In the Supreme Court
State of Georgia

SCAPA DRYER FABRICS, INC.	)
	)
Petitioner,	)
	)
v.	)
	)
ROY KNIGHT AND MILVA KNIGHT	)
	)
Respondents.	)

BRIEF OF *AMICI CURIAE* COALITION FOR LITIGATION JUSTICE, INC., CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA, NATIONAL ASSOCIATION OF MANUFACTURERS, AMERICAN TORT REFORM ASSOCIATION, AND NFIB SMALL BUSINESS LEGAL CENTER

IN SUPPORT OF PETITION FOR CERTIORARI

Case No. S15C1278

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INTEREST OF *AMICI*

Amici are organizations whose members include asbestos defendants and their insurers. Accordingly, *Amici* have a substantial interest in ensuring that expert evidence admitted in asbestos cases is consistent with sound science and public policy. *Amici* regularly file briefs before state and federal appellate courts to explain the science behind today's low-dose asbestos lawsuits and to encourage the courts to move asbestos litigation back into the world of mainstream medical knowledge and the ordinary requirements of toxic tort legal causation standards. The decision below violates these basic principles, and, if allowed to stand, would adversely impact *Amici*'s members.

INTRODUCTION

Amici support the petition for certiorari filed by Scapa Dryer Fabrics, Inc. ("Scapa") so that the Court can address the necessity of determining a causative dose in low-exposure asbestos cases. Unlike historical asbestos litigation, which typically involved plaintiffs with years of heavy exposure to friable asbestos such as insulation, much of asbestos litigation today operates in a world of ultra-low and speculative exposures. Those claimed exposures frequently consist of nothing more than a few instances of handling asbestos material or sometimes merely passing by or witnessing an asbestos-containing product or operation.

Georgia's intermediate appellate court has now addressed this class of asbestos case twice – and produced two polar opposite opinions. The court that decided the 2012 *Butler*[1] case soundly and correctly rejected the theory that every workplace exposure contributes to causation. The *Scapa* dissent followed *Butler.* In contrast, the five-judge *Scapa* majority let the experts testify to the same theory. In the process, the *Scapa* court let a jury verdict stand where no Plaintiff expert even attempted to determine how much exposure Mr. Knight received at Scapa's facility and whether it constituted enough exposure to cause mesothelioma.

The extent of dose received from a particular jobsite or work activity, however, is the critical question in a multiple exposure case such as *Scapa*. As this brief will demonstrate, it is not true that every contact with asbestos in Mr. Knight's life was a contributing cause. Exposures across a work history can differ dramatically, some in the more substantial realm (*e.g.*, extensive insulation work) and some trivial and inconsequential. Expert testimony is necessary to sort through these exposures and guide the jury in its decision. Declaring all such exposures as causative is wrong on the science and unhelpful to the jury.

Because of *Scapa,* the Georgia Court of Appeals is now deeply divided on how to address causation in asbestos cases involving limited exposures and

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[1] *Butler v. Union Carbide Corp.*, 310 Ga. App. 21, 712 S.E.2d 537 (Ga. App. 2011).

multiple worksites.[2] And that confusion will create a crisis situation for Georgia trial courts – which opinion to follow? – because the next two decades of asbestos cases will increasingly involve the sort of speculative exposures with no dose assessment that the *Scapa* court would apparently find sufficient and the *Butler* court clearly would not. This Court needs to provide timely guidance on the criteria for expert testimony in low exposure asbestos litigation.

The first step in that guidance is to return asbestos cases to the fundamental principle of *dose* – plaintiff experts must demonstrate, through a competent scientific assessment, that plaintiff received a dose sufficient to cause the disease at issue – in this case, mesothelioma. As the concurrence in *Butler* stated, "The first question *Daubert* requires judges to ask is "where are the data?" and failure to produce them should result in exclusion of the expert opinion."[3] The *cumulative any exposure* theory espoused by Plaintiffs' lead medical causation expert, Dr. Jerold Abraham, instead substitutes vague terms like "substantial" and "proximity"

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[2] "Low" exposure cases as used in this brief is intended to refer generally to those exposures for which epidemiology studies have not documented an increased risk of disease. Such exposures typically involved bonded products or only tangential or infrequent work with asbestos-containing materials, as opposed to the years of employment in dusty trades and insulation work that have produced the vast majority of mesothelioma cases. "Low" exposure cases often involve exposures below even today's OSHA standard of 0.1 f/cc and frequently cannot be distinguished from the background exposures that all persons experience.

[3] *Id*. at 45.

for real data and instead simply assumes that every workplace contact with asbestos is part of the cause.

The second step in restoring asbestos litigation to a sound foundation is to ensure that trial judges are not forced to perform the role that experts like Dr. Abraham have abdicated – namely, assisting the jury in determining how much exposure from a particular workplace event is enough. The *Scapa* majority substituted itself for this missing expert testimony by deciding that the Scapa facility exposures were "substantial," with no assistance from Dr. Abraham on such a complex industrial hygiene and medical issue. The court should instead have functioned as gatekeeper – to ensure that *the experts do their job* and do it competently. The *Scapa* court should have dismissed the case, not rescued it.

Amici file this brief to explain why science mandates rejection of *any exposure* testimony. The contrary approach adopted by the *Scapa* majority will expand asbestos litigation into uncharted and unscientific territory. The Court should remedy this situation before jury verdicts in low dose cases become increasingly out of touch with medicine and tort principles.

ARGUMENT

The majority opinion in *Scapa* departed from well-accepted scientific principles and toxic tort causation law in two key ways. First, the court allowed Dr. Abraham to testify that Mr. Knight's work at the Scapa facility caused his

disease, without ever asking and answering the questions *how much exposure did he receive* and *was this enough to cause cancer?* Second, since Dr. Abraham failed to do the expert's job in this regard, the majority stepped in and decided for itself that Mr. Knight's Scapa exposures were "substantial" and "not de minimis." Op. at 10.

The Court should grant certiorari to instruct lower courts to follow the analysis in the *Butler* opinion and thus ensure that future asbestos litigation in Georgia does not go off the rails of a good scientific foundation.

I. *Any Exposure* Testimony Is Not Consistent with Toxic Tort Causation and the Tenets of Science.

Dr. Abraham engages in circular reasoning to reach his opinion as to which defendants' products or work activity the jury should consider a cause of mesothelioma. If a plaintiff has mesothelioma, Dr. Abraham reasons that asbestos is known to cause this disease, and asbestos fibers accumulate in the lung, so it must be true that every exposure, no matter how small, is part of causation. Thus, rather than answering the pressing question here – which of Mr. Knight's many workplace exposures during his career were sufficient actually to cause mesothelioma and which were inconsequential enough to exclude – he simply assumes that all of them were contributory. Claiming that all exposures contribute

to causation just because they are cumulative is like assuming that a bucket of water thrown in the ocean contributes meaningfully to the size of the ocean.[4]

Dr. Abraham's reliance on this *cumulative exposure/any exposure theory* is illogical and inconsistent with the most basic principles of science. It is thus unreliable and inadmissible under *Daubert.* Many courts, including the *Butler* court, have recognized the unscientific nature of *any exposure* testimony and required the experts to demonstrate a causative dose. In the coming wave of low-dose cases, such a standard will be critical to Georgia's asbestos jurisprudence.

A. Carcinogens Such as Asbestos Are Dose Dependent – Not Every Exposure Is Causative.

Asbestos, like any toxin including carcinogens (*e.g.*, radiation or tobacco smoke), requires some level of overall dose to produce disease. The human body is capable of defending itself against a whole array of daily exposures to known toxins, up to a point. Disease results when those exposures reach a level that overwhelms our defenses, called the "threshold" point. Aspirin, alcohol, sunlight, even known "poisons" like arsenic are only poisonous if the dose is high enough to make them so. At lower doses, they are either harmless or beneficial. For this reason, since the time of Paracelsus, toxicology has rested on the bedrock principle

[4] *Moeller v. Garlock Sealing Tech.*, 660 F.3d 950, 955 (6th Cir. 2011).

that "the dose makes the poison."[5] For toxicologists "[d]ose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect."[6]

This dose principle holds true for carcinogens like asbestos just as much as it does for any other toxin:

> Most chemicals that have been identified to have "cancer-causing" potential (carcinogens) do so only ***following long-term, repeated exposure for many years. Single exposures or even repeated exposures for relatively short periods of time (e.g., weeks or months) generally have little effect*** on the risk of cancer, unless the exposure was remarkably high and associated with other toxic effects.[7]

Airplane passengers receive doses of radiation at high elevations beyond background, but scientists don't ascribe cancer to those flights.[8] Foods often contain low levels of natural carcinogens not known to cause any harm. Science

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5 FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, REFERENCE GUIDE ON TOXICOLOGY at 403 (the "fundamental tenet" of toxicology). The "father of toxicology," physician and philosopher Paracelsus, first articulated this principle in the 16th century, stating: "All substances are poisonous—there is none which is not; the dose differentiates a poison from a remedy." David L. Eaton, *Scientific Judgment and Toxic Torts—A Primer In Toxicology For Judges And Lawyers*, 12 J.L. & POL'Y 5, 11 (2003). The Eaton article is an excellent primer of how science and toxic tort litigation intersect – it is included as Exhibit A to this brief.

6 Eaton, *supra*, at note 7.

7 *Id*. at 9 (emphasis added).

8 *See* Health Physics Soc'y, *Radiation Exposure During Commercial Airline Flights* (2014), *at* http://www.hps.org/publicinformation/ate/faqs/commercial-flights.html; Health Physics Soc'y, *Airport Screening Fact Sheet* (2011), *at* http://hps.org/documents/airport_screening_fact_sheet.pdf (compiling studies).

has cleared these "exposures" through the use of epidemiology studies that have found no link between such low-level exposures and cancer, even when the substance is without question a carcinogen at high doses.[9]

Asbestos is no different. Asbestos fibers are ubiquitous in the environment and are part of the normal background exposure to toxic substances we all receive. These "background" levels have never been shown to cause mesothelioma. In addition, many workers have received minor or low level asbestos exposures with no apparent harm. The cohorts that have exhibited documented levels of asbestos disease are typically those who worked in heavy exposure industries – the old "dusty trades" such as shipbuilding and repair, asbestos factories, and asbestos mining.[10] Some worker populations have not shown any increased asbestos disease despite working with asbestos their entire careers. For example, multiple

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[9] Epidemiology is universally recognized as the "most desirable evidence" for assessing causation in the science of toxicology. Michael Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of the Agent Orange and Bendectin Litigation*, 86 NW. U. L. Rev. 643, 646 (1992); *see also id.* at 648 ("The most desirable evidence is epidemiologic, because it can best be generalized to support inferences about the effect of an agent in causing disease in humans."); Bert Black, *Epidemiologic Proof in Toxic Tort Litigation*, 52 FORDHAM L. REV. 732, 736 (1984) ("[E]pidemiology is the only generally accepted scientific discipline . . . to identify and establish the causes of human diseases."); Mary Andrues, *Proof of Cancer Causation in Toxic Waste Litigation: The Case of Determinacy Versus Indeterminacy*, 61 S. CAL. L. REV. 2075, 2088 (1988) ("The only valid way to identify human carcinogens and establish medical causation is to observe differences in the incidence of cancer between humans exposed to toxic wastes and those who are not.").

[10] *See* Deborah Hensler *et al*., *Asbestos Litigation in the U.S.: A New Look at an Old Issue* (RAND Corp. 2001).

studies of vehicle mechanics who worked with chrysotile-containing brake pads have never found a consistent increased incidence of mesothelioma.[11] South African chrysotile miners likewise have not demonstrated a single case of mesothelioma despite decades of heavy mining exposures.[12] Chrysotile is the same fiber type found in Scapa's dryer felts. OSHA's asbestos standard today is ***not*** zero – it is 0.1 f/cc on an 8-hour time-weighted basis, meaning this is an "acceptable exposure" for a 45-year work life. The U.S. Environmental Protection Agency allows school children back into an asbestos-remediated school if exposures are below 0.01 f/cc.[13]

Thus, it is ***not true*** that every exposure to asbestos has been shown to cause disease, or that there is no "safe" dose of asbestos, certainly not in the sense of

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[11] Most of the studies are summarized and discussed in Francine Laden *et al*., *Lung Cancer and Mesothelioma Among Male Automobile Mechanics: A Review*, 19 REVS. ON ENVTL. HEALTH 39 (2004); and Michael Goodman *et al*., *Mesothelioma and Lung Cancer Among Motor Vehicle Mechanics: A Meta-analysis*, 48 ANNALS OCCUP. HYGIENE 309 (2004). *See also* Julian Peto *et al*., *Occupational, Domestic and Environmental Mesothelioma Risks in Britain: A Case-Control Study*, UK HEALTH & SAFETY EXEC., at x (2009); Christine Rake *et al., Occupational, Domestic and Environmental Mesothelioma Risks in the British Population: A Case Control Study*, 100 BRIT. J. CANCER 1175, 1182 (2009).

[12] *See* David Rees, *Case Control Study of Mesothelioma in South Africa*, 35 AM. J. INDUS. MED. 213, 220 (1999).

[13] Asbestos Hazard Emergency Response Act (AHERA), 40 CFR Pt. 763, §763.90(i)(5).

actual causation.[14] Experts who come into court should be required to do more than rely on speculation that every exposure has contributed to disease. In both asbestos and other contexts, scientists regularly answer the critical question *how much is enough* by conducting exposure studies, from which they can determine whether those exposures reached the levels found to cause disease in comparable epidemiology studies (*e.g.*, of the same fiber type and similar exposure circumstances).[15] Expert testimony on carcinogens requires a reasonable assessment of the likely range of dose received by the worker and a determination as to whether this dose is comparable to amounts known (not speculated) to cause disease.[16] Georgia law requires no less. The science behind this is not simple, but

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[14] *Butler*, 310 Ga. App. at 41 ("The claim that there is no known safe level of exposure does not mean that none exists; it simply means that science today has not or cannot … determine what that level of exposure is.").

[15] Courts routinely require plaintiffs to demonstrate not just some exposure, but "evidence from which the trier of fact could conclude that the plaintiff was exposed to levels of toxins ***sufficient to cause the harm complained of.***" *Wintz v. Northrop Corp.*, 110 F.3d 508, 513 (7th Cir. 1997) (citing Reference Manual on Scientific Evidence) (emphasis added); *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1241 (11th Cir. 2005) ("In toxic tort cases, [s]cientific knowledge of the harmful level of exposure to a chemical, plus knowledge that plaintiff was exposed to such quantities are minimal facts necessary to sustain plaintiff's burden.).

