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May 9, 2009

Ms.Gail C. Ford
Vorys, Sater, Seymour and Pease LLP
52 East Gay Street
Columbus, Ohio 43216-1008

RE: Case No. 2007-11-8033; Bonnie L. Mallory, Executrix of the Estate of Robert E. Mallory, Deceased v. The Goodyear Tire & Rubber Company, et al. Court of Common Pleas of Summit County, Ohio

Dear Ms. Ford,

Thank you for allowing me to review the medical records, three sets of bone marrow slides, and additional materials that you provided to me, concerning the above action. As you are aware, I am a Board-certified hematologist in clinical practice at The Methodist Hospital, in Houston, Texas, where I also serve as Director of the Transitional Residency Program and Chairman of one of two Internal Review Boards (IRBs). I have clinical faculty appointments to Baylor College of Medicine, University of Texas Health Science Center at Houston and Weill Cornell Medical College. I am a member of the Board of Directors of the Christus/Stehlin Foundation for Cancer Research, and of the Gulf Coast Regional Blood Center where I chair the Education and Research Committee. I am a past President of the Gulf Coast Hematology Society and of the Houston Society of Internal Medicine. I have more than 40 years experience in clinical hematology and am familiar with the hematological disorders classified as leukemias, including the various ***de novo*** and **secondary** forms of acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS) and chronic myeloproliferative disorders (MPD), and what is known concerning their etiology, diagnosis, clinical course and therapy. The opinions expressed herein are my own and should not be construed in any way to also represent the opinions and/or judgments of The Methodist Hospital System or any of its associated institutions and subsidiaries. My Texas medical license is current and on file with the appropriate authorities. You have a copy of my curriculum vitae and a listing of my prior trial testimony. My testimony has never been excluded by any court.

This action concerns Mr. Robert E. Mallory (DOB 01-25-1938, SSN 234-56-2518, DOD 02-01-2007) who is described as initially a rigger and later a machine repair mechanic working over many years at various Goodyear facilities in Akron, Ohio, until his retirement, circa year 2000. He sought medical attention in November of 2005, with sudden complaints of right flank pain, and was admitted to the hospital because his routine blood counts showed a moderate anemia and severe leukopenia with a normal platelet count. Immature white blood cells (*blast forms*) were noted on his peripheral blood film. His illness appeared fairly sudden in onset, as he claimed to have recently been walking 3 miles per day every morning. His physical examination was described as unremarkable. A bone marrow examination done on 11-23-2005, and numbered B-05-0016, was abnormal, and interpreted as representing a high-risk myelodysplastic syndrome (MDS) consistent with the terminology of refractory anemia with excess blasts (RAEB). Apparently, no cytogenetic (*chromosome*) analysis of the bone marrow cells was attempted on this study.

Mr. Mallory was described as having smoked until 3 or 4 years prior to this admission. The duration and quantity of his smoking is not detailed in the material I have received. He claimed some exposures to benzene and asbestos. One interviewing physician thought his description of this chemical exposure was minimal, and another chart note indicates he had no specific chemical exposures. His mother and a brother had died from cancer. There was no mention of a family history of hematological disease. You have provided employment records which included his blood counts up until year 2000, but none from the period 2000 – 2005. He was referred to the Cleveland Clinic for a second opinion concerning his hematological condition and recommendations on its therapy, and he was seen there in December of 2005.

You have provided me with slides of his initial bone marrow examination. The peripheral blood film shows normal-appearing erythrocytes. There is a severe leukopenia and neutropenia, but those neutrophils and lymphocytes present are normal in morphology. On scan of the blood film it is not difficult to fine typical myeloblasts with some degree of maturation. The platelet count is normal, but rare very large platelets, as are occasionally seen in myeloproliferative disorders (MPD) are evident. The bone marrow biopsy is normocellular, but the marrow aspirate films suggest the bone marrow may actually be hypercellular (*if a biopsy is obtained from the same general area as the prior aspirate, such a discrepancy in apparent bone marrow cellularity is occasionally observed*). As mentioned in the pathology report, a striking feature in this bone marrow is a maturation arrest of the granulocytic series with virtual absence of mature neutrophils. Overall, the myeloid cell population is substantial and consists of increased blast forms, along with myelocytes and promyelocytes. There is some erythroid hyperplasia with a predominance of orthochromatophilic (*late stage*) normoblasts. As also mentioned in the pathology report, there is little erythroid dyspoiesis, and certainly far less than 10 % of the erythroid elements show any significant dyspoietic features. Storage iron is present in normal amounts, but the quality of the slides and their histological staining is poor, and it would be difficult to know if ringed sideroblasts are present. They were not described in the report. Particularly, the myeloid elements are

