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Epidemiological Uncertainty, Causation, and Drug Product Liability

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Article abstract

Epidemiological evidence is regularly presented to courts in determining proof of causation in medicinal product liability litigation. Building on the foundations of the author's previous monograph, which supported the use of epidemiological evidence in dealing with problems of proof of causation in alleged cases of adverse drug reactions, this paper revisits this perennial problem of the role of epidemiological evidence in assessing causation in product liability cases in a twenty-first century context, examining recent cases in the United Kingdom, United States, Australia, and Canada. It seeks to determine the extent to which the courts in the highlighted cases have been pragmatic and fair in their interpretation and utilization of epidemiological evidence, from the perspective of both consumers and pharmaceutical manufacturers. The paper examines the apparent tension between the levels of proof required in law and science, including the relationship between levels of statistical significance and the claimant's burden of proof; and it assesses the wisdom of using a doubling of the risk rule as a threshold to any recovery. It explores the ways in which probabilistic methods, including statistical refining with individual risk factors, can be used in conjunction with epidemiological evidence to determine specific causation. The paper supports the view that logistic regression techniques and other forms of statistical refining mechanisms using specific risk factors can and do help in the process of giving quantitative or quasi-quantitative expression to conclusions about the cause of disease in an individual drug product liability claim that is based on epidemiological evidence.

EPIDEMIOLOGICAL UNCERTAINTY, CAUSATION, AND DRUG PRODUCT LIABILITY

*Richard Goldberg**

Epidemiological evidence is regularly presented to courts in determining proof of causation in medicinal product liability litigation. Building on the foundations of the author's previous monograph, which supported the use of epidemiological evidence in dealing with problems of proof of causation in alleged cases of adverse drug reactions, this paper revisits this perennial problem of the role of epidemiological evidence in assessing causation in product liability cases in a twenty-first century context, examining recent cases in the United Kingdom, United States, Australia, and Canada. It seeks to determine the extent to which the courts in the highlighted cases have been pragmatic and fair in their interpretation and utilization of epidemiological evidence, from the perspective of both consumers and pharmaceutical manufacturers. The paper examines the apparent tension between the levels of proof required in law and science, including the relationship between levels of statistical significance and the claimant's burden of proof; and it assesses the wisdom of using a doubling of the risk rule as a threshold to any recovery. It explores the ways in which probabilistic methods, including statistical refining with individual risk factors, can be used in conjunction with epidemiological evidence to determine specific causation. The paper supports the view that logistic regression techniques and other forms of statistical refining mechanisms using specific risk factors can and do help in the process of giving quantitative or quasi-quantitative expression to conclusions about the cause of disease in an individual drug product liability claim that is based on epidemiological evidence.

La preuve épidémiologique est régulièrement présentée pour démontrer la causalité dans les litiges en matière de responsabilité pour les produits thérapeutiques.

En se fondant sur l'une des monographies précédentes de l'auteur, qui appuie le recours à la preuve épidémiologique pour traiter des difficultés à prouver la causalité dans des affaires portant sur les effets indésirables de médicaments, cet article réexamine, dans le contexte du XXIe siècle, le problème constant du rôle de la preuve épidémiologique dans les questions de causalité en matière de responsabilité du fabricant. Il analyse à cette fin la jurisprudence du Royaume-Uni, des États-Unis, de l'Australie et du Canada. Cet article cherche à cerner jusqu'à quel point les tribunaux ont adopté, dans les affaires étudiées, une approche pragmatique et juste en interprétant et en utilisant la preuve épidémiologique, tant du point de vue des consommateurs que de celui des fabricants de produits pharmaceutiques. Il examine la tension entre les niveaux de preuve nécessaire dans les domaines scientifique et juridique, y compris la relation entre les niveaux de signification statistique et le fardeau de la preuve du demandeur, et évalue la possibilité d'utiliser la règle de doublement du risque comme seuil pour un recouvrement judiciaire. Il explore les façons dont les méthodes probabilistes, telles que l'affinage des statistiques avec des facteurs de risque, peuvent être utilisées en conjonction avec la preuve épidémiologique afin de déterminer la causalité spécifique. Cet article avance que les techniques de régression logistique, ainsi que d'autres mécanismes de raffinement statistique se servant de facteurs de risque spécifiques, peuvent aider à donner une expression quantitative ou quasi-quantitative aux conclusions portant sur la causalité dans une réclamation en responsabilité pour un produit thérapeutique basé sur la preuve épidémiologique.

* Professor of Law, Durham University, UK. Earlier drafts of this paper were delivered to the Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, April 2011 under a Carnegie Research Grant, and to the first meeting of the *Technological Innovations, Uncertainty, and Responsibility* network, Faculty of Law, McGill University, 5 July 2012. The author wishes to thank Professors Philip Dawid and David Goldberg for helpful discussions.

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Introduction

Proof of causation in toxic tort litigation is an inherently difficult problem, which regularly requires time-consuming analysis of complex scientific evidence.[1] The difficulties in proving both general causation (whether a product was capable of causing the damage alleged) and specific causation (whether the product did so in the individual case) are magnified in the context of medicinal products.[2] As Harvey Teff and Colin Munro have highlighted:

> Drugs are always potentially dangerous due to their toxicity. They are often taken by people who are already ill and who may be unusually susceptible to further ailments. Unlike many other products, they may cause injury in unpredictable ways, depending on the individual user's constitution. They may not be taken according to the instructions. The user may be allergic to a particular drug. Alternatively, what appears to be an allergy may in fact be a toxic reaction.[3]

With a multitude of new kinds of drugs emerging as a harvest of the scientific and technological revolutions of both the twentieth and early twenty-first centuries, the cases have become even more complex, demanding much from lawyers and scientific experts on both sides and from judges themselves.[4]

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1 See CJ Miller & RS Goldberg, *Product Liability*, 2d ed (Oxford: Oxford University Press, 2004) at para 17.05.

2 Richard Goldberg, *Causation and Risk in the Law of Torts: Scientific Evidence and Medicinal Product Liability* (Oxford: Hart Publishing, 1999) 5 et seq [Goldberg, *Causation and Risk in the Law of Torts*].

3 Harvey Teff and Colin Munro, *Thalidomide: The Legal Aftermath* (Farnborough: Saxon House, 1976) at 135–36. "Clearly it is often harder to prove that one's injuries are due to an adverse drug reaction than that they have been caused by a faulty machine" (Harvey Teff, "Regulation Under the Medicines Act 1968: A Continuing Prescription for Health" (1984) 47:3 Mod L Rev 303 at 322). Professor Teff also notes "[t]he synergistic effects of certain combinations (for example, barbiturates and alcohol, anti-histamines and cheese) may prove fatal" (Harvey Teff, "Products Liability in the Pharmaceutical Industry at Common Law" (1974) 20:1 McGill LJ 102 at 115).

4 See e.g. *Bonthrone v Secretary of State for Scotland*, 1987 SLT 34, Jauncey LJ, cited in Diana Brahams, "Pertussis Vaccine and Brain Damage: Two Claims Before the Courts" (1985) 326 Lancet 1137 (on the existence of cryptogenic (unknown) causes to eliminate any possible causal connection between the pertussis vaccine and brain damage); see also *Loveday v Renton* (1988), [1990] 1 Med LR 117 (QB) at 185 [*Loveday*], Stuart-Smith LJ, discussed in Goldberg, *Causation and Risk in the Law of Torts*, *supra* note 2 at 137–43 (after examining complex scientific evidence and arguments, Lord Stuart-Smith held that the plaintiff had failed to prove on a balance of probabilities that the pertussis (whooping cough) vaccine could cause permanent brain damage in young children); *Kay v Ayrshire and Arran Health Board*, [1987] 2 All ER 417, 1987 SC 145 (HL Eng) (penicillin overdose was held to be not capable of causing or aggravating deafness). Consider also the US mass tort litigation concerning Bendectin (Debendox),

The practical significance of establishing causation in a medicinal product liability case cannot be overstated. In the United Kingdom, whether the claim is in negligence or under the strict liability provisions of the *Product Liability Directive*,[5] proof of causation will often lead to ei-

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the anti-nausea drug used in pregnancy. In contrast to thalidomide, where many lines of evidence have shown that the drug caused phocomelia malformations (see Henning Sjöström & Robert Nilsson, *Thalidomide and the Power of the Drug Companies* (Harmondsworth: Penguin, 1972) at 156–59), no causal link has ever been scientifically established between Bendectin and birth defects. The Bendectin litigation demonstrated a persistent failure by plaintiffs' lawyers to prove causation. Joseph Sanders wrote the seminal paper on this topic: "The Bendectin Litigation: A Case Study in the Life Cycle of Mass Torts" (1992) 43:2 Hastings LJ 301. For a discussion of the litigation's implications in the United Kingdom, see Goldberg, *Causation and Risk in the Law of Tort*, *supra* note 2 at 102–31. The litigation spawned two formative monographs: Michael D Green, *Bendectin and Birth Defects: The Challenges of Mass Toxic Substances Litigation* (Philadelphia: University of Pennsylvania Press, 1996); Joseph Sanders, *Bendectin on Trial: A Study of Mass Tort Litigation* (Ann Arbor: University of Michigan Press, 1998). Thirty years after Bendectin's withdrawal from the market, the drug (now renamed Diclegis) has won Food and Drug Administration approval as the only FDA-approved treatment for morning sickness (FDA News Release, "FDA approves Diclegis for pregnant women experiencing nausea and vomiting", online: US Food and Drug Administration <www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm347087.htm>, accessed 13 April 2013; Associated Press, "Morning Sickness Drug Returns", *The New York Times* (8 April 2013), online: The New York Times <www.nytimes.com/2013/04/09/us/morning-sickness-drug-returns.html?emc=tnt&tntemail1=y&_r=0&pagewanted=print>).

5 EC, *Council Directive 85/374/EEC of 25 July 1985 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Concerning Liability for Defective Products,* [1985] OJ, L 210/29. By article 4 of the Directive, and section 2(1) of the *Consumer Protection Act* 1987 (UK), c 43, s 2(1), the person injured by a defective medicinal product must prove the damage, the defect, and the causal relationship between them. The damage must have been caused "wholly or partly by a defect" in the medicinal product. Thus the formal distinction between negligence and strict liability is that with negligence, it must be proven that breach of a duty caused the harm, whereas under the 1987 *Act*, it must be proven that a defect caused the damage (see Pamela R Ferguson, *Drug Injuries and the Pursuit of Compensation* (London: Sweet & Maxwell, 1996) at 125). It appears that each member state will rely on its own theory of causation as established in its civil liability system, though it has been observed that some kind of semi-autonomous European understanding of causation could be established from common elements of the member states' legal systems (see Simon Whittaker, "The EEC Directive on Product Liability" (1985) 5 YB Eur L 233 at 247). The argument that causation is likely to be defined and interpreted by national law and assessed by national courts is strengthened by the decision of the European Court of Justice in *Henning Veedfald v. Århus Amtskommune*, where the Court concluded that it was for the national court to decide whether a claim was to be categorized in respect of personal injury, property damage, or non-material damage (C-203/99 [2001] ECR I-3587 at I-3599–3600). This is subject to a qualification founded on the principle of effectiveness, in that national laws must not by their interpretation of causation render ineffective either the protection of injured persons or the restraints on liability of producers, since both reflect the "fair apportionment of risk" of the Directive. In so doing, however, courts will take into consideration the extent to which these causal issues combine issues of fact and their evaluation and questions of law (see Simon Whittaker, *Liability for Products: Eng-*

ther a settlement or a successful claim.[6] Conversely, a failure to establish a causal link between a medicinal product and, for example, the alleged medical conditions of claimants, may lead to such claims being struck out as an abuse of the process of the court on the basis that each claim has no real prospect of success.[7]

Epidemiology is defined as "the field of public health and medicine that studies the incidence, distribution and etiology of disease in human populations."[8] Epidemiological evidence is regularly presented to courts in determining proof of causation in medicinal product liability litigation. Building on the foundations of the author's previous monograph, which supported the use of epidemiological evidence in dealing with problems of proof of causation in alleged cases of adverse drug reactions,[9] this paper revisits the perennial problem of the role of epidemiological evidence in assessing causation in product liability cases in a twenty-first century context, examining recent cases in the United Kingdom, United States, Australia, and Canada. In essence, it seeks to determine the extent to which the courts in the highlighted cases have been pragmatic and fair in their interpretation and utilization of epidemiological evidence, from the perspective of both consumers and pharmaceutical manufacturers.

