

UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 07-11944-GAO

BRIAN K. MILWARD and LINDA J. MILWARD,  
Plaintiffs,

v.

ACUITY SPECIALTY PRODUCTS GROUP, INC., AMERICAN GREASE STICK COMPANY, ARISTECH CHEMICAL CORPORATION, BERRY PRODUCTS, INC., BOSTIK, INC., BOYLE-MIDWAY, INC., THE CLOROX COMPANY, CRC INDUSTRIES, INC, HENKEL CORPORATION, LA-CO INDUSTRIES, INC./MARKAL, LPS INDUSTRIES, INC., NCH CORPORATION, CHEMSEARCH DIVISION, NICUS CORPORATION, NUCALGON WHOLESALER, INC., RADIATOR SPECIALTY COMPANY, RUST-O-LEUM CORPORATION, SHERWINWILLIAMS COMPANY, THE STECOCORPORATION, SUNNYSIDE CORPORATION, UNITED STATES STEEL CORPORATION, USX CORPORATION, WD-40 COMPANY, and ZEP MANUFACTURING COMPANY,  
Defendants.

OPINION AND ORDER

July 31, 2009

O'TOOLE, D.J.

In their first amended complaint, the plaintiffs allege that over time Brian Milward “was exposed to products manufactured and/or sold by Defendants which included benzene as an ingredient or contaminant” and that “[a]s a direct and proximate result of [his] exposure to benzene . . . and other benzene-containing products . . . , he developed Acute Promyelocytic Leukemia . . . .” (First Am. Compl. ¶¶ 31, 33.) The plaintiffs propose to prove a central proposition necessary to their claims—that benzene can cause acute promyelocytic leukemia (“APL”)—through the testimony of Dr. Martyn Smith, a toxicologist, to be offered under the authority of Federal Rule of Evidence 702. The defendants have objected that Dr. Smith’s

proposed testimony does not meet Rule 702's standard for admissibility, as elucidated in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), and subsequent cases.

On this issue, both sides have presented affidavits and supporting materials, including a large number of articles published in respected, peer-reviewed journals. In addition, Dr. Smith and defense witnesses Drs. David Garabrant, David Pyatt, and John Bennett all testified at an evidentiary hearing. Upon consideration of the evidence submitted, I conclude that Dr. Smith's proffered testimony that exposure to benzene can cause APL lacks sufficient demonstrated scientific reliability to warrant its admission under Rule 702.

### **I. Relevant Legal Principles**

Rule 702 provides:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

When a party's proffer of expert scientific evidence is objected to by an opponent,

the trial judge must determine at the outset, pursuant to Rule 104(a), whether the expert is proposing to testify to (1) scientific knowledge that (2) will assist the trier of fact to understand or determine a fact in issue. This entails a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.

Daubert, 509 U.S. at 592-93. This "gatekeeping" by the trial court, see id. at 597, ensures "that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand," id. at 598.

The requirement that the testimony be "reliable" comes from Rule 702's reference to "scientific . . . knowledge." Id. at 590.

In order to qualify as “scientific knowledge,” an inference or assertion must be derived by the scientific method. Proposed testimony must be supported by appropriate validation—i.e., “good grounds,” based on what is known. In short, the requirement that an expert’s testimony pertain to “scientific knowledge” establishes a standard of evidentiary reliability.

Id. It is important to note that the necessary “reliability” is *evidentiary* reliability, in the usual sense that the evidence must be sufficiently trustworthy for a jury to be permitted to rely on it. Id. at 590 n.9. Evidentiary reliability depends on the scientific validity of the testimony. Id.

The need for the testimony to be “relevant” derives from Rule 702’s requirement that it “assist the trier of fact to understand the evidence or to determine a fact in issue.” Id. at 591; see also Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co., 161 F.3d 77, 81 (1st Cir. 1998) (“To be admissible, expert testimony must be relevant not only in the sense that all evidence must be relevant, but also in the incremental sense that the expert’s proposed opinion, if admitted, likely would assist the trier of fact to understand or determine a fact in issue.”) (internal citation omitted). The scientific validity of the proposed testimony thus relates to both the “relevance” and “reliability” requirements because the testimony can only assist the trier of fact if it has “a valid scientific connection to the pertinent inquiry.” See Daubert, 509 U.S. at 592.

