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Mr. Ross Asher
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RE: Cause No. 2:04CV72679; Paul Lee Schrader, and his wife, Joann Schrader; In the United States District Court Eastern District of Michigan.

Dear Mr. Asher,

Thank you for allowing me to review the medical records, personnel files and associated materials you provided concerning the above-numbered action. As you are aware, I am a board-certified hematologist in private practice at Christus St. Joseph Hospital, in Houston, Texas, where I also serve as Academic Chief of Medicine and Director of the Transitional Internship Program. I am a member of the Board of Directors of the Stehlin Foundation for Cancer Research, at Christus St. Joseph Hospital, and of the Gulf Coast Regional Blood Center where I chair the Education and Research Committee. I am the current and a past President of the Gulf Coast Hematology Society. I have more than 35 years experience in clinical hematology and am familiar with the disorders classified as **de novo** and **secondary** acute myeloid leukemia (AML) and, specifically, with what is known concerning the etiology, diagnosis, clinical course and therapy of the various leukemias including hematological illnesses classified under the title of myelodysplastic and myeloproliferative syndromes. My medical license is current and on file with the appropriate authorities. Appended is a copy of my curriculum vitae as well as a listing of cases in which I have offered testimony over the past several years. I have never been excluded as an expert witness by any court.

These records concern Mr. Paul L. Schrader (DOB 5-7-48, SSN 385-48-2838) who is described as a laboratory analytical specialist particularly involved in quality control. He had smoked cigarettes for a long period of time, not clearly defined in the medical records, but personnel records document his smoking in 1974. His blood counts were normal in 1995, but on 10-26-96, pancytopenia was first evident. On 10-27-97 his total leukocyte count was 2,200/cu mm (normal value 5-10,000/cu mm), platelet count 103,000/cu mm (normal value 150-250,000/cu mm) and hemoglobin concentration 13.5 gm/dl. This was discussed with Mr. Schrader, and he was referred for hematological consultation. A bone marrow examination, done on 11-28-97, was consistent with myelodysplasia (MDS) with normal cytogenetics (chromosomes) and contained 3 % blast cells. His blood counts gradually worsened, and he was treated with colony stimulating factors. On 8-20-99, he became quite ill and was admitted to the hospital. At that time his hemoglobin concentration was 6.4 gm/dl, total leukocyte count

1,400/cu mm and platelet count 17,000/cu mm. A repeat bone marrow now contained 15 – 20 % blast forms and was more cellular than a bone marrow done in January of 1999 (all of these bone marrow specimens showed normal cytogenetics). He was thought to have refractory anemia with increased blasts (a sub-classification of MDS), possibly in transition to frank AML, and he received chemotherapy with drugs including Topotecan and cytosine arabinoside. However, he developed renal difficulties and failed to enter a remission. For this reason, he underwent an unrelated donor stem cell transplant around 5-6-2000.

A complication of the transplant was that he developed some degree of graft vs. host disease, particularly associated with pulmonary problems. This was aggravated by underlying emphysema (chronic obstructive pulmonary disease, COPD) caused by years of smoking and his inability to stop smoking, even following the transplant. Nevertheless, from the hematological standpoint he has done well, and the last notes are from January 2005, which indicate he remains in remission and is still smoking. He is no longer receiving immunosuppressive medications.

Additional medical history mentions that he is an adopted child, and a full medical background is not available. His personnel files indicate some dermatitis from exposure to a "rubber accelerator" and some exposure to tear gas. They also specifically record that he worked with carbon tetrachloride, solvents containing chlorine, toluene, phenol, and aldehydes, but there is no mention of him working with benzene. As I understand it, he now alleges that his diagnosis of myelodysplasia (refractory anemia with increased blasts)/AML is a consequence of occupational exposure to benzene.

It is difficult to assign a specific cause for myelodysplasia (MDS) or AML, which is a common sequel to MDS, in any particular individual. Its frequency increases dramatically with advancing age, and, in most instances, the cause of MDS is considered unknown, and not related to any particular chemical exposures (1-4). This is particularly true for certain specific hematological disorders, such as acquired refractory anemia with ringed sideroblasts and chronic myelomonocytic leukemia, which have been included in the general category of myelodysplastic syndromes. Benzene and other myelotoxic agents have the capacity to cause MDS/AML after certain types and intensities of exposures. In the case of benzene, the cumulative dose is generally considered the determining risk factor, and estimates of at least 200 ppm years, or even higher, are thought necessary to potentially cause AML, and with no conclusive evidence that low dose exposures may cause the illness (5-7).

