EXPERT REPORT OF

RICHARD A. PARENT, PHD, DABT, FATS, RAC, ERT

IN THE MATTER OF

[redacted] ***et al.***

VS.

[redacted]**.,** ***et al.***

IN THE

UNITED STATES DISTRICT COURT

DISTRICT OF MINNESOTA

CAUSE NO. [redacted]

CONSULTOX, LIMITED

DAMARISCOTTA, MAINE

JANUARY 10, 2007

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QUALIFICATIONS

I, Richard A. Parent, PhD, DABT, FATS, RAC, ERT, am a board certified toxicologist with over 12 years' experience in the field of industrial toxicology and an additional 23 years' experience in litigation support for both the plaintiff and the defense. I have testified in local and federal courts as an expert in toxicology and have given expert testimony in the disciplines of toxicology and chemistry. During my career, I have spent 10 years in research on organic chemicals at American Cyanamid Company. In the field of toxicology, I have initiated and carried out an active program in product safety relating to toxicology for the Xerox Corporation. I have directed two contract toxicology laboratories: Food and Drug Research Laboratories, Inc. and Gulf South Research Institute, Life Sciences Division. In 1984, I established Consultox, Limited, a toxicology consulting firm, and have since consulted in product safety for various industries and have designed toxicology studies to assess the safety of materials being considered for use in various products. For litigants, I have provided toxicological support and have addressed causation issues for the plaintiff as well as the defense. I am board certified by the American Board of Toxicology, the Academy of Toxicological Sciences, and the Regulatory Affairs Professional Society. I am a recognized expert in toxicology in France and the European community. I present myself to the Court as an expert in the fields of toxicology and chemistry. For the Court's information, I offer my curriculum vitae in Appendix A and a listing of my testimony in past depositions and trials in Appendix B.

MATERIALS REVIEWED

- Literature references cited in this report (See Appendix C)
- API Toxicological Review, Benzene, September 1958 by Marshall Clinton, M.D. under direction of Prof. Philip Drinker; Harvard
- Chemical Safety Data Sheet SD-2, Benzene: 1960, third revision; MCA
- National Safety Council MSDS for Benzene, Data Sheet D-308; 1950
- Testimony of Claiborne D. Smith, Environmental and Training Manager for the DuPont Company at a Public Hearing on the Proposed Amendment for Occupational Exposure to Benzene before the Occupational Safety and Health Administration, dated May 24, 1978, in Washington DC
- OSHA, "Occupational Exposure to Benzene", Emergency Temporary Standards; Hearing; published in Federal Register, May 3, 1977, and May 27, 1977
- OSHA "Occupational Exposure to Benzene, Occupational Safety and Health Standards", Federal Register, vol 43, no 29, pp 5918-, Friday February 10, 1978; Part II
- OSHA, "Exposures to Benzene Liquid Mixtures", Amendment to Rule; Federal Register, vol 43, no 124, June 27, 1978; Part III
- "A Survey of Methods and Instrumentation for the Analysis of Benzene in the Workplace Air"; prepared for NIOSH, April 1972
- Final Report "A Study of Possible Associations Between Exposure to SBR Processes and Mortality from Leukemia and Related Diseases Based on Toxicologic,

Industrial Hygiene, and Epidemiologic Considerations" (for workers in the 1964 Cohorts and deaths from 1964 to 1973); Occupational Health Studies Group, School of Public Health, by John Taulbee, *et al.* Univ. North Carolina, July 1976

- Report on Studies Investigating the Relationship of Cancers of the Lymphatic and Hematopoietic Systems to Work-Environment Exposure within the Firestone Tire and Rubber Company; A. J. McMichael, MD, PhD, *et al.*, School of Public Health, Univ North Carolina, September 1974
- Letter from Norton Nelson of NYU Medical Center to Eula Bingham of OSHA dated August 9, 1977, describing findings of leukemia in animal models treated with benzene
- "Criteria for a recommended standard . . . Occupational Exposures to Benzene; CDC/NIOSH; HEW Publication No (NIOSH) 74-137, 1974; 10 ppm, 25 ppm ceiling
- OSHA "Economic Impact Statement, Benzene"; Vol I, US DOL, May 1977
- Threshold Limit Documents from the American Conference of Governmental Industrial Hygienists for 1958; (benzene, 25 ppm); for 1974 (intended change to 10 ppm)
- Copy of Complaint dated September 12, 2005
- Deposition of [redacted] taken June 5, 2006
- Medical records of [redacted] from January 1, 2001, to May 20, 2005
- Various Material Safety Data Sheets, labels from products and product information brochures from [redacted]
- Plaintiffs' Objections and Responses to Defendants' Master Set of Interrogatories and Requests for Production dated January 10, 2006
- [redacted]Inc's Objections and Responses to Plaintiffs Request for Production dated July 26, 2006
- [redacted] Inc's Objections and Responses to Plaintiffs' Request for Production dated July 27, 2006
- Defendant [redacted]Company's Responses to Plaintiffs' June 15, 2006, Request for Production of Documents dated October 18, 2006
- Defendant [redacted]Chemical Company's Answers to Plaintiffs' Interrogatories undated
- Deposition of [redacted] taken on October 31, 2006
- Deposition of [redacted] taken on December 12, 2006
- Expert report of [redacted], PhD, dated January 6, 2007