In Daubert, the Supreme Court cautioned that because the “overarching subject” of the admissibility inquiry under Rule 702 “is the scientific validity—and thus the evidentiary relevance and reliability—of the principles that underlie” the proposed testimony, “[t]he focus, of course, must be solely on the principles and methodology, not on the conclusions that they generate.” Id. at 594-95. This admonition emphasizes that scientifically valid evidence cannot be excluded simply because the trial judge is not persuaded that the witness’s conclusions are correct. See Ruiz-Troche, 161 F.3d at 85 (“Daubert does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert’s assessment of the

situation is correct.”). Whether the opinion is ultimately persuasive on the issue to which it is relevant is a matter for the trier of fact, not the gatekeeper. Id.

To the extent that the Court’s statement in Daubert may have suggested a clear dichotomy between “methodology” and “conclusions,” it was a bit too stark. The Court later modulated the point by noting that “conclusions and methodology are not entirely distinct from one another.” Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997). In Joiner, the trial court had excluded a proffered expert opinion because the expert’s conclusions were not sufficiently supported by the published studies upon which he relied. In holding that it was not an abuse of discretion to exclude the evidence, the Court said:

Trained experts commonly extrapolate from existing data. But nothing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.

Id. In other words, “while methodology remains the central focus of a Daubert inquiry,” it may be necessary for the trial judge to evaluate whether the conclusions drawn by the expert have adequate support in the scientific principles upon which the expert purports to rely. See Ruiz-Troche, 161 F.3d at 81. As the court of appeals has put it:

[E]ven though Daubert and its progeny require trial judges to evaluate the level of support provided by complex scientific studies and experiments in myriad disciplines, reliability and relevance remain legal judgments. Trial judges cannot abdicate the responsibility for making those judgments by delegating them to the scientific community.

Id.

## **II. Dr. Smith’s Testimony**

The plaintiffs would call Dr. Smith as a witness to establish “general causation”—that is, the general principle that exposure to benzene can cause APL. In brief, his opinion is based

primarily on his conclusion that benzene as a cause of APL is “biologically plausible.” He further finds support for this conclusion in the limited number of epidemiological studies containing data about the possible causal relationship between exposure to benzene and the development of APL. All told, Dr. Smith would testify that the “weight of the evidence” supports a conclusion that exposure to benzene is a cause of APL. (See generally Pls.’ Br. in Supp. of the Admissibility of Their Expert Evidence on Gen. Causation Exs. 3 [hereinafter Smith Decl.] & 7 [hereinafter Smith Supp. Decl].)

The defendants do not challenge Dr. Smith’s professional qualifications. He holds a Ph.D. in biochemistry and is a professor of toxicology in the School of Public Health at the University of California at Berkeley. He is an author of more than 200 research articles published in peer-reviewed scientific journals, as well as scores of other publications, including book chapters, reviews, and technical reports.

A. Some Uncontested Scientific Background

Leukemia is a cancer of the human blood. It is marked by the uncontrolled proliferation within the blood of cancerous, or leukemic, cells. Because the blood includes a variety of differentiated cells, various forms of leukemia are described by reference to the type of cell affected. As a general matter, differentiated blood cells are classified either as myeloid cells, stemming from a common myeloid progenitor cell, or as lymphoid cells, stemming from a common lymphoid progenitor cell. Similarly, the various forms of leukemia are classified broadly as myeloid or lymphoid leukemias depending on the cells affected. In turn, the leukemias are further classified as either acute or chronic. Accordingly, any particular form of leukemia falls within one of four general classes: acute myeloid leukemia (“AML”), chronic myeloid leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia.

APL, at issue here, is one of seven or eight subtypes of AML, which are sub-classified, by convention, as types M0 through M7. APL is type M3. AML of any type is relatively rare, with an annual incidence of about six to eight cases per 100,000 people, and APL cases are about five to ten percent of all AML cases.

