05 level. For cumulative exposure, the risks were not monotonically increased, and in fact, the highest (non-significant) OR were found near the lowest levels - 0.18-0.49 ppm-years, 0.23-5.49 ppm-years, 0-0.49 ppm-years, 0-0.45 ppm-years and 0-0.90 ppm-years, depending upon the cut points chosen.
3. The authors concluded that the results were consistent with insufficient power to detect a small effect, or a lack of effect for low benzene exposure, particularly between 0.1 - 1.0 part per million.
4. The highest risk of leukemia was found in the managerial/professional category which should have had limited, or no potential for benzene exposure beyond the background levels.
5. There was limited amount of smoking information available and therefore this potentially confounding variable was not controlled for in the analysis. However, smoking was one of two strongest predictors for leukemia risk. Seven of the 14 cases were ever smokers and the remaining persons had an unknown smoking status.
6. There was no breakdown of leukemia by cell type.
7. By their own validation exercise, exposure estimates were within 22%. In addition, some of the exposure data was extrapolated from other facilities. In addition, the exposure assessment did not include personal monitoring, so the actual exposure level of each case and control is unknown.
8. There was missing work information for 25% of the 115 workers included in this analysis. Of that number, 19% were missing some information and 6% were missing more than halve. This could have introduced error due to mistakes made in the interpolation of jobs from other information.

9. The authors eliminated 2/16 cases of leukemia due to missing job information, thus further limiting the power of the study.

Armstrong, T. W., E. D. Pearlman, et al. (1996). "Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution worker epidemiology study." <u>Am Ind Hyg Assoc J</u> **57**(4): 333-43. (Armstrong, Pearlman et al. 1996)

High quality industrial hygiene monitoring data were only available from the early 1970s forward. As has been done in other similar industrial studies, the authors evaluated current jobs and then applied modifying factors to take into account historical process information and estimate "tenable" quantitative estimates of past exposure to benzene and hydrocarbons. The modifying factors were categorized into four types: workplace (control technology, product throughput), task (loading frequency, work practices), environment (wind speed, ambient temperature) and material (benzene content, volatility). The total values derived from the modifying factors was added to a base estimate for a task, tasks were tabulated by day for each worker and this was then culminated in a total worker exposure.

Where sufficient measurements were available log normality was verified. All data sets evaluated were statistically consistent with log normality. The Maximum Likelihood Estimator (MLE) was used to estimate the population arithmetic mean from the sample data for base estimates. MLE has been generally used when arithmetic means were reported with data and it was believed that consistency was needed in the study. The modified Cox calculation was used to derive 95% confidence intervals. The confidence intervals were used to evaluate precision of estimates, evaluate uncertainty as well as sensitivity and to assist with the validation exercise.

Base estimates were derived from some internal industrial hygiene measurements (170) as well as select literature sources. However, average shift measurements were only available after the 1970s. Company records supplied base estimates for the following job titles: agent, gauger, loader, checker, delivery driver, barrel washer, barrel filler, marine deck attendant, and marine pump man. The number of measurements used to ascertain the base estimates ranged from 3 for marine pumpman to 1335 for general population background data. A significant portion of the exposures in areas involved either general population exposure or facility background exposure with low or no direct occupational exposure to the products distributed at the facilities.

A limited validation of the exposure estimating algorithm was performed using available monitoring data. Criteria for selection included documentation of the survey methods and results, as well as measurements of exposure and adequate descriptive information on the operations and job titles of central interest to the study. When estimating exposure validation the results were generally within the estimated confidence intervals for the exposure estimates. Excluding one estimate, the average difference between the estimate and the sampling data was < 15% for the benzene exposures. With that said, the authors noted that validation was limited by the availability of measured exposure data, especially for jobs or conditions that diverged from the base estimate conditions. The only measured exposure data

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available for validation was for modern operations with relatively consistent technology work practices and materials. The confidence intervals for the measured data in this test exercise were not shown because the intervals are very wide and only based on a few measurements, as was the case with the measured data available here. Earlier operations had different exposure potential, but measured data from those earlier, more varied, operations are not available.

The sensitivity analysis of principal exposure modifiers indicated that percent benzene in the fuel and loading technology could increase the exposure estimates greatly as seen in Table 51 below.

Table 51 - Sensitivity Analysis of Principal Exposure Modifiers		
Principal Exposure Modifier	**Estimated Range of Values**	**Impact on Benzene Exposure Estimates**
Percent Benzene in Fuel	0.7 to 3.7[A]	-30% to +370%
Loading Technology	1 or 3	0% or +300%
Task	0.1[B] to 2	-90% to +200%
Temperature	0.63 to 1	-37% to 0%
Fuel Volatility	0.75 to 1	-25% to 0%
Product Mix	0.77 to 1.3	-23% to 30%

[A]Without benzole addition.
[B]For foreman.

T.W. Armstrong, E.D. Pearlman, A.R. Schnattter, S.M. Bowes, N. Murray and M.J. Nicolich. 1996. Retrospective Benzene and Total Hydrocarbon Exposure Assessment for a Petroleum Marketing and Distribution Worker Epidemiology Study. *American Industrial Hygiene Association Journal.* 57: 333-343.

Limitations:
1. Close scrutiny of the base estimates revealed that several of the most highly exposed workers (barrel washer and loader) were derived from limited numbers of measurements, derivations from total hydrocarbon content and short term measurements. For instance, the loader base estimate (historic) was derived from the total hydrocarbons and (14) short term measurements. The calculated benzene concentration used for this category was 2.6 ppm. The highest base estimate was for the barrel washer, yet the benzene concentration was derived from the total hydrocarbon level and (4) short term measurements.
2. The limited validation exercise did not include measurements of benzene exposure in highly exposed workers. Only the total hydrocarbons were estimated in those workers and they varied as follows: -21%, -9%, -11%, -49%, +220% and +85%. Alternatively, the benzene measurements varied as follows: 33%, 10%, 130%, 4.5%,

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0, 0, 0, 14.3% and -14%. Obviously, with a more highly exposed worker a hypothetical percent difference is of far greater importance than in a worker with only background exposure. In addition, all of the confidence intervals used in the validation exercise were very wide. The only jobs evaluated were route sales, loader and plantman.

7. The Caprolactam, Italian Shoe Worker and Gas/Electric Utility Worker Studies

Swaen, G. M., T. Scheffers, et al. (2005). "Leukemia risk in caprolactam workers exposed to benzene." Ann Epidemiol **15**(1): 21-8. (Swaen, Scheffers et al. 2005)

Cohort Description and Methods:

This study was composed of Dutch chemical industry association members. Pure benzene is used to extract the caprolactam from the neutralized caprolactam ammonium sulphate solution. Benzene extraction was performed indoors and rather primitive in the early years of production. According to former employees this resulted in high background exposures with peak and skin exposure due to technical problems and limitations.

There were 311 caprolactam workers who had been employed in the caprolactam plant at some time between January 1, 1951 and December 31, 1968. These workers were followed for mortality and the end date of the follow-up was January 1, 2001, covering a maximum risk period of follow-up of 40 years and a minimum risk period of 32 years in case a person survived until the end of the study.

Individual exposure estimates were constructed for 275 of the 311 workers. Workers with no exposure assessment were treated as a separate group in the analysis with a supposed equal exposure distribution. Cumulative individual exposure was assessed as a summation of exposures per cohort year. Modifying factors were derived from the expert judgment process. The factors 1 (low) to 6 (high) are assigned to the percentiles of the benzene exposure distribution of available exposure data in the 1970s and 1990s. The factors 2 to 6 are assumed to be within the 25-75 percentile range of the exposure distribution. Three additional factors were assigned to take into account major changes in the production process between 1951 and 1968.

Regarding the expert judgment process, a group interview was held with 7 former employees to reconstruct past exposure to benzene of workers at the caprolactam factory. The panel consisted of the following employees: two heads of shift, instructor, chemical analyst, chief of production, and two production workers. The following four issues were discussed: the job location and timeframe at the caprolactam factory from 1951 to 1968, the influences of process and work practices changes on benzene exposure, workplace air exposure to benzene during regular production incidence and stops, ranking of jobs related to the workplace air concentrations.

The cohort time period of 1951 to 1968 was split in three periods on the basis of major changes in the production process. Period 1 was from 1951 to 1957; Period 2 was from 1957 to 1962; and Period 3 was 1962 to 1968. In total 30 changes that had an affect on benzene concentrations in the caprolactam factory were identified.

A factor was used as a modifier in the assessment of the background concentration of benzene in the caprolactam factory. Intensity of the benzene exposure was divided into three classes: low, middle, and high. To achieve consensus in the interpretation of the exposure classes, the following definitions were employed: none to low exposure – no smell of benzene; middle – a weak benzene smell; and high – strong benzene odor. However, it should also be noted that the odor threshold for benzene varies between persons.

To derive individual exposure estimates, the main task name and the description of

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the job as it appears in the planning work were used. The job time concentrations were established and checked using the exposure assessment expert system (EAES). The first period (1951-1957) the exposure factors were determined at the panel meeting, the history recommended workplace levels, and the exposure measurements conducted in the factory from 1978 to 1988.

Benzene measurements from 1978 to 1980 and later were used to establish the base estimate distribution of benzene exposure ppm.

Results:

The total cumulative exposure of the 275 cohort members was 43,725 ppm-years, and 49,500 ppm-years when extrapolated to the total cohort. The daily mean workplace exposure was 20.9 ppm per person. The average number of exposure years was 9.6 with a standard deviation of 6.0 and a range from 1 to 18 years.

It was clear that exposure fell over time. For example, average daily mean exposures in the early period (1951-1957) were estimated to be over 26 ppm, compared with 0.6 in the 1963-1968 period. For 47% of the workers, the cumulative exposure was < 50 ppm-years and for 28% higher than 200 ppm-years with a maximum of 1,080 ppm-years. The highest contribution in ppm was found for the operator extraction. The highest contribution in term of number of years of contribution was observed for the job descriptions reserve (219 years) and chemical analyst (168 years).

According to former employees, it is likely that there was extensive and frequent dermal exposure to benzene. Former workers helped us to identify jobs and time periods with daily and weekly skin contact. Relevant skin exposure occurred primarily in the early years. An arbitrary 2% to 10% ppm-years of the air exposure was added if the job was identified with a weekly or daily skin contact. This approach led to the addition of 1,654 ppm-years to the cohort.

Next all exposed workers were classified into three cumulative dose groups: low, medium, and high. The cut-off points of the three dose groups were chosen in such a way that all three dose groups contained one-third of the cohort. Of the 311 workers included in the study, 121 had died before the end date of the follow-up. One hundred eighty (180) or 57.9% were still alive, and 8 or 2.6% had emigrated. For workers who emigrated, the person years at risk accumulated was stopped at emigration date. Two (1.1%) of employees were lost to follow-up. The workers who had emigrated or were lost to follow-up had no particular exposure pattern. Of the 121 deceased workers, 5 or 4.1% could not be linked to the particular cause of death.

Regarding total mortality, the SMR was 85.9 with a 95% confidence interval of 71.3 to 102.6. Only one death from leukemia was observed compared with an expected number of 1.17. The leukemia found was a non-ANLL type. The one leukemia death was not found in the highest exposure group.

We applied three quantitative risk estimates to the data of the caprolactam cohort to see which of these earlier risk assessments are compatible with the findings in the caprolactam cohort. Of the risk models applied to the caprolactam cohort, two overestimate the leukemia risk from benzene exposure in such a way that they predict benzene-induced excesses from leukemia that are statistically significant, but different from our findings.

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The authors stated that their study added some support for a threshold dose.

<u>Limitations:</u>

1. This is a very small study with only one leukemia case, so the conclusions drawn from it are necessarily limited.
2. The exposure assessment was based upon very limited industrial hygiene measurements with a great deal dependant upon "expert" judgment.
3. Eight of the workers emigrated, two were lost to follow-up and five did not have a particular cause of death. This is 5.4% unaccounted for from the original cohort. The addition of even one case would drastically alter the conclusions from this study.

B. Studies with Only Qualitative Exposure Measurements

1. Petroleum Industry Studies

(Please see the following pages for the charts containing the petroleum studies)

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Table 52 - Gulf Oil and Chevron Oil Company Studies								
Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Cont rol (#)	Statistical Measure CI or p-value	Comment s
(Tsai, Wen et al. 1983) Refinery	Retrospec tive Cohort, Mortality, 09/15/52-01/01/78	US General Populatio n	454 workers (all male workers ever employed during the period who worked directly on benzene, ethylene, aromatic distillate hydrogenatio n or cumene units.	All Lymphop oietic Cancer	0	0.42	SMR=0.00 (0.00-8.73)	
				Leukemia and Aleukemi a	15	27.8 9	SMR=0.54 9 (0.30-0.89)	
(Wen, Tsai et al. 1983) Refinery	Longitudi nal, Mortality, 01/01/37-01/01/78	US General Populatio n	16,880 hourly and salaried workers	Lymphati c and Hematopo ietic Cancer	80	78.7 1	SMR=1.02 (0.80-1.26) Adjusted SMR= 1.08	
				Lymphos arcoma and Reticulos arcoma	4	16.3 6	SMR=0.24 (0.07-0.63) Adjusted SMR=0.26	
				Hodgkin' s Disease	16	11.0 2	SMR=1.45 (0.83-2.36) Adjusted SMR=1.55	
				Leukemia and Aleukemi a	38	33.2 8	SMR=1.14 (0.81-1.57) Adjusted SMR=1.22	
				Cancer of Other Lymphati c Tissue	20	17.4 4	SMR=1.15 (0.70-1.77) Adjusted SMR=1.22	
(Dagg, Satin et al. 1992) 2 Petroleum Refineries	Retrospec tive Cohort, Mortality, 01/01/50-12/31/86	US Populatio n	14,074 workers (operating and maintenance, clerical, technical	Lymphati c and Haematop oietic System	Total=88 Richmon d=61 El Segundo= 27		Total SMR=106 (86-132) Richmond SMR=117 (90-151) El Segundo	

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			supervisory or administrativ e)			SMR=92 (60-133)	
				Lymphos arcoma and Reticulos arcoma	Total=18 Richmon d=14 El Segundo= 4		Total SMR=106 (63-167) Richmond SMR=129 (71-217) El Segundo SMR=66 (18-168)	
				Hodgkin' s Disease	Total=8 Richmon d=5 El Segundo= 3		Total SMR=88 (38-173) Richmond SMR=86 (28-200) El Segundo SMR=94 (19-274)	
				Leukemia and Aleukemi a	Total=33 Richmon d=21 El Segundo= 12		Total SMR=98 (67-137) Richmond SMR=98 (61-150) El Segundo SMR=99 (51-172)	
				Other Lymphati c tissue	Total=28 Richmon d=20 El Segundo= 8		Total SMR=136 (90-197) Richmond SMR=154 (94-238) El Segundo SMR=108 (46-212)	

