EXPERT REPORT OF

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IN THE MATTER OF

[redacted]

VS.

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

IN THE

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF [redacted]

JACKSON DIVISION

CIVIL ACTION NO.: [redacted]

CONSULTOX, LIMITED

DAMARISCOTTA, MAINE

April 1, 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 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

- Openly published literature on vinyl chloride monomer back to at least 1930 and comprising a database of at least 673 citations (References cited as well as additional references may be found in Appendix C.)
- Medical records of Mr. [redacted] dating from 4/16/69 to 8/12/03 (Appendix D)
- Job history of Mr. [redacted] dating from 4/21/69 to present
- Second amended complaint dated May 19, 2003, by Douglas Mercier
- Numerous internal industrial documents dating from 1953 to August of 1995
- Personal telephone interview with [redacted] (Appendix E)
- Internal industry documents relating to vinyl chloride and used in the construction of a timeline (Appendix F) related to the [redacted] facility and Mr. [redacted] exposure scenario

INTRODUCTION

Vinyl chloride (VCM) and its polymerization products have been produced since the early 1940s.[1] Polyvinyl chloride or PVC is one of the major products produced from VCM and has been used in a number of products including plastic piping.

The PVC production facility in [redacted], was originally built in 1963 by Thompson-Apex Company and consisted of 20 small PVC polymerization reactors. The plant went though several name changes including Thompson-Apex a/k/a Monroe manufacturing whose ownership was transferred to Conoco around 1973 or 1974. The

company was taken over by DuPont around 1981; in 1983 became Vista Chemicals; in 1989 became Condea Vista; and subsequently Georgia Gulf since 1997. Around 1975, large reactors replaced the smaller ones, and by 1982 the plant production capacity reached 455 MM pounds per year of PVC.

Mr. [redacted] worked in the [redacted], plant which produced PVC plastic from vinyl chloride. Mr. [redacted] was involved in various aspects of the PVC production process from 1969 to the present. In a personal telephonic interview, I had occasion to secure from him descriptions of his various job duties and other details about his workplace. My notes of this conversation are contained in Appendix E but are worthy of some comment here.

In his initial assigment as a "Trainee" and "Vinyl Utility" person at the age of 21 years, Mr. [redacted] described his duties in cleaning the autoclaves for 8 hours per day. He recounts smelling VCM which he described as "sweet smelling", except he would lose his sense of smell when he went into the reactors. He indicated that he did not wear any respiratory protection during this period. It should be noted here that the odor threshold for VCM is somewhere between 2,000 and 4,000 parts-per-million (ppm) as described in internal industry documents (see Appendix F, 2/69, 8/8/74, 9/19/74 and 5/2/75 entries) and from 1,330 to 3,912 ppm as described in the literature.[2] Mr. [redacted] describes tingling in his body during his work inside of the reactors and times when he would have to come out of the reactors for air. The tingling and drowsiness are symptoms consistent with exposures above 1,000 ppm,[3,4] and that level of exposure in autoclave cleaners is consistent with published literature up to 1975.[5,6] It should be noted that the current permissible exposure level to VCM is 1 ppm.[4]

Mr. [redacted] reports that in his subsequent job assignments, he still smelled VCM on a regular basis, and as an "A" operator he would help out cleaning the reactors and would do a lot of reactor cleaning on overtime. His current assignment in the laboratory does not involve the extent of VCM exposure experienced in his other job assignments. Thus, over a period of about 26 years, from 1969 to 1995, Mr. [redacted] was exposed to levels of VCM that he could smell, indicating exposures from about 2,000 to 4,000 ppm. His exposures in the early years obviously were greater than more recent exposures because of new regulations and the elimination of the smaller reactors.

As it will become clear in the information presented below, vinyl chloride monomer (VCM) is causally linked to a rare liver disease called hepatic angiosarcoma, a disease which has been diagnosed in Mr. [redacted]. I will describe this relationship in some detail, and I will relate Mr. [redacted]'s VCM exposure experience to his disease. In considering whether or not there is any safe level of exposure to VCM, Sir Richard Doll, a respected industry consultant wrote, "It must indeed, be presumed that some risk of developing the disease [angiosarcoma] will persist from exposures to doses that are even lower than the current industrial levels of 5 ppm or less, as vinyl chloride has been shown to act as a mutagen, and it cannot be assumed that a threshold exists below which no carcinogenic risk persists".[7]
The literature on VCM is extensive, and there are many fine reviews that have been written describing its toxicological and carcinogenic effects.[1,3,5,8-40] Published

epidemiology studies have indicated increased risks of developing hepatic angiosarcoma between 1.36 and 57 times in VCM workers versus unexposed controls,[41-59] and many case reports have been published.[6,60-86] It should be noted that some of the epidemiological studies cited here and elsewhere[45,48,51,53] are based on a cohort of US workers which is not totally representative of the entire worker population (selection bias). Although the bias is toward lower prevalence of chronic disease, the information contained in these studies is still useful if viewed in this context.

VCM also has been reported to be a mutagen[20,87-93] and to cause chromosomal damage.[94-105] VCM reacts with DNA to form adducts[106-114] which cause genetic mutations, evidence of which can be found in the hepatic angiosarcoma tumors and in the blood of those exposed to VCM.[115-124] Hepatic angiosarcomas also have been reported as a result of controlled exposure studies in several animal species.[30,32,125-136] Many of the above cited studies will be discussed below in more detail.

In order that there will be no doubt of a causal relationship between exposure to VCM and hepatic angiosarcoma, I have conducted a causation analysis using the criteria of Sir Bradford Hill.[137] Causation analysis using these criteria has become an accepted approach to the establishment of causal relationships by the International Agency for Research on Cancer, the Surgeon General of the United States, and others.

