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Joseph V. Rodricks

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EVALUATING DISEASE CAUSATION IN HUMANS EXPOSED TO TOXIC SUBSTANCES

Joseph V. Rodricks, Ph.D., D.A.B.T. [*]

INTRODUCTION

Individuals claiming they have been harmed by exposures to chemical substances may seek compensation by bringing lawsuits against those whose actions caused the exposures to occur. Exposures may involve specific products, such as pharmaceuticals, foods and many other consumer products, or industrial chemicals used by workers in commercial operations of many types, or chemicals emitted to the environment during their manufacture, distribution, use, or disposal. Under our judicial system, those making claims of harm, i.e. plaintiffs, are generally required to offer evidence, through experts in medicine, epidemiology, toxicology, and perhaps several other scientific disciplines, that a causal relationship exists between the exposures they have allegedly experienced and the specific type of medical injury or disease they claim to have incurred. Defendants in such cases will also seek out experts to evaluate and, if possible, counter the evaluations of experts engaged by plaintiffs. Plaintiffs are generally not faced with the scientifically impossible burden of demonstrating causality with absolute proof; rather, the legal standard is typically expressed as a need to demonstrate that causality is demonstrable with a reasonable degree of scientific certainty, or that it is more likely true than not true that the harm

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[*] Joseph V. Rodricks is a Founding Principal in the Arlington, Virginia office of ENVIRON International Corporation. A version of this paper was presented at Brooklyn Law School, Science for Judges seminar on April 1, 2005.

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was caused by the exposure at issue.[1]

This paper is devoted to certain aspects of the problem of evaluating disease causality in individuals when the putative cause is a chemical substance. Not all of the elements of a causality analysis will be discussed, must notably those concerning medical diagnosis of a plaintiff's condition and the often complex and multifaceted problem of evaluating the nature, timing and magnitude of the plaintiff's exposure to the chemical(s) of interest. Exposure analysis, which is a critical component of the evaluation of causation, may be relatively straightforward in the case of certain products, but may become exceedingly complex if it involves reconstructing exposures arising from contaminated environments, especially when there is evidence that the exposures have been ongoing for long periods of time. Experts in exposure evaluation come from many disciplines—chemistry, chemical and environmental engineering, modeling of the movement of chemicals through air or water or into the food supply, and industrial hygiene—and even a partial discussion of the nature of their work would significantly distract from the principal concerns of this paper. For this presentation it is assumed that accurate medical diagnoses can be achieved, and that reasonably accurate estimates of plaintiff's exposures can be derived.

The subjects of this paper pertain to the types of scientific evidence that are useful for a determination of *general causation* and *specific causation*, and of methods appropriate to evaluate that evidence. The question of general causation is directed at an evaluation of evidence that the chemical(s) at issue has been established, through appropriate scientific studies, *to cause the type of injury or disease* the plaintiff has developed. In the absence of convincing evidence of general causation, it would not be possible for a plaintiff, on the basis of the best available scientific knowledge, to make a reasonably convincing case that his or her specific disease was caused by exposure to the chemical at issue. If, on the other hand, a reasonably convincing case could be made

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[1] FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 383, 547 n. 278, 547-48 n. 280, 548 n. 282 (2d ed. 2000) *available at* http://www.fjc.gov/public/pdf.nsf/lookup/sciman00.pdf/$file/sciman00.pdf.

that general causation has been established, the scientific evaluation can move to the question of plaintiff-specific causation: did the plaintiff incur sufficient exposure to the chemical at issue to allow the conclusion that the plaintiff's specific medical condition was more likely than not caused by that exposure?[2] For example, an individual who was diagnosed with acute myelogeneous leukemia and had experienced exposure to benzene would have a compelling case for general causation. But if that individual's exposure were very low, it may not be possible for an expert to show convincingly that specific causation can be established. Benzene is not the only cause of this type of leukemia and a demonstration that some undefined level of benzene exposure had occurred is a far from adequate basis for establishing specific causation.[3]

Even if general and specific causation have been established, there may remain other factors in the plaintiff's life that are even likelier explanations for his or her condition; the subject of "alternative causation" is also outside the scope of this paper, but will be briefly discussed in a later section. General and specific causation are thus the topics to be covered.

This paper shall begin in Part I with some general background on chemical toxicity and the scientific methods used to identify the toxic properties of specific chemicals. The use of toxicological information by public health and regulatory authorities for purposes of public health protection merits discussion because there are certain parallels between the types of questions these authorities pursue and those arising in a tort setting. In this regard, the question of the utility of experimental data on toxicity, typically derived from studies in laboratory animals, requires close

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[2] In some cases, a plaintiff may have been a member of a specific population exposed to the chemical at issue and the subject of some type of direct epidemiology study. Evaluating the likelihood that such a study could provide evidence of both general and specific causation in the plaintiff requires methods that are not discussed in this paper. This paper focuses on the far more typical situation in which such studies have not been conducted.

[3] In fact, because of its presence in gasoline, human exposure to some level of benzene is virtually ubiquitous.

scrutiny. Part II addresses how public health and regulatory scientists evaluate the potentially adverse health consequences of chemical exposures within a framework called *risk assessment*. That same framework is useful for evaluating disease causation in individuals, but we shall see that some of the types of scientific evidence used commonly in the regulatory context may not be appropriate for evaluating causation in individuals. Following that discussion, in Part III, the evaluative methods used to understand general and specific causation are outlined. This paper concludes in Part IV with a discussion of the attendant limitations of general and specific causation.