In order to establish factual causation in the context of medicinal product liability, claimants must prove both general causation ("whether a substance is capable of causing a particular injury or condition in the general population") [10] and specific causation ("whether a substance

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lish Law, French Law, and European Harmonisation (Oxford: Oxford University Press, 2005) at 512–13). The European Commission believes that "injured parties can establish the causal link in cases where a defective product causes damage irrespective of the differences between national procedural rules" (EC, *Fourth Report on the Application of Council Directive 85/374/EEC of 25 July 1985 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Concerning Liability for Defective Products* (Brussels: EC, 2011) at 11), though it has noted the views of consumers that there is difficulty in "proving the causal link between the defect and damage when such damage is complex in nature" (*ibid* at 7). Consumers believe that the burden of proof should be reversed (*ibid*).

6 Mark Mildred, "Representing the Plaintiff" in Geraint G Howells, ed, *Product Liability, Insurance and the Pharmaceutical Industry: An Anglo-American Comparison* (Manchester: Manchester University Press, 1991) 24 at 27.

7 See Miller & Goldberg, *supra* note 1 at para 17.02.

8 Michael D Green, D Michal Freedman & Leon Gordis, "Reference Guide on Epidemiology" in *Reference Manual on Scientific Evidence*, 3d ed (Washington: National Academies Press, 2011) 549 at 551 [Green, "Epidemiology"].

9 See generally Goldberg, *Causation and Risk in the Law of Torts*, *supra* note 2.

10 *Merck & Co v Garza*, 347 SW (3d) 256 at 262 (Tex 2011) [*Garza*], citing *Merrell Dow Pharmaceuticals v Havner,* 953 SW (2d) 706 at 714 (Tex 1997) [*Havner*].

caused a particular individual's injury").[11] Since epidemiology is based on the study of populations and not individuals, it focuses on the question of general causation rather than specific causation.[12] Epidemiological evidence may identify an association between a drug and a disease, but whether such an association is causal requires an evaluation of the evidence, with emphasis on the extent to which weaknesses of a study's design and implementation compromise its findings and inferences about causation.[13]

The results of epidemiological studies cannot *per se* conclusively prove specific causation. However, several cases have focused on the role that epidemiological evidence plays in determining proof of specific causation, which is a legal question addressed by courts.[14] This paper explores the ways in which probabilistic methods, including statistical refining with individual risk factors, can be used in conjunction with epidemiological evidence to determine specific causation.

Part IA explores the apparent tension between the levels of proof required in law and science, including the relationship between levels of statistical significance and the claimant's burden of proof. Part IB assesses the wisdom of using a "doubling of the risk" rule as a threshold to any recovery. Notwithstanding the problems with the doubling of risk theory in the United States, its usage appears to be gaining ground in the United Kingdom. Moreover, in particular, the doubling of risk theory has come to recent attention in the context of the utilization and value of epidemiological or statistical evidence alone in determining causation on a balance of probabilities, with discussion by the UK Supreme Court in *Sienkiewicz v. Greif*.[15] A cautious attitude toward the use of the doubling of risk rule in the context of both general and specific causation is seen from the case law explored. In examining the distinction between association and causation, Part IC discerns two main reasons for this judicial scepticism about epidemiological evidence, namely the propriety of drawing causal inferences from observed associations (a general causation issue) and the propriety of drawing causal inferences in individual cases from concededly

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11 See *ibid*; *Garza*, *supra* note 10. See also Michael D Green, "The Future of Proportional Liability: The Lessons of Toxic Substances Causation" in M Stuart Madden, ed, *Exploring Tort Law* (New York: Cambridge University Press, 2005) 352 at 366 [Green, "Proportional Liability"].

12 See Green, "Epidemiology", *supra* note 8 at 552; Steve Gold, "Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence" (1986) 96 Yale LJ 376 at 379–80.

13 Green, "Epidemiology", *supra* note 8 at 552–53, 598.

14 *Ibid* at 609.

15 *Sienkiewicz v Greif*, [2011] UKSC 10, [2011] 2 WLR 523 [*Sienkiewicz*].

causal associations observed in samples of populations (a specific causation issue). These reasons are discussed in an analysis of the controversial Scottish case of *McTear v. Imperial Tobacco Ltd*[16] and the decision of the Federal Full Court of Australia in *Merck Sharp & Dohme (Australia) Pty Ltd v. Peterson*.[17] In the context of *McTear*, Part ID discusses the necessity of requiring something more than a doubling of the risk to permit the claimant to recover, and it stresses the role of judges in resolving this issue.

Part IE discusses the implications for specific causation, in the context of *McTear*, of epidemiology being based on the study of populations and not individuals. It suggests that the limitations of epidemiological evidence in determining specific causation as described by the trial judge are somewhat inaccurate since, in establishing specific causation, epidemiologists can and do adjust for potentially confounding factors through logistic regression techniques and other forms of statistical refining mechanisms. Part IF therefore concludes with an examination of such statistical refining methods in determining specific causation in medicinal product liability cases, including the use of Bayes' theorem to help us understand how statistical risks can be refined using personal risk factors. The paper does not argue that Bayes' theorem is necessarily the answer to the problem of establishing specific causation in the context of epidemiological evidence. Nonetheless, while recognizing the limitations of Bayes' theorem, the paper supports the view that logistic regression techniques and other forms of statistical refining mechanisms using specific risk factors can and do help in the process of giving quantitative or quasi-quantitative expression to conclusions about the cause of disease in an individual drug product liability claim that is based on epidemiological evidence. Finally, the paper illustrates the increasing support for the refining and personalizing of epidemiological evidence in cases of individual causation involving medicinal products, as evidenced by the decision of the Ontario Superior Court of Justice in *Andersen v. St Jude*.[18]

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16 *McTear v Imperial Tobacco Ltd*, [2005] CSOH 69, 2 SC 1 (Ct Sess Scot) [*McTear*].

17 *Merck Sharp & Dohme (Australia) Pty Ltd v Peterson*, [2011] FCAFC 128, 284 ALR 1, leave to appeal to HCA refused, [2012] HCA Trans 105 [*Peterson*].

18 See *Andersen v St Jude Medical, Inc*, 2012 ONSC 3660 (available on CanLII) at paras 542, 544, 555, 558–59 [*Andersen*].

I. Reconciling the Standards of Proof in Law and Science in the United Kingdom

A. Evidence of Causation for Purposes of Science and for Purposes of Law

There is an apparent tension between the levels of proof required in law and in science. For the law of negligence, it is sufficient to show that the balance of probabilities—meaning more than fifty per cent, or on a preponderance of the evidence—indicates a causal connection. It is sometimes erroneously assumed by lawyers that scientists regard an association as causal if it is ninety-five per cent certain.[19] However, this is a misinterpretation of the so-called *p* value, which is merely the level of statistical significance used to exclude the possibility that when something transpires in a cohort of cases, it does so by chance (i.e., the null hypothesis). When the *p* value falls below the threshold of 0.05, the investigator is able to reject the null hypothesis since there is a less than one in twenty chance that the link between exposure and disease is random.[20] While there is no generally accepted standard of scientific proof for causation,[21] and neither the claimant nor the defendant is required to apply scientific standards of proof when determining causation on a balance of probabilities,[22] such a standard must be "much more than marginal".[23] In light of this apparent tension between the balance of probabilities standard and

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19 See Green, "Epidemiology", *supra* note 8 at 577 n 81. Equating statistical significance with the legal burden of proof has been described as being "like trying to find the shortest path from Oxford to Cambridge by scrutinizing a map of London" (DH Kaye, "Apples and Oranges: Confidence Coefficients and the Burden of Persuasion" (1987) 73:1 Cornell L Rev 54 at 66). Kaye demonstrates the distinction between statistical significance and the civil burden of persuasion by using a hypothetical case (*ibid* at 66–73). There is often judicial reference to a statement that the level of 0.05 for statistical significance is a much higher burden of proof than the civil burden of a preponderance of the evidence or balance of probabilities (that is, greater than fifty per cent): see Green, "Epidemiology", *supra* note 8 at 577, citing *In re Ephedra Products Liability Litigation*, 393 F Supp (2d) 181 at 193 (SD NY 2005); *Marmo v IBP, Inc*, 360 F Supp (2d) 1019 at 1021 (D Neb 2005); Peter Feldschreiber, Leigh-Ann Mulcahy & Simon Day, "Biostatistics and Causation in Medicinal Product Liability Suits" in Richard Goldberg, ed, *Perspectives on Causation* (Oxford: Hart, 2011) 179 at 190. Recent case law has referred to Wyeth's citation of the Reference Manual on Scientific Evidence to point to the erroneous nature of this approach (see *Giles v Wyeth, Inc*, 500 F Supp (2d) 1048 at 1056–57 (SD Ill 2007)).

20 Feldschreiber, Mulcahy & Day, *supra* note 19 at 184, 190.

21 See *Loveday*, *supra* note 4 at 124, Stuart-Smith LJ.

22 See *Carter v Basildon and Thurrock University Hospitals NHS Foundation Trust*, [2007] EWHC 1882 at para 92 (available on BAILII) (QB) [*Carter*].

