No. 06-865

IN THE
Supreme Court of the United States

HERCULES INCORPORATED,

Petitioner,

v.

UNITED STATES OF AMERICA,

Respondent.

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

BRIEF OF AMERICAN CHEMISTRY COUNCIL AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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CORPORATE DISCLOSURE

American Chemistry Council – The American Chemistry Council is a trade association representing U.S. chemical companies. The American Chemistry Council has no publicly owned parent corporation, and no publicly owned corporation owns more than 10% of its stock.

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INTEREST OF AMICUS[1]

Amicus the American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. The business of chemistry is a $558 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in U.S. exports.

Amicus and its members have a strong interest in ensuring that the federal government's regulation of chemicals is based on the most accurate and up-to-date scientific information regarding the effects of exposure to chemicals and other products. It thus has a strong interest in opposing actions such as those taken by the U.S. Environmental Protection Agency here that regulate the disposal and treatment of chemicals without basing that regulation on an adequate scientific foundation and without subjecting that regulation to judicial review as Congress intended. The American Chemistry Council participates regularly in federal court litigation both as a party and as amicus curiae.

SUMMARY OF ARGUMENT

The issues presented in the petition are of paramount importance. As noted in the petition, the Environmental Protection Agency ("EPA") consistently applies a standard potency factor for dioxin that effectively dictates the remedial actions required at chemical disposal sites around the country. That potency factor, however, has never been subjected to notice-and-comment rulemaking. The EPA has

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[1] No person or entity other than amicus and their counsel made a monetary contribution to the preparation or submission of this brief. Counsel of record for the parties have consented to the filing of this brief, and letters of consent have been filed with the clerk.

thus never had to consider the full range of scientific evidence that bears on the dioxin potency standard; nor has it ever had to satisfy any level of independent judicial review in holding to that factor.

That is of critical importance here because EPA has its science wrong. Despite several decades of intensive epidemiological research on populations of production workers and military personnel who may have had high exposures to dioxin, there is no scientific consensus that exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin ("TCDD" or "dioxin") causes soft-tissue sarcoma, non-Hodgkin's lymphoma, multiple myeloma, or any other cancer. To the contrary, the best-designed studies refute any assertion of causation. Indeed, more than thirty years of serious scientific analysis and scores of epidemiological studies have failed to demonstrate even a consistent *association* between exposure to dioxin and any particular cancer.

The federal courts examining the scientific literature involving dioxin have consistently recognized the lack of evidence showing a causal link between dioxin exposure and cancer risks. Judge Weinstein, for example – who has presided over 20 years of Agent Orange[2] litigation in the District Court for the Eastern District of New York – has repeatedly found that plaintiffs in that litigation lack scientific support for their causation theories, and the Second Circuit has consistently echoed those findings.

These court decisions are backed by science, not speculation. For example, a recent Institute of Medicine Report expressly disclaims any conclusions as to causation

[2] Agent Orange was a 50/50 mixture of two concentrated herbicides (2,4-Dichlorophenoxyacetic acid and 2,4,5-Trichlorophenoxyacetic acid). Neither is considered a carcinogen, but the latter contained trace amounts of TCDD. Hence, the Agent Orange litigation, insofar as the claims are based on cancer, indirectly focuses on TCDD.

and, moreover, expressly recognizes that "it is impossible to quantify the degree of risk likely to be experienced by veterans because of their exposure to herbicides in Vietnam." Institute of Medicine, *Veterans and Agent Orange: Update 2004 at* 17 (2005) ("2004 IOM Report"). Similarly, there is no coherent and consistent evidence for a link between dioxin and cancer risk in heavily-exposed dioxin production workers. There is simply no substantial scientific support for the hypothesis that dioxin causes cancer in humans.

Despite this uncertain evidence regarding highly exposed persons, the EPA continues to employ a cancer potency factor that is based on a linear, no-biological-threshold model to extrapolate laboratory animal findings to persons with the very lowest levels of dioxin exposure. This model, which has been routinely criticized even by EPA's own Scientific Advisory Boards and other independent scientific panels, assumes that, if a high exposure to something increases cancer risk, then (1) there is no "safe" or "threshold" exposure below which there is no cancer risk (i.e., any exposure increases cancer risk) and (2) cancer risk increases linearly with exposure. This model, however, is not supported by the science. This is, in short, a situation in which full notice-and-comment rulemaking followed by judicial review would make a difference.