CAUSATION - THE HILL CRITERIA

A. B. Hill[137] 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. I will apply this criteria to the possible establishment of a causal connection between exposure to VCM resulting from the PVC production process and a rare liver cancer described as a hepatic angiosarcoma, which has been diagnosed in 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.

When dealing with this criterion, it is important to consider the statistical significance of the findings, preferably in humans, in support of a causal relationship. There are many cases where such data is either non-existent or limited to only case-reports and animal

data. In this case, the human data is plentiful, and the statistical power is great. Consider the following statistically significant (ss) data supporting a causal relationship between VCM exposure and hepatic angiosarcoma, a condition being experienced by Mr. [redacted].

On January 22-23, 1974, BF Goodrich announced that three workers had died of hepatic angiosarcoma, and later that year the information was published by Creech and Johnson.[65] Although several studies of the BF Goodrich's Louisville plant have been made as a part of more comprehensive studies, a recent (2003) re-analysis of the data, separating it from overlapping cohorts, resulted in some new dose-response relationships for liver and biliary cancer. The overall cohort produced an SMR of 359 (ss = statistically significant), but the Louisville cohort resulted in an SMR of 400 (ss). For those hired before 1950 the SMR was 357 (ss); for those with 20+ years of employment SMR was 364 (ss); and for latency from 20-29 years, the SMR was 694 (ss).[43] An SMR of 694 means that a person subjected to similar circumstances has about a 7-times-risk of contracting liver or biliary cancer than an unexposed person. Another study of the Louisville cohort reported an odds ratio (OR) of 11 (ss) for liver and biliary cancer in VCM workers from Louisville and Calvert City.[46] An odds ratio (OR) or risk ratio (RR) is a direct expression of approximate risk of having the disease. In this case, the reported risk in contracting liver or biliary cancer would be 11 times greater than in a comparable unexposed person.

A study sponsored and edited by the Chemical Manufacturers Association (CMA) was reported by Wong and was based on a cohort of 10,173 men who had worked at least one year in jobs involving VCM exposure in the United States. Although the study suffers from selection bias, fifteen deaths from hepatic angiosarcoma were reported. For the overall cohort, SMR = 641.2 (ss) for liver and biliary cancer, but for 20+ years of exposure, SMR = 1,284.9 (ss). The SMRs also increase in a dose-response manner with latency and inversely with age at first exposure.[53] Another study of essentially the same cohort of 10,109 men and suffering the same selection bias was sponsored by the CMA and reported dose-related increase in SMRs relating to exposure period resulting in an SMR = 688 (ss) for greater than 20 years of exposure and an SMR of 434(ss) for induction time from first exposure of greater than 30 years.[51] A NIOSH retrospective cohort study of four plants with VCM/PVC production for at least 15 years with exposed subjects having at least five years of exposure resulted in SMR = 1,155 (ss) for biliary and liver cancer and for those employees with greater than 15 years latency, SMR = 1,606 (ss).[47] This represents an increased risk of 16 times over non-exposed workers. Examination of Union Carbide's South Charleston Facility from 1974 to 1983 resulted in an SMR = 592 ss for hepatic angiosarcoma.[57]

A recent (2003) Italian study involving 41,037 persons and 248 deaths observed from January of 1973 to July of 1999 reports an SMR of 2.78 ss (equivalent to an SMR of 278) for hepatic angiosarcoma and mortality from angiosarcoma statistically increasing with latency period (time from initial exposure to diagnosis) and duration of cumulative

exposure.[42] Another recent study involved a multi-national meta-analysis based on six studies. While it did not analyze specifically for angiosarcoma of the liver, it did report SMRs for liver cancer in VCM workers ranging from 1.36 (ns) to 57.1 (ss) representing a risk approximating 1.4 to 57 times greater than unexposed workers.[41]

An update of a 1974 Chinese report of a cohort of VCM polymerization workers from a plant which operated from 1942 to 1974 calculated an SMR of 300 (ss) for liver cancer. When employment was between 10-15 years, the SMR was reported to be 1429 (ss). Response generally related to dose in terms of period of exposure.[49] Another study of 451 workers exposed to VCM versus 870 controls, where only workers with 5+ years of experience between 1948 and 1972 were included, showed an SMR of 5,714 (ss) for cancers of the liver, particularly angiosarcoma.[50] A Swedish cohort of PVC/VCM workers demonstrated an Odds Ratio of 413 (ss) for angiosarcoma with disease incidence increasing with latency period.[52] A recent (2001) European study of 12,700 male VCM workers that reported 37 angiosarcoma, and 10 hepatocellular carcinomas, calculated relative risks (RR) of angiosarcomas in autoclave cleaners up to 88.2 (ss) based on cumulative exposures in ppm-years. Dose-response also was reported for hepatocellular carcinomas.[138]

A study done in the UK reported 7 angiosarcomas and an SMR = 567 (ss) for liver cancer and an SMR = 1842 (ss) for autoclave workers with hepatic angiosarcoma.[55] Other studies include a report of another Italian cohort where the pooled mortality from primary liver cancer from the three cohorts resulted in an SMR = 346 (ss),[56] and a German study reporting an SMR = 1523 (ss) for liver cancer in PVC/VCM production workers with risk increasing with duration of exposure to a maximum SMR = 2828 (ss).[58]

