No. 11-316

IN THE
Supreme Court of the United States

UNITED STATES STEEL CORP., et al.,
Petitioners,

v.

BRIAN K. MILWARD AND LINDA J. MILWARD,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the First Circuit

RESPONDENTS' BRIEF IN OPPOSITION

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QUESTION PRESENTED

Whether the district court abused its discretion in excluding expert testimony that falls within the range where experts might reasonably differ?

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INTRODUCTION

The First Circuit's opinion in this case reflects a fact-intensive application of settled legal principles regarding the admissibility of expert testimony. That opinion recites and applies the appropriate legal standards, as established by Federal Rule of Evidence 702 and this Court's precedent, including *General Electric Co. v. Joiner*, 522 U.S. 136 (1997).

At bottom, the First Circuit's decision recognizes that the district court abused its discretion by excluding expert testimony that "falls within the range where experts might reasonably differ." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 153 (1999). To the extent that expert testimony meets that broad standard, "the jury must decide among the conflicting views of different experts." *Id.*

Based on the admissions of Petitioners' own expert witnesses, the record establishes that, at the very least, the expert testimony of Dr. Martyn Smith at issue here falls within the range where experts might reasonably disagree. Petitioners' own experts testified that reasonable experts can and do agree with key portions of Dr. Smith's opinions– including portions that the district court nonetheless determined were not scientifically reliable. Moreover, the *amicus curiae* brief filed in the court of appeals by 27 distinguished scientists underscores that Dr. Smith's view that benzene exposure can cause Acute Promyelocytic Leukemia ("APL") is not only scientifically reasonable, but correct.

Notably, despite Petitioners' protests that Dr. Smith's "weight of the evidence" methodology for

assessing causation is inherently unreliable, Petitioners' own toxicologist admitted that he applies the same method in making causal determinations. This admission should come as no surprise, in light of the unrebutted evidence demonstrating that the "weight of the evidence" method is universally accepted by scientists as the proper approach for assessing whether a chemical can cause cancer. In recognition of the broad scientific acceptance of this approach, both the American Law Institute's *Restatement (Third) of Torts* and the Federal Judicial Center's recently-published third edition of the *Reference Manual on Scientific Evidence* have endorsed the "weight of the evidence" method for evaluating causation in a toxic tort case.

Moreover, certiorari is also unwarranted because of the interlocutory stage of the proceedings. This Court generally declines to exercise certiorari jurisdiction over interlocutory decisions, absent extraordinary circumstances that do not exist here.

The decision below neither creates a split of authority nor sanctions the use of a scientifically inappropriate methodology. In light of the fact-intensive nature of the First Circuit's review, and that court's application of well-established legal principles, review by this Court is not merited.

STATEMENT

I. THE EVIDENCE RELATING TO THE "WEIGHT OF THE EVIDENCE" METHODOLOGY EMPLOYED BY DR. MARTYN SMITH

Brian Milward suffers from APL. He and his wife Linda allege in this action that his workplace exposure to benzene-containing products manufactured or supplied by Petitioners caused Brian's APL. With regard to methodological issues, the Milwards offered the testimony of both Dr. Carl Cranor and Dr. Smith, the expert attacked by Petitioners.

A. Dr. Cranor's Testimony Regarding the Scientific Methodology for Assessing "General Causation."

Carl Cranor is a full professor in the Department of Philosophy at the University of California at Riverside. For the last 27 years, Dr. Cranor's research has focused on issues concerning the interplay between science and the law regarding risks posed by toxic substances. Since about 1985, Dr. Cranor has published approximately 50 articles or book chapters on these issues. Many of these articles and two of the books are on the use of scientific evidence in regulatory and toxic tort law. Dr. Cranor has served on many scientific, governmental, and regulatory committees on the risks posed by toxins. *See* JA VI:3078-80 (Report of Dr. Carl Cranor ¶¶4-10)

("Cranor Report").[1]

Dr. Cranor offered opinions regarding the methods used by scientists in assessing "general causation" issues—that is, whether a particular chemical is capable of causing a particular disease. According to Dr. Cranor, scientists who investigate and assess whether a particular chemical exposure may cause a particular disease apply a nondeductive reasoning process known as "inference to the best explanation." JA VI:3082 (Cranor Report ¶13). Dr. Cranor explained that scientists evaluating causation use the reasoning process of "inference to the best explanation." "There is widespread agreement that *all scientifically relevant information* bearing on possible explanations [for incidence of a particular disease] must be considered in drawing a conclusion about which explanation is most likely." JA VI:3084-3085 (Cranor Report ¶14E) (emphasis in original). In the context of assessing causation, such evidence will include "human epidemiology studies, case reports, reviews describing a group of epidemiological studies, studies of effects of the exposure on animals, and a wide variety of experimental data—often conducted on intact animals, human cells *in vitro* and on model systems such as yeast, bacteria and mammalian cell lines—showing the biological mechanisms through which the chemical may cause a disease, along with the metabolic pathways of the chemical in animals and humans." JA VI:3085 (Cranor Report ¶14E(i)).