INTRODUCTION

Initially, I will describe some of the findings of peer-reviewed, published literature causally relating leukemias to benzene exposure in man and provide some information on supportive studies in experimental models involving animals. Upon completion of this brief summary of the literature, I will present a formal causation analysis using the Hill criteria, after which I will describe relevant information on Mr. [redacted], the

plaintiff in this case. I will conclude with a discussion of the relationships between the plaintiff's exposures to benzene and his diagnosed acute myelogenous leukemia (AML), culminating with my opinion on specific causation.

BENZENE

General

The literature I have reviewed provides me with sufficient scientific information about benzene to make an informed expert opinion on the potential for causal connections between benzene exposure and blood dyscrasias.

In 1985, Aksoy[1] made the following statement, "Today there seems to be sufficient data to incriminate benzene as a potent carcinogenic agent causing leukemia, malignant lymphoma, multiple myeloma, and lung cancer". Goldstein and Shalat[2] recently stated: "Within a few years, it became overwhelmingly obvious that benzene in fact does cause acute myelogenous leukemia and there is now virtually no argument regarding benzene as a known cause of cancer in humans". I will provide some support for these bold statements in the discussions below. In addition, there are many reviews on the subject that may be of some interest.[1,3-22]

Exposure Scenarios

Since benzene is a volatile solvent, it would appear obvious that the most likely mode of exposure would be via inhalation of benzene vapors. This is indeed the case;[23] however, "Several recent studies, both in animals and in humans, conclusively demonstrate that benzene is absorbed through the skin".[23] One study suggests that dermal absorption may contribute as much as 10-25% to a worker's total dose of benzene.[18] Although dermal absorption of benzene has been known long before 1950[24], recent studies have provided more definitive data.[23,25-32] One study in guinea pigs reported that benzene passed through the skin at the rate of 0.4 mg/cm^2.[33] Based on this information, it becomes clear that when considering a worker's exposure to benzene, dermal contact must be a factor in assessing total exposure.

Symptomatology

Benzene is an intermediate and solvent that has been in use for many years. As with other solvents, inhalation of elevated levels of benzene can result in headaches,[3,4,34-36] lassitude,[4,36] weakness,[4,34,35] nausea,[3,36] staggering gait,[3] loss of appetite,[34,35] paralysis,[3] convulsions,[3] unconsciousness,[3] pallor due to anemia,[34,35] bleeding from nose,[34,35] and other effects.

Historical Perspective

The hematotoxicity of benzene has been known for a long time, "Benzene has been a known hematological poison since the nineteenth century".[4] "It [benzene] has been recognized as an industrial carcinogen since 1928",[21] resulting from the discovery of acute lymphoblastic leukemia in a worker exposed to benzene for five years.[37] A 1920 publication describes leukopenia, a potential precursor to leukemia, in rabbits exposed to benzene,[38] while a 1932 publication describes a leukemia resulting from benzene exposure.[39] A 1950 scientific publication describes aplastic anemia and agranulocytosis as a result of chronic benzene poisoning,[24] while an even earlier publication in 1942 cited anemia, aplastic anemia, eosinophilia, and leukocytosis from benzene exposure.[40]

As part of an American Petroleum Institute Review of benzene in 1948, the following statement appears ". . . reasonably well documented instances of the development of leukemia as a result of benzene exposure have been cited".[41] In 1950 the National Safety Council published the following comment, "Chronic benzene poisoning affects the blood and blood-forming organs producing serious degeneration in bone marrow".[42] Interestingly, a recent publication by a respected scientist who has long been familiar with the toxicity of benzene suggests that petrochemical industry representatives have often withheld information and misinterpreted positive information on the toxicity of benzene even from their own research.[43]

The quotes above-referenced are a very small number of the many very old scientific papers which show that the blood and bone marrow are the target tissues of benzene and that it should be no surprise to anyone that benzene causes the blood dyscrasias which are the subject of this report.

Bone Marrow as a Target Organ

It should be noted at this point that benzene is a well known human leukotoxin,[11,44-47] producing leukopenia in man;[34,35,40,48] and this topic will be discussed at greater length in the sections of this report that follow. Numerous accounts of hematotoxicity have been related to benzene exposure[3] resulting in the following published statements, "Benzene is a potent bone marrow toxin in animals and man";[49] "Epidemiological evidence has shown that benzene is a potent hematotoxin and leukemogenic agent in humans";[50] and "Occupational exposure to benzene has long been associated with bone marrow depression and an increased incidence of blood dyscrasias including leukopenia, lymphocytopenia, thrombocytopenia, pancytopenia, leukemia and lymphoma".[51] A more recent quote states ". . . the causal relationship between benzene and acute myelogenous leukemia is unequivocal."[52]