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Table 53 – Chevron Oil Company Studies								
(Satin, Wong et al. 1996) Oil Refinery	Retrospective Cohort, Mortality, 01/01/37-12/31/83	General population in Texas and US Population	17,844 workers	Cancer of All Lymphatic, Haemotopoietic Tissue	138	TX= 131.7 US= 135.6	TX SMR=104.8 (88.0-123.8) US SMR=135.6 (85.5-120.3)	
				Lymphosarcoma and Reticulosarcoma	13	TX= 23.0 US= 25.4	TX SMR=56.5 (30.1-96.5) US SMR=51.2 (27.3-87.6)	
				Hodgkin's Disease	18	TX= 12.7 US= 14.2	TX SMR=141.3 (83.7-223.3) US SMR=127.1 (75.0-200.9)	
				Leukemia and Aleukemia	57	TX= 55.9 US= 55.0	TX SMR=102.0 (77.3-132.2) US SMR=103.7 (78.6-134.4)	
				Cancer of All Other Lymphopoietic Tissue	50	TX= 40.1 US= 41.1	TX SMR=124.7 (92.6-164.5) US SMR=121.7 (90.3-160.4)	

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Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Control (#)	Statistical Measure CI or p-value	Comments
				Baton Rouge				
(Hanis, Holmes et al. 1982) Refinery and Chemical Plant	Retrospective Cohort, Mortality 01/01/70-12/31/77	US Death rates	8,666 regular employees who worked at least one month, plus retirees who were alive as of 01/01/70.	All Lymphopoietic	25	23.0	SMR=109 (70-161)	
				Lymphoreticular Sarcoma	5	4.2	SMR=119 (39-278)	
				Leukemia	9	9.3	SMR=97 (44-184)	
				Other Lymphatic Tissue	7	7.2	SMR=97 (39-200)	
(Hanis, Shallenberger et al. 1985) 3 Refinery and Chemical Plants	Retrospective Cohort, Mortality, 01/01/70-12/31/77	US Population	21,698 workers	All Lymphopoietic	55	61.8	SMR=89 (67-116)	
				Lymphosarcoma/Reticulosarcoma	13	11.4	SMR=114 (61-196)	
				Leukemia	20	25.9	SMR=77 (47-119)	
				Other Lymphatic Tissue	15	18.6	SMR=81 (45-133)	
(Hanis, Shallenberger et al. 1985)3 Refinery and Chemical Plants	Retrospective Cohort, Mortality, 01/01/70-12/31/77		21,698 workers	All Lymphopoietic	Potentially Exposed=45 Non-Exposed=9	Potentially Exposed=4.4 Non-Exposed=3.8		
				Lymphosarcoma/Reticulosarcoma	Potentially Exposed=10	Potentially Expo		

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					Non-Exposed=3	sed=0.9 Non-Exposed=…		
				Leukemia	Potentially Exposed=15 Non-Exposed=4	Potentially Exposed=1.7 Non-Exposed=…		
(Shallenberger, Acquavella et al. 1992) 3 Refinery and Chemical Plants	Retrospective Cohort, Mortality, 01/01/70-12/31/82	General populations in Louisiana, Texas and New Jersey	25,321 workers (including retirees and terminated employees)		Baton Rouge=50 Baytown=32 Bayway/Bayonne=30 Total Population=111		Baton Rouge SMR=125 Baytown SMR=103 Bayway/Bayonne SMR=99 Total Population=110	The comparison population state was matched to the same state where the plant was located.
					Baton Rouge=23 Baytown=15 Bayway/Bayonne=9 Total Population=46		Baton Rouge SMR=129 Baytown SMR=114 Bayway/Bayonne SMR=68 Total Population=104	
					Baton Rouge=9 Baytown=6 Bayway/Bayonne=6 Total Population=21		Baton Rouge SMR=156 Baytown SMR=117 Bayway/Bayonne SMR=111 Total Population=21	
					Baton Rouge=17 Baytown=9 Bayway/		Baton Rouge SMR=122 Baytown SMR=84 Bayway/Ba	

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					Observed	Expected	SMR	Comments
					Bayonne=14 Total Population=40		yonne SMR=141 Total Population =116	
(Huebner, Schnatter et al. 1997) Petrochemical	Retrospective Cohort, Mortality, 01/01/79-12/31/92	US Population adjusted for gender, race and calendar time.	81,746 former and current petrochemical company employees.	All Lymphatic/Hematopoietic	Males=123 Females=15	Males=128.5 Females=17.4	Males SMR=0.96 (0.80-1.14) Females SMR=0.86 (0.48-1.42)	
				Lymphosarcoma/Reticulosarcoma	Males=5 Females=2	Males=12.3 Females=1.5	Males SMR=0.41 (0.13-0.95) Females SMR=none listed (none listed)	
				Hodgkin's Disease	Males=7 Females=3	Males=8.4 Females=1.4	Males SMR=0.83 (0.33-1.71) Females SMR=none listed (none listed)	
				Leukemia/Aleukemia	Males=60 Females=2	Males=58.7 Females=7.1	Males SMR=1.02 (0.78-1.32) Females SMR=0.28 (0.03-1.02)	
				All Other Lymphopoietic	Males=23 Females=8	Males=20.2 Females=7.3	Males SMR=1.14 (0.72-1.71) Females SMR=1.09 (0.47-2.15)	
				Multiple Myeloma	Males=18 Females=4	Males=15.0 Females=2.4	Males SMR=1.20 (0.71-1.90) Females SMR=none listed (none listed)	
(Lewis, Gamble et al. 2000) 3 Refinery/Petrochemic	Retrospective Cohort, Mortality, 01/01/70-12/31/82	National and State Population for the respective states of	19,075 Active/Terminated workers.	Lymphatic and Hemopoietic Tissue	116	95.2	SMR=122 (101-146)	Data was only provided for males.

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al Plants		each plant.						
				Lymphosarcoma and Reticulosarcoma	13	11.4	SMR=114 (61-196)	
				Leukemia	56	37.3	SMR=150 (113-195)	
				Other Lymphopoietic Tissue	45	41.0	SMR=110 (80-147)	
(Gamble, Lewis et al. 2000) 3 Refinery/Petrochemical Plants	Retrospective Cohort, Mortality, 01/01/70-12/31/82	US and State Population	6,238 male retirees from the three plants (almost all deceased)	Lymphatic and Hemopoietic Tissue	98	86.8	SMR=113 (92-138)	
				Lymphosarcoma and Reticulosarcoma	13	11.0	SMR=118 (63-202)	
				Leukemia	35	39.1	SMR=90 (62-124)	
				Other Lymphopoietic Tissue	46	33.6	SMR=137 (100-182)	
(Huebner, Wojcik et al. 2004) 2 Refinery/Petrochemical Plants	Retrospective Cohort, Mortality 01/01/70-12/31/97	General Populations for Louisiana (for Baton Rouge Plant) or Texas (Baytown Plant). US rates were also used for comparison purposes	7,637 Baton Rouge Employees and 7,007 Baytown Employees. Predominantly white males.	Malignant Neoplasms of Lymphatic and Hematopoietic Tissue	BR=81 B=54	BR=55.17 B=49.32	BR SMR=1.47 (1.17-1.82) B SMR= 1.10 (0.82-1.43)	BR=Baton Rouge B=Baytown
				Hodgkin's Disease	BR=0 B=1	BR=2.70 B=2.25	BR SMR= - (-) B SMR= - (-)	
				Non-Hodgkin's	BR=29 B=15	BR=19.77	BR SMR=1.47 (0.98-2.11)	

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				Lymphoma		B=17.85	B SMR= 0.84 (0.47-1.39)	
				Multiple Myeloma	BR=13 B=11	BR=10.001 B=9.03	BR SMR=1.30 (0.69-2.22) B SMR= 1.22 (0.61-2.18)	
				Leukemia	BR=37 B=27	BR=21.92 B=19.56	BR SMR=1.69 (1.19-2.33) B SMR= 1.38 (0.91-2.01)	
				Acute Non-lymphocytic	BR=11 B=12	BR=7.23 B=5.62	BR SMR=1.52 (0.76-2.72) B SMR=2.13 (1.10-3.73)	
				Chronic Myelocytic	BR=5 B=4	BR=2.75 B=2.61	BR SMR=1.82 (0.59-4.25) B SMR= 1.54 (0.42-3.93)	
				Acute Lymphocytic	BR=2 B=2	BR=0.89 B=1	BR SMR= - (-) B SMR= - (-)	
				Chronic Lymphocytic	BR=10 B=5	BR=4.13 B=4.07	BR SMR=2.42 (1.16-4.45) B SMR= 1.23 (0.40-2.87)	
				Other and Unspecified Leukemia	BR=9 B=4	BR=6.90 B=6.22	BR SMR=1.30 (0.60-2.48) B SMR= 0.64 (0.18-1.65)	
(Wong, Harris et al. 2001) Petroleum Refinery	Retrospective Cohort, Mortality 01/01/59-12/31/97	US Population	3,328 workers	Cancer of all Lymphatic, Hemopoietic Tissue	19	18.65	SMR=101.9 (61.3-159.1)	
				Lymphosarcoma and Reticulosarcoma	1	2.11	SMR=47.4 (1.2-264.3)	

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				Hodgkin's Disease	1	1.13	SMR=88.4 (2.2-492.8)	
				Leukemia and Aleukemia	5	7.37	SMR=67.8 (22.0-158.3)	
				Cancer of all other Lymphopoietic Tissue	12	8.04	SMR=149.2 (77.1-260.6)	
(Lewis, Yarborough et al. 1999) Petrochemical researchers	Retrospective Cohort, Mortality, 01/01/64-12/31/92	US and New Jersey Populations	13,188 New Jersey USA based employees	All Lymphopoietic Cancer	Males=33 Females=2	Males=36.2 Females=4.8	Males SMR=91 (63-128) Females SMR= - (-)	
				Lymphosarcoma, Reticulosarcoma	Males=2 Females=0	Males=4.6 Females=0.5	Males SMR= - (-) Females SMR= - (-)	
				Hodgkin's Disease	Males=1 Females=0	Males=3.5 Females=0.7	Males SMR= - (-) Females SMR= - (-)	
				Leukaemia, Aleukaemia	Males=14 Females=0	Males=13.5 Females=1.8	Males SMR=103 (57-174) Females= - (-)	
				All Other Lymphopoietic	Males=16 Females=2	Males=14.6 Females=1.7	Males SMR=110 (63-178) Females SMR= - (-)	

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Table 55 – Mobil Oil Company Studies								
Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Control (#)	Statistical Measure CI or p-value	Comments
(Collingwood, Milcarek et al. 1991) 2 Refinery Plants	Retrospective Cohort, Mortality 01/01/45-12/31/78	US Males	2,467 workers in lubrication products and blending (97% male)	Lymphosarcoma and Reticulosarcoma	0		SMR=0 (0-121)	
				Hodgkin's Disease	1		SMR=58 (2-324)	
				Leukemia and Aleukemia	6		SMR=106 (39-230)	
				Other Lymphatic Tissue	5		SMR=149 (49-349)	
(Raabe, Collingwood et al. 1998) Petroleum Refinery	Retrospective Cohort, Mortality, 01/01/45-12/31/87	US Age specific mortality rates	7,119 workers	Lymphatic and Hematopoietic Cancer	TP=65 WM=54	TP= 48.7 WM =40.2	TP SMR=133 (103-170) WM SMR=134 (101-175)	TP= Total population WM = White Males
				Lymphosarcoma and Reticulosarcoma	TP=9 WM=7	TP= 8.6 WM =7.4	TP SMR=105 (48-199) WM SMR=95 (38-196)	
				Hodgkin's Disease	TP=3 WM=3	TP= 4.5 WM =3.8	TP SMR=66 (14-194) WM SMR=79 (16-230)	
				Leukemia and Aleukemia	TP=28 WM=24	TP= 20.1 WM =16.9	TP SMR=139 (92-201) WM SMR=142 (91-211)	
				Other Lymphatic Tissue	TP=24 WM=19	TP= 15.2 WM =11.9	TP SMR=158 (101-235) WM SMR=160 (96-249)	
(Wong, Harris et	Retrospective	US Populatio	7543 workers	All Lymphati	83	69.49	SMR=119.4 (95.1-	

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al. 2001) Petroleum Refinery	Cohort, Mortality, 01/01/45-12/31/96	n		c, Hemopoie tic Tissue			148.1)	
				Lymphos arcoma and Reticulos arcoma	9	9.74	SMR=92.4 (42.3-175.5)	
				Hodgkin's Disease	3	5.14	SMR=58.4 (12.0-170.6)	
				Leukemia and Aleukemi a	39	28.07	SMR=138.9 (98.8-189.9)	
				Cancer of All Other Lymphop oietic Tissue	32	26.56	SMR=120.5 (82.4-170.1)	

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Table 56 - Shell Oil Company Studies

Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Control (#)	Statistical Measure CI or p-value	Comments
(McCraw, Joyner et al. 1985) Petroleum Refinery	Retrospective Cohort Mortality 01/01/73-12/31/82	US	3,976 men Hourly & Salaried	Leukemia	14	6.6	SMR=213 (117-358)	Subjects not in area with highest benzene levels
				Acute Myeloid	8	2.0	SMR=394 (172-788)	No exposure data
				Acute Monocytic	1	0.2	SMR=661 (6-2,782)	
				Chronic Myeloid	1	0.8	SMR=121 (2-696)	
				Acute Lymphatic	1	0.3	SMR=340 (4-1,854)	
				Chronic Lymphatic	1	1.3	SMR=73 (1-428)	
				Other and Non-Specified	2	2.0	SMR=100 (11-361)	
(Austin, Cole et al. 1986) Oil Refinery	Case Control Mortality 01/01/73-12/31/82	50 matched controls	14 cases with leukemia (8 cases with AML) All white males with leukemia who worked or had worked at the refinery for at least 6 months.	Leukemia	14	8		4 controls matched to each case on year of birth (plus or minus 2 years). Controls had to have worked for at the refinery for at least 6 months and could not have died from lymphoma or diseases of the blood-forming organs. Controls

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								had to have survived at least as long as their matched case.
				Acute Myeloid Leukemia	8	2		These 8 were included in the original count of 14 cases of leukemia.
(Tsai, Dowd et al. 1991) Petroleum/ petrochemical Refinery	Prospective Cohort, Morbidity, 01/01/81-12/31/88		2132 full-time male (1380 production and 752 staff employees of the Shell Oil Company)	All Neoplasms	Production-46, Staff-17	Production-44.2, Staff -15.2	SMR= Production-104, Staff-112	No CI was given.
(Wongsric hanalai, Delzell et al. 1989) Petroleum Refinery	Retrospective and Case Control, Mortality, 01/01/42-01/01/84	US White Men	9,484 white men who worked at the petroleum refinery.	All Lymphatic and Hematopoietic Tissue	90		SMR=126 (101-155)	Three deaths attributed to myelofibrosis are included in the category of "all lymphatic and hematopoietic tissue", but not in any of the other subcategories.
				Lymphosarcoma	14		SMR=99 (54-166)	
				Hodgkin's Disease	9		SMR=114 (52-216)	
				Leukemia	44		SMR=149 (108-200)	
				Other Lymphatic and Hematopoietic	20		SMR=105 (64-162)	