This process of evaluating all available evidence

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[1] "JA" refers to the Joint Appendix filed in the First Circuit.

on causation is often referred to as the "weight of the evidence" process. JA VI:3088 (*Id.* at ¶14I). A "weight of the evidence" review is used by regulatory agencies and scientific bodies that evaluate cancer risks posed by chemicals, including the National Toxicology Program and the International Agency for Research on Cancer ("IARC"). *Id.*

In evaluating the "weight of the evidence" relating to causation, scientists often look to nine considerations: 1) the strength of an association between an exposure and a particular disease; 2) consistency of the association across different researchers studying the problem in different circumstances at different times; 3) any specificity of the association (whether an exposure is associated with a unique or highly unusual disease, as asbestos is associated with mesothelioma); 4) temporality (the cause must precede the effect); 5) biological gradient or dose-response (whether greater exposure is associated with a greater disease rate); 6) the biological plausibility of an association (whether the association is biologically plausible given existing scientific knowledge); 7) coherency of the association (whether the association is consistent with or conflicts with what is known about the disease and its natural history); 8) any relevant experimental data (whether any experimental data or semi-experimental data assists the inference for causation); and 9) analogy (whether any biological analogies to other diseases or associations assist the inference for causation). JA VI:3089 (Cranor Report ¶16); Pet. App. 9a-10a.

Dr. Cranor cautions that these considerations,

referred to as the "Hill factors" after the scientist who first articulated them, must be evaluated with a few "important qualifications in mind." JA VI:3089 (Cranor Report ¶16). First, with the exception of temporality, none of the considerations is a *sine qua non* for a causation determination. Second, the "factors are asymmetric. If they are present or applicable to the issue … they tend to strengthen the inference for causation, but if they are absent or inapplicable, they tend not to weaken it much [with the exception of the temporality consideration]." *Id.*

Throughout the process of evaluating the individual pieces of evidence and integrating that evidence to reach an overall conclusion, scientists evaluating causation must exercise judgment:

> [S]cientific judgment has a crucial role at several points, not just in drawing a final conclusion. An expert reviews the body of data that appear to bear on causal judgments, selects the scientifically relevant data, assesses and weighs studies for their quality, weighs the importance of different kinds of data vis-à-vis one another (e.g., animal studies versus human studies versus short-term studies versus structure-activity relationships versus mechanistic evidence versus any case studies and so on), and brings her background understanding of biology and toxicology, as well as her understanding of the phenomena, to the causal issues. Scientific judgment also enters into integrating all the data and how it bears on evaluating different possible explanations

> in light of all the evidence and the particular phenomena to be explained (e.g., a disease).

JA VI:3087 (Cranor Report ¶14F(ii)).

Critically, "professionals may disagree at various stages of reasoning in an inference to the best explanation, and thus may have disagreements about their overall view of the scientific conclusions." JA VI:3087 (Cranor Report ¶14F(iii)). Different scientists often attach different degrees of importance, significance, or weight to commonly-held considerations that guide scientific inquiry. "An end result is that there is reason to expect they will disagree about whether one theory or view is acceptable or not compared with another. And, this disagreement is quite reasonable among respectable scientists." JA VI:3095 (Cranor Supp. ¶3); *see also* Pet. App. 12a (noting that "an evaluation of data and scientific evidence to determine whether an inference of causation is appropriate requires judgment and interpretation") (quoting *Restatement (Third) of Torts* § 28 comment c(1) (2011)).

B. The Testimony of Plaintiffs' General Causation Expert, Dr. Martyn Smith

Dr. Martyn Smith is one of the world's most well-published, well-respected scientists in the field of benzene toxicology. He is a Professor of Toxicology in the Division of Environmental Health Sciences, School of Public Health, University of California at Berkeley, where he has been a faculty member since 1982. *See* JA VI:3105 (Report of Dr. Martyn Smith ¶4) ("Smith Report"). Dr. Smith received his Bachelor of Science Degree in Biology

from Queen Elizabeth College, University of London (1977) and his Ph.D. in Biochemistry from the Medical College of St. Bartholomew's Hospital, London, England (1980). He performed post-doctoral research in the Department of Toxicology at the Karolinska Institute, Stockholm, Sweden (1980-1981) under the supervision of perhaps the world's leading toxicologist, Professor Sten Orrenius. JA VI:3106 (Smith Report ¶5).

In 1994, Dr. Smith was elected a Fellow of the American Association for the Advancement of Science for his outstanding contributions to the field of environmental toxicology, especially with regard to developing scientific understanding of the mechanisms of benzene toxicity. From 2000 to 2003, Dr. Smith served on the National Advisory Environmental Health Sciences Council, which advises the National Institute of Environmental Health Sciences of NIH on all decisions and future directions. JA VI:3106 (Smith Report ¶6).

Dr. Smith has devoted his career to the study of the toxic effects of chemicals and drugs on the human body, with particular emphasis on the mechanisms by which benzene and its metabolites cause damage at the cellular level and to the human organism as a whole. The research in Dr. Smith's laboratory focuses on the causes of leukemia and lymphoma. His research on benzene is funded by the National Institutes of Health and has been extensively peer-reviewed. JA VI:3110 (Smith Report ¶10). Since 1979, Dr. Smith has authored or co-authored over 215 articles in peer-reviewed journals in the field of toxicology, 37 book chapters, and more than 150 abstracts, as well as

technical reports for the United States Environmental Protection Agency and the California Environmental Protection Agency. Many of these publications are on the subject of benzene toxicity. JA VI:3107 (Smith Report ¶8); *see also* JA VI:3130-3148 (Curriculum Vitae of Dr. Smith).

In reaching his opinions in this case, Dr. Smith applied the "weight of the evidence" methodology described by Dr. Cranor. In applying this method, Dr. Smith emphasized that epidemiological evidence provides only one type of evidence among the several that should be considered in assessing causation: "The term WOE [weight of the evidence] has come to mean not only a determination of the statistical and explanatory power of any individual study (or the combined power of all the studies) but the extent to which different types of studies converge on the hypothesis." JA VI:3150.