Much of our detailed information about chemical-induced AML comes from study of several thousands of patients who have manifested secondary AML after receiving chemotherapy and radiation for illnesses such as Hodgkin's disease and breast cancer, or as immunosuppressive agents. This type of therapy-induced AML (t-AML) is thought to be essentially identical with the AML/MDS potentially induced by high cumulative exposures to benzene, which, itself, is an obsolete genotoxic and radiomimetic chemotherapy drug (3, 8-9). In general, the appearance of most forms of t-AML (or forms of myelodysplasia which may precede overt t-AML) typically occur within a few years (mean, about 60 months) after the last exposure, and the increased incidence of t-AML returns to the baseline values observed in the general population by 10-12

years post-exposure (3, 10-11). As stated in a recent review, **"The risk of leukemia starts to increase two years after stopping therapy, appears to be maximum in the 5- to 9-year follow-up period, and then drops to near zero after the 10th year of follow-up"** (11). The latency period between chemical exposure and appearance of AML is much shorter in the form of AML referred to as acute promyelocytic leukemia (t-APL), and may also be shortened after very intense chemical exposures, as given in preparation for bone marrow transplantation, for example (12-13).

One of the consistent features of chemical-induced secondary forms of AML/MDS has been the presence of chromosomal abnormalities. As generally defined, **"The term secondary leukemia is usually employed to indicate both forms of acute myeloid leukemia (AML) evolving from previous myelodysplasia and forms of acute leukemia developing after exposure to environmental or therapeutic toxins or radiation (therapy-related)"** (11). AML and MDS may also appear **de novo**, as they occur, without known cause, in the general population. In **de novo** AML chromosome analysis is found to be normal in around 50 % of patients, even when studied by modern molecular leukemic DNA probes (FISH) in addition to conventional cytogenetics (11, 14-21). By contrast, in **secondary** forms of AML or MDS, including those associated with benzene exposure, demonstrable clonal cytogenetic (chromosomal) defects are evident in more than 90% of patients (11, 20, 22). The most common of the clonal abnormalities in chemical-induced **secondary** forms of AML/MDS involve chromosomes 5 and 7, perhaps seen in as many as 75% of cases, but a wide number of abnormalities have been described (1, 8, 20, 22-23). When chromosome aberrations are present in **de novo** AML, Trisomy 8 is among the most common defects seen along with certain balanced translocations (1, 23-24). Trisomy 8 is the most frequent numerical chromosomal aberration in AML and occurs at a frequency of 10-15%. Mr. Schrader repeatedly had normal chromosome studies. These findings, alone, greatly favor **de novo** AML/MDS, in his case.

A number of studies, including the Surgeon General's 2004 report, indicate that cigarette smoking may at least double the risk of AML, and other studies suggest the same is true of MDS (25-27). While cigarette smokers are exposed to ten times the amount of benzene non-smokers experience, it is not clear that this is the one of many carcinogens cigarette smokers are exposed to, which causes the disease. A heavy smoker may have a cumulative dose of 5-6 ppm years, but this level of exposure is not considered enough to cause AML. For example, in one recent study of a petrochemical cohort, with mean exposures of 40 ppm years, no statistically significant increase in AML was evident (28). Moreover, the particular features (classification of the type of AML, incidence and type of chromosomal abnormalities, etc.) of smoking-induced AML, remain unknown. Nevertheless, cigarette smoke, both active and passive, may account for the majority of Mr. Schrader's benzene exposure. It is unclear to me, from Mr. Schrader's file, how he could have accumulated a major laboratory exposure to benzene. Pipefitters and mechanics in the petrochemical industries, and in other sections of industry, and who have used lubricating agents containing varying amounts of benzene, and solvents containing some benzene, have not shown a statistically significant increase in the incidence of AML for many years, in developed countries (18-24).

A three year remission from AML is generally considered tantamount to a cure (36). Hopefully, this will be the case with Mr. Schrader. Cigarette smoking, aside from potentially causing AML, has been associated with lessening remission rates in AML and prolonging recovery from chest infections (37). Certainly, he has significant lung disease, and continued smoking will likely cause him further disability in the future.

Thus, in consideration of the rarity of finding a chemical (benzene)-induced AML with normal chromosomes, the rarity of benzene-induced AML in the general petrochemical and other industries for many years, the lack of any information concerning benzene exposures in his personnel file, and the confounding variable of cigarette smoking, it is clear that we must conclude that, in all medical probability, the AML/MDS suffered by Mr. Schrader is without defined causation, as it commonly appears in the general population.

Please let me know if I can supply you with any additional information. I would be pleased to review the bone marrow slides, but there appears to be no dispute about the accuracy of the diagnosis of AML.

Cordially yours,

Ethan A. Natelson, M.D.

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