poorly stained throughout the several Wright/Giemsa-stained slides of the bone marrow films and a blast count is difficult to accurately assess, but I would not dispute the 11 % figure clamed in the report (*normal value, 1-2 %*). Apparently, the blast estimate by flow cytometry was 14 %. Because of the necessary preparation of the bone marrow cells for flow cytometry analysis, discrepancies between the blast percentage by direct visual count and by flow cytometry are the rule. Some also argue the point as to whether the blast cell percentage should be restricted to the myeloid cell line or include the total nucleated cell count (1). However, by any estimate the myeloblast percentage is clearly greatly increased over normal.

For many years, the results of properly performed cytogenetics have been essential in determining the classification, prognosis and treatment of neoplastic bone marrow hematological disorders. For example, "**Cytogenetics have become of crucial importance for diagnosing and treating patients with MDS and AML**" (2). And, "**Bone marrow aspiration...bone marrow biopsy...and cytogenetic investigations...are all mandatory for diagnosis and prognosis**" (3). As an arbitrary number, the World Health Organization currently lists 20 % blast forms as a qualifier for a diagnosis of acute myeloid leukemia (AML) but much lesser blast numbers allow a diagnosis of AML if certain types of chromosome aberrations are also present (4). Thus, if we had cytogenetics available in this case, depending upon their results this bone marrow could represent AML (*and is consistent with an M3 or M4 AML morphology under the now disappearing FAB classification system*). A diagnosis of AML would be supported by the sudden nature of the illness and the absence of macrocytosis and other morphological abnormalities among the circulating erythrocytes and granulocytes. However, I would agree that the bone marrow could also represent MDS, as concluded by the interpreting pathologist. However, with certainty, this bone marrow study does not represent erythroleukemia (*M6 AML under the FAB classification system*). Apparently, the physicians at the Cleveland Clinic felt as I did in reviewing these slides, and told Mr. Mallory and his family that his hematological illness could actually represent AML, and not MDS, and suggested a typical AML protocol (*referred to as the 7 and 3 regimen*) as one possible form of his initial therapy.

I am unsure if a second bone marrow was performed at the Cleveland Clinic in December of 2005. There is reference to a bone marrow report numbered S05-77762, but no pathology report under this designation is present among the medical records I received. Of the two sets of marrow slides I received from the Cleveland Clinic, none has an S05 designation. There is also no mention of the results of a chromosome analysis report on a repeat bone marrow study prior to starting his therapy. It seems likely, then, that the original outside slides were re-numbered with an S05 designation, and retained in the Cleveland Clinic pathology department. If this is so, in my opinion, his medical care fell well below the general standards. I say this because his therapy would then have been initiated with an experimental treatment protocol containing arsenic trioxide, when the consulting hematologist freely admitted the correct hematological diagnosis was uncertain, based on the initial bone marrow study, and there were no cytogenetic reports available for study. As previously mentioned, it has been well-known for many years

that, depending upon the cytogenetics in both MDS and AML syndromes, entirely different treatments are favored, and such information provides the patient with the best chance of an optimal response and often dictates prognosis (2).