In assessing whether benzene exposure may cause APL, Dr. Smith applied the nine Hill considerations. As described above, the consensus methodological approach to analyzing general causation issues requires examination of the weight of the evidence from all available modalities or types of studies. Epidemiology studies provide an important piece of the puzzle, but the absence of epidemiology confirming strong mechanistic evidence does not preclude a determination of causation in every instance. JA VI:3116 (Smith Report ¶22); *see also* Pet. App. 10a ("Although Hill identified nine viewpoints, it is generally agreed that this list is not exhaustive and that no one type of evidence must be present before causality may be inferred"). In addition, consideration of

epidemiology in isolation, without concurrent exploration of mechanistic evidence, conflicts with mainstream scientific practice. JA VI:3116 (Smith Report ¶22).

A compelling line of mechanistic evidence demonstrating that exposure to a certain chemical leads to cancer effects would lead "most but not all scientists [to] conclude that such data provides indisputable evidence of human cancer risk despite a lack of epidemiological results specific to that agent."[2] "National and international agencies that provide evaluations of human health risks do not rely solely on associations observed in epidemiological studies. Most often, no adequate studies have been performed, especially on newly introduced chemicals. Rather, expert multidisciplinary panels use all available and relevant scientific evidence in reaching their overall conclusions." JA VI:3159 (Melnick 2005 Article at S32). For example, with respect to TCDD, the most potent form of dioxin and dioxin-like compounds, both the International Agency for Research on Cancer and the National Toxicology Program have concluded that TCDD is a known human carcinogen, based on compelling mechanistic evidence supported by more limited evidence from epidemiology. JA VI:3117 (Smith Report ¶23).

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[2] JA VI:3157-3161 (Melnick 2005 Article, Ronald L. Melnick, PhD, *A* Daubert *Motion: A Legal Strategy to Exclude Essential Scientific Evidence in Toxic Tort Litigation*, 95 Am. J. Public Health No. S1 at S 32 (2005)). Dr. Melnick is a former scientist at the Environmental Toxicology Program, National Institute of Environmental Health Sciences, National Institute of Health. ("Melnick 2005 Article").

II. THE FOUR-PART BASIS FOR DR. SMITH'S CONCLUSION THAT BENZENE EXPOSURE CAN CAUSE APL.

Dr. Smith concluded that benzene exposure can cause APL on the basis of four lines of evidence: 1) the strong, consistent, dose-responsive relationship demonstrated in the epidemiological literature between benzene exposure and Acute Myeloid Leukemia ("AML"); 2) the scientific evidence showing that all of the various sub-types of AML begin to develop with genetic changes at the level of a common "progenitor" or "pluripotent stem" cell; 3) the substantial body of literature showing that the metabolites of benzene inhibit an important DNA-related enzyme, which is called topoisomerase-II; and that other chemicals that inhibit topoisomerase-II, including chemotherapeutic agents, are known to cause APL; and 4) the small body of epidemiological literature that has examined the relationship between benzene exposure and specific subtypes of AML, including APL. Following an introductory section describing some uncontested, background information about AML and APL, each of these four lines of evidence is described below.

A. The Nature of Acute Myeloid Leukemia, Including Acute Promyelocytic Leukemia.

Leukemia is a cancer of the blood-forming system and is defined as the uncontrolled proliferation of bone marrow progenitor cells. Due to their common stem cell origin, the various types of leukemias are related diseases that have common mechanisms of development and share a common general pathogenesis. They are, however,

generally classified into four major types by the level of differentiation and cell type: acute or chronic myeloid leukemia (AML or CML) and acute or chronic lymphocytic leukemia (ALL or CLL). AML is the major form of acute non-lymphocytic leukemia (ANLL), which also includes biphenotypic leukemia with characteristics of both myeloid and lymphoid leukemia as well as AML. JA VI:3111 (Smith Report at ¶13).

AML is sub-divided and classified morphologically, according to the French-American-British classification system, by the degree of differentiation along different cell lines and the extent of cell maturation. M1, M2, and M3 show predominantly granulocytic differentiation and differ from one another in the extent and nature of granulocytic maturation; M4 shows both granulocytic and monocytic differentiation; M5 shows predominantly monocytic differentiation; and M6 shows predominantly erythroblastic differentiation. M7 is associated with leukemic megakaryocytes. JA VI:3112 (Smith Report ¶14).

AML-M3 is known as acute promyelocytic leukemia, or APL, a bone marrow cancer involving a deficiency of mature blood cells in the myeloid line of cells and an excess of immature cells called promyelocytes. JA VI:3112-3113 (Smith Report at ¶16). APL accounts for 5%-10% of cases of AML. The U.S. National Cancer Institute SEER Program estimates that, in 2008, 13,290 men and women will be diagnosed with AML, and 8,820 men and women will die of it. JA VI:3113 (Smith Report ¶17).

B. Epidemiology Studies of Benzene-Exposed Populations Have Unequivocally Established That Benzene Exposure Causes AML.

The first of the four lines of evidence supporting Dr. Smith's conclusion that benzene can cause APL are epidemiology studies that establish the causal relationship between benzene and AMLs as a group. Many epidemiologic studies have been conducted of benzene-exposed workforces. These studies generally show increased occurrences of AML among exposed workers when compared to unexposed workers or the general population. The increased incidence of AML among the exposed workers in these studies is often statistically significant and dose-response relationships have been determined. Based on these multiple epidemiologic studies, governmental agencies and knowledgeable experts all generally accept that benzene causes AML. *See* JA II:701 (Tr. 4/21/09 at 21:12-15).