Other more recent studies have confirmed the increased risk of leukemia related to benzene exposure including Chinese[53] and Australian[54-56] studies of industrial exposures, exposures in a rubber plant,[57,58] an oil and gas plant,[59] a shipyard,[60] and

environmental exposure.[61] Case reports describe use of gasoline to degrease automobile parts resulting in two cases of AML[62] and eight cases of AML in South Korea where mean benzene exposure concentration was 0.094 ppm.[63] Some of the other studies cited above also suggest that low concentrations of benzene produces an increased leukemia risk. The 2005 environmental study cited[61] was carried out in a city where the average exposure to benzene (0.002 ppm) resulted in an increased risk of leukemia. One of the Australian nested case-control studies of the petroleum industry based on 33 leukemias and exposures over 20 years reported statistically significantly elevated risks (odds ratio[OR] = 51.9 (ss) [statistically significant]) of leukemia in those exposed to greater than 16 ppm-years or 0.8 ppm.[54] A cohort study of the oil and gas industry was based on 72 cases of leukemias and 285 matched controls where the cumulative exposure to benzene was at or equal to 16.8 ppm-years resulted in an increased risk of leukemia (OR = 3.6 (ss)), and a dose response relationship was noted with an OR = 1.2 (ss) per 10 ppm-years of exposure.[59] In 2002, Silver, *et al.*[57] reported on benzene-related Standard Mortality Ratios (SMRs) for leukemia in a rubber plant as high as 13.55 (ss), while in the same year, Rinsky, *et al.*[58] reported SMRs for leukemia of 3.37 (ss) and 2.56 (ss) in another rubber plant and attributed this increased incidence of disease to exposure to benzene.

Recent reviews relating benzene exposure to AML and other leukemias have appeared in the literature.[64-68] One review of nine cohort and 13 case-control studies showed AML risks related positively to benzene dose across all studies.[69] Another review points out that only benzene and ionizing radiation have been demonstrated conclusively to be carcinogenic to the hematopoietic system.[70]

Myelogenous Leukemias in Man

From the many reviews on the subject,[1,3-22] it becomes clear that the most frequent blood dyscrasia related to human exposure to benzene is acute myelogenous leukemia (AML) and its precursor, myelodysplastic syndrome (MDS).[71,72] From some of the references, we have noted increased incidences of AML related to benzene exposure,[26,73] including increased risk of MDS,[20,26,74-82] a precursor to AML.[26,71,72] Still other studies demonstrate this increased risk. One study of workers exposed to 1 to 30 ppm benzene for 8 to 9 years reported a risk ratio for AML of 3.75 (ss),[83] while another study reported an SMR of 337(ss) for leukemias[84] and increasing SMRs with dose of benzene rising as high as 6,637 (ss) in the highest exposure group.[84] Still other reports relate an SMR of 444 for AML related to benzene exposure[85] and a RR of 3.6 (ss) in Swedish service station attendants exposed to benzene.[86] Aksoy, *et al.* reported increased incidences of AML in Turkish shoe workers.[87]

Many reports in the literature cite epidemiology studies that report data based on total leukemias including AML and chronic myelogenous leukemia (CML). This includes a study by Hayes, *et al.*[26] showing a statistically significant (ss) relative risk (RR) of 2.6 for total leukemias; a study by Fu, *et al.*[88] reporting standard mortality ratios (SMRs) of 536

(ss) and 245 (ss); an American Petroleum Institute study by Paxton, *et al.*[89] who reported SMRs of 2.38 to 3.81 (ss); a study by Ireland, *et al.*[90] reporting an SMR of 2.3 with 95% confidence intervals (CI) of 0.7 to 5.3; a study of shoe workers showing a risk ratio of 2.2 (ss) by Askoy, *et al.*[91]; studies by Rinsky, *et al.*[84] reporting an SMR of 337 (ss), and 2,100 (ss) for those employed more than five years,[92] and 6,639 (ss) for those exposed to benzene for more than 400 ppm-years;[84] studies by Yin, *et al.*[80,93] reporting an SMR of 5.74 (ss) and an RR of 2.6 (ss) for leukemia in Chinese workers; a study by Ciccone, *et al.*[81] reporting an odds ratio (OR) of 1.7 (ss) for leukemia resulting from benzene exposure; a study by Infante *et al.*[94] reporting an OR of 1.38 (ss); an additional study by Paxton, *et al.*[95] describing an SMR of 3.6 (ss) and finally an Australian study[96] which reported a standardized incident ratio (SIR) of 2.8 (ss) and an SMR of 2.0 (ss).

