EXPERT REPORT OF

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

IN THE MATTER OF

[redacted] **AND** [redacted]**, PLAINTIFFS**

VS.

SAFETY-KLEEN CORPORATION, SAFETY-KLEEN CANADA, INC., RADIATOR SPECIALTY COMPANY, USX CORP. and HEXCEL CORP.

IN THE

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF VIRGINIA

NORFOLK DIVISION

CIVIL ACTION NO. [redacted]

CONSULTOX, LIMITED

DAMARISCOTTA, MAINE

JULY 22, 2004

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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 20 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 and a separate benzene bibliography (See Appendix C)
- Summary of medical records of [redacted] January 18, 1995 to August 10, 2003 (See Appendix D)
- Summary of medical records of [redacted] May 26, 1988 to August 12, 2003 (See Appendix D)
- Summaries of information relating to the chemical composition of Liquid Wrench and its components (See Appendix E)
- Material Safety Data Sheets on components of Liquid Wrench (See Appendix E)
- Timeline of knowledge relating to the toxicity of benzene with references (See Appendix F)
- Letter Report from [redacted] III, CIH, CSP, PE, DEE to Mr. [redacted] dated July 17, 2004 (See Appendix G)
- Deposition of [redacted] taken July 1, 2003
- Deposition of [redacted] taken on November 8, 2000, with attachments
- Continuation of Wells deposition dated January 25, 2001
- Deposition of [redacted] taken on February 25, 1999
- Deposition of [redacted] dated November 2, 2000 in the matter of B. D. Gregory vs Burlington Northern, Santa Fe *et al.*
- Letter from J. C. Graeber, Supervisor Tech Services, USS Chemicals to Dr. T. Tames of Radiator Specialty Company dated May 25, 1977
- Letter from Frank Sedlack, Manager Tech Service, USS Chemicals to G. K. Kologiski, Chief Chemist, Radiator Specialty Company dated June 10, 1963

- Laboratory report from Solder Seal entitled "Eliminate Benzene from Liquid Wrench No. 1, Standard Formula", dated March 24, 1978
- 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
- NSC MSDS for Benzene, Data Sheet D-308; 1950
- Testimony of [redacted], 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
- Raffinate Purchases from US Steel by Radiator Specialty Company from April 1967 to 1978
- 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; Bates# USS 2120
- OSHA, "Exposures to Benzene Liquid Mixtures", Amendment to Rule; Federal Register, vol 43, no 124, June 27, 1978; Part III; Bates# USS 2184
- "A Survey of Methods and Instrumentation for the Analysis of Benzene in the Workplace Air"; prepared for NIOSH, April 1972; Bates# USS 1739
- 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; Bates# 1758-1808
- 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; Bates# USS 559-600
- 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
- Various reproduction of "Liquid Wrench" labels and cans
- Various Acute Toxicology studies on "Liquid Wrench" by Foster D. Snell, Inc.
- Various documents and presentations made at the International Workshop on Benzene, November 9-11, 1976; Paris, France
- OSHA "Economic Impact Statement, Benzene"; Vol I, US DOL, May 1977 (Bates # USS 690)
- Threshold Limit Documents from the American Conference of Governmental Industrial Hygienists for 1958; (benzene, 25 ppm); for 1974 (intended change to 10 ppm)

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 each of the plaintiffs. I will conclude with a discussion of the relationships between the plaintiffs' exposures to benzene and their diseased states, culminating with my opinion on causation.

BENZENE

General

The scientific 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], and I have included in Appendix F, a timeline of published literature with references relating to the toxic and carcinogenic properties of benzene.

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], more recent studies have provided more definitive data.[23,25-30] One study in guinea pigs reported that benzene passed through the skin at the rate of 0.4 mg/cm^2.[31] 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. It may be appropriate at this point to examine an Expert Report by [redacted] III, which is attached as Appendix G and describes in some detail the exposures experienced by the Plaintiffs in this case, Mr. [redacted] and Mr. [redacted]

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,[3,4,32-34] lassitude,[4,34] weakness,[4,32,33] nausea,[3,34] staggering gait,[3] loss of appetite,[32,33] paralysis,[3] convulsions,[3] unconsciousness,[3] pallor due to anemia,[32,33] bleeding from nose,[32,33] 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.[35] A 1920 publication describes leukopenia, a potential precursor to leukemia, in rabbits exposed to benzene,[36] while a 1932 publication describes a leukemia resulting from benzene exposure.[37] 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.[38]

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".[39] 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".[40]

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. Further details about timely knowledge relating to the hematotoxicity of benzene are presented in a timeline found in Appendix F.