C. Toxicological Evidence Demonstrates That All of the Subtypes of AML Have a Common Pathology, and That Benzene Exposure Causes Damage To the Progenitor Stem Cell From Which All of the Subtypes of AML Develop.

The second line of evidence relied on by Dr. Smith comes from toxicology studies showing that: 1) all of the subtypes of AML have a common origin in the bone marrow that begins with genetic changes to a progenitor or stem cell that is a common "ancestor" of all myeloid blood cells; and 2) benzene and its metabolites cause genetic damage at these progenitor and stem cell levels.

According to Dr. Smith, all AMLs derive from a genetically damaged pluripotent stem cell, which can differentiate into all of the different myelogenous cell types and proliferate, ultimately resulting in the development of the various AML subtypes. Because the subtypes of AML all derive from this common origin of a genetically damaged pluripotent stem or progenitor cell, they likely have a common pathogenesis. JA VI:3121 (Smith Report ¶28a). The pathogenic process for APL, like all forms of AML, is for leukemic stem cells to be generated through the accumulation of chromosomal mutations and epigenetic changes. *See* JA VI:3178-3179 (Supplemental Declaration of Martyn Smith ¶33) ("Supp. Smith Decl."); *see also* JA IV:2161 (peer-reviewed article on leukemic stem cells, stating in the abstract that "numerous studies demonstrate that acute myeloid leukemia arises from mutations at the level of stem cell"); JA IV:2193 (peer-reviewed article regarding leukemic stem cells).

Many toxicology studies have established that the metabolites of benzene cause significant chromosomal damage at the stem cell level in the bone marrow. *See* JA VI:3169 (Supp. Smith Decl. ¶13); JA VI:3125-3127; *see also* JA II:1090 (Transcript 4/23/09 at 126:10-25) (Testimony of Defendants' expert hematopathologist, Dr. John Bennett, agreeing that "there have been innumerable studies that demonstrate that benzene actually works at multiple levels to create damage to the DNA structure of this hematopoietic stem cell").

Thus, the epidemiological evidence has established conclusively that benzene exposure is capable of causing AMLs as a group. That same body of epidemiological evidence, when coupled with the pathological mechanism evidence described above, also strongly supports the conclusion that benzene exposure is capable of causing APL and the other specific subtypes of AML. JA VI:3112 (Smith Report ¶15). Indeed, Dr. Smith testified that active researchers in the field of benzene toxicology do not even debate the issue of whether benzene exposure is capable of causing all of the subtypes of AML. JA VI:3178-3179 (Supp. Smith Decl. ¶33).

D. The Fact That Benzene Inhibits the Enzyme Topoisomerase-II Provides Substantial Additional Evidence That Benzene Exposure Causes APL.

Dr. Smith's third line of evidence that benzene can cause APL is based on the facts that the metabolites of benzene inhibit the enzyme topoisomerase-II and inhibition of that enzyme has been shown to cause APL.

Topoisomerase-II is an enzyme essential for the maintenance of proper chromosome structure and segregation; it removes knots and tangles from genetic material by passing an intact double helix through a transient double-stranded break that it creates in a separate segment of DNA. JA VI:3122 (Smith Report ¶29). A variety of widely prescribed anticancer drugs, such as etoposide, kill cells by increasing physiological levels of topoisomerase-II-DNA cleavage complexes. These drugs are referred to as topoisomerase-II poisons (to distinguish them

from catalytic *inhibitors* of the enzyme) because they convert this essential enzyme to a potent cellular toxin. *Id.*

Numerous studies have shown that topoisomerase-II inhibitors induce APL. As one recent, peer-reviewed article notes: "Therapy-related acute promyelocytic leukemia (t-APL) with the t(15;17) translocation is a well-recognized complication of cancer treatment with agents targeting topoisomerase-II." JA VI:3122-3123 (Smith Report ¶31); JA IV:2016.

Like the chemotherapeutic agents that have been shown to cause APL, reactive benzene metabolites also inhibit the functionality of topoisomerase-II. JA VI:3125-3126 (Smith Report ¶34). Recent studies have now convincingly shown that the benzene metabolites 1,4-hydroquinone and 1,4-benzoquinone enhance DNA cleavage mediated by human topoisomerase-II. JA VI:3126-3127 (Smith Report ¶35); *see also* JA VI:1976; 1829; 1868; and 2024 (various peer-reviewed publications showing that benzene's metabolites inhibit topoisomerase-II). Those studies show that reactive metabolites of benzene not only inhibit functionality of topoisomerase-II but are also potent topoisomerase II poisons.[3] Since topoisomerase II poisons not only cause AML, but also induce chromosomal translocations associated

[3] The Agency for Toxic Substances and Disease Registry, a subagency of the U.S. Department of Health and Human Services, has endorsed Dr. Smith's view that benzene's metabolites inhibit topoisomerase-II, in its "Toxicological Profile for Benzene." JA III:1650. Indeed, that document cites Dr. Smith in support of that conclusion. *Id.*

with APL, and because metabolites of benzene have been shown to be topoisomerase inhibitors and poisons, there is strong biological and mechanistic evidence that exposure to benzene causes APL with its associated chromosome translocations involving the retinoic acid receptor-alpha (*RARa*) gene on Chromosome 17. JA VI:3127 (Smith Report ¶36).

Notably, a published, peer-reviewed article reviewing the literature on "Genotoxicity of benzene and its metabolites" concludes:

> The genotoxic effects produced by BZ and its metabolites are most consistent with inhibition of topoisomerase-II or ribonucleotide reductase inhibition. The chromosomal abnormalities in human leukemia produced therapeutically by topoisomerase-II inhibitors also implicate this mechanism in BZ-induced leukemia.