23 See *Dingley v The Chief Constable, Strathclyde Police*, 1998 SC 548 at 603 (Ct of Sess), [1998] GWD 677, Lord Prosser [*Dingley* cited to SC], aff'd 2000 SC (HL) 77, cited in *Sienkiewicz*, *supra* note 15, Lord Phillips.

the standard of statistical significance, courts must be alert to the problem that may be faced by an expert "in readjusting his focus from the ninety-five per cent confidence limit approach to the balance of probabilities test."[24] However, in *Vadera v. Shaw*[25] the English Court of Appeal reconciled the legal standard of proof on a balance of probabilities with the scientific standard of statistical significance, in holding that a failure to establish a statistically significant connection between the oral contraceptive Logynon and the occurrence of strokes was fatal to the establishment of proof of causation on a balance of probabilities. Lord Justice Henry stated:

> The judge concluded, and in our respectful view was right on the evidence to conclude, that the studies carried out and referred to by Dr Lidegaard [for the plaintiff] did not establish a statistically significant connection between Logynon and strokes. Such evidence cannot be ignored by a judge. It is as common sense a conclusion as one could wish to say that if the connection between A and B cannot be shown with confidence to be other than a coincidence, then it cannot be held on a balance of probabilities that A caused B. This is not to allow scientists or statisticians to usurp the judge's function, but rather to permit him to use their skills to discern a connection, or a lack of connection, between two phenomena.[26]

B. Doubling of Risk Theory

Epidemiologists investigating disease causation measure the association between exposure to an agent and the incidence of disease by using the concept of relative risk. Relative risk is defined as the ratio of the incidence of a disease in a population exposed to the agent to the incidence of disease in a population that has not been exposed.[27] For example, if ten per cent of all people exposed to a drug develop a disease, compared with five per cent of people who are unexposed, the disease occurs twice as frequently among the exposed people. The relative risk is ten per cent/five

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[24] See *Carter*, *supra* note 22 at para 97. A confidence interval or confidence limit is a range of values within which the true value is likely to fall (see Green, "Epidemiology" *supra* note 8 at 621; Goldberg, *Causation and Risk in the Law of Torts, supra* note 2 at 137; American Law Institute, *Reporters' Study: Enterprise Responsibility for Personal Injury,* vol 2: *Approaches to Legal and Institutional Change* (Philadelphia: American Law Institute, 1991) at 324–28).

[25] *Vadera v Shaw* (1998), 45 BMLR 162 (CA), (2000) 8 Med LR 316.

[26] *Ibid* at 174. However, it is suggested that there was a failure by the trial judge and the Court of Appeal to scrutinize adequately the scientific evidence in respect of causation in this case (see Richard Goldberg, "The Contraceptive Pill, Negligence and Causation: Views on *Vadera v. Shaw*" (2000) 8 Med L Rev 316 at 331–35).

[27] Green, "Epidemiology", *supra* note 8 at 566, 627; Green, "Proportional Liability", *supra* note 11 at 366.

per cent (i.e., two). A relative risk of one shows no association between exposure and disease.[28]

A significant attempt to reconcile the apparent tension between the balance of probabilities standard and the standard for epidemiology has emerged with the theory that causation can be proven on the balance of probabilities by reference to the doubling of risk of injury theory. That theory has long been recognized in the United States,[29] where it has been said that "[t]he use of scientifically reliable epidemiological studies and the requirement of more than a doubling of the risk strikes a balance between the needs of our legal system and the limits of science."[30] However, the theory has also been subject to trenchant criticism.[31] In particular, academics have argued that judges have adopted "substantive changes in causation law through the rubric of evidentiary admissibility decisions"[32] and "have frequently conflated admissibility decisions and sufficiency of

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[28] See *ibid*; Green, "Epidemiology", *supra* note 8.

[29] See especially *Daubert v Merrell Dow Pharmaceuticals*, 43 F (3d) 1311 (9th Cir 1995), 63 USLW 2420, cert denied, 516 US 869, 116 S Ct 189 (1995) [*Daubert II*]. In that case, the Court of Appeals, on remand from the Supreme Court of the United States, held that the plaintiffs had to show not merely that Bendectin *increased* the likelihood of injury, but that it more likely than not *caused* their injuries. In terms of statistical proof, it had to be shown that plaintiffs' mothers' ingestion of Bendectin more than doubled the likelihood of birth defects (*ibid* at 1320). This was reaffirmed by the Supreme Court of Texas in *Havner*, *supra* note 10 at 716–18. The Supreme Court of Texas has now expanded on its holding in *Havner* and adopted the position that a doubling of risk is a necessary but not sufficient condition to prove causation (see *Garza*, *supra* note 10 at 265). Vermont has also adopted the doubling of risk theory in a slightly diluted form in the context of specific causation (see *Blanchard v Goodyear Tire and Rubber*, 30 A (3d) 1271, 2011 VT 85 (Vt Sup Ct) at 1275–77). For an excellent discussion of the implications of both cases, see Steve C Gold, "Revisiting Relative Risk Rules: *Garza*, *Blanchard*, and the Ever Evolving Role of Epidemiologic Proof in Toxic Tort Cases" (2012) 40 Prod Safety & Liab Rep (BNA) 50 [Gold, "Revisiting Relative Risk Rules"].

[30] *Havner*, *supra* note 10 at 718 (echoing the views of the court of appeals in *Daubert II*, *supra* note 29).

[31] See e.g. Lucinda M Finley, "Guarding the Gate to the Courthouse: How Trial Judges Are Using Their Evidentiary Screening Role to Remake Tort Causation Rules" (1999) 49:2 DePaul L Rev 335 (criticizing the doubling–in–risk evidentiary requirement for epidemiological proof, describing the trend as "seriously scientifically and legally misguided" at 348); Margaret A Berger, "Upsetting the Balance Between Adverse Interests: The Impact of the Supreme Court's Trilogy on Expert Testimony in Toxic Tort Litigation" (2001) 64:2–3 Law & Contemp Probs 289 (criticizing the doubling of the risk rule as "a legal invention that creates a hard and fast rule that disposes of cases efficiently but rests on assumptions that cannot be scientifically validated at this time" at 304–06); Sander Greenland & James M Robins, "Epidemiology, Justice, and the Probability of Causation" (2000) 40:3 Jurimetrics J 321 at 325–26; Mark Geistfeld, "Scientific Uncertainty and Causation in Tort Law'" (2001) 54:3 Vand L Rev 1011 at 1015, 1018, 1020.

[32] Finley, *supra* note 31 at 336.

evidence decisions."[33] Those courts which require plaintiffs to produce epidemiological studies with a relative risk of two are making a "legal policy determination to equate epidemiology, relative risk, general causation, and the burden of proof on individual causation."[34] Moreover, while the total number of judicial opinions that at least mention the concept of doubling of risk has increased, US courts disagree as to the proper role of the doubling of risk theory in deciding questions of both sufficiency and admissibility of scientific evidence of causation in toxic tort cases. They do not agree on whether to adopt the doubling of risk as a threshold, nor do they agree on the meaning of such a threshold.[35] As the reporters for the American Law Institute's *Restatement Third of Torts* have noted:

> Many courts accept the doubling of the incidence of disease in group studies; some courts insist on doubling of risk as a minimum threshold for establishing specific causation. Others have recognised that if other known causes can be identified and eliminated, something less than a doubling would still be sufficient to find specific causation. [36]

Accordingly, the requirement of a relative risk of two for the admissibility or sufficiency of epidemiological evidence has been subject to much scepticism.[37] The reporters for the *Restatement Third of Torts*, in discussing the considerations that affect the appropriateness of determining the probability of specific causation based on the outcome of group studies, have concluded that a judicial requirement that plaintiffs show a threshold increase in risk (or a doubling of incidence in a group study) to satisfy the burden of proof of specific causation is "usually inappropriate".[38]

Notwithstanding the problems with the doubling of risk theory in the United States, its existence appears to be gaining ground in the United

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[33] *Ibid*; see also Jean Macchiaroli Eggen, "Clinical Medical Evidence of Causation in Toxic Tort Cases: Into the Crucible of *Daubert*" (2001) 38:2 Hous L Rev 369 at 378–79; Michael D Green, "The Future of Proportional Liability: The Lessons of Toxic Substances Causation" in M Stuart Madden, ed, *Exploring Tort Law* (Cambridge: Cambridge University Press, 2005) 352 at 368–69. A recent instance of the conflation of both admissibility and sufficiency of evidence requirements is *Garza, supra* note 10, discussed in Gold, "Revisiting Relative Risk Rules", *supra* note 29 at 53 (where he argues that by framing a totality of evidence test as a matter of reliability, *Garza* explicitly conflated rules of admissibility and substantive sufficiency in the weighing of evidence).

[34] Finley, *supra* note 31 at 362.

[35] Russellyn S Carruth & Bernard D Goldstein, "Relative Risk Greater Than Two in Proof of Causation in Toxic Tort Litigation" (2001) 41:2 Jurimetrics Journal 195 at 199, 202–03.

[36] *Restatement (Third) of the Law of Torts* §28(a) (2010) [*Restatement*].

[37] See Carl F Cranor, *Toxic Torts: Science, Law and the Possibility of Justice* (Cambridge: Cambridge University Press, 2007) at 234–38, 281.

[38] *Restatement*, *supra* note 36.

Kingdom. Of particular significance was the case *XYZ v. Schering Health Care Ltd*,[39] a trial of seven lead cases in group litigation against three pharmaceutical companies in respect of cardiovascular injuries coming under the collective description of venous thromboembolism (VTE). The claimants alleged that their injuries were caused by taking the defendants' different brands of third-generation combined oral contraceptives. The claimants alleged that the products they took were defective under the *Consumer Protection Act 1987* and the *Product Liability Directive*. While the cause of action was based on strict liability, the requirement common to both negligence and strict liability of proving a causal link between the product and the damage (i.e., the issue of general causation) emerged as the first central issue requiring determination.

Justice Mackay stated that the claimant could prove that an exposure to risk caused injury if that exposure had more than doubled the risk of the injury occurring.[40] This method of proving causation had previously been applied in a case of bladder cancer, where the claimant had been tortiously exposed to carcinogens and non-tortiously exposed to cigarette smoke, both of which are potent causes of the condition.[41] However, it has been argued that since the doubling of risk approach is only valid where the risk estimate represents "*mutually exclusive* ways in which the injury may have been caused" and is sought "to estimate the likelihood it was one way which had operated in a particular case rather than one of the

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39 70 BMLR 88, [2002] EWHC 1420 (QB) [*XYZ*].

40 *Ibid* at para 21, Mackay J. See also Miller & Goldberg, *supra* note 1 at paras 17.06–17.08.

41 See *Cookson v Novartis Grimsby Ltd*, [2007] EWCA Civ 1261, [2007] All ER (D) 465 (Nov) at para 74, Smith LJ. See also *Ministry of Defence v AB*, [2010] EWCA Civ 1317, 117 BMLR 101 at 149 [*AB*]. In the appeal for *AB* (*AB v Ministry of Defence*, [2012] UKSC 9, [2013] 1 AC 78 [*AB* UKSC]), the UK Supreme Court found the doubling of risk theory relevant in the context of examining the strength of claimants' cases on causation and in determining whether the trial court's exercise of discretion under section 33 of the *Limitation Act 1980* was appropriate. The trial judge was found to have wrongly exercised his discretion. In dismissing the claimants' appeals, the Supreme Court observed that it was undesirable that a court which conducts an inquiry into whether a claim is time-barred should, even when it considers its power under section 33 of the 1980 *Act*, have detailed regard to the evidence with which the claimant aspires to prove its case. Nonetheless, because of the complexity of the claims placed before the trial judge and the nature of the submissions about knowledge in section 14(1) of the 1980 *Act*, the trial judge was able to make a "microscopic survey of the written evidence," especially in respect of causation. The Court of Appeal had been unusually well-placed in exercising its discretion under section 33 to assess the claimants' prospects of establishing causation. Since the Court of Appeal had concluded that the claimants' faced "very great difficulties" in establishing causation, and the claimants had no real prospects of success, it had been correct not to exercise its discretion to allow the claims to proceed. To have done so would have been absurd (*ibid*, Lord Wilson at 100).

other possible ways."[42] As such, the doubling of risk approach is not validly applicable as a method to cases of bladder cancer, where the mechanism by which an agent (e.g., amines) present in two sources (e.g., occupational amine exposure and amines contained in cigarette smoke) causes bladder cancer is unknown.[43] By contrast, such comparisons of risk estimates in the doubling of risk approach would be statistically valid where the estimates relate to mechanisms which, even if their details are not understood, are known to involve different agents, such as a birth defect that may be attributable *either* to a medicinal product *or* to a background risk.[44]

"The utilization and value of epidemiological or statistical evidence alone in determining causation on a balance of probabilities was subject to some interesting debate in the [UK] Supreme Court in *Sienkiewicz v. Greif*."[45] The reason for this discussion, as pointed out by Baroness Hale,[46] was the presence of an *obiter* observation by Lady Justice Smith in her judgment in *Sienkiewicz* that "in a case of multiple potential causes, a claimant can demonstrate causation by showing that the tortious exposure has at least doubled the risk arising from the non-tortious cause or causes."[47] Their Lordships were postulating the scenario where, having established general causation between the toxic agent and the disease, epidemiological evidence might be used to establish specific causation. While their Lordships held unanimously that there was no room for introducing the doubling of risk approach to "single exposure"[48] mesothelioma cases or multiple defendant mesothelioma cases,[49] differences in view emerged

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[42] Jane Stapleton, "Factual Causation, Mesothelioma and Statistical Validity" (2012) 128:2 Law Q Rev 221 at 223–25 [emphasis added].