The continuing retrospective cohort study of 26,319 benzene workers in China cited above[97] reported 32 cases of leukemia of which 23 were AML and 7 were chronic myelocytic leukemia (CML) with a mean latency period of 11.4 years versus 4 cases of leukemia in the matched control population. Another retrospective epidemiology study of benzene exposure in "Pliofilm" production plants reported 7 deaths from leukemia whereas only 1.4 were expected.[94] Four of the seven deaths were defined as AML.[94,98] In a follow-up of the same cohort, an SMR of 560 ($p<0.001$) for leukemia deaths was reported and included cases of AML. In another follow-up study,[89] combined leukemias and multiple myelomas were still elevated, and dose-related relationships were established. When workers were exposed to benzene for five or more years, the SMR increased to 2,100.[92] In reviewing many of these studies, the Agency for Toxic Substances and Disease Registry (ATSDR) in its draft Toxicological Profile for Benzene made the following statement, "Case reports and epidemiological studies of workers have established a causal relationship between benzene exposure and acute myelogenous leukemia".[3]

It is clear that the epidemiological information cited above leaves little doubt that there is a strong causal connection between exposure to benzene and the development of blood dyscrasias, including the myelogenous leukemias.

Animal Studies

The most definitive information regarding the potential for a causal relationship between benzene exposure and various types of malignant blood dyscrasias, including leukemias, multiple myelomas, and lymphomas, comes from studies in man. Many of these studies are cited above. Much has been done to assess the hematopoietic toxicity of benzene in animals, and some of that work is presented below.

The fact that benzene is carcinogenic in mice and rats has been well described.[99-101] Sprague-Dawley rats treated by gavage with benzene showed Zymbal gland tumors, hemolymphoreticular neoplasias, and mammary carcinomas.[102-103] Other tumors have been noted as a result of benzene inhalation studies.[104] Some studies have even

reported leukemias and lymphomas in animals;[4,100,105-107] see also studies cited in OSHA Final Rule document.[23]

There is little doubt that the hematopoietic system is a primary target organ for benzene. The target effects have been described as having "adverse hematological effects in animals"[50] and "a potent bone marrow toxin in animals and man".[49] Consistent with observations in humans,[34,35,40,48] leukopenia, lymphomas, and other blood dyscrasias have been reported in animals.[3,108] Dogs,[109-110] rats,[48,110,111] guinea pigs, rabbits, and monkeys[112] have been reported to show leukopenia as a result of being treated with benzene. Thymic lymphomas, a 15% incidence, have been reported in C57B1 mice.[100] Other lymphomas have been reported in another study.[105] Malignant lymphomas were reported also in mice studied by the National Toxicology Bioassay Program.[107] Other hematopoietic dysplasias noted in animals include lymphocytopenia, anemia, and bone marrow hypoplasia in rats and mice exposed to benzene;[51,100,113] stem cell suppression in mice;[101,114] and reduced numbers of total bone marrow cells, progenitor cells, differentiating hematopoietic cells, and most blood parameters reported in a Chemical Institute of Toxicology study of the effects of benzene on B6C3F1 mice. These studies clearly demonstrate that the bone marrow is a target tissue for benzene.[115] These are only a few of the published studies which support a causal link between benzene exposure and various blood dyscrasias. For descriptions of additional studies, refer to reviews by OSHA and NIOSH.[3,23]

Considering the information cited above and statements such as, "Today there seems to be sufficient data to incriminate benzene as a potent carcinogenic agent causing leukemias, malignant lymphoma, multiple myeloma and lung cancer";[1] and "Within a few years, it became overwhelmingly obvious that benzene does in fact cause acute myelogenous leukemia and there is now virtually no argument regarding benzene as a known cause of cancer in humans";[2] and "Epidemiological evidence has shown that benzene is a potent hematotoxin and leukemogenic agent in humans",[50] it is my opinion within a reasonable degree of scientific certainty that there exists a clear causal association between benzene and various blood dyscrasias, including acute myelogenous leukemia. Additional support for these conclusions may be found in the many reviews which have been published.[1,3-22,52,64-70]

CAUSATION - THE HILL CRITERIA

A. B. Hill[116] describes criteria for establishing general causation. These criteria have been refined somewhat since his original paper but have not changed significantly. The Hill criteria are widely accepted, and the International Agency for Research on Cancer uses many of these criteria as part of their classification scheme for carcinogens. The Hill criteria apply to human studies and propose a set of requirements to be met in order to establish causation. Some of the criteria allow for the use of data from controlled animal studies in order to establish the target organs and mechanisms of

action of particular toxicants. We will apply this criteria to the possible establishment of a causal connection between occupational exposure to benzene and the acute myelogenous leukemia suffered by Mr. [redacted]

1. Strength of Association

The essence of this criteria involves an assessment of the extent to which a particular disease coincides with a particular exposure. The incidence of the disease does not have to be high in order to establish a strong association. In the case of a rare disease, the finding of even a few cases within a small population who have been treated with a particular drug would be of great significance.

In the discussions above, I have clearly established a causal connection between benzene and acute myelogenous leukemia. Some of the pertinent human data to illustrate the strength of this causative connection are reiterated below.