Moreover, the stakes are high, as this case demonstrates. EPA applied its scientifically unsupported standard to impose over one hundred million dollars in clean-up costs on Hercules, and EPA itself has acknowledged that dioxin-related litigation and regulatory response expenditures have likely exceeded $100 billion. Given the stakes, EPA may not cling to its no-threshold model and the resulting potency standard while maintaining that the standard is immune from all judicial review. Review by this Court is thus appropriate.

ARGUMENT

I. COURTS RECOGNIZE THAT DIOXIN EXPOSURE HAS NOT BEEN SHOWN TO CAUSE CANCER.

EPA's cancer potency factor is based on the flawed premise that dioxin has been shown to cause cancer. However, as recognized by a number of courts that have examined the science behind dioxin, despite decades of litigation there has been no credible evidence presented even in highly exposed persons that dioxin actually causes cancer.

The seminal decisions involving Agent Orange (and thus dioxin) exposure have been issued by Judge Weinstein in the Eastern District of New York. Judge Weinstein, more than any other sitting federal judge, has been steeped in the scientific literature associated with Agent Orange and dioxin for well over twenty-five years and has been uniquely situated to evaluate that literature as a result of handling that consolidated Agent Orange litigation. While his recent opinion, *In re "Agent Orange" Production Liability Litigation,* 304 F. Supp. 2d 404, 424-42 (E.D.N.Y. 2004), focuses primarily on how the government contractor defense forecloses plaintiffs' claims, in the course of that opinion, the court offered a tentative assessment of plaintiffs' claims that their diseases – principally multiple myeloma and non-Hodgkin's lymphoma – resulted from their exposure to Agent Orange while serving in the U.S. military in Vietnam. Judge Weinstein noted that "[i]n earlier waves of such suits in the 1970s, 1980s and 1990s, the courts concluded that none of the available evidence would support a finding to a more-probable-than-not standard of causality between exposure to Agent Orange and disease (except for a quickly

discoverable and curable form of skin irritation, chloracne)."[3] *Id.* at 407. He went on to note that "[t]he scientific basis for that conclusion of lack of any substantial proof of causality, either general or specific to individuals, remains much the same." *Id.* (citing Institute of Medicine, *Veterans and Agent Orange: Update 2002* (2003)). This conclusion was based on his continuing review of the scientific literature on dioxin and Agent Orange in connection with the ongoing litigation in *In re "Agent Orange" Production Liability Litigation,* MDL No. 381.[4]

It is also in the context of this Agent Orange litigation that the Second Circuit has gained considerable experience in addressing the scientific causation issues. That court first addressed the issue in 1987 when it affirmed the certification and settlement of class actions brought in the initial wave of Agent Orange litigation. *See In re "Agent Orange" Production Liability Litigation*, 818 F.2d 145 (2d Cir. 1987). Writing for a unanimous court, Judge Winter noted that "the clear weight of scientific evidence casts grave doubt on the

[3] Chloracne is linked to dioxin exposure, but not exposure to the basic herbicides.

[4] The docket sheet in the Agent Orange MDL reflects more than 150 entries from 1984 through 2005 describing scientific journals and articles relating to Agent Orange and the health consequences of exposure that Judge Weinstein has read and of which he has taken "judicial notice." Throughout the mid-1990s, for example, Judge Weinstein took notice of reports such as the EPA Health Assessment Documents for Tetrachlorodibenzo-p-Dioxin and Related Compounds on Oct. 21, 1994 (docket entry 14679); EPA Review Draft Documents for Public Review for 120 day public review and comment (docket entry 14790); Estimating Exposure to Dioxin-Like Compounds Volume 1 Executive Summary (docket entry 14791); Health Assessment Document for 2,3,7,8 TCDD and Related Compounds (docket entry 14792); Estimating Exposure to Dioxin Like Compounds, Volume 11, Properties, Sources, Occurrences and Background Exposures (docket entry 14794); and EPA Review Draft Estimating Exposure to Dioxin Like Compounds (docket entry 14795).