I. CHEMICAL TOXICITY AND SCIENTIFIC METHODS USED TO IDENTIFY TOXIC PROPERTIES OF SPECIFIC CHEMICALS

Scientists undertaking toxicological risk assessments in the regulatory setting commonly disagree on the interpretation of specific study results, but they nevertheless work within a common understanding of the types of scientific evidence appropriate for such assessments. This common understanding has resulted from half a century of scientific dialogue, much of it guided by many expert reports on this topic issued by various arms of The National Academies since the early 1980's.[4] No such history of scientific discourse has informed the risk assessment process as it relates to disease causation in individuals, and it is difficult to discern anything remotely like a scientific consensus on how different types of scientific evidence should be used in such assessments. What is presented here might represent the thinking of most

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[4] The National Academies has issued hundreds of reports on specific issues of chemical toxicity. For a recent example, see NAT'L RESEARCH COUNCIL, HEALTH IMPLICATIONS OF PERCHLORATE INGESTION (2005), *available at* http://www.nap.edu/books/030904894X/html/. For a broad view of approaches to risk assessment, see COMM'N OF LIFE SCI., NAT'L RESEARCH COUNCIL, SCI. AND JUDGMENT IN RISK ASSESSMENT (1994) [hereinafter SCIENCE AND JUDGMENT], *available at* http://www.nap.edu/books/030904894X/html/; COMM'N OF LIFE SCI., NAT'L RESEARCH COUNCIL, THE NAT'L RES. COUNCIL'S COMMITTEE ON TOXICOLOGY: THE FIRST 50 YEARS (1997), *available at* http://www.nap.edu/books/ 030904894X/html/.

scientists, but no scientist writing on this topic would claim that it represents a consensus, or that there are no alternative approaches that might have utility. If an appropriate government sponsor could be found, the subject of scientific evidence and disease causation in individuals could surely benefit from a study by The National Academies.

A. Chemical Toxicity

All chemical substances, whether of natural or synthetic origin, can cause toxicity—some type of harm to the structure or functioning of the body—under some conditions of exposure; thus, as a technical matter, all chemicals can be said to be toxic.[5] The types of adverse health effects and the conditions of exposure necessary to cause those effects vary widely among chemicals.[6] The conditions under which we are exposed to most of the millions of natural and synthetic chemicals that surround us are such that their toxic properties are never expressed, but we recognize perhaps hundreds of chemicals that do present some risk of toxicity and that we are exposed to many more chemicals that have yet to be investigated for their risk potential. Regulatory agencies, such as the Environmental Protection Agency, the Occupational Safety and Health Administration, and the Food and Drug Administration, develop, for various administrative purposes, lists of hazardous (toxic) substances.[7] Chemicals so listed are usually those with

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[5] *See* PRINCIPLES AND METHODS OF TOXICOLOGY (A. Wallace Hayes ed., 4th ed. 2001); JOHN TIMBRELL, INTRODUCTION TO TOXICOLOGY (3d ed. 2001). The standard might be CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS (Curtis Klaassen ed., 6th ed. 2001) [hereinafter CASARETT AND DOULL'S]. The general background provided in this section is also provided, in extended form, in JOSEPH RODRICKS, CALCULATED RISKS: UNDERSTANDING THE TOXICITY AND HUMAN HEALTH RISKS OF CHEMICALS IN OUR ENVIRONMENT (1992).

[6] Dose, duration, timing, route of entry into the body, etc. David L. Eaton & Curtis D. Klaassen, *Principles of Toxicology*, *in* CASARETT AND DOULL'S, *supra* note 5, at 11, 13-14, 17-26.

[7] Data on the toxic properties of most of the chemicals regulated by the EPA can be found at http://www.epa.gov/iris/subst/index.html. OSHA's listing

well-recognized toxic properties and to which large numbers of people are or could be exposed. It should be recognized that many substances not listed as hazardous may well pose health risks under some conditions and that not all listed substances will pose health risks under all conditions of exposure.[8] This topic will be developed more fully in the later section on risk assessment.

Toxicity expresses itself in many different ways. Some chemicals cause harm to the respiratory or nervous systems, while others can harm the liver or the kidneys. Some chemicals may cause harm to several different organs or systems of the body, although the conditions of exposure necessary to cause harm in different organs or systems often vary even for a specific chemical. Many chemicals, which we label carcinogens, can cause malignant tumors to appear in different cells of the body. There are chemicals that can adversely affect immune or endocrine functions, or that can interfere with reproductive processes. The developing embryo or fetus is a target for some chemicals. In recent years much attention is being devoted to the ways chemicals such as a lead and methyl mercury, found in fish, can put children at risk of impaired cognitive development or cause behavioral abnormalities. There is an immense body of scientific literature concerning the adverse effects of chemical exposures and the conditions under which they occur, and it is now growing at a relatively rapid pace.[9] Moreover,

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of regulated workplace chemicals can be found at http://www.osha-slc.gov/SLTC/pel/index.html. The FDA has several centers that regulate different categories of chemicals. *See* U.S. FOOD AND DRUG ADMIN., NAT'L CTR. FOR TOXICOLOGY RESEARCH Home Page, http://www.fda.gov/nctr/index.html. A comprehensive, integrated database on chemical toxicity can be found at http://risk.lsd.ornl.gov/tox/tox_values.shtml. The Agency for Toxic Substances and Disease Registry (ATSDR) provides comprehensive toxicity reviews on many important chemicals. *See* ATSDR, TOXICOLOGICAL PROFILE INFO. SHEET, http://www.atsdr.cdc.gov/toxpro2.html.

[8] *See* Eaton & Klaassen, *supra* note 6, at 13-16. *See also* SCIENCE AND JUDGMENT, *supra* note 4, at 25-42.

[9] The National Toxicology Program is a multi-agency activity of the Department of Health and Human Services and is both an important toxicology and epidemiology research center and a source of information on the many growing areas of research and testing of chemicals. *See generally* NATIONAL

many basic scientists have turned their attention to the difficult scientific tasks of understanding the fine details of the chemical and biological processes that take place after a chemical enters the body and to the point at which its toxicity becomes detectable; much progress is being made in understanding "toxic mechanisms."[10]

Although we are exposed to many thousands of chemicals, including a large share of natural origin, present mostly as the non-nutritive constituents of food, it appears that we are not harmed by most of these exposures.[11] The absence of harm is probably attributable to the fact that chemical toxicity does not express itself under all conditions. Toxic responses are a function of the magnitude of the dose[12] and it is established with high certainty that toxic responses do not appear until a so-called threshold dose is exceeded;[13] they increase in incidence, severity, or both, as the dose increases above the threshold, but we are protected from harm

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TOXICOLOGY PROGRAM, http://ntp-server.niehs.nih.gov.

[10] *See generally* Harvey Clewell, *Use of Mode of Action in Risk Assessment: Past, Present, and Future*, 42 REG. TOXICOLOGY AND PHARMACOLOGY 3-14 (2005).

