

Statement of Dr. Ronald Hoffman

Members of the Committee on Science and Technology

US House of Representatives

My name is Dr. Ronald Hoffman. I am the Albert A. and Vera G. List Professor of Medicine at the Tisch Cancer Institute of the Mount Sinai School of Medicine in New York, NY. At that institution I am Director of the Myeloproliferative Disorders Program. For over 31 years I have been a practicing clinical hematologist. Hematology is the study of the diseases of the blood. In addition, I am a laboratory based scientist who has investigated the stem cell origins of blood cancers. I am an author of over 400 scientific papers and have served as the President of both the International Society of Experimental Hematology and the American Society of Hematology. I am the lead editor of the textbook Hematology, Basic Principles and Practice which is in its 5th edition and is the leading textbook of hematology in the United States and Europe. I have held prior faculty positions at Yale University School of Medicine, Indiana University School of Medicine, Stanford University School of Medicine and the University Of Illinois College Of Medicine.

For the last 30 years my research and clinical practice has revolved around the investigation of a group of chronic blood cancers, termed the myeloproliferative disorders with include polycythemia vera, essential thrombocythemia and primary myelofibrosis. These disorders are characterized by excessive production of red cells, platelets and white blood cells. These disorders are frequently associated with excessive blood clotting or bleeding and evolution to acute leukemia. These disorders are now known to be blood cancers which originate at the level of blood stem cells. In 2005 a mutation of an intracellular kinase termed JAK2 was found to be present in patients with myeloproliferative disorders. JAK2 is responsible for transmitting signals to blood cell elements inducing them to produce greater numbers of such cells in response to hormones that normally regulate blood cell production. The JAK2 mutation was discovered by a group in France headed by Dr. William Vainchenker. The mutation allows blood cell production to occur in myeloproliferative disorder marrow cells in the absence of the signals provided by the hormones that normally control blood cell production, thereby leading to the production of too many red cells, white cells or platelets in patients with these blood cancers. This JAK2V627F mutation also been shown to provide an almost fool proof means of diagnosing patients with myeloproliferative neoplasms since it can be detected using molecular methods in over 95% of patients with polycythemia vera, and 50% of patients with essential thrombocythemia and primary myelofibrosis. Previously, polycythemia vera was diagnosed based upon a variety of costly diagnostic tests as well as relatively nonspecific clinical signs and symptoms. Since there are numerous other causes of too many red cells or polycythemia other than this form of blood cancer, physicians frequently had great difficulty in definitively making this diagnosis. With the advent of the molecular test for

JAK2V617F, the accuracy of definitively diagnosing polycythemia vera has been greatly enhanced. Although blood cells with the JAK2V617F are occasionally observed in patients with other kinds of blood cancers it is rarely if ever observed in normal people.

My first contact with the Agency for Toxic Substances and Disease Registry (ATSDR) began in the summer in 2006. Dr. Vince Seaman, an epidemiologist and toxicologist at ATSDR first called me to ask me some questions about the nature of polycythemia vera and about the possibility of environmental insults increasing in the incidence of this blood cancer. I had never heard of the ATSDR and at that time had not been previously acquainted with Dr. Seaman. I was a bit skeptical about the significance of a cluster of polycythemia vera patients that Dr. Seaman and his colleagues were then investigating in Carbon, Luzerne and Schuylkill counties in Eastern Pennsylvania in response to an invitation made by the Pennsylvania Department of Public Health. After a series of phone calls with Dr. Seaman, I gained a greater degree of comfort with these investigations and became concerned about this high incidence of polycythemia vera in this area that had been initially identified by the Pennsylvania Department of Public Health. I thought that this cluster was potentially important from a scientific point of view and that it presented a possible public health danger to the citizens of Pennsylvania. In the past, links between environmental toxic exposures and clusters of polycythemia vera had not been well documented. In my discussions with Dr. Seaman I emphasized the difficulty of making the clinical diagnosis of polycythemia vera and that the newly described molecular assay for JAK2V617F would provide a simple inexpensive means of making this diagnosis with certainty merely by testing blood drawn from the study subjects. Dr. Seaman agreed and we set about to create a means of obtaining blood specimens from the subjects who agreed to participate in the study. Specimens were collected in Tamaqua, shipped to my laboratory and analyzed for JAK2V617F during the period from December 2006 through April 2007. These specimens were shipped in a deidentified manner to my laboratory and the assays were performed without knowledge of the patient source. Initially I had asked that ATSDR to provide some support to cover the expenses for the performance of these assays. To my surprise the agency administrators were unwilling to supply such funds and were actually resistant to their performance. Their unwillingness to receive input about the significance of the extraordinarily large numbers of patients with this hematological cancer in this small area of Pennsylvania or to consider the value of a molecular epidemiological tool to make their task easier surprised me. Their lack of comfort in collaborating with scientists outside their community or their area of expertise and to readily incorporate new scientific advances into their research efforts while investigating a possible cluster of blood cancer patterns seemed odd, and closed minded in nature. I frequently felt that the members of the Agency management team viewed that this molecular epidemiological approach was overkill and unnecessary since they had already concluded that the cluster was not significant or worthy of further investigation. We proceeded with the JAK2V617F testing without the support of the Agency due to my belief that these studies were the state of the art in 2009 and were required to confirm the diagnosis of polycythemia vera. The molecular testing for JAK2V617F was supported with funds that I had received from the Myeloproliferative Disorders Research Foundation for different purposes. The Foundation agreed to this diversion of resources. Dr. Seaman