The International Agency for Research on Cancer (IARC) has reported on a large multicentric cohort study involving plants in Italy, Norway, Sweden, and the UK. Thirty-seven plants and 17 companies were involved. For the total cohort, an SMR of 286 (ss) was calculated for liver cancer, and an SMR of 311 (ss) in PVC/VCM production areas. A dose-response is noted with latency with a maximum SMR = 896 (ss). Based on actual person-years of exposure, again, a dose-response is presented with a maxi-mum relative risk (RR) of 17.1 (ss). When a sub-cohort of autoclave workers is considered, SMR = 1358 (ss).[54]

There should be little doubt that the strength of the causal connection between VCM/PVC processing and liver cancer, specifically angiosarcoma is significant. The risks of developing hepatic angiosarcoma from VCM exposures are huge. It also should be obvious that those involved in the PVC polymerization process are at highest risk, particularly those whose duties involved cleaning autoclaves even for relatively short periods. Mr. [redacted] was involved in cleaning autoclaves during his early Aberdeen employment and, as will be clear when temporality is discussed, the timing between his exposure and his development of angiosarcoma is consistent with what has been published in the peer-reviewed literature.

2. Consistency of Association

Hill[137] *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.*

Because the published literature on this subject is overwhelming, the best approach to address this topic is to cite some of the many case reports linking VCM exposure to hepatic angiosarcoma[6,44,58,60-71,80,85,139,140] and to describe different situations resulting in liver cancer and hepatic angiosarcoma in VCM-exposed individuals.

Although there appears to be a minimum latency period, earliest age at diagnosis ranges from 36 years of age[72] to 45[62] to 51,[82] all the way to a man aged 71 who was exposed to VCM for over 20 years.[141] The 45-year-old male chemical worker was exposed to 195 to 630 ppm VCM over 248 months.[62] Seven cases of hepatic angio-sarcoma were reported from a Louisville study where the ages ranged from 36 to 58 years of age,[72] while another study of 20 VCM workers with angiosarcoma were reportedly exposed from 3-29 years.[74] Nineteen additional cases of liver cancer were reported with a latency from 12-34 years.[75]

Other studies reported in the peer-reviewed literature included fifteen cases of angio-sarcoma of the liver resulting from exposures ranging from 4 to 28 years;[76] two cases of angiosarcoma resulting from a study of 7,000 workers exposed between 1940 and 1974 in Great Britain;[77] ten cases of angiosarcoma reported in Canadian workers;[78] twelve cases of hepatic angiosarcoma, mostly in autoclave cleaners with exposures around 500 ppm;[142] two workers exposed from 11 to 12 years to PVC production developed hepatic angiosarcomas;[83] 38 cases of hepatic angiosarcoma from Canada, Czechoslovakia, France, Great Britain, Italy, Norway, Rumania, Sweden, US, and West Germany;[84] and 64 cases of angiosarcoma from PVC polymerization workers as of October, 1977.[86] Environmental exposure also has produced nine cases of hepatic angiosarcoma which were reported in England and Wales from 1979 to 1986 in non-occupationally exposed residents living next to a VCM production facility.[73]

The consistency of the causal association between VCM exposure and hepatic angio-sarcomas knows no international boundaries. Consider, for example, studies from Quebec, Canada,[78] Great Britain,[73,77,143] Italy,[42,56,63,79,144] Germany,[23,69,75,81,83] Sweden,[44,52,145] China,[49] France,[67,146] Australia,[61] Russia,[147] Norway,[85] Japan,[93] Croatia,[142,148] and Taiwan.[70,124,149]

Given the industrial exposure typical of PVC production facilities and the appropriate induction period, there is little doubt that the risk of hepatic angiosarcoma is very significant. Workers laboring in industrial facilities all over the world have developed this terminal disease as a result of being exposed to VCM. It should be clear that the consistent appearance of hepatic angiosarcoma in the VCM/PVC industry has been demonstrated in all ages of workers worldwide. In addition, animal studies which will be presented below, also have shown a consistent response to VCM in developing hepatic angiosarcomas in several species (see "Experiment" section).

Thus, I believe that we have met Hill's criterion of consistency both domestically and internationally. In addition, the same response, hepatic angiosarcoma, has been found consistently in animals as indicated below.

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.

Hepatic angiosarcoma is an extremely rare lesion occurring in about 0.5 to 2.5 cases/MM persons.[39] Other causes besides VCM have been identified as being related to the development of hepatic angiosarcoma, including exposure to arsenial medications and exposure to inorganic arsenic in vineyard workers.[88,150-153] The early use of Thorocrast (thorium dioxide) for arteriography also has been identified with angiosarcoma.[150-152,154,155] In addition, androgenic-anabolic steroids[152] and therapeutic irradiation[151] were thought to be linked to hepatic angiosarcoma. Mr. [redacted] has not been exposed to any of these alternative causes making them irrelevant in this case.

Hepatic angiosarcoma is described as a vascular lesion involving dilated sinusoidal spaces containing red blood cells with the sinusoids lined by enlarged and proliferating tumor cells.[150] It has been reported that endothelial sinusoidal cells have a lower capacity to detoxify VCM metabolites[156] and that biopsies of VCM workers are reported to show 90% incidence of proliferation of cells lining the hepatic sinusoids.[156] Microscopic examination of human tissue from hepatic angiosarcoma reveals that hyperplastic changes occur in the sinusoidal cells where hepatic cells were replaced by fibrous tissue forming trabeculae with areas that are infiltrated with angiosarcoma cells.[34] In another report the authors compare VCM liver lesions with those from arsenic describing, "activation of the sinusoidal lining cells accompanied by fibrosis in the portal tracts . . ." and proposing "a fibrotic precursor lesion progressed to angiosarcoma by focal dilitation of the sinusoids with even greater activation but dedifferentiation of the lining cells. This evolution is identical with that following prolonged exposure to organic arsenials".[88] In addition to these alternative causes, hepatic angiosarcoma has been produced in mice as a result of treatment with vinylidene chloride,[90] a chemical similar in structure to vinyl chloride.