[11] "Appears" is used here because it is extraordinarily difficult to acquire knowledge about such potential risks. There is no way to document this assertion because there has been no systematic study of most of the many thousands of natural and synthetic chemicals to which all of us are exposed daily, over our full lifetimes. But most human disease is attributable to the major life-style factors—smoking, nutritional practices, alcohol abuse, infectious diseases, lack of exercise—so it seems reasonable to conclude that we are able to tolerate most chemical exposures without adverse consequence. *See generally* WORLD HEALTH ORG., THE WORLD HEALTH REPORT: REDUCING RISKS, PROMOTING HEALTHY LIFE 82 (2002) (summarizing the major sources of human morbidity and mortality).

[12] *See* Eaton & Klaassen, *supra* note 6, at 17-24 (explaining that dose refers to the amount of chemical taken that actually enters the body usually per unit of time as a result of exposure).

[13] *Id.* at 19. *See also* INT'L PROGRAMME ON CHEM. SAFETY, PRINCIPLES FOR THE ASSESSMENT OF RISKS TO HUMAN HEALTH FROM EXPOSURE TO CHEMICALS, ENVTL. HEALTH CRITERIA 210, at 4.3.1, *available at* http://www.inchem.org/documents/ehc/ehc/ehc210.htm [hereinafter INT'L PROGRAMME].

if the threshold dose is not exceeded. This "threshold hypothesis" is well-documented, although it is not possible to claim the hypothesis holds for every chemical or type of toxicity. In fact, as shall be seen below, there is evidence it may be incorrect for certain types of carcinogens.[14] The issues of thresholds and dose-response relationships are critical in the evaluation of specific causation.[15]

B. Identifying Toxic Properties

It is, of course, unethical to test chemicals for toxicity in humans. Pharmaceutical substances are delivered to human subjects in controlled clinical trials, but only after there is sufficient experimental animal data to provide high assurance that the toxic properties associated with every drug will not be expressed at the doses used in a trial. Adverse side effects may occur during a trial, occasionally with a frequency or severity that may require the trial to be halted. Clinical trials are conducted under a set of internationally recognized ethical codes, which recognize the important health benefits drugs confer.[16] Such controlled trials are clearly not appropriate for studying toxicity.

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[14] *Compare* Steve E. Hrudey & Daniel Krewski, *Is There a Safe Level of Exposure to a Carcinogen?*, 29 ENVTL. SCI. & TECH. 370A (1995) (summarizing the evidence on both sides of the "no-threshold" debate on carcinogens), *with* Samuel M. Cohen, *Human Carcinogenic Risk Evaluation: An Alternative Approach to the Two-Year Rodent Bioassay*, 80 TOXICOLOGICAL SCI. 225 (2004) (providing several examples of threshold mechanisms for carcinogens). *See also* Elaine M. Faustman & Gilbert S. Omenn, *Risk Assessment*, *in* CASARETT AND DOULL'S, *supra* note 5, at 83, 92-99.

[15] *See* sources cited s*upra* note 5 (explaining that exposure refers to the contact between an individual and the environmental medium in which a chemical is present; dose refers to the amount of chemical that actually enters the body usually per unit of time as a result of exposure; dose-response refers to the quantitative relationship between dose and toxic response). *See also* INT'L PROGRAMME, *supra* note 13, at 4.1 and 5.2 (respectively explaining dose-response, exposure and dose).

[16] WORLD MED. ASS'N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MED. RESEARCH INVOLVING HUMAN SUBJECTS (1964) (amended 2004), *available at* http://www.wma.net/e/policy/pdf/17c.pdf.

Much can be learned about chemical toxicity by careful observation of groups of individuals who experience common exposures, usually incident to their occupations.[17] Other discrete, non-occupational cohorts may also be subject to such observational studies.

Epidemiologists have developed several investigative methods to conduct such studies and can design them in ways to build-in some type of control group; however, none of these epidemiological studies (cohort, case-control) are ever "controlled" in the same way a laboratory experiment or clinical trial is controlled.[18] Only in well-controlled experiments can cause-effect relationships be established with reliability. Individual epidemiology studies are at best designed to identify whether a *statistical association* exists between a chemical exposure and a specific disease or toxic injury outcome – that is, to determine whether one event, such as chemical exposure to a chemical, occurs together with a second event, such as a specific disease or toxic injury, more frequently than would be expected without such

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[17] These types of exposures are typically greater than those occurring in the general population. Petroleum refinery workers are exposed to benzene in the range of 0.5 to 1 ppm. The general population averages about 0.01 ppm. This type of difference is typical for hundreds of industrial chemicals. There are many reasons for these differences, but the major one is occupational situations involving direct contact with and handling of chemicals. Emissions of these same chemicals to the environment (air, water, food) results in significant dilution. Alon Rosenthal, George M. Gray & John D. Graham, *Legislating Acceptable Cancer Risk from Exposure to Toxic Chemicals*, 19 ECOL. L.Q. 269, 280 (1992) (discussing the need to extrapolate from high dose occupational exposures to low levels of environmental exposure).

[18] Clinical trials are inherently not as well-controlled as experiments involving animals, where environments, diet, and genetic characteristics in test and control groups are virtually identical except for the presence of the chemical under test. Brian L. Strom, *Study Designs Available for Pharmacoepidemiology Studies*, *in* PHARMACOEPIDEMIOLOGY 17, 17-29 (Brian L. Strom ed., 3d ed. 2000). *See also* LEON GORDIS, EPIDEMIOLOGY chs. 7, 12 (2d ed. 2000) (on randomized trials and comparing cohort and case-controlled studies); Nelson H. Wilson et al., *Short-Term, Subchronic, and Chronic Toxicology Studies*, *in* PRINCIPLES AND METHODS OF TOXICOLOGY, *supra* note 5, at 917, 932, 936-38 (discussing well-controlled animal studies).

chemical exposure. Other factors that may bias or confound any observed association also need to be identified and, if possible, eliminated as alternative explanations for the association.[19]

Although epidemiological studies are highly relevant to identifying the toxic properties of chemicals that are of concern for our species, no single study is sufficient to establish causation. Epidemiologists await a body of evidence from several studies, ideally involving different study methods, investigators, and population groups. Consistency among study outcomes and clear evidence that risk increases with increasing exposure (dose), strong statistical associations, and supporting experimental data, are considered the necessary hallmarks of true causality; nonetheless, causality can never be determined with complete certainty.[20] Expert groups, such as those convened by bodies such as the International Agency for Research on Cancer (IARC), a unit of the World Health Organization, or the federal National Toxicology Program, periodically review evidence and typically assign weights to it.[21] The IARC, for example, describes the

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[19] Michael D. Green et al., *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, *supra* note 1, at 333.