[16] *Parker v. Brush Wellman, Inc.*, 1:08-CV02725, 2010 WL 3730924 at *4 (N.D. Ga. 2010) (applying Georgia law) (in order to carry burden of proof, "a plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure to the defendant's toxic substance before he or she may recover"), *quoting Wright v. Willamette Indus.*, 91 F.3d 1105, 1106 (8th Cir. 1996), *aff'd on other grounds, Parker v. Schmiede Mach. and Tool Corp.*, 445 F. App'x. 231 (11th Cir. 2011); *see*

the requirement of a dose assessment is as basic as it gets – no one would conclude that taking aspirin caused someone's death without first *at least asking the question* how many aspirin are involved.

The *any exposure* theorists' notion that all exposures must be considered causative simply because they accumulate is also illogical and unscientific. As even those experts will admit, the human body has many defenses in place to prevent ordinary exposures to carcinogens from producing cancerous tumors. As a result, as Professor Eaton instructs in his article above, many exposures are simply too small and inconsequential to contribute to any disease. A match thrown into a burning forest may "cumulate" into the single fire, and it is in some sense not possible to separate the match's fire from the rest – but the match's input into the overall fire is completely inconsequential. The many rainstorms preceding Hurricane Katrina added water to the levees and water bodies around the City, but those storms certainly did not contribute to the destruction of New Orleans in any meaningful way, for the fundamental reason that the City's systems were perfectly capable of handling that level of inflow. The human body works the same way. No expert should be permitted to find "cause" in every input to a cumulative event.

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also Butler, 310 Ga. App. at 39-40 (concurring opinion) (similarly quoting *Wright*).

To meet the reliability standard of *Daubert,* then, it is incumbent on experts like Dr. Abraham to answer, in a scientifically reliable manner, the "how much" question. If background isn't enough, and if many exposed cohorts do not seem to incur asbestos disease, how much asbestos, and of what fiber type, must a specific work activity contribute to be meaningful for a causation analysis? And did plaintiff's exposures at a particular job site cross this threshold?

It is true that the exact level of causation for asbestos is unknown (a point Plaintiffs misstate to claim there is "no safe level of exposure"), but that does not mean the general range of causative and non-causative exposures is impossible to ascertain. Like many other toxic substance, for which the exact demarcation between disease and no disease is not crystal clear, scientists routinely make judgments about "safe" levels of exposure based on epidemiology and other studies. And asbestos is likely the most studied toxin in human history. There is no reason that these testifying experts should be allowed to jump to the unjustified conclusion that every occupational exposure, no matter how minimal, has to be a contributing cause. They do so for litigation purposes – to draw into lawsuits every possible defendant's product, regardless of actual degree of contribution.

B. Multiple Courts Have Rejected the *Any Exposure* Theory Because It Does Not Account for the Primacy of Dose.

Since 2005 many of the old asbestos thermal insulation manufacturers have gone into bankrupty as a result of asbestos litigation. As a result, the plaintiffs' bar

has target bonded product and significantly lower-dose exposure scenarios in reliance on the *any exposure* theory with no credible science to support the causation arguments. In response, many courts nationwide have rejected the *any exposure* theory or similar *cumulative exposure* approach in asbestos and other toxic tort litigation.[17] The courts rejecting this theory include the Sixth Circuit Court of Appeals, the highest courts of Texas, New York, Pennsylvania, Nevada, and arguably Virginia, and trial and appellate courts in Florida, Delaware, Ohio, Louisiana, Mississippi, Utah, California, Washington, and Pennsylvania. Some highlights of those rulings include the following:

- The Supreme Court of Pennsylvania has soundly rejected *any exposure* testimony three times, calling the theory a "fiction" and requiring experts to prove a causative dose. *See Betz v. Pneumo Abex LLC*, 44 A.3d 27 (Pa. 2012). *See also Gregg v. V-J Auto Parts Co.*, 943 A.2d 216 (Pa. 2007); *Howard ex rel. Estate of Ravert v. A.W. Chesterton, Inc.*, 78 A.3d 605 (2013).[18]

[17] For a survey of *any exposure* opinions and issues, *see* Mark Behrens & William Anderson, *The "Any Exposure" Theory: An Unsound Basis for Asbestos Causation and Expert Testimony*, 37 Sw. U. L. Rev. 479 (2008); William Anderson, Lynn Levitan & Kieran Tuckley, *The "Any Exposure" Theory Round II – Court Review of Minimal Exposure Expert Testimony in Asbestos and Toxic Tort Litigation Since 2008*, 22 Kan. J. L. & Pub. Policy 1 (2012).

[18] Some of these courts, such as Pennsylvania, rely on the *Frye* standard rather than *Daubert.* Although the analysis is analytically distinct, these *Frye* courts provide valuable criticisms of the scientific basis and lack of logical thinking behind the *any exposure* theory that applies across all jurisdictions. *See Butler*, 310 Ga. App. at 27 (relying on *Frye* decision as lending "credence" to the conclusion that the "no threshold" theory was unscientifically reliable).

- The Virginia Supreme Court held that experts "must opine as to what level of exposure is sufficient to cause mesothelioma, and whether the levels of exposure at issue . . . were sufficient." *Ford Motor Co. v. Boomer*, 736 S.E.2d 724, 733 (Va. 2013). *See also Wannall v. Honeywell Int'l, Inc*., 292 F.R.D. 26 (D.D.C. 2013) (applying *Boomer*), *aff'd*, 775 F.3d 425 (D.C. Cir. 2014).

- The Texas Supreme Court (twice) and two Texas intermediate courts have considered multiple aspects of the *any exposure* theory and plaintiff arguments for it, and have rejected all of them. *See Bostic v. Georgia-Pacific Corp.*, 439 S.W.3d 332 (Tex. 2014); *Flores v. Borg-Warner Corp.*, 232 S.W.3d 765, 772 (Tex. 2007); *Georgia-Pacific Corp. v. Stephens*, 239 S.W.3d 304 (Tex. App.-Houston 2007); *Smith v. Kelly-Moore Paint Co., Inc.*, 307 S.W.3d 829 (Tex. App. 2010).

- The federal Sixth Circuit Court of Appeals has rejected *any exposure* testimony four different times, both in asbestos cases and otherwise. *See Bartel v. John Crane, Inc*., 316 F. Supp. 2d 603 (N.D. Ohio 2004), *aff'd sub nom. Lindstrom v. A-C Prod. Liab. Trust*, 424 F.3d 488 (6th Cir. 2005); *Moeller v. Garlock Sealing Tech., LLC*, 660 F.3d 950 (6th Cir. 2011); *Martin v. Cincinnati Gas & Elec. Co*., 561 F.3d 439 (6th Cir. 2009); *Pluck v. BP Oil Pipeline Co.*, 640 F.3d 671 (6th Cir. 2011) (benzene).

- Multiple federal district courts have rejected *any exposure* testimony under the same standard, *Daubert*, that applies in Georgia.[19]

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[19] *See Smith v. Ford Motor Co.*, No. 2:08-CV-630, 2013 WL 214378 (D. Utah Jan. 18, 2013); *Anderson v. Ford Motor Co*., 950 F.Supp.2d 1217 (D. Utah 2013); *Sclafani v. Air & Liquid Sys. Corp.*, No. 2:12-CV-3013, 2013 WL 2477077 (C.D. Cal. May 9, 2013); *In re W.R. Grace & Co*., 355 B.R. 462 (Bankr. D. Del. 2006), *appeal denied*, 2007 WL 1074094 (D. Del. Mar. 26, 2007); *Newkirk v. ConAgra Foods, Inc*., 727 F. Supp. 2d 1006 (E.D. Wash. 2010), *aff'd*, 438 F. App'x. 607 (9th Cir. 2011) (diacetyl); *Henricksen v. ConocoPhillips Co*., 605 F. Supp. 2d 1142 (E.D. Wash. 2009) (benzene); *Comardelle v. Penn Gen. Ins. Co.*, No. 13-6555, 2015 WL 64279 (E.D. La., Jan. 5, 2015); *Davidson v. Georgia Pacific*, No. 12-1463, 2014 WL 801342 (W.D. La., Feb. 28, 2014).

Other key opinions include *Holcomb v. Georgia Pacific*, 289 P.3d 188 (Nev. 2012) ("cumulative exposure" testimony insufficient); *Free v. Ametek*, 2008 WL

This is, in fact, not the first time an appellate court has examined *any exposure* testimony as applied to Scapa's dryer felts. The Ninth Circuit Court of Appeals last year reversed an $11 million trial verdict rendered in part against Scapa, on the grounds that the trial judge did not perform a sufficiently rigorous *Daubert* review of expert testimony. That failed rigor included plaintiff expert's reliance on the *any exposure* approach. *See Estate of Barabin v. AstenJohnson, Inc.*,740 F.3d 457, 464-65 (9th Cir.), *cert. denied*, 135 S. Ct. 55 (2014). The *Scapa* court's cursory examination of Dr. Abraham's approach likewise does not meet *Daubert's* requirements.[20]

Recent opinions continue to extend the reach of the courts refusing to allow *any exposure* testimony. In April of this year one of the New York City asbestos docket judges excluded all *cumulative exposure* testimony in brake cases. *See Juni v. A.O. Smith Water Prods*., __ N.Y.S.3d __, 2015 WL 1840006 (N.Y. Sup. Ct. New York Cnty., Apr. 13, 2015). As that court stated: "That mesothelioma is

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728387 (Wash. Super. Ct., King Cnty., Feb. 28, 2008); *McPhee v. Ford Motor Co*., 135 Wash. App. 1017, 2006 WL 2988891 (Wash. App. Div. 1 Oct. 16, 2006).

[20] The *Scapa* panel seemed to pay at most lip service to a true *Daubert* analysis by summarily concluding that Dr. Abraham used a "scientific investigation" to reach his conclusions. Op. at 14. Yet the court did not examine a single one of Dr. Abraham's studies or the lack of referenced support for his methodology, or test or examine the logic of any of his conclusions. Nor did the Court apply any of the Supreme Court's four *Daubert* factors to Dr. Abraham's methodology. The *Scapa* panel's approach is much more akin to the cursory trial court approach in *Barabin* than a serious *Daubert* analysis of any exposure testimony, as in the recent Louisiana cases *Comardelle* and *Davidson* and Utah *Smith* opinion.

caused only by exposures to asbestos does not dispose of the issue of whether a defendant's product caused the mesothelioma … which depends on the sufficiency of the exposure, if any, to asbestos in the defendant's product and whether that exposure is capable of causing mesothelioma." *Id.* at *15. The same point applies to the alleged Scapa exposures in this premises case.

There are many reasons, set forth in detail in the above opinions, that so many courts have rejected precisely the type of testimony Dr. Abraham provided here. *Cumulative any exposure* testimony (1) is illogical because it ignores these experts' own admission that background exposures also accumulate in the lungs but are *not* causative; (2) assumes improperly that disease caused at high levels of exposure would also occur at much lower doses with no evidence that it does; (3) disregards the difference in fiber potency by treating chrysotile exposures (*e.g.*, Mr. Knight's dryer felt) the same as amphibole exposures such as insulation; (4) and has no epidemiology studies to support the notion that the lowest exposure is causative. The *any exposure* theory eliminates plaintiff's ordinary burden of proof – plaintiff need only claim breathing "dust," and then defendants must prove those exposures non-causative. In fact, none of these experts has ever published the

notion that any amount of workplace exposure must be considered causative – they only express this opinion in court.[21] Georgia law should require more.[22]

C. Georgia Law Needs to Reflect Basic Causation Principles to Avoid a Flood of Trivial Exposure Cases.

Amici urge the Court to accept Scapa's petition. The contrast between the *Scapa* and *Butler* opinions, and the divergence of *Scapa* from the dominant law in other jurisdictions, begs for a resolution before this Court. Georgia law needs to incorporate a more reasonable causation rule than "every exposure counts" because

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[21] The *Scapa* panel and Dr. Abraham referenced the Helsinki guidelines as support for an *any exposure* approach, but that document nowhere declares what these experts say in court. Helsinki explicitly states that exposures must be "significant" for attribution and does not attribute disease to "any" or "all" workplace exposures. *Consensus report: Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution,* 23 SCAND. J. WORK ENVIRON. HEALTH (1997). The reliance on this document is specious to begin with because it is a publication by nineteen hand-picked researchers and does not represent any form of scientific consensus. The *Butler* court also rejected reliance on the Helsinki document because "this report did not address whether a component of a cumulative exposure of asbestos is causative." 310 Ga. App. at 26-27. *See also* Concurring Opinion at 43 (Helsinki criteria were not formulated "with the *Daubert* test in mind").

[22] *Parker v. Brush-Wellman,* 2010 WL 3730924 at *5 ("It is not … Defendant's responsibility to disprove exposure; rather, it is Plaintiff's burden to prove *actual* exposure."). *See* David E. Bernstein, *Getting to Causation in Toxic Tort Cases,* 74 BROOK. L. REV. 51, 59 (2008) ("The recent, increasingly strict exposure cases . . . reflect a welcome realization by state courts that holding defendants liable for causing asbestos-related disease when their products were responsible for only *de minimis* exposure to asbestos, and other parties were responsible for far greater exposure, is not just, equitable, or consistent with the substantial factor requirements of the *Restatement (Second)* and *Lohrmann* [*v. Pittsburgh Corning Corp*., 782 F.2d 1156 (4th Cir. 1986)].").

the asbestos docket is quickly becoming a never-ending stream of speculative and trivial exposure cases. Mr. Knight, for instance, unlike the insulators common in prior year asbestos cases, apparently did not even handle much, if any, asbestos material himself. His case seems to be largely built on the idea that he was in the vicinity (with no actual distances provided) of material that contained asbestos, and even then only on a few occasions. Opinion p. 5; *see* Scapa Opening Brief at 20-25. These "mere presence" cases involve very little exposure, if any, and that is why experts like Dr. Abraham avoid assessing the dose – there is not enough to support the case.