The process in which blood cells form, mature, and differentiate, called hematopoiesis, begins with hematopoietic stem cells (“HSCs”) and culminates with mature differentiated cells that serve a particular purpose, such as granulocytes, a category of white blood cells. HSCs are pluripotent, meaning that they can potentially differentiate into any of a number of specialized cells. During the cell maturation process, there are intermediate stem cells, sometimes termed “multipotent” or “oligopotent,” that still have some potential, but less than HSCs, to develop into various specialized cells. However, some possibilities are eliminated at progressive stages of maturation. For example, the myeloid progenitor cell (identified as CFU-GEMM) may lead to any of the differentiated myeloid cells, but not to any lymphoid cells. APL occurs in committed myeloid cells.

In almost all cases of APL, there is a characteristic genetic alteration. As Dr. Smith describes it in his affidavit:

[T]he retinoic acid receptor-alpha (RAR $\alpha$ ) gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukemia gene (PML) on chromosome 15, a translocation denoted as t(15;17) (q22;q12). . . . The resultant fusion proteins disrupt the function of the RAR $\alpha$  which blocks the normal maturation of granulocytes. The chromosomal translocation involving RAR $\alpha$  is believed to be the initiating event in APL and may be essential to the development of this subtype of AML.

(Smith Decl. ¶ 18.) The t(15;17) translocation is necessary, but not sufficient in itself, to induce APL. In fact, APL occurs in only about ten percent of persons with that chromosomal

translocation. In rare cases of APL, the chromosomal translocation is different, but in all cases chromosome 17 is involved.

B. The Contested Opinions

Dr. Smith's opinion is that it is "biologically plausible" that exposure to benzene can cause APL. This opinion rests on a three-part foundation:

First, the subtypes of AML are, in fact, subtypes of one disease in as much as they all derive from a genetically damaged pluripotent stem cell which can differentiate into all myelogenous cell types and proliferate, developing the various AML subtypes. Since the subtypes of AML all derive from a genetically damaged pluripotent stem or progenitor cell, they likely have a common pathogenesis.

(Id. ¶ 28.a.)

Second, APL is characterized by a chromosome translocation involving chromosome 17 and a partner chromosome in which the two chromosome pairs undergo double-stranded breaks and rearrangement. Since benzene is clastogenic and has the capability of breaking and rearranging chromosomes, it is biologically plausible for benzene to cause this cytogenic abnormality.

(Id. ¶ 28.b.)

Third, it is biologically plausible that exposure to benzene actually induces the chromosome translocations that result in APL through the inhibition of an enzyme called topoisomerase II.

(Id. ¶ 28.c.)

In addition to his conclusions about the biological plausibility of a causal relationship between exposure to benzene and APL, Dr. Smith would opine that epidemiological studies showing a causal relationship between benzene exposure and other AML subtypes also support a causal relationship with respect to APL. (See id. ¶¶ 24-27, 28.c.) Some epidemiological studies with data bearing on whether benzene causes APL show a positive association between benzene exposure and APL, but the associations shown are not statistically significant. See, e.g., Nat'l Investigative Group for the Survey of Leukemia & Aplastic Anemia, Countrywide Analysis of

Risk Factors for Leukemia and Aplastic Anemia, 14:3 Acta Academiae Medicinae Sinicae (1992) [hereinafter Acta Study]. Nonetheless, Dr. Smith would testify that these studies are suggestive of a causal connection and thus count positively in its favor in a weight of the evidence evaluation.

### **III. Conclusions**

#### **A. Dr. Smith's Opinion that All AMLs, Including APL, Have a Common Pathogenesis Because They All Derive from a Common Genetically Damaged Stem Cell Is Not Supported by Sufficient Reliable Facts and Data.**

There is no dispute that, in the words of the defendants' expert toxicologist, Dr. Pyatt, "[s]cientific and medical evidence . . . supports a causal link between benzene and the development of AML." (Defs.' Daubert Submission in Opp'n to Pls.' Proffered Experts Ex. 29, ¶ 13 [hereinafter Pyatt Decl.].) Dr. Smith relies on that broadly described causal link between benzene and AML to support his opinion that APL, a particular subtype of AML, must also be caused by exposure to benzene.