[43] *Ibid* at 226.

[44] *Ibid* at 223.

[45] Richard Goldberg, "Using Scientific Evidence to Resolve Causation Problems in Product Liability: UK, US and French Experiences" in Richard Goldberg, ed, *Perspectives on Causation* (Oxford: Hart Publishing, 2011) 149 at 153.

[46] See *Sienkiewicz*, *supra* note 15 at para 169.

[47] *Ibid* at para 63 (quoting Smith LJ in the Court of Appeal, [2010] QB 370).

[48] *Ibid* at para 67. As Lord Kerr noted, "[t]he use of the expression 'single exposure' may be misleading in this context" (*ibid* at para 199). It is probably better expressed as "single tortious exposure cases" (*ibid* at para 173, Hale B). These are cases where only one defendant exposed the victim to asbestos and there was only one possible tortious source for the exposure, and the only other exposure creating a risk of developing mesothelioma was environmental exposure to low level asbestos dust in the general atmosphere (*ibid* at paras 113, Lord Rodger; 199, Lord Kerr; 207, Lord Dyson).

[49] *Ibid* at paras 106, Lord Phillips; 160, Lord Rodger; 169, Hale B; 188, Lord Mance; 203, Lord Kerr; 220, Lord Dyson. In such cases, the *Fairchild v Glenhaven Funeral Services Ltd* ([2002] UKHL 22, [2003] 1 AC 32) and *Barker v Corus (UK) plc* ([2006] UKHL 20, [2006] 2 AC 572) exception for mesothelioma applied to provide the claimant with an

with the *obiter* discussion of the general applicability of the doubling of risk theory using epidemiological evidence to determine proof of causation in personal injury cases.

Lord Phillips discussed the *XYZ* decision and took the view that, while the case contained "a detailed and illuminating discussion of epidemiology," it did not afford any direct assistance to the question whether the "doubles the risk" test—as he called it—was appropriate for determining causation in a case of multiple potential causes.[50] His reasoning was somewhat obscured by his misclassification of the contraceptives in this case. He stated that the issue "was whether a second generation of oral contraceptives more than doubled the risk of causing deep vein thrombosis (DVT) that was created by the first generation of contraceptives ... It was not whether the DVT suffered by the claimants had been caused by the second generation of oral contraceptives."[51]

In fact, the issue was whether the claimants had proved that *third* generation combined oral contraceptives caused a true excess risk of VTE, which was more than twice the risk caused by *second* generation combined oral contraceptives. Both sides in *XYZ* agreed that if the claimants failed to prove this, the action could not succeed. However, both parties had also agreed that if the claimants could prove a true excess risk of VTE, they would also succeed on the second issue, which was whether the relevant products were defective within the meaning of section 3 of the *Consumer Protection Act 1987* (i.e., that their safety would not be such as persons generally were entitled to expect)[52]. The test of defectiveness under section 3(2)(a) of the *Act* includes consideration of instructions or warnings associated with the product. Thus, the reasoning behind the doubling of risk theory's relevance to establishing that the third generation contraceptives were defective was that if the UK Supreme Court ruled that the true risk of VTE was more than doubled with third generation combined oral contraceptives, women and their prescribers were entitled to be told this before making their decisions or giving their advice, respectively—and they had not been.[53]

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action if it proved that the defendant materially increased the risk that the claimant might develop mesothelioma (see *Sienkiewicz*, *supra* note 15 at paras 103, 107, Lord Phillips). But now see the Supreme Court decision in *Durham v BAI (Run Off) Ltd* ([2012] UK SC 14, [2012] 1 WLR 867), where the Supreme Court held that the actual development of mesothelioma was an essential element of the cause of action (*ibid* at paras 52, 65–66, Lord Mance; see also para 124, Lord Phillips, dissenting).

50 *Sienkiewicz*, *supra* note 15 at para 74.

51 *Ibid.*

52 See *XYZ*, *supra* note 39 at para 20.

53 *Ibid* at paras 20–21. See also Miller & Goldberg, *supra* note 1 at paras 17.06–17.08.

Lord Phillips' reasoning seems to ignore the fact that causation was *inherently behind* the court's approach. As Justice Mackay explained in *XYZ*:

> The reason why the Claimants accept, through Lord Brennan QC, that this first issue is capable of disposing of the claims should be set out. It is not because an increase of less than two would fail to render the product defective within the meaning of the Act, though the Defendants would so argue if they had to. It is for reasons of *causation* that he accepts this burden, correctly in my view. If factor X increases the risk of condition Y by more than two when compared with factor Z, it can then be said, of a group of say 100 with both exposure to factor X and the condition, that as a matter of probability more than 50 would not have suffered Y without being exposed to X. If medical science cannot identify the members of the group who would and who would not have suffered Y, it can nevertheless be said of each member that she was more likely than not to have avoided Y had she not been exposed to X [emphasis added].[54]

While Lord Phillips concluded[55] that there was no scope for the doubling the risk test in cases where two agents operated cumulatively and simultaneously in causing the onset of a disease, since in such cases the material contribution rule in *Bonnington Castings v. Wardlaw*[56] would apply, he submitted[57] that there was no reason in principle why the "doubles the risk test" should not be applied where the initiation of a disease was dose-related and there had been consecutive exposures to an agent or agents that cause the disease (e.g., *McGhee v. National Coal Board*).[58] Lord Phillips regarded *Hotson v. East Berks Area Health Authority*[59] as an example of the latter situation.[60]

However, neither Lord Rodger nor Baroness Hale took such a view, both holding that a doubling of risk approach was not an appropriate test of causation.[61] Lord Rodger stressed that where statistical evidence established that exposure to a substance more than doubled the *risk* of a disease, this would not amount to proof, on the balance of probabilities, that the exposure actually *caused* the disease.[62] Meanwhile, Lord Dyson did

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54 *XYZ*, *supra* note 39 at para 21.

55 See *Sienkiewicz*, *supra* note 15 at para 90.

56 *Bonnington Castings Ltd v Wardlaw,* [1956] AC 613 (HL) at 620, Lord Reid.

57 See *Sienkiewicz*, *supra* note 15 at para 93.

58 *McGhee v National Coal Board*, [1972] UKHL 7, [1973] 1 WLR 1.

59 *Hotson v East Berkshire Health Authority*, [1988] UKHL 1, [1987] 1 AC 750 [*Hotson*].

60 See *Sienkiewicz*, *supra* note 15 at para 93.

61 *Ibid* at paras 156, 158, 161, Lord Rodger; 170, 173, Hale B.

62 *Ibid* at para 156.

not "find it necessary to decide whether there are any circumstances in which, as a matter of English law, causation can be proved on the basis of epidemiological evidence alone."[63] He expressed the view that "there [was] no *a priori* reason why, if the epidemiological evidence [was] cogent enough, it should not be sufficient to enable a claimant to prove his case without more."[64] By contrast, Lord Kerr stressed the need to treat the use of epidemiological evidence to seek to establish any specific proposition in an individual case with great caution.[65] He felt that there was a real danger that "so-called 'epidemiological evidence' [would] carry a false air of authority."[66]

Finally, Lord Mance felt that whether and when epidemiological evidence could prove a case was "a question best considered not in the abstract but in a particular case, when and if that question [arises]."[67] If it could arise, he would hope and expect that this would only occur in the rarest of cases.[68]

This cautious attitude toward the use of the doubling of risk rule in the context of specific causation has been reflected in medicinal product liability litigation concerning the anti-inflammatory drug Vioxx. In *Merck Sharp & Dohme (Australia) Pty Ltd v. Peterson*,[69] plaintiffs alleged in representative proceedings that consumption of Vioxx increased the risk of a myocardial infarction (heart attack) and that Vioxx had caused or contributed to the myocardial infarction of the class representative, Mr. Peterson.[70] The trial judge, Justice Jessup, had held that the epidemiological evidence had demonstrated that Vioxx had doubled the risk of heart attack across the population as a whole,[71] and that consumption of Vioxx materially contributed to Peterson's heart attack.[72] Yet in upholding Merck Australia's appeal on the issue of causation, the Full Court criticized the doubling of risk approach as being "apt to mandate an award of

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63 *Ibid* at para 221.

64 *Ibid* at para 222.

65 *Ibid* at para 205.

66 *Ibid* at para 206.

67 *Ibid* at para 192.

68 *Ibid*.

69 *Peterson*, *supra* note 17.

70 *Ibid* at 2.

71 *Merck Sharp & Dohme (Australia) Pty Ltd v Peterson* (2010), 184 FCR 1 at para 570, [2011] FCAFC 128; see generally Claudia Newman-Martin, "Manufacturers' Liability for Undiscoverable Design Flaws in Prescription Drugs: A Merck-Y Area of the Law" (2011) 19:1 Torts Law Journal 26.

72 *Peterson*, *supra* note 17 at para 772.

compensation to applicants who have not, in truth, been injured by the respondent."[73] It also noted that, while a relative risk of two might imply a fifty per cent probability that the risk had been realized in a typical case, a relative risk of less than two would imply a probability of less than fifty per cent. The trial judge's finding of relative risk had been "about two".[74]

C. Association Versus Causation

It is arguable that it would be an oversimplification to think that the views of Lord Phillips in *Sienkiewicz* will help to signal a green light to the establishment of proof of causation on a balance of probabilities by a mere doubling of relative risk. The matter was addressed in *Merrell Dow Pharmaceuticals, Inc. v. Havner*[75] where, having stated that a balance between the needs of the legal system and the limits of science could be achieved by the use of scientifically reliable epidemiological studies and the requirement of more than doubling the risk, the Supreme Court of Texas added the caveat:

> We do not hold, however that a relative risk of more than 2.0 is a litmus test or that a single epidemiological test is legally sufficient evidence of causation. Other factors must be considered. As already noted, epidemiological studies only show an association. There may in fact be no causal relationship even if the relative risk is high.[76]

The latter sentence is of particular importance, and while Lord Phillips in *Sienkiewicz* referred to the caveat expressed in *Havner*,[77] he omitted that last sentence and ignored its import in his final analysis. Unlike Lord Phillips, Lord Rodger stressed the importance of the distinction between *association* and *causation*. In this context, Lord Rodger's reason for

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[73] *Ibid* at para 110. This would be the case since "those applicants who were actually injured by causes other than the respondent's actionable conduct will be able to recover compensation because, for them too, a relative risk of greater than 2 can be said to imply probability of greater than 50% that the respondent's actionable conduct was the cause of their loss" (*ibid*). However, this criticism is misconceived, since the problem of compensation to those not injured by a defendant is generic in any system that uses a preponderance of the evidence rule and has no relevance to the type of evidence employed to determine whether the plaintiff has met the preponderance threshold.