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				tissue				
(Honda, Delzell et al. 1995) Petroleum Manufactu ring Plant	Retrospec tive Cohort, Mortality, 01/01/42-1989	US White Men	9,796 white male hourly and salaried workers	All Lymphop oietic Cancer	104		SMR=114 (93-138)	Individuals had to have worked at the plant at least 6 months before 1990
				Lymphos arcoma	14		SMR=89 (49-149)	
				Hodgkin's Lymphom a	9		SMR=106 (48-200)	
				Leukemia	46		SMR=123 (90-164)	
				Other Lymphop oietic Tissue	29		SMR=99 (66-142)	
(Tsai, Gilstrap et al. 1993) Two Refinery and Petrochem ical Plants	Retrospec tive Cohort Mortality 01/01/73-12/31/89	California Mortality Rates	4,585 MMC and WMC full-time male employees who worked at least 6 months prior to 12/31/89, were actively employed as of 01/01/73 and were pensioners who were alive as of 01/01/73.	Lymphati c and Hematopo ietic Tissue	MMC=14 WMC=12 Combine d=26		MMC SMR=1.04 (0.57-1.74) WMC SMR=1.04 (0.54-1.82) Combined SMR=1.04 (0.68-1.52)	The two plants were Martinez Manufactu ring Complex (MMC) and Wilmingto n Manufactu ring Complex (WMC)
				Lymphos arcoma and reticulosa rcoma	MMC=2 WMC=0 Combine d=2		MMC SMR=1.21 (0.15-4.37) WMC SMR=none listed. Combined SMR=0.65 (0.08-2.36)	
				Hodgkin's Disease	MMC=2 WMC=0 Combine d=2		MMC SMR=3.66 (0.44-) WMC SMR=none listed. Combined	

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							SMR=1.99 (0.24-7.18)	
				Leukemia	MMC=2 WMC=7 Combined=9		MMC SMR=0.36 (0.04-1.29) WMC SMR=1.47 (0.59-3.02) Combined SMR=0.87 (0.40-1.65)	
				Other Lymphatic Tissue	MMC=8 WMC=5 Combined=13		MMC SMR=1.39 (0.60-2.75) WMC SMR=1.02 (0.33-2.39) Combined SMR=1.22 (0.65-2.09)	
Shell in Louisiana								
(Tsai, Gilstrap et al. 1997) Petrochemical Company	Prospective Cohort, Mortality 01/01/73-01/01/94	United States, Louisiana and/or Surrounding Tri-Parish area.	3,803 Refinery and Petrochemical Workers (active and retired)	All Lymphatic and Hematopoietic tissue	9	12.2	SMR=0.74 (0.34-1.41)	Must have worked at least 6 months prior to 01/01/94.
				Leukemia and Aleukemia	4	5.0	SMR=0.81 (0.22-2.07)	
				All Lymphatic and Hematopoietic tissue	8	US= 11.3 LA= 11.5 Tri-Parishes= 11.2	US SMR=0.71 LA SMR=0.70 Tri-Parishes SMR=0.71	With at least 10 years time since first employment
				Leukemia and Aleukemia	3	US= 4.6 LA= 4.7 Tri-Parishes= 4.3	US SMR=0.66 LA SMR=0.63 Tri-Parishes SMR=0.70	With at least 10 years time since first employment
(Tsai, Wendt et al. 2003) Refinery and Chemical	Prospective Mortality Surveillance (01/01/73	US, Louisiana and the seven parish region	Morbidity Study = 4,221 employees and retirees Mortality	All Lymphatic and Haematopoietic Tissue	15	18.0	SMR=0.83 (0.47-1.38)	

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Facility	- 12/31/99) and Morbidity : (1990-1999)		Study= 2,203 individuals who ever worked at the plant during this period.					
				Lymphosarcoma and Reticulosarcoma	3	1.3	SMR=2.32 (0.48-6.79)	
				Hodgkin's Disease	0	0.9	SMR= - (0.00-4.24)	
				Leukaemia and Aleukamia	4	7.0	SMR=0.57 (0.16-1.46)	
				All other Lymphopoietic Tissue	8	8.8	SMR=0.91 (0.39-1.79)	
				All Lymphatic and Hematopoietic tissue	14	US= 16.2 LA= 17.1 Industrial Corridor= 17.6	US SMR=0.87 LA SMR=0.82 Tri-Parishes SMR=0.79	With at least 10 years of employment
				Leukemia and Aleukemia	3	US= 6.3 LA= 6.8 Industrial Corridor= 7.0	US SMR=0.48 LA SMR=0.44 Tri-Parishes SMR=0.43	With at least 10 years of employment
Shell Deer Park								
(Marsh, Enterline et al. 1991) Petroleum Refinery and Chemical Plant	Retrospective Cohort, Mortality, 01/01/48-12/31/72	US, Texas and Harris County populations	6,831 male and female hourly and salaried workers who were employed for at least 3 months during the period studied.	All Lymphopoietic Tissue	36		US SMR=110 TX SMR=115 Harris County SMR=110	
				Lymphopoietic Tissue	26=Refinery Only 9=Chemi		127=Refinery Only 111=Chemi	Harris County Compariso

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					cal Plant Only 1=Both Plants Combined		cal Plant Only 25=Both Plants Combined	n Only
				Lympho-Reticulosarcoma	9=Refinery Only 1=Chemical Plant Only 0=Both Plants Combined		189=Refinery Only 59=Chemical Plant Only - =Both Plants Combined	Harris County Comparison Only
				Hodgkin's Disease	3=Refinery Only 0=Chemical Plant Only 0=Both Plants Combined		135=Refinery Only - =Chemical Plant Only - =Both Plants Combined	Harris County Comparison Only
				Leukemia	8=Refinery Only 3=Chemical Plant Only 0=Both Plants Combined		97=Refinery Only 93=Chemical Plant Only - =Both Plants Combined	Harris County Comparison Only
				Other Lymphopoietic (residual)	7=Refinery Only 5=Chemical Plant Only 1=Both Plants Combined		120=Refinery Only 237=Chemical Plant Only 1=Both Plants Combined	Harris County Comparison Only
(Tsai, Dowd et al. 1992) Petroleum and Chemical Plant	Prospective Cohort, Morbidity 01/01/81-12/31/88	All manufacturing employees of the Shell Oil Company	3,422 male employees	Lymphatic and haematopoietic Tissue	Production=4 Staff=2		Production SMR=124 (33-340) Staff=91 (10-379)	
(Tsai, Gilstrap et al. 1996) Petroleum Refinery and	Retrospective Cohort, Mortality, 01/01/48-12/31/89	Death rates for Harris County, Texas	9,720 hourly and salaried employees with routine field or laboratory	All Lymphatic and Hematopoietic Tissue	Refinery=39 Chemical=17 Total=56		Refinery SMR=122.0 (87-167) Chemical SMR=92.3	

Chemical Plant			assignments				(54-148) Total SMR=111.2 (84-144)
				Lymphosarcoma and Lympho-Reticulosarcoma	Refinery=9 Chemical=1 Total=10		Refinery SMR=169.5 (77-322) Chemical SMR=34.7 (1-194) Total SMR=122.1 (59-225)
				Hodgkin's Disease	Refinery=4 Chemical=0 Total=4		Refinery SMR=137.0 (37-351) Chemical SMR= - (-) Total SMR=84.2 (23-215)
				Leukemia and Aleukemia	Refinery=14 Chemical=7 Total=21		Refinery SMR=109.4 (60-84) Chemical SMR=98.3 (39-202) Total SMR=105.4 (65-161)
				All Other Lymphopoietic (residual)	Refinery=12 Chemical=9 Total=21		Refinery SMR=109.8 (57-192) Chemical SMR=136.9 (63-260) Total SMR=120.0 (74-183)
(Tsai, Ahmed et al. 2007) Petroleum Refinery	Retrospective Cohort, Mortality, 01/01/48-12/31/03	Harris County, Texas Population	10,621 employees who worked for at least 3 months during the	All Lymphatic, Hematopoietic Tissue	Refinery=62 Chemical=41 Total=103		Refinery SMR=0.98 (0.75-1.25) Chemical SMR=0.94 (0.67-1.27)

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			period studied.				Total SMR=0.96 (0.79-1.17)	
				Hodgkin Diseases	Refinery= 4 Chemical =0 Total=4		Refinery SMR=1.16 (0.32-2.97) Chemical SMR= - (0.0-1.63) Total SMR=0.70 (0.19-1.79)	
				Non-Hodgkin Lymphoma	Refinery= 27 Chemical =13 Total=40		Refinery SMR=1.13 (0.74-1.64) Chemical SMR=0.75 (0.40-1.28) Total SMR=0.97 (0.69-1.32)	
				Leukemia, Aleukemia	Refinery= 23 Chemical =18 Total=41		Refinery SMR=0.95 (0.60-1.42) Chemical SMR=1.10 (0.65-1.73) Total SMR=1.01 (0.72-1.36)	

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Table 57 - Texaco Oil Company Studies								
Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Control (#)	Statistical Measure CI or p-value	Comments
(Divine, Barron et al. 1985) Refining, Petrochemical or Research Facility	Retrospective Follow-up, Mortality, 01/01/47-12/31/77	US White male population	19,077 white men - All employees of Texaco Inc., who worked at the refinery, petrochemical or research facilities.	Lymphosarcoma	20	22.2	SMR=90 (55-139)	To be included, employees had to have worked at least 5 years prior to 12/31/77.
				Hodgkin's Disease	13	12.0	SMR=108 (58-185)	
				Leukemia	48	40.7	SMR=118 (87-156)	
				Cancer of the Lymphatic Tissue	25	21.8	SMR=115 (74-170)	
(Divine and Barron 1986) Refining, Petrochemical or Research Facility	Cohort, Mortality, (01/01/47 - 12/31/77)	US white male population of similar age and calendar time.	18,798 persons employed 5 years or more at a Texaco refinery, petrochemical plant or research laboratory.	Lymphosarcoma	OM >1 year=6 OM >5 years=4 O >1 year=13 O >5 years=8 M >1 year=6 M >5 years=2 L >1 year=1 L >5 years=1 PB >1 year=5 PB >5 years=3		OM >1 year SMR=78 CI=(28-169) OM >5 years SMR=64 CI=(17-163) O >1 year SMR=106 CI=(56-181) O >5 years SMR=82 CI=(22-210) M >1 year SMR=46 CI=(17-101) M >5 years SMR=24 CI=(3-88) L >1 year SMR=42 CI=(1-236) L >5 years SMR=53	Office/Manager=OM Operators=O Maintenance=M Laboratory=L Pipefitters/ Boilermakers=PB

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							CI=(1-293) PB >1 year SMR=117 CI=(38-274) PB >5 years SMR=133 CI=(27-387)	
				Hodgkin's Disease	OM >1 year=1 OM >5 years=1 O >1 year=7 O >5 years=4 M >1 year=6 M >5 years=6 L >1 year=1 L >5 years=1 PB >1 year=1 PB >5 years=1		OM >1 year SMR=27 CI=(0-150) OM >5 years SMR=34 CI=(0-188) O >1 year SMR=106 CI=(43-219) O >5 years SMR=82 CI=(22-210) M >1 year SMR=86 CI=(31-186) M >5 years SMR=138 CI=(50-299) L >1 year SMR=72 CI=(1-403) L >5 years SMR=90 CI=(1-498) PB >1 year SMR=46 CI=(1-256) PB >5 years SMR=88 CI=(1-488)	
				Leukemia	OM >1 year=18 OM >5 years=11 O >1 year=31 O >5 years=21		OM >1 year SMR=124 CI=(74-197) OM >5 years SMR=93	

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					M >1 year=27 M >5 years=14 L >1 year=3 L >5 years=3 PB >1 year=17 PB >5 years=12		CI=(46-167) O >1 year SMR=137 CI=(93-194) O >5 years SMR=120 CI=(74-184) M >1 year SMR=115 CI=(76-167) M >5 years SMR=93 CI=(51-156) L >1 year SMR=74 CI=(15-218) L >5 years SMR=94 CI=(19-274) PB >1 year SMR=212 CI=(123-339) PB >5 years SMR=285 CI=(147-498)	
				Cancer of the Lymphatic Tissue	OM >1 year=8 OM >5 years=6 O >1 year=16 O >5 years=12 M >1 year=18 M >5 years=13 L >1 year=1 L >5 years=0 PB >1 year=7 PB >5 years=1		OM >1 year SMR=97 CI=(67-136) OM >5 years SMR=92 CI=(34-201) O >1 year SMR=132 CI=(75-214) O >5 years SMR=127 CI=(66-223) M >1 year SMR=142	

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							CI=(84-225) M >5 years SMR=161 CI=(86-275) L >1 year SMR=43 CI=(1-242) L >5 years SMR=0 CI=(0-199) PB >1 year SMR=164 CI=(66-338) PB >5 years SMR=44 CI=(1-246)	
(Divine and Barron 1987) Producing or Pipeline Location	Retrospective follow-up, Mortality, 01/01/46-12/31/80	US white male population	11,098 white men who were employed for at least 6 months.	Lymphosarcoma	7	11.8	SMR=59 (24-122)	
				Hodgkin's Disease	4	6.6	SMR=60 (16-154)	
				Leukemia	25	22.7	SMR=110 (71-163)	
				Cancer of Other Lymphatic Tissue	12	13.5	SMR=89 (46-155)	
(Divine, Hartman et al. 1999) Refining, Research and Petrochemical Facilities	Retrospective follow-up, Mortality, 01/01/47-12/31/93	US Population	28,480 employees	Lymphatic and Haematopoietic Cancer	White Men=226 Non-White Men=3 All Women=11		White Men=99SMR= (87-113) Non-White Men= SMR=36 (7-106) All Women= SMR=131 (65-234)	
				Lymphosarcoma and Reticulosarcoma	White Men=26 Non-White Men=0 All Women=0		White Men= SMR=75 (49-110) Non-White Men= SMR=0 (0-417) All	

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							Women= SMR=0 (0-309)	
				Hodgkin's Disease	White Men=17 Non-White Men=0 All Women=0		White Men= SMR=98 (57-156) Non-White Men= SMR=0 (0-615) All Women= SMR=0 (0-618)	
				Leukemia	White Men=93 Non-White Men=0 All Women=4		White Men= SMR=101 (81-123) Non-White Men= SMR=0 (0-122) All Women= SMR=129 (35-331)	
				Other Lymphatic Tissue	White Men=85 Non-White Men=3 All Women=7		White Men= SMR=109 (87-135) Non-White Men= SMR=81 (16-237) All Women= SMR=209 (84-431)	
(Divine, Hartman et al. 1999) Refining, Research and Petrochemical sites	Retrospective follow-up, Mortality, 01/01/47-12/31/93	US Population	28,840 workers (employed for ≥5 years)	Non-Hodgkin's Lymphoma	74		SMR=88 (69-111)	Data was provided only on white men for all of the leukemias.
				Multiple Myeloma Leukemia	36		SMR=101 (70-140)	
				Acute Lymphocytic Leukemia	5	4.9	SMR=101 (32-235)	
				Chronic	15	18.6	SMR=80	