However, clear differences exist among AML subtypes that may make inappropriate a broad extrapolation from AML generally to APL specifically. For instance, as Dr. Smith himself acknowledges, APL is a unique clinical or therapeutic entity, distinguished biologically from other subtypes of AML by the characteristic t(15;17) translocation and its amenability to treatment by all-trans retinoic acid. (Smith Supp. Decl. ¶ 2.) In addition, other subtypes of AML that apparently occur secondary to alkylating chemotherapy administered to patients with a primary cancer also appear to have their own unique chromosomal characteristic—deletions at chromosomes 5 and 7—that is not seen either in APL or, perhaps more significantly, in cases of primary AML. (Pyatt Decl. ¶ 12.) Questions arise, therefore, about how similar and how

different various AML subtypes may be in ways that matter for Dr. Smith's opinion that benzene is a common cause for all AML subtypes.

Dr. Smith's answer is that the mutating effect of the benzene exposure occurs at an early stage of cell development, before differentiation has proceeded very far; therefore, this mutation has the potential to impact all myeloid cell lineages and all subtypes of AML. Because any leukemia involves uncontrolled proliferation of leukemic cells, the leukemia-initiating cell must have the self-renewing properties of a stem cell. For this reason, it is not unreasonable to suspect that the leukemic stem cell is a genuine stem cell, whether pluri-, multi-, or oligopotent, that has incurred a leukemia-inducing transformation.

Recent research, however, has led investigators to think that the "leukemic stem cell" may exist in more mature, differentiated cell lines. See, e.g., S. Wojiski et al., [PML-RAR \$\alpha\$  Initiates Leukemia by Conferring Properties of Self-Renewal to Committed Promyelocytic Progenitors](http://www.nature.com/leu/journal/vaop/ncurrent/index.html#26032009), *Leukemia* (Mar. 26, 2009), available at <http://www.nature.com/leu/journal/vaop/ncurrent/index.html#26032009> (last visited July 30, 2009) [hereinafter Wojiski]. In other words, the "leukemic stem cell" may not be a stem cell in the usual sense, but rather a differentiated cell that has somehow acquired the ability to reproduce itself, as a stem cell can. Describing such a cell as a "stem cell" is, strictly speaking, inaccurate, but the term is apparently used as a shorthand way of referring to the reproducing capability of the leukemic cell. The proposed "leukemic stem cell" is more precisely a leukemic cell capable of self-renewal.

At this time, there is no scientific consensus about the leukemic stem cell and at what stage of cell maturation it may occur. Investigation continues. The debate is evident in several published articles admitted into evidence at the hearing. For instance, in a recent review article published in *Leukemia*, a respected, peer-reviewed journal, Misaghian and others wrote:

“Numerous investigations have provided evidence that AML arises from genetic mutations. It is not currently known for certain whether the mutations occur in the normal stem cells or in more differentiated cell types, which then acquire stem cell-like features.” N. Misaghian et al., Targeting the Leukemic Stem Cell: The Holy Grail of Leukemia Therapy, 23 *Leukemia* 25, 25 (2009). Other researchers claim that evidence tends to show affirmatively that the leukemic transformation leading specifically to APL occurs not at a primitive stem cell level, but rather at the level of a committed, differentiated cell. See A.G. Turhan et al., Highly Purified Primitive Hematopoietic Stem Cells Are PML-RAR $\alpha$  Negative and Generate Nonclonal Progenitors in Acute Promyelocytic Leukemia, 85 *Blood* 2154, 2154 (1995). Another paper, while noting that transformations leading to some forms of AML appear to occur at the HSC level, reported that the transformation leading to APL may occur at the level of a more mature, committed cell:

Although HSCs are often the target of genetic events leading to malignant transformations, committed progenitors or even differentiated cells may also become transformed. In [APL] patient samples, the M3 subtype of AML, it has been shown that the [APL]-associated fusion gene PML/retinoic acid receptor  $\alpha$  (RAR $\alpha$ ), which results from the t(15;17) balanced reciprocal translocation, was present in [CD34-CD38+] cell populations but not in [CD34+CD38-] HSC-enriched cell populations. This observation suggests that in [APL] the transformation process may involve a more differentiated cell type than HSCs and/or pluripotent progenitors that have been implicated in other AML subtypes.