After having received 24 courses of arsenic trioxide, along with a monoclonal antibody form of chemotherapy, Mylotarg, the first Cleveland Clinic bone marrow examination was done, in March 2006. This bone marrow slide preparation is excellent and well-stained. It shows a hypercellular bone marrow with increased blasts and continuing erythroid hyperplasia with mild dyspoiesis. The iron stain shows ringed sideroblasts. I think that it is entirely possible that the ringed sideroblasts might also have been present on the initial bone marrow but not able to be identified on a poorly made and stained slide. The presence of ringed sideroblasts and this marrow morphology makes one think of another entirely different diagnostic consideration, namely a JAK-2 positive myeloproliferative disorder (MPD) with ringed sideroblasts, a recently recognized entity (5). However, some of these morphological findings could be iatrogenically caused by his recent chemotherapy. Arsenic trioxide is a mitochondrial poison and potential leukemogen and is capable of producing chromosomal damage (6-7). It is in the mitochondria that iron may accumulate in the form of ringed sideroblasts, in acquired sideroblastic syndromes.

The routine chromosome studies on this second bone marrow sample did not yield enough metaphases for accurate cytogenetic analysis, and no FISH (*fluorescent in situ hybridization studies*) probe studies were apparently ordered on the specimen. When a remission of the hematological disorder had not occurred following this treatment, no additional therapy was given aside from a short course of Vidaza, at the patient's request. A third bone marrow study was performed in July of 2007. The results of this study are somewhat similar to the prior one, but also show a definite increase in eosinophils in both the peripheral blood and the bone marrow. Certain AML syndromes, such as inversion 16 AML, may often be associated with eosinophilia. Cytogenetic studies were allegedly ordered on this third bone marrow study, but the results are not found in the medical records I received. This third marrow study had a myeloperoxidase stain applied to the bone marrow biopsy which gave a strongly positive result, confirming a myeloid AML and excluding erythroleukemia. Over time, Mr. Mallory's blast cell count gradually rose in the peripheral blood, and he died in February of 2007. The death certificate lists the cause of death as acute myelogenous leukemia (*a synonym for acute myeloid leukemia*), which would appear appropriate, based upon these medical records.

In attempting to assign causation in AML, in no instance can the specific etiology of an individual case of AML be confirmed with complete certainty, but particular characteristics of the leukemia and the clinical setting in which it appears offer clues with which to provide an evidence-based scientific opinion. Some of these aids include the age of the patient, the specific type or subset of AML, the family history, the cytogenetic (*chromosome*) pattern of the leukemic cells, the presence or absence of certain myelodysplastic syndromes preceding the onset of AML, and the response to specific therapy. In addition, if a chemical or environmental toxic etiology is suspected, the

cumulative dose of the toxin received and the latency period between achievement of a dose sufficient to cause AML, and the onset of AML, are also of major importance (2, 8-9). In the modern era, it has become well-accepted that, "**Acute myelogenous leukemia (AML) is not a homogenous disorder but encompasses many different entities that are distinguished by the morphology of the leukaemia cells, specific chromosome aberrations, gene rearrangement patterns, and different clinical courses and response to therapy...it is critically important to study each entity specifically, in an attempt to decipher epidemiological clues as to aetiology...AML in general comprises multiple molecular subgroups which may have different aetiologies and pathogenesis.**" (10). In consideration of these important caveats I will comment first about causation of AML in general, and then focus on the hematological disorder in Mr. Mallory.

It should be noted that perhaps 80-85 % of all AML cases are thought to be ***de novo***, in appearance, and unrelated to any known causative events such as prior chemotherapy, underlying hematological disease and potential chemical exposure (2, 8-13). With certain specific forms of AML, such as those exhibiting the inversion 16 chromosome, perhaps 95 % of cases may be ***de novo***. No particular occupation, patient age, or general state of health makes one immune to ***de novo*** AML, and it always must remain an etiologic consideration in any given case. The term, ***de novo***, when applied to AML, not only refers to its sudden onset without known cause, but to certain additional characteristic features of the leukemia (*vide infra*). Of the **secondary**, or perhaps 15-20 % of event-related examples of AML that appear today, most are thought to occur as a consequence of prior treatment with chemotherapeutic drugs or radiation, or as evolution from underlying myelodysplastic syndromes (MDS), which, themselves, may also be either ***de novo*** or **secondary** hematological disorders.