A Standard Mortality Ratio (SMR) for leukemia has been reported to be 5.74 after exposure to about 25 ppm for about 9 years,[97] and risk ratios (RRs) have been reported as 3.2,[117] 2.26 in shoe workers,[87,118] and 2.5 in Chinese benzene workers.[26] In an earlier Chinese study, an SMR of 574 was reported for leukemia. Other reports include elevated SMRs for lymphosarcomas, myeloid leukemias, and lymphatic leukemias,[119] RRs 3.1 for AML, RRs of 3.75,[83] an SMR of 560[92] for AML, and 3.93 for lymphatic and hematopoietic cancers in benzene workers.[97] One study reported an SMR of 2,100 for AML in those exposed to benzene for more than 5 years.[92] For total leukemias related to benzene the following statistically significant findings have been cited in the peer-reviewed literature: RRs of 2.6,[26] 2.2,[91] 1.7,[84] 2.6;[80] SMRs of 536 and 245,[88] 2.0,[96] 2.38 to 3.81,[89] 337,[84] 2,100,[92] 6,637,[84] 5.74,[93] 3.6;[95,120] ORs of 1.7,[81] 1.38;[94] and a reported SIR of 2.8.[96] A 1996 Chinese cohort study of 74,828 benzene-exposed workers and 35,805 unexposed controls followed from 1972 to 1987 reported statistically significant excesses of leukemias and a RR of 2.3 (ss).[121]

A recent study by Glass, *et al.*[56] resulted in a OR of 11.3 (ss) in workers exposed to 8 ppm-years cumulative exposures, and a recent study done in Shanghai involving a case-control design with 486 leukemia cases and 502 controls reported an OR of 1.7 (ss) for association with benzene exposures.[122] An Italian study published in 2003 reports the calculation of an SMR of 7.0 (ss) in workers exposed to a cumulative exposure 200 ppm-years.[123] Studies published in the past few years continue to show elevated ORs and SMRs attributable to benzene exposures. [53-61] In reviewing this data, the

International Agency for Research on Cancer (IARC) finds sufficient evidence for carcinogenicity of benzene in man, particularly for leukemia.[5,124,125] I, too, find the evidence to be convincing.

2. Consistency of Association

Hill[116] asks the question, "Has it been repeatedly observed by different persons, in different circumstance and times?" In other words, have similar findings been observed by different observers in different situations? This criteria tends to rule out other possible causes that may be related to a specific situation.

While I have cited many studies which report elevated rates of hematopoietic cancers related to benzene exposure, there are also industry-sponsored studies in which the authors attempt to show that no relationship exists between hematopoietic cancers and benzene exposure.[117,126-132] It might appear that this information would somewhat cloud the issue of consistency; however, a closer look reveals data that supports causal links between benzene exposure and hematopoietic cancers. For example, Wong, a consultant for the petrochemical industry and the Chemical Manufacturers Association, reports a relative risk of 3.93 for lymphatic and hematopoietic cancers and even demonstrates a dose-response relationship.[117] Many of the industrial studies demonstrate less than significant RRs and SMRs because of the healthy worker effect where the disease incidence in workers is generally lower than that in an overall population and because some of the studies were designed to look only at populations with very minimal exposure to benzene. In 2006 Infante[43] published a manuscript suggesting that the petrochemical industry withheld information about benzene and even misinterpreted some of its positive findings.

There is certainly a preponderance of studies demonstrating causal relationships between hematopoietic lesions such as leukemias and benzene exposure.[3,6,26,73,87,89-91,93,117-119,133-138] Goldstein and Shalat,[2] commenting on Exxon-sponsored studies by Wong and Raab[3] and Thorpe,[129] state that, ". . . there is now virtually no argument regarding benzene as a known cause of cancer in humans". Regarding the Thorpe study, ". . . includes many individuals who have only minimal exposure to benzene making it very difficult to detect a proven benzene effect." Even considering the attempts to discredit a causal connection between benzene and human hematopoietic cancers, the published data is clearly consistent with such a causal connection.

3. Specificity of Association

The specificity of an association describes the precision with which the occurrence of one variable will predict the occurrence of another. This criterion overlaps the strength of association to some extent but focuses more on the direct link between a specific disease and a specific cause for that disease. When dealing with human populations, this specificity is rare. Consider, for example, the well established association between vinyl chloride exposure and angiosarcoma of the liver, a rare disease.[139-142] It did not take observers much time to realize that the few cases of angiosarcoma observed at a vinyl chloride plant were noteworthy because of the rarity of the lesions.

In the case of benzene exposure, we are dealing with a specificity that is quite pronounced. Benzene attacks the hematopoietic system which resides, in part, in the bone marrow. In man alone, there are many very early reports of benzene causing hematotoxicity,[34,35,40,48] including the statement that "Benzene has been a known hematological poison since the nineteenth century.[4] A 1950 statement by the National Safety Council states, "Chronic benzene poisoning affects the blood and blood-forming organs producing serious degeneration in bone marrow.[71] Many other publications describe benzene as a hematotoxin in both man and in animals.[3,11,21,24,34,37-39,41,44,45,47-51,100,101,108-114] Thus, it is clear that although it may produce other systemic effects, benzene targets blood and bone marrow resulting in a predictable sequence of events leading to cancer of the blood in the form of leukemias, lymphomas, and myelomas. A recent review by Descatha, *et al.*[70] suggests that only benzene and ionizing radiation have been identified as causative agents in cancer of the hematopoietic system in man.