JA VI:2364.

E. APL-Specific Data Available From Published Epidemiological Studies Supports the Conclusion That Benzene Can Cause APL.

Dr. Smith also considered a fourth and final line of evidence, which is the small amount of APL-specific data from the published epidemiological studies on benzene and AMLs generally. Dr. Smith testified that he did not need APL-specific epidemiology to reach a "weight of the evidence" conclusion that benzene can cause APL. According to Dr. Smith, the first three lines of evidence described above were enough. In other words, Dr. Smith determined that the weight of the evidence shows that benzene can cause APL based on the

evidence that: 1) benzene is an established cause of AML; 2) all subtypes of AML have a common cell of origin and benzene causes genetic damage to that ancestral progenitor cell; and 3) benzene inhibits topoisomerase-II, and inhibition of that enzyme is known to cause APL. JA II:718-720 (Transcript 4/21/09 at 38:18-40:3).

As Dr. Smith testified, the rarity of APL makes it difficult to study by traditional epidemiological methods. JA VI:3165 (Supp. Smith Decl. ¶7); *see also* Pet. App. 25a-26a and n. 18 (stating that "[t]he difficulty of performing such a study has even been expressly affirmed in the scientific literature"). AML itself is a relatively rare disease, about 6 to 8 cases per 100,000 population annually. Because APL comprises about 5%-10% of AML, the incidence of APL can be estimated at about 3 to 8 cases per 1,000,000. JA VI:3117-3118 (Smith Report ¶24). Unfortunately, most epidemiological studies of AML causation are death certificate studies, and the specific subtype is usually not listed or studied. It is very rare to find an epidemiological study that separates out the different sub-types of AML. The most well-known epidemiological cohort studies of benzene exposed workers outside of China do not provide information about different sub-types of AML and consider AML as one disease. JA VI:3165 (Supp. Smith Decl. ¶7).

APL has been reported among benzene-exposed workers in a number of epidemiologic studies:

(a) In a multi-center case-control study of 1257 leukemia cases in China, odds ratios were calculated for benzene and certain AML

subtypes. The odds ratio for APL was 1.42, which was close to the odds ratios for subtypes M2a (1.58) and M5 (1.55) and greater than the other subtypes (1.20). JA IV:1835-1836. Thus, this study reported a greater than 40% increased risk of APL in benzene-exposed workers. JA VI:3118 (Smith Report ¶25(a)).

(b) In a cohort study of 74,828 workers exposed to benzene in various factories in China, 32 cases of acute leukemia were found. Histopathologic data were evaluated for 9 exposed workers with AML. Of these, three were diagnosed with AML M2, one was diagnosed with AML M2 or M4, four were diagnosed with AML M3, and one was diagnosed with AML M4 or M5. JA IV:2352. Thus, in this study, APL was the most common form of AML diagnosed in the benzene-exposed workers. JA VI:3118-3119 (Smith Report ¶25(b)).

(c) A multi-center Italian case-control study of 38 cases of APL showed a strong association with shoe-making (odds ratio = 6.3, 95% confidence interval = 1.3 - 31.1). JA IV:2157. This study implicates benzene in the causation of APL, because for many years benzene was used as an adhesive in shoemaking in both Italy and Turkey. Indeed, the authors of this study stated, "If these data are confirmed by further studies, the high risk of developing AML after benzene exposition could be largely

attributed to the APL subset." JA VI:2159.

Moreover, a more recent study, published after the district court's hearing, found a stronger association between benzene and APL than between benzene and any other subtype of AML. *See* Amended Brief of *Amici Curiae*, the Council for Education and Research on Toxics and 27 individual scientists (hereinafter "Scientists' *Amici* Brief"), filed in the court below on May 10, 2010 (Dkt. No. 00116048742), at 23-24 & Appendix 2.

Taking into account all of the available and relevant scientific evidence described above, Dr. Smith reached his "weight of the evidence" opinion that benzene exposure is capable of causing APL. JA VI:3127 (Smith Report ¶37).

F. As Petitioners' Own Experts Testified, Dr. Smith's Opinions Fall Within the Range Where Reasonable Experts Might Differ.

Although they disagreed with Dr. Smith's ultimate conclusion, Petitioners' own experts conceded that Dr. Smith's opinions fall within the range where reasonable experts might differ. These concessions came in two key areas. First, Petitioners' experts agreed that the "weight of the evidence" method that Dr. Smith applied here is generally accepted by the relevant scientific community, and the experts' disagreement was thus limited to application of that method. Second, Petitioners' experts acknowledged that reasonable experts in the field agree with Dr. Smith's opinions about both the common cellular origin of all types of AML and the significance of inhibition of topoisomerase-II as a cause of APL. This

acknowledgement is particularly significant in light of the district court's holding that both of those opinions are unreliable. *See* Pet. App. at 46a; 51a.

Petitioners' expert toxicologist, Dr. David Pyatt, testified that the "weight of the evidence" approach used by Dr. Smith in this case is *exactly* how scientists are trained to analyze causation. Indeed, Dr. Pyatt himself applies the "weight of the evidence" methodology. JA II:1210-11 (Pyatt testimony).