capacity of Agent Orange to injure human beings," *Id.* at 149, and that "[e]pidemiological studies of Vietnam veterans, many of which were undertaken by the United States, Australian, and various state governments, demonstrate no greater incidence of relevant ailments among veterans or their families than among any other group." *Id.*; *see also In re "Agent Orange" Production Liability Litigation*, 818 F.2d 187, 193 (2d Cir. 1987) (noting that "epidemiological studies of those very personnel and their families fail to show that Agent Orange was hazardous"). The Court observed that the pertinent question was "'What will Agent Orange do to friendly personnel exposed to it?'" The epidemiological studies provided an answer: "'Nothing harmful so far as can be told.'" *Id.*

The Second Circuit revisited the issue in 1993, when it affirmed Judge Weinstein's conclusion that the initial Agent Orange class settlement barred plaintiffs' claims in the so-called "second wave" of Agent Orange litigation. *In re "Agent Orange" Production Liability Litigation*, 996 F.2d 1425 (2d Cir. 1993). Again speaking unanimously, the court quoted scientific literature making clear that "'[t]o date, there has been no conclusive evidence that exposure to Agent Orange is carcinogenic, mutagenic or teratogenic in humans. Furthermore, no deaths attributable solely to exposure to Agent Orange and its dioxin contaminant have been reported.'" *Id.* at 1437 (quoting 13B Arthur L. Frank, *Courtroom Medicine: Cancer* § 25A.00, at 25A-4 (1992)).

The conclusions at that time were based in part on the extensive scientific record that Judge Weinstein had compiled and analyzed. In 1985, for example, Judge Weinstein surveyed the evidence advanced by the plaintiffs. Focusing in particular on epidemiological studies, Judge Weinstein concluded that "[n]o acceptable study to date of Vietnam veterans and their families concludes that there is a causal connection between exposure to Agent Orange and the

serious adverse health effects claimed by plaintiffs." *In re "Agent Orange" Production Liability Litigation*, 611 F. Supp. 1223, 1231 (E.D.N.Y. 1985), *aff'd on other grounds*, 818 F.2d 187 (2d Cir. 1987). The court concluded that there was simply no "credible evidence of a causal link between exposure to Agent Orange and the various diseases from which [the plaintiffs] are allegedly suffering." *Id*. at 1229.

Judge Weinstein's lengthy and scholarly opinion addressing the claims brought by the Vietnam Association for Victims of Agent Orange/Dioxin reflects the same thorough grounding in the relevant scientific literature. *See In re "Agent Orange" Production Liability Litigation*, 373 F. Supp. 2d 7, 19, 22-23, 32 (E.D.N.Y. 2005) (discussing recent scientific articles and explaining why they do not alter the court's conclusions as to lack of proof of exposure or causation). He noted that "[p]roof of causal connection depends primarily upon substantial epidemiological and other scientific data, particularly since some four million Vietnamese are claimed to have been adversely affected," and that plaintiffs' "[a]necdotal evidence . . . can not suffice to prove cause and effect." *Id.* at 32. Although the case was dismissed on other grounds, Judge Weinstein noted that epidemiological studies regarding Vietnamese plaintiffs are not available "with the richness of demographic and other data published in the United States," and he cited recent articles suggesting that the existing body of epidemiological literature was insufficient. *Id*.

Although Judge Weinstein has had the most experience with such cases, his decisions do not stand-alone. For example, in *Chemical Weapons Working Group, Inc. v. United States Department of the Army*, 935 F. Supp. 1206 (D. Utah 1996), *aff'd,* 111 F.3d 1485 (10th Cir. 1977), an environmental group sought an injunction to stop the U.S. Army's proposed operation of a facility to incinerate chemical warfare agents, which would create TCDD as a