Additional less frequent examples of **secondary** AML eventuate from certain myeloproliferative disorders, such as polycythemia vera and may also be associated with pernicious anemia (*a hereditary deficiency of vitamin B-12*), which may cause abnormal cell replication with associated chromosomal aberrations. Other rare causes of AML are constitutional chromosomal disorders, such as Down's syndrome. Aside from AML as a consequence of cigarette smoking, and possibly causation related to hepatitis C infection, environmental toxin-induced MDS/AML in developed countries in the modern era is thought to account for only a very small number of cases (8-16).

Under normal conditions, bone marrow cells must replicate at an extremely rapid pace. For example, the entire circulating white blood cell granulocyte population is replaced daily, multiple times. The nature of blood cell replication, which requires programmed DNA fracture followed by DNA duplication and reassembly, and chromosome realignment may lead to chromosome damage that is not immediately corrected by the existing multiple cellular reparative processes. This is why some authors suggest the terms primary or ***de novo*** AML to be synonymous with endogenous AML causation, and to be distinguished from **secondary** or event-related, or exogenous induction of AML. In a 2008 publication, we may read, "**The infrequency of an**

Exogenous cause: It is likely that most blood cancers are the results of cellular misadventures in blood-forming cells or lymphocytes, aberrations of normal cell processes, such as spontaneous mutations resulting in oncogene formation and inadequacies of DNA repair mechanisms. Chemical: Only a small proportion of blood cancers have a cause related to exogenous or environmental factors. The only blood cancer for which there is convincing scientific evidence of an avoidable environmental cause is AML (and the closely related disease myelodysplasia), and only in a minority of cases" (13). Thus, it should not be surprising that a defined external or environmental cause for AML induction is infrequently evident in patients with newly diagnosed AML and cannot be assumed to ever have been a factor in causation.

In terms of exposures to benzene or to solvents or paints and other petrochemical products containing trace amounts of benzene, as alleged in the Mallory legal action as causative of his hematological disorder, numerous large, serial epidemiologic studies involving hundreds of thousands of workers, with potential for benzene and other hydrocarbon exposures, have failed to show any statistically significant increase in the incidence of AML, in developed countries, for many years (17-31). The cumulative dose of benzene necessary to predispose to AML is extremely high, with statistically significant evidence of risk estimated to require at least a 200 ppm year exposure (32-33). In one modern study of individuals working with benzene-related synthesis, no statistically significant evidence of increase in the incidence of AML was evident with mean cumulative exposure levels about 40 ppm years (28). In another small, but carefully studied group exposed to pure benzene, and with mean exposures of 159 ppm years, the incidence of AML was also not increased (29). And, yet in another modern cohort report, there was no statistically significant increase in AML incidence below cumulative exposures of 250 ppm years (34).

Plaintiff's experts often cite a questionnaire and interview based sub-set exposure analysis of the AML cases reported in the Australian Health Watch Study cohort, and published several years ago by Dr. Glass, as evidence that low-dose cumulative benzene exposure may cause AML. The Health Watch Cohort consists of about 18,000 petrochemical workers recruited from 1980 to 2000, when the study was closed for long-term follow up. The mean cumulative benzene exposure in this cohort is estimated at 4.9 ppm years with a range of up to 57 ppm years. In the most current (13th) follow up analysis of the Health Watch Study cohort reported in 2007, Glass reports 11 cases of ANLL (*acute non-lymphocytic leukemia, a seldom- used designation in the United States where it has become a synonym for AML*) with an expected number of 12.7 ANLL cases, based upon standard mortality rates for AML in the Australian population. **Thus, a deficit of AML has been identified in this benzene-exposed cohort**. Moreover, she now reports that there is no statistically significant increased incidence of ANLL for any worksite designation in this cohort and too few ANLL cases for statistical analysis according to duration of employment or increasing hydrocarbon exposure. Pooling all forms of leukemia in the cohort, in order to increase statistical power, she now tells us that there is no association between length of employment and/or increasing hydrocarbon

exposure among leukemia, as a single designation (31).

In my opinion, to continue to site this cohort, which actually exhibits a deficit of AML cases, as proof of an increased incidence of AML at low benzene exposures, is disingenuous. The earlier Glass report simply demonstrates the power of recall bias, when used in epidemiology in the cancer field. Interviewing patients with AML (*or other forms of cancer*), who wish their illness to have been caused by something or some exposure they had no control over, and comparing this information with the recall of healthy patients, who have no need to search their memory and/or embellish their prior chemical exposure history, frequently leads to statistical misinformation (35-36).