[20] GORDIS, *supra* note 18, at 184-218 (providing a thorough discussion of approaches to evaluating causality). *See also* sources cited *infra* note 21 (referencing reports on causality of carcinogens from the International Agency for Research on Cancer, Environmental Protection Agency, and U.S. Department of Health and Human Services).

[21] The International Agency for Research on Cancer (IARC), a division of the World Health Organization (WHO), issues expert reports on causes of cancer. Reports on occupational and other sources of carcinogens each contain descriptions of how epidemiological and experimental evidence is evaluated in each instance to reach conclusions regarding causation. *See* IARC, http://www.iarc.fr (last visited Oct. 27, 2005). *See also* RISK ASSESSMENT FORUM, ENVTL. PROTECTION AGENCY, GUIDELINES FOR CARCINOGEN RISK ASSESSMENT (1999) [hereinafter RISK ASSESSMENT FORUM], *available at* http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=439797 (providing EPA's framework for assessing possible cancer risks); U.S. DEP'T OF HEALTH & HUMAN SERV., NAT'L TOXICOLOGY PROGRAM, REPORT ON CARCINOGENS (11th ed. 2005), *available at* http://ntp-server.niehs.nih.gov/ index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709 CB4C932 (discussing agents, substances, mixtures, and exposure circumstances that may pose a

evidence on specific substances, or sometimes mixtures of chemicals or even certain occupational settings in which the specific causative chemical(s) has not been identified, as sufficient when causal criteria are judged to have been met by the agency's expert panels.[22] The IARC's expert panels also describe evidence on other substances as sufficient to establish an association but insufficient to establish causation, or as only insufficient.[23] At the present time, the IARC lists 95 substances, mixtures, or occupations as causally related to cancer, based on epidemiological data.[24] It can be said that any substance so listed qualifies as a

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hazard to human health by virtue of their carcinogenicity).

[22] *See, e.g.*, 77 IARC, WHO, MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: SOME INDUSTRIAL CHEMICALS (2000) [hereinafter SOME INDUSTRIAL CHEMICALS], *available at* http:www-cie.iarc.fr/htdocs/indexes/vol77index.html (describing studies of sixteen specific chemicals where there was insufficient evidence to establish causation in humans). *But see* 62 IARC, WHO, MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: WOOD DUST FORMALDEHYDE 35 (1998), *available at* http://www-cie.iarc.fr/htdocs/monographs/vol62/wood.html (finding sufficient evidence of cancer causation in humans in case of wood dust, based on a large body of case-control and cohort studies).

[23] IARC, WHO, MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: PREAMBLE (1999), *available at* http://www-cie.iarc.fr/monoeval/eval.html (listing categories used to classify the degree of evidence related to carcinogenicity in specific organs or tissues). Evidence regarding specific substances may fall into these categories if some, but not all, of the criteria described in the opening sentences of this paragraph are met. Expert committees provide descriptions of the available evidence and why it may fail to meet criteria for causation. *See also* SOME INDUSTRIAL CHEMICALS, *supra* note 22 (listing IARC descriptions of the evidence for any of the 16 chemicals evaluated and reasons why causation criteria were not met).

[24] In all, IARC expert panels have evaluated 900 individual substances, chemical mixtures, and occupational exposure situations. IARC, WHO, LISTS OF IARC EVALUATIONS (2004), *available at* http://www-cie.iarc.fr/monoeval/grlist.html. The evidence that each substance, mixture, and occupational exposure causes cancer is rated on a scale of 1-4; 1 is for agents that definitely cause cancer and 2A is for those that probably cause cancer. *Id*. Categories 1 and 2A may be sufficient to establish general causation as a matter of law. *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, *supra* note 1 & accompanying text. Roughly 20 percent of evaluated substances, mixtures, and occupational exposures fall into category 1 or 2A. IARC, WHO, OVERALL EVALUATIONS OF

general cause of the specific type(s) of cancer for which it is listed, although experts can be found who will have reasons to question the IARC's listings. In any event, there is no stronger evidence for general causation of chemical toxicity than that obtained from a body of epidemiological evidence meeting causation criteria.[25] Exceptions to this rule may apply in the case of pharmaceutical or other medical products, because controlled clinical trials are more readily useful for establishing causation (or its absence) than are epidemiological studies.[26]

Epidemiological studies cannot be conducted until after chemical products are introduced into commerce and for some diseases, such as cancers with latency periods of many years or decades, much time must pass before results can be collected and evaluated. For these and other reasons, toxicologists have developed and continue to improve various methods for collecting toxicity data in laboratory animals. Toxicology studies in animals began to be used in the 1930's and for a time focused on relatively

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CARCINOGENICITY TO HUMANS (2004), http://www-cie.iarc.fr/monoeval/crthall.html.

[25] Differential diagnoses are frequently used by examining physicians to identify the cause of a medical condition in individual patients. In most cases, the physician relies upon *established* knowledge regarding the various causes of specific conditions. In some cases, a physician may think he or she has identified a *new* (previously unreported) cause for a disease or injury and may seek publication in medical journals of the findings. Such "case reports," especially if a series of similar reports appears over time, can be of high value in generating hypotheses about causal relations. Such hypotheses can then be studied epidemiologically, but establishing causal relationships based only on such reports is highly problematic because in the absence of controls, it is nearly impossible to determine whether the condition would also have occurred in the individual patient in the absence of exposure to the suspect chemical. *See* GORDIS, *supra* note 18 (describing why such case reports are of highly limited utility in establishing causation); Judith K. Jones, *Determining Causation from Case Reports*, *in* PHARMACOEPIDEMIOLOGY, *supra* note 18, at 525-38 (discussing the limitations and the potential value of such reports). *See also* STROM, *supra* note 18, at 22.