Most of the real asbestos-induced mesothelioma cases are disappearing from the docket because the workers who were exposed to significant amounts of asbestos (*i.e.*, those prior to the advent of OSHA in 1971) are aging out. Instead, the bulk of today's docket increasingly consists of younger persons, including many women, who can only claim extremely minor exposures such as watching a husband perform a few backyard brake jobs, or who can only speculate that they may have breathed some asbestos because it was in a building somewhere. These mesotheliomas are not the result of asbestos exposures.[23]

[23] An increasing proportion of these cases are likely spontaneous, produced by errors in the human body's transcription of DNA billions of times in reproducing cells. The medical literature fully documents the existing of spontaneous cases. B.T. Mossman *et al.*, *Asbestos: Scientific Developments and Implications for Public Policy*, 247 SCIENCE at 294 (1990) ("approximately 20 to 30% of

Nevertheless, the *any exposure* theory permits these trivial or minimal exposure cases to get to a jury. Many states, as noted above, have decided to draw the line on this unwarranted expansion of asbestos litigation. Without *any exposure* testimony, plaintiffs would have to meet the same standard any other plaintiff would in a toxic tort case – *i.e.*, by proving a causative dose. In contrast, the *any exposure* theory, if allowed to support a case like *Scapa*, would place a strict liability legal obligation on a premises owner like Scapa – Scapa would be obliged to compensate anyone who could claim to have been "in proximity" (with no standard for that term) of asbestos in its plant, or who merely saw "dust" in the plant, with no further proof of negligence or causation. The Court should draw the line against this testimony as other courts have.[24]

The Court should also eliminate the loose usage of highly general terms such as "in proximity," "visible dust," and "substantial exposure" – the language of Dr.

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mesotheliomas occur in the general population in adults not exposed occupationally to asbestos"); Weill, H., et al., *Changing Trends in US Mesothelioma Incidence,* H, 61 OCCUPATION ENVIRONMENTAL MED. 438 (2004) ("only about 20% of all mesotheliomas in women in the United States can reasonably be linked to asbestos exposure"). *See, e.g., Butler*, 310 Ga. App. at 41.

[24] The *any exposure* theory also does not suffice under Georgia's "contributing factor" test as set forth in *John Crane, Inc. v. Jones*, 278 Ga. 747 (2004). The expert and court must still draw a line between exposures that meaningfully contribute and those that do not – "proximate cause is an essential element of the plaintiff's case…." *Id.* at 751.

Abraham and the *Scapa* court – from the lexicon of Georgia's asbestos cases.[25] As used in cases like *Scapa*, these intentionally vague terms allow plaintiffs and their experts to whitewash their lack of any real exposure evidence. Georgia law requires, *at a minimum*,[26] "close proximity" for an asbestos case to proceed, but this standard surely requires at least some testimony on how close or how far plaintiff was from the source – not just a magic incantation of those words. The "close proximity" test also must be viewed as a floor – not the full extent of plaintiff's obligations. In addition to proximity, the actual distance from the source is critical, as is the actual dose associated with the claimed exposure based on the duration, extent, and frequency of the exposures, and the potency of the fiber type.

Amici thus request that the Court use this opportunity to clarify that in low-dose litigation plaintiffs must assess and establish a causative dose before proceeding to trial, even if plaintiff can claim to have breathed "dust" or seen asbestos-containing materials in some number of workplace occasions.

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[25] *See, e.g., Parker v. Mobile Oil Corp.*, 7 N.Y.3d 434, 449-50 (N.Y. 2006) (expert's opinion that plaintiff was "frequently" exposed to "excessive" amount of benzene, without foundation, "cannot be characterized as a scientific expression of Parker's exposure level"); *Sterling v. P&H Mining Equip.*, No. 1006 EDA, 2015 WL 1743156 at *4 (Pa. Super. Apr. 17, 2015), at 8 (plaintiff testimony that he "saw dust" insufficient with no proof that dust contained asbestos, multiple potential other sources of dust in industrial facility, no testimony as to distance from dust, etc.).

[26] *Hoffman v. AC&S Inc.*, 248 Ga. App. 608, 611 (2001); *but see Butler*, 310 Ga. App. at 31 (*Hoffman* "close proximity test" is "the basic, threshold requirement for recovery;" declining to allow case to proceed on mere exposure testimony).

II. The *Scapa* Court Departed from Toxic Tort Causation Principles and Improperly Took on the Role Abandoned by Plaintiffs' Experts.

The *Scapa* panel departed from standard scientific principles and toxic tort causation rules by deferring to Dr. Abraham's opinions rather than testing them. This approach is the exact opposite of what *Daubert* requires. The court then compounded the error by supplying the missing element of Dr. Abraham's testimony – the *court itself* determined that the exposures were sufficient for causation in this case (and that those in *Butler* were not). These two errors are more than sufficient to reverse the ruling and instead to adopt the analysis and approach in *Butler*, which is consistent with the overwhelming number of decisions in other courts.

A. The Court Should Have Required a Dose Assessment Rather than Merely Contrasting the *Butler* and *Scapa* Exposure Scenarios.

The *Scapa* court's ruling turns on a distinction between this case and *Butler* – that *Butler* involved only trivial or de minimis exposures and *Scapa* involved "substantial" exposures. Simply applying labels to different exposure scenarios, however, is not a substitute for a competent assessment of the dose. A scientific assessment to test this conclusion would have involved an analysis of many factors that the court did not even begin to address – all of them essential in determining whether in fact Mr. Knight's exposures at Scapa were substantial in a causative sense rather than inconsequential:

- *Exposure at the source:* The analysis has to start with the level of exposure at the source itself. No plaintiff expert even commented on this factor, and the court relied instead on the presence of mere "dust." (Scapa's evidence indicated that exposures immediately next to these felts were well below regulatory standards.)

- *Distance from the source:* Mr. Knight did not handle the dryer felts himself, so the next critical component is his distance from the source. Exposures drop to inconsequential levels quickly the farther from the source the worker is. Neither Dr. Abraham nor the court required any evidence of Mr. Knight's actual distance or its effect on exposures.

- *Duration and frequency of exposure:* Dr. Abraham and the court failed to assess the duration and frequency of Mr. Knight's supposed exposures. A few limited exposures to carcinogens are unlikely to produce disease. Mr. Knight's testimony indicates that his contact with asbestos, if any, was of short duration and only occurred on a few instances.

- *Fiber potency differences:* Dr. Abraham and the court also failed to consider the actual potency of the fiber types involved. Dryer felt is made from chrysotile, a very weak carcinogen that only causes mesothelioma, if at all, in cohorts with enormous exposure.[27] Mr. Knight

[27] Chrysotile is at best only a very weak carcinogen, and one that has not produced mesothelioma at all except in the very highest exposed worker groups. *See, e.g.*, *In re Garlock Sealing Tech., LLC*, 504 B.R. 71,76, 78 (Bank. W.D.N.C. 2014) ("[I]t is clear under any scenario that chrysotile is far less toxic than other forms of asbestos," and the "most reliable and probative" peer-reviewed scientific reports "confirm[] that exposure to asbestos from end users of encapsulated asbestos products is minimal."); *Bartel v. John Crane, Inc*., 316 F. Supp. 2d at 605 ("[I]t is generally accepted that it takes a far greater exposure to chrysotile fibers than to amphibole fibers to cause mesothelioma."); *In re Asbestos Litig*., 911 A.2d 1176, 1181 (Del. Super. Ct. 2006) ("[I]t is generally accepted in the scientific community and among government regulators that amphibole fibers are more carcinogenic than serpentine (chrysotile) fibers."). *See also* Christine Rake *et al.*, *Occupational, Domestic and Environmental Mesothelioma Risks in the British Population: A Case Control Study*, 100 BRIT. J. CANCER 1175 (2009) ("The mesothelioma risk caused by amosite (brown asbestos) is two orders of magnitude greater than that by chrysotile (white asbestos).").

> could not possibly have achieved such exposures at Scapa, yet neither Dr. Abraham nor the court credited the potency differential in any way.

There is nothing scientific about this approach. It ignores every standard precept of industrial hygiene. The outcome is pure speculation – that Mr. Knight *may* have breathed *some* asbestos fibers at *an unknown level* only a few times. This is not dose assessment. And the guesswork that results is why many courts are rejecting this approach and requiring a real assessment of the dose.

Plaintiff and the *Scapa* panel decided that no dose assessment was necessary for several reasons, all of which are difficult to understand. For example, Plaintiffs assert that no dose assessment is possible because no one measured Mr. Knight's actual exposures at the time. A professional industrial hygienist would scoff at this claim, because these professionals routinely reconstruct historical doses by working from studies of similar occupations and work experiences.[28] To give only one example, a recent article, relying on a set of historical exposure studies of asbestos workers, developed a very detailed assessment of the amount of exposure

[28] This rationale is also very convenient – it is unlikely in the extreme that a specific plaintiff in litigation today will have his or her own exposures tested in the 1950s, 1960s, or 1970s. Many of the scenarios in today's litigation involve exposures well below the OSHA standards of the time that would never have even necessitated any testing. Thus, plaintiffs' experts can justify their speculation in every single case. If this rationale is accepted, then the more reasonable conclusion is that plaintiffs' experts have no exposure assessment on which to base their opinions.

likely to have occurred based on distance from the source.[29] Dr. Abraham ignored this and similar studies. Based on published literature and Scapa's own air monitoring, it is likely that Mr. Knight's actual dose would fall below background levels given that Scapa could not detect measurable asbestos only feet away from the dryer felts.

Likewise, Plaintiffs argued in their brief below that Georgia does not require an exact quantification of the dose. Perhaps, but that is a long way from abandoning any attempt at all to assess the range of possible exposures. Mr. Knight's approximate range of exposures can potentially be characterized in fiber/cc year levels given sufficient testimony on his activities, location, and duration of work. And if there is no such testimony, then plaintiff cannot recall sufficient direct contact with asbestos to prove a case, and the case should not proceed. Even the case Plaintiffs cite – *Fulmore* – stands only for the proposition that plaintiffs do not need to provide a "specific measurement" of the worker's actual exposures – *i.e.*, an actual air monitoring record of the plaintiff himself. But *Fulmore* and other Georgia cases mandate that experts at least assess and estimate the dose in a competent way and prove that it was enough to be causative.[30]

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[29] Ellen Donovan, *et al*., *Evaluation of Bystander Exposures to Asbestos in Occupational Settings: A Review of the Literature and Application of a Simple Eddy Diffusion Model,* 1 CRITICAL REV. TOXICOLOGY 1 (2010).

[30] *Parker v. Brush Wellman, Inc.,* 2010 WL 37300924 at *4; *Butler,* 310 Ga. App. at 39-40 (concurring opinion).

B. The *Scapa* Panel Erred in the Grounds It Asserted for Accepting *Any Exposure* Testimony.

Given the widespread rejection of testimony like Dr. Abraham's in other courts, reversal is justified here because the *Scapa* court allowed such testimony to supplant the need for an assessment of Mr. Knight's actual exposures. A review of the court's grounds for doing so only bolsters the need for reversal.

The *Scapa* majority relied first and foremost on a distinction between *Butler's* "trivial" exposures and Mr. Knight's alleged "substantial" exposures. But the appellate court's fundamental distinction is in error, because *any exposure* testimony left the court without any assessment of Mr. Knight's actual exposures sufficient to make that critical distinction. No one can say that an exposure is "substantial" without assessing the dose to begin with and comparing it to published health standards for asbestos or to health studies of populations that actually got asbestos disease. "Substantial" is totally meaningless otherwise. This is exactly how New York's highest court handled the *Parker* benzene case, when the experts simply used qualitative words like "excessive" instead of determining plaintiff's dose. *Parker v. Mobil Oil*, 7 N.Y.3d 434, 449-50 (N.Y. 2006).

To add to this error, the distinction the *Scapa* court tried to draw between the exposure scenarios of *Butler* and *Scapa* is nearly nonexistent. In fact, just the opposite assessment – that Mr. Knight's exposures were in fact *less substantial* than in *Butler* – is easy to construct. Mr. Butler *directly handled* the asbestos

containing material (molding compound pellets containing up to 30 percent asbestos) (310 Ga. App. at 21), whereas Mr. Knight apparently was only in some undefined "proximity" to known asbestos-containing material. Mr. Butler handled *135,000 pounds of asbestos containing materials* (*id.* at 22); Mr. Knight apparently directly handled very little, if any, asbestos- containing material. Mr. Butler worked with the asbestos-containing pellets daily for over seven years (*id.*); Mr. Knight was only in the presence of asbestos materials a handful of times at Scapa. An expert in *Butler* testified that his exposures would have exceeded the two fibers/cc OSHA standard of the time (*id.* at 22-23) – there was no such assessment in *Scapa*. The material Mr. Butler used without question contained asbestos (*id.* at 22); but Mr. Knight could only speculate that the dust on the HVAC equipment and insulation he worked with contained asbestos, because he did not know and no expert ever confirmed this.

The point of this comparison is to show the fallacy in using words like "substantial" unaccompanied by any dose assessment. The *Scapa* court's approach would permit wildly different asbestos judgments on similar sets of facts and leave defendants at the mercy of whether a judge, in his or her own layperson's perspective, thought the exposures were substantial or not. The actual *Butler-Scapa* comparison if anything only undercuts the justification of the *Scapa* court–

the exposures in both *Butler* and *Scapa* were equally inconsequential. *Any exposure* testimony was no more justified in one than the other.

C. The Court Should Not Have Substituted Its Own Judgment for the Missing Expert Testimony Needed to Support Causation.

With no guidance from Dr. Abraham on how to determine which of Mr. Knight's exposures in his career were sufficient for causation, the *Scapa* court should have dismissed the case against Scapa because of the lack of competent expert causation testimony.[31] The court instead committed a second fundamental error. The panel determined for itself that the exposures at the Scapa facility were "substantial" and therefore sufficient to allow *any exposure* testimony.

The error in this approach is that the court has taken on the complex and difficult role of determining how much exposure is enough to be considered "substantial" and causative. The trial judge, however, should be the gatekeeper of expert testimony, not sit in the expert's seat and render a causation determination. Decisions on the degree and type of exposure necessary to cause mesothelioma are the subject of hundreds of scientific articles and intense medical debate in the literature. Professionals in several fields – epidemiology, toxicology, occupational

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[31] *Butler,* 310 Ga. App. at 30 ("Causation is an essential element of a toxic tort case …. Absent reliable expert testimony that exposure to a … product contributed to the development of Mr. Butler's mesothelioma, there is insufficient evidence to create a jury issue as to causation."); *Parker v. Brush-Wellman,* 2010 WL 3730924 at *8 (excluding expert; "this is not a case which could be informed by the juror's human experience alone to prove causation").

medicine, oncology, industrial hygiene, and others – regularly apply their expertise and extensive knowledge to assess, for instance, whether a long-term exposure to chrysotile could ever be considered a cause of mesothelioma.[32] For the court here to simply declare Mr. Knight's exposures "substantial" is quite a leap, given the degree of scientific knowledge necessary to make such a determination.[33] The court's leap is even more dramatic given the complete lack of any industrial hygiene analysis by either Dr. Abraham or the *Scapa* panel – the level of exposure at the source, the distance from the source, the quantity of exposure over time, the infrequency of the exposure, any comparison with health standards or lifetime exposures authorized by health authorities.