and his team sent us fifty six blood specimens which we evaluated for the JAK2V617F mutation. Over half of these specimens were JAK2V617F positive and an additional 5 patients from the area were shown to be JAK2V617F positive based upon information present in their medical records; I also assisted ATSDR in establishing a committee of medical experts to examine the medical records of the participants in the study to be certain that the clinical characteristics of these individuals were consistent with a diagnosis of polycythemia vera.

By the end of April 2007 these molecular analyses had been completed showing that about 53% of the subjects in the study area fulfilled both clinical and molecular diagnostic criteria of having polycythemia vera. One patient had diagnostic features of polycythemia vera as determined by our committee of experts but did not have the JAK2V617F mutation. The confirmed cases appeared to be clustered around the EPA superfund sites and sites of waste coal power plants in the tri-county area. Remarkably, four of the reported cases of polycythemia vera were located along Ben Titus Road, a stretch of about 100 homes scattered over a distance of a mile; each of these cases was confirmed as being JAK2V617F positive indicating that these patients did indeed have polycythemia vera. Remarkably, the greatest numbers of cases of polycythemia vera were in the Tamaqua area, a sparsely populated area, not in the area of greatest population density near Wilkes-Barre where the cancer registry data (which is based upon diagnoses being made using clinical criteria) had indicated that the greatest numbers of patients had lived. With this data in hand, I and Dr. Seaman wrote an abstract in August 2007 for consideration for presentation at the 2007 meeting of The American Society of Hematology Meeting which was to be held in December 2007 in Atlanta, Georgia. Over 20,000 hematologists from around the world usually attend this meeting. Several conference calls were held with numerous members of the ATSDR staff who checked the data and went over the content of the abstract word by word and agreed with the data and the conclusions of the abstract vocally during these numerous conversations prior to its submission. The abstract was then submitted for consideration for presentation at the American Society of Hematology Meeting. Although numerous ATSDR staff were aware of this submission and its content, Dr. Seaman, without my knowledge, apparently did not have the abstract formally cleared by the agency. Dr. Seaman explained to me that he was new at the Agency and was not fully aware of the clearance process for documents of this type. This omission was surprising to me and appeared to represent a technicality since so many of the ATSDR staff had gone over the content of this abstract and had already agreed with its content during our numerous phone conversations. In October of 2007 I attended a community meeting dealing with this subject which was organized by the ATSDR and the Pennsylvania Department of Health in Hazelton, Pennsylvania. Prior to the meeting I had lunch with many of the junior staff of ATSDR who had come to Hazelton. My collaborator at the agency, Dr. Vince Seaman was noticeably absent. Several weeks prior to the meeting he had been sent to Mozambique for a mandatory training period dealing with agency business. I felt that the timing of Dr. Seaman's trip was odd and showed poor judgment on the part of the agency. Dr. Seaman had participated in the field of work that led to the report and had the confidence and trust of the community. Many of the community members saw Dr. Seaman as a so called "straight shooter". At the lunch many of the junior staff of the ATSDR bemoaned Dr.