[26] *See* STROM, *supra* note 18, at 26-27 ("Randomized clinical trials are 'the gold standard' by which other designs must be judged.").

intense exposures of limited duration.[27] Nowadays, studies typically involve several species, extend over the animals' lifetimes, and involve an examination of reproductive and developmental effects. Every manifestation of a chemical's toxicity can be uncovered using animals through detailed tissue pathology (this is not even remotely possible in human studies). As noted earlier, because such studies are strictly controlled, they can be used to identify cause-effect relationships with greater reliability.

C. Utility of Animal Data

Rats, mice, dogs, and pigs are commonly used in toxicology experiments and, although there is extensive work underway to identify test systems that will not require the use of whole animals, it is likely such experiments will continue to be carried out, because of the intense interest in the United States and in the European Union (the EU) to acquire more complete toxicology data on ever greater numbers of chemicals.[28] The primary uses of such data are to identify the toxic properties of chemicals, the threshold doses for toxicity, and, through the use of a method termed 'risk assessment,' exposure levels (doses) that will not pose toxic risks to human populations.

While regulatory agencies prefer to use epidemiological evidence to identify protective levels for human populations, they will not hesitate to use animal toxicology data when human data are limited or altogether lacking.[29] There is substantial scientific

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[27] Joseph F. Borzelleca, *The Art, the Science, and the Seduction of Toxicology: An Evolutionary Development*, *in* PRINCIPLES AND METHODS OF TOXICOLOGY, *supra* note 5, at 1-22.

[28] The regulators of the European Union (the EU) are in the process of developing a Registration, Evaluation, and Assessment of Chemicals program (REACH). At present, it targets thousands of chemicals for testing. Whether this ambitious goal is retained in the program's final form is unknown. *See generally* REACH, *at* http://europa.eu.int/comm/environment/chemicals/reach.htm.

[29] *See* ENVTL. PROTECTION AGENCY [hereinafter EPA], INTEGRATED RISK INFORMATION SYSTEM [hereinafter IRIS], *available at* http://www.epa.gov/

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basis for this regulatory policy.[30]

First, factors that influence toxicity are generally similar across mammalian species, as are cells, cellular components, and extracellular environments.[31] Thus, biological factors that influence a chemical's behavior in the body and its interaction with the specific sites where it causes damage are generally similar across all mammalian species. These basic biological similarities suggest that chemicals that produce specific forms of toxicity in animals will also do so in humans, given a sufficient dose; however, similar does not equate to identical.[32]

While there appears to be a concordance between the types of toxic responses seen in animals and that observed in humans for those cases in which both human and animal data are available, often for unexplained reasons the specific manifestations of toxicity (e.g., type of cancer) differ across species.[33] Thus, while

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iris/subst/index.html. The EPA has evaluated the toxic properties of hundreds of chemicals and derived toxicity risk factors based on either human or animal evidence. Animal evidence is the primary source for these risk factors, because human evidence is either lacking or is inadequate. Good examples of chemicals listed in the IRIS database that are regulated based on animal data are acrylamide, acrylonitrile, and carbon disulfide. *See* EPA, OFFICE OF THE SCI. ADVISOR, RISK ASSESSMENT PRINCIPLES & PRACTICES 76-77 (2004) [hereinafter EPA, RISK ASSESSMENT PRINCIPLES & PRACTICES], *available at* http://www.epa.gov/osainter/pdfs/ratf-final.pdf (providing examples of four substances for which some human data on toxicity were available but were not used for IRIS toxicity evaluations. In each case, the agency used animal data to derive toxicity factors).

[30] The clearest exposition of the basis for this regulatory policy can be found in a volume published by a committee of the National Research Council. *See generally*, COMM. ON THE INSTITUTIONAL MEANS FOR ASSESSMENT OF RISKS TO PUB. HEALTH, NAT'L RESEARCH COUNCIL, RISK ASSESSMENT IN THE FED. GOV'T: MANAGING THE PROCESS (1983) [hereinafter RISK ASSESSMENT IN THE FEDERAL GOVERNMENT] (establishing the risk assessment framework that is used by regulatory and public health institutions throughout the world).

[31] *I.e.*, Anatomy, physiology, and biochemical processes. *See* RISK ASSESSMENT PRINCIPLES & PRACTICES, *supra* note 29, at § 4.

[32] *See* RISK ASSESSMENT IN THE FEDERAL GOVERNMENT, *supra* note 30.

[33] Harry Olson et al., *Concordance of the Toxicity of Pharmaceuticals in Humans and Animals*, 32 REGULATORY TOXICOLOGY AND PHARMACOLOGY, 56, 56-67 (2000) (discussing a careful study on this issue and also providing

regulators may be on solid ground to conclude that an animal carcinogen may be a human carcinogen, they would be on much shakier ground if they were to conclude that the specific type of cancer (or other toxicity) that occurs in animals is also likely to occur in sufficiently exposed humans.[34]

For regulatory purposes—that is, for purposes of developing standards to limit exposures to ensure protection of human populations—it is not essential to know which specific type of cancer or other disease is caused by a chemical. For public health protection, that particular type of scientific uncertainty is not important, or so the regulators have traditionally held.[35]

Another factor limiting the use of animal data for drawing strong inferences about humans concerns the doses necessary to cause adverse effects. Here, animal-human differences seem to be significant, and the magnitudes of those differences are generally unpredictable. For example, even if a chemical established as causing liver injury in rodents is assumed to be a liver toxicant in humans, identifying the human dose necessary to cause that toxicity is not possible without imposing incompletely tested assumptions.

Thus, while animal data are routinely used for public health protection, they are of limited utility for establishing general causation in humans. They may be used to buttress findings from human studies, but when no human data are available, it would seem to stretch scientific understanding beyond its limits to conclude that specific health effects found in animals will with a reasonable degree of scientific certainty be expected to occur in

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examples). *See also* RODRICKS, *supra* note 5, at 137 tbl. 7 (citing animal-human differences in cancer-types related to the same chemical).

[34] *See* 2 INSTITUTE OF MEDICINE OF THE NAT'L ACADEMIES, BOARD ON HEALTH PROMOTION & DISEASE PREVENTION, GULF WAR AND HEALTH: INSECTICIDES AND SOLVENTS 98-349 (2003) (providing an extended discussion on this issue and evaluating the general disease causation for chemical substances to which U.S. military personnel may have been exposed during the Gulf War).