Consider what trial judges must now do in Georgia if the *Scapa* decision holds. Trial judges will have to decide with no help from *any exposure* experts whether ten brake jobs is enough to be "substantial" and thus suffice for *any exposure* testimony. And what if the next case involves only five? Would six

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[32] *See, e.g.,* Hodgson, J. & Darnton, A., *The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure*, 46 ANN. OCCUP. HYG. 565 (2000) (extensive analysis of level and types of fibers causing asbestos disease); Peto and Rake articles, *supra* n. 11.

[33] The Maryland Court of Appeals in *Dixon* (cited by Plaintiffs) fell into this trap – the court decided one year of brake work was enough, under that state's "frequency, regulatory, and proximity test" for asbestos causation, with no reference to any science or foundation for such line-drawing. *Dixon v. Ford Motor Co.*, 70 A.3d 328, 335-38 (Md. 2013). *Dixon* is inapposite here because Georgia does not use the frequency, regularity and proximity test, and thus Plaintiff has cited to it erroneously. In any event, the court should not have succumbed to the temptation to place itself in the expert's role.

months of work in a facility, with only one or two identified contacts with asbestos suffice? Or should the court require daily contact in such a circumstance?

The answers to these and an infinite number of similar questions lie in the science of dose, exposure, and epidemiology. A trial court, given an expert attempt to make such decisions, can perform the required gatekeeping function and decide whether the expert's analysis of the data is based on a reliable methodology. But where the expert, like Dr. Abraham, simply refuses to perform this analysis at all, there is nothing for the court to work with. The court should not have tried to fill in the gap created by this testimony, and instead should have dismissed the case for lack of adequate expert causation testimony.

CONCLUSION

Georgia should follow the lead of so many other *Daubert* jurisdictions and require experts to perform their required role – assess the dose, demonstrate why it is causative, and forego merely claiming all of plaintiff's cumulative exposures are causative. *Any exposure* testimony is unscientific and cannot help the jury make the hard decisions in these cases. The *Butler* court got it right, the *Scapa* court did not, and *Amici* request that the Court accept Scapa's petition to avoid the *Scapa* impact of extending asbestos cases into ever more trivial and speculative exposure scenarios without scientific foundation.

Respectfully Submitted,

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CERTIFICATE OF SERVICE

This is to certify that I served all counsel of record with a copy of this BRIEF OF *AMICI CURIAE* COALITION FOR LITIGATION JUSTICE, INC., CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA, NATIONAL ASSOCIATION OF MANUFACTURERS, AMERICAN TORT REFORM ASSOCIATION, AND NFIB SMALL BUSINESS LEGAL CENTER by e-mail, addressed as follows:

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SCIENTIFIC JUDGMENT AND TOXIC TORTS—A PRIMER IN TOXICOLOGY FOR JUDGES AND LAWYERS

*David L. Eaton, Ph.D., DABT, FATS**

I. GENES, ENVIRONMENT AND DISEASE

Remarkable progress has been made in the past decade in understanding the molecular basis of many chronic diseases such as cancer, degenerative neurological diseases (Alzheimer's, Parkinson's), heart disease, and asthma. Although the molecular basis for such diseases has become more apparent, the exact "cause" is seldom identified for a disease in general, and especially for a disease in an individual. It is now recognized, however, that most such chronic diseases result from a complex interplay between our genes and our environment. While our parents predetermine our genes, our environment is somewhat controllable, and thus identifying "environmental risk factors" for chronic diseases holds great promise for disease prevention. It should be noted that "environment" in this context represents virtually everything in the world around us that is not "in our genes." Thus environmental factors include lifestyle choices such as smoking, drug use and alcohol consumption, exposure to infectious agents (viruses, bacteria), as well as diet and nutrition, environmental pollution (air, water), and even behavioral and social factors such as exercise, reproductive choices, sexual activity, etc.

There is currently great scientific effort committed to

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identifying specific genetic characteristics (so-called "genetic polymorphisms") that make one individual more susceptible to something in the environment than another.[1] This area of research is sometimes referred to as "ecogenetics," or the study of "gene-environment interactions."[2] There are many classic examples of genetic characteristics that make an individual sensitive to something in his environment. For example, the rare genetic disease, phenylketonuria (PKU), makes individuals with this genetic trait very sensitive to a normal component of our diet—phenylalanine. Phenylalanine is a normal building block of proteins, and in most people is an important nutrient in the diet. For a small part of the population with a mutation in the PKU gene, however, regular "doses" of phenylalanine found in the normal diet can lead to serious mental retardation if infants are exposed to phenylalanine. Because of this, genetic testing for PKU is mandatory in most states in the United States and is part of normal newborn screening. Those rare individuals who test positive for PKU can lead normal lives by following special diets and avoiding foods rich in phenylalanine.

Another common example of a "gene-environment" interaction occurs in many people of Asian descent who carry a genetic variant of a gene involved in alcohol metabolism. Normally, alcohol is fairly rapidly detoxified in the liver. But individuals with a variant form of the gene for an enzyme called "aldehyde dehydrogenase" (ALDH2) are less able to eliminate a toxic by-product of alcohol metabolism, acetaldehyde. If a person with the variant ALDH2 gene consumes even modest amounts of alcohol, toxic amounts of acetaldehyde can accumulate in the blood, causing a very uncomfortable reaction ("flushing" of the skin from vasodilatation, nausea, headache). Not surprisingly, alcoholism and alcohol-related diseases such as cirrhosis of the liver occur very

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[1] *See* Samir N. Kelada, David L. Eaton, Sophia S. Wang, Nathaniel R. Rothman & Mhuin J. Khoury, *The Role of Genetic Polymorphisms in Environmental Health*, 111 ENVTL. HEALTH PERSP. 1055-64 (2003).

[2] Gilbert S. Omenn, *Public Health Genetics: An Emerging Interdisciplinary Field for the Post-Genomic Era,* 21 ANN. REV. OF PUB. HEALTH 1, 1-13 (2000); Daniel W. Nebert & Michael J. Carvan, III, *Ecogenetics: From Ecology to Health*, 13 TOXICOLOGY AND INDUSTRIAL HEALTH 163, 163-92 (1997).

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infrequently in people with this genetic trait.

There is currently a great deal of interest in identifying common genetic traits that might combine with factors in our environment to cause disease. It is hoped that, one day, physicians will be able to characterize, or "genotype," the entire genetic code of a person, and based on the results (kept on a personal microchip medical card), identify whether the patient is at increased risk for certain diseases and potentially identify specific dietary, workplace, or other environmental factors that should be avoided to lower risk. While we are still a decade or more away from having scientifically validated tests for "environmental susceptibility" to most environmental/occupational hazards, similar approaches for identifying how individuals respond to *therapeutic drugs* is just around the corner (the field of "Pharmacogenomics"). Indeed, there are now several relatively widespread genetic tests that can identify in advance patients who are likely to have adverse reactions to otherwise "normal" therapeutic doses of specific drugs.[3] The concept of "designer drugs" is becoming a reality, but so far in a limited way. For example, there is a common genetic variant in a gene called "N-acetyl transferase." This gene is involved in the detoxification of a variety of therapeutic drugs, and people with the "slow" genetic variant exhibit increased toxicity (but also enhanced therapeutic effects at lower doses) to a variety of common drugs. Knowing this predisposition in advance allows physicians to prescribe the proper dose.

How will such genetic information be used in the courtroom? In the realm of genetic testing for drug sensitivity, there will be medical malpractice claims filed against physicians who fail to order genetic tests before prescribing certain drugs, once such procedures become the standard of care.[4] Drug companies will

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[3] Rafael Valdes Jr., Mark W. Linder & Saeed A. Jortani, *What Is Next in Pharmacogenomics? Translating It to Clinical Practice*, 4 PHARMACOGENOMICS 499, 499-505 (2003).

[4] Jan van Aken, Mechteld Schmedders, Gunter Feuerstein & Regine Kollek, *Prospects and Limits of Pharmacogenetics: The Thiopurine Methyl Transferase (TPMT) Experience*, 3 AM. J. OF PHARMACOGENOMICS 149, 149-55 (2003); Mark A. Rothstein & Sharona Hoffman, *Genetic Testing, Genetic Medicine, and Managed Care*, 34 WAKE FOREST L. REV. 849 (1999).

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attempt to increase drug safety and limit liability by identifying in advance drugs that may elicit adverse responses in small segments of the population because of genetic sensitivity. In the environmental and occupational arena, employers might use genetic tests as a way of identifying and removing "sensitive" individuals from certain workplace exposures.[5] While such practice might conceivably lower the occurrence of chemical-induced occupational diseases, it is obviously also a means of employment discrimination. It is also likely that plaintiff and defense attorneys will utilize genetic susceptibility as an argument for, or against, causation in toxic tort cases. Currently, however, the scientific data supporting the use of genetic susceptibility information in toxic tort litigation is extremely limited.[6] In the vast majority of circumstances, specific and measurable genetic "susceptibility markers" often do little more than shift a person "up" or "down" the dose-response curve. Such differences tend to be modest (less than a two-fold difference in susceptibility), and the impact of the genetic trait is often lost in the "noisy background" of poor exposure assessment.[7] That is, if one can only "guess" the dose, duration, and frequency of exposure to a specific chemical within a factor of 5 or 10 (not uncommon in toxic tort cases), a genetic factor that theoretically doubles or halves the risk from a given dose will not be particularly informative against the high level of uncertainty of the actual "exposure." Thus, although genetic information will increasingly find its way into toxic tort

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[5] Robert J. McCunney, *Genetic Testing: Ethical Implications in the Workplace*, 17 OCCUPATIONAL MED. 665, 665-72 (2002); Steve M. Bartell, Raphael A. Ponce, Tim K. Takaro, Richard O. Zerbe, Gilbert S. Omenn & Elaine M. Faustman, *Risk Estimation and Value-of Information Analysis for Three Proposed Genetic Screening Programs for Chronic Beryllium Disease Prevention*, 20 RISK ANALYSIS 87, 87-99 (2000).

[6] Gary E. Marchant, *Toxicogenomics and Toxic Torts*, 20 TRENDS IN BIOTECHNOLOGY 329, 329-32 (2002).

[7] Werner K. Lutz, *Differences in Individual Susceptibility to Toxic Effects of Chemicals Determine the Dose-Response Relationship and Consequences of Setting Exposure Standards*, 126 TOXICOLOGY LETTER 155, 155-58 (2002); Marilyn J. Aardema & James T. MacGregor, *Toxicology and Genetic Toxicology in the New Era of "Toxicogenomics": Impact of "-Omics" Technologis*, 499 MUTATATION RES. 13, 13-25 (2002).

litigation, the fundamental concepts of toxicology and epidemiology continue to serve as the foundation for establishing causation in toxic tort claims.[8] The following information is provided as a "primer" in basic toxicology, as it relates to toxic tort litigation. For a more detailed discussion of considerations of how the science of toxicology and epidemiology should be used in the courtroom, the reader is referred to the Federal Judicial Center's *Reference Manual on Scientific Evidence*.[9] This publication includes chapters devoted to toxicology and epidemiology, as well as medical testimony and use of DNA in the courtroom.

II. BASIC TOXICOLOGY RELEVANT TO TOXIC TORT LITIGATION

Toxic substances may take many forms, including both human-made (synthetic) and natural chemicals. Although the adverse effects of physical agents such as ionizing radiation fall under the broad rubric of toxicology, this discussion will focus on chemical agents. There are many "sub-disciplines" within the field of toxicology, and a variety of approaches and techniques are used to evaluate the toxicological characteristics of chemicals. A detailed review of the basic principles of toxicology is beyond the scope of this article.[10] The following brief review highlights some of the key principles of toxicology that must be considered in any attempt to establish whether a chemical exposure was causally related to a specific adverse effect or disease in an individual.

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[8] Mark Parascandola & Douglas L. Weed, *Causation in Epidemiology*, 55 J. EPIDEMIOLOGY COMMUNITY HEALTH 905, 905-12 (2001); *see* Marchant, *supra* note 6.

[9] FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (2d ed. 2000).

[10] A number of fundamental textbooks are available that review the principles of toxicology in depth. *See* J. MARK ELWOOD, CAUSAL RELATIONSHIPS IN MEDICINE (1988); ALFRED S. EVANS, CAUSATION AND DISEASE (1993); KENNETH J. ROTHMAN, CAUSAL INFERENCE (1988); MERVYN W. SUSSER, CAUSAL THINKING IN THE HEALTH SCIENCES (1973).

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A. Types of Adverse Effects Produced by Chemicals

Virtually all substances are capable of inducing some form of toxic effect, and the type and nature of effects will vary depending on the

- dose (amount of substance that finds its way into the body)
- route (i.e., oral, inhalation, skin; injection)
- duration (days, weeks, months, years) and
- frequency (how many times per day, week, month, year)

of exposure.

A given chemical does not cause every possible effect, and the ability of a chemical to cause a particular effect depends upon a variety of factors, as discussed below. Typically, a specific chemical elicits a characteristic pattern of toxic (adverse) effects, although the appearance of specific effects will depend on the dose and other characteristics of exposure. Sometimes chemicals of a common type cause a generalized adverse response. For example, nearly all organic solvents derived from petroleum products (including mixtures such as gasoline or kerosene, or individual solvents such as benzene, hexane, or toluene) share some (but not all) symptoms in common: "defatting" of the skin following dermal exposure, and central nervous system depression (inebriation, loss of consciousness) following relatively high levels of inhalation exposure. However, even though different chemicals of the same general type (e.g., solvents) may have some common effects, they may also differ dramatically in other effects. For example, the industrial solvents benzene and toluene are very similar chemically, and share many common toxic effects noted above for solvents, but benzene is toxic to the bone marrow and can increase the risk of leukemia in workers, whereas these serious toxic effects have not been found for toluene. Thus, some chemicals act in very specific ways at the cellular level, and their effects may be largely limited to a characteristic type of response. As an example, the widely-used class of insecticides known as "organophosphates" inhibit a specific enzyme in the nervous system (acetylcholinesterase), and most of the signs and symptoms of toxicity can be attributed to this one mode of action. However, even small differences in chemical structure can sometimes make

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very large differences in the type of toxic response that is produced. This is especially true for chemicals that cause birth defects (teratogens) or chemicals that increase the risk of cancer (carcinogens).