Bone Marrow as a Target Organ

It should be noted at this point that benzene is a well known human leukotoxin,[11,41-44] producing leukopenia in man;[32,33,38,45] 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";[46] "Epidemiological evidence has shown that benzene is a potent hematotoxin and leukemogenic agent in humans";[47] 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".[48]

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).[49,50] From some of the references, we have noted increased incidences of AML related to benzene exposure[26,51] including increased risk of MDS,[20,26,52-60] a precursor to AML.[26,49,50] 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),[61] while another study reported an SMR of 337(ss) for leukemias[62] and increasing SMRs with dose of benzene rising as high as 6,637 (ss) in the highest exposure group.[62] Still other reports relate an SMR of 444 for AML related to benzene exposure[63] and a RR of 3.6 (ss) in Swedish service station attendants exposed to benzene.[64] Askoy *et al.*[65] reported increased incidences of AML in Turkish shoe workers.[65]

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.*[66] reporting standard mortality ratios (SMRs) of 536 (ss) and 245 (ss); an American Petroleum Institute study by Paxton *et al.*[67] who reported SMRs of 2.38 to 3.81 (ss); a study by Ireland *et al.*[68] 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.*[69]; studies by Rinsky *et al.*[62] reporting an SMR of 337 (ss), and 2,100 (ss) for those employed more than five years,[70] and 6,639 (ss) for those exposed to benzene for more than 400 ppm-years;[62] studies by Yin *et al.*[58,71] 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.*[59] reporting an odds ratio (OR) of 1.7 (ss) for leukemia resulting from benzene exposure; a study by Infante *et al.*[72] reporting an OR of 1.38 (ss); an additional study by Paxton *et al.*[73] describing an SMR of 3.6 (ss) and finally an Australian study[74] 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[75] 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.[72] Four of the seven deaths were defined as AML.[72,76] 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,[67] 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.[70] 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 is 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.[77-79] Sprague-Dawley rats treated by gavage with benzene showed Zymbal gland tumors, hemolymphoreticular neoplasias, and mammary carcinomas.[80-81] Other tumors have been noted as a result of benzene inhalation studies.[82] Some studies have even reported leukemias and lymphomas in animals;[4,78,83-85] 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"[47] and "a potent bone marrow toxin in animals and man".[46] Consistent with observations in humans,[32,33,38,45] leukopenia, lymphomas, and other blood dyscrasias have been reported in animals.[3,86] Dogs,[87-88] rats,[45,88,89] guinea pigs, rabbits, and monkeys[90] 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.[78] Other lymphomas have been reported in another study.[83] Malignant lymphomas were reported also in mice studied by the National Toxicology Bioassay Program.[85] Other hematopoietic dysplasias noted in animals include lymphocytopenia, anemia, and bone marrow hypoplasia in rats and mice exposed to benzene;[48,78,91] stem cell suppression in mice;[79,92] 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.[93] 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]

CONCLUSIONS

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".[47] It is my opinion within a reasonable degree of scientific probability that there exists a clear causal association between benzene and various blood dyscrasias including acute and chronic myelogenous leukemia and that the bone marrow is a primary target for benzene toxicity. Additional support for these conclusions may be found in the many reviews which have been published.[1,3-22]

CAUSATION - THE HILL CRITERIA

A. B. Hill[94] 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 leukemias diagnosed in [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 the myelogenous leukemias. 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,[75] and risk ratios (RRs) have been reported as 3.2,[95] 2.26 in shoe workers,[65,96] 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,[97] RRs 3.1 for AML, RRs of 3.75,[61] an SMR of 560[70] for AML, and 3.93 for lymphatic and hematopoietic cancers in benzene workers.[75] One study reported an SMR of 2,100 for AML in those exposed to benzene for more than 5 years.[70] 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,[69] 1.7,[62] 2.6;[58] SMRs of 536 and 245,[66] 2.0,[74] 2.38 to 3.81,[67] 337,[62] 2,100,[70] 6,637,[62] 5.74,[71] 3.6;[73,98] ORs of 1.7,[59] 1.38;[72] and a reported SIR of 2.8.[74] 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.[99]

A recent study by Glass *et al.*[100] 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.[101] 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.[102] In reviewing this data, the International Agency for Research on Cancer (IARC) finds sufficient evidence for carcinogenicity of benzene in man, particularly for leukemia.[5,103,104] I also find the evidence to be convincing.