Vinyl chloride clearly attacks the vascular system, and this is quite consistent with numerous reports of other vascular lesions such as Raynaud's phenomenon, acroosteolysis and scleroderma.[5,51,157-176] Some reports have noted scleroderma[177,178,179] and systemic sclerosis.[180] While it is clear that these also are vascular lesions consistent with the vascular target for VCM in the liver, it is believed that there is also an immune component to some of these conditions.[148,164,181-185] Not surprisingly, these lesions occur most frequently in autoclave cleaners.[162,172,186]

One recent multi-centric international study addresses specificity directly with the following statement: "The relationship between vinyl chloride exposure and angiosarcoma of the liver is also one of the most specific industrial chemical carcinogenic associations commonly seen with no other known risk factors (and therefore no potential confounders)."[41]

Considering the rarity of the hepatic angiosarcoma lesion, the limited number of alternative causes of the disease, the strong causal link to VCM, and the other indications that VCM attacks the vascular system, the "Specificity" criteria has been satisfied.

4. Temporality

Hill[137] *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 being addressed.*

Temporality is not difficult to describe in this case since the development of hepatic angiosarcoma requires a period of exposure to VCM followed by an appropriate latency period during which time the tumor is developing. There are many examples that describe both the exposure period and latency periods. Consider the following studies all of which describe hepatic angiosarcoma.

EXPOSURE PERIOD	LATENCY PERIOD	REFERENCE
12+ yrs	10+ yrs	42
3+ yrs	12+ yrs	47
5+ yrs	15+ yrs	49
5-9 yrs	10-19 yrs	51
4.2+ yrs	<20 yrs	53
3+ yrs	15+ yrs	54
13-16 mos.	–	58
5+ yrs	11+ yrs	50
3+ yrs	9-35 yrs	74
6+ yrs	12+ yrs	75
4+ yrs	–	76
4+ yrs	8+ yrs	84
3.5+ yrs	8+ yrs	187

Although additional information could be cited, the above-listed studies should suffice to make it clear that in order to be at significant risk of hepatic angiosarcoma from exposure to VCM, a relatively brief exposure period is sufficient. One of the above studies found that as little as a 13 month exposure period was sufficient to increase the risk of acquiring hepatic angiosarcoma. Exposures to vinyl chloride monomer while cleaning autoclaves have been estimated to be as high as 15,000 ppm in the 1950s.[52] Obviously, other job responsibilities related to the polymerization of PVC entail additional exposures to PVC monomer.[3,6,9,18,23,55,64,148,188] Thus, a short-term exposure (perhaps less than a year) to the very high concentrations of VCM while cleaning a reactor could be very significant relative to the risk of contracting hepatic angiosarcoma from the exposure. In the paragraph below, I will indicate some of the extraordinary exposure levels that have been measured in PVC production facilities similar to those where Mr. [redacted] has worked.

The induction time is another matter in that it may be dependent on the age at first exposure as well as other factors. One study reports an SMR of 1,611 (ss) for those who were exposed in the VCM/PVC industry when they were under 25 years old,[53] as is the case with Mr. [redacted]. Other studies have noted the sensitivity to age at first exposure relative to increased risk for hepatic angiosarcoma.[75]

Mr. [redacted] was about 21 years of age when he began working at the Aberdeen plant. For approximately the first 26 years of his employment he worked on processes which caused him to be exposed to significant concentrations of VCM, including the cleaning of reactors. As a result of being exposed to VCM at such a young age and having been exposed for more than 26 years to significant concentrations of VCM, it is not surprising that on June 13, 2001, 32 years after his initial exposure, Mr. [redacted] was diagnosed with hepatic angiosarcoma after exhibiting the classical symptoms of right upper quadrant pain and transient elevations of liver enzymes.

During his employ, Mr. [redacted] was employed as a trainee and autoclave cleaner, a dryer operator, an "A" reactor operator, a UR "A" operator, UR Lead Operator, then he was assigned in 1966 to unloading railroad cars and working in the lab doing QC testing. During Mr. [redacted]'s performance in all of these jobs with the exception of the laboratory job, he noted smelling VCM regularly at an exposure level of from 2,000 to 4,000 ppm. There have been reports in the literature that may describe some of the exposure situations to which Mr. [redacted] was subjected. One study describes exposures between 10,000 and 15,000 ppm VCM during reactor cleaning.[52] Other reports describe exposures to 1,000 ppm prior to 1955, 300-500 ppm from 1955-1970 and 100-200 ppm from 1970-1974.[9] A similar study reported about 1,000 ppm from 1945-1955, 400-500 ppm from 1955-1960, 300-400 ppm from 1960-1970, about 140 ppm in 1973, and 5 ppm in 1975.[18,23] A study of UK VCM workers showed the following estimated exposures: for autoclave workers 500-800 ppm VCM from 1940-1955; 150-500 ppm from 1956-1974; for baggers/driers <400 ppm from 1940-1955 and <40 ppm from 1956 to 1974.[55] Exposures before 1975 were as high as 1,000 ppm,[5] resulting in slight anesthesia, drowsiness, slight visual disturbances, faltering gait, numbness and tingling