Cigarette smoking is now well-accepted as a cause of adult AML, and some believe this toxic exposure may cause around 9 % to even more than 20 % of all AML cases (14-15, 37-42). The relative risk from smoking is generally reported as 1.2-2.3 times the incidence in the general population, depending upon the amount smoked (11). The 2004, Surgeon General's report concludes that a 20 pack year smoking history doubles the risk of AML (40). In a recent editorial on this subject, the author states, "**Studies measuring population-attributable risk, the proportion of all cases of AML that can be attributed to cigarette smoking, have reported values ranging from 14 to 31%. If the lowest value is true, cigarette smoking would be the most prevalent exogenous cause of AML**" (14). The causative factors or chemicals leading to the appearance of AML in smokers are unknown (14, 41-42). Cigarette smokers are thought to be exposed to ten times the benzene dose of non-smokers. Estimates of this cumulative benzene dose among heavy smokers range from 0.5 ppm years to as much as 3-6 ppm years, both estimates far less than the statistically significant cumulative benzene dose thought necessary to cause AML. The specific chromosomal pattern seen in smoking-induced AML remains undefined, with certainty, but complex chromosomal aberrations and defects related to chromosome 8 are cited, and appear somewhat different from those seen following benzene exposures (11, 14). I have not received any information concerning the years and amounts Mr. Mallory smoked, but he stopped only a short while prior to the development of his hematological disorder, and I will assume he had at least a 20-pack year history. Because the risk of AML attributed to smoking does not promptly return to baseline with smoking cessation, it remains a potential cause for his AML or MDS, depending upon his original hematological diagnosis (40).

In addition to the importance of the cumulative dose of a potentially myelotoxic agent, the latency period (*the time interval between accumulation of a dose with sufficient potential to cause AML, and the appearance of AML*) is an important consideration. Information on such latency is best known through careful study of literally thousands of cases of **secondary** AML following administration of varying types of chemotherapeutic agents with the ability to damage DNA. Among these examples of **secondary** AML, it has been repeatedly observed that the cumulative dose, given either orally or intravenously (*rather than peak levels achieved after a single pulse administration*), determines the incidence of **secondary** AML (8, 43). This chemotherapy model for latency is especially accurate, and reproducible, not only because of the large number of

cases studied, and the certainty of dose, but because the initial and the final administration of chemicals are typically spaced only several months apart. Therefore, although the actual time of latency onset may not be accurately known in each case, whether one chooses to arbitrarily define latency from the date of administration of either the first, or of the last dose of the chemical (s), to the onset of **secondary** AML, the calculated latency period will vary by only a few months.

With careful study of such latency periods, it has been repeatedly demonstrated that there is a characteristic window of opportunity to develop **secondary** AML following a toxic exposure to bone marrow cells that is generally described as around 2-10 years (8-12). Additionally, depending upon the mechanism of action of the specific chemical administered (*for example, topoisomerase II inhibitor vs. alkylating agent*), this latency interval may be closer to the shorter or to the longer end of the 2 to 10 year span. AML attributed to benzene also appears to be associated with a latency period, quite similar to the modern-day chemotherapy model (8, 44-47). Recent benzene exposures are thought to more likely relate to a new diagnosis of benzene-induced AML/MDS than remote exposures (44-45, 47). Since the benzene concentrations in many petrochemical products have been regulated for many years, such potential exposures would make it difficult to achieve a leukemogenic dose during the modern era (48). If the bulk of his alleged benzene exposures were remote, Mr. Mallory would not fit the usual chemical-induced latency pattern. However, I would need to defer to the defense toxicologists who might attempt to model his total cumulative benzene dose on a year by year basis.