Petitioners' experts questioned Dr. Smith's conclusion that all of the subtypes of AML have a common origin. However, both of Petitioners' experts on the "biological mechanism" of APL, Dr. David Pyatt and Dr. John Bennett, acknowledged that reasonable scientists in the field agree with Dr. Smith's conclusion on this issue, which is "consistent with most of the evidence." *See* JA II:1202-1203 (Pyatt testimony, Transcript 4/24/09 at 100:20-101:14); JA II:1093-1094 (Bennett testimony, Transcript 4/23/09 at 129:22-130:1). Dr. Bennett also testified that the hematopoietic stem cell is "sort of the mother cell" from which all the other types of blood cells originate. JA II:1093 (Transcript 4/23/09 at 126:20-25).

Dr. Pyatt further acknowledged that the "hematopoietic progenitor cell population is a target tissue for benzene toxicity." JA VI:3195. He also admitted that this fact, taken together with the conclusion that all subtypes of AML have a common origin, provides evidence that benzene exposure is capable of causing APL. JA VI:3195-3196.

Defendants' hematopathologist, Dr. John Bennett, agreed with Dr. Smith that two of benzene's metabolites—hydroquinone and benzoquinone—are topoisomerase II inhibitors. JA VI:3241. Dr. Bennett further acknowledged that chemotherapeutic compounds that inhibit topoisomerase II can cause APL. JA II:1070 (Transcript 4/23/09 at 106:4-16).

The *Amicus Curiae* brief in the court below provides further indication that Dr. Smith's analyses and conclusions have broad acceptance in the scientific community. *See* Scientists' *Amici* Brief. That brief was joined by 27 individual scientists working in the field of public health, including epidemiologists, hematologists-oncologists, occupational medicine physicians, medical toxicologists, toxicologists, industrial hygienists, and a chemist. The list of individual *amici* is a who's who among scientists who research and publish in the areas of leukemia, benzene, and environmental and occupational toxicology and epidemiology. *See* App. 1 to Scientists' *Amici* Br.

The credentials, breadth, and depth of knowledge among these *amici* scientists regarding the causes of leukemia cannot reasonably be questioned. Through the filing of their brief, those scientists spoke out strongly and unanimously in support of the scientific analysis and conclusions of Dr. Smith in this case. As their "Interests of *Amici*" section concludes: "*Amici* believe that there is currently a general consensus of the medical and scientific community that benzene is a human carcinogen and that occupational exposure to benzene is known and recognized to cause Acute

Myelogenous Leukemia (AML) and variants of AML, including APL." Scientists' *Amici.* Br. at 2. By contrast, no scientists stepped forward to support the position taken by Petitioners.

III. THE DECISIONS BELOW

The district court held that Dr. Smith's opinions were not sufficiently reliable to satisfy the requirements of Federal Rule of Evidence 702. The court examined each of the discrete lines of evidence relied on by Dr. Smith and found that none provided reliable support for his opinion within the meaning of Rule 702 and *Daubert*.

On appeal, the First Circuit determined that the district court had "crossed the boundary between gatekeeper and trier of fact." Pet. App. 20a. The court of appeals identified three problematic conclusions by the district court. First, the district court determined that Dr. Smith's opinion that all forms of AML likely share a common origin is "at best a plausible hypothesis," and was therefore unreliable. *Id.* Second, the district court held that there was insufficient support for Dr. Smith's inference that benzene can probably cause the type of chromosomal translocation typically associated with APL. Pet. App. 19a. Third, the district court determined that there was insufficient evidence to support Dr. Smith's inference that benzene metabolites inhibit topoisomerase-II in such a way as to cause the APL-related chromosomal translocation. Pet. App. 20a.

The court of appeals held that the district court had applied the wrong legal standard in reaching

each of these three conclusions. According to the First Circuit, the district court "took sides on questions that are currently the focus of extensive debate—and on which reasonable scientists can clearly disagree. In this, the court overstepped its authorized bounds as gatekeeper." Pet. App. 21a. The court of appeals explained that, under Rule 702, "the fact that another explanation might be right is not a sufficient basis for excluding Dr. Smith's testimony." Pet. App. 21a.

The court of appeals rebuffed the district court's conclusion that "sound epidemiological studies are ordinarily needed to confirm, by consistent observation, an hypothesis of causation." Pet. App. 24a-25a. The proposition that epidemiological evidence is always necessary to prove causation has been explicitly rejected by other federal courts of appeals and by the *Restatement (Third) of Torts*. *See* Pet. App. 25a.

Finally, the court of appeals noted that the district court appeared to misunderstand Dr. Smith's testimony regarding the probability that benzene is capable of causing APL. Dr. Smith's reliance on evidence relating to the mechanism by which benzene exposure can cause APL falls within Sir Austin Bradford Hill's "biological plausibility" consideration. Seizing on the word "plausibility" from the Hill factors the district court determined that "the sum of Dr. Smith's testimony, fairly understood, is that benzene *might* be a cause of APL." Pet. App. 53a. Nonetheless, as the court of appeals determined, the record shows that "the sum of his testimony was that a weighing of the Bradford Hill factors, including biological

plausibility, supported the inference that the association between benzene exposure and APL is genuine and causal." Pet. App. 28a.

REASONS FOR DENYING THE WRIT

I. THERE IS NO CONFLICT AMONG THE COURTS OF APPEALS.

Petitioners stretch in vain to manufacture a conflict among the circuits. In each of the circuit court decisions cited by Petitioners, as in the decision below, the courts applied the same, well-settled principles established by this Court to varying sets of complex, scientific facts. The varied results in the cases reflect differences in the facts, not a conflict on the law.