B. Concepts of Dose and Exposure

"Dose" refers to the amount of chemical that enters the body. The units of dose are typically expressed as an amount of substance per kg of body weight (mg/kg bw). Thus, if a 132 lb woman (60 kg) absorbed 60 milligrams of a chemical in a glass of contaminated water, she would have a dose of 1 mg/kg bw. Dose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect. Indeed, the basic dictum of toxicology was stated by the Sixteenth Century Physician/Philosopher, Paracelsus, considered the "father of toxicology": "*All substances are poisonous—there is none which is not; the dose differentiates a poison from a remedy.*"[11]

1. Relationship between "Exposure Concentration" and "Dose"

Dose and "exposure" in terms of media (e.g., air, water, soil) concentration are related, but not identical, terms. Exposure may be referred to as the presence of a chemical in a medium (e.g., air, water, food) that allows for direct contact with potential sites of absorption (e.g., gastrointestinal tract, lungs, skin). The units of such exposure are usually expressed as concentrations—e.g., milligrams of chemical per liter of water (mg/L), milligrams of chemical per cubic meter of air (mg/m^3), milligrams of chemical per kilogram of food (mg/kg). Frequently, such concentrations are expressed as "parts per million" (ppm) or "parts per billion" (ppb). For chemicals dissolved in water, 1 part per million is the same as 1 milligram of chemical dissolved in 1 liter of water. One part per billion (1 ppb) is a thousand times less—1 milligram dissolved in a thousand liters of water, or 1 microgram of chemical dissolved in 1

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[11] CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS Chs. 1, 4 (Curtis D. Klaassen ed., McGraw Hill 6th ed. 2001) (emphasis added).

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liter of water. A part per trillion (ppt), is 1,000 times less than a part per billion. To provide some perspective on these units, consider the following:

- 1 ppm=1 penny in $10,000, or 1 inch in the distance of 15.8 miles
- 1 ppb=1 penny in $10 million, or 1 inch in 15,800 miles
- 1 ppt=1 nickel of Bill Gates net worth (assuming $50 billion), or 6 inches in the distance between the earth and the sun.

Analytical tools developed in the past several decades make it possible to measure substances in water, food, soil or air at the ppt and even parts per quadrillion (ppqd; 1,000 times less than a ppt). It is evident from these simple analogies that, when discussing exposure to chemicals in drinking water, air, or soil, it is critically important that the relationship between exposure, as expressed as a concentration of a pollutant in a medium (measured in ppm, ppb, ppt or even ppqd) and the *actual dose to a person* not be lost. The science of toxicology can help understand whether the dose of a substance achieved following a particular exposure has any relationship to toxicity or disease.

2. Frequency and Duration of Exposure

Frequency and duration of exposure are important elements of "dose." Effects caused by chemicals may differ depending on whether exposure was short-term (e.g., acute, single dose or a few days) or long-term (chronic, repeated over years). The dose of a chemical required to produce health effects also differs with frequency and duration of exposure. When exposure occurs repeatedly over weeks, months, or years, the dose is usually expressed as a dose rate, with units of mg of chemical per kg of body weight per day. The dose necessary to produce deleterious effects with short-term exposure is higher than the dose that produces toxic effects when repeated over a long time period. The body can usually tolerate or recover from high doses with brief short-term exposure as compared to long-term repeated exposure. For example, one night of moderate drinking may give you no more than a headache the next day, but heavy drinking frequently

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for years could lead to liver cirrhosis and possibly liver cancer. However, it is also possible that repeated, low dose exposures—even for many years—will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage. This concept of "thresholds" will be discussed in more detail later.

Most chemicals that have been identified to have "cancer-causing" potential (carcinogens) do so only following long-term, repeated exposure for many years. Single exposures or even repeated exposures for relatively short periods of time (e.g., weeks or months) generally have little effect on the risk of cancer, unless the exposure was remarkably high and associated with other toxic effects. Relatively infrequent exposure may also have negligible health consequences even if continued over time because of recovery between doses.

3. Pathways and Routes of Exposure

"Pathways" are the means by which an environmental chemical may reach an "exposed" person. Chemicals can enter the body by four fundamental "routes": (1) via oral exposure (e.g., ingestion of the toxic substance directly, or in food or drinking water), (2) via inhalation (e.g., breathing air or inhaling dust contaminated with the toxic substance), (3) via direct contact with the skin (e.g., spilling of a pesticide mixture on the skin), or (4) by direct injection into the body (e.g., introduction of a drug by intravenous injection). The "bioavailability"—or ability of the chemical to be taken into the blood stream—differs by route of entry. Most drugs and toxic chemicals will be well absorbed from the gut when ingested in a soluble form versus in other media such as soil. Many chemicals, however, are only slightly absorbed, if at all, if applied to the skin. However, fat-soluble chemicals in high concentration may be well absorbed across the skin, and this can lead to an important pathway of exposure for those using concentrated solutions in the workplace. The extent of inhalation absorption of chemical vapor will depend on a variety of factors, including the relative solubility of the chemical in blood versus air, the rate of breathing, and even whether one breathes through the nose or

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mouth.

4. Site of Action in the Body

Ultimately, what matters is the actual concentration of a toxic substance at the "site of action" in the body. The concentration of a chemical in any given organ/tissue in the body is determined by complex interactions between the rates of exposure, and rates of absorption, distribution, metabolism, and excretion. Because chemicals differ in their solubility in body fluids/tissues, in how they are metabolized, and in what cellular processes are altered, toxic effects of a chemical may be limited to specific tissues or organs, referred to as its "target tissue." For example, lead and mercury typically produce toxic effects associated with the brain and kidneys, whereas certain chlorinated solvents such as chloroform and carbon tetrachloride affect predominantly the liver (although in high doses they also affect the brain).

Many factors determine whether a chemical will be toxic to a particular organ. Some organs metabolize (biotransform) chemicals to toxic intermediates, leading to toxicity in that organ. In such instances, the relative ability of an organ or tissue to metabolize the chemical may determine whether the toxic effect is seen in that tissue. Certain tissues may also accumulate a chemical from the bloodstream at higher rates than other tissues, leading to toxicity in just that tissue. This is particularly true for tissue with a function (e.g., liver), but not necessarily for storage tissue, i.e., fat, which accumulates fat-soluble chemicals such as DDT, but is not directly injured. Metabolic pathways and the amount and type of toxic by-products produced or accumulated may also differ depending on the amount of chemical in the blood stream (which, of course, is directly related to dose). For example, metabolic pathways at low doses that result in chemical detoxification may be overwhelmed at high doses leading to accumulation of toxic intermediates or production of greater amounts of toxic by-products by alternative pathways.

5. Dose-response Relationship

As noted above, the relationship between dose and effect (dose-response relationship) is the hallmark of basic toxicology. The "dose-response" in a given individual describes the relationship between the magnitude or severity of the effect(s) and the dose. In many instances, especially for acute toxicity, the slope of the dose-response curve is quite steep. That is, once a sufficient dose has been achieved to induce a toxic response, further increases in the dose may produce large increases in the response. In the individual, the nature of the response may change with increasing dose. For example, ingestion of one or two glasses of wine will result in an apparent "stimulatory" effect on the nervous system, often expressed as slight changes in personality or character. Further consumption of alcohol will lead to loss of coordination and reaction time, slurred speech, etc. Continued consumption of alcohol beyond this level of intoxication may result in loss of consciousness and even death.

Although individuals within a population may respond differently to the same dose of chemical, the reaction of the population as a whole nevertheless follows a "dose-response relationship" such that the number of people in a population that respond to a chemical exposure increases with dose. Inherent in this concept is that, for the vast majority of chemicals and types of responses, there are doses below which no individual will respond (e.g., a "threshold") and doses above which nearly everyone responds. For example, no one would exhibit any detectable adverse effect of a few drops of wine or beer (e.g., the dose is below the threshold), yet most everyone in a population would show signs of intoxication after ingestion of an entire bottle of wine (over a relatively short period of time). In between these two extremes, there are clearly differences in the level of intoxication between individuals consuming one, two, three, or four glasses of wine. In a similar fashion, there is inherent human variability in response to chronic exposures to chemicals. Dose-response relationships in populations also exist for both acute and chronic exposures to toxic substances.

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6. *Concept of "Thresholds"*

For most types of dose-response relationships following chronic (repeated) exposure, thresholds exist, such that there is some dose below which even repeated, long term exposure would not cause an effect in any individual. Most toxicological responses, including neurological, reproductive, and developmental effects, exhibit thresholds (e.g., there is a dose below which the probability of an individual responding is essentially zero). One key objective in toxicology is to identify doses for a population below which no one will respond. However, in the case of chemical carcinogens, particularly those that increase risk of cancer by causing direct damage to DNA in cells, many regulatory agencies assume that there are no "thresholds," and that risk is proportionate to dose at all levels of exposure—e.g., as the dose of carcinogen increases, the probability of developing cancer increases in a proportionate, "linear" fashion.

Nonetheless, many scientific and practical reasons indicate that, at very low doses, the significance of such risks, if real, become trivial and are lost in the background of other daily risks. For example, it is well known that cigarette smoking is strongly associated with increased risk for lung and bladder cancer (and other types), and that the probability of developing such smoking-related cancers is related to both the amount (cigarettes per day) and the frequency (years of smoking) of smoking over a life-time.[12] It is also recognized that the carcinogenic properties of cigarette smoke are strongly related to the ability of components of cigarette smoke to damage DNA (cause mutations), and thus it might be assumed that the dose-response relationship for smoking would be a "non-threshold" (linear at low doses) response.[13] However, while a linear, non-threshold response to cigarette smoke may be hypothesized on theoretical grounds, from a practical

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[12] *See* OFFICE OF THE SURGEON GENERAL, U.S. PUB. HEALTH SERV., DHHS PUB. NO. (CDC) 90-8416, THE HEALTH BENEFITS OF SMOKING CESSATION: A REPORT OF THE SURGEON GENERAL (1990).

[13] Ralph Zito, *Low Doses and Thresholds in Genotoxicity: from Theories to Experiments*, 20 J. EXPERIMENTAL CLINICAL CANCER RES. 315, 315-25 (2001).

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perspective one's level of increased risk from smoking one cigarette over a lifetime, or even one cigarette a month for a lifetime, is not likely to be distinguishable from "background" risk for cancer from all other causes, known and unknown.

Not all chemical carcinogens increase cancer risk by causing mutation. For such "non-genotoxic" carcinogens, it is generally thought that the dose-response relationship follows a typical threshold-type response. Thus, it is often important to distinguish between "genotoxic" (particularly those that act directly on DNA to cause mutations) and "non-genotoxic" carcinogens for regulatory and risk assessment purposes. Practical thresholds may also exist for "genotoxic" carcinogens that damage DNA by indirect mechanisms (e.g., production of sufficient "reactive oxygen species" to cause oxidative damage, or sufficient inhibition of DNA repair mechanisms), because a sufficient amount of the chemical is needed before enough damage to the DNA occurs to lead to cancerous cells.

C. Chemical Exposures and Chronic Diseases

Traditional toxicology tests in laboratory animals are designed to identify toxic responses following various periods of exposure.[14] Acute toxicity studies examine the toxic effects after single, high doses and are useful to understand the specific organ systems affected by the chemical, as well as the general "potency" of its effect (e.g., does it require microgram, milligram, or gram quantities to produce evidence of toxicity?). Additional "sub-chronic" (usually ninety days of daily exposure) and "chronic" (usually lifetime, or two years of continuous daily exposure) studies are often done to further examine whether the chemical is capable of causing other types of toxic effects following repeated exposures. Such studies may demonstrate that repeated exposure to a chemical could cause liver or kidney or brain damage, for example. Special "3-generation" studies may be done in animals to determine if the chemical can cause reproductive effects and/or

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[14] CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, *supra* note 11, at chs. 2, 11-34.

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birth defects. Today, new chemicals entering commerce, such as a new pesticide, may be subjected to specialized tests to determine if it can cause neurological effects on learning and behavior, or cause toxicity to the immune system. Each of these toxicological end-points can be the subject of toxic tort litigation. However, regardless of the end-point, the basic concept of "dose-response" remains essential in evaluating a causal connection between an alleged exposure and a particular disease. As noted above, for non-cancer end points, it is generally accepted that "thresholds" exist, and that doses below the threshold represent no risk. However, determining the "true" threshold for humans is difficult, if not impossible, and requires consideration of human variability. Thus, regulatory agencies often determine "safe" levels of exposure for non-cancer endpoints by dividing the highest dose that does not cause any evidence of toxicity upon repeated exposure to a group of laboratory animals (the so-called "No Observable Adverse Effect Level," or NOAEL) by some "uncertainty" factor.[15] Usually the factor is 100 or 1000, although the choice of what uncertainty factor to use is dictated by the nature of the toxic response, the quality and quantity of the experimental animal data, and the level of understanding of the mechanism of action of the toxic substance.

Determining the causal relationship between a chemical exposure and a particular chronic disease requires careful consideration of a variety of factors, some of which may be unique to the particular end point in question. For example, establishing an association between a particular drug or chemical and a birth defect requires careful consideration of the exact timing of exposure during pregnancy. Thalidomide, responsible for development of thousands of limb malformation in Europe many decades ago, requires that exposure occur during a very specific period—as short as a few days—early in pregnancy.[16] Exposure to the drug after the critical period during embryonic development

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[15] *Id.* at ch. 4.

[16] Joseph M. Lary, Katherine L. Daniel, J. David Erickson, Helen E. Roberts & Cynthia A. Moore, *The Return of Thalidomide: Can Birth Defects be Prevented?*, 21 DRUG SAFETY 161, 161-69 (1999).

when the limb buds are forming will not produce that particular birth defect, regardless of dose. Likewise, because the drug is relatively rapidly eliminated from the body, exposure very early in pregnancy—but that was stopped several days prior to the period of limb bud development—also would not produce the birth defect.