Seaman's absence, but were energized by the findings that had resulted from the collaboration between Dr. Seaman and my laboratory . About 75 – 100 community members attended the meeting and there were a series of presentations, some by the professionals in the community, by ATSDR senior staff and by myself. The conclusions articulated by the ATSDR spokesperson seemed at odds with the results summarized in our abstract that had just been submitted to the American Society of Hematology. The ATSDR claimed that groups of polycythemia vera cases were scattered throughout the tri-county area in no predictable pattern. They also emphasized that only half of the reported cases actually had polycythemia vera based upon our molecular analyses but failed to mention that even with this caveat in mind that the incidence of polycythemia vera was still extraordinarily high in this region. ATSDR appeared to minimize the importance of these findings and concluded that it would be virtually impossible to identify the inciting agent that might possibly have led to the polycythemia vera cluster. The ATSDR spokesperson seemed to feel that this was a fruitless effort and was not really worthy of further attention. I was impressed by the anger of the community at the meeting, there sense of futility and betrayal. At the meeting I mentioned to the audience that we have submitted an abstract to the American Society of Hematology about our findings and that the scientific community would assess the validity of our conclusions. I attempted to inform them that if this material was found scientifically meritorious that the scientific community would demand further investigation of the problem. They appeared skeptical. As I drove back to New York that evening with my scientific colleague at Mount Sinai, Dr. Mingjiang Xu we talked about the experiences of the day. We commented how we felt, that the ATSDR had misinterpreted and prematurely drawn conclusions about the data that we had participated in generating. We commented that many of the ATSDR management were unwilling to think out of the box and how their unwillingness to investigate the unknown or to address difficult problems was the antithesis to the type of scientific investigation that we were so familiar with in the biological and medical sciences. Also we questioned if there was some outside constituency who ATSDR was responding to that made them act like they just wanted this whole matter to go away. Instead of viewing this as a challenging and important scientific problem of possible importance, we felt that they had concluded that it was not important or that it was futile to try to further investigate its origins.. Their lack of familiarity with the power of modern cellular and molecular biology and their unwillingness to apply these tools in an innovative fashion to this problem was surprising to me. I concluded that this type of nihilism was antithetical to the performance of good science.

In the middle of November I was emailed by the American Society of Hematology that our abstract had been accepted as an oral presentation. Only 12% of the thousands of abstracts submitted to this meeting receive a high enough grade to be presented at an oral session. I immediately informed Vince Seaman of the acceptance. Vince was in Mozambique on assignment but he and several other ATSDR staff members helped me create the presentation and reviewed its content and repeatedly altered the content until they approved it and the written speech that I was to present at the meeting. There were repeated attempts and requests on the part of ATSDR management to avoid showing

maps which might indicate a geographic relationship between the cases of polycythemia vera and the known EPA super fund sites.

A representative of the agency management team was to appear at the presentation but at the last moment, although he was based in Atlanta, he stated that it was not necessary and that he would not be attending. Several days prior to my presentation at the Atlanta meeting the ATSDR - unknownst to me - issued a press release stating that the abstract presented results that were premature and scientifically flawed. Medical colleagues in Hazelton called me and informed me about this disclaimer by the agency, reports of which had appeared in the local press in Pennsylvania and asked me what I was going to do. I was a bit shocked and was incredulous about the lack of forthrightness demonstrated to me by my presumed scientific collaborators at ATSDR. I told the physicians in Hazelton that I still believed that the data were correct and that I intended to present the information and let the scientific community evaluate its merit. I must tell you I felt betrayed by the leadership of ATSDR since I had made great efforts to get these leaders involved in the content of the abstract and obtain their approval. After my arrival in Atlanta, I was contacted on my cell phone on repeated occasions by officials of ATSDR requesting that I either withdraw the abstract entirely, state prior to my presentation that the agency disagreed with my conclusions or present an abridged version of the data. I was intimidated by these frequent calls by government officials which created a great degree of stress and anxiety for me. I was also outraged at this obvious attempt at intimidation. I refused to alter the presentation and presented it in its entirety although ATSDR continued to undermine its validity in the press. I felt justified in these actions since numerous members of the Agency had previously repeatedly approved the content of the abstract. The presentation was well received and the scientific community accepted the possibility that environmental contaminants might play a role in the development of polycythemia vera in the patients in the Tamaqua area.

After receiving this positive feedback from the members of the American Society of Hematology, I realized that the only way that I could further validate the data was for it to be published in a peer reviewed journal so that once and for all this data would be in the public domain and be open to further scientific input and criticism. Upon Dr. Seaman's return from Mozambique we began writing this manuscript. The senior leadership of the agency continued to doubt these conclusions and insisted that the agency's biostatisticians perform sophisticated geospatial analyses to further test the validity of our findings. I strongly agreed with their scientific rigor not wanting to be associated with incorrect information. This cluster analysis was done using Satscan, a geospatial software tool developed by the National Cancer Institute for the detection of cancer clusters. The chance of the likelihood of the polycythemia vera cluster being a random event based on the total number of cases in the tri-county area was calculated by the agency statisticians independently of my input or that of Dr. Seaman. A single statistically significant cluster of polycythemia vera patients ($p < 0.001$) was identified near the geographic center of the three counties. The incidence of polycythemia vera in the cluster area was 4.3 times higher than that in the rest of the county. The probability of one finding greater than 15 cases of polycythemia vera in this area and 18 cases in the remainder of the tri-county area was 1 in 220,000. The probability of the cluster being a