of extremities. With more elevated exposure in the range of 8,000 to 20,000 ppm, symptoms included dizziness, giddiness, euphoria, ataxia, headaches and narcosis.[3] These are symptoms that have been observed in some autoclave cleaners. A 1975 publication based on BFG plant states: "Thus, peak exposures may often have exceeded 1,000 ppm during acute episodes and may have approached 10,000 ppm in the production facility".[6] A 1976 Italian study described levels up to 2,000 ppm of VCM monomer in resin and about 90 ppm concentration in reactor vessels after 30 air exchanges per hour.[188] Finally, a report from Dow Chemical Company describes 8-hour Time Weight Averages (TWAs) for reactor operators from 120-365 ppm with peaks to 4,000 ppm during the period from 1950 to 1959. They comment on tank car unloaders showing TWAs of 100 ppm with peaks to 4,000 ppm. Operators are thought to be exposed from 25-80 ppm TWA with peaks to 500 ppm with tank car unloaders to 25 ppm during the period of 1960 to 1963.[64]

Mr. [redacted]'s own comments from my conversation of March 17, 2004, with him confirm what is described above regarding his exposures as an autoclave cleaner in 1969 and continuing with overtime autoclave cleaning through 1973. He described smelling VCM regularly during these periods up to 1996 when he took a job in the laboratory. I have already mentioned that the odor threshold for VCM is between 2,000 and 4,000 ppm according to internal company documents described in Appendix F (see entries for 2/69, 8/8/74, 9/19/74 and 5/2/75) and from 1,330 to 3,912 ppm in the published literature.[2] In addition, he worked for a period of time unloading VCM-laden tank cars, an activity described above as involving exposure to as much as 4,000 ppm VCM.[64]

Thus, the temporality of Mr. [redacted] relative to his exposure and development of hepatic angiosarcoma is clearly consistent with that which is published in the peer-reviewed literature as are his exposure scenarios. He was first exposed to VCM as an autoclave cleaner at a young age and subsequently exposed heavily for an additional 23 years, resulting in a diagnosis of hepatic angiosarcoma some 32 years after his initial exposure. I have provided an indication of the extent of exposure to which Mr. [redacted] was subjected and feel that this requirement of the Hill Criteria has been fulfilled.

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.

There is a wealth of information relative to dose-response in both humans and animals. Allow me to elaborate on the human data. A historical cohort study of 10,109 men, although suffering from selection bias, demonstrated the following dose-response relationships: for those exposed from 1-4 years, from 5-9 years, from 10-19 years, and for greater than 20 years, the Standard Mortality Ratios (SMRs) were 83 (ns), 215 (ss),

679 (ss), 688 (ss), respectively.[51] Another analysis of the American cohort of VCM workers suffering from the same bias, by Wong reported SMRs for exposures of less than 10 years to be 182.1 (ns), for 10-20 years 1,235.6 (ss), and for 20+ years 1,284.9 (ss), an impressive dose-response relationship.[53] One study used an index of VCM exposure and 23 cases of hepatic angiosarcomas to develop a relationship between exposure intensity and the development of angiosarcoma with a correlation coefficient of p = 0.0038 (ss).[189,190] An updated Chinese study reported the following SMRs from date of first exposure: for less than 5 years SMR = 83 (ns); from 5-10 years SMR = 455 (ss); from 10-15 years SMR = 1429 (ss); from 15-20 years SMR = 1,000 (ss); from 20-25 years SMR = 1,200 (ss); and for greater than 25 years SMR = 833 (ss).[49]

A study by the IARC addressed this issue in several ways. Looking at actual person-years of exposure versus relative risk (RR), they reported RR = 1 (baseline), then for 500-1,999 ppm-years exposure, RR = 1.2 (ns); from 2,000-5,999 ppm-years, RR = 4.6 (ss); from 6,000-9,999 ppm-years, RR = 12.2 (ss); for greater than 10,000 ppm-years exposure, RR = 17.1 (ss). In addition, they calculated the SMRs from low, medium, and high exposures at SMR = 244 (ss), 551 (ss), 719 (ss), respectively, and specifically for hepatic angiosarcoma with greater than 10,000 ppm-years of exposure, RR = 45.5 (ss),[54] an impressive set of dose-response relationships. A similar European study based on exposure levels reported exposures from 0-734 ppm-years with RR = 1; from 735-2,379 ppm-years, RR = 6.56 (ss), from 2,380-5,188 ppm-years, RR = 13.6 (ss); and for 7,532 ppm-years RR = 88.2 (ss). They also analyzed risk of never being an autoclave cleaner, RR = 1, and being an autoclave cleaner, RR = 25.5 (ss).[138] This study states that if you were ever a PVC autoclave cleaner, your risk of developing hepatic angiosarcoma is 25 times that of an unexposed person. Other epidemiology studies also have shown dose-response relationships.[42,58,104,138,191]

Equally as impressive is that various animal studies have demonstrated dose-response relationships with VCM. One study in rats, mice, and hamsters shows a definite dose-response with increasing angiosarcomas with dose and earlier age at first exposure;[135] other studies in Wistar rats and other rat strains produced both hepatic angiosarcomas and hepatocellular carcinomas in a dose-dependent manner.[130,134] Even as early as 1975, Maltoni produced angiosarcomas in the livers of mice, rats and hamsters at exposures down to 50 ppm.[33] Many other studies were reported also to produce dose-response relationships in animals exposed to VCM.[30,127,130-136,192]