Although there is great interest in understanding how environmental factors might contribute to chronic neurological diseases such as Alzheimer's and Parkinson's disease, there are relatively few examples where environmental exposures have been shown to contribute to these diseases. Perhaps the most notable example is that of a batch of synthetic heroin that was contaminated with a substance known as MPTP, and subsequently sold on the streets of San Francisco. Numerous young men (under the age of 30) presented with "rapid onset" symptoms essentially identical to Parkinson's disease. On detailed investigation, it was learned that they had all used a synthetic heroin substance shown later to have contained MPTP.[17] This substance is selectively toxic to certain nerve cells in the brain. These same cells, called "dopaminergic neurons," are lost progressively with age in all people, resulting in Parkinson's disease in some (those with a somewhat accelerated loss of cells). Thus, the street drug was able to do in weeks what normally takes a lifetime of "normal" aging. There is now great interest to find other environmental factors that might contribute to the enhanced rate of loss of dopaminergic neurons that seems to be the hallmark of Parkinson's disease. One environmental chemical, an herbicide called "paraquat," has a strong structural similarity to the active metabolite of MPTP, and thus there has been substantial toxicological and epidemiological inquiry into whether environmental or occupational exposure to paraquat might contribute to Parkinson's disease. At this point in time, there is limited toxicological and epidemiological data suggestive of a link between paraquat exposure and Parkinson's disease, but there remains great controversy and uncertainty over whether paraquat or other pesticides represents a substantial risk factor for Parkinson's disease.

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[17] J. William Langston, *The Etiology of Parkinson's Disease With Emphasis on the MPTP Story,* 47 NEUROLOGY (6 Suppl 3) 153, 153-60 (1996).

There is also substantial interest in how chemicals might modify the immune system. There are three ways by which chemical interactions with the immune system could be important. In the first, the chemical may cause direct toxicity to cells of the immune system, thereby interfering with normal immune functions. Numerous chemicals, including "dioxin," have the ability to interfere with normal immune function, and at sufficient doses, may disrupt immune function.[18] This could lead to enhanced susceptibility to infection, or perhaps even increased risk of cancer, since the immune system plays an important role in destroying pre-cancerous and cancerous cells. Establishing whether a particular chemical has induced immune dysfunction in an individual, however, would require application of the same basic principles of toxicology and epidemiology as for any other type of toxic effect, including "dose-response" and the concept of thresholds.

The second way in which a chemical might interact with the immune system is through the development of an "allergic" reaction to the chemical itself. This is illustrated by the common allergies to penicillin. Some chemicals are capable of triggering the immune system to develop antibodies against the chemical (or, more accurately, to a protein in the body that has been modified by the chemical), and subsequent exposures to that chemical can induce an allergic response. This is a major concern for many drugs, as allergic responses can be fatal. Once "sensitization" has occurred (e.g., the individual has developed antibodies to a specific chemical), relatively small doses of the chemical may be sufficient to trigger a response. Thus, people with allergic sensitization to a specific chemical may respond at a dose much lower than the "average" person, and the response will be qualitatively different (e.g., rather than causing liver damage at a high dose seen in most people, the "allergic" individual may have an asthmatic attack, or develop skin rashes or GI disturbances, at much lower doses). One of the most controversial areas in toxicology and environmental medicine is that related to a number of syndromes such as

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[18] Michael I. Luster, Michael F. Ackermann, Dori R. Germolec & Gary J. Rosenthal, *Perturbations of the Immune System by Xenobiotics*, 81 ENVTL. HEALTH PERSP. 157, 157-62 (1989).

"Multiple Chemical Sensitivity" (MCS), Gulf-War Syndrome, Sick Building Syndrome, Chronic Fatigue Syndrome, etc., for which an immunological basis may be involved.[19] As noted by Kipen and Fiedler:

> Symptoms, and especially those without clear underlying medical explanations, account for a large percentage of clinical encounters. Many unexplained symptoms have been organized by patients and practitioners into syndromes such as chronic fatigue syndrome, multiple chemical sensitivity, sick building syndrome, Gulf War syndrome, and the like. All these syndromes are defined solely on the basis of symptoms rather than by medical signs. Some of the above-described conditions overlap strongly with explained conditions such as asthma. The relationship of such symptoms and syndromes to environmental exposure is often sharply debated, as is the distinction between the various syndromes.[20]

Litigation in this area often pits toxicologists, epidemiologists, and/or environmental and occupational medicine specialists against another group of physicians identified as "clinical ecologists." As noted by Goldstein and Henefin:

> Clinical ecologists . . . have offered opinions regarding multiple-chemical hypersensitivity and immune-system responses to chemical exposures. These physicians generally have a background in the field of allergy, not toxicology, and their theoretical approach is derived in part from classic concepts of allergic responses and immunology. This theoretical approach has often led clinical ecologists to find cause-and-effect relationships or

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[19] *See* Dalia Racciatti, Jacopo Vecchiet, Annalisa Ceccomancini, Francesco Ricci & Eligio Pizzigallo, *Chronic Fatigue Syndrome Following a Toxic Exposure,* 270 SCI. TOTAL ENV'T 27, 27-31 (2001); *see also* Roberto Patarca, *Cytokines and Chronic Fatigue Syndrome*, 933 ANNALS N.Y. ACAD. SCI. 185, 185-200 (2001).

[20] Howard Kipen & Nancy Fiedler, *Environmental Factors in Medically Unexplained Symptoms and Related Syndromes: The Evidence and the Challenge*, 110 (Suppl 4) ENVTL. HEALTH PERSP. 597, 597-99 (2002).

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low-dose effects that are not generally accepted by toxicologists.[21]

A third way that chemical exposures might involve the immune system involves the development of autoimmune diseases such as lupus, rheumatoid arthritis, and scleroderma. These are important and disabling diseases, yet our understanding of why the immune system sometimes goes awry is limited. Autoimmune diseases arise when the immune system begins to recognize normal tissues as "abnormal" and mounts an attack to destroy the tissue (similar to transplant rejection, where the transplanted organ is recognized as foreign by the immune system). Because the etiology of autoimmune disease is largely unknown and unpredictable, there have been many efforts to identify environmental factors that contribute to the development of autoimmune diseases. Probably the most extensively studied disease in this regard is lupus (Systemic Lupus Ereythematosus, SLE). About a half a dozen drugs have been definitively linked with lupus, with dozens more implicated.[22] However, the list of non-drug "environmental" chemicals that have been definitively shown to cause lupus (or other autoimmune diseases) is much shorter. Some inorganic substances, in particular silica, gold, cadmium, and mercury, have been shown to induce autoimmunity in animals and humans. There is suggestive data that exposure to organic solvents, certain chlorinated hydrocarbons such as vinyl chloride, trichloroethylene, and hexachlorobenzene, can also induce autoimmunity, although the scientific evidence (both toxicological and epidemiological) for this is marginal. It remains an area of scientific interest and controversy.

D. Environment and Cancer Risk

Claims of cancer, or increased cancer risk, or fear of cancer,

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[21] Bernard D. Goldstein & Mary Sue Henefin, *Reference Guide on Toxicology, in* FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 401, 416 (2d ed. 2000).

[22] Evelyn V. Hess, *Environmental Chemicals and Autoimmune Disease: Cause and Effect*, 181-182 TOXICOLOGY 65, 65-70 (2002).

following chemical exposures are often key elements of toxic tort litigation, and thus I will devote a substantial amount of space to this particular form of toxic response. While it is clear that some chemical pollutants (potentially found in air, food, and/or water) have the ability to cause cancer in either or both experimental animals and humans, deciding whether a particular chemical exposure has "more probably than not" been a "substantial contributing factor"—or whatever the relevant burden of proof might be—in a particular person's cancer (or risk of cancer, or fear of cancer) is a major challenge for scientists, lawyers, judges, and jurors. To facilitate an understanding of the scientific challenges that are faced in such litigation, it is perhaps useful to look at the "big picture" of what scientists know—and don't know—about the causes of cancer.

1. Major Causes (Risk Factors) of Cancer

Over the last fifty or so years, a tremendous amount of epidemiological data has been collected on the relationship between a variety of "environmental factors" and the incidence of cancer. Studies comparing cancer risks in different populations with various lifestyle, genetic, cultural, dietary, and behavioral characteristics have led to a reasonable understanding of the major "risk factors" for cancer. These data are of course based on the incidence of cancer in large populations, and thus it is difficult to ascribe "individual" risk to a specific person from these data. Based on such analyses, it has been stated that 85-90% of all cancers are "environmentally-related" and thus potentially preventable. It should again be emphasized, however, that the term "environmentally-related" in this context refers to everything *other than* genetics (including smoking, diet, lifestyle, etc.) and does not equate directly to "environmental pollution."

As illustrated in Table 1, approximately 35-40% of all cancer deaths are attributable to tobacco products.[23] While much of this is

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[23] Richard Doll & Richard Peto, *The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today*, 66 J. NAT'L CANCER INST. 1191, 1191-308 (1981). Most estimates are derived from the

lung cancer (the leading cause of cancer-related deaths in both men and women in most developed parts of the world), smoking also increases risk of oral, bladder, kidney, and several other cancers.

TABLE 1—"BEST ESTIMATES" OF THE MAJOR RISK FACTORS FOR CANCER

Factors	Best Estimate (%)	Range (%)
Tobacco	35	25 – 40
Diet	35	10 – 70
Cultural and Lifestyle factors	10	1 – 13
Infectious agents	10	5 – 20
Genetics	5	2 – 10
Occupation	4	2 – 8
Alcohol	3	2 – 4
Geophysical factors (e.g., radon)	3	2 – 4
Medicines/medical procedures	1	<1 – 3
Pollution	2	<1 – 5
Industrial Products	<1	<1 – 2
Food additives	<1	- 5 – 2

The next most important factor—roughly equal in importance to smoking—is "diet." What it is about diet that is so important remains uncertain. What is clear is that there are many aspects of the diet that can either increase or decrease cancer risk. For example, diets high in fruits and vegetables have consistently been shown to lower the risk of a variety of cancers.[24] In some studies,

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seminal work of Sir Richard Doll. *Id.* Recognition of infectious agents as a substantial contributor to several types of cancer, especially for cervical and stomach cancer, became evident in the past decade. *Id.* The American Cancer Society also discusses the major causes of cancer in their book, entitled: CANCER: WHAT CAUSES IT, WHAT DOESN'T (2003), available for purchase at http://www.cancer.org.

[24] *See* John D. Potter, *Diet and Cancer: Possible Explanations for the Higher Risk of Cancer in the Poor*, 138 INT'L AGENCY FOR RES. ON CANCER SCI. PUBLICATIONS 265, 265-83 (1997); Eli Riboli & Teresa Norat, *Epidemiologic Evidence of the Protective Effect of Fruit and Vegetables on Cancer Risk*, 78 (3 Suppl) AM. J. CLINICAL NUTRITION 559S, 559S-569S (2003); Antonia Trichopoulou, Androniki Naska, Antonis Antoniou, Sharon Friel, Ku Trygg & Alessandro Turrini, *Vegetable and Fruit: The Evidence in Their Favour and the Public Health Perspective*, 73 INT'L J. FOR VITAMIN NUTRITION

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diets high in animal fat have been associated with increased risk of some common cancers (e.g., breast), but the relationship is not always seen, and it remains unclear whether the amount and/or type of fat in the diet are important risk factors. There are also some chemical contaminants in the diet that may increase cancer risk, but again for most populations it is not clear how important natural dietary carcinogens (cancer-causing chemicals) are to overall cancer risk. In some parts of the world, however, a common mold contaminant of corn and peanuts—called "aflatoxin"—is certainly an important contributor to the very high incidence of liver cancer. It has been shown that aflatoxin is much more dangerous in populations where hepatitis B viral infections are common.[25]

The third most important category of risk factors revolves around cultural and lifestyle factors, which includes sexual practices and reproductive factors. Often these cultural factors interact with other environmental factors, such as viruses. For example, it is now recognized that almost all cervical cancer is due to infection with the human papilloma virus (HPV), which is transmitted through sexual activity. For reasons that are unclear, cervical tissue in teenage women seems more susceptible to HPV infection than that in older women. Thus, sexual activity at a young age is a major risk factor for cervical cancer. While this disease is relatively easily diagnosed (via Pap smear) and treated if detected early, large differences in access to medical care and sex education can make a huge difference in the mortality of this disease across populations.

Breast cancer is the second leading cause of cancer-related deaths among women in the United States and many other developed countries, trailing only smoking-related lung cancer. The major risk factor for breast cancer appears to be a constellation of reproductive factors that influence a woman's "lifetime dose" of unopposed estrogen. Thus, the age of onset of menstruation, the

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RES. 63, 63-69 (2003).

[25] Thomas W. Kensler, Gang-Sun Qian, Jiang-Guo Chen & John D. Groopman, *Translational Strategies for Cancer Prevention in Liver*, 3 NATURE REV. CANCER 321, 321-29 (2003).

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age of onset of menopause, the number of children, the age of first pregnancy, and the extent of breast-feeding, all influence breast cancer risk. Thus, it is not surprising that breast cancer incidence and mortality is much lower in countries and cultures where women have their first children early in life, have multiple children, breast feed for extended periods, and often have dietary habits that postpone (or, at least don't accelerate) the onset of menstruation, compared to a typical "suburban U.S." lifestyle. Recently, there has been much public press coverage of the discovery of several "breast cancer genes" (BRCA1, BRCA2, BRCA3).[26] Although there is little question that women who carry variant forms of the genes are at substantially increased risk of developing breast cancer (especially at a younger age), the overall contribution of these rather rare genetic causes of breast cancer is probably substantially less than 10% of all breast cancers. Thus, the large majority of breast cancers seem not to have major genetic contributors. But it remains uncertain whether there are important "environmental susceptibility" genes that might interact with environmental factor(s) to substantially increase breast cancer risk.

Of the various identifiable "environmental" factors not associated with diet or lifestyle, infectious agents seem to play a more important role than was expected only a decade ago. It is now clear that well over 90% of cervical cancers are due to HPV infections.[27] Many cases of stomach cancer are directly attributable to a chronic bacterial infection from *helicobacter coli.*[28] Most cases

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[26] *See* Peg Brickley, *Repairing BRCA1 Science DNA-Repair Researchers Trying to Separate Sound Science from Allegedly False Data in Retracted Papers*, THE SCIENTIST, June 18, 2003; Jeffrey Krasner, *Marketing of Cancer-Gene Test Raises Ethical Medical Concerns: Gene Test Ads Prompt Concern*, BOST. GLOBE, Mar. 26, 2003, at D1; Rick Weiss, *2 Genes Make Cancer Risk Soar; Women's Odds Not Tied to Family Health, Study Finds,* WASH. POST, Oct. 24, 2003, at A1.

[27] *See* F. Xavier Bosch & Silvia de Sanjose, *Human Papillomavirus and Cervical Cancer—Burden and Assessment of Causality*, 31 J. NAT'L CANCER INST. MONOGRAPHS 3, 3-13 (2003); Steven E. Waggoner, *Cervical Cancer*, 361 LANCET 2217, 2217-25 (2003).