Many authors have considered **secondary** AML developing as a consequence of either chemotherapy exposure or benzene toxicity to be quite similar, or even identical. This is not surprising since, in reality, benzene was employed as an early chemotherapeutic agent, administered orally in an olive oil base at doses of 2-5 grams daily. It was particularly effective in chronic forms of leukemia and in polycythemia vera (49-50). Its administration over several weeks can lower an elevated total leukocyte count from the 200,000 to 400,000/cu mm level into the normal range (5,000 to 10,000/cu mm), much like chronic oral therapy with the later-introduced alkylating agents. Persistent bone marrow damage, and even aplastic anemia, following its prolonged administration, was well-known. Arsenical and radioactive compounds were similarly used as early forms of chemotherapy and are also leukemogenic (51). Thus, linking the potential hematologic consequences of modern day chemotherapy, benzene and other environmental toxins, "**The AML cases arising after DNA-damaging chemotherapeutic agents and the AML cases caused by diverse environmental factors (e.g., benzene, petroleum, organic solvents, and arsenical pesticides) are genotypically similar; the majority are characterized by deletions of all or part of chromosomes 5 and/or 7...**" (53).

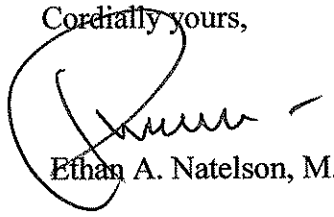
Routine cytogenetics on bone marrow myeloid cells show abnormalities in at least 90 % of patients with **secondary** AML consequent to modern chemotherapy agents or hematotoxins, such as benzene (8, 11, 52-54). By contrast, in ***de novo*** AML 40-50 % will have normal (*diploid*) chromosome patterns and often balanced chromosome translocations {*reciprocal exchange of DNA segments between two chromosomes*).

Still another feature which may be helpful in distinguishing between ***de novo*** and **secondary** AML is the presence or absence of a clearly defined period of myelodysplasia (MDS) preceding the diagnosis of frank AML. This typically takes the form of a persistent, progressive, and unexplained anemia. In **secondary** AML, about two thirds of patients exhibit a period of MDS prior to the appearance of AML, while this phenomenon is lacking in most ***de novo*** forms of AML, which typically occur abruptly (2, 8). There is no laboratory data in the material I received describing progressive prior blood count abnormalities during the critical period of 2000 to 2005, which might suggest a preceding MDS in Mr. Mallory. Clinically, his disease had a sudden onset with lack of preceding symptoms and as evidenced by only a moderately reduced hemoglobin concentration with normal mature granulocyte and red blood cell morphology and a normal platelet count on his first hospital visit in 2005. In most instances, the group of disorders under the general heading of MDS are fairly rapidly progressing illnesses (3). As previously discussed, because of the lack of cytogenetic data on his initial bone marrow examination, the original pathological diagnosis of MDS versus AML (*and even versus a form of myeloproliferative disease*) cannot be definitive with the information we have. The myeloproliferative disorders (MPD) are not liked to either prior benzene or chemotherapy exposures.

In summary, and in my opinion, and in all medical probability, the most likely cause for the specific diagnosis of AML present at death, in Mr. Mallory, is ***de novo*** AML. This is, by far, the most common form of AML that we see in the general population at large, regardless of occupation. His cigarette smoking remains another potential etiology for his diagnosis of AML that cannot be eliminated. **Secondary** AML from benzene exposure is highly unlikely in his case because of the rarity of this illness in the modern era, among his peers in industry, and the unlikely possibility that Mr. Mallory might have been exposed in the modern era to the large cumulative dose exposures necessary to predispose to AML (48, 55).

Please let me know if you require any additional information. I have photographed the pertinent features of all three sets of bone marrow slides in a powerpoint format. I reserve the right to amend this report as new or additional materials such as estimations of dose-exposure levels and additional clinical material concerning Mr. Mallory becomes available.

Cordially yours,



Ethan A. Natelson, M.D.

REFERENCES:

1. Wang SA, et al. Erythroid-predominant myelodysplastic syndromes: enumeration of blasts from nonerythroid rather than total marrow cells provides superior risk stratification. Modern Pathol 2008;21:1324-1402.

2. Pedersen-Bjergaard J, et al. Genetic pathways in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. American Soc Hematol Educational Program Book 2007:392-397.

3. Cazzola M, Malcovati L. Myelodysplastic syndromes-coping with ineffective hematopoiesis. New Eng J Med 2005;352:536-538.