byproduct. Discussing the science on dioxin, the court noted that "[a]lthough plaintiffs argue that any increase in the levels of dioxin exposure is unacceptable, the danger associated with relatively small increases is far from certain, and the evidence presented by plaintiffs is insufficient to support a finding that such danger is likely to be significant." *Id.* at 1213. The court also critiqued the assessment done by Utah's Department of Environmental Quality, noting that "[u]ltimately, the court finds that the Utah DEQ assessment is intended to show an area of safety, not predict an actual level of risk. Although plaintiffs have shown that the assumptions applied in the State's health risk assessment may indicate a higher level of risk for some hypothetical persons, this does not constitute a showing that there is an actual risk to some person or persons posed by the emissions levels predicted for the facility." *Id.* at 1214. As a matter of law, the court concluded that "the asserted risks of harm due to dioxin exposure are too speculative to qualify as irreparable harm to plaintiffs." *Id*. at 1215.

II. THERE IS NO CONSISTENT PATTERN OF ELEVATED CANCERS IN STUDIES OF INDUSTRIAL WORKERS EXPOSED TO DIOXIN

Production workers exposed to dioxin in industrial settings are generally considered to have the highest documented exposures of any of the cohorts studied in the epidemiological literature.[5] Most members of this group were exposed during the course of their work in industrial plants. However, even for these high levels of exposure, the results of the major epidemiological studies remain largely

[5] Higher exposure levels have been reported in rare instances of intentional dioxin poisoning. *See, e.g.,* Alexandra Geusau, et al., *Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Intoxication: Clinical and Laboratory Effects*, 109 Envtl. Health Persp. 865 (2001).

negative, with occasional weak and inconsistent findings. In fact, among humans, the only disease found to be causally related to TCDD is chloracne, which is a reversible skin condition that develops shortly after high levels of exposure to dioxin. *In re "Agent Orange" Production Liability Litigation*, 304 F. Supp. 2d at 407.[6]

A relatively recent comprehensive review article on the evidence relating to the "hypothetical cause-effect relationship" between 2,3,7,8-TCDD and cancer concludes that "[t]he long-term accumulation of negative, weak, and inconsistent findings suggests that TCDD eventually will be recognized as not carcinogenic for humans." Philip Cole, et al., *Dioxin and Cancer: A Critical Review*, 38 Reg. Toxicology & Pharmacology 378, 378 (2003). Cole et al. examined the scientific research on dioxin from three perspectives: (1) an analysis of the evidence available through 1997, with emphasis on the review done by the International Agency for Research on Cancer (IARC) in its 1997 Monograph 69, (2) a review of epidemiologic reports issued after 1997 Monograph was published, and (3) an evaluation of the EPA's ongoing risk assessment. Cole et al. concluded that "[i]t is clear from this review that the evidence does not support the IARC's classification of TCDD as a Group 1 carcinogen. In fact, the evidence

[6] Indeed, studies done in worker populations who were exposed to dioxin at sufficient levels to develop chloracne show "no clear evidence of a causal association between any cause of mortality and potential occupational exposures to the higher chlorinated phenols, derivative products, or the chlorinated dioxins." *See* Gregory G. Bond, et al., *Update of Mortality among Chemical Workers with Potential Exposure to the Higher Chlorinated Dioxins*, 31 J. Occupational Med. 121, 123 (1989); Cole et al., *supra*, at 383 ("Interestingly, even chloracne has not been associated with significant risks of cancer as would be expected if moderate to high TCDD exposures were carcinogenic.").

indicates that TCDD is not carcinogenic to human beings at low levels and that it may not be carcinogenic to them even at high levels. Cole et al., *supra*, at 386. The conclusion of this recent, comprehensive review of the dioxin literature is directly contrary to the EPA's use of its no-biological-threshold model, which is derived from the weak and inconsistent findings for the most highly exposed industrial worker cohorts, to fix a supposed level of cancer risk in humans with low exposures—without any support in the actual epidemiological literature for such low exposure populations.

Cole et al. also addressed the question of how, "in the absence of sufficient epidemiologic evidence, a conclusion of human carcinogenicity was drawn." *Id.* at 381.