[28] Jon R. Kelley & John M. Duggan, *Gastric Cancer Epidemiology and Risk Factors*, 56 J. CLINICAL EPIDEMIOLOGY 1, 1-9 (2003).

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of liver cancer worldwide can be attributable to hepatitis B (and probably C) viral infections, and alcohol consumption.[29] Even the HIV virus responsible for AIDS is associated with substantially increased risk for certain types of cancer.[30] It is possible, although still not proven, that a significant fraction of human blood-related cancers (leukemias and lymphomas) have a viral etiology, as several leukemia viruses have been identified in animals.

What role do "man-made" chemical pollutants, such as heavy metals, pesticides, industrial solvents, asbestos, etc., play in overall cancer risk? As indicated in Table 1, "occupation" is thought to be responsible for 3-5% of all cancers, although there is reasonable hope and expectation that this will decline substantially as the long history of high-level occupational exposures to cancer-causing substances becomes a relic of the past.[31] But the incidence of asbestos-related lung cancer and mesothelioma, derived from occupational exposures that occurred predominantly in the '40s, '50s, '60s and early '70s has not yet peaked, since latency period (time from first exposure to the development of clinical disease) may be as long as fifty to sixty years in some individuals. Greatly improved awareness and early identification of potential cancer-causing chemicals, coupled with significant improvements in workplace controls, monitoring, and worker education (at least in developed countries) should result in a drastic reduction in the incidence of occupationally related cancers in the future.

Probably the most uncertain and controversial contributor to cancer risk is that associated with environmental pollution.[32]

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[29] Renuka Bhattacharya & Margaret C. Shuhart, *Hepatitis C and Alcohol: Interactions, Outcomes, and Implications*, 36 J. CLINICAL GASTROENTEROLOGY 242, 242-52 (2003); Timothy M. Block, Anand S. Mehta, Claus J. Fimmel & Robert Jordan, *Molecular Viral Oncology of Hepatocellular Carcinoma*, 22 ONCOGENEOLOGY 5093, 5093-107 (2003).

[30] Eliabeth Y. Chiao & Susan E. Krown, *Update on Non-acquired Immunodeficiency Syndrome-Defining Malignancies*, 15 CURRENT OPINIONS ONCOLOGY 389, 389-97 (2003).

[31] *See supra* note 23 & Tbl. 1.

[32] *See* Julia G. Brody & Riuthann A. Rudel, *Environmental Pollutants and Breast Cancer,* 111 ENVTL. HEALTH PERSP. 1007, 1007-19 (2003); Shuanfang Li, Stephen D. Hursting, Barbara J. Davis, John A. McLachlan & J. Carl Barrett,

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Although it is very difficult to make reasonable "estimates" of the contribution of environmental pollution to overall cancer incidence and mortality, most experts place the number at only a few percent, at most. However, even 1% of 500,000 deaths a year is not an insignificant number (5000) of potentially preventable deaths, so efforts to reduce the use and release of chemical carcinogens are not ill-founded. The challenge comes in balancing the potentially real, but very low, risks of cancer in a large population against the societal benefits that come from the industrial and consumer activities that contribute to the pollution. The basic ways that chemicals can increase cancer risk (chemical carcinogenesis) and the process of "carcinogenic risk assessment" for chemical pollutants are discussed in more detail below.

One example in the area of environmental carcinogenesis that has been the subject of substantial tort and regulatory litigation is that of "dioxins."[33] Dioxins represent a group of industrial by-products produced inadvertently in the chemical manufacture of trichlorophenol (TCP). TCP was widely used in the synthesis of the herbicide, 2,4,5 trichlorophenoxy acetic acid (2,4,5-T), a component of Agent Orange. TCP was also used in the manufacture of the antibacterial soap ingredient, hexachlorophene, so many antibacterial soaps were also contaminated with trace amounts of dioxins. Although there are more than a dozen specific "dioxin" chemicals, the term is generally used to refer to one

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Environmental Exposure, DNA Methylation, and Gene Regulation: Lessons from Diethylstilbesterol-Induced Cancers, 983 ANNALS N.Y. ACAD. SCI. 161, 161-69 (2003); William G. Thilly, *Have Environmental Mutagens Caused Oncomutations in People?*, 34 NAT'L GENETICS 255, 255-59 (2003).

[33] *See* Andrew Blum, *Dioxin Cases: Lengths and Results Vary*, 10 NAT'L L.J. 3 (1988); Richard Pliskin, *Dioxin Case Ends with a Whimper:* Ironbound Health Rights Advisory Commission v. Diamond Shamrock Chemicals Co., 130 N.J.L.J. 1 (1992); *Verdict in One of Nation's Longest Trials Reached a Year Ago Saturday (*Kemner v. Monsanto*)*, 134 CHIC. DAILY L. BULL. 1 (1988); John Deakle & Nicholas Varchaver, *Muddy Waters; Georgia-Pacific is Mired in Mississippi, Facing 8,800 Plaintiffs and Billions of Dollars in Potential Liability, Thanks to Dioxin-Emitting Paper Mill and a Local Plaintiffs Lawyer Who Won't Go Away*, 15 AM. LAW. 52 (1993); William Boyd, *Controlling Toxic Harms: The Struggle Over Dioxin Contamination in the Pulp and Paper Industry*, 21 STAN. ENVTL. L.J. 345 (2002).

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highly toxic form, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). When tested in experimental animals, TCDD is extremely toxic, causes cancer and birth defects at extraordinarily low doses, and is generally considered the most toxic and carcinogenic man-made chemical ever studied. Dioxins represent an interesting challenge to the courts for several reasons. First, there are very large species differences in susceptibility to the toxic—and presumably carcinogenic—effects of TCDD. For example, the single lethal dose of dioxin in guinea pigs is approximately 0.1 micrograms per kg of body weight, whereas the lethal dose in hamsters is more than 10,000 times greater. Second, although studies in rats and mice provide consistent evidence that "dioxin" is a potent and effective carcinogen, human epidemiology studies are less convincing. Furthermore, dioxin is not appreciably metabolized in the body, nor does not cause mutations, and the "mechanism" by which it causes cancer is uncertain. Because it is very soluble in fat and is not metabolized in the body, it remains in the body for many years following exposure. Because potentially tens of thousands of military personnel were exposed to dioxin during the Vietnam War, and because of the widespread use of certain herbicides containing small amounts of dioxins in agriculture, forest practices, utility and highway right of ways, and even residential property, it has been the subject of extensive toxic tort litigation.[34] Although it is probably one of the most extensively studied chemical carcinogens, there remains substantial scientific uncertainty as to the actual levels of cancer risk to humans exposed to trace levels of dioxins in the environment.

2. *General Mechanisms of Chemical Carcinogenesis*

Chemicals that cause an increased incidence of cancer in a population (experimental animals or humans) following exposure are referred to as "carcinogens."[35] The process of chemical carcinogenesis is "multi-stage," such that several events must

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[34] *See* sources cited *supra* note 33.

[35] CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, *supra* note 11, at Ch. 8.

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occur before a normal cell is transformed into a malignant (cancer) cell. Typically, the process of carcinogenesis is divided into four general stages: (1) initiation, (2) promotion, (3) progression and (4) metastasis. A chemical carcinogen may increase the incidence of tumors by acting at any or all of these various stages. One of the most important ways that a chemical may act as a carcinogen is by interacting with DNA in somatic cells to cause mutations. (Somatic cells refer to all cells in the body except sperm and egg cells (ova)). Mutations in somatic cells may lead to permanent changes in the DNA that result in critical changes in the way the cell controls its rate of cell division. Such a permanent alteration in DNA of a somatic cell is referred to as "initiation," and represents the first stage of chemical carcinogenesis. Because initiation results in a permanent change in the DNA of a cell that is subsequently passed on to all "daughter" cells following division of the mutated cells, initiation is generally considered to be an irreversible process, and initiated cells may accumulate in the body throughout life.

By definition, all chemicals that are "initiators" are mutagenic, and thus short-term tests that demonstrate the mutagenic ability of a chemical make it a suspect carcinogen.[36] However, not all chemicals that test positive in mutagenicity assays are carcinogenic for a variety of reasons. Nevertheless, a chemical that consistently tests positive in numerous different short-term mutagenicity assays is more likely to be carcinogenic than a chemical that routinely tests negative. However, as with all toxicological responses, the "dose-response" for mutagenesis is critically important to consider. Thus, when considering the potential health significance of exposure to chemical mutagens that may act as carcinogens, it is important to keep the total or cumulative "dose" in mind, as the critical issue is whether there *is a biologically relevant* increase in the "background" rate of DNA damage from all other sources over the lifetime of an individual.

Although initiation is an essential first step toward cancer, most initiated cells do not go on to become cancers because they usually require additional genetic changes and other external stimuli to

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[36] *Id.*

become true cancer cells. An initiated cell is analogous to a car whose accelerator is stuck part way on. As long as the brakes work, the speed and control of the car can be adequately maintained. However, if a second change occurs, resulting in the loss of the brakes, then the car can no longer be controlled. It should be recognized that the vast majority of mutations in a cell do not have any effect on cell growth and regulation, just as most mechanical malfunctions in a car do not result in a stuck accelerator or loss of brakes.

The second step of carcinogenesis, referred to as "promotion," occurs when some external stimuli, including exposure to certain chemicals, increases the rate of cell proliferation of initiated cells or otherwise enhances the ability of an initiated cell to become cancerous, but does not directly interact with DNA. A chemical that increases cancer risk by acting as a promoter of carcinogenesis is generally considered to be less of a concern because the promoting stimulus goes away when the exposure stops—e.g., promotion is "reversible." The process of promotion can be viewed as a relatively early stage in carcinogenesis where an initiated cell is stimulated to divide repeatedly to give rise to a small colony of initiated cells (a "preneoplastic" lesion).

The third stage of carcinogenesis, referred to as progression, represents the long period of time where the small colony of initiated cells acquires additional mutations that further transform the cell from a normal cell to a cancer cell. To return to the car analogy, additional mutations damage the cell's "brakes," "steering," or other critical functions necessary to properly maintain control.

The probability of a single cell acquiring all of the necessary genetic changes to convert it from a normal cell to a cancer cell depends on a variety of factors, including the dose and duration of exposure to mutagenic substances. Exposure to man-made mutagenic chemicals can increase cancer risk. However, it should be recognized that the vast majority of DNA damage that occurs in our cells results from normal metabolic processes and exposure to natural components in the diet or to UV radiation in sunlight. As a cell "burns" sugars to produce energy it generates reactive by-products of oxygen. These by-products, called "free radicals" or

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"reactive oxygen species" (ROS) can and do directly damage DNA. In addition, common chemicals found naturally in the diet and/or formed during cooking can also damage DNA (e.g., act as mutagens). Fortunately, the cells of the body have remarkable processes that can reduce the damage to DNA from ROS and mutagenic chemicals (both natural and man-made), as well as repair damaged DNA. Many vitamins and certain chemicals found naturally in the diet (especially in fruits and vegetables) act as "antioxidants" and can help protect cells from the DNA damaging effects of ROS and chemicals (both man-made and natural) that damage DNA. This is one reason why diet is so important in lifetime cancer risk. Many studies have demonstrated that diets high in fruits and vegetables lower the risk of many types of cancer.[37]

Because the probability of a single somatic cell acquiring all of the necessary genetic changes (mutations) to become a cancer cell is quite small and is a function of the period of time that a cell has to acquire such mutations, cancers that occur because of exposure to a carcinogen are both relatively rare in an exposed population and are usually not seen until many years after the initial period of exposure. For cancers caused by prolonged or repeated exposure to a chemical, the time frame from first exposure to when the disease becomes clinically evident is referred to as the "latency" period. In general, the latency period is somewhat inversely related to the extent of exposure (dose). For most human cancers that are related to chemical carcinogen exposure (e.g., cancers related to cigarette smoking), the latency period is usually twenty to forty years. Certain cancers (mesotheliomas) that arise from occupational exposure to asbestos typically are not seen for thirty or more years after first exposure.[38] The shortest latency period possible appears to be at least a couple of years following very high levels of exposure to mutagenic chemicals used to treat cancers, especially leukemias.[39] Because latency seems to be inversely related to dose,

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[37] *See* sources cited *supra* note 24.

[38] Mark Britton, *The Epidemiology of Mesothelioma,* 29 SEMINARS ONCOLOGY 18, 18-25 (2002).

[39] Richard A. Larson, Michelle M. LeBeau, James W. Vardiman & Janet D.

very low levels of exposure to mutagenic chemicals may be of little practical consequence to an individual because (1) the extent of DNA damage is very small, relative to the "background" rate that occurs from all other sources, and (2) the latency period for developing a cancer is very long and may exceed normal life expectancy. Although these are very important practical biological considerations, they are often not considered in quantitative risk assessment of low dose carcinogen exposures by regulatory agencies, who usually assume that risk is directly proportional to dose at low doses (the "linearized dose-response" approach to cancer risk assessment).

Another factor that affects the occurrence of a cancerous cell is the rate of cell turnover, or "cell proliferation."[40] Because all cells have a background incidence of spontaneous mutations, the likelihood of a cell becoming mutated is related to the rate of cell replication, analogous to rolling dice. The more often the dice are rolled the more likely a specific number is to appear. This factor is especially important in considering the use of high doses of chemicals in laboratory animal test for cancer-causing potential. When doses of the test chemical are so high that they cause tissue damage (and thus stimulate cell division to repair the damage)—which usually would not occur at low doses—direct extrapolation of the rate of tumor formation in the animals given high doses to humans exposed to much lower doses that don't cause tissue damage is of questionable scientific value.[41] The particular rodent strains used also often have a high background rate of spontaneous tumors.[42] Thus, any chemical that damages cells and causes considerable regeneration (i.e., cell proliferation) may increase the

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Rowley, *Myeloid Leukemia After Hematotoxins*, 104 (Suppl 6) ENVTL. HEALTH PERSP. 1303, 1303-07 (1996).

[40] Samuel M. Cohen, *Cell Proliferation and Carcinogenesis,* 30 DRUG METABOLISM REV. 339, 339-57 (1998).

[41] Samuel M. Cohen, *Urinary Bladder Carcinogenesis,* 26 TOXICOLOGY PATHOLOGY 121, 121-27 (1998); Lois S. Gold, Thomas H. Slone & Bruce N. Ames, *What Do Animal Cancer Tests Tell Us About Human Cancer Risk? Overview of Analysis of the Carcinogenic Potency Database*, 30 DRUG METABOLISM REV. 359, 359-404 (1998).