Emmanuelle Passagué et al., Normal and Leukemic Hematopoiesis: Are Leukemias a Stem Cell Disorder or a Reacquisition of Stem Cell Characteristics?, 100 *Proceedings of the Nat'l Acad. of Science USA* 11842, 11846 (2003).

In any event, a paper to be published in Leukemia later this year sums up the state of the science regarding the level at which the leukemic transformation for APL occurs: “[O]ur results do not formally address the target cell of transformation in APL in which the initial PML-RAR $\alpha$

mutation occurs, *a question that remains unanswered in the APL field.*” Wojiski, *supra*, at 8 (emphasis added).

What is the target cell for the leukemic transformation that leads to APL? The evidence indicates that the answer at this time remains, “We don’t know.” Dr. Smith has a theory, and that theory may be correct. Or it may be correct in some instances and not others. It is a point in his favor that, as noted above, the fact that the leukemic cell proliferates has tended to support the idea that the leukemic stem cell was a true stem cell, existing early in the maturation process. On the other hand, however, more recent research has led some scientists to think that differentiated cells, at a stage of development later than the common myeloid progenitor, may also acquire the ability to proliferate, akin to a stem cell, though they are not in fact stem cells. Significantly, some research indicates this may be particularly true in APL.

Based on the present state of “scientific knowledge,” Dr. Smith’s theory is at best a plausible hypothesis; it might be true. There are other plausible hypotheses that might be true as well, including the hypothesis that the genetic mutation that leads to APL occurs in relatively mature cells, not in a common progenitor cell of all myeloid lineages. The evidence presented here does not support a conclusion that, at the current state of knowledge, Dr. Smith’s opinion that the mutation that causes all AML subtypes, including APL, occurs in a common progenitor stem cell is based on sufficient facts and data to be accepted as a reliable scientific conclusion, as distinguished from an hypothesis. The opinion is not admissible under Rule 702.

**B. Dr. Smith’s Opinion that Because Benzene Has Been Shown to Cause Some Chromosomal Damage, It Probably Also Causes the t(15;17) Translocation Is Only an Hypothesis and Not a Conclusion that Has Been Shown To Be Reliably Established.**

As noted above, the parties agree that exposure to benzene has been established as a cause of some subtypes of AML other than APL. The chromosomal damage in such cases has

been identified to chromosomes 5 and 7 or 8 and 21. See Luoping Zhang et al., Nonrandom Aneuploidy of Chromosomes 1, 5, 6, 7, 8, 9, 11, 12, and 21 Induced by the Benzene Metabolites Hydroquinone and Benzenetriol, 45 *Envtl. & Molecular Mutagenesis* 388, 389 (2005) [hereinafter Zhang] (“[W]e have reported that the loss of chromosomes 5 and 7 (monosomy 5 and 7) and the gain of chromosomes 8 and 21 (trisomy 8 and 21) are significantly increased in benzene-exposed workers in comparison with controls.”). No evidence has been published making a similar connection between benzene exposure and the t(15;17) translocation, characteristic of APL.

Dr. Smith’s opinion is that “[s]ince benzene is clastogenic and has the capability of breaking and rearranging chromosomes, it is biologically plausible for benzene to cause” the t(15;17) translocation. (Smith Decl. ¶ 28.b.) This is a kind of “bull in the china shop” generalization: since the bull smashes the teacups, it must also smash the crystal. Whether that is so, of course, would depend on the bull having equal access to both teacups and crystal. If the teacups were easily knocked over, but the crystal securely stored away, a reason would exist to question, if not to reject, the proposition that the crystal was in as much danger as the teacups.

One way there might be equal damage-causing access would be if it appeared that the damage was not specifically directed to vulnerable areas, but was randomly experienced. Thus, if benzene metabolites were observed to damage chromosomes randomly, then the fact that it damages some might lead one to infer, at least provisionally, that it could damage all. On the other hand, if benzene metabolites were observed to cause selective damage, then one would want to identify the mechanism of selection in order to see what unobserved selective damage might be inferred. Without understanding why some chromosomes were selected for damage,

one could not decide whether or which other chromosomes would also be susceptible to damage. One could not draw the general conclusion that Dr. Smith seems to draw.