> There are four reasons why so much attention has been focused on TCDD. First, TCDD is the most toxic PCDD. Even though toxicity and carcinogenicity are different, the high toxicity of TCDD has contributed to its overall notoriety. Second, TCDD has been linked closely to a major war (Vietnam) and to a major industrial accident (Seveso), both of which attracted widespread attention and increased suspicion that TCDD imposes a risk of cancer. Third, TCDD is an animal carcinogen, although for tumor types that bear little relationship to those allegedly linked to it in humans. Generalizing to humans from animals is fraught with difficulty, and animal evidence is often not a good predictor of human carcinogenicity. Fourth, the original epidemiologic studies of TCDD were represented as positive. However, these early studies, all by Hardell

> et al., have not been confirmed by other investigators. Nevertheless, it is difficult to erase from the collective consciousness the widely publicized early studies.

Id. at 381-82.

As aptly described by Cole et al., virtually the only "science" behind the suspicion that TCDD may cause cancer are the so-called "Hardell studies" conducted initially in the late 1970s by a group of Scandinavian epidemiologists/oncologists. The Hardell studies were case-control studies of pesticide applicators that focused on soft-tissue sarcoma and malignant lymphoma. Importantly, however, in the 20-plus years since these studies were conducted, no other investigators have been able to replicate the results, and contemporaneous case-control studies by other investigators "uniformly produced non-significant associations." Cole et al., *supra*, at 383. Courts have also recognized the limitations of the Hardell studies. Judge Weinstein, after examining these studies in depth expressly noted:

> The parties, and especially plaintiffs, rely on over one hundred epidemiological studies not conducted by government officials and as such not subject to the 803(8)(C) exception. . . . Most of the studies rely on inapposite data and would be excluded under Rules 401 to 403. Some of them on industrial exposure have been recognized as flawed. *See*, *e.g., Palmer v. Nova Scotia Forest Industries*, 60 N.S.R. (2d) 271, 352-53, 2 D.L.R. (4th) 397 (S.Ct. Nova Scotia, 1983) (Nunn, J.) (refusing to enter injunction against spraying of 2-4-D, 2,4,5-T-phenoxy herbicides in part *because expert*

> *studies, such as Hardell's, showing alleged adverse health effects were widely recognized as flawed).*

In re "Agent Orange" Prod. Liab. Litig., 611 F. Supp. at 1241 (emphasis added).

Studies of industrial workers further weaken any suggested links between TCDD and cancer in humans. The study by Manolis Kogevinas, *Cancer Mortality in Workers Exposed to Phenoxy Herbicides, Chlorophenois, and Dioxins*, 145 Am. J. Epidemiology 1061 (1997), which involved "'the largest overall cohort of 2,3,7,8,-TCDD-exposed workers'" Cole et al., *supra*, at 381, (quoting IARC Monograph at 161), found an overall relative risk of 1.1 Cole et al., *supra*, at 381, (citing Kogevinas et al. at 144 (1997)).[7]

This lack of consistent evidence of increased cancer risk associated with TCDD is further supported by the results of a recent study examining the long-term mortality experience of a cohort of 2187 male chemical plant production workers. The cohort of workers, which was a subset of the Kogevinas cohort, had previously been exposed to substantial levels of dioxin prior to 1983. K.M. Bodner, et al., *Cancer Risk for Chemical Workers Exposed to 2,3,7,8-*

[7] The Kogevinas study did show a slight, but statistically significant increase in the rate of overall cancers associated with high-levels of occupational exposure. As Cole et al. noted, however, it is unprecedented that a chemical would increase the risk of all cancers, but not increase the risk of any specific cancer. "There is . . . no single chemical that is known to cause cancer at many organ sites." Cole et al., *supra*, at 380. Even the International Agency for Research on Cancer (IRAC) acknowledged that "this lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiology data must be treated with caution. . ." Int'l Agency for Research on Cancer, World Health Org., *IARC Monograph on the Evaluation of Carcinogenic Risks to Humans* at 337, 338 (1997).

tetrachlorodibenzo-p-dioxin, 60 Occup. and Envtl. Med. 672-75 (2003). The Bodner study was the most recent in a series examining the cohort, and therefore has the most current mortality statistics and involves the longest latency period. e mortality rates were compared with both national figures and with a pool of coworkers in unrelated production jobs. The study showed that all cancers combined for this cohort were at or below expected levels.[8] The Bodner study also noted that workers who developed chloracne -- presumably the workers who had the highest exposure levels generally -- had very low all-cancer rates. The report concluded that "[d]espite some unanswered questions, we find no coherent evidence that this cohort has an increased risk of cancer collectively, or of any particular type of cancer that can be attributed to dioxin exposure." *Id*. at 675.