[42] *See* Gold, *supra* note 41; *see also* Zito, *supra* note 13.

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likelihood of a cancerous cell occurring.

E. Use of Toxicological Data to Assess Chemical Risks in Populations and Individuals

It is important to recognize that the procedures commonly used in "risk assessment" for the purposes of establishing public health guidelines that represent "acceptable" exposure levels for large populations are often, in this author's opinion, of marginal relevance to estimating "causation" in an individual—e.g., whether a particular chemical caused or contributed to a particular disease or illness in a given person. Although toxicological data—and the basic principles of toxicology outlined above—are useful for both (establishing guidelines for protection of public health and establishing "causation"), there are substantial differences in approach. Thus, use of toxicological data for these two distinct purposes will be discussed separately in the following sections.

F. Use of Toxicological Data to Establish "Acceptable" Levels of Exposure for Large Populations (Public Health)

Much of the available dose-response criteria for assessing chemical toxicity and risks to human health are based on protective guidelines developed by federal (e.g., EPA, ATSDR) and sometimes state agencies. The federal government and national organizations using similar approaches also set occupational health guidelines and standards for protection of workers. Guidelines for protection of the general public are usually more stringent than for workers, who are assumed to be part of a healthier and less sensitive population. Public health guidelines, however, should not be interpreted as predicting exact levels at which effects would occur in a given individual. Because a number of protective, often "worst-case" assumptions (e.g., exposure to any dose of a carcinogenic chemical based on animal studies confers a risk of cancer in humans, high daily exposure for a lifetime) are made in estimating allowable exposures for large populations, these criteria and the resulting regulatory levels (e.g., MCLGs, MCLs) generally

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overestimate potential toxicity levels for nearly all individuals. Furthermore, because these guidelines are intended to be protective of all individuals in a population, including the very young, the very old, and other potentially "sensitive" individuals, the theoretical risks from exposure at the guideline level is likely to be substantially overestimated for the large majority of individuals in the population. Nevertheless, they can provide useful guidance to public health agencies that have the responsibility of protecting all individuals in large populations.

Public Health criteria developed by the EPA for individual chemicals usually include determination of non-cancer reference doses and "cancer potency" or "slope factors." Non-cancer reference doses represent the dose below which no adverse health effects are expected, even in sensitive individuals exposed repeatedly at the defined level for many years. Reference doses are usually derived from "No Observable Adverse Effect Levels" (NOAELs) or "Lowest Observable Adverse Effect Levels" (LOAELs) in the toxicological literature. NOAELs and LOAELs are usually determined from experimental animal studies, rather than human exposures. The term "Reference Dose" is frequently used to refer to a dose of a chemical to humans that could be consumed on a daily basis for a lifetime with no chance of anyone exhibiting an adverse response (the specific definition of such "safe" doses varies from agency to agency and regulation to regulation). Reference Doses are obtained by dividing the "NOAEL" dose determined in animal studies by an Uncertainty Factor. Uncertainty Factors usually range from 100 to 1000, depending on the amount of uncertainty in, for example, extrapolating from animals to humans, short-term to long-term effects, average to sensitive members of the population.[43] Generally, the more uncertainty factors required, the more likely it is that the Reference Dose will be lower than what would actually be necessary for protection of humans because each uncertainty factor errs on the side of overprotection. Thus, although health authorities can confidently expect that exposures below reference dose levels will not result in adverse effects, the converse is not

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[43] *See* sources cited *supra* notes 13 & 14.

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true. Exposures in a given individual that exceed a reference dose level do *not* signify that effects are likely to occur because of the margin of "safety" built into these Reference Doses which are intended to provide guidance for protecting even sensitive members of the population. Thus, such regulatory levels are of substantial value to public health agencies charged with ensuring the protection of the public health, but are of limited value in judging whether a particular exposure was a substantial contributing factor to a particular individual's disease or illness.

G. Determining Regulatory Guidelines for Chemical Carcinogens for Protection of Public Health

For carcinogens, most regulatory agencies have used "default" assumptions about the dose-response relationship such that it is assumed that the risk of developing cancer is proportionate to dose at all doses (e.g., there is no "threshold" dose).[44] Thus, to establish socially acceptable levels of exposure to carcinogens commonly found in food, air and water, the EPA, FDA, and other regulatory agencies have established guidelines for conducting risk assessments.[45] Using such procedures, "acceptable," "tolerable," "permissible," or "safe" levels of exposure to a specific chemical are often established based on regulatory policy decisions on allowable risk, or tradeoffs between risk reduction and cost.[46] For contaminants in drinking water, such levels are referred to as "Maximum Contaminant Levels," or MCLs. The EPA has a long-standing policy that dictates that the desired level of cancer risk for a contaminant in drinking water is zero.[47] Thus, for carcinogens the EPA has established MCLGs (Maximum Contaminant Level Goals) of zero. However, because zero levels are generally not

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[44] *See* ENVTL. PROT. AGENCY, EPA 630/P-03/001A, NCEAA-F-0644A, DRAFT FINAL GUIDELINES FOR CARCINOGEN RISK ASSESSMENT (2003). Earlier adopted versions also have assumed linearity at low dose. *Id.*

[45] *See id.*; Zito, *supra* note 13.

[46] *See* ENVTL. PROT. AGENCY, *supra* note 44.

[47] *See* U.S. Envtl. Prot. Agency, Setting Standards for Safe Drinking Water, *at* http://www.epa.gov/safewater/standard/ setting.html (last modified Aug. 7, 2003).

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achievable by modern technology, the actual drinking water standards, MCLs, are usually based on other considerations such as technical feasibility, cost-benefit analysis, and background levels. However, even if the standard is based primarily on a technology or cost, MCLs for most such chemicals in drinking water must still be within an acceptable range of health risk. For cancer risk from chemicals in drinking water, the EPA has stated this range to be an excess lifetime risk of cancer over background of one in 1,000,000 to one in 10,000. However, there are some exceptions where MCLs have been established that yield theoretical excess lifetime cancer risks much greater than one in 10,000. The recent adoption of an MCL for arsenic in drinking water of 10 ppb is such an example.[48]

Because the lifetime probability of dying from cancer for someone living in the United States is about 1 in 4 (25%, or 0.25 lifetime probability), a theoretical increase in lifetime cancer risk (mortality) of 1 in 100,000 would provide a potential increase in overall lifetime probability of dying from cancer from approximately 0.25 to approximately 0.25001. Thus, when citizens are confronted with evidence that their drinking water is contaminated with a "cancer causing chemical" at levels that exceed federal regulatory limits, it becomes important to ensure that the public understands how such standards are derived and the significance of the potential increase in risk, relative to other common risks encountered daily.

EPA cancer "slope factors" represent the slope of the dose-response relationship statistically extrapolated from studies of high dose exposure and cancer in laboratory animals or human populations. The EPA default assumption in these slope factors is that no dose of a carcinogenic chemical is without some risk of cancer and that one can extrapolate high dose exposures and the risk of cancer to low doses. The use of a slope factor in this

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[48] *See* U.S. Envtl. Prot. Agency, Arsenic in Drinking Water, *at* http://www.epa.gov/safewater/arsenic.html (last modified July 14, 2003); SUBCOMMITTEE TO UPDATE THE 1999 ARSENIC IN DRINKING WATER REPORT, NAT'L RES. COUNCIL, ARSENIC IN DRINKING WATER: 2001 UPDATE (2001), *available at* http://www.nap.edu/catalog/10194.html (last visited Dec. 5, 2003).

manner ignores the ample evidence that for many carcinogenic chemicals, practical thresholds may exist for significant cancer risk because of detoxification mechanisms at low doses (e.g., difference in metabolism of the chemicals at high dose versus lower doses) or because of the mechanisms of action. Therefore, these slope factors cannot be expected to accurately predict a risk of cancer, if any, in a given individual at low doses. Although they may be somewhat useful to make crude estimates of individual risk, many assumptions go into the determination of the cancer slope factor, and it is important to consider the relevance of the particular animal study from which the slope factor was determined when attempting to use such values in individual risk calculations.

H. Use of Toxicological Data in Assessment of Individual Causation

When assessing whether a particular potentially toxic substance is a substantial contributing factor to an *individual's* disease or illness, the "regulatory approach" is of little value, although much of the same toxicological and epidemiological data may be used in evaluating causation. The key scientific criteria used to establish causation between an alleged chemical exposure and a particular disease or illness includes the following basic concepts:

1. *The toxic substance in question must have been demonstrated to cause the type of illness or disease in question.* This addresses the issue of general causation as well as specific causation, and may be demonstrated either in humans following known exposures (usually from accidents, occupational exposures, or intentional exposures), or, in the absence of human data, in experimental animals intentionally exposed to the agent in question. Because most chemicals that are widely encountered in the environment, such as pesticides, metals, and industrial solvents, are manufactured, workplace exposure to humans may occur. Occupational health and safety regulations require workplace monitoring, and thus there is frequently a substantial amount of toxicologically relevant data from workplace monitoring that can

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be used to assess whether a particular chemical is capable of causing a particular disease or illness. Indeed, virtually all synthetic chemicals identified by EPA or International Agency for Research on Cancer as "known human carcinogens" have been identified as such through studies of workers exposed to the chemical in the workplace. Workplace exposures are typically hundreds to thousands of times greater than incidental environmental exposures that might occur from contamination of drinking water, or off-site migration of chemicals via the air.

2. *The individual must have been exposed to a sufficient amount of the substance in question to elicit the health effect in question.* As noted above, the main tenant of toxicology is the "dose-response" relationship. If criterion (1) above has been established for a given chemical, then it must be established that the individual's dose over a defined period of time was sufficient to cause the alleged health effect. It is not adequate to simply establish that "some" exposure occurred. Because most chemically induced adverse health effects clearly demonstrate "thresholds," there must be reasonable evidence that the exposure was of sufficient magnitude to exceed the threshold before a likelihood of "causation" can be inferred. For carcinogenic chemicals that act via mutagenic action, a threshold may not be evident. Thus, although any level of exposure will theoretically increase the probability of developing the disease, the risk follows a dose-response relationship, and the dose must be sufficient to "significantly" elevate the risk above the background. What represents a "significant" increase in cancer risk is of course subjective and influenced by many factors. However, as noted above, because the process of chemical carcinogenesis is always associated with a "latency," and the latency period is generally inversely related to dose, at very low doses of even "direct acting," mutagenic carcinogens, the latency period might exceed life expectancy, thereby imparting a "practical" threshold.

3. *The chronological relationship between exposure and effect must be biologically plausible.* If a disease or illness in an individual preceded the established period of exposure, then it cannot be concluded that the chemical caused the disease, although it may be possible to establish that the chemical aggravated a pre-

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existing condition or disease. For cancer cases, diagnosis of the cancer in a time frame close to the beginning period of exposure (i.e., within a few years) argues strongly against a causal relationship, since, as noted above, chemically-induced cancers have latency periods that are nearly always in excess of five years, and are somewhat inversely related to dose.

4. *The likelihood that the chemical caused the disease or illness in an individual should be considered in the context of other known causes.* Although this consideration may not be essential to establish *general* causation, it is a critical consideration in the quantitative assessment of whether the substance was "more likely than not" a cause or substantial contributing factor to the disease or illness in a specific person. This is especially important in cancer causation, because cancer is by its very nature a multi-factorial disease. As discussed above, chemicals that are mutagenic have the theoretical potential to increase cancer risk even at very low doses, although there is a point at which the theoretical risk is trivial, relative to all other causes, known and unknown. As there are literally hundreds, if not thousands, of mutagenic naturally-occurring chemicals present at low levels in our diet and thus also present theoretical cancer risks, it becomes important to put such theoretical, "low dose" risks in perspective.[49]

J. Multiple Exposures/Mixtures

Another area of relevance to human risk assessment for environmental pollutants is the fact that, unlike experimental animals, humans may be exposed to multiple different chemicals, diets, and lifestyle factors that affect the dose-response relationship for a given chemical. For chemical carcinogens, it is often assumed that the risks are additive even though they may not act through similar mechanistic pathways. That is, the risk for each chemical in a mixture is calculated separately, and the total risk from exposure to the mixture is simply the sum of the risks for each individual chemical. While there are examples of non-additive responses (both "synergistic," where the response of two chemicals is greater

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[49] *See* Kipen & Fiedler, *supra* note 20.

than predicted from adding the individual response alone, and "antagonistic," where one chemical appears to reduce the risk of the second), unless there is compelling evidence to the contrary, additivity of risks for all carcinogens is generally assumed. However, for carcinogens that act via different modes (e.g., genotoxic vs. non-genotoxic carcinogens), additivity is less certain, and mechanistic data may warrant consideration of non-additive models for interaction.

EPA risk assessment guidelines also consider non-cancer effects of chemicals to be additive, particularly if they effect the same endpoint at lower doses. If the chemicals act by the same mechanism, then their action could be additive even when exposure to each is below a dose that would cause effects.

III. FUTURE SCIENTIFIC OPPORTUNITIES AND CHALLENGES IN TOXIC TORT LITIGATION

The past decade has seen a tremendous advance in DNA-based technologies that offer exciting challenges and opportunities to the field of toxicology. The growing area of "toxicogenomics"—the application of new molecular technologies to understand how chemicals cause adverse responses in cells, tissues, and organisms—will eventually play an important role in toxic tort litigation. Rather than examining the effect of a chemical on one or a few biochemical pathways, the tools of toxicogenomics provide a means to examine the global response of a cell to a chemical stimulus, resulting potentially in a "fingerprint" alteration in expression of thousands of different genes (transcriptomics), proteins (proteomics), or cellular metabolites (metabonomics). The potential exists for such tools to provide convincing proof that a particular disease was related to a specific chemical exposure, through unique changes that potentially can be measured years after the exposure occurred. As noted by Marchant, however, "many obstacles and uncertainties remain to be resolved before toxicogenomics data should be used outside the research context for practical, regulatory or legal applications."[50] Until such time as

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[50] *See* Marchant, *supra* note 6; *see also* John C. Childs, *Toxicogenomics:*

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these new scientific approaches to linking specific diseases or illnesses to specific exposures can be proven reliable, judges, lawyers, and jurors must rely upon the basic scientific principles of toxicology and epidemiology to establish causation in toxic torts.

New Chapter in Causation and Exposure in Toxic Tort Litigation, 69 DEF. COUNCIL J. 441, 441-46 (2002).

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