random event based on the total number of confirmed cases in the tri-county area was 1/2000. Several sources of hazardous materials were located in or near the high rate area of polycythemia vera. Seven of the 16 waste coal power plants in the United States are located in or within this area or within a few miles of the area. Seven U.S Environmental Protection Agency super fund sites are contained within this area and another possible cluster area that was identified. This manuscript was completed and revised on numerous occasions with the participation of members of the ATSDR and the Epidemiology Branch of the Pennsylvania Department of Public Health. Numerous revisions were made on the manuscript based upon the suggestions of the ATSDR and the Pennsylvania Department of Public Health without compromising the validity of the information presented. The manuscript was reviewed and revised word by word during several teleconferences. This manuscript was accepted by the peer reviewed journal, Cancer, Epidemiology, Biomarkers and Prevention published in February 2009. During the submission process, a number of minor changes were made in the manuscript to accommodate the Journal's reviewers and specific publication format requirements. This is a routine process and ATSDR did not require the final version of the manuscript to be re-cleared. After the manuscript was published, the chief epidemiologist at the Pennsylvania Department of Health, who had actively participated in the word-by-word editing of the manuscript even though he was not an author, became very upset when he found that the manuscript had been altered. He made numerous calls to high-placed officials at ATSDR in an effort to get them to discredit the manuscript. The ATSDR management resisted these efforts as they recognized that the manuscript contained factual, scientifically valid information and there was no basis for the claims being made by the Pennsylvania Department of Health.

I also participated in a round table discussion of expert researchers convened by ATSDR and the Pennsylvania Department of Public Health in Philadelphia later in 2008 to identify research priorities about further investigating the extent of the cluster of cases of polycythemia vera in the tri-county area and determining possible factors that might have led to this cluster. The data that was presented in the paper published in Cancer, Epidemiology, Biomarkers and Prevention I believe is important and valid. I believe that it provides information which justifies continued realistic concerns that there is a relationship between a cluster of cases of polycythemia vera and serious environmental exposures in the tri-county area. This concern clearly merits careful, additional, detailed objective rigorous scientific investigation to better define the magnitude of this problem and what are the possible causes of such an event. This information is of potential importance not only for the population of this tri-county area but to all citizens of the United States because it provides a possible link between the environment and blood cancers, an association that has not to date been well documented.

ATSDR is the leading federal public health agency responsible for determining human health effects associated with toxic exposures, preventing continued exposures and mitigating associated human health risks at the 1200 National Priorities hazard waste sites targeted for cleanup by the US Environmental Protection Agency. The mission of the ATSDR is stated to be "to generate and communicate credible scientific information about the relationship between hazardous substances and adverse human health effects and to promote responsive public health actions." My experience was that in the case of

the polycythemia vera cluster in Eastern Pennsylvania that ATSDR accomplished this goal only because of the relentless prodding to complete the needed investigations due in part to the efforts of some of the talented staff at the agency working in collaboration with our group at the Mount Sinai School of Medicine in New York and the continued input of the physicians in the tri-county area and of course the residents of this area. My sense was that if the agency was left to themselves they would have preferred to ignore the whole problem. ATSDR seemed committed to a course of ignoring and discrediting a mounting body of evidence which suggested the presence of a cluster of polycythemia vera patients in the tri-county area. The agency appeared to be overly responsive to possible outside influences which compromised its ability to evaluate the severity of this problem. Rather than questioning the validity of this cancer cluster in a pro-active manner, their initial response was to discount its significance and to express on numerous occasions the futility in attempting to link the cluster of these cases of polycythemia vera to any specific environmental toxins. This type of work is obviously difficult and time consuming but appears to be the core function of this agency. If the agency is not willing to evaluate such clusters in a pro-active and objective fashion and closely interact with individuals with different and complementary areas of expertise then the possibility of their accomplishing their stated goals is very small. The scientific nihilism and lack of respect for the integrity of scientific investigation initially displayed by members of the agency surely compromises the stated mission of this agency. Their unwillingness to look objectively at the compelling data generated by our investigations is puzzling and disturbing to me. The agency has many talented, skilled energetic professionals in its ranks who have expressed to me frustration and concern about their being held back from fully investigating the polycythemia vera cluster in Pennsylvania. The reasons for these actions and their rationale remain unclear. Most recently the agency has become increasingly more committed to more vigorously investigating the polycythemia vera cluster and its causes. I congratulate them on this recent change in policy. This behavior is much more appropriate and consistent with the stated mission of the agency and will likely to lead to a growth of a valid body of information that will provide new insight into the significance of the polycythemia vera cluster in Eastern Pennsylvania and its possible causes. In addition these investigations will likely provide new information about a possible link between blood cancers and environmental toxins. Such information will hopefully be helpful in decreasing in the future the incidence of such deadly cancers in areas of such high risk for exposure to environmental toxins.