4. Temporality

Hill[116] asks "Which is the cart and which is the horse?" If a disease state exists prior to exposure to a medication, the exposure may exacerbate the disease but may not have caused the disease. The appearance of a diseased state must follow treatment with the medication or exposure to the toxicant being addressed.

While one can easily see from the studies cited in the literature, exposure clearly preceded the observed disease state. One of the premises for conducting epidemiology studies is the elimination of those subjects having preexisting conditions prior to the exposure being studied; thus, temporality is a requirement of any scientifically sound epidemiology study. In addition, animal studies cited herein also demonstrate temporal responses with regard

to hematotoxic effects resulting from treatment with benzene; thus, temporality is a "given" in the studies cited.

5. Biological Gradient

Dose-response is the foundation of good toxicological studies. The higher the dose or the longer the treatment, the more severe the response or the more prevalent the response. Dose cannot only be expressed as a single dose producing an acute response, but also by specifying the daily dose and treatment period. The latter is more appropriate in this situation.

Several studies mentioned herein describe dose-related responses to benzene exposure. A retrospective cohort study of benzene exposure reported a dose-response relationship for risk of leukemia,[93] while another study reported relative risks (RR) for ANLL (Acute Non-Lymphatic Leukemias) including the myelogenous leukemias, increasing from 3.2 for exposure to <10 ppm benzene, to 5.1 for exposures between 10 and 24 ppm, and 7.1 for exposures exceeding 25 ppm benzene.[26] One study which reported on SMRs for combined leukemias and multiple myelomas demonstrated dose-response relationships from three prior studies citing SMRs as high as 20.[89]

A recent report by Glass, *et al.*[56] demonstrated a dose-related increased risk of leukemia beginning at cumulative exposures above 2 ppm-years with an OR of 11.3 (ss) in those with greater than 8 ppm-years cumulative exposures. Another recent study, a population-based, case-control study of 486 leukemia cases compared to 502 unexposed controls, reported a dose-response relating duration of exposure to benzene and leukemia.[122] A recently published Italian study reported a progressive increase in SMR in a cohort of 1,687 men with cumulative exposures beginning at 40 ppm-years to 200 ppm-years.[123]

A study of Swedish seamen involved with the transport of benzene showed a dose-related increase in lymphatic and hematopoietic malignancies related to benzene exposure.[143] Chemical workers exposed to benzene also demonstrated dose-related increases in lymphatic and hematopoietic cancers.[117] SMRs for deaths related to leukemia or acute myelogenous leukemia increased from 560 to 2,100 when the exposure period was extended for five or more years.[92] In another study, SMRs were found to increase in the following sequence related to benzene dose levels: 109, 322, 1,186, 6,637.[84] Delzell, *et al.*[144] was able to show that relative risk of NHL increased with length of employment. More recent publications describe this relationship between benzene exposures and leukemias.[59,68,69] These are only a few of the many dose-related increases in blood-related diseases linked to

benzene exposure. Refer to an OSHA document for more in-depth discussions and comments on dose-response relationships between benzene and blood dyscrasias.[23]

6. Plausibility/Coherence

Hill[116] defines plausibility as biological plausibility based on the level of timely scientific knowledge; however, if the concepts presented are new, they should not be dismissed out of hand. They should be considered within the scope of current scientific knowledge and concepts. He states the following with regard to coherence, ". . . the cause and effect interpretation of our data should not seriously conflict with generally known facts of the natural history or biology of the disease".

The hypothesis considered in this report is that benzene causes leukemia and other dysplasias of the blood and blood-forming elements. Hypotheses based on sound scientific principles should be presented to explain the phenomena under consideration to demonstrate the logic in the causal conclusions being reached. It is desirable to provide experimental evidence to support the hypothesis. In essence, does the hypothesis make sense? Yes, it does. Is it consistent with current scientific knowledge? Yes, it is.

As a way of demonstrating both the plausibility and coherence of the stated hypothesis, it may be appropriate to address possible mechanisms which may explain the toxicity and carcinogenicity of benzene as it pertains to the hematopoietic system. Benzene is lipophilic and therefore concentrates in tissues that have high fat content including the bone marrow.[21] Benzene has been shown to be metabolized in the liver by a specific isoenzyme, CPY2E1, to one or more reactive metabolites which are transported to the target tissue including bone marrow.[145,146] Benzene oxide is considered to be a possible reactive intermediate.[145,146] Activation of benzene is required for the development of both cytotoxicity and genotoxicity.[73] Once the reactive benzene metabolites reach the bone marrow, further metabolism is thought to occur as a result of myeloperoxidase, resulting in p-benzoquinone or the semiquinone radical.[21] Depression of bone marrow function results from induction of apoptosis (programmed cell death) in hematopoietic cells and through effects of these reactive metabolites on stromal macrophages. Prostaglandin E2 also is increased within the bone marrow resulting in a down regulation of hematopoiesis.[21]