The Zhang paper reported findings that two particular benzene metabolites cause selective, rather than random, chromosomal aberrations. The authors, who include Dr. Smith, wrote that their experimental data “support[s] the idea that benzene can initiate or promote leukemia induction by a nonrandom selective effect on the ploidy status of specific chromosomes.” Zhang, *supra*, at 390. The results of this study do not establish that benzene does *not* cause the specific chromosomal translocation t(15;17) characteristic of APL, but they do tend to defeat the generalization that because it has been shown that benzene causes damage to some chromosomes, it is “biologically plausible” that it causes damage to other chromosomes.

Since general extrapolation is not justified and since there is no direct observational evidence that benzene causes the t(15;17) translocation, Dr. Smith’s opinion—that because benzene is an agent that can cause some chromosomal mutations, it is “plausible” that it causes the one critical to APL—is simply an hypothesis, not a reliable scientific conclusion.

C. Dr. Smith’s Opinion that Benzene Metabolites Inhibit Topoisomerase II in Such a Way as to Cause the Chromosomal Translocation Seen in Cases of APL Is an Hypothesis and Not a Conclusion that Has Been Shown To Be Reliably Established.

Topoisomerase II (“topo II”) is an enzyme that facilitates the replication of DNA without damage. If the protective effect of the enzyme is inhibited, damage to DNA could occur, possibly resulting in leukemia-initiating genetic or chromosomal mutations. Various substances inhibit the action of topo II, including some benzene metabolites. It has also been shown that some topo II inhibitors have been associated with particular chromosomal aberrations and hence particular subtypes of AML, including APL.

Evidence is lacking, however, to support Dr. Smith's conclusion that the inhibition of topo II by benzene metabolites leads to APL, as distinguished from other AML subtypes. There are different classes of topo II inhibitors and the different classes have been associated with different AML subtypes. For instance, the epipodophyllotoxin class of topo II inhibitors has been associated with AML subtypes M4 and M5; whereas, the dioxopiperazine class has been associated with subtypes M2 and M3 (APL). See David Eastmond et al., Topoisomerase II Inhibition by Myeloperoxidase-Activated Hydroquinone: A Potential Mechanism Underlying the Genotoxic and Carcinogenic Effects of Benzene, 153-154 *Chemico-Biological Interactions* 207, 212-13 & tbl.2 (2005). In the former class, the M4 and M5 leukemias are characterized by a reciprocal translocation involving the q23 region of chromosome 11, whereas in the latter case, the M2 and M3 leukemias are characterized by a reciprocal translocation between chromosomes 8 and 21 and 15 and 17, respectively. Id. at 213. To the extent that Dr. Smith's opinion rests on the proposition that all topo II inhibitors act similarly to cause a similar effect, then, it does not appear to be based on reliable scientific knowledge.

To the contrary, evidence exists that the topo II inhibition effected by benzene metabolites is affirmatively different from that effected by other classes of topo II inhibitors. The Eastmond article reports:

[L]eukemias induced by the known classes of topoisomerase inhibitors . . . differ significantly from each other by class and by their mechanism of topo II inhibition. . . . As outlined in Table 2, the leukemias induced by benzene do not appear to exhibit the defining characteristics of any of the four classes [of topo II inhibitors] described above.

Id. It concludes: "Given the overall variability reported, it is not possible at this point to confidently identify the mechanisms underlying benzene-induced leukemias in humans." Id.

What seems clear from the evidence is that researchers are working very hard to discover the biological mechanisms that induce the various forms of leukemia. Some questions have now been answered with sufficient convincingness that it is fair to say they represent a consensus in the scientific community. As to other questions, however, answers remain elusive, and while hypotheses are possible, consensus has not occurred. Consensus is not the exclusive litmus test, of course, since the demise of the Frye rule. See Daubert, 509 U.S. at 583-97 (displacing the standard for admissibility of expert scientific testimony articulated in Frye v. United States, 293 F. 1013 (1923)). It is, however, a factor that scientists accept as relevant, among others, in deciding whether a causal relationship has been reliably established between an agent and an effect. See Kimho Tire Co. v. Carmichael, 526 U.S. 137, 149-50 (1999); Daubert, 509 U.S. at 593-94.