[74] *Ibid* at para 111. See also *Seltsam Pty Ltd v McGuiness*, [2000] NSWCA 29, 49 NSWLR 262, Spigelman CJ (while in Australian law the test of actual persuasion did not require epidemiological studies to reach the level of risk of 2.0, "the closer the ratio approaches 2.0, the greater the significance that can be attached to the studies for the purposes of drawing an inference of causation in an individual case. The 'strands in the cable' must be capable of bearing the weight of the ultimate inference" at para 137).

[75] *Havner*, *supra* note 10.

[76] *Ibid* at 718.

[77] *Supra* note 15 at para 88.

scepticism about epidemiological evidence concerns the propriety of drawing causal inferences from observed associations (a general causation issue); yet there is seemingly a further reason for scepticism in his speech, regarding the propriety of drawing causal inferences in individual cases from concededly causal associations observed in samples of populations (a specific causation issue).[78] Lord Rodger's speech is more compelling in that it shows a greater understanding of both the significance and the limitations of epidemiological evidence, and it demonstrates a reluctance to support the general application of the doubling of risk theory to determining proof of both general and specific causation in personal injury cases.[79] Lord Rodger accepted that epidemiological and statistical evidence may form an important element in proof of causation, and he supported the utilization and value of epidemiological evidence where a claimant was required to prove his case on a balance of probabilities.[80] However, he emphasized that, since by its very nature statistical evidence does not deal with the individual case, the court should not proceed to find a causal relationship *in that particular case* without further non-statistical evidence (e.g., evidence of temporality of the appearance of results of the exposure).[81] In so doing, he cited *Phipson on Evidence*, which states that "[w]here there is epidemiological evidence of association, the court should not proceed to find a causal relationship without further, non-statistical

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78 This can be contrasted with the other reason for judicial scepticism about epidemiological evidence, namely the propriety of drawing causal inferences from observed associations. It is often difficult to tease out from the decisions which form of judicial treatment is taking place.

79 See *Sienkiewicz*, *supra* note 15 at paras 163, Lord Rodger; 173, Hale B.

80 *Ibid* at para 163, Lord Rodger.

81 *Ibid*. Baroness Hale also opined that "the existence of a statistically significant association between factor X and disease Y does not prove that in the individual case it is more likely than not that factor X caused disease Y" (*ibid* at para 170). Lord Mance accepted that epidemiological evidence, used with proper caution, could be admissible and relevant in conjunction with specific evidence related to the individual circumstances and parties. The significance a court might attach to it depended "on the nature of the epidemiological evidence, and of the particular factual issues before the court" (*ibid* at para 191). Lord Kerr considered that "[i]t is an essential and minimum requirement ... that there be evidence connecting avowedly relevant statistical information produced by the epidemiological studies to the facts of the case" (*ibid* at para 205). Lord Dyson also stressed the association/causation dichotomy, stating that "epidemiology ... seeks to establish associations between alleged causes and effects ... However, in an individual case, epidemiology alone cannot *conclusively* prove causation" (*ibid* at para 218). See also the recent discussion by the High Court of Australia in *Amaca Pty Ltd v Booth*, [2011] HCA 53, 283 ALR 461 at para 49 [*Amaca*] (where French CJ distinguished between mere statistical correlation between conduct and injury and the need to establish causal connection between the conduct and injury).

evidence."[82] Lord Rodger illustrated his example of evidence of temporality in the context of a medicinal product and an adverse effect, where there was "a strong epidemiological association between a drug and some condition that could have been caused in some other way."[83] He submitted that epidemiological evidence, "along with evidence that the claimant developed the condition immediately after taking the drug," could be sufficient to allow the judge to conclude that the drug caused the condition on the balance of probability.[84]

The Federal Full Court of Australia's decision in *Peterson* is another example of courts' reluctance to draw inferences from a population to an individual in the context of medicinal products.[85] There the Full Court upheld the "but for" test of causation and found that the trial judge's findings of fact were insufficient to sustain the position that, on the balance of probabilities, but for the consumption of Vioxx, Peterson's myocardial infarction would not have occurred.[86] The court concluded that while the epidemiological evidence meant that it was *possible* Vioxx had caused Peterson's myocardial infarction, there were other strong potential causes, such as "age, gender, hypertension, hyperlipidaemia, obesity, left ventricular hypertrophy and [a] history of smoking."[87] Peterson was therefore "a member of a group within the community, 25% of whom were expected by ... cardiologists to suffer a heart attack within 5 years."[88] These personal circumstances seriously diminished the strength of the epidemiological evidence as a strand in the cable of circumstantial proof.[89] Accordingly, the Full Court held that it was not more probable than not that Vioxx, whether alone or in combination with Peterson's personal risk factors, was a necessary condition of the occurrence of his heart attack.[90] While a relative risk of two could be converted into a fifty per cent statistical likelihood that Vioxx was causally implicated in the occurrence of a myocardial infarction, there were other candidates as causes of the injury. The strength of the epidemiological strand did not rise above the possibility that it was "in the mix" of factors which may have caused Peterson's heart

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82 Hodge M Malek, ed, *Phipson on Evidence*, 17th ed (London, UK: Thomson Reuters Legal, 2010) at paras 34–27.

83 *Sienkiewicz*, *supra* note 15 at para 163.

84 *Ibid*.

85 *Peterson*, *supra* note 17.

86 *Ibid* at paras 103–05.

87 *Ibid* at para 120.

88 *Ibid*.

89 *Ibid* at para 113.

90 *Ibid* at para 120.

attack.[91] While the fact that the plaintiff in *Peterson* suffered from several personal risk factors prima facie cuts against recovery, this mere fact alone does not resolve the import of the epidemiological evidence. The difficulty lies with the fact that epidemiological evidence conflates people with different underlying conditions, and it may not be known what the relative risk is for those individuals with no history of heart disease compared to individuals, such as Peterson, with a long history of heart disease. Indeed, there is a strong argument, based on Merck's own VIGOR study of Vioxx, that the relative risk of taking Vioxx is equally strong in both subgroups and that Vioxx could have caused a heart attack even in someone with a history of heart disease.[92] There is thus no data to support the Full Court's conclusion that personal circumstances seriously diminish the strength of the epidemiological evidence. Accordingly, the court's approach was arguably a *guess* by a sceptical court that Vioxx is incapable of being identically implicated both in cases of individuals with pre-existing heart problems and in cases of those without.

In light of Lord Rodger's observations in *Sienkiewicz*, and from the perspective of the propriety of drawing causal inferences from observed associations, the mere existence of a statistically significant association is insufficient to establish a causal relationship without the presence of further non-statistical evidence. To establish a causal relationship, factors such as those enumerated by Sir Austin Bradford Hill would need to be utilized to determine whether a reported association is causal.[93] This point

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91 *Ibid* at para 123. Special leave to appeal to the High Court of Australia was refused since the applications were deemed not suitable vehicles for the consideration of the relevant questions of principle that would warrant the grant of leave, "having regard to the findings of fact of the primary judge and the Full Court's treatment of them" (*Peterson*, *supra* note 17, leave to appeal to HCA refused, [2012] HCATrans 105).

92 See *McDarby v Merck & Co*, 949 A2d 223 at 234 (NJ Super App Div 2008) [*McDarby*] (noting that the results of the VIGOR study in March 2000 revealed a higher incidence of adverse cardiovascular events with those who received rofecoxib (Vioxx) than with those patients who received naproxen, "in patients with and without a history of atherosclerotic cardiovascular disease, and in patients with or without classic risk factors for cardiovascular disease" at 234). See also Gold, "Revisiting Relative Risk Rules", *supra* note 29. Consider the following hypothetical. For those with no pre-existing heart problems, taking Vioxx raises the risk of heart attacks 101%, more than doubling the risk from 1% to 2.01%. For those with pre-existing heart conditions like Peterson, taking Vioxx raises the risk of heart attacks 101%, from 10% to 20.01%. Vioxx is identically implicated in both scenarios.

93 Sir Austin Bradford Hill, "The Environment and Disease: Association or Causation?" (1965) 58:5 Proceedings of the Royal Society of Medicine 295 at 295 [Hill, "Association or Causation"]. These aspects of association (that is, strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy) are utilized to determine whether a reported association is causal or non-genuine. For recent support for the Bradford Hill factors as providing a guide to the

was emphasized by the Scottish Court of Session in *McTear v. Imperial Tobacco Ltd*,[94] a decision which takes a cautious approach to the use of epidemiological evidence and stresses the impossibility of applying epidemiological studies to determine causation in individual cases. The case illustrates the court's scepticism about the epidemiological evidence, as the court questioned the propriety of drawing causal inferences from observed associations when determining general causation. The court was also sceptical about the propriety of drawing causal inferences in individual cases from causal associations observed in samples of populations. While this case concerns tobacco products, its implications are particularly pertinent to problems involving medicinal products, where the role of epidemiological evidence in proving both general and specific causation is prominent.

UK developments in this area have often focused on the difficulty in proving general and specific causation using epidemiological evidence[95] derived from trends in general populations. This was graphically illustrated by *McTear*. In that case, the pursuer, the widow of a smoker, sought to recover damages from the defenders, who had manufactured the John Player brand cigarettes that the pursuer's late husband had smoked. The pursuer's husband had contracted squamous cell carcinoma of the lung, and the pursuer averred both that cigarette smoking could cause lung cancer (an issue of general causation) and that her husband's lung cancer was caused by his smoking (an issue of individual or specific causation).

The problem of establishing a general causal link between cigarette smoking and cancer was exacerbated by the fact that, unlike all the cigarette companies in the United States and all the other cigarette companies in the United Kingdom, Imperial Tobacco had not accepted that there

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kind of considerations that lead to an inference of causal association, see *Amaca*, *supra* note 81 at para 49.

94 *McTear*, *supra* note 16 at para 6.158. However, the presentation of the list of factors in textbooks as "criteria" for inferring causality or associations in a way as to imply that all the conditions are necessary has been described as "unfortunate" (Sander Greenland, ed, *The Evolution of Epidemiologic Ideas: Annotated Readings on Concepts and Methods* (Los Angeles: Epidemiology Resources Inc, 1987) at 14). As Greenland correctly observes, Sir Austin Bradford Hill expressly stated that he did not intend to lay down "hard and fast rules of evidence that must be obeyed before we accept cause and effect" (*ibid*, citing Hill, "Association and Causation", *supra* note 93 at 299). Hill added that "[n]one of [his] nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*" (*ibid* at 299 [emphasis in original]). See also Cranor, *supra* note 37 at 102–05.