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				Lymphoc ytic Leukemia			(45-133)
				Acute Myelogen ous Leukemia	20	15.5	SMR=129 (78-199)
				Chronic Myelogen ous Leukemia	12	11.4	SMR=105 (54-183)
				Acute Unspecifi ed Leukemia	15	5.4	SMR=276 (154-455)
				Cell-Type Unspecifi ed Leukemia	15	6.5	SMR=231 (129-381)
(Divine and Hartman 2000) Crude Oil Production site	Retrospec tive follow-up, Mortality, 01/01/46-12/31/94	US populatio n	24,124 workers broken up into two groups: white men, on-white men and all women	Lymphati c and Haematop oietic	Employed <5 yrs=8 Employed 5-9 yrs=10 Employed 10-19 yrs=19 Employed ≥20 yrs=79		<5 yr SMR=54 (23-107) 5-9 yrs SMR=86 (41-159) 10-19 yrs SMR=89 (53-139) ≥20 yrs SMR=102 (81-128)	Data was provided only on white men for all of the leukemias.
				Lymphos arcoma and Reticulos arcoma	Employed <5 yrs=2 Employed 5-9 yrs=0 Employed 10-19 yrs=3 Employed ≥20 yrs=5		<5 yr SMR=111 (12-401) 5-9 yrs SMR=0 (0-235) 10-19 yrs SMR=83 (16-243) ≥20 yrs SMR=46 (15-107)	
				Hodgkin's Disease	Employed <5 yrs=1 Employed 5-9 yrs=0 Employed 10-19 yrs=0 Employed ≥20 yrs=4		<5 yr SMR=50 (0-278) 5-9 yrs SMR=0 (0-249) 10-19 yrs SMR=0 (0-159) ≥20 yrs SMR=97 (26-248)	

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				Leukaemia	Employed <5 yrs=3 Employed 5-9 yrs=3 Employed 10-19 yrs=8 Employed ≥20 yrs=35		<5 yr SMR=52 (10-153) 5-9 yrs SMR=66 (13-194) 10-19 yrs SMR=94 (40-185) ≥20 yrs SMR=111 (77-154)	
				Other Lymphatic Tissue	Employed <5 yrs=2 Employed 5-9 yrs=7 Employed 10-19 yrs=5 Employed ≥20 yrs=31		<5 yr SMR=40 (4-147) 5-9 yrs SMR=184 (73-379) 10-19 yrs SMR=75 (24-176) ≥20 yrs SMR=109 (74-155)	

				Table 58 - Union Oil Company Studies					
Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Control (#)	Statistical Measure CI or p-value	Comments
(Sathiakumar, Delzell et al. 1995)Petroleum Company	Case-Control, Mortality, (1976-1990)	284 matched by year of birth (±2 years) and (active employees who had worked for at least 1 year or retired employees)	69 cases of leukemia (any cohort member who had leukemia listed on death certificate.					For those individuals who died while actively working, they were matched with an actively working employee with the same birth year (±2 years) and race. For those individuals who died after retirement, they were matched by a birth year (±2 years) and retiree status.

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2. Studies Conducted in Various Industries with Benzene Exposure

(Please see the following pages for the charts containing various industrial studies)

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Table 59 - Various Industry Studies								
Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Cont rol (#)	Statistical Measure CI or p-value	Comment s
Highway Maintenance Workers								
(Bender, Parker et al. 1989) Highway Maintenance Worker (HMW)	Occupational Cohort, Mortality, 01/01/45-12/31/84	White Male Minnesota Mortality Experience	4,849 men with 1 or more years of experience as a HMW for the Minnesota DOT	Lymphore ticular	34	35.7	SMR=95 (66-133)	
				Lymphosarcoma	7	6.2	SMR=113 (45-233)	
				Hodgkin's Disease	2	3.4	SMR=58 (7-209)	
				Leukemia	17	15.9	SMR=107 (62-171)	
				Multiple Myeloma	3	5.7	SMR=53 (11-155)	
				Other Lymphore ticular	5	4.5	SMR=110 (36-257)	
Shoe Manufacturing Plants								
(Paci, Buiatti et al. 1989) Shoe manufacturing plant	Historical Cohort, Mortality, 01/01/39-12/31/84	National Italian Mortality rates specific for cause, age, sex and calendar period, plus the mortality data bank of the World Health Organization.	2,014 individuals who worked or had ever worked at the plant during the period, but that were still employed in or after January 1950.	Leukemia	Men=6 Women=-	Men = 1.5 Women =0.9	Men SMR=400 (146-870) Women SMR=0 (..)	
				Other Lymphatic and Hematopoietic Neoplasms	Men=1 Women=1	Men = 1.8 Women =0.9	Men SMR=55 (..) Women SMR=111 (..)	
(Walrath, Decoufle	Case-Control,	US Populatio	4,374 deceased	Lymphosarcoma	Male=13 Female=9	Male =	Male PMR=110	

				and Reticulosarcoma		11.9 Female= 5.3	Female PMR=171	
et al. 1987) Shoe manufactu ring company	Mortality 01/0160-12/31/79	n	former employees who died during the period of time identified.					
				Hodgkin's Disease	Male=3 Female=2	Male= 4.2 Fem ale= 1.7	Male PMR= - Female PMR= -	
				Multiple Myeloma	Male=10 Female=8	Male= 5.2 Fem ale= 2.3	Male PMR=193 Female PMR=346	
				Other Lymphati c Tumors	Male=10 Female=6	Male= 9.2 Fem ale= 4.1	Male PMR=109 Female PMR=148	
				Leukemia	Male=22 Female=7	Male= 25.6 Fem ale= 8.8	Male PMR=86 Female PMR=79	
(Lehman and Hein 2006) 2 Shoe manufactu ring plants	Retrospec tive Cohort, Mortality, 01/01/40-12/31/79	US Populatio n	7,828 men and women who had worked at one of the 2 plants for one month or more during the period.	Neoplasm s of Lymphati c and Hematopo ietic Tissue	Male=20 Female=4 6 Combine d=66		Male SMR=0.74 (0.45-1.15) Female SMR=1.10 (0.81-1.47) Combined SMR=0.96 (0.74-1.22)	
				Leukemia and Aleukemi a	Male=8 Female=1 9 Combine d=27		Male SMR=0.72 (0.31-1.42) Female SMR=1.22 (0.74-1.91) Combined SMR=1.01 (0.67-1.48)	
(Fu, Demers et al. 1996) 2 Shoe manufactu	Retrospec tive Cohort, Mortality,		Total: 6,223: 4,215 male shoemakers from England and	Non-Hodgkin's Lymphom a	English=6 Italian=2		English SMR=55 (20-120) Italian SMR=106	English cohort time period: 1939-1991

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ring plants			2,008 male and female shoemakers from Italy				(13-382)	– but only those alive in 1950 could participate. Italian cohort: 1939-1984, but only those who had worked between 1950-1984.
				Leukemias	English=16 Italian=8		English SMR=89 (51-145) Italian SMR=214 (92-421)	
				Multiple Myeloma	English=8 Italian=3		English SMR=104 (45-206) Italian SMR=288 (60-843)	
Filling or Service Stations								
(Lagorio, Forastiere et al. 1994) Filling Station Attendants	Cohort, Mortality, 01/01/81-07/31/91	Regional Population	2,665 service station managers in Italy – both men and women.	Lymphohematopoietic	Men=5 Women= - Total=5	Men = 6.7 Women =0.7 Total =7.3	Men SMR=75 (29-157) Women SMR= - (-) Total SMR=68 (27-143)	
				Non-Hodgkin's Lymphoma	Men=3 Women= - Total= - 3	Men = 1.7 Women =0.2 Total =1.9	Men SMR=173 (47-448) Women SMR= - (-) Total SMR=158 (43-408)	
				Leukemia	Men=2 Women= - Total=2	Men = 3.3 Women =0.3 Total =3.6	Men SMR=61 (11-192) Women SMR= - (-) Total SMR=56 (10-175)	

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(Lynge, Andersen et al. 1997) Service Stations	Cohort, Mortality, ~15 years with start and end dates dependent upon country.	National Incidence Rates	19,000 service station workers from Denmark, Norway, Sweden and Finland	Non-Hodgkin's Lymphoma	Male: D=8 N=9 S=18 F=2 T=37 Female: D=1 N=1 S=0 F=0 T=2	Male: D=5.98 N=9.25 S=16.90 F=2.47 T=34.60 Female: D=1.31 N=1.02 S=1.11 F=0.18 T=3.62	Male: D SIR=1.3 N SIR=1.0 S SIR=1.0 F SIR=0.8 T SIR=1.1 (0.8-1.5) Female: D SIR=0.8 N SIR=1.0 S SIR= - F SIR= - T SIR=0.6 (0.0-2.0)	Start and End Dates: Demark: 11/09/70-11/08/87 Norway: 01/01/71-12/31/91 Sweden: 11/01/70-12/31/89 Finland: 12/31/70-12/31/85
				Hodgkin's disease	Male: D=3 N=2 S=5 F=0 T=10 Female: D=0 N=0 S=0 F=0 T=0	Male: D=2.86 N=2.00 S=4.85 F=1.03 T=10.24 Female: D=0.41 N=0.15 S=0.23 F=0.05 T=0.85	Male: D SIR=1.3 N SIR=1.0 S SIR=1.0 F SIR= - T SIR=1.0 (0.5-1.8) Female: D SIR= - N SIR= - S SIR= - F SIR= - T SIR= - (-)	D=Denmark N=Norway S=Sweden F=Finland T=Total
				Multiple Myeloma	Male: D=2 N=3 S=3 F=1	Male: D=2.60 N=5.	Male: D SIR=0.8 N SIR=0.6 S SIR=0.4 F SIR=1.1	

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					T=9 Female: D=0 N=0 S=2 F=0 T=0	35 S=7.13 F=0.91 T=15.99 Female: D=0.52 N=0.56 S=0.50 F=0.07 T=1.65	T SIR=0.6 (0.3-1.1) Female: D SIR= - N SIR= - S SIR=4.0 F SIR= - T SIR= - (-)	
				Leukemia	Male: D=5 N=9 S=12 F=0 T=26 Female: D=2 N=0 S=0 F=0 T=2	Male: D=6.74 N=6.58 S=13.69 F=2.15 T=29.16 Female: D=1.32 N=0.63 S=0.88 F=0.16 T=2.99	Male: D SIR=0.7 N SIR=1.4 S SIR=0.9 F SIR= - T SIR=0.9 (0.6-1.3) Female: D SIR=1.5 N SIR= - S SIR= - F SIR= - T SIR=0.7 (- 0.1-2.4)	
				Acute Myeloid Leukemia	Male: D=1 N=4 S=8 F=0 T=13 Female: D=0 N=0	Male: D=2.18 N=2.33 S=3.86 F=0.8	Male: D SIR=0.5 N SIR=1.7 S SIR=2.1 F SIR= - T SIR= 1.4 (0.8-2.4) Female: D SIR= - N SIR= -	

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					S=0 F=0 T=0	T=9.14 Female: D=0.57 N=0.26 S=0.33 F=0.1 T=1.23	S SIR= - F SIR= - T SIR= - (-)
				Chronic Lymphatic Leukemia	Male: D=2 N=2 S=4 F=0 T=8 Female: D=2 N=0 S=0 F=0 T=2	Male: D=2.63 N=1.83 S=5.06 F=0.6 T=10.16 Female: D=0.34 N=0.14 S=0.24 F=0.0 T=0.75	Male: D SIR=0.8 N SIR=1.1 S SIR=5.06 F SIR= - T SIR=0.8 (0.3-1.6) Female: D SIR=5.9 N SIR= - S SIR= - F SIR= - T SIR=2.7 (0.3-9.6)
				All Other Leukemia	Male: D=2 N=3 S=0 F=0 T=5 Female: D=0 N=0 S=0 F=0 T=0	Male: D=1.93 N=2.42 S=4.77 F=0.8 T=9.87 Female:	Male: D SIR=1.0 N SIR=1.2 S SIR= - F SIR= - T SIR=0.5 (0.2-1.2) Female: D SIR= - N SIR= - S SIR= - F SIR= - T SIR= - (-)

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							D=0.41 N=0.23 S=0.33 F=0.1 T=1.04	
Printing								
(Zoloth, Michaels et al. 1986) Printing	Retrospective Cohort, Mortality, 01/01/58-12/31/81	US Population	1,401 white male deceased commercial pressmen	All Lymphatic and Hematopoietic	27	22.2	SMR=122 (83-178)	
				Other Lymphatic Cancer	11	5.2	SMR=209 (117-375)	
				Leukemia and Aleukemia	9	10.0	SMR=89 (47-173)	
Chemical Workers								
(Decoufle, Blattner et al. 1983) Chemical Plant	Retrospective Cohort, Mortality, 01/01/47-12/31/77	US Population	259 male employees who worked between 01/01/47-12/31/60	Lymphatic and Hematopoietic Tissue	4	1.06	(1.09-10.24)	No SMR was given.
(Arnetz, Raymond et al. 1991) Petrochemical Commercial Research and Development Personnel	Dynamic Cohort, Mortality Surveillance Study, 01/01/64-12/31/86	New Jersey Population	13,250 present and former New Jersey based employees in the Exxon Research and Engineering Company and the Chemical Technology Dept. of Exxon Chemical Co.	Leukemia and Lymphatic Cancer	26	29.7	SMR=87 (57-128)	
				Lymphosarcoma and Reticulosarcoma	2	5.3	SMR=37 (4-135)	
				Hodgkin's Disease	2	3.6	SMR=55 (6-201)	
				Leukemia	8	12.1	SMR=66	

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				and Aleukemia			(28-130)	
				Cancer of all other Lymph. Tissue	14	8.7	SMR=161 (87-270)	
Sweden and Finland								
(Gustavsson, Hogstedt et al. 1986) Rubber Industry	Retrospective Cohort, Mortality and Incidence, Morality: 1952-1981 Cancer Incidence: 1959-1980	National Population	12,212 workers from 2 Swedish rubber manufacturing companies.	Cause of death: Lymphoma and Myeloma	8	8.92	SMR=90 (38-176)	
				Cause of Death: Leukemia	6	6.58	SMR=91 (33-198)	
				Incidence of Cancer: Multiple Myeloma	5	3.90	SMR=128 (41-299)	
				Incidence of Cancer: Leukemia	7	7.46	SMR=94 (37-193)	
(Jarvholm, Mellblom et al. 1997) Transport and Refinery Industry	Retrospective Cohort, Morbidity, 1958-1987	General population	4,128 Men and 191 women who had worked at least one year in the petroleum industry	Lymphoma	≥1 y; ≥1 y=9 ≥1 y; ≥20 y=3 ≥10 y; ≥20 y=2		≥1 y; ≥1 y SIR=0.93 (0.48-1.6) ≥1 y; ≥20 y SIR=0.65 (0.18-1.7) ≥10 y; ≥20 y SIR=0.48 (0.08-1.5)	Explanation of categories: Duration of exposure; time since onset of exposure ≥1 y; ≥1 y ≥1 y; ≥20 y ≥10 y; ≥20 y
				Leukemia	≥1 y; ≥1 y=6 ≥1 y; ≥20 y=3 ≥10 y; ≥20 y=3		≥1 y; ≥1 y SIR=1.4 (0.59-2.7) ≥1 y; ≥20 y SIR=1.4 (0.39-3.7) ≥10 y; ≥20 y SIR=1.5	Data presented is on males only. No data was available for females.