Since the mechanism of cancer production by VCM is thought to involve a mutagenic event, dose-response relationships also are reported in a variety of mutagenesis assays.[20,87-92] One such assay is for the K-ras mutation pattern from workers exposed to VCM which is expressed in a statistically-significant dose-dependent manner in French workers.[146] It is noteworthy that mutations of the p53 gene have been considered by some to be a biomarker for hepatic angiosarcoma.[118-121] Numerous other mutation assays have been carried out using vinyl chloride and several good reviews have been published.[20,87-92] These assays range from single strand breaks in mice liver after VCM exposure at 500 ppm[94] to Dominant-Lethal assays in mice and rats[193,194] to the study of

mutagenic response in reverse mutation assays in bacteria.[93] Many of these assays have been carried out on lymphocyte cultures in exposed humans.[95] Exposure-related increases in chromosomal aberrations in 11 VCM workers vs. controls.[95] Several studies have reported increased chromosomal aberrations and breaks in VCM exposed populations versus controls.[97-103,105] One study of 57 VCM exposed workers demonstrated an inverse dose-response relationship in that the chromosomal aberrations frequency decreased with decreasing exposure to VCM.[104]

Thus, the biological gradient issue has been demonstrated in man, animals, and in *in-vitro* assays and should suffice to satisfy this criterion.

6. Plausibility and Coherence

> *I will consider these criteria together since they impinge on the same theme voiced by Hill[137] 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". In addition, hypotheses based on sound scientific principles should be presented to explain the phenomena under consideration and to demonstrate the plausibility of the causal conclusions being reached. It is desirable to provide experimental evidence to support the hypothesis, but this is not always available.*

Does it make scientific sense that VCM is capable of producing a rare liver lesion called an angiosarcoma in man and animals? Does this hypothesis violate any known and accepted biological premise? We need to first understand how VCM is metabolized and where it is metabolized and to what is it metabolized. Although VCM is also capable of producing the more common hepatocellular carcinomas,[70,79,195-198] it also is capable of producing a very rare liver tumor called an angiosarcoma, as we have seen in the many references cited above. Are we able to describe and demonstrate mechanisms by which VCM can produce these rare lesions? These are the questions that must be addressed in order to fulfill the requirements of this criterion.

Vinyl chloride monomer (VCM) is a mutagen that attacks the liver via a genotoxic pathway. It is first metabolized in the liver via a CYP4502E1 mediated pathway[199,200] to a reactive metabolite, chlorethylene oxide (CEO). CEO then binds to DNA form-ing adducts that lead to mutations,[115-121,124,146,201] uncontrolled cell growth and tumor formation at multiple sites.[41-45,47,49,50,52,53,72,75,199] The formation of CEO has been confirmed, and it is considered the ultimate carcinogen in VCM exposures.[111] It is further metabolized in the liver to another reactive metabolite, chloracetaldehyde.[199,202,203] Although the aldehyde can form protein adducts, it is not thought to be mutagenic by some,[199] and yet it has produced positive mutagenic responses in some assays.[202] Although this represents a simplistic picture of a more complex metabolic scheme involving multiple organ systems, the basic steps and intermediates are the same.[203-205] The critical point for hepatic cancer is the formation of chlorethylene oxide in the liver and its reaction with hepatic macromolecules including DNA and RNA[206,207] resulting in mutagenic events[20,87-92,146,208-210] as discussed below.

As a highly reactive metabolite of VCM, chlorethylene oxide (CO) reacts with DNA forming a variety of adducts which have been isolated from VCM-exposed livers.[106-110,112-114,199] The results of these DNA lesions are mutated genes which express proteins that have actually been found in hepatic angiosarcoma tissue taken from man and animals.[115-123] One of the genes mutated by VCM is the p53 tumor suppressor gene.[118-123,146,201,211] This event is thought to have serious implications relative to the development of angiosarcomas. A particularly interesting study involving N^2,3-ethenoguanine (EG), an adduct which has been found to be abundant in hepatic angiosarcomas in animals and man, demonstrated a supra-linear dose-response with the number of adducts increasing 42-fold in the livers of treated rats.[110]

Now that I have provided some limited insight into the molecular mechanisms that lead to hepatic angiosarcoma as a result of VCM exposure, I will consider its pathogenesis. Biopsies from VCM workers show a 90% incidence of cell prolifer-ation in cells lining the hepatic sinusoids[156] which are part of the hepatic vascula-ture. Another report describes dilated sinusoidal spaces containing red blood cells and lined by tumor cells.[150] While it is clear that hepatic angiosarcomas originate from the endothelial cells lining the hepatic sinusoids,[212] histopathological examin-ation of human hepatic angiosarcomas suggest that the lesion develops as a result of hyperplastic changes in the sinusoidal cells where hepatic cells were replaced by fibrous forming trabeculae which were infiltrated with angiosarcoma cells.[34] This is not surprising since endothelial sinusoidal cells have a 50 to 500 times lower capacity to detoxify VCM metabolites (that is, CEO) than do hepatocytes.[10] In addition, hepatocytes can readily repair DNA lesions, but there is little information available relative to DNA repair in endothelial sinusoidal cells.[10]

It is obvious that hepatic angiosarcoma is a vascular lesion. Interestingly, other vascular problems also result from exposure to VCM. Consider the other problems of VCM workers such as Raynaud's phenomenon,[5,157-176] dissolution of bone tissue in the distal phalanges,[158-160] scleroderma-like lesions,[177-179] and systemic sclerosis[180,213] all related to the vascular system.

The fact that hepatic angiosarcomas from VCM exposure form in the hepatic sinusoidal vasculature presents a problem in diagnosing the disease as is obvious in the medical records of Mr. [redacted] (See Appendix D). Proliferative lesions involving the hepatocytes send up red flags of extreme elevations of liver enzymes released from the hepatocytes, however, hepatic angiosarcomas only involve hepatocytes in the later stages of development. Consequently, liver enzymes are not obviously elevated in an alarming manner as is in the case of Mr. [redacted]. This difficulty in diagnosis provides even further evidence of the sinusoidal endothelial origin of the vinyl chloride cancer.