95 Epidemiology has been defined as "the study of patterns of disease occurring in human populations and the factors that influence these patterns" (*McTear*, *supra* note 16 at para 6.157).

was a causal link between smoking and disease, especially lung cancer.[96] In respect of establishing general causation, Lord Nimmo Smith concluded that, in the absence of such an admission, and indeed of any evidence that this was an inference that should be drawn, the burden of proof lay on the pursuer to show that cigarette smoking could cause lung cancer.[97] In the absence of support from animal experiments, proof of causation between cigarette smoking and lung cancer depended on what was proven before the court about epidemiological studies.

Lord Nimmo Smith held that, in accordance with the Scots law of expert evidence, it was necessary to consider whether the evidence of any expert witness had imparted to the court special knowledge of the subject matter of epidemiology so as to enable the court to draw its own conclusions from epidemiological evidence. Accordingly, it was not open to the court to form its judgment on the evidence without being taught how to analyze the epidemiological evidence to a sufficient extent, and without being provided with sufficient factual material to enable proof on the balance of probabilities not only that there was an association between cigarette smoking and lung cancer, but also that the proper conclusion to be drawn from this was that there was a *causal connection* between them.[98] This distinction between association and causation in the context of the general causation issue lay at the heart of Lord Nimmo Smith's conclusions. In his view, when an association between an exposure and a condition was judged to be statistically significant, that *in itself* did not constitute a judgment that there was a causal connection between an exposure and a condition.[99] He explained:

> The finding of an association between an exposure and a condition or disease, even if judged to be statistically significant, does not of itself connote that a causal connection between the two is established. This is a matter for further exercise of judgment, taking account of

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96 See *ibid* at paras 2.58, 2.76, 6.30. This was notwithstanding the generally accepted view for over 50 years that cigarette smoking could cause lung cancer (see Richard Doll & A Bradford Hill, "Smoking and Carcinoma of the Lung: Preliminary Report" [1950] 4682 Brit Med J 739; Richard Doll & A Bradford Hill, "The Mortality of Doctors in relation to their Smoking Habits: A Preliminary Report" [1954] 4877 Brit Med J 1451; *McTear*, *supra* note 16 at para 5.208 (evidence of Sir Richard Doll)). The defence in *McTear* admitted that the World Health Organization, along with United Kingdom and United States governments, had accepted for years that cigarette smoking can cause lung cancer. However, they averred that "[c]igarette smoking has not been scientifically established as a cause of lung cancer and, although various theories have been advanced, the cause or causes of lung cancer are unknown and the mechanism or mechanisms whereby lung cancer develops are unknown" (*ibid* at para 2.7).

97 See *ibid* at paras 2.78, 2.80.

98 See *ibid* at para 6.155.

99 See *ibid* at para 6.158.

> such criteria as the consistency, the strength, the specificity, the temporal relationship and the coherence of the association ... This must, I think, especially be so when, in the view of Sir Richard Doll ... cigarette smoking is not a necessary cause nor a sufficient cause of lung cancer[.][100]

Lord Nimmo Smith then addressed the concept of relative risk, concluding that even a relative risk derived from comparison of the incidence of lung cancer in smokers and non-smokers, of a magnitude such that a positive association may be judged to be strong enough to establish causation between the two, did not connote the establishment of a causal link.[101]

As we shall now see, this scepticism about epidemiological evidence and questions about the propriety of drawing causal inferences from observed associations was not the only problem that the pursuer had in establishing general causation in *McTear*. The court also had to be taught the relevant epidemiology.

D. Teaching Courts Epidemiology

In respect of general causation, Lord Nimmo Smith held that the pursuer had failed to prove, in accordance with the requirements of the Scots law of evidence relating to expert witnesses, that cigarette smoking could cause lung cancer.[102] This was because the pursuer had failed to lead sufficient evidence, in the form of primary epidemiological literature that drew a causal connection between cigarette smoking and lung cancer, to impart to the court special knowledge of the subject matter so as to enable the court to form its own judgment about it and the conclusions to be drawn from it.[103] Lord Nimmo Smith stated that "a fundamental defect in the presentation of the pursuer's case" was the failure to present in court any of the primary literature that had concluded that there was a causal connection between cigarette smoking and lung cancer.[104] In his view, this was a missed opportunity:

> This could have been done: it is clear that the survey of British doctors, on which Sir Richard Doll and colleagues have worked for many years, is regarded as a classic of its kind, both because of the pioneering nature of the research, a preliminary report of which was published as Doll and Hill (1950), and because this has been followed

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[100] *Ibid*.

[101] See *ibid* at para 6.159.

[102] *Ibid* at paras 6.170.

[103] *Ibid* at paras 6.155, 6.162–6.163.

[104] *Ibid* at para 6.163.

> up with subsequent papers over several decades. I could at least have been shown these papers, which I assume disclosed the data, the statistical techniques and all the other considerations which led to the authors' conclusions, so that I could see for myself whether these conclusions were soundly based. The opportunity was there, with Sir Richard Doll in the witness box, and indeed Prof[essor] Friend for one thought that evidence would be given about this survey. Warning had been given on behalf of [Imperial Tobacco Ltd] ... that Sir Richard Doll's data were of potential interest to the court. But in the event no attempt was made to show me the data.[105]

A recent Scottish case, *Smith v. McNair*,[106] reaffirms this cautious approach to the interpretation of epidemiological evidence.[107] It stresses the need for experts to teach a court how to analyze epidemiological evidence before it can come to a judgment by interpreting that evidence. While acknowledging that medical witnesses are entitled to refer to medical literature—in particular to published papers by epidemiologists—even if they themselves are not epidemiologists,[108] Lord McEwan in *McNair* stressed the need to look at such evidence critically because its writers could not be cross-examined themselves. Such scientific evidence only becomes a factor for consideration if it is "intelligible, convincing and tested".[109] Accordingly, in Scotland, the cases are at one in emphasizing that where a pursuer seeks to rely on epidemiological evidence of disease to prove causation, the pursuer must impart to the court special knowledge of the subject matter of epidemiology, so that the court can form its reasoned judgment on the epidemiological evidence.[110]

Such a cautious approach to epidemiological evidence was central to the decision in *McNair*. While sympathetic to the experts who were "out-

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105 *Ibid* at para 6.162.

106 [2008] CSOH 154 (available on WL UK) (OH Scot) [*McNair*]; see also Richard Goldberg, "Causation, Idiopathic Conditions and the Limits of Epidemiology" (2009) 13:2 Ed L Rev 282.

107 See *Dingley*, *supra* note 23 at 555, Lord President Rodger; 604, Lord Prosser, concurring; *McTear, supra* note 16 at 5.11, Lord Nimmo Smith.

108 *Main v McAndrew Wormald Ltd* (1988), [1988] SLT 141 at 142.

109 *McNair*, *supra* note 1086 at para 18, citing *Davie v Magistrates of Edinburgh* (1952), 1953 SC 34 at 40, 1953 SLT 54 Ct Sess (Scot).

110 See also United States, the Advisory Committee Note (2000 Amendment) to Fed R Evidence 702. The Amendment not only stresses that the expert conducts the application of principles and methods to the facts of cases reliably, but also reiterates the "venerable practice of using expert testimony to educate the factfinder on general principles" (*ibid*). It notes that it might be important in some cases for an expert to *educate* the finder of fact about general principles, without ever attempting to apply these principles to the specific facts of the case (*ibid*).

with their chosen discipline and abroad in the field of epidemiology,"[111] Lord McEwan concluded nonetheless that the experts were unable to explain the studies, which seemed to him to "raise more questions than answers."[112] Unlike *McTear*, however, *McNair* shows less of an impression of what Chris Miller has described as a "dogmatic aversion"[113] to statistical evidence. Lord McEwan felt that many of the concerns about the evidence might have been assuaged if the authors of the reports had been called to testify and if there had been some statistical evidence presented. Without such assistance, the judge was "at once disabled from being able properly to evaluate the worth of the study or to draw the proper conclusions."[114] In his view, therefore, this was an appropriate case for epidemiologists to give evidence and for experts to explain their studies. He did not, however, believe that this was always the case, and he suggested that reliance on doctors and epidemiologists "can almost lead the court unwittingly into a kind of satellite litigation on issues away from the pursuer's case."[115] He seemed to regard *McTear* and another Scottish decision, *Dingley*,[116] as two recent examples of this.[117] However, the use of statistics in determining causation is hardly satellite litigation. In both *McTear* and *Dingley*, it was a primary issue which required resolution in the face of scientific uncertainty. The concern with Scots law taking such a cautious approach to epidemiological evidence is therefore that such an approach may make it harder to even discern that there is any possible reconciliation of the legal standard of proof on a balance of probabilities with the scientific standard of statistical significance.

Even more importantly, there is also concern that the placing an obligation on a plaintiff to teach epidemiology to a court suggests that the court can remain passive in this process. This is surely an unhelpful approach in cases such as *McTear* and in cases involving adverse reactions allegedly caused by medicinal products. In such cases, there is a clear social expectation that judges will resolve these matters to the satisfaction of both parties. As a leading American judge has observed about cases where judges preside over non-jury trials:

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111 *McNair*, *supra* note 106 at para 80.

112 *Ibid* at para 81.

113 Chris Miller, "Causation in Personal Injury: Legal or Epidemiological Common Sense" (2006) 26:4 LS 544 at 566 [Miller, "Causation in Personal Injury"].

114 *McNair*, *supra* note 106 at para 80.

115 *Ibid* at para 16.

116 *Dingley*, *supra* note 23.

117 *McNair*, *supra* note 106 at paras 27, 29.

> Passivity of the court is no virtue when serious scientific questions of more than passing importance are involved. The court owes an obligation to the parties, to society, and to itself to assist in obtaining the best possible answers to the scientific questions before it. That will mean forcing the parties to gather and present evidence effectively, calling upon other experts as necessary, and studying to obtain the understanding needed to maintain effective control.[118]

Had the pursuer in *McTear* explained the epidemiological evidence properly, and had Lord Nimmo Smith been more receptive to evidence of relative risk as well as taken a more active role in forcing the pursuer to present her evidence effectively, it would seem that general causation could have been established. Moreover, Lord Nimmo Smith should have given more weight[119] to the surely important fact that the defenders admitted that the World Health Organization, along with the governments of the United Kingdom and the United States, had accepted for many years that cigarette smoking can cause lung cancer.[120]

Of course, irrespective of the conclusions on general causation, there remained the problem of establishing individual causation in the context of "naked statistical evidence".[121] It is to this that we now turn.

E. The Statistical Chance/Personal Chance Dichotomy

It has been argued that there is a dichotomy between two kinds of chances—one "statistical" and the other "personal". A statistical chance is a figure collected from "previous unconnected outcomes, giving a probabil-

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[118] Jack B Weinstein, "Improving Expert Testimony" (1986) 20:3 *U Rich L Rev* 473 at 495–96. Judge Weinstein also encourages judges presiding over non-jury trials "to become familiar with the scientific background by reading about the issues and discussing them with the experts" (*ibid* at 494). Weinstein is cited in *Snyder v United States (Department of Health & Human Services)* 2009 WL 332044 at 2 (Ct Fed Cl 2009).

[119] Counsel for the pursuer had submitted (unsuccessfully) that considerable weight should be placed on the fact that this proposition had come to be generally accepted (see *McTear*, *supra* note 16 at para 6.41).