[35] *See* RISK ASSESSMENT FORUM, *supra* note 21. The EPA recognizes that animal cancer data may not predict specific cancer types in humans, but frequently uses such data for human cancer risk assessment. *Id*. § 2.2.2.1.

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sufficiently exposed humans; and identifying sufficient exposure from the animal data is even more problematic.[36]

II. REGULATORY RISK ASSESSMENTS

"Risk assessment" is a framework within which data regarding the adverse health effects caused by chemicals derived from epidemiological and experimental studies, and information regarding the conditions under which human populations are or could be exposed to those chemicals, are integrated to yield a description, usually quantitative in nature, of the likelihood that those adverse effects will occur in the exposed populations.[37] That likelihood of adverse effects occurring in the exposed populations is called a risk.[38] Risk assessment serves to bridge the gap between research and the needs of so-called risk managers; the latter are typically regulatory and public health decision-makers. Research findings and other forms of data arise from diverse sources, have varying degrees of utility and quality, and are not infrequently contradictory; risk assessors have the difficult task of making sense of such data and using the results to present risk managers with as coherent a description of risk as the underlying science allows.

Risk assessments are typically directed at an existing exposure situation, such as the risks incurred by populations residing in the vicinity of a manufacturing or hazardous waste facility, or at the exposure situation expected if certain regulatory actions are taken.[39] Those actions are usually taken if the existing risks are judged excessive; risk assessors' goal is to reduce risks to acceptably low levels, the technical definition of safe levels.[40]

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[36] *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, *supra* note 1.

[37] *See* RISK ASSESSMENT IN THE FEDERAL GOVERNMENT, *supra* note 30, at 18.

[38] *Id.*

[39] EPA, RISK ASSESSMENT PRINCIPLES & PRACTICE, *supra* note 29, at 99-112 (providing a thorough description of how the agency approaches all the human exposure circumstances associated with a typical (and complex) hazardous waste site, as the focus of its risk assessment process).

[40] "Safe" is often taken to mean the complete absence of a risk. As a

Often, risk assessors evaluate the epidemiology, toxicology, and dose-response information for purposes of establishing a safe exposure level for a specific chemical.[41] Those safe levels are then used to establish standards for the chemical that apply to specific environmental media—allowable limits on the concentrations of the chemical in water, air, food, or soil, or in workplace environments. Measured concentrations of chemicals in these media can be compared with the standards to determine whether a risk exists.

The foundations for current approaches to risk assessment were set forth in a study produced in 1983 by the National Academy of Sciences.[42] The study authors noted that, given the current state of scientific understanding, which has improved in the past 20 years but has not overcome the basic problems in risk assessment, and also given the compelling need to conduct risk assessments for public health protection, regulators would be required to invoke certain assumptions in the conduct of risk assessments.[43] These assumptions address the limits of our knowledge and may not have firm scientific support, but risk assessments cannot be completed without them.

In the context of regulatory risk assessment three such issues stand out: 1) the need to extrapolate from epidemiological and

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technical matter such situations—which require proof of a negative condition—cannot be demonstrated to exist. Completely safe conditions may actually exist, but there is no scientifically rigorous method for identifying them. RODRICKS, *supra* note 5, at 204-11 (providing a discussion of the relationship between safety and risk). The toxicity risk factors ("Reference Doses") derived and presented by the EPA in its IRIS database are used as maximum "safe" exposure levels for chemicals. *See* IRIS, *supra* note 29. The Reference Dose is, however, not characterized by the agency as safe, but rather as a dose at which the probability of an adverse toxic response is negligibly small. *See* Barbara D. Beck et al., *The Use of Toxicology in the Regulatory Process*, *in* PRINCIPLES AND METHODS OF TOXICOLOGY, *supra* note 5, at 23, 47.

[41] Beck et al., *supra* note 40, at 23. The entire chapter is devoted to the methods used to establish the safe (negligible risk) doses set forth in EPA's IRIS database. Nearly identical methods are used by other agencies. *See also* sources cited *supra* note 13.

[42] RISK ASSESSMENT IN THE FEDERAL GOVERNMENT, *supra* note 30.

[43] *Id.* at 51-85. *See also id*. at 7 (Recommendation B).

experimental results obtained at doses substantially greater than those incurred by populations that are the typical subjects of risk assessments; 2) the need to extrapolate from experimental results to human beings; and 3) the need to deal with the known potential for variability in response to chemical exposures among a large, diverse human population. Scientific knowledge in these areas is limited. Other such limitations exist regarding the nature and extent of human exposures. Regulators have responded to the National Academy of Sciences study by describing the usual default assumptions to be used, while noting that in specific cases scientific knowledge may exist to permit departures from those assumptions.[44] Risk assessment is, thus, not a scientific activity in the usual sense; moreover, in many cases, testing the results of a risk assessment by additional epidemiological investigations is beyond current scientific capabilities.[45] In the absence of any attempt to assess risks, it is not possible to have an understanding of whether public health is adequately protected, or whether new products can be safely introduced into commerce.

The approach to chemical risk assessment used by regulatory authorities is designed to evaluate risks to what might be called "generic" individuals.[46] It is recognized that responses to chemical

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[44] *See* RISK ASSESSMENT FORUM, *supra* note 21.

[45] Regulatory and public health policies attempt to ensure that risks are controlled at levels substantially below those that can be identified using the best available epidemiology tools. Arhtur C. Upton, *Perspectives on Individual and Community Risks*, *in* ENVIRONMENTAL TOXICANTS 905-11 (Morton Lippman ed., 2nd ed. 2000). Public health policies are limited to detecting relatively large risks. Some scientists argue that precious resources are wasted in regulating "non-detectable risks" (i.e., those that are estimated using the regulatory risk assessment approach), but regulatory and public health officials have generally interpreted our laws as requiring the cautious approach to public health protection. *See* Gary Taubes & Charles Mann, *Epidemiology Faces its Limits*, 269 SCIENCE 164, 164-69 (1995).