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							(0.41-3.9)	
(Pukkala 1998) Oil refinery	Retrospective Cohort, Morbidity, 01/01/71-12/31/94	Finish population.	7,512 men and 1,942 women	Hodgkin's Disease	7	5	SMR=1.35 (0.54-2.79)	
				Non-Hodgkin's Lymphoma	12	10	SMR=1.24 (0.64-2.17)	
				Leukemia	9	9	SMR=1.02 (0.47-1.93)	
Italian								
(Dario Consonni 1999)Petroleum Refinery Industry	Retrospective Follow-up Cohort, Mortality, 01/01/49-12/31/82	Lombardy Region Population	1,583 male workers	Lymphatic and Hematopoietic	15	8.4	SMR=179 (100-295)	
				Lymphoma	7	3.7	SMR=190 (76-391)	
				Hodgkin's Disease	2	1.3	SMR=151 (17-544)	
				Non-Hodgkin's Lymphoma	5	2.4	SMR=212 (68-495)	
				Leukemia	8	3.6	SMR=225 (97-443)	
UK								
(Sorahan, Kinlen et al. 2005) Plant workers	Retrospective Historical Cohort, Mortality, 01/01/68-12/31/02	Serial mortality rates for England and Wales	5,514 (5,130 men and 384 women) individuals who had been exposed at work to benzene	Hodgkin's Disease	3	2.8	SMR=108 (22-317)	Workers came from factories in Wales and in England.
				Non-Hodgkin's Lymphoma	15	15.9	SMR=94 (53-156)	
				Multiple Myeloma	6	9.5	SMR=63 (23-137)	
				Leukaemia	22	16.1	SMR=137 (86-207)	
				Lymphoid	5	5.05	SMR=99	

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				Leukaemia			(32-231)
				Acute Lymphoid Leukaemia	0	0.83	SMR=0 (0-444))
				Chronic Lymphoid Leukaemia	5	4.04	SMR=124 (40-289)
				Other/Unspecified Lymphoid Leukaemia	0	0.18	SMR=0 (-)
				Myeloid Leukaemia	14	9.41	SMR=149 (81-250)
				Acute Myeloid Leukaemia	12	6.60	SMR=182 (94-318)
				Chronic Myeloid Leukaemia	2	2.57	SMR=78 (9-281)
				Other/Unspecified Myeloid Leukaemia	0	0.24	SMR=0 (-)
				Monocytic Leukaemia	0	0.34	SMR=0 (-)
				Acute Monocytic Leukaemia	0	0.25	SMR=0 (-)
				Chronic Monocytic Leukaemia	0	0.05	SMR=0 (-)
				Other/Unspecified Monocytic Leukaemia	0	0.04	SMR=0 (-)
				Other and Unspecified Cell Types	3	1.28	SMR=234 (48-685)

				Acute Other and Unspecified Cell Types	2	0.80	SMR=250 (30-904)	
				Chronic Other and Unspecified Cell Types	1	0.05	SMR=1843 (47-10271)	
				Other and Unspecified Cell Types	0	0.43	SMR=0 (-)	
				Acute Non-Lymphocytic Leukaemia (ANLL)	14	7.65	SMR=183 (100-307)	
				All Leukaemias excluding ANLL	8	8.43	SMR=95 (41-187)	
Oil, Chemical and Atomic Workers International Union (OCAW Union)								
(Thomas, Decoufle et al. 1980) Petroleum Refining and Petrochemical Plants	Cause-Specific Mortality, 1947-1977	US General Population and Texas Male Population	3,105 active deceased members of the OCAW Union	Lymphatic and Hematopoietic Tissue	White Males=63 Non-White Males=7	White Males=54.4 Non-White Males=6.3	White Males PMR=1.16 Non-White Males PMR=1.11	
(Thomas, Waxweiler et al. 1984) Oil Refineries	Proportionate Mortality Study,	Active and Retired union members who worked at the same refinery, were of the same race and sex and died of other causes.	2,132 deceased members of the OCAW Union employed in three Texas Oil Refineries.	Leukemia	34 (employed at least 1 day, with a median duration employed 28.2 years)	96 (employed at least 1 day, with a median duration employed 31.8 years)		

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				DOW Chemical				
(Bond, McLaren et al. 1987) Chemical Company	Cause-Specific Mortality, 01/01/40-12/31/82	US, Michigan or Seven Local Counties	37,682 male employees with 3 or more days of service at Midland or Bay City, Michigan locations of Dow Chemical. (Majority were hourly workers)	Lymphatic and Hematopoietic Cancer	114	US= 100.7 MI= 107.6 7C= 111.1	US SMR=113 MI SMR=106 7C SMR=103	US=United States MI=Michigan 7C=7 Counties
				Lymphosarcoma and Reticulosarcoma	21	US= 18.4 MI= 18.8 7C= 20.4	US SMR=114 MI SMR=112 7C SMR=103	
				Hodgkin' Disease	5	US= 8.7 MI= 9.3 7C= 10.8	US SMR=57 MI SMR=54 7C SMR=46	
				Leukemia and Aleukemia	49	US= 37.6 MI= 42.2 7C= 42.1	US SMR=130 MI SMR=116 7C SMR=116	
				Cancer of Other Lymphatic Tissue	37	US= 32.5 MI= 35.7 7C= 37.1	US SMR=114 MI SMR=104 7C SMR=100	
				Rubber Industry				
(Monson and Nakano 1976) Rubber Industry	Mortality Experience, 01/01/40-06/30/74	US White Males	13571 white male rubber workers in an Akron, OH rubber plant.	Lymphatic and Hematopoietic	4	3.8		
(Monson and Nakano 1976) Rubber Industry	Mortality Experience, 01/01/40-06/30/74	US Population	5816 Females, 986 black males and 3727 white salaried males in an Akron, OH rubber Plant.	Lymphatic and Hematopoietic	14	11.8		

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(Delzell and Monson 1981) Rubber plant	Cause-Specific Mortality, 01/01/40-07/01/78	US Population	29,087 men and women who worked at least 2 years at a large rubber manufacturing facility.	Lymphatic and Multiple Myeloma	WM=76 NW=6 F=11 SM=15 SF=10		WM SMR=109 (86-137) NW SMR=171 (62-372) F SMR=74 (37-133) SM SMR=101 (57-167) SF SMR=88 (42-162)	WM=White Male F=All Females NW=Non-White Male SM=Salaried Males SF=Salaried Females
				Leukemia	WM=68 NW=no data provided F=8 SM=7 SF=1		WM SMR=121 (94-153) NW SMR=no data provided F SMR=79 (34-156) SM SMR= 139 (56-287) SF SMR=29 (1-162)	

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Table 60 - Meta Analysis								
Author/Year Industry & Workers	Study Type Endpoint & Years	Comp pop	Total Pop (#)	Disorder	Cases (#)	Cont rol (#)	Statistical Measure CI or p-value	Comments
(Wong and Raabe 1989) Petroleum Industry	Over 100 studies were examined	Different for each study	Different for each study					Multiple studies compared, with a quantitative meta-analysis by cancer site.
				Lymphop oietic	460	448. 71	SMR=1.03 (0.94-1.13)	p-value=0.85 MIN SMR=1.12
				Lymphos arcoma	97	111. 75	SMR=0.87 (0.71-1.06)	p-value=0.16 MIN SMR=1.25
				Leukemia	279	253. 54	SMR=1.10 (0.97-1.23)	p-value=0.10 MIN SMR=1.16
				Other Lymphati c Tissue	122	106. 39	SMR=1.15 (1.15-0.95)	p-value=0.13 MIN SMR=1.25

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C. Evaluation of Animal Studies with Quantitative Exposure

1. Sub-chronic Toxicity in Animals

Animal studies have revealed that mice are more sensitive to hematopoietic insult by benzene than rats. (Zhu, Li et al. 1995; Henderson 1996)   While all species appear to have similar mechanisms of detoxification, mice have greater capacity, relative to their size, for metabolism versus either monkeys or rats. Mice preferentially metabolize more benzene to hydroquinone metabolites, particularly at low doses. However, in all non-human species a greater portion of benzene is converted to hydroquinone and other ring-breaking metabolites at lower doses. This potentially presents problems when attempting to extrapolate studies utilizing a "high" dose of benzene to the predicted toxicity at a "low" dose. In addition, it has been noted that mice bone marrow stromal cells are more susceptible to cytotoxicity induced by hydroquinone and benzoquinone. This may be the result of decreased (50%) glutathione levels and quinine reductase (28 times less) activity in mice stromal cells versus rat stromal cells. (Zhu, Li et al. 1995) There are significant intra-species and strain differences in rodents, which makes comparison of results challenging, and in many cases, impossible.

The simplest parameters to evaluate in human and animal studies of hematopoiesis are measures in peripheral blood, including erythroctytes and lymphocytes. A number of studies have measured these values in benzene exposed animals. Baarson and colleagues exposed C57Bi mice to 10 ppm for 6 hours a day, 5 days a week (Baarson, Snyder et al. 1984). They saw a gradual decrease in a erythroid progenitor cell, the colony-forming unit-erythroid (CFU-E) after 178 days of exposure. Prior to that point, they saw a 45% depression of burst forming cell growth at 66 days that returned to control level at 178 days. In addition, the animals had a depression of splenic nucleated red cells, circulating red blood cells, as well as circulating lymphocytes.

In 1978, researchers at New York University began reporting on various hematological abnormalities following benzene exposure. In the first study, Sprague-Dawley rats and AKR/J mice were exposed to 300ppm benzene for 6 hours a day, 5 days a week for life (Snyder, Goldstein et al. 1978b). The rats developed lymphocytopenia, mild anemia, and moderately decreased survival. The mice also had severe lymphocytopenia, as well as anemia accompanied by granulocytosis and reticulocytosis. There was no indication of leukemia or preleukemia in any animals. In a follow-up study reported in 1980, AKR/J and C57BL/6J mice were given duplicate lifetime exposures for 100ppm and 300ppm, respectively (Snyder, Goldstein et al. 1980). All of the AKR mice had anemia and lymphocytopenia, and 20% developed bone marrow hypoplasia (2% in controls). However, these abnormalities were not as severe as those seen at 300ppm. The C57BL/6J mice had anemia, lymphocytopenia and neutrophilia with a left shift. Thirty-three percent of animals   developed bone marrow hypoplasia. Snyder *et al*. also reported significant hematological abnormalities in a study of Sprague-Dawley rats and three species of mice (CD-1, AKR, C57BL) exposed to either 100ppm or 300 ppm for 6 hours a day, 5 days a week for life (Snyder, Erlichman et al. 1981). All of the mice exposed at 300ppm had decreased survival, blood lymphocytopenia and neutrophilia with intermittent immature granulocytes. At 100ppm, the AKR mice had blood

lymphocytopenia and anemia. The rats exposed to 300ppm had slightly decreased survival and peripheral lymphocytopenia. This same group of researchers reported myeloblast and promyelocyte proliferation in the bone marrow of male CD-1 mice exposed to 300ppm benzene for 6 hours a day, 5 days a week for 26 weeks (Snyder, Green et al. 1981). Utilizing this same exposure protocol (300 ppm), they also found significantly (± 2 S.E.) depressed levels of peripheral red blood cells and lymphocytes (Snyder, Goldstein et al. 1982).   This was in addition to Howell-Jolly bodies at 7 days, anisocytosis after 22 days, poikilocytosis at 92 days and a shift to immature myeloid cells at 217 days. (Howell-Jolly bodies are basophilic DNA remnants found in circulating red blood cells. Typically, they are removed by the spleen. Anisocytosis is different size red blood cells, typically found in anemia. Poikilocytosis is evidence of abnormally shaped red blood cells.) Neoplasia free animals also had a higher incidence of bone marrow hypoplasia and bone marrow hyperplasia compared to control animals.

Another research group, Cronkite and colleagues, exposed C57B1/6 mice to 10, 25 and 100 ppm for 6 hours a day, five days per week for 2 weeks (Cronkite, Drew et al. 1985). The animals in the 10 and 25 ppm groups did not have any decrease of nucleated cells in bone marrow, decrease in stem cells (CFU) or decrease in stem cells synthesizing DNA. At 100ppm there was significant ($p<0.001$) depression of bone marrow cellularity and number of stem cells. However, there was a slight (non-significant) increase in the fraction of stem cells in DNA synthesis. At 400ppm there was also a significant ($p<0.0004$) decrease in stem cells and a non-significant increase in stem cells in DNA synthesis. In a previous study of 400ppm for up to 9.5 weeks, bone marrow cellularity and stem cell count were also depressed (Cronkite, Inoue et al. 1982).   However, stem cells in DNA synthesis were significantly increased. There was also significant depression of red and white blood cells throughout the exposure, which persisted for at least 14 days after the cessation of exposure. In the 1984 study, following inhalation of 10, 25, 100 or 400ppm for 6 hours a day, 5 days a week for 2 weeks, there was no significant effect on hematocrit at 10 or 25ppm. At 100 and 400ppm, there was a significant effect with a dose-effect relationship. There was no effect on lymphocytes at 10ppm; however, there was a dose-effect relationship with higher doses. No effect on granulocytes was noted at any dose. In another arm of the same study, stem cell numbers were evaluated after exposure to 300ppm benzene for 2, 4, 8 or 16 weeks. There was no effect after 2 or 4 weeks. At 8 weeks of exposure, the stem cell numbers were ~50% of age matched controls. Three days after 16 weeks of exposure the stem cell numbers were 27% of controls, but this increased to 60% at 16 weeks post exposure and 92% at 25 weeks post exposure. Blood lymphocytes did not show any effects after 2 weeks of exposure to 300ppm benzene. Following 4 weeks of exposure, there was a significant deficit of blood lymphocytes at 2 and 4 weeks post exposure which resolved by 8 and 16 weeks post exposure. The same was true after 8 weeks of exposure ($p<0.0002$). After 16 weeks of exposure, this was also the case ($p<0.008$). In a 1989 study, Cronkite *et al.* exposed CBA/Ca mice to 10, 25, 100, 300, 400, and 3000 ppm for 6 hours a day, 5 days a week for 2-16 weeks (Cronkite, Drew et al. 1989). Two weeks of inhaling 10 ppm produced no hematologic effects, while 25 ppm induced a significant lymphopenia. Inhalation of 100, 300, and 400 ppm produced dose-dependent decreases in blood lymphocytes, bone marrow cellularity, marrow content of spleen colony-forming units (CFU-S) and an increased fraction of CFU-S

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in DNA synthesis. Exposure to 300 ppm for 2, 4, 8, and 16 weeks produced severe lymphopenia and decrease in bone marrow CFU-S. Recovery was rapid and complete after 2 and 4 weeks of exposure. However, after 8 and 16 weeks of exposure, recovery of lymphocytes took 8 weeks. It took 16 weeks for the CFU-S to recover to that of the age-matched controls after 8 weeks of exposure and 25 weeks to recover to age-matched after 16 weeks of exposure. Interestingly, the authors also examined damage Inhalation of 3000 ppm for 8 days created less hematological damage than inhalation of 300 ppm for 80 days. It was suggested that saturation of metabolizing enzymes with 3000 ppm resulted in reduced metabolites and resultant hematotoxicity.