2. Consistency of Association

Hill[94] 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.[95,105-111] 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.[95] 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.

There is certainly a preponderance of studies demonstrating causal relationships between hematopoietic lesions such as leukemias and benzene exposure.[3,6,26,51,65,67-69,71,95-97,112-117] Goldstein and Shalat,[2] commenting on

Exxon-sponsored studies by Wong and Raab[3] and Thorpe,[108] 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.[118-121] 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,[32,33,38,45] 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.[49] Many other publications describe benzene as a hematotoxin in both man and in animals.[3,11,21,24,32,35-37,39,41,42,44-48,78,79,86-92] 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.

4. Temporality

Hill[94] 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. In the cases of Mr. [redacted] and Mr. [redacted] we have demonstrated appropriate temporality in that their work histories and exposures preceded their development of leukemias, and the agent to which they were exposed, benzene, clearly was involved in their early exposures as indicted in Appendix G.

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,[71] 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.[67]

A recent report by Glass *et al.*[100] 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.[101] 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.[102]

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.[122] Chemical workers exposed to benzene also

demonstrated dose-related increases in lymphatic and hematopoietic cancers.[95] 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.[70] In another study, SMRs were found to increase in the following sequence related to benzene dose levels: 109, 322, 1,186, 6,637.[62] Delzell *et al.*[123] was able to show that relative risk of NHL increased with length of employment. These are only a few of the many dose-related increases in blood-related disease 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[94] 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.[124,125] Benzene oxide is considered to be a possible reactive intermediate.[124,125] Activation of benzene is required for the development of both cytotoxicity and genotoxicity.[51] 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[126] 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. In rats, benzene exposure has been reported to show increased incidences of Sister Chromatid Exchanges (SCEs) and micronuclei,[127,128] micronuclei and chromosomal aberrations in mice,[127,128] high incidence of chromosomal aberrations in rabbits,[129] cytogenetic effects in mice,[130] elevated micronuclei in mice and hamsters,[131] increased frequency of SCEs in bone marrow cells and inhibited marrow cellular proliferation in mice,[132] and other cytogenetic effects.[133,134] Several studies have been carried out in man[23] resulting in chromosomal abnormalities in lymphocytes and bone marrow cells of benzene-exposed workers,[135,136] statistically significantly higher chromosomal aberrations in benzene-exposed rotogravure workers,[137] and other cytogenetic effects in man.[138,139]

Thus, 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 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 already presented convincing evidence that human exposure to benzene results in various hematological lesions including leukemia,[6,23,26,51,65,67-69,71,75,77,95-97,112-117,124,140-144] and acute myelogenous leukemia (AML),[3,62-65,72,76] 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.[1,5,32,40,46,103,104] 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[3,23,45,47,48,77-85,87-93] Further, I have presented experimental data which show that benzene can be absorbed through the skin.[18,23,24,27-31] (see also Appendix G). I have described some experimental work directed toward understanding the mechanisms of action of benzene on the blood forming elements[18,21,51,124] and cytogenetic studies demonstrating the ability of metabolic products of benzene to cause chromosomal damage.[23,127,128,130-139] 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, and congenital or genetic origins.[53] Neither Mr. [redacted] nor Mr. [redacted] have shown any significant potential for having been subjected to any of these alternative risk factors for leukemia.

CONCLUSIONS ON GENERAL CAUSATION

At this point, sufficient evidence has been presented to support a causal relationship between benzene and blood dyscrasias, including the leukemias. I have quoted statements from the literature including, "There is no doubt about the leukemogenic effect of benzene in man";[96] "Benzene is now recognized as a cause of leukemia in humans . . .";[141] and, "A causal relationship between chronic occupational exposure to benzene and development of leukemia has now been established beyond doubt".[69] I have referenced the conclusions of the International Agency on Cancer indicating that benzene is a human carcinogen.[5,103,104] There should be no doubt about the causal link between benzene and hematopoietic cancer in man.

CASE-SPECIFIC CAUSATION

Plaintiffs

The two individuals involved as plaintiffs in this case are [redacted] and [redacted] Both are about the same age and have had similar occupational exposures to benzene in the same workplace and have been diagnosed with leukemias as can be seen below.