4. Arber DA, et al. Acute myeloid leukemia with recurrent genetic abnormalities. Chap 6, pp 112-114, In World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissue, 4th Edition, Eds, Swerdlow SH, et al. IARC, Lyon, 2008.

5. Natelson EA. Benzene exposure and refractory sideroblastic erythropoiesis: Is there an association? Am J Med Sci 2007;334:356-360.

6. Amadori S, et al. Use of arsenic trioxide in haemtological malignancies:insight into the clinical development of a novel agent. Current Med Research and Opinions 2005;21:403-411.

7. Patlolla AK, Tchounwou PB. Cytogenetic evaluation of arsenic trioxide toxicity in Sprague-Dawley rats. Mut Res 2005;587:126-133.

8. Natelson EA. Benzene-induced acute myeloid leukemia: A clinician's perspective. Am J Hematol 2007;82:826-830.

9. Deschler B, Lübbert M. Acute myeloid leukemia: epidemiology and etiology. Cancer 2006;107:2099-2107.

10. Douer D. The epidemiology of acute promyelocytic leukemia. Best Practices & Research Clin Haematol 2003:16:357-367.

11. Estey E, Döhner H. Acute myeloid leukemia. Lancet 2006;368:1894-1907.

12. Leone G, Mele L, Pulsoni A, et al. The incidence of secondary leukemias. Haematol 1999;84:937-945.

13. Lichtman MA. Battling the hematological malignancies. The 200 years' war. The Oncologist 2008;13:126-138.

14. Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. Leukemia 2007;21:1137-1140.

15. Danaei G, Vander Hoorn S, Lopez AD, et al. Causes of cancer in the world: Comparative risk assessment of nine behavioural and environmental risks factors. Lancet 2005;366:1784-1793.

16. Anderson LA, et al. Hematopoietic malignancies associated with viral and alcoholic hepatitis. Cancer Epi Biomarkers Prev 2008;17:3069-3075.

17. Wong O, Raabe GK. Cell-type specific leukemia analyses in a combined cohort of more than 208,000 petroleum workers in the United States and the United Kingdom, 1937-1987. Reg Toxicol 1995;21:307-321.

18. Satin KP, Bailey WJ, Newton KL, et al. Updated epidemiological study of workers at two California petroleum refineries, 1950-1995. Occup Environ Med 2002;59:248-256.

19. Lynge E, Andersen A, Nilsson R, et al. Risk of cancer and exposure to gasoline vapors. Amer J Epidemiol 1997;145:449-458.

20. Wong O, Harris F, Rosamilia K, et al. An updated mortality study of workers at a petroleum refinery in Beaumont, Texas, 1945-1996. J Occup Environ Med 2001; 43:384-401.

21. Lewis RJ, Schnatter AR, Drummond I, et al. Mortality and cancer morbidity in a cohort of Canadian petroleum workers. Occup Environ Med 2003;60:918-928.

22. Graff JJ, Sathiakumar N, Macaluso M, et al. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. J Occup Environ Med 2005;47:916-932.

23. Sorahan T, Nichols L, Harrington JM. Mortality of United Kingdom oil refinery and petroleum distribution workers, 1951-1998. Occup Med 2002;52:333-339.

24. Satin KP, et al. A 50-year mortality follow-up of a large cohort of oil refinery workers in Texas. J Occup Environ Med 1996;38:492-506.

25. Divine BJ, Hartman CM, Wendt JK. Update of the Texaco mortality study 1947-93: Part II. Analyses of specific cause of death for white men employed in refining, research, and petrochemicals. Occup Environ Med 1999;56:174-180.

26. Tsai SH, Ahmed FS, Wendt JK, et al. A 56-year mortality follow-up of Texas petroleum refinery and chemical employees, 1948-2003. J Occup Environ Med 2007;49:577-567.

27. Gun RT, Pratt N, Ryan P, et al. Update of mortality and cancer incidence in the Australian petroleum industry cohort. Occup Environ Med 2006;63:476-481.

28. Bloemen LJ, Youk A, Bradley TD, et al. Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. Occup Environ Med 2004; 61:270-274.