In a study involving CD-1 mice and Sprague Dawley rats, inhalation exposure to 1, 10, 30 and 300 ppm benzene for 6 hours a day, five days per week for 13 weeks produced significant hematological changes at 300 ppm (Ward, Kuna et al. 1985). The findings in mice included decreased hematocrit, total hemoglobin, erythrocyte count, leukocyte count, platelet count and myeloid/erythrocyte ratio, while the rats only showed a decrease in lymphocyte count and a slight increase in neutrophil count. Histopathological changes noted in the mice included myeloid hypoplasia of the femoral bone marrow and slightly decreased marrow cellularity in rats. It was noted that in male mice the incidence, severity and timing (earlier) was greater. This is in direct contrast to earlier research which indicated a greater susceptibility to hematological abnormalities in female rats and mice, following benzene exposure (Leong 1977).

In 1996, Farris and colleagues evaluated benzene-induced hematotoxicity following exposure to a low concentration of benzene (Farris, Robinson et al. 1996). Male B6C3F1 mice were exposed to 0, 1, 10, 100, or 200 ppm benzene by inhalation for 6 hours a day, five days per week for 1, 2, 4, or 8 weeks. At each milestone, they evaluated primitive and committed progenitor cells, differentiating and maturing lineage-specific cells, and stromal cells in the bone marrow; T and B lymphocytes of the spleen and thymus; micronucleated reticulocytes and erythrocytes; and standard blood parameters. At the regulatory limit of 1ppm, there was no significant effect on any parameter. At 10 ppm, the only parameter affected was a transient reduction in the number of splenic B lymphocytes. This value reverted to the control value by 4 weeks. At 100 and 200 ppm benzene, there were rapid (5 day) and significant reductions in number of reticulocytes in the blood, B lymphocytes in the bone marrow and spleen, and an increased frequency of micronucleated reticulocytes in the bone marrow. At 100 ppm, there was a return towards control values at week 8 versus those values noted at 2 and 4 weeks. This indicated compensation of the bone marrow to continued exposure. At two weeks of exposure to 100 ppm benzene, the B lymphocytes were 26% of control and at 8 weeks 38%. Once again, this was viewed as evidence of compensation by increased progenitor cell replication and replenishment. This same research group re-examined a similar question in a paper the following year. Once again B6C3F1 mice were exposed to benzene; however, a 5ppm dose was added. There were no significant effects on hematopoietic measures at ≤ 10 ppm. At 100 and 200 ppm, benzene reduced the total number of bone marrow cells, progenitor cells, differentiating hematopoietic cells, and most blood parameters. Replication of primitive progenitor cells in the bone marrow was increased during the exposure period as a compensation for the cytotoxicity induced by 100 and 200 ppm benzene. In mice exposed to 200 ppm benzene, the primitive progenitor cells

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maintained an increased percentage of cells in S-phase through 25 days of recovery compared with controls. The authors suggested that these processes were a plausible mode of action for benzene-induced leukemia in humans exposed to high concentrations.   In a related study, they found that B6C3F1 mice exposed to 100–200 ppm benzene for eight weeks showed persistent reductions in femoral bone marrow B-lymphocytes, splenic T- and B-lymphocytes, as well as, Thymic T-lymphocytes (Farris, Robinson et al. 1997).   The percentage of apoptotic femoral B-lymphocytes and thymic T-lymphocytes was increased 6 and15-fold by 200 ppm benzene.   At both 100 and 200 ppm exposure femoral B-lymphocytes were increased in a compensatory fashion.   At ≤10 ppm benzene there was no significant effect on the numbers or replication of the lymphocyte populations.   The authors concluded that a reduced number of splenic B-lymphocytes after 2 weeks of exposure to benzene appeared to be the most sensitive end point and time point for evaluating benzene cytotoxicity in this study.

A number of additional research groups have examined the effects of benzene exposure on the immune system.   At 50 ppm of inhaled benzene for 6 hours a day and 7 consecutive days, Aoyama found that BALB/c mice T and B lymphocyte levels in both the blood and spleen were depressed.   The level of B lymphocytes was dose dependent and more intense than that of T lymphocytes. The ability to form antibodies was suppressed by benzene at all exposure levels, but the cell mediated immune response was resistant to benzene inhalation and actually enhanced at 200 ppm exposure for 14 days.   Rozen *et al.* reported a significant decrease in bone marrow B-lymphocytes, splenic B-lymphocytes, as well as thymic and splenic T-lymphocytes in male C57BL/6J mice exposed to 300 ppm for 6 hours a day, five days a week after 6, 30, and 115 days of exposure (Rozen and Snyder 1985).   In addition, mitogen-induced proliferation of B-lymphocytes in the thymus and spleen were progressively depression to zero at the 115th exposure.   Bone marrow cellularity increased 3-fold and the numbers of thymic T-cells increased 15-fold in benzene-exposed mice between the 6th and 30th exposure.   Prior to that study, they had found depressed mitogen-induced blastogenesis of B-lymphocytes in male B57BL mice exposed to 6 days for 6 hours a day of 10ppm benzene, although the overall number of B-lymphocytes was not decreased (Rozen, Snyder et al. 1984).   At 31ppm for the same time period, splenic T-lymphocyte mitogen-induced blastogenesis was significantly reduced.

2. Carcinogenicity in Animals

Although data from animal models are frequently used in risk assessments, including benzene, it must be understood that extrapolation from animal studies to humans is fraught with potential error and misunderstandings. For instance, some of the earliest animal studies by Maltoni and colleagues indicated significant elevation of Zymbal gland carcinomas in Sprague-Dawley rats (Maltoni, Cotti et al. 1982).   With that said, humans do not have a Zymbal gland and therefore this finding is of questionable relevance to human carcinogenesis.   In further work, Maltoni and colleagues reported additional cancers in Sprague Dawley rats, (carcinomas of the oral cavity, carcinomas of the nasal cavities, carcinomas of the skin, hepatocarcinomas and increased incidence of total malignant tumors)

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as well as, cancers in Swiss mice (Zymbal gland carcinoma, mammary carcinomas in females, lung tumors and increased total malignant tumors (Maltoni and Scarnato 1979; Maltoni, Conti et al. 1982; Maltoni, Cotti et al. 1982; Maltoni, Conti et al. 1983; Maltoni, Conti et al. 1985; Maltoni, Conti et al. 1988; Maltoni, Ciliberti et al. 1989). Through this data, and that of additional research groups in the United States (Huff, Haseman et al. 1989), it was concluded that benzene is a multipotential rodent carcinogen that can produce cancerous lesions in multiple species and organs by different routes, including ingestion, injection and inhalation. Early studies looking for evidence of benzene-induced myelogenous leukemia in laboratory animals, did not find any evidence of leukemogenesis at a variety of doses and routes in mice, guinea pigs, rats and rabbits (Ward, Weisburger et al. 1975; Leong 1977)

In 1982, Goldstein and Snyder reported four cases of myelogenous leukemia in rats and mice (Goldstein, Snyder et al. 1982). Sprague-Dawley rats, AKR mice, C57B1 mice and CD-1 mice were exposed to either 100ppm or 300ppm of inhaled benzene for 6 hours a day, five days a week for life. Semimonthly hematological surveys were drawn in 10 animals in each group, including the control group. As noted in previous studies, mice were more susceptible to the aplastic effects of exposure, particularly the AKR strain (Snyder, Goldstein et al. 1980). Although not statistically significant, one Sprague-Dawley rat developed chronic myelogenous leukemia at 100 ppm during the 35th week of exposure. In addition, three CD-1 mice developed myeloproliferative disorders, including 1 case of acute (exposure week 29) and 1 case of chronic myelogenous (exposure week 26) leukemia, as well as, 1 case of granulocytic hyperplasia (exposure week 38). All cases occurred in the 300ppm group. Sprague-Dawley rats and CD-1 mice are not known to have a background rate of myelogenous leukemia, and it was assumed by the authors that their findings were related to benzene exposure.

Further research by another group, Cronkite *et al*. reported an increase of leukemia in female C57B1/6 mice following a 16 week exposure to 300ppm for 6 hours a day and 5 days per week (Cronkite, Bullis et al. 1984). Unlike earlier studies which utilized lifetime exposures, this study allowed for hematopoietic recovery. At 64 weeks, 8% of exposed animals had thymic lymphoma. Although the authors described lymphoma-leukemia, both entities were collated in one group "leukemia". There was no evidence that animals had myelogenous "leukemia" in the exposed groups; however, the sham exposure groups had three cases. C57B1/6 mice carry a radiation leukemia virus which makes them susceptible to thymic lymphomas. Cronkite and colleagues also found an increase in myelogenous (resembles acute myeloblastic and chronic granulocytic) leukemia following the inhalation of 300ppm benzene 6 hours a day for 16 weeks in male CBA/Ca mice (Cronkite, Drew et al. 1989). This increased incidence appeared shortly after exposures started. Eventually, 19.3% of animals developed a myelogenous neoplasm. Inhalation of 100 ppm benzene for the same exposure period did not significantly increase (2.4 exposed, 0.0 control, p=0.19) the incidence of myelogenous leukemia. The authors concluded,

> Our data suggest that there may be an effective time-dose relation (or concentration) of benzene that may not increase the incidence of myelogenous neoplasms, but will induce other neoplasms. Our data suggest that exposure

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to 100ppm benzene 6hr/day, 5 days/week for 16 weeks may be close to such a time-dose threshold for myelogenous leukemias.

Farris *et al.* exposed CBA/Ca mice to 300 ppm benzene via inhalation for 6 hours a day, 5 days per week for 16 weeks and then maintained the exposed and control groups for 18 months (Farris, Everitt et al. 1993). Fourteen exposed animals developed lymphoma (lymphoblastic, lymphocytic, or mixed) as compared to only 2 sham-exposed mice. Moderate to marked granulocytic hyperplasia was present in exposed animals (36% in bone marrow/6% in spleen), compared to control levels of 8% and 0% respectively. There were no cases of granulocytic leukemia sham-exposed with 8 and 0%, respectively. Interpretation of the granulocytic response as a direct effect of benzene was complicated by the presence of inflammation in the mice. Although inhaled benzene was clearly carcinogenic in CBA mice, it did not induce granulocytic leukemia.

Chapter Four: Discussion

1. General Comments from this Investigation

In the course of conducting this research, over 450 scientific articles and studies on benzene exposure, health effects, biomarkers and physiology were critically evaluated. Of these 450, approximately 50 articles were critical to understanding the issue of a possible threshold dose associated with benzene exposure. Most important are the seven groups of human studies that have compared the measured or estimated dose of average and cumulative benzene dose to the risk of hematologic neoplasm formation. These seven groups included: 1) The Pliofilm Cohort, 2) The Chinese (NCI-CAPM) Study Series, 3) The Chemical Industry Studies, 4) The Australian Petroleum Industry Studies, 5) The United Kingdom Petroleum Industry Studies, 6) The Canadian Petroleum Industry Studies and 7) Various Small Studies (The Caprolactam, Shoe Workers and Gas/Electric Utility Studies). In addition, a large number of qualitative studies that did not measure or estimate exposure were analyzed to understand the prevailing evidence which suggests that only acute myelogenous leukemia (and closely related acute non-lymphocytic leukemia) is associated with benzene exposure. This close association with only myelogenous leukemia is further substantiated by the fact that myelogenous leukemia has been found to "drive" the risk of leukemia. From a mechanistic standpoint this also makes sense, as hydroquinone, a benzene metabolite increases the recruitment and propagation of myeloid progenitor cells (Irons, Stillman et al. 1992). Following evaluation of the human studies, relevant animal research was examined. It was clear from this extensive analysis that not all studies are created equally, and close scrutiny is required to elucidate proven facts from suggestive anomalies or artifacts of statistical evaluation, i.e. – significance is the guidepost to eliminating chance as long as study power is adequate to support the conclusions.

Prior to any discussion regarding a possible threshold dose of benzene, I believe it is in imperative to restate some of the obvious limitations in the data set. The most glaring item that is present in every single human study is the difficulty in retrospectively assigning exposure assessments. This is particularly true for the Pliofilm cohort. At this point, there are several "interested" parties that trade upon the continuing refinement of the exposure assessment process. There does not appear to be any more information that will be discovered, so continuing efforts will focus on the interpretation of what is known and unknown.

2. Results from the Seven Quantitative Groups and the Animal Studies

In summary, the authors of the human studies with a quantitative exposure assessment came to the following conclusions:

1. ***The Pliofilm Cohort*** – There are three generally accepted exposure matrices that each generate different levels of risk; however, all consistently reveal a statistically significant relationship with leukemia mortality. Up through 1996, there were 22 (10 acute myeloid line, 1 myeloid–unspecified, 3 chronic myeloid line, 1 acute lymphoid and 2 unspecified) leukemia cases and 8 multiple myeloma cases. Regardless of the exposure matrix utilized, none of the three exposure matrices (Rinsky, Crump & Allen and Paustenbach) shows a significant elevation of leukemia risk at <50 ppm year (Paxton, Chinchilli et al. 1994). When further refined to only acute myelogenous leukemia, significance is only achieved at >200 ppm-years (Wong 1995).

2. ***The Chinese (NCI-CAPM) Study Series*** – The authors of the 1997 case-control study found a non-significant elevation of acute non-lymphocytic leukemia (2.0 95% CI: 0.6 – 7.0) in (7) cases with <10 ppm average exposure and a non significant elevation of risk in cases (5) exposed for <40 ppm-years (1.9 95% CI: 0.5 – 7.0). Significance was only achieved with cumulative exposure to 40-99 ppm-years (4.2 95% CI: 1.1-11.6) (Hayes, Yin et al. 1997).