In addition to these epigenetic events, benzene, through its reactive metabolites induced mutagenic and chromosomal events[147] which led to the OSHA statement, ". . . benzene exposure is also clearly associated with

chromosomal damage".[23] Supporting this statement are many studies which demonstrate this relationship.[148,149] Chromosomal aberrations, sister chromatid exchanges, and micronucleii have been observed in lymphocytes of benzene exposed workers.[150] Other perspectives on the mechanism of induction of leukemia by benzene include the suggestion that benzene initiates cancer by forming ortho-quinones that react with DNA in cells and generate mutations that lead to cancer;[151] that p-benzoquinone, a benzene metabolite, damages DNA by forming exocyclic base adducts which are highly mutagenic;[152] and that the repair mechanism proceeds by a unique mechanism.[153]

In rats, benzene exposure has been reported to show increased incidences of Sister Chromatid Exchanges (SCEs) and micronuclei,[154,155] micronuclei and chromosomal aberrations in mice,[154,155] high incidence of chromosomal aberrations in rabbits,[156] cytogenetic effects in mice,[157] elevated micronuclei in mice and hamsters,[158] increased frequency of SCEs in bone marrow cells and inhibited marrow cellular proliferation in mice,[159] and other cytogenetic effects.[160,161] Other studies in mice suggest a dysfunction of the p53 gene as being involved in the mechanism of leukemia production from benzene exposure,[162] and one study using microarray analysis[163] reports benzene induction of expression of p21, an interlocking counterdevice for cell cycle due to upregulation of p53 thereby inducing the immediate suppression of the kinetics of hemopoietic progenitors followed by the prominent suppression of hemopoiesis leading to leukemia. Others suggest that benzene induced DNA lesions can lead to changes in hematopoietic stem cells that give rise to leukemic clones based on experimentation in mice.[164]

Benzene metabolites studied in human peripheral blood have been shown to produce aneuploidy (gain and loss of chromosomes) which has been suggested as a possible mechanism of leukemia induction.[165]

Several other studies have been carried out in man[23] resulting in chromosomal abnormalities in lymphocytes and bone marrow cells of benzene-exposed workers,[166,167] statistically significantly higher chromosomal aberrations in benzene-exposed rotogravure workers,[168] and other cytogenetic effects in man.[169,170]

We have determined that benzene and its metabolites reach the target tissue resulting in potential down-regulation of hematopoiesis within the marrow and chromosomal damage within the blood-forming elements.
Several possible mechanisms, among others, have been suggested and are described as follows.

1) DNA adducts which represent heritable carcinogenic damage to the somatic cell line
2) Cytotoxicity of benzene metabolites resulting in a compensating proliferation of stem cells
3) Cytotoxic damage to the stromal microenvironment including stromal macrophages causing impairment of ability to regulate stem cell proliferation and differentiation
4) Cytotoxic damage to the immune system, including lymphocytes and stromal macrophages allowing tumor cells to proliferate
5) Chromosomal aberrations in stem cells induced by hydroquinone or benzoquinone resulting in activation of oncogenes.[27]

While the exact mechanism or mechanisms of action of benzene on the bone marrow may not be elucidated at this time, I believe that there is adequate evidence that benzene and its active metabolites affect the bone marrow via several plausible mechanisms resulting in hematotoxicity and malignant transformations. I have described this evidence in terms consistent with current scientific thinking and have not violated any biological principles regarding the origin of the diseases in question since they clearly represent pathological responses to a chemical insult.

7. Experiment

Although human clinical trials are relied upon to establish the efficacy of drugs, and epidemiolgy studies are used in establishing causation relating to adverse drug reactions, animal experimentation is extremely useful in demonstrating concepts used to explain some of the human findings. Studies of the effects of chemicals on cellular processes also have proven useful in being able to understand the mechanisms involved in the toxicological processes being studied.

I have presented convincing evidence that human exposure to benzene results in various hematological lesions including leukemia,[6,23,26,73,87,89-91,93,97,99,117-119,133-138,145,171-175] and acute myelogenous leukemia (AML),[3,84-87,94,98] and I have gleaned from the literature quotations from learned organizations and bodies stating that the fact that benzene causes cancers, including leukemias and lymphomas.[1,5,34,42,49,124,125] These selected statements were based on human data or epidemiological information and a number of animal studies describing blood dyscrasias as a result of treatments with benzene.[3,23,48,50,51,99-107,109-115] Further, I have presented experimental data which show that benzene can be absorbed through the skin.[18,23,24,27-30,33] I have described some experimental work directed toward understanding the mechanisms of action of benzene on the blood forming elements[18,21,73,145] and cytogenetic studies demonstrating the ability of metabolic products of

benzene to cause chromosomal damage.[23,154,155,157-160,161,166-170] In presenting some of the available experimental information on benzene, I have provided a solid foundation to support a causal relationship between benzene and malignant lesions of the bone marrow and blood.