[120] *Ibid* at paras 2.7, 6.30.

[121] As Gary Wells has observed, the term "naked statistical evidence" is ill-defined in the legal literature (see e.g. David Kaye's use of the term in in David Kaye, "Naked Statistical Evidence", Book Review of *Quantitative Methods in Law: Studies in the Application of Mathematical Probability and Statistics to Legal Problems* by Michael Finkelstein, (1980) 89:3 Yale LJ 601 at 603; David Kaye, "The Limits of the Preponderance of the Evidence Standard: Justifiably Naked Statistical Evidence and Multiple Causation" (1982) 7:2 Law & Soc Inquiry 487 at 488), though it typically refers to probabilities that are not case specific to the events in issue "but rather existed prior to or independently of the particular case being tried" (Gary L Wells, "Naked Statistical Evidence of Liability: Is Subjective Probability Enough?" (1992) 62:5 Journal of Personality and Social Psychology 739 at 739).

ity of that outcome in any non-individual case," whereas a personal chance is "peculiar to a particular individual."[122] A statistical chance has no compensatory value, until the data is "personalised".[123]

The impossibility of applying statistics derived from epidemiological studies to determine causation in individual cases was cited as the principal reason for the pursuer's failure to prove individual, or specific, causation in *McTear*. Epidemiological evidence could not prove that it was more likely than not that but for his smoking of cigarettes, the deceased would not have contacted lung cancer.[124] As Lord Nimmo Smith put it:

> The information provided in an observational epidemiology is generally such that it can neither confirm nor refute a causal relationship, particularly when the exposure in question is not specifically associated with a certain condition (ie the exposure is always associated with the condition, and vice versa). Epidemiology cannot provide information on the likelihood that an exposure produced an individual's condition. The population attributable risk is a measure for populations only and does not imply a likelihood of disease occurrence within an individual, contingent upon that individual's exposure. The fact that cases and non–cases can emerge both from the unexposed and the exposed groups show that the likelihood of the individual occurrence cannot be reliably predicted from his or her exposure group membership alone. The group estimates obscure the underlying heterogeneity of the population, so that it is entirely possible that other group memberships besides exposure, like genetic profile, socio-economic status, workplace, diet and other exposures make a major contribution to disease occurrence. The question of using epidemiological data for individual causation raises the problem of identifying a particular individual who was harmed by the exposure. While models such as the assigned share concept, derived from attributable fractions, have attempted to deal with this, they suffer from the limitations mentioned by Dr Lewis. The attempt to identify exposure as the sole cause of disease in an individual produces a statement counter to fact in that it implies that the individual would have remained healthy if the exposure had not occurred. This, as Dr Lewis said, is not provable and cannot be derived from epidemiological data.[125]

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[122] Timothy Hill, "A Lost Chance for Compensation in the Tort of Negligence by the House of Lords" (1991) 54:4 Mod L Rev 511 at 512 [Hill, "Lost Chance"].

[123] *Ibid* at 518. See also *Hotson v East Berkshire AHA*, [1987] 2 WLR 287, 303769, Croom-Johnson LJ.

[124] See *McTear*, *supra* note 16 at paras 6.180, 6.184–6.185. See also the above discussion in *Sienkiewicz*, *supra* note 15 at paras 163, 170, 191, 205, 218. As in the UK, US courts often bifurcate both specific and general causation elements (see Joseph Sanders, "The Controversial Comment *C*: Factual Causation in Toxic-Substance and Disease Cases" (2009) 44:4 Wake Forest L Rev 1029 at 1032).

[125] *McTear*, *supra* note 16 at para 6.180.

Lord Nimmo Smith concluded that, given there were other possible causes of lung cancer other than cigarette smoking, and given that lung cancer could occur in a non-smoker, it was not possible to determine in any individual case whether *but for* an individual's cigarette smoking he probably would not have contracted lung cancer.[126] In doing so, Lord Nimmo Smith referred to "[t]he fallacy of applying statistical probability to individual causation."[127]

However, his dicta require closer scrutiny. While Lord Nimmo Smith was correct to observe that there are limitations to epidemiological evidence, his description of these limitations is somewhat inaccurate. In stating that "group estimates obscure the underlying heterogeneity of the population, so that it is entirely possible that other group memberships besides exposure, like genetic profile, socio–economic status, workplace, diet and other exposures make a major contribution to disease occurrence,"[128] he fails to appreciate that epidemiologists can and do adjust for these potentially confounding factors through logistic regression statistical techniques.[129] Notwithstanding Lord Nimmo Smith's doubts about causal proof based on population estimates of relative risk, these estimates are relevant to individual cases, even though they do not directly measure the probability of causation in an individual case.[130] Moreover, Miller has suggested that, while Lord Nimmo Smith's "dogmatic aversion to statistical evidence" means that epidemiology alone will never secure recovery in respect of specific causation in such cases,[131] use of epidemiological evidence that satisfies the criteria developed by Sir Austin Bradford Hill would seem to be hard to gainsay.[132] Thus, Miller has argued that if an individual had been one of the cases in a case control study that yields strength of association (relative risk), then in light of such strength of association and other Bradford Hill criteria, "it seems perverse to hold

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[126] *Ibid* at paras 6.184–6.185.

[127] *Ibid* at para 6.184. For the need to exercise caution in the use of general statistics in establishing causation, and the importance of looking at the claimant's individual circumstances, see the observations of Brooke LJ in *Wardlaw v Farrar*, [2003] EWCA Civ 1719, [2003] 4 All ER 1358. See also *Amaca Pty Ltd v Ellis*, [2010] HCA 5 at para 62, 263 ALR 576; *Sienkiewicz, supra* note 15 at paras 152, 163, Lord Rodger; 170, 172, Hale B; 190–92, Lord Mance; 204–06, Lord Kerr.

[128] *McTear*, *supra* note 16 at para 6.180.

[129] See also Kenneth J Rothman & Sander Greenland, *Modern Epidemiology*, 2d ed (Philadelphia, Lippincott-Raven Publishers, 1998) at 394–95.

[130] See Steve C Gold, "When Certainty Dissolves Into Probability: A Legal Vision of Toxic Causation for the Post-Genomic Era" (2013) 70:1 Wash & Lee L Rev 237 at 281, 303 [Gold, "Certainty Dissolves"]; Greenland & M Robins, *supra* note 31 at 321–22.

[131] See Miller, "Causation in Personal Injury", *supra* note 113 at 566.

[132] *Ibid*.

that it is *less* probable than not that the exposure caused that individual's condition."[133] I contend that Miller is correct in concluding that a causal relationship would exist in such circumstances. Indeed, Sir Austin Bradford Hill emphasized that "[n]one of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*,"[134] and this has been judicially approved in the United States.[135] Sir Austin Bradford Hill specifically cautioned against overly emphasizing the importance of specificity at the expense of strength of association, referring specifically to smoking and lung cancer. [136] In doing so, he provided a particularly apt example:

> Coming to modern times the prospective investigations of smoking and cancer of the lung have been criticized for not showing specificity—in other words the death rate of smokers is higher than the death rate of non-smokers from many causes of death. ... But here surely one must return to my first characteristic, the strength of association. If other causes of death are raised 10, 20 or even 50% in smokers whereas cancer of the lung is raised 900–1,000% we have specificity—a specificity in the magnitude of the association.
>
> ...
>
> We must also keep in mind that diseases may have more than one cause.
>
> ...
>
> In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.[137]

I suggest that Lord Nimmo Smith in *McTear* undervalued the significance of the widely accepted magnitude of strength of association between cigarette smoking and cancer, and that he was wrong to treat the Bradford Hill factors as criteria that *all* needed to be satisfied before such an association could amount to a causal connection between smoking and lung cancer. In his discussion of the impossibility of applying statistics derived from epidemiological studies to determine causation in individual cases, Lord Nimmo Smith failed to appreciate that, in determining specific causation, epidemiologists can and do adjust for potentially confounding

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[133] *Ibid* [emphasis in original].

[134] Hill, "Association or Causation", *supra* note 93 at 299 [emphasis in original].

[135] See *Cook v Rockwell Intern Corp*, 580 F Supp 2d 1071 at 1098 (D Colo 2006).

[136] Hill, "Association or Causation", *supra* note 93 at 297. The High Court of Australia has recently stressed that reference to relative risk ratio may act as an indicator of strength of association (see *Amaca*, *supra* note 81 at para 49).

[137] Hill, "Association or Causation", *supra* note 93 at 297.

factors through logistic regression techniques and other forms of statistical refining mechanisms. It is to these techniques that we now turn.

F. Overcoming the Statistical Chance/Personal Chance Dichotomy: Statistical Refining Mechanisms Using Specific Risk Factors

The problem of using statistics deriving from trends in general populations to prove causation in an individual case has been recognized judicially by the House of Lords in *Hotson v. East Berkshire Area Health Authority*[138] and in *Gregg v. Scott*,[139] and by the UK Supreme Court in *Sienkiewicz v. Greif*.[140]

Yet it is arguable that while epidemiological evidence reaches conclusions on the incidence of a disease in a population in the form of relative risk, this relative risk can be refined to draw conclusions about the cause of disease in an individual using specific risk factors,[141] such as those present in Mr. McTear's case and in Mr. Peterson's case. This has been accepted by American courts in the context of pharmaceutical product liability litigation.[142] In *McDarby v. Merck & Co, Inc.*,[143] a case involving the drug Vioxx, epidemiological evidence was combined by experts with the presence of the plaintiff's personal heart attack risk factors, namely his age, low levels of "good" cholesterol, weight, and diabetes. The New Jersey court regarded this as ample evidence to support an increased risk resulting from the combined effects of diabetes and Vioxx, and concluded that Vioxx had been a substantial contributing factor to the plaintiff's heart at-

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[138] *Hotson*, *supra* note 59 at 789, Lord Mackay.

[139] See *Gregg v Scott*, [2005] UKHL 2, [2004] 2 AC 176 at paras 26–33, Lord Nicholls; 153, Lord Phillips.

[140] *Sienkiewicz*, *supra* note 15 at paras 152, 163, Lord Rodger; 170, 172, Hale B; 190–92, Lord Mance; 205, Lord Kerr.

[141] See Berger, *supra* note 31 at 306.

[142] Green, "Epidemiology", *supra* note 8 at 616, citing *Havner*, *supra* note 10 at 720; see also *Smith v Wyeth Ayerst Laboratories Co*, 278 F Supp (2d) 684 at 708–09 (WDNC 2003) (discussing an expert's attempt to apply principles of relative risk from an epidemiological study on the relationship between diet drugs and primary pulmonary hypertension (PPH) to the risk faced by the individual plaintiff, who developed PPH after taking prescription appetite suppressants based on specific risk characteristics (duration of use and timing of use). The expert's opinion was deemed unreliable).

[143] *McDarby*, *supra* note 92 at 270.

tack.[144] In so concluding, the court applied a substantial factor standard in the context of concurrent causation, in preference to the "but for" test.[145]

In this context, I have suggested that statistics regarding evidence of general causal links between a drug and an injury (a statistical chance) could be refined into statistics establishing a specific causal link between the drug and the adverse reaction in the case at issue (a personal chance)[146] using logistic regression techniques and other forms of statistical refining mechanisms.[147]

Logistic regression techniques identify determinants of a particular outcome and assess the extent of the contribution of these determinants, adjusting for confounding factors[148] that may influence the contribution.[149] Logistic regression is also closely linked to other forms of statistical refining, such as Bayes' theorem. Bayes' theorem can modify evaluations of probability based on initial assumptions in the light of more data that later becomes available. It expresses the relationship between the probability of a proposition (A) evaluated *before* the utilization of new data (B) (prior probability), and the probability of the same proposition evaluated *after* the utilization of the new data (posterior probability).