[redacted]

Mr. [redacted] was born on September 6, 1953. It is my understanding that Mr. [redacted] began working at Union Camp, now International Paper, in July 1972 as a spare hand on a paper machine. After about six months, Mr. [redacted] transferred into the Maintenance Department where he worked until approximately 1980, during which time his most extensive exposure to benzene is thought to have occurred.

[redacted]

Mr. [redacted] was born on April 15, 1956. He began working in 1975 at the same location as Mr. [redacted] as a truck driver. After a few months, he was working in maintenance at International Paper.

Job Descriptions (see Appendix G)

Both Messrs. [redacted] and [redacted] worked for most of their careers as mechanics/millwrights. In a paper mill, this work involved maintaining and fixing pumps, engines, turbines, paper machines and other machinery, as well as tearing down, fixing, and reassembling equipment. During these activities, Mr. [redacted]

described using large quantities of solvents including "Liquid Wrench" for washing down and polishing the interior of turbine shells, cleaning and soaking valves in a 500-gallon tank enclosed in a small room and using an air stream to agitate the solvent reservoir. Twelve-hour shifts performing these tasks were not unusual. Mr. [redacted] complained that his hands turned white and his skin would crack and bleed as a result of dermal exposure to the solvents.

Mr. [redacted] shared many of the same experiences; but, he also spent full time from 1973 to about 1978 cleaning pumps and pump parts with solvents throughout his shifts. He described using several 10-quart buckets of solvent each day. In contrast to Mr. [redacted] s duties, Mr. [redacted] only worked on one turbine rebuild project where he cleaned parts.

Both Messrs. [redacted] and [redacted] used quantities of "Liquid Wrench" ranging from small squirts from a can or aerosol dispenser to several 10-quart buckets in the course of the day. These procedures resulted in solvent-saturated gloves because they were not furnished with solvent impervious gloves, nor were they provided with protective clothing or respirators. Further, I have no record that they were tested for benzene exposure; nor am I aware that they were warned of the dangers of benzene exposure. Toxicological properties related to the blood were well known for many years prior to that time (see Appendix F).

In a deposition dated July 1, 2003, Mr. [redacted], mechanic/millwright for 30-32 years at International Paper, recounted job duties similar to those of Messrs [redacted] and [redacted] as described above involving the use of "liquid Wrench" solvent. He recounted rebuilding gear motors, replacing gears and shafts, and servicing all moving parts of the paper machine. He recalled the use of 5-gallon buckets full of solvent taken from a 55-gallon drum. He recalled using bundles of rags and a cleaning bucket without respiratory protection from the "Liquid Wrench" solvent. Mr. [redacted] also developed leukemia, apparently as a result of his benzene exposures. This testimony would appear to corroborate the working conditions described by Messrs. [redacted] and [redacted]

Exposures

It is clear from the above discourse that both Messrs. [redacted] and [redacted] were exposed to significant quantities of "Liquid Wrench" solvent mixture from the time of their initial employment to at least 1979 and beyond. The main component of the "Liquid Wrench" formulation used during that period (raffinate) is said to contain from 1 to 14% benzene with a typical content of 5% (memo from J. G. Graeber to T. Tames of Radiator Specialty dated May 25, 1977; see Appendix E, also Table 2 in Appendix G, and Exhibit #9 of the Wells Deposition of November 8, 2000, as cited in the "Materials Reviewed" section of this report). That benzene is a significant part of the formulation is not surprising since the formulation during that time frame was made up largely of a

coal tar distillate called raffinate which was purchased by Radiator Specialty Company from US Steel Corporation in very large quantities as indicated below.

Apr. to Dec. 1967	139,100 gals.
1968 year-to-date	187,700 gals.
1969 year-to-date	198,200 gals.
1970 year-to-date	179,600 gals.
1971 year-to-date	180,700 gals.
1972 year-to-date	214,400 gals.
1973 year-to-date	232,700 gals.
1975 year-to-date	193,200 gals.
1976 total	264,600 gals.
1977 year-to-date	216,100 gals.
1978 year-to-date	31,400 gals.