29. Swaen GMH, Scheffers T, Jr., et al. Leukemia risk in caprolacam workers exposed to benzene. Ann Epidemiol 2005;15:21-28.

30. Sorahan T. Mortality of UK oil refinery and petroleum distribution workers, 1951-2003. Occup Med 2007;57:77-185.

31. Sim M, et al. Health Watch. The Australian Institute of Petroleum Health Surveillance Program. Thirteenth Report. Nov. 2007. pp 1-89. Monash University, Melbourne Australia ISBN 978-0-9804448-0-3.

32. Wong O. Investigations of benzene exposure, benzene poisoning and malignancies in China. Reg Toxicol Pharm 2002;35:126-135.

33. Bergsagel DE, Wong O, Bergsagel PL, et al. Benzene and multiple myeloma: Appraisal of the scientific evidence. Blood 1999; 94:1174-1182.

34. Costantini AS, Quinn M, Consonni D, et al. Exposure to benzene and risk of leukemia among shoe factory workers. Scand J Work Environ Health 2003;29:51-59.

35. Boffetta P, et al. False-positive results in cancer epidemiology: A plea for epistemological modesty. J Natl Cancer Instit 2008;100:100:988-995.

36. Savage L. (Editorial) Skepticism and greater awareness of epidemiology's limitations could reduce impact of false-positive results. J Natl Cancer Instit 2008;107.

37. Moorman AV, Roman E, et al. Smoking and the risk of acute myeloid leukemia in cytogenetic subgroups. Brit J Cancer 2002;86:60-62.

38. Kane EV, Roman E, et al. Tobacco and the risk of acute leukaemia in adults. Brit J Cancer 1999;81:1228-1233.

39. Pasqualetti P, et al. Tobacco smoking and risk of haematological malignancies in adults: A case control study. Brit J Haematol 1997;97:659-662.

40. Carmona, R. The Surgeon General's 2004 report, The Health Consequences of Smoking. Chap 2, p 254.

41. Chelghoum Y, et al. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. Ann Oncol 2002;13:1621-1627.

42. Thomas X, Chelghoum Y. Cigarette smoking and acute leukemia. Leuk Lymph 2004; 45:1103-1109.

43. Praga C, Bergh J, Bliss J, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: Correlation with doses of epirubicin and cyclophosphamide. J Clin Oncol. 2005;23:4179-4191.

44. Richardson DB. Temporal variation in the association between benzene and leukemia mortality. Environ Health Perspect 2008;116:370-374.

45. Silver SR, Rinsky RA, et al. Effect of follow-up time on risk estimates:A longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort. Am J Indust Med 2002;42:481-489.

46. Morgan GJ, et al. Benzene and the hemopoietic stem cell. Chem-Biol Interact 2005;153-154:217-222.

47. Hayes RB, et al. Benzene and the dose response incidence of hematologic neoplasms. J Natl Can Instit 1997;89:1065-1071.

48. Williams PRD, et al. Occupational exposures associated with petroleum derived products containing trace levels of benzene. J Occup Environ Health 2008;5:565-574.

49. Wintrobe MM. *Clinical Hematology*, 1st Edition, Lea & Febiger, Philadelphia, pp 663, 1942.

50. Kalapos I. Die Wirkung des Benzols bei der Leukämie. Klin Wochen. 1935; 15:864-867.

51. Beutler E. The treatment of acute leukemia: past, present, and future. Leukemia. 2001;15:658-661.

52. Smith MA, McCaffrey RP, Karp JE. The secondary leukemias: challenges and research directions. J Natl Can Instit 1996;88:407-418.

53. Applebaum FR, LeBeau, MM, Willman CL. Secondary leukemia. Hematology. Am Soc Heme Education Booklet 1996; pp33-47.

54. Larson RA, Le Beau MM. Therapy-related myeloid leukemia: A model for leukemogenesis in humans. Chemico-Biol Interact 2005;153-154:189-195.

55. Silver RT, Bennett JM, Goldman JM, et al. The third international congress on myeloproliferative and myelodysplastic syndromes. Leuk Res 2007;31:11-17.