III. STUDIES ON MILITARY PERSONNEL EXPOSED TO DIOXIN CONSISTENTLY FAIL TO DEMONSTRATE A CAUSAL LINK BETWEEN DIOXIN AND CANCER

The Air Force has spent hundreds of millions of dollars following the health histories of the group of Vietnam veterans who clearly were the most highly exposed individuals during that conflict—the Operation Ranch Hand personnel who loaded and sprayed Agent Orange. That ongoing study of the Ranch Hand veterans has shown no marked excess of cancer even now, thirty-five to forty years after the exposure.[9]

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[8] Although the rates for soft tissue sarcoma and non-Hodgkin's lymphoma were greater than expected during the prior study period, the rates of these cancers did not increase at the expected rate during the update period.

[9] The 2005 report of this study concludes that "the significant associations between herbicide exposure or dioxin levels and the likelihood of developing cancer were seen primarily for Ranch Hand

The Ranch Hand study examined veterans who serviced, loaded, and flew the fixed-wing aircraft used for herbicide spraying missions in Vietnam and compared them to veterans who flew similar aircraft in Southeast Asia during the time of the Vietnam War but never flew herbicide missions and were not exposed to Agent Orange in their missions. Elevated serum levels of dioxin confirmed that the Ranch Hand group had been exposed to Agent Orange. Logically, if one were to find an increased risk from Agent Orange exposure in any group of Vietnam veterans, it would first show up in the most heavily exposed Ranch Hand group. However, study of the Ranch Hand veterans has not found any cancer-related health effects caused by Agent Orange exposure, *see* Joel E. Michalek *et al., The Air Force Health Study: A Summary of Results*, 54 Organohalogen Compounds 396 (2001), and the overall cancer mortality rate is similar to the comparison group, See Fatema Z. Akhtar *et al., Cancer in U.S. Air Force Veterans of the Vietnam War*, 42 J. Occupational & Envtl. Med. 123 (2004).[10]

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officers and Ranch Hands in the low dioxin category, which were the lower-exposed subgroups, on average. Some of these associations also may have been due to chance or to a lack of adjustment for a factor not considered in these analyses." Science Applications Int'l Corp., *Air Force Health Study Final Report*, *An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides – 2002 Follow-up Examination and Results*, 10-138 (2005).

[10] Akhtar et al., *supra*, conducted a comparison of cancer incidence in a cohort of Ranch Hand and Comparison veterans relative to the general United States white population and found a positive association with prostate cancer and melanoma in both groups of veterans. However, some researchers question whether a comparison of these cohorts is scientifically valid. Both melanoma and prostate cancer are frequently undiagnosed for many years in the general population, leading to a detection bias in favor of the Ranch Hand veterans. *See* Marian Pavuk, et al., *Prostate Cancer in US Air Force Veterans of the Vietnam War*, 16 J. Exposure Sci. & Envtl. Epidemiology, 184, 188 (2006) ("Air Force

Similar findings were made in the most recent Institute of Medicine ("IOM") Report, which concluded that "in general, *it is impossible* to quantify the degree of risk likely to be experienced by veterans because of their exposure to herbicides in Vietnam." 2004 IOM Report at 17 (emphasis added); *see also Id.* at 7 (noting that the "lack of adequate data on Vietnam veterans themselves makes it difficult to reach conclusions about increased risk of disease among Vietnam veterans"). The Report highlights the inadequacy of the current state of the scientific record, decrying "the lack of data on Vietnam veterans, the large uncertainties about the magnitude of potential risk posed by exposure to herbicides in epidemiologic studies, the inadequate control for other important risk factors in many epidemiologic studies, and the uncertainty about the nature and magnitude of exposure to herbicides in Vietnam." *Id*. at 7. Indeed, far from reflecting a scientific consensus that Agent Orange has caused cancer in Vietnam veterans, the Report highlights the need "for additional scientific studies to resolve continuing scientific uncertainties about the health effects of the herbicides used in Vietnam and their contaminants." *Id.* at 10.