For example, in *Allen v. Pennsylvania Engineering Corp.*, 102 F.3d 194 (5th Cir. 1996), the Fifth Circuit expressed misgivings relating to the "weight of the evidence" method, which had purportedly been applied by the experts in that case. 102 F.3d at 198. Nonetheless, as the First Circuit recognized below, *Allen* did not hold that "the weight-of-the evidence approach is per se unreliable." Pet. App. 13a n.9. "Rather, the court rejected its use in that case—a case in which it found that the experts' conclusion was 'at best weakly supported, if not contradicted, by the evidence on which they rely,' and in which the experts 'all declined to say that they would subject their findings to the test of peer review for publication.'" *Id.*

Moreover, reading *Allen* as Petitioners do–to mandate an absolute prohibition against use of the "weight of the evidence" method–would render the

Fifth Circuit an outlier. After all, any *per se* rule against use of the "weight of the evidence" method would flout the indisputable reality of how scientists actually reach causation determinations. The unrebutted record in this case, subscribed to by Petitioners' own experts, reflects that the weight of the evidence method is the *only* scientifically accepted method for analyzing general cancer causation issues like the one at issue here. *See* JA VI:3082-3088 (Cranor Report describing the "WOE" or "inference to the best explanation" method, and explaining that such method is employed by the various regulatory agencies and scientific bodies that evaluate cancer risks posed by chemicals); *see also* JA II:1210 (testimony by Petitioners' toxicology expert that scientists generally use the "weight of the evidence" method to assess causation).

The other circuit court decisions cited by Petitioners do not raise even a shadow of a conflict. For instance, the Eleventh Circuit's decision in *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233 (11th Cir. 2005), does not mention the "weight of the evidence" method and does not recite any legal standard in conflict with the standards applied by the court below. Instead, *McClain* involved a lengthy, highly fact-specific evaluation of expert testimony relating to whether ephedrine can cause heart attacks and strokes. 401 F.3d at 1241-55. The court held that such testimony was unreliable because, for example, the experts "failed to rely upon reliable sources," *id.* at 1255, and failed to show that their methods comported "with those standards otherwise utilized by experts in the field of toxicology." *Id.* at 1251.

Similarly, the decision in *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665 (6th Cir. 2010), *cert. denied*, 121 S. Ct. 2454 (2011), also involved a highly fact-specific evaluation of scientific evidence—this time relating to a *specific causation* question—whether manganese exposure had caused the plaintiff's illness, which resembled Parkinson's Disease. 620 F.3d at 668-69. The Sixth Circuit held that the expert testimony was not reliable based on the expert's failure to rule out the likelihood that the plaintiff had suffered Parkinson's Disease from genetic or other causes, besides manganese exposure. *Id.* at 670 (noting that the expert "barely explained why he thought manganese caused the disease"). As in *McClain*, *Tamraz* includes no discussion of the "weight of the evidence" method, nor any statement of law that conflicts with the decision below. The same is true of each of the other circuit court decisions cited by Petitioners. *See* Pet. 23-25.

II. THE COURT OF APPEALS APPLIED WELL-SETTLED LEGAL PRINCIPLES TO THE FACTS OF THIS CASE.

The First Circuit's decision is faithful to *General Electric Co. v. Joiner*, 522 U.S. 136 (1997), and this Court's other relevant precedents. The opinion below relies on and quotes from *Joiner* in several places. First, the opinion acknowledges that, under *Joiner*, a court of appeals is required to review a district court's decision regarding admissibility of expert testimony for abuse of discretion. Pet. App. 3A (quoting *Joiner*, 522 U.S. at 146). Next, the opinion quotes *Joiner* for the propositions that 1) "conclusions and methodology are not entirely

distinct from one another"; 2) "a district court properly may exclude expert testimony if the court concludes too great an analytical gap exists between the existing data and the expert's conclusion"; and 3) "nothing in either *Daubert* [*v. Merrell-Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993)] 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." Pet. App. 5a (quoting *Joiner*, 522 U.S. at 146); *see also id.* at 22a (quoting reference to *Joiner* in *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1230 (9th Cir. 1998)).

Nothing in the court of appeals' decision conflicts with any of these legal principles enunciated in *Joiner*. The court of appeals did not, as the Petition (at 31-32) suggests, mandate the admissibility of all expert testimony that invokes the "weight of the evidence" method. Instead, the court of appeals determined only that because the record established that Dr. Smith's opinions at least fell within the range where reasonable experts can differ, his "opinion was based on a reliable methodology and substantial evidence that he explained." Pet. App. 22a. Thus, any supposed "analytical gap" in that expert opinion "was of the district court's making." *Id.*

Moreover, the court of appeals' criticism of the district court's "atomistic" analysis of Dr. Smith's testimony does not conflict with *Joiner*. *See* Pet. App. 22a-23a. In *Joiner*, the Court concluded that the evidence was insufficient to support the experts' conclusions, whether the various pieces of evidence were viewed "individually or in

combination." 522 U.S. at 146-47. Here, by contrast, the court of appeals held that, when viewed as a whole, the evidence relied on by Dr. Smith was clearly sufficient to support his opinion. In other words, the court of appeals applied the same legal standards applied in *Joiner*, to a different set of facts, which, unremarkably, generated a different outcome.

At bottom, the decision below rests on application of the well-settled legal principle that trial courts should not exclude expert testimony that "falls within the range where experts might reasonably differ." *Kumho Tire Co. v. Carmichael*, 526 U.S. at 153. To the extent that expert testimony meets that broad standard, "the jury must decide among the conflicting views of different experts." *Id.*

Here, as explained above (at 20-22), even Petitioners' own experts recognized that Dr. Smith's opinions at least fall within the realm where experts might reasonably differ. Petitioners' toxicologist admitted that even he uses the "weight of the evidence" method for assessing causation, and that, in general, scientists use that approach. He further admitted that reasonable experts agree with Dr. Smith that all types of AML have a common origin, and that the progenitor cells from which the various types of AML arise is a target for benzene toxicity. Finally, he acknowledged that, taken together, these facts suggest that benzene is capable of causing APL. Likewise, Petitioners' hematopathologist acknowledged that metabolites of benzene inhibit topo-II, and that

chemotherapeutic agents that act on topo-II in a similar fashion are established causes of APL.