Although the mechanistic aspects of hepatic angiosarcoma are complex and are not yet fully understood, it should be clear that there is a scientific logic to the relationship between VCM and the development of hepatic angiosarcoma. It also should be clear that sound scientific principals and tests have been applied in the establishment of these relationships and that no biological premise has been violated.

7. Experiment

Although human clinical trials are relied upon to establish the efficacy of drugs, and epidemiology 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. In addition, 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.

Although there may have been earlier animal studies involving VCM, a 1930 study reported hyperemia in the livers of exposed guinea pigs.[214] A particularly pertinent 1961 study in animals was carried out by Dow Chemical. Guinea pigs, rats, rabbits, and dogs were exposed to VCM and showed increased liver weight and liver pathology.[215] One of the first studies to show that VCM could be carcinogenic was published in 1971 and reported tumors at multiple sites in Wistar rats.[216,217] Maltoni and his colleagues also were actively researching the chronic effects of VCM in animal models finding hepatic angiosarcomas in mice, rats, and hamsters with dose-response down to 50 ppm VCM[30,32,33,132] and at exposures as low as 10 ppm.[30] Hepatic angiosarcomas in response to VCM exposure were found in mice exposed by inhalation for 8 months,[125] in rats and mice exposed for 12 months,[126,127] in rats and mice exposed for 6 months and showing a dose-response relationship,[134] in Wistar rats fed VCM in two lifetime feeding studies resulting in a dose-dependent response,[130,136] and in Syrian Golden Hamsters, F-344 rats, Swiss CD-1 mice, and B6C3F1 mice.[129] Some studies demonstrated a greater sensitivity to VCM in younger animals[128,135] which appears consistent with the human experience.[53] Most animal studies have demonstrated a dose-dependency.[127,129-133,135] In one of the studies, Maltoni described VCM as being a "multi-potential carcinogen" after observing liver angiosarcomas, Zymbal gland carcinomas, nephroblastomas, brain cancers, mammary cancers and forestomach tumors.[30]

As is the case with the studies of human exposure to VCM, the experimental support in animals alone is sufficient to convince anyone that VCM is a carcinogen, producing hepatic angiosarcoma and brain cancers[47,53,54,80] among other malignant lesions. There are still other experimental studies supporting the carcinogenicity of VCM including its ability to form DNA adducts[106-109] and gene mutations[115-121,124,146,201] both of which are thought to be involved in the pathogenesis of hepatic angiosarcoma. In addition, there are numerous experimental reports describing the other mutagenic[20,87-90,218] and cytogenetic[94-105,219] properties of VCM, but to elaborate beyond this would be somewhat redundant.

VCM has been identified experimentally and on the basis of human exposure studies as being carcinogenic. I have previously cited many controlled human epidemiological studies that could easily be considered as experimental, but it would be redundant to re-iterate those studies since the experimental data in animals alone is sufficient to identify vinyl chloride monomer as being a carcinogen. The combination of the human data plus the animal data and other experimental work has identified VCM as an animal and human carcinogen beyond any doubt as declared by the IARC,[199,220-223] by the US EPA[4] and by the American Conference of Governmental Industrial Hygienists (ACGIH).[4]

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?

In discussing his criteria, Hill[137] makes it clear that all of the criteria need not be met in order to establish causation. In attempting to find an analogous relationship to the VCM-angiosarcoma causal link, one quickly realizes that there is none. The closest analogy would be arsenic which is described as having a pathogenesis for hepatic angiosarcoma which is very similar as that described for VCM exposures.[88] Vinylidene chloride, which is identical in chemical structure as VCM except it has an extra chlorine atom attached, also has been shown to produce hepatic angiosarcomas in mice.[90] Neither of these afford a satisfactory analogy. Clearly, the causal connection between VCM exposure and hepatic angiosarcoma is unique.

CONCLUSIONS AND OPINIONS

Mr. [redacted] has been involved in the production of PVC from vinyl chloride since April of 1969. As a young man of 21 years, he began working as a utility person cleaning VCM reactors all day and sometimes resulting in his body exhibiting a tingling sensation according to his own comments described in Appendix E. As we have mentioned, this symptom has been experienced by others and is thought to involve airborne concentrations of VCM in excess of 1,000 ppm.[3] This was not an unusual occurrence in the industry considering a 1975 publication based on the BF Goodrich plant stating: "Thus, peak exposures may often have exceeded 1,000 ppm and, during acute episodes, may have approached 10,000 ppm in the production facility".[6] Mr. [redacted] told me that he witnessed others being dragged out of the reactors close to unconsciousness, and he relates having to take periodic breaks to "come up for air".

Mr. [redacted] was quickly promoted to Dryer Operator during which time his responsibilities changed but his exposures to VCM continued. He described smelling VCM on a regular basis and, as mentioned above, the odor threshold for VCM is thought to range from 2,000 to 4,000 ppm (see 2/69, 8/8/74, 9/9/74 and 5/2/75 entries in Appendix F, see also Reference #2). Shortly thereafter in December of 1969, he became an "A" operator which involved running the reactors. During this period, Mr. [redacted] related smelling VCM on a regular basis. He talked about helping to clean the reactors on many occasions during the day and working overtime cleaning reactors. He advanced to "Lead Operator" and then to "Large Lead Operator" in March of 1974. It was apparently about that time that his exposures to VCM were reduced because of new regulations and because the large reactors did not require frequent cleaning. He still relates smelling VCM during that period and during the subsequent time he spent in the rail yard unloading VCM loaded tank cars.