For public policy reasons, Congress created a program of compensation for Vietnam veterans without requiring reliable scientific evidence of the health effects of Agent Orange exposure. Pursuant to the Agent Orange Act of 1991, the IOM was directed to "provide scientific information for the Secretary of Veterans Affairs" to aid in the implementation of the compensation program. *Institute of Medicine, Veterans and Agent Orange: Health Effects of*

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veterans have been more closely followed than the general population and underwent repeated medical examinations that may partly explain excesses seen in that study."); Akhtar et al., *supra*, at 133 (acknowledging the potential for detection bias in the melanoma findings).

Herbicides Used in Vietnam at 227 (1994) ("1994 IOM Report"). The IOM's periodic reports – the first was published in 1994, and the IOM has issued updated reports every two years since – have done just that. The IOM, however, has expressly disclaimed any intent to make causation assessments, noting that its "charge was n[ot] to focus on questions of causation," *Id.*, and explaining that its categorization of diseases was "based on 'statistical association,' not on causality as is common in scientific reviews," *Id.* at 246; *see also e.g.*, 1994 IOM Report at 7, 572; 2004 IOM Report at 7 ("As mandated by PL 102-4, the distinctions among categories are based on statistical association, not on causality."). As the Federal Judicial Center's *Reference Manual on Scientific Evidence* explains, however, "an association is not equivalent to causation":

> An association identified in an epidemiologic study may or may not be causal. Assessing whether an association is causal requires an understanding of the strengths and weaknesses of the study's design and implementation, as well as a judgment about how the study findings fit with other scientific knowledge.

Federal Judicial Center, *Reference Manual on Scientific Evidence* 336-37 (2d ed. 2000) (footnote omitted).[11]

[11] The peril of conflating association with causation is not unique to the dioxin context. In some early epidemiological studies, for example, coffee drinking was associated with lung cancer. However, coffee drinking used to be highly associated with smoking cigarettes, thus smoking was a "confounding" variable. Once smoking was controlled for, the association between coffee drinking and lung cancer disappeared. *See* Junius C. McElveen, Jr. & Chris Amantea, *Legislating Risk Assessment*, 63 U. Cin. L. Rev. 1553, 1581 (1995).

The vast gulf between association and causation has been well established in the context of Agent Orange. As described in *Nehmer v. United States Veterans' Administration*, 712 F. Supp. 1404, 1407-08 (N.D. Cal. 1989), the Veterans Administration ("VA") initially adopted a causation standard to govern eligibility for disability benefits under the Veterans' Dioxin and Radiation Exposure Compensations Standards Act of 1984. Applying that standard, the VA denied more than 31,000 claims for compensation in the first three years of the program. *Id.* at 1408. That causation standard was declared invalid in *Nehmer*, *see id.* at 1416-20, and was replaced with a standard requiring only a "significant statistical association," *id*. at 1420. Under that more relaxed standard, the VA has granted thousands of claims and is paying hundreds of millions of dollars in Agent Orange benefits.

The distinction between association and causation is particularly significant in the present context because of the congressional mandate to assess only the former. The IOM thus considers the link between chemical exposure and disease to be sufficient when "a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence." *Institute of Medicine, Veterans and Agent Orange: Update 2002* at 8 (2002) ("2002 IOM Report"). "Several small studies that are free of bias and confounding" may be sufficient evidence of an association when the results are "consistent in magnitude and direction," *Id.* at 14, even if larger and more reliable studies fail to replicate the small studies and even report results to the contrary.

There is, in short, nothing even approaching a "scientific consensus" that Agent Orange has caused cancers in Vietnam veterans, and nothing in the IOM Report suggests otherwise. As the record in the Agent Orange litigation

indicates, the Ranch Hand Study and the other studies of Vietnam veterans "effectively rule out the possibility of widespread health effects in Vietnam veterans due to Agent Orange."