In a memo from J. Wells to distribution dated 3/30/78, it is stated that the supply of benzene-containing raffinate will be exhausted by the end of April of 1978 (see Appendix E). Thus, it would appear that benzene was present in significant quantities in the "Liquid Wrench" formulation during a period when it was used heavily by both Messrs. [redacted] and [redacted] What is quite surprising is that one sample of "Liquid Wrench" (sample# A3-27535-001A), analyzed by Armstrong Forensic Laboratories in October 2003, contained 30% benzene (see Appendix E). This raises the question as to whether or not Radiator Specialty resumed the use of benzene in their formulation or, if this was an old sample, then the limits of 1-14% as previously indicated may be too low. Attachment #8 of [redacted] November 8, 2000, deposition indicates several memos and comments which would suggest that "Liquid Wrench" did contain as much as 30% benzene in 1977 ([redacted] report dated October 5, 1977, document # 14-0163, Bates #MOB 037859; another document from W. T. Gregg to M. A. Mehlman dated October 6, 1977, states "J. L. Wescoat of the Beaumont Refinery, had a laboratory analysis made of this product and found the benzene content to be 30%, Bates #MOB 03785, document #14-016)

For additional exposure information, refer to the report by Frank M. Parker, III, a Certified Industrial Hygienist (CIH), which contained an in-depth analysis of the exposures of Messrs. [redacted] and [redacted] and the inadequacy of hazard communications and personal protection afforded these workers.

Effects

Summaries of medical records for Messrs. [redacted] and [redacted] may be found in Appendix D of this report.

[redacted]

The records available to me on Mr. [redacted] date back to May 26, 1988, and conclude on August 12, 2003, (see Appendix D). From these records it would appear that Mr. [redacted] began experiencing high white blood cell counts as early as February 10, 1989, and also had high counts on May 13, 1991, November 11, 1998, and April 16, 2001. He was not diagnosed with acute myelogenous leukemia until April 20, 2001. Up to late 1979, "Liquid Wrench" contained up to 30% benzene (see Appendix G, Table 2). Subsequent to that time, "Liquid Wrench" still contained benzene but at lower levels. Thus, Mr. [redacted] was most heavily exposed since the beginning of his employment as a mechanic in early 1973 to 1979. This would suggest a latency period of 22 years from the last heavy exposure in 1979 to diagnosis, or as little as 10 years from the last heavy exposure to the first signs of elevated white blood counts. This finding would appear to be consistent with the literature which suggests anywhere from two to greater than 20 years latency period for developing leukemia from benzene exposure.[20,68,72,97]

[redacted]

I have reviewed Mr. [redacted]'s medical records beginning on January 19, 1985, to August 10, 2003(see Appendix D). Mr. [redacted] was born on April 15, 1956. His Father is still living and his mother may have died of an aneurysm at age 52. His brothers and sisters are in good health, but other relatives have diabetes, hypertension, heart disease, and stroke. On October 31, 1985, his white blood count (WBC) and hemoglobin and hematocrit (H&H) are normal. Again, he presents in October 1988 with a normal WBC and H&H, but in November of 1990 his WBC is elevated probably due to an infection. On April 24, 2001, his WBC is very elevated, and on the following day he is diagnosed with chronic myelogenous leukemia (CML).

He is diagnosed with leukemia about 26 years after beginning his employment at International Paper and his exposure to benzene via his use of "Liquid Wrench" as described in Appendices D and G. The timing of his exposure to significant quantities of benzene in "Liquid Wrench" and his presentation with CML is consistent with latency periods described in the literature.[20,68,72,97]

CONCLUSIONS AND OPINIONS

I have provided a detailed report causally linking exposure to benzene to the development of leukemia in man. This causal relationship is generally accepted in the international scientific community and government agencies as well. I have met all of the criteria put forth by Hill[94] which are accepted by numerous agencies involved in risk assessment, including the International Agency for Research on Cancer (IARC) and the Office of the Surgeon General of the United States. I have described the exposures to "Liquid Wrench" suffered by Messrs. [redacted] and [redacted] with the aid of an excellent report by [redacted] CIH, and numerous other documents available to me. I have

provided ample evidence for the benzene content of "Liquid Wrench" to be as high as 30%. Thus, in consideration of all the facts presented, including the fact that Messrs. [redacted] and [redacted] are similar in age and have suffered similar exposures to "Liquid Wrench", I opine within reasonable scientific probability that the leukemias being experienced by them have been caused by their exposure to benzene in "Liquid Wrench" during a period of time when it contained high concentrations of benzene. I reserve the right to supplement this report should additional materials become available.

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CONSULTOX, LIMITED

Date