[46] By use of the term generic, I mean hypothetical individuals within populations that are the subjects of risk assessments that are *assumed* to be equally sensitive to the hazardous effects of a chemical. "Generic" is my short-hand. *See* SCIENCE AND JUDGMENT, *supra* note 4, ch. 10 (discussing the issue of variability at length). Inspection of the process used by EPA (IRIS data base) reveals how the risk assessment process is designed to focus on the high-risk

exposures are variable within populations, and regulators target those generic individuals who are at the high end of sensitivity. If standards are developed to protect those individuals, then all others in the population, who are less sensitive, can be assumed to be protected. Moreover, regulators estimate population exposures by making assumptions that target those similarly generic individuals at the high end of the range of population exposures.[47]

It is not possible to determine, except in unusual circumstances, which actual individuals in a population are at the high end of sensitivity and also at the high end of exposure. In this sense it can be said that regulatory risk assessments apply to generic, as opposed to actual individuals. This fact alone limits significantly the applicability of regulatory risk assessments and the various standards derived from them to the evaluation of general and specific causation in actual individuals. Further, for at least those regulatory risk assessments and standards that are based primarily on experimental animal data, the relevance to individual causation analysis is highly dubious.[48]

A final point regarding regulatory risk assessments is that the so-called safe levels are derived from the epidemiological or experimental toxicity data by the use of assumptions[49] that have the effect of placing those levels at a very small fraction of the observed threshold levels.[50] The reasons for this effect are

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(most sensitive) responders in the population. *See* IRIS, *supra* note 29.

[47] *See* SCIENCE AND JUDGMENT, *supra* note 4, 43-55 (in particular, note the section entitled Maximally Exposed Individual at 46).

[48] *See* discussion *supra* Part I.C.

[49] Sometimes expressed in the form of certain mathematical models. It is common, for example, to use what is called a linear, no-threshold model to estimate low dose cancer risks, based on data obtained at high doses. *See* Faustman & Omenn, *supra* note 14, at 75-88 (describing such a model); Beck et al., *supra* note 40.

[50] Regulators assume, in the absence of evidence to the contrary, that carcinogenic chemicals act through mechanisms that disobey the general "threshold" rule for toxicity. This does not translate to the sometimes expressed view that any level of carcinogen exposure can cause cancer. *See* sources cited *supra* note 14. *See also* Upton, *supra* note 45 (describing regulated risk levels). Instead, it means only that any exposures to carcinogens will increase cancer

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complex, and will not be described here, but they are related to general knowledge regarding the behavior of chemicals when they are present at toxic levels, and the lack of specific knowledge pertaining to the magnitude of human variability, animal-to-human and high-to-low dose extrapolation, and many other aspects of a risk assessment. Because of this and because the regulatory standards are designed to protect the generic, highest risk individuals, it is likely that actual individuals in a population exposed at levels less than those standards are not at risk. Exposures at levels in excess of regulatory standards will not necessarily lead to toxic injury or disease; knowledge that such exposures have occurred is, by itself, completely inadequate to establish disease causation in individuals. This is not an expression of lack of concern for situations in which regulatory standards are exceeded. It is rather a statement regarding the lack of utility of this kind of information for assessing injury causation in actual individuals.

III. GENERAL AND SPECIFIC CAUSATION IN ACTUAL INDIVIDUALS

There are models of evaluation, similar conceptually but not in actual execution to the regulatory risk assessment model, that are useful for evaluating general and specific causation in actual individuals. Assuming that a plaintiff has been properly diagnosed as having a specific disease or injury, and assuming that the legal standard for establishing causation is the more likely than not criterion, a court may proceed through the evaluation using the following lines of inquiry:

i. To what chemical was the plaintiff exposed?

ii. Is there sufficient evidence in the scientific literature to support a causal relationship between exposure to the

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risk and that the magnitude of the risk increases with increasing exposures. Regulators do not become concerned until lifetime (calculated) cancer risks reach probabilities of one-in-one million or greater. The no-threshold approach is not based on highly certain scientific knowledge, and there may be many exceptions to it. *See* RISK ASSESSMENT FORUM, *supra* note 21.

chemical and the specific type of injury or disease the plaintiff has incurred?

If the answer to (ii), the general causation question, is no (using the scientific criteria for judging general causation from epidemiological studies, described above), then the inquiry ends. If the answer is to (ii) is yes, then the inquiry continues. It might also continue if the answer were "strong associations established, if not causation, and supporting evidence from experimental studies," because additional evaluation might assist in dealing with such an ambiguity. Thus, the next inquiry:

> iii. What is the likelihood that someone having the plaintiff's characteristics (age, sex, race, smoking habits, alcohol consumption rates, etc.) would have the specific injury or disease in the absence of exposure to the suspect chemical?

Very few diseases or injuries have unique causes; most have multiple causes including, in our hypothetical case, the suspect chemical. Even if alternative causes are unknown, it may be understood that many individuals acquire the condition in the absence of exposure to the suspect chemical.[51] Health statistics may be available to help answer inquiry (iii) with a reliable degree of quantification, especially in the case of cancer. Plaintiff's condition may be vary rare, in which the likelihood of demonstrating specific causation (inquiry (iv), *infra*) increases; it becomes difficult to establish specific causation if the plaintiff's condition is a very common one. Thus, this next inquiry:

> iv. Did the plaintiff incur exposures to the suspect chemical of sufficient magnitude and duration to make it more likely true than not that the chemical, and not some other factor, was the cause of the plaintiff's medical condition?

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[51] Very few chemicals are known to be both necessary and sufficient causes of human disease. For example, although benzene is said by IARC to be a cause of certain types of human leukemias, it is by no means the only such cause and, in fact, most cases occur in the absence of benzene exposure. This same pattern exists for virtually all chemical carcinogens. *See* sources cited *supra* note 19 and *infra* note 54.