IV. EPA'S SCIENCE ADVISORY BOARD AND THE NATIONAL ACADEMY OF SCIENCE HAVE BOTH NOTED THE ABSENCE OF ANY CONSISTENT, REPLICABLE PATTERN OF INCREASED CANCERS IN THE EPIDEMIOLOGY LITERATURE.

In 1995, EPA's Science Advisory Board ("SAB") issued a powerful critique of the agency's Dioxin Reassessment. Among other criticisms, the SAB stated that "the presentation of scientific findings portrayed in the draft document's conclusions is not balanced vis-à-vis the possible risks posed by exposure to dioxin, with a tendency to overstate the possibility for danger." JA18028. The SAB further noted that the evidence "for the purported mechanisms that link receptor binding to toxic effects in humans" was "quite mixed," making it "difficult to document a dioxin-cancer relationship." JA18066. Although the SAB concluded that EPA had fairly summarized the findings, strengths and weaknesses of the relevant epidemiological studies, the SAB was quite firm in its additional conclusions that "TCDD is not a complete carcinogen" and that the risk-specific dose estimate supplied by EPA's cancer potency factor "is not supported by the available data." JA18077, 18101.

In addition to the findings above, SAB recommended that EPA revise the dioxin risk characterization and the dose-response modeling chapters of its report.[12] Because of the

[12] SAB also recommended that EPA develop of a new section on dioxin toxicity equivalence factors (TEF).

complexity of the science issues related to dioxin, the SAB suggested that the subsequent draft undergo an additional level of review by independent external peer reviewers before being brought back to the SAB for review.

In 2000, a revised reassessment was submitted to SAB. Surprisingly, despite the prior criticism of its cancer potency factor, EPA did not revise its flawed no-threshold model. SAB was again critical of EPA's dioxin risk characterization, noting (1) the lack of consensus about the strength of the epidemiological data suggesting that dioxin is carcinogenic in humans; (2) the lack of consensus on a single value for a dioxin potency factor; and (3) EPA's failure to assess non-cancerous affects to establish a reference dose characterization. *See generally*, EPA, *Dioxin Reassessment - on SAB Review of the Office of Research & Development's Reassessment of Dioxin* 2-11 (2001). EPA undertook further revisions. At this point, the Department of Agriculture, concerned that enforcement of EPA's cancer potency factor could imperil large portions of the country's food supply, assembled an Interagency Working Group made up of representatives from seven federal agencies that recommended further review of EPA's 2003 revision of the Dioxin Reassessment. EPA then asked the National Research Council (NRC), the operating arm of the National Academy of Sciences, to convene an expert committee to review independently EPA's Reassessment. National Research Council, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment*, at 9(July 2006).

The NRC strongly criticized EPA's continued reliance on the linear, no threshold model:

> [S]election of the default linear extrapolation approach for carcinogenicity emerged as one of the most critical decisions in the 2003 Reassessment. The committee

> concludes that EPA did not support its decision adequately to rely solely on this default linear model and recommends that EPA add a scientifically rigorous evaluation of a nonlinear model that is consistent with receptor-mediated responses and the recent NTP cancer bioassay studies. The committee determined that the available data support the use of a nonlinear model, which is consistent with receptor-mediated responses and a potential threshold. . . .

Id. at 17.

Although the NRC made no effort to calculate a cancer potency factor using a non-linear model, it seems clear that any such calculation will yield a factor which will be much lower than the 16-fold reduction that Hercules proposed in the Administrative Records of this case. *See, e.g.*, JA17583 (proposing slope factor of 9,700 $(mg/kg\text{-}day)^{-1}$, using linear model and then-recent histopathology results), JA17585 (noting that other nations had dramatically higher Acceptable Daily Intake (ADI) standards than EPA). Moreover, a "nonlinear model" with "a potential threshold," means that there is some lower level of exposure below which any cancer risk becomes insignificant. And, all the risk models leave open the ever-increasingly likely possibility that dioxin does not cause human cancer even at the highest levels of exposure.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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