3. ***The Chemical Industry Studies*** - ***(Dow Chemical)*** In the initial study published in 1978, there was a non-significant rise in leukemia (3 cases of myelocytic) at estimated cumulative doses of 45.4, 1.5 (The individual only worked for 18 months at <2 ppm TWA.) and 25.4 ppm-years (Ott, Townsend et al. 1978). A follow-up study found a non-significant rise in all leukemia; however, four of the cases were myelogenous and this was a significant finding (p=0.011) (Bond, McLaren et al. 1987). The forth case was in addition to the three previously found in the first study and the individual had an estimated cumulative exposure of 351 ppm-years. A final follow-up in 2004 found no new cases of ANLL and the SMR was non-significant (1.11 95% CI: 0.30 – 2.83) (Bloemen, Youk et al. 2004). At all levels of cumulative exposure (<28.3, 28.3-79.1 and >79.1 ppm-years) there was a non-significant elevation of risk. ***(Monsanto/Salutia)*** The initial study in 1997 reported a non-significant elevation in leukemia (SMR=2.3 95% CI: 0.7 – 5.3) and multiple myeloma (SMR=2.3 95% CI: 0.7-9.4). Three workers with leukemia were exposed to benzene at ≥6 ppm-years (SMR=4.6 95% CI:0.9 – 13.4), as was one worker ANLL (SMR=4.5, 95% CI: 0.1 – 25.3) (Ireland, Collins et al. 1997). In a 2003 follow-up study, the authors suggested that peak exposure frequency was a better predictor of risk than cumulative exposure (Collins, Ireland et al. 2003). At >40 days of >100 ppm peak exposure there was a non-significant elevation of ANLL (SMR=4.1 95% CI: 0.5 – 14.9) with two workers vs. 0.5 expected, and leukemia (SMR=2.7, 95% CI:0.8 – 6.4) with five workers vs. 1.8 expected. ***(Chemical Manufacturers Association)*** In 1987, Wong found that SMRs were non-significant for all leukemia; however, with internal analysis the association between continuous exposure to benzene and leukemia was significant. In addition, the trend for increasing exposure

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was significant (Wong 1987). There were 3 cases of myeloid leukemia out of 22 total lymphohematopoietic cancer cases and this subtype was not analyzed specifically.

4. ***The Australian Petroleum Industry Studies*** – A case-control study with age matched controls found that risk of leukemia was increased at >2 ppm-years. For the 13 cases with >8 ppm-years the odds ratio=11.3 (95% CI: 2.85 – 45.1) (Glass, Gray et al. 2003). There were 11 cases of ANLL (9 AML and 2 acute undifferentiated leukemia) and when ≤4 ppm-years was the reference category, >4-8 ppm-years (OR=0.52, 95% CI: 0.05-5.0) and >8 ppm-years (OR=7.17, 95% CI: 1.27-40.4). They did not find an association with multiple myeloma or non-Hodgkin's lymphoma. There was also a strong association between leukemia risk and benzene concentrate. In 2006, the authors re-analyzed the data in a 2006 update (Glass, Gray et al. 2006) and attempted to take into account high exposure events (HEEs) that resulted from spillage and poor work practices. These estimates were added to the previously calculated cumulative exposures for cases and controls. The odds ratios were recalculated and this increased the exposure for 25% of subjects. For most individuals the increase was <5%. With the added HEEs the odds ratio for leukemia with matched analyses went from 1.10 (95% CI: 1.04-1.16) to 1.03 (95% CI: 1.01 – 1.05). When treated as a categorical variable the odds ratio in the 7 cases of leukemia with >16 ppm-years was 98 (8.8 -1090), when compared to individuals with <0.5 ppm-years cumulative exposure. When the two lowest groups of exposure <1 ppm-years were compared with the highest exposure group the odds ratio was 51.9 (5.6 – 477) without HEEs and 7.79 (2.34 – 25.89) with HEEs. It was thought that the odds ratio fell because leukemia is associated with higher exposures and thus the risk per ppm year is reduced. They did not report recalculated results for ANLL with HEEs.

5. ***The United Kingdom Petroleum Industry Studies*** – There was no significant increase in leukemia risk with cumulative exposure or intensity of exposure; however, risk doubled with employment >10 years (Rushton and Romaniuk 1997). There was a non-significant increase (OR=2.82 95% CI: 0.8-9.4) for acute myeloid/monocytic leukemia (31 total cases) with a cumulative exposure 4.5 – 45 ppm-years (9 cases) when compared to the <.0.45 group (7). For the exposure category 0.45 – 4.5 ppm-years (15 cases) the OR=2.17 (95% CI: 0.77-6.09). The average exposure for all 31 cases was 3.7 ppm-years, while the controls had 3.8 ppm-years. There were no cases with a cumulative exposure >45 ppm-years. They found weak evidence of an association between acute myeloid/monocytic leukemia and peaked exposure.

6. ***The Canadian Petroleum Industry Studies*** – Leukemia risk was not increased in this case-control study for increasing cumulative exposure (Schnatter, Armstrong et al. 1996). Average benzene concentrations ranged from 0.01 to 6.2 ppm. There were a total of 14 leukemia cases, after excluding 2 because of inadequate work histories.

7. ***Various Small Studies - (The Caprolactam Workers Study)*** – There was one death due to leukemia in this retrospective cohort mortality study of 311 men, versus the expected rate of 1.17 (Swaen, Scheffers et al. 2005). The estimated exposure for the group was 159 ppm-years. The daily mean exposure was 20.9 ppm. ***(Italian Shoe Workers Study)*** - This was a study of 1687 shoe workers with cumulative benzene exposure ranging from 0 - >500 ppm-years (Seniori Costantini, Quinn et al. 2003).

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The SMR for leukemia in men was significantly elevated for with >200 ppm-years cumulative exposure to benzene (7.0, 95% CI: 1.9 – 18.0). There were non-significant elevations at <40 (1.4, 95% CI: 0.2-5.0), 40-99 (3.7, 0.1 – 20.6) and 100-199 (3.0, 95% CI: 0.4-10.9). The mean cumulative exposure for men and women was 71.8 ppm-years and 43.4 ppm-years, respectively. The following cases were detailed: 1 reticulum cell sarcoma, 1 other primary malignant neoplasm of lymphoid tissue, 3 multiple myeloma, 3 chronic lymphatic leukemia, 1 acute myeloid leukemia (22.8 ppm-years), 1 chronic myeloid leukemia, 4 unspecified acute leukemia (41.2, 251.9, 285.4 and 98.8 ppm-years), 1 acute erythemia (108.2 ppm-years) and 2 unspecified leukemia (380.4, 140.4 ppm-years). In addition, the authors found an elevated risk of leukemia with peak exposures ≥30 ppm (6 cases vs. 1.7, SMR=3.5, 95% CI: 1.3 – 7.6 for men and women - 6 cases vs. 1.3, SMR=4.5, 95% CI: 1.1 – 9.9 for men only). *(Gas/Electric Utility Workers)* – This was a nested-case control study of 72 leukemia cases within a cohort of 170,000 workers (Guenel, Imbernon et al. 2002). They use a relative value exposure matrix. The risk of leukemia increased in workers with an estimated cumulative exposure ≥16.8 ppm-years (OR=3.6, 95% CI: 1.1-11.7). There was an indication of a dose response relationship with every 10 ppm-years increase in exposure (OR=1.2, 95% CI: 1.0-1.5). The link with benzene was more pronounced for acute leukemia versus chronic leukemia. There were 20 cases of AML with no exposure, 1 with 0-<5.5 ppm and 5 with ≥5.5 ppm. In addition, there were 3 cases of acute leukemia of unknown cytology.

Unfortunately, animal studies have little to offer when evaluating the potential for a threshold dose of leukemogenesis. In order to induce leukemia in rodents, a relatively high dose must be used simply because the lifespan is too short to allow normal induction intervals as seen in human beings. However, animal studies are extremely valuable for studying the mechanisms and metabolism of benzene. As noted in the animal study section above, doses of 100-300 ppm were necessary in order to induce leukemia in mice and rats.

3. Limitations of the Seven Quantitative Study Groups

The section above lists the interpretation of the various studies as reported by the authors. In some cases, limitations of the studies were frankly stated in the Discussion section of the respective studies; alternatively, some authors minimized or did not even address potential limitation(s) of their study. The following text is critical in order to put the findings of the studies into context.

The Pliofilm Cohort:

The overwhelming limitation with the Pliofilm cohort is the lack of quality industrial hygiene data, particularly from the earliest periods of operation. Although it is still contended by Rinsky, most evidence points to significantly higher levels of exposure in the various Pliofilm plants during the 1940s and 1950s. Quality, periodic industrial hygiene data collection only became available during the mid-1970s. However, there were some very limited grab samples taken at several points up to that time. In many ways, these limited

samples have only complicated matters by providing reference points that may or may not be valuable. That has led to very contentious debate about the purpose, quality, methodology, placement and relevance of these measurements. For example, in one report it was mentioned secondhand that exposures were thought to have followed the appropriate regulatory level of the time. That is, the plant was operating within the accepted limits, such as 100 ppm. With each successive reduction in the PEL, the company complied. Alternatively, there is some documentation to suggest that there was the opportunity for limited time, very high exposures that were far greater than the acceptable limit. This in fact happened to one of the early cases of leukemia. It is impossible to come to a concrete answer for all of these variables – literally the "facts" are unverifiable. In addition, the samples that are available came from one plant, while most of the cases came from a plant with little industrial hygiene information. Once again, this creates a point of contention – Is one plant the same as the other plant? In addition to the poor industrial hygiene data, there are also questions about what, if any, ventilation was available during the 1940s. There are some cryptic comments and records about the ventilation function; however, they are very limited and not particularly enlightening. Although it was mentioned that the ventilation kept local levels to 0 or 10-15 ppm, this was only apparently measured once. In addition to the limitations of the industrial hygiene data, some assumptions were initially made about areas of exposure (wet-side) versus (dry-side) operations. Although the dry-side workers very likely had lower exposures, their levels were not zero, as originally assumed by the National Institute of Occupational Safety and Health (NIOSH) research team.

There is some limited information, once again incomplete, that consisted of peripheral blood samples collected from the late 1940s onward. These blood samples were at the center of several studies (Kipen, Cody et al. 1988; Hornung, Ward et al. 1989; Cody, Strawderman et al. 1993; Ward, Hornung et al. 1996) that examined the change in white blood cell counts over time with benzene exposure. The interpretation by Kipen and Cody is most consistent with relatively high level benzene exposure and this has been co-opted to support the higher estimates by Crump and Allen, as well as Paustenbach. Unanswerable questions still remain as to the exact methodology used to measure the various blood counts.

Some additional factors that have been brought up in the analyses have been the effect of shutdowns during World War II due to lack of rubber, the effect of dermal absorption on cumulative benzene exposure, as well as, personal protection use and function.

The Chinese (NCI-CAPM) Study Series:

The Chinese NCI-CAPM study has a number of problems that in many ways potentially invalidate the findings, or at least significantly diminish the usefulness of the data. Although this is a very large study that could potentially offer much good data, these workers are not exposed to only benzene, unlike the Pliofilm Cohort. The factories being studied are a mixture (64% paint manufacture/use) of industrial types, including rubber production, printing, paint, etc. that have the potential for a very wide range of chemical exposures. The major weakness of this study is the lack of confidence that the research team had in the existing industrial hygiene measurements. Similar to the Pliofilm Cohort, in many cases when measurements were collected during the early years of the study the purpose, technology, sample time and other factors were not documented. Short term grab samples

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were often the only source of industrial hygiene data. The research team developed a confidence rating system for the measurements and a high level of confidence was ascribed to only 2% of measurements in the 1940s. During the periods when most of the workers who eventually developed cancer were working, the confidence in the measurements was very low. The level of confidence rose slowly in the succeeding years and reached 42% after 1985. In addition, there was no central team of industrial hygienists to evaluate all of the ~700 factories involved in the study, and estimates of exposure depended upon local industrial hygienists at each factory, although there was "uniform" training of all study members.

In a related matter, there are persistent allegations that the levels of exposure estimated by the research team are not consistent with the Chinese occupational literature, or the results of their own co-investigators. Although the lead researchers have explained many of the incidentally elevated levels as isolated inconsistencies, there is good documentation of elevated benzene levels in many industries in China (Wong 2002; Vermeulen, Li et al. 2004). In addition, related questions have been raised about the level of ventilation, personal protection, length of the workday, number of days worked per week and benzene content of produces used in manufacturing. All of these factors have significant bearing on the dose estimation and thus the study outcomes.

There are inconsistencies in data collection and documentation of disease status in a significant proportion of leukemia cases; particularly ANLL, the type of leukemia most closely associated with benzene exposure. In addition, there are questions about acquisition of cases and possible bias. There are also problems with unexposed rates of disease in the control population and the effect they have on statistical stability. The highest level of benzene exposure categorization is 50 ppm, yet there is significant documentation that levels far higher are frequently encountered in Chinese industrial settings. This will introduce substantial misclassification and an overestimation of risk.

In summary, potentially major problems in the Chinese (NCI-CAPM) studies include: scientifically unsound industrial hygiene practices, unreliable data sources and collection techniques, flawed epidemiologic practices, misclassification and a narrow/incomplete scope when considering exposures and resulting diseases.

The Chemical Industry Studies - (Dow Chemical, Monsanto/Salutia, and Chemical Manufacturers Association)

A common weakness of these studies was a lack of personal, time-weighted industrial hygiene measurements. Concurrently the exposure history was based upon estimated ranges from area sampling, not individualized data which would include work practices, personal protective equipment use and operator specific factors. In each of the study groups, the populations had the opportunity for innumerable chemical exposures, in addition to benzene. In addition to the underlying problems with a lack of personal monitoring data, most were unable to take important factors such as peak exposure levels and frequency into account. Peak exposures can add significant amounts of benzene to cumulative exposure; in addition, they have been consistently linked to an increased risk of leukemia. Another problem frequently found in these studies was inadequate exposure estimates from the early years of production, particularly before the 1950s.

Another common problem among the chemical cohort studies was the use of the U.S. population as the control group. This practice introduces the possibility of the "healthy worker" effect, which tends to lower standardized mortality ratios artificially and may obscure any significant findings. In addition, many of the studies did not control for potential confounders and modifying factors, such as smoking. In one study, where confounding variables such as cigarette smoking were not accounted for, there was a clear excess of lung cancer deaths in the unexposed cohort of workers. Also problematic was incomplete follow-up of the cohort members, resulting in missing data and possibly skewed data due to non-differential effects.

There were also limitations that resulted from the ascertainment of leukemia diagnoses. For several of the studies, the leukemia diagnoses were obtained from death certificates, without verification of diagnosis, much less the particular cell type of the disorder. If the types of leukemia are not broken down by cell type, the analysis is limited. Misclassification of even one case within the various subtypes of leukemia can drastically change the outcome of a study with few cases. In addition, if a person died of an alternative cause, besides a lymphohematopoietic disorder, this may have been excluded from the death certificate if it was not the "cause" of death. For instance, if a person was in the early stages of lymphohematopoietic disorder without clinical signs, this may have simply been missed without an autopsy.