8. Analogy

Are there other drugs, chemicals or conditions that simulate the causal relationship which is under scrutiny? Are there other similar situations that parallel the events relating to the causal connection addressed herein?

There are other chemicals for which I could establish a causal relationship with leukemias and lymphomas, but clearly, the causal relationships established here are the strongest. There are also leukemias and lymphomas that are of genetic origin; however, a familial history of these lesions is usually present in those cases. Some of the alternative causes of these leukemic blood dyscrasias include radiation exposure, pesticide exposure (possible benzene involvement), viruses, alkylating drugs, smoking[176-179] and congenital or genetic origins.[75]

CONCLUSIONS ON GENERAL CAUSATION

At this point, sufficient evidence has been presented to support a causal relationship between benzene and acute mylogenous leukemia. I have quoted statements from the literature including, "There is no doubt about the leukemogenic effect of benzene in man";[118] "Benzene is now recognized as a cause of leukemia in humans . . .";[172] and, "A causal relationship between chronic occupational exposure to benzene and development of leukemia has now been established beyond doubt".[91] I have referenced the conclusions of the International Agency on Cancer indicating that benzene is a human carcinogen.[5,124,125] There should be no doubt about the causal link between benzene and hematopoietic cancer in man.

CASE-SPECIFIC CAUSATION

[redacted]

Mr. [redacted] was born on June 11, 1964, and worked in the printing industry from about 1984 to the present. He worked at [redacted] from about March of 1984 to January of 2000, at [redacted] from April 2000 to July 2000, at [redacted] Company from July 2000 to June of 2003, and at [redacted] from January 2004 to the

present. In all of these jobs, he was employed as a pressman and, as a result of his duties, he was regularly exposed to a number of different products containing aromatic hydrocarbons and petroleum distillates which contained benzene. In his deposition he testified that he would occasionally wear gloves but never a respirator and that he received little if any safety guidance. He was never warned about benzene, and his employers never encouraged him to read the MSDSs or the labels on the containers.

Mr. [redacted]'s father is alive and well at age 84, and his mother previously had died of lung cancer. There is no history of any blood dyscrasias that he is aware of in his family. Mr. [redacted] started smoking when he was 14 years old at a rate of 12-15 cigarettes per day according to his testimony. Mr. [redacted] was diagnosed in September 2001 with acute myelogenous leukemia (AML) at the age of 37 years. At this point in his life, Mr. [redacted] had a 17-year work history as a printer during which time he was continuously exposed to benzene which was a contaminant in many of the solvents used in the printing process and for cleaning the presses. During his time in the printing industry, he did not read material safety data sheets (MSDSs), and, even if he did, there was little on those sheets to reflect any real danger from exposure to benzene. Many of the sheets that I examined from [redacted] did not even mention benzene as a contaminate of any of the solvents except when forced to do so as a result of Proposition 65 in California. Many of the sheets contained the phrase "contains no carcinogens" to further mislead the reader.

In the depositions of [redacted], a chemist for [redacted] International, and [redacted] Chemicals, it has become obvious that neither of these companies made any effort to analyze for benzene. Mr. [redacted] on Page 87 of his deposition alluded to the fact that they used conductivity and refractive index to determine benzene. It should be noted that it is not technically possible to determine benzene as a contaminant in complex mixtures by these techniques. Mr. [redacted] said that they used gas chromatography to analyze their solvents, but on Page 60 of his deposition he admits that they looked for other things using gas chromatography, not benzene. Both Mr. [redacted] did readily admit that benzene is a contaminant in the solvents that are used in their products.

It should be noted that an increased risk of leukemia has been reported in cases of cumulative exposures to benzene as low as 2 ppm-years.[56.] Since Mr. [redacted] had a 17-year work history, that would amount to an average exposure of 0.12 ppm benzene during the time of his employment. These findings would appear to be consistent with another study which reported on 8 cases of AML where the mean benzene concentration was 0.094 ppm,[63] and an environmental exposure study which reported an increased risk of leukemia at a mean concentration of 0.002 ppm.[61] It seems appropriate to note that the National Institutes of Safety and Health (NIOSH) has recommended a time weighted average (TWA) concentration for exposure to benzene of 0.1 ppm and that ". . . benzene be treated as a potential human carcinogen.".[180]

CONCLUSIONS AND OPINIONS

According to the Expert Report by Dr. [redacted], Mr. [redacted] was exposed to benzene from individual products ranging from 13.3 ppm down to 2.1ppm and these estimates, according to Dr. [redacted], are at the lower limits of exposure. Assuming this to be true, and considering the published information cited above, it would appear that Mr. [redacted] was at significant risk of developing AML as a result of being exposed to the products described above. While his smoking may have contributed to his risk for AML, within a reasonable degree of scientific probablity, it is my opinion that the most likely cause of Mr. [redacted]'s AML was his occupational exposure to benzene through his use of defendants' printing chemicals as specified above. I reserve the right to alter the opinions expressed in this expert report should new information become available.

Richard A. Parent, PhD, DABT, FATS, RAC, ERT
CONSULTOX, LIMITED

Date

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