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In the absence of some measure of exposure conditions,[52] it is difficult, if not impossible, to establish specific causation. This conclusion stems from the fact that the risk of toxicity changes with dose and does not become even minimally significant until the threshold for toxicity is exceeded for sufficient periods of time.[53]

It is not scientifically possible to determine, for a specific individual, what the threshold value is; but examination of the dose-response data from the epidemiological studies used to demonstrate general causation should reveal the magnitude of exposure necessary to increase risk above background levels.[54] Some have addressed the more likely true than not criterion by identifying, from the dose-response data, the so-called risk doubling dose: the dose required to double the background risk.[55] Thus, for example, if the specific plaintiff's risk of developing his or her specific disease in the absence of exposure to the suspect chemical is one-in-one thousand, examination of the dose-response data from the epidemiological data can reveal the magnitude of the dose necessary to increase risk by a factor of one-in-one thousand. If the exposure experts can demonstrate that the plaintiff incurred

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[52] I.e., dose, duration, timing relative to injury, route of entry into the body, etc. *See* discussion *supra* Part I.A.

[53] *See supra* Part I.A. *See also* Philip S. Guzelian et al., *Evidence-Based Toxicology: A Comprehensive Framework for Causation*, 24 HUMAN AND EXPERIMENTAL TOXICOLOGY 161, 161-201 (2005). This paper contains an excellent (though complex) discussion of the general problem of causation, as well as specific guidance regarding toxicological questions.

[54] Dose-response relationships identified in epidemiology studies provide information regarding the extent of disease risk increase that is associated with a given increment in exposure. Epidemiologists collect information on exposures incurred by the populations under study and typically distinguish subpopulations having exposures of different magnitudes and duration. Evidence that disease risk increases as exposure increases is used as supportive of a causal relationship. *See* GORDIS, *supra* note 18. *See also* sources cited *supra* note 21.

[55] Phillip Cole, *Causality in Epidemiology, Health Policy, and Law*, 27 ENVTL. LAW REP. 10279 (1997). In the determination of general causation, epidemiologists often use the risk-doubling criterion as a rule-of-thumb in establishing reliable statistical associations. This use of the criterion is different from that described here for examining specific causation.

exposures leading to a dose of at least that magnitude, then it can be concluded that exposure to the suspect chemical increased plaintiff's disease risk to a level of at least two-in-one thousand (1/500). Thus, it may be concluded that, since the plaintiff actually has the disease, then the risk has been realized, and it is more likely that it was caused by the chemical than by whatever other factors cause the condition. This conclusion derives from the fact that, since the plaintiff's risk was greater than two-in-one thousand, and that factors other than the suspect chemical contributed less than half of the plaintiff's total risk (no more than one-in-one thousand), then there was a greater than 50% chance his or her condition was due to the chemical exposure and not other factors. If the exposure incurred by the plaintiff does not create a risk doubling dose, then under the criteria used here, it cannot be claimed specific causation has been demonstrated.[56]

This sketch of how the analysis of specific causation may proceed is meant to describe the type of analysis necessary—the scientific method to be used—and is not intended to describe a strict set of inflexible criteria (such as, for example, a strict risk-doubling standard). A degree of scientific judgment is necessarily involved, especially since the data required to conduct a careful, quantitative evaluation of the plaintiff's exposures and epidemiological dose-response relationships are almost never without uncertainty. Alternative approaches, including what epidemiologists call attributable risk analysis (similar conceptually to what has been described but somewhat different in form) may also be applied. Whatever is undertaken in the analysis of specific causation, it should be clear that the mere fact that the plaintiff can demonstrate some exposure to a substance for which general causation has been established is hardly sufficient, even if that exposure exceeds some applicable regulatory standard.

There is a role for additional analysis in certain cases, because it is possible that alternative and even more likely causes of a specific plaintiff's harm can still be found, even if criteria for specific causation seem to be satisfied. This enters the domain of

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[56] *Id.*

what is sometimes called differential medical diagnosis, which I leave to others, except to say such diagnoses, whether they are intended to demonstrate causation or its lack, are by themselves inadequate evaluative tools.[57]

IV. LIMITS IN PROVING CAUSATION

The framework outlined for evaluating general and specific causation consists of elements that parallel those contained in the risk assessment framework used by regulatory agencies. It consists of an examination of the toxic effects produced by a chemical, the conditions of exposure necessary to produce those effects, the relationships between dose and effect, and the conditions under which humans (populations or individuals) have been or may become exposed. Some important differences between the types of scientific evidence used to conduct risk assessments in the tort and regulatory or public health contexts also exist, and the results from regulatory risk assessments will, in most cases, be of highly limited utility in the examination of individual disease causation.

Although the general process described here for undertaking an evaluation of general and specific causation may have broad acceptance, it seems clear that nothing approaching the uniformity of scientific approaches that can be discerned in the regulatory context exists in connection with the evaluation of individual exposures and responses. The relative weights given to different types of scientific information may vary greatly among experts, and there appears to have been little substantive discussion of the problem of individual disease causation in the scientific, as against the legal, literature.[58]

One issue that transcends the scientific literature concerns the question of the potentially excessive burden placed upon plaintiffs if they are required to show with a reasonable degree of scientific rigor that their injuries or diseases have been caused by chemical exposures. Although legal standards would seem to call for such

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[57] *See* sources cited *supra* note 26.

[58] A recent publication by Philip Guzelian and associates perhaps signals a break in this trend. Guzelian, *supra* note 53, at 161-201.

rigor, the data requirements necessary to apply appropriate scientific methods can sometimes be substantial, difficult, and costly to develop. Establishing general causality for any chemical requires extensive scientific investigation. Plaintiffs can, of course, incorporate existing scientific knowledge regarding those chemicals for which general causal relations with certain injuries or diseases have been established, but they are still required to develop evidence to support specific causation. For substances for which general causal relations have not been substantiated, it is difficult to imagine circumstances in which plaintiffs could develop such evidence. This conclusion must, however, be qualified by noting that it is premised on the view that establishing general causation requires the types of evidence described in this paper; clearly scientists may disagree on this matter. It is also likely that, in considering the types and strengths of different sources of scientific evidence necessary to establish causation, scientists can be influenced by their own, non-scientific views of how burdens of proof should be distributed between plaintiffs and defendants.

A study of general and specific causation by The National Academies could be of high value. This institution, through reports of its expert committees, plays a leading role in the United States in developing scientific consensuses, and does so through processes that eliminate, to a high degree, the influence of individual biases. I suggest the scientific community would greatly benefit from the kind of guidance The National Academies provide, and the judicial system will in turn benefit from a clearer picture of the types of scientific evidence that are appropriate to bring before juries in matters such as those that are the subject of this paper.