In one study, there were two cases of ANLL in the unexposed category and three in the exposed category – such limited numbers in both the unexposed and exposed categories lead to very unstable estimates of risk and severely limit any conclusions being drawn from this study. Likewise, in another study the use of a relatively small internal comparison group introduced statistical instability and lead to the appearance of significance where it was not true. There were only seven cases of leukemia, six in the continuously exposed and one in the intermittent grouping. There was a deficit of leukemia in the comparison group (0 observed vs. 3.4 expected) which magnified the relative risk of the exposed.

In the Chemical Manufacturers Association Study, two of the seven plants did not include 1946-1957 – years which have historically been associated with higher exposures in other studies. The unexposed group was missing 14 death certificates (4.29% vs. 1.12% and 1.32%) versus the two groupings (based upon different exposure groups, thus the two percentages) of exposed workers that were missing 9 death certificates. This could have potentially affected analysis, particularly given the small numbers in each disease category.

The Australian Petroleum Industry Studies

The Australian Petroleum Industry Studies had numerous problems. As in other studies, there were problems related to collecting the work history/data collection, small numbers of cancers that led to potentially unstable estimates of risk and possible problems with the exposure assessment.

There were a relatively small number of hematological cancer cases and only 33 leukemia cases. Of the leukemia cases, only 11 were acute non-lymphocytic leukemia, while another 11 were chronic lymphocytic leukemia. These small numbers limit the power to detect excess risk, particularly in individual leukemia subtypes. In addition, misclassification of just a few cases from the lowest groups to a higher group would markedly change the dose

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response curve.

Information about lower exposed jobs was far greater than information available for the highly exposed jobs. Exposure estimates were derived from monitoring data that was collected after 1975. While work history information was collected from contemporary co-workers versus the cases in order to limit recall bias, this likely led to significant under-ascertainment of exposure related to personal work habits and accidents, spills and other short-term high level exposures. If the co-worker only described a job/task as it would have been optimally carried out, without consideration of these factors, it would have the effect of smoothing the peaks and potentially lowering the estimates for each case.

The base estimates which are the beginning of all exposure estimation in this study were questionable even by the author's estimation. When they were compared to relevant exposure data in the literature 12 were not available, 19 were validated, four were adjusted and 14 were not confirmed by the literature. However, the 14 not confirmed were judged to be inadequate and were ignored. The exposure level categories were very small and seemingly insignificant errors in exposure estimation could markedly affect the placement of cases into different exposure levels. This was noted by the research team in a later publication and several of the lower exposure values were combined.

The United Kingdom Petroleum Industry Studies

The United Kingdom Petroleum studies had limited value for several reasons. For many of the cases and controls, the work history was incomplete. Data was extrapolated from the existing records. As noted in other studies, there were different patterns used for taking work histories. Work histories were taken mainly from personnel records, if they still existed. Alternatively, a significant number of records were incomplete and they had to be reconstructed through additional information gathering that would not be specific to the individual, and through extrapolation from existing data. In addition, ~95% of the terminals where work had historically taken place were closed by the time of the study. This required the extrapolation of data from similar terminals still in operation and reliance upon tertiary literature and materials that were also used to fill in information gaps.

The Canadian Petroleum Industry Studies

Although no significant leukemic effect was found in this study, significant limitations were still present. The study was small and thus had limited power to predict disease outcomes. If benzene exposure caused a two fold increase in risk for >45 ppm year category, the study would have only a 16% chance of discovering the relationship at a 20% exposure rate and a 5% significance level. In order to attain 80% power, 90 cases would have been needed. None of the odds ratios for cumulative exposure were significant at the p=0.05 level. For cumulative exposure, the risks were not monotonically increased, and in fact, the highest (non-significant) odds ratios were found near the lowest levels - 0.18-0.49 ppm-years, 0.23-5.49 ppm-years, 0-0.49 ppm-years, 0-0.45 ppm-years and 0-0.90 ppm-years, depending upon the cut points chosen. The authors concluded that the results were consistent with insufficient power to detect a small effect, or a lack of effect for low benzene exposure, particularly between 0.1 - 1.0 part per million.

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The case-control study eliminated 2 of the 16 identified leukemia cases due to incomplete work histories. In addition, smoking status was largely unknown and unaccounted for in the analysis. However, smoking was one of two strongest predictors for leukemia risk. Of the 14 cases of leukemia, seven were ever smokers and the smoking status of the remaining seven was unknown.

The highest risk of leukemia was found in the managerial/professional category which should have had limited, or no potential for benzene exposure beyond the background levels.

As in other studies, there was limited or no industrial hygiene measurement data available and they had to be estimated with an exposure matrix. By the authors' own validation exercise, exposure estimates were within 22%. In addition, some of the exposure data was extrapolated from other facilities.

Data collection was also problematic. Work information for 25% of the 115 workers who were included in the analysis was missing. Of that number, 19% were missing some information and 6% were missing more than half.

The third study had critical problems related to measurement data. Close scrutiny of the base estimates revealed that several of the most highly exposed workers (barrel washer and loader) were derived from limited numbers of measurements, derivations from total hydrocarbon content and short term measurements. For instance, the loader base estimate (historic) was derived from the total hydrocarbons and (14) short term measurements. The calculated benzene concentration used for this category was 2.6 ppm. The highest base estimate was for the barrel washer, yet the benzene concentration was derived from the total hydrocarbon level and (4) short term measurements. Further, the limited validation exercise did not include measurements of benzene exposure in highly exposed workers. Only the total hydrocarbons were estimated in those workers and they varied as follows: -21%, -9%, -11%, -49%, +220% and +85%. Alternatively, the benzene measurements varied as follows: 33%, 10%, 130%, 4.5%, 0, 0, 0, 14.3% and -14%. Obviously, with a more highly exposed worker a hypothetical percent difference is of far greater importance than in a worker with only background exposure. In addition, all of the confidence intervals used in the validation exercise were very wide. The only jobs evaluated were route sales, loader and plantman.

Various Small Studies - (The Caprolactam Workers Study) – (Italian Shoe Workers Study) - (Gas/Electric Utility Workers)

These were all very small studies, particularly the Caprolactam study which had only one case of leukemia. In addition, both the Caprolactam and Shoe Worker studies had estimated exposure assessments based primarily on expert judgment. In the Caprolactam study the researchers utilized a panel of employees. The modifying factor was determined based upon the strength of several subjective measures following process changes and the base estimate was derived from industrial hygiene measurements collected in 1978-1988. A similar method was used to estimate the exposures in the Shoe Worker Study because there were very limited industrial hygiene measurements. The Gas/Electric Utility Workers Study utilized a relative value system to estimate benzene exposure. It is not clear how they established there baseline value, which they modified as the concentration of benzene in the glue changed with time.

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The Caprolactam Study also had a significant number of workers unaccounted for in the analysis. Of the workers, eight emigrated, two were lost to follow-up and five did not have a particular cause of death. This reduced the original cohort by 5.4%, which had the potential of dramatically affecting the conclusions if just one more case were added.

4. Evidence for a Threshold Dose – Use of the Hill Criteria

Strength

Although there will always be questions regarding the Pliofilm Cohort, it is apparent that the Crump and Allen model, as well as, the Paustenbach 1992 model explain the mortality in the cohort better than the Rinsky 1987 model. Interestingly, Williams and Paustenbach revised the estimations of the Paustenbach (1992) model in a recent article (Williams and Paustenbach 2003). Using Monte Carlo techniques, they found that many of the very highest levels were most likely not realistic. However, they concluded that their revised analysis did not markedly change the earlier findings, although the article failed to calculate new individualized dose estimates for the 22 cases of lymphohematopoietic cancer. Perhaps the strongest evidence for a threshold dose in this cohort is the observation by Paxton (1994) that regardless of the estimating model, there have been no cases found in persons with <50 ppm-years of cumulative exposure. Wong (1995) took this even farther when he re-analyzed the data specifically for acute myeloid leukemia and determined that no cases occurred with <200 ppm-years cumulative exposure using the Rinsky (1987) estimations. Although this appears to fully answer the question unconditionally, it is important to realize that the Pliofilm has a small number of cases and it is underpowered to detect an excess of cancer at lower cumulative doses.

The Chinese (NCI-CAPM) clearly has multiple methodological limitations which make the conclusions drawn at very low doses questionable. Nevertheless, the authors reported a non-significant risk for ANLL, which includes acute myelogenous leukemia, below 40 ppm-years cumulative exposure. Given the very real weaknesses in the exposure methodology and the reported findings of the study, it is not unreasonable to conclude that the study is within the range of the Paxton (1994) estimation of 50 ppm-years cumulative dose of benzene.

The Dow Chemical Studies revealed a significant elevation of myelogenous leukemia; however, the numbers were so small that this study has the potential for significant statistical instability. Three of the cases had significant cumulative exposures (45.4167, 25.4167 and 350.9167 ppm-years) based upon estimates that were primarily based upon expert judgment and some limited industrial hygiene measurements which were most likely conservative according to the original report. One other case had a cumulative exposure of 1.5 ppm-years and he worked only 18 months in a low exposure (> 2 ppm) job. It is probable that this case was not related to benzene exposure. By the second update, the SMRs were non-significant and near baseline rates. The Monsanto/Salutia studies reported relatively low levels of cumulative exposure; however, the leukemia risks were all non-significant. The data did suggest that peak exposure frequency may be associated with leukemia risk. The Chemical Manufacturers Association study did not find an elevated SMR for leukemia and there were only 3 myeloid cases in the cohort.

The Australian Petroleum Industry Studies are the strongest evidence contradicting the findings of the Pliofilm Cohort. They found a highly elevated and significant risk of leukemia at >8 ppm-years cumulative exposure, as well as a significant risk for ANLL at that same level. Interestingly, although this is the third study to use the base estimate X modifying factor exposure estimating methodology, estimates of peak exposures were not

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taken into account in the initial (2003) case-control study. In a subsequent re-analysis with added high level exposures (HHEs) the risk for leukemia was only highly significant at >16 ppm-years. The revised risk for ANLL was not reported. Besides the limited number of cases in the referent group, which creates potential instability in the statistical measures, the missing peak exposures cast some doubt on the exact level of risk, if any, associated with the original measurements. It is possible with further study that this will still be the case; however, it is not a foregone conclusion of irrefutable evidence for risk at these low levels.

The United Kingdom Petroleum Industry Studies did not reveal any elevated risk of leukemia. However, there was a non-significant increase in risk for acute myeloid/monocytic leukemia with a cumulative exposure range of 4.5 – 45 ppm-years. The upper limit of the interval is within the same range suggested by Paxton (1994). The author noted, "The present study, along with these other studies, suggests that risks under about 50 ppm-years are either small or nonexistent."

The Canadian Petroleum Industry Studies did not find an elevated risk for leukemia; however, the exposures were on the low side (0.01 – 6.2 ppm).

The Various Other Studies including the Caprolactam workers, Italian Shoe Workers and Gas/Electric Utility Workers were all small studies. The Caprolactam and Shoe Worker studies both suggested little or no risk at low levels of exposure. However, there was only one case of leukemia in the Caprolactam study, thus it was not too informative. The Italian Shoe Workers only had an elevated risk at > 200 ppm-years cumulative exposure. There were non-significant elevations at doses >40 ppm-years exposure, which is consistent with the suggested level proposed by Paxton (1994). The Gas/Electric Utility Workers study showed an elevated risk at or above their extrapolated value of 16 ppm-years cumulative exposure. However the number of cases was very small and it is not clear if the ppm-years calculation was a relative versus absolute value. They did not measure any benzene levels.

As you can see from the above discussion, the argument for little to no risk for leukemia and acute myelogenous leukemia in the range of 40-50 ppm-years cumulative dose is strong. Although the Australian study suggests that there is significant risk at a lower level, this estimate has already been revised. Nevertheless, I believe that there is strong support for a threshold that most likely fall around 40-50 ppm-years. It will be potentially enlightening if the UK, Canada and Australian cohorts are even combined, as was suggested by the Institute of Medicine in 2005.

Consistency

There is no epidemiologic evidence that suggests an individual with only a background level of benzene exposure is at any risk of developing leukemia of any type. By default, this answers the part of the question that was originally posed in this investigation – Is there evidence for a threshold dose of benzene? However, I believe that the studies noted above clearly show a high level of consistency, except for the Australian outlier.

Specificity

Throughout the collection of case reports, case series and epidemiologic studies, the acute myelogenous leukemias (ANLL) have been consistently and specifically associated with benzene exposure, unlike the remaining types of leukemia. The Pliofilm Cohort is one

of the strongest pieces of evidence for the specificity of benzene related cancer. Pliofilm workers were exposed to little else besides benzene and the overwhelming type of leukemia was acute myelogenous leukemia. There is no other group, regardless of whether exposure was quantified that had this singular solvent exposure.

Temporality

There is a background rate of all subtypes of leukemia, including acute myelogenous leukemia. It was interesting that the Gas/Utility Electric Study had 20 cases of AML in non-exposed workers. Many of the cases with very low exposure to benzene probably do not have a benzene related neoplasm.

Biological Gradient

Once the threshold dose is reached, acute myelogenous leukemia incidence and mortality rises rapidly. However, below that dose there is no expectation of risk.

Plausibility

Although sub-chronic effects such as chromosomal aberrations and hematological changes have been widely reported at a variety of doses, their presence is not necessarily a direct link to leukemogenesis. For instance, the vast majority of persons who develop the aforementioned sub-chronic effects return to their baseline values very quickly. For those persons with persistent abnormalities, there is scientific proof that they will inevitably proceed to leukemogenesis. Even individuals who develop aplastic anemia from very high level exposures do not necessarily develop leukemia, although their risk is certainly elevated.

Coherence

As mentioned earlier, animal data cannot be directly extrapolated to human beings; however in lifetime inhalation studies there does appear to be a threshold dose at a dose dependant on the species and breed.

Experiment

Many of the quantitative and qualitative epidemiologic studies have been updated and invariably any elevated risk found in the previous investigation has fallen with decreasing exposure. In most studies, the risk falls to insignificance and in many it return to background rates.

Analogy

Unfortunately, benzene is the only known leukemogen that has been studied so thoroughly. In addition, although leukemogenesis is most likely related to the quinone metabolites of benzene, the exact mechanism of action has not been fully elucidated.

Chapter Five: Conclusions, Limitations and Recommendations

The purpose of this investigation was to determine whether there is a threshold where no theoretical risk for benzene-related leukemogenesis exists. From the evidence examined and with an understanding that there are limitations in any data set, this investigation revealed that there is a threshold dose for benzene-induced carcinogenicity. The threshold dose where a theoretical risk for benzene-induced leukemogenesis is around 50 ppm-years, although it may be higher based upon information presented in other studies.

This investigation utilized secondhand data from the publically available medical and scientific literature; as such, it is dependent upon and subject to the inherent limitations of the underlying data sets.

Future research on this important topic is certainly encouraged. A meta-analysis of the UK, Canadian and Australian (Health Watch) data would be worthwhile and potentially offer further clarity to the potential for adverse health outcomes in petroleum industry workers.

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