Although Mr. [redacted]'s heaviest exposures undoubtedly occurred when he was cleaning the small reactors, his continuing exposure to VCM started in April of 1969 and ended in 1996, an exposure period of about 26 years. On or about June 13, 2001, 32 years after his first VCM exposure in Aberdeen, Mr. [redacted] was diagnosed with angiosarcoma of the liver. Studies cited in the peer-reviewed literature describe VCM exposure periods of 13 months to greater than 15 years for VCM-exposed workers with hepatic angiosarcoma,[47,49-51,53,54,58,224] and latency periods (time from first exposure to disease) of 8 years as a minimum.[47,49,51,53,54,224] Again, Mr. [redacted] was exposed for a period of 26 years with several years of heavy exposure in the autoclaves and developed cancer 32 years after his initial exposure. Mr. [redacted]'s disease development is highly consistent with what is known and published for hepatic angiosarcoma resulting from VCM exposure. Further, one epidemiology study reported that those exposed to VCM when younger than 25 years of age exhibited an even higher risk of hepatic angiosarcoma with an SMR of 1,611 (ss), than those exposed at an older age,[53] an observation confirmed in animal studies.[128,135] Another study looked at risks for autoclave cleaners and calculated a statistically-significant relative risk of 25.5 for ever-cleaners versus never-cleaners.[138] Mr. [redacted] worked in a job having the highest risk of developing hepatic angiosarcoma, and he worked there at an early age when he was most susceptible to developing the disease from VCM exposure.

One of the few ways that Mr. [redacted] was informed about the dangers of exposure to VCM was through the Material Safety Data Sheets on VCM. The SD-56 Material Safety Data Sheet (MSDS) that the industry started using in 1953 stated "Vinyl chloride presents no very serious problem in general handling aside from the risk of fire and explosion. The presently accepted upper limit of safety as a health hazard is 500 ppm". Furthermore, the odor threshold contained on the 1953 MSDS was 260 ppm (see Appendix F, 1953 entry). Thus, anyone who smelled VCM would assume that they were being exposed to 260 ppm VCM instead of the 2,000-4,000 ppm which is the real odor

threshold.[2] Thus, when workers said that they smelled VCM, no one was alarmed because they thought that the odor threshold was 260 ppm. It should be noted that the SD-56 MSDS was not changed until 1972. Even the revised version contained erroneous information including an odor threshold of 200 ppm (see Appendix F, 1972 entry). Mr. [redacted] read the SD-56 MSDS which was posted at his workplace, and the only thing that he remembers from it is the explosion hazard related to VCM. As early as 1959, toxicologist V.K. Rowe of Dow, wrote to BF Goodrich stating, "We feel quite confident, however, that 500 ppm is going to produce rather appreciable injury when inhaled 7 hours a day, 5 days a week for an extensive period," (see 5/12/59 entry in Appendix F). Mr. [redacted] did indeed become injured.

In Appendix F, I have attached a timeline that I personally have constructed relating to the events pertinent to Mr. [redacted]'s exposures in his workplace. The 7/17/74 entry of Appendix F describes the passive air sampling method in use at the Aberdeen plant (3M-OV passive dosimeters based on adsorption on charcoal) as producing concentrations that are low by a factor of ten or more and that VCM concentrations at Aberdeen were ranging from less than 1 ppm to greater than 40,000 ppm. This is consistent with an 11/15/93 Vista interoffice memo from Penny to Grumbles stating, "air levels typically in the thousands of parts per million" and a 5/17/74 interoffice memo from Kennedy to Schuster acknowledging VCM odor in the workplace "occasionally" from 1963 to 1974. Note that the odor threshold for VCM is around 2,000 to 4,000 ppm (see entries dated 2/69, 8/8/74, 9/19/74, and 5/2/75 in Appendix F). This threshold is consistent with literature indicating a range from 1,330 to 3,912 ppm.[2] Other entries in Appendix F which also describe exposure situations include those dated 6/28/74, 8/16/74, 3/25/75, 5/14/75 and 12/30/80.

In conclusion, I believe that I have successfully demonstrated that a definitive causal relationship exists between exposure to VCM and the development of hepatic angiosarcoma. I also have shown that Mr. [redacted] labored in an environment that has been well characterized in the industry as being heavily contaminated with airborne VCM. I have provided ample peer-reviewed literature and references to internal documents to indicate the extent of Mr. [redacted]'s exposure. I have discussed Mr. [redacted]'s employment experience with him and found that his comments were very consistent with exposures that have been characterized in the literature under similar circumstances. Mr. [redacted] was exposed to VCM for a period of about 26 years with the heaviest exposures occurring at the young age of 21 years during the cleaning of autoclaves and at an age that he was most susceptible to the effects of VCM. Thirty-two years after his initial exposure, Mr. [redacted] was diagnosed with an extremely rare cancer, hepatic angiosarcoma, a lesion which has been causally related to VCM exposure. Both Mr. [redacted]'s period of exposure and latency for the development of hepatic angiosarcoma are highly consistent with existing knowledge. In addition, I have taken care to dismiss alternative causes of this rare liver lesion such as exposures to arsenic,

Thorocrast, steroids, and radiation. I therefore opine with a high degree of scientific certainty, that the development of Mr. [redacted]'s hepatic angiosarcoma is the direct result of his extensive exposure to vinyl chloride monomer, particularly in the early years of his career. I reserve the right to supplement this report as additional information becomes available.

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Date