This and similar testimony led the court of appeals to the straightforward conclusion that the district court had exceeded its legal authority by taking "sides on questions that are currently the focus of extensive scientific research and debate—and on which reasonable scientists can clearly disagree." Pet. App. 21a. This Court's jurisprudence, together with the unanimous view of the circuits, supports this rule of law.

Moreover, despite Petitioners' efforts to vilify Dr. Smith's use of the "weight of the evidence" methodology, that method enjoys unanimous acceptance from the relevant scientific community. For this reason, both the American Law Institute and the Federal Judicial Center have endorsed use of the approach in toxic tort litigation. *See Restatement (Third) of Torts: Phys. & Emot. Harm* § 28, comment c (2010) ("Scientists first systematically gather all of the studies that have been conducted and that are relevant to the causal question being investigated. When multiple studies exist, they are synthesized …"); *Reference Manual on Scientific Evidence* (3d ed. 2011) at 651 ("The hazard identification process often uses 'weight of evidence' approaches in which the toxicological, mechanistic, and epidemiological data are rigorously assessed to form a judgment regarding the likelihood that the agent produces a specific effect").

Although the decision below approves the use of the "weight of the evidence" method in this case, the decision does not create a rule of law that

would insulate an expert's opinion from review solely because the expert has invoked that method. In this case, Dr. Smith applied that method by reviewing and analyzing a massive quantity of peer-reviewed data, published in scientific journals and by government and scientific agencies, such as the Environmental Protection Agency and the IARC . Dr. Smith's inferences from that data were reasonable, as Petitioners' own experts conceded. Under these circumstances, the First Circuit determined that Dr. Smith had appropriately applied the weight of the evidence method.

At the same time, if an expert purporting to apply the weight of the evidence method failed to review critical data or made an inference with which no reasonable expert would agree, the First Circuit's decision would permit exclusion of that testimony consistent, with this Court's decisions in *Daubert*, *Joiner*, and *Kumho Tire*.

III. THE LACK OF FINALITY OF THE FIRST CIRCUIT'S RULING UNDERSCORES THAT REVIEW SHOULD BE DENIED.

Petitioners ignore another compelling reason to deny review: the interlocutory nature of the ruling below. Although this Court has jurisdiction to review interlocutory decisions of federal courts of appeals under 28 U.S.C. § 1254(1), "[o]rdinarily, in the certiorari context, 'this court should not issue a writ of certiorari to review a decree of the circuit court of appeals on appeal from an interlocutory order, unless it is necessary to prevent extraordinary inconvenience and embarrassment in the conduct of the cause.'" Robert L. Stern, et al., *Supreme Court Practice* § 4.18, at 258 (8th ed.

2002) (quoting *Am. Constr. Co. v. Jacksonville, T. & K.W. Ry. Co.*, 148 U.S. 372, 384 (1893) (emphasis added)); *see also*, *e.g.*, *Hamilton-Brown Shoe Co. v. Wolf Bros. Co.*, 240 U.S. 251, 258 (1916) (interlocutory decisions are reviewed only "in extraordinary cases").

The posture of this case is anything but extraordinary. The Milwards filed a garden-variety state-law toxic tort suit. The Milwards consented to the district court's entry of judgment on behalf of Petitioners because, absent evidence that exposure to benzene could cause APL, the Milwards could not prevail on the merits. The district court did not consider specific causation–that is, whether benzene actually caused Mr. Milward's APL. It considered no other defenses, and it held no trial. The First Circuit reversed solely on the ground that Dr. Smith's testimony regarding general causation should have been admitted. On remand, Petitioners will retain any other legal defenses that they may have, and the trier of fact may decide in favor of either party, *including on issues of general causation*. If Petitioners prevail before the jury or win the case on any other ground, review on the question presented in the petition would not be necessary (or appropriate).

This case is a less appropriate vehicle for immediate, interlocutory review than was *Virginia Military Institute v. United States*, 508 U.S. 946 (1993) (*VMI*). There, the Fourth Circuit had issued a final decision holding that the Commonwealth of Virginia's sponsorship of a military college for men only was unconstitutional, but the district court had yet to rule on the appropriate remedy. The

Court denied certiorari on the ground that the decision was not sufficiently final because the remedy phase had not been completed. *See id.* at 946 (Scalia, J., concurring). The Court recognized that there would be time enough to review the decision, if necessary, after the remedial portion of the case had concluded, *id.*, and, in fact, it later did so. *See United States v. Virginia*, 518 U.S. 515 (1996). Here, there is no decision regarding liability, let alone the appropriate remedy.

Of course, the Milwards believe that they will prevail on the merits. If they do, Petitioners may appeal from the final decision and, ultimately, petition the Court on the Rule 702 question on which they now seek premature review (and on any other properly preserved federal issue). *See VMI*, 508 U.S. 946 (Scalia, J., concurring). Moreover, unlike *VMI*, which was sui generis, here, if Petitioners are correct that the issue presented is important and recurs frequently, *see* Pet. 31-33, there will be any number of appropriate future vehicles that would allow this Court to resolve the issue after entry of a final decision. In the meantime, the Court should stay its hand and allow the Milwards' case to run its course.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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