Dr. Smith's opinion that because benzene metabolites inhibit topo II and because some classes of topo II inhibitors appear to have a causal relationship to APL, therefore benzene has a causal relationship to APL is at best a theory and at worst an error. It does not constitute reliable "scientific knowledge" qualified for admission under Rule 702.

D. Dr. Smith's Opinion that Epidemiological Evidence Supports the Existence of a Causal Relationship Between Exposure to Benzene and APL Is Not the Result of an Application of Reliable Methodology to Valid Data and Gives Inappropriate Weight to Association Evidence that Is Not Statistically Significant.

To answer the question whether a suspected or known toxic agent is the cause of a particular disease, scientific researchers look to evidence from epidemiological studies. The plaintiffs may be correct that epidemiological evidence is not always essential to a scientific conclusion that a cause and effect relationship exists, but the defendants are also correct that sound epidemiological studies are ordinarily needed to confirm, by consistent observation, an hypothesis of causation. Dr. Smith's attempt to find support in epidemiological studies for a

causal link between exposure to benzene and APL is unpersuasive. The studies he relies on do not give the support he claims.

At the hearing, the defendants' epidemiological expert, Dr. Garabrant, persuasively demonstrated that the several published articles on which Dr. Smith relied, when properly understood, do not support his opinion. First, none of the studies purports to give direct support to the proposition that benzene causes APL. Some, in fact, such as the Chinese "Acta" case control study and the Pliofilm cohort study, tended to show no association. See generally Acta Study, supra; Robert A. Rinsky et al., Leukemia in Benzene Workers, 2 Am. J. of Indus. Med. 217 (1981). Second, it appears that Dr. Smith made unduly favorable assumptions in reinterpreting the studies, such as that cases reported as AML could have been cases of APL. This may have been because he was overly eager to find evidence to support his hypothesis, a tendency that sound scientific inquiry should control. Finally, Dr. Garabrant convincingly demonstrated, especially with respect to the Golomb and Travis papers, that Dr. Smith's conclusions that there was a positive association between exposure to benzene and APL were based on faulty calculations of odds ratios. See generally H.M. Golomb et al., Correlation of Occupation and Karyotype in Adults with Acute Nonlymphocytic Leukemia, 60 Blood 404 (1982); Lois B. Travis et al., Hematopoietic Malignancies and Related Disorders Among Benzene Exposed Workers in China, 14 Leukemia & Lymphoma 91 (1994).

In any event, even to the extent some of the data reported in the various studies could be properly understood to suggest a positive association, the findings are not statistically significant. It does not appear that the plaintiffs now seriously contend otherwise, but rather argue that evidence of an association between benzene and APL "suggests" a causal relationship, and such

a suggestion is further support for Dr. Smith's opinion that the relationship exists because it is biologically plausible.

A "suggestion" may give rise to a plausible hypothesis, but not a reliable inference. That is why scientists are careful only to rely on data that is shown to have statistical significance. In this case, Dr. Smith's attempt to support his conclusion with data that concededly lacks statistical significance is a deviation from sound practice of the scientific method. In short, what Dr. Smith has is an epidemiological hypothesis to go with his biological hypothesis. What is lacking is sufficient evidence—whether biological or epidemiological—to warrant a reliable scientific inference.

#### **IV. Order**

The plaintiffs' proffer of Dr. Smith's opinions must be rejected for failure to satisfy the prerequisites to admissibility established by Rule 702. While Dr. Smith's hypotheses are, to use his term, "plausible," they remain hypotheses, the validity of which has not been reliably established. As such, they are not admissible as "scientific knowledge" under Rule 702. Moreover, the sum of Dr. Smith's testimony, fairly understood, is that benzene *might be* a cause of APL. This is an assertion of possibility, not probability. As such, it would not assist the trier of fact to resolve the question of causation, and the testimony is thus not relevant in the necessary sense.

The defendants' objection to the admission of Dr. Smith's opinions is sustained.

It is SO ORDERED.

/s/ George A. O'Toole, Jr.  
United States District Judge