Thus:

$$\text{Posterior Probability of A given B} = \frac{\text{Prior Probability of A}}{1} \times \frac{\text{Probability of B given A}}{\text{Unconditional Probability of B}}$$

$$\text{i.e. } P(A/B) = P(A) \times [P(B/A) / P(B)]$$

Prior probabilities can therefore be updated in the light of new data from epidemiological studies as they accumulate, providing both fact find-

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144 *Ibid* at 269–70.

145 *Ibid* (applying the substantial factor standard, causation was appropriately demonstrated by long term use of Vioxx and "medical and/or scientific proof of a nexus between [that use] and ... plaintiff's condition" at 271).

146 Hill, "Lost Chance", *supra* note 122 at 518.

147 This builds on the author's discussion in Goldberg, *Causation and Risk in the Law of Torts, supra* note 2 at 39–40.

148 A confounding factor is a factor that is both a risk factor for the disease and one associated with the exposure in issue. "Confounding" refers to the situation where an association between an exposure and an outcome is all or partly due to a factor that affects the outcome but which is unaffected by the exposure (see Green, "Epidemiology", *supra* note 8 at 621).

149 Rothman & Greenland, *supra* note 129; O Caster et al, "Logistic Regression in Signal Detection: Another Piece Added to the Puzzle", Letter to the Editor, (2013) 94:3 Clinical Pharmacology & Therapeutics 312.

ers in individual product liability cases, and policy-makers such as the Food and Drug Administration and the European Medicines Agency, with an update of the estimated risk.[150] The main difficulty with such posterior probabilities is that frequentist statisticians[151] who rely on epidemiological evidence regard them as necessarily subjective, since they reflect not only data but also subjective prior probabilities.[152] However, "objective Bayesians"[153] use Bayes' theorem without eliciting prior probabilities from subjective beliefs, avoiding the charge of subjectivism.[154] This has been supported in the pharmaceutical product liability context by Professor Joseph Gastwirth, who has adopted a data-based approach to ensure that the choice of prior distribution is objective and unbiased. He uses the first case control study or an analysis of adverse event and case reports to determine two prior distributions, one the most favourable to the defendant, and the other centred on or near the estimated relative risk from the first study. This method of determining two prior distributions restricts the degree of subjectivity that an analyst can insert into a Bayesian approach. This is very important in the legal context, where lawyers would likely choose the expert who obtains the more favourable result for them. The data-based approach helps to avoid bias in the choice of prior distribution.[155] Others have also tried to apply Bayes' theorem in the evaluation of the reliability of medical and scientific evidence in toxic tort cases.[156]

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150 See Joseph L Gastwirth, "Should Law and Public Policy Adopt 'Practical Causality' as the Appropriate Criteria for Deciding Product Liability Cases and Public Policy?" (2013) 12:3 Law, Probability and Risk 169 [Gastwirth, "Practical Causality"]; see also Patrick Ryan et al, "Learning from Epidemiology: Interpreting Observational Database Studies for the Effects of Medical Products" (2013) 5:3 Statistics in Biopharmaceutical Research 170 at 178 (supporting a Bayesian framework to interpret observational database studies for the effects of medical products and suggesting that future work can extend the Bayesian framework to include such elements as the Bradford Hill factors).

151 Frequentist statisticians are those who define probability as the frequency of a certain measurement or observation. The frequentist approach focuses on the probability of the data, given the hypothesis. See Maarten HP Ambaum, "Frequentist vs Bayesian Statistics—A Non-Statisticians [sic] View" (July 2012), online: Department of Meteorology, University of Reading, UK <www.met.reading.ac.uk/~sws97mha/Publications/Bayesvsfreq.pdf>.

152 See David H Kaye & David A Freedman, "Reference Guide on Statistics" in *Reference Manual on Scientific Evidence*, 3d ed (Washington, DC: National Academies Press, 2011) 211 at 258, 273.

153 Bayesian statisticians define probability as the plausibility of a hypothesis given incomplete knowledge or data (see Ambaum, *supra* note 150).

154 Kaye & Freedman, *supra* note 152 at 259 n 123.

155 Gastwirth, "Practical Causality", *supra* note 150.

156 See e.g. Neal C Stout & Peter A Valberg, "Bayes' Law, Sequential Uncertainties, and Evidence of Causation in Toxic Tort Cases" (2005) 38:4 Mich JL Reform 781 at 787 (submitting that judges should apply Bayesian probabilistic approaches in toxic tort

However, the strongest criticism of Bayes' theorem is the difficulty of arriving at a sufficiently accurate evaluation of a pre-existing probability to which experimental data can be applied.[157]

Bayes' theorem tells us that the value of a piece of evidence in testing a particular assertion is determined by its likelihood ratio. The likelihood ratio (LR) is the probability of the evidence supposing our assertion is true, divided by the probability of the evidence if the assertion is not true.[158] The Centre for Evidence Based Medicine at the University of Oxford provides a helpful example of the LR in the following:

> [Y]ou have a patient with anaemia and a serum ferritin of 60mmol/l and you find in an article that 90 per cent of patients with iron deficiency anaemia have serum ferritins in the same range as your patient (= sensitivity) and that 15 per cent of patients with other causes for anaemia have serum ferritins in the same range as your patient (1 – specificity). This means that your patient's result would be six times as likely (90/15) to be seen in someone with, as opposed to someone without, iron deficiency anaemia, and this is called the LR for a positive test result.[159]

An alternative statement of Bayes' theorem explains it in terms of odds.[160] Bayes' theorem expresses the relationship between the odds in favour of a hypothesis *before* the utilization of new data (prior odds) and the odds in favour of the hypothesis after taking into account the new data (posterior odds). The prior odds must be multiplied by the likelihood ratio of the new piece of data to generate the posterior odds.

Thus:

> Posterior Odds = Prior Odds x Likelihood Ratio

Applying this to the *Peterson* case,[161] "Vioxx-induced MI" could be compared with a catch-all alternative, "no Vioxx-induced MI". Alternative-

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cases when evaluating the reliability of medical and scientific evidence, and in so doing permitting the fact finder to decide only those toxic tort claims for which there is reliable and relevant scientific support for each link in the causal chain).

157 See Sir Richard Eggleston, *Evidence, Proof and Probability*, 2d ed, (London, UK: Weidenfeld and Nicolson, 1983) at 171.

158 See Bernard Robertson & GA Vignaux, *Interpreting Evidence: Evaluating Forensic Science in the Courtroom* (Chichester, UK; John Wiley & Sons 1995) at 17.

159 Centre for Evidence Based Medicine, "Likelihood Ratios", online: CEBM <www.cebm.net/?o=1043>.

160 The relationship between odds and probability is:

> Odds = Probability / (1 – Probability)

Thus the probability of 0.9 = odds of 9:1.

161 *Peterson*, supra note 17.

ly, one could compare "Vioxx-induced MI" with some specific alternative, such as "diet-induced MI", "totally uncaused MI", or "no MI". The likelihood ratio would then be the ratio of the probabilities of developing MI under these two hypotheses.[162]

A statistical chance could be refined and personalized into a personal chance using specific factors which are embodied in the likelihood ratio. The probabilities in the likelihood ratio can be decomposed into factors in the light of specific case information in respect of patient history. Such factors could include the risk factors in *Peterson*,[163] namely Peterson's age (LR (Ag)), gender hypertension (LR (Gh)), hyperlipidaemia (LR (Hypl), obesity (LR (Ob)), left ventricular hypertrophy (LR (LVH)), and a history of smoking (LR (Hs)).[164] The likelihood ratio is then found by obtaining the product of all the individual likelihood ratio factors.

Diagrammatically this can be expressed by:

LR = LR (Ag) x LR (Gh) x LR(Hypl) x LR(Ob) x LR(LVH) x LR(Hs)

(Caveat: components, i.e. Ag etc., must be statistically independent)

The use of all these factors is dependent on the specific case information available. If all specific case information in respect of the factors is available, the posterior odds are calculated as follows:

Posterior Odds = Prior Odds x LR = LR (Ag) x LR (Gh) x LR(Hypl) x LR(Ob) x LR(LVH) x LR(Hs)

Thus the posterior odds can be further refined by combining the prior odds, based on background information, with the likelihood ratios, based on case-specific information, to produce as accurate a posterior probability as possible.[165] The nature of each risk factor likelihood ratio can represent a particularistic property of the individual claimant, provided they can be determined in the case in issue.[166] There is therefore a need to obtain sta-

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[162] I am grateful to Professor Philip David for his explanation of this point.

[163] *Peterson*, *supra* note 17.

[164] *Ibid* at para 120.

[165] See B Donatini, I Le Baye & P Krupp, "Causality Assessment of Spontaneous Reporting: Correlation Between Bayesian and Other Approaches" (1993) 7:4 Pharmaceutical Medicine 255 at 256.

[166] Personal Communication, Professor Philip David, Statistical Laboratory, Centre for Mathematical Sciences, Cambridge University, 12 July 2013; Robertson and Vignaux advocate that scientific evidence concerning an issue should be combined with other ev-

tistics with an evidentiary foundation before such likelihood ratios can be calculated.[167]

This would seem to be a possible tool that can improve probabilistic precision in the *Peterson*–type case and in other cases involving medicinal products. In so doing, this tool can overcome the difficulties associated with the statistical chance/personal chance dichotomy.

It is clear that while Bayes' theorem could provide a normative approach to legal decision making in the context of causation and medicinal products, implementing the theorem, in practice, is likely to be difficult.[168] We have seen that Bayes' theorem assumes the presence of conditionally independent new evidence to update the previous evidence, but this new evidence is absent in many cases involving alleged adverse drug reactions. This complicates the application of the theorem. The use of individual risk factor likelihood ratios in respect of individual items of evidence is potentially valuable, but these may be difficult to calculate in practice. It should also be conceded that if sample sizes are so small that one cannot disaggregate data to provide information on individual risk factors, then the statistical refining process will fail. Moreover, while more detailed individual ratios might improve the accuracy of the posterior odds, the introduction of too many additional quantities with imperfect estimation could degrade it.[169] However, the basic point here is not to suggest that Bayes' theorem is necessarily the answer to the problem of establishing specific causation in the context of epidemiological evidence. It is rather that logistic regression techniques and other forms of statistical refining mechanisms using specific risk factors can and do help in the process of giving quantitative or quasi-quantitative expression to conclusions about the

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idence relating to the same issue, and that the most effective way of doing so is to express the evidence in likelihood ratio form for it to be subsequently combined with other evidence (Robertson & Vignaux, *supra* note 158 at 220). In addition, they have observed that the likelihood ratio's importance is that it determines relevance and probative value, the key determinants of admissibility of expert evidence (*ibid* at 22). Robertson and Vignaux have submitted that it is not essential to have precise numbers for each of the probabilities to assess the likelihood ratio (*ibid*). However, this would seem arguable in complex cases involving the establishment of causation with medicinal products (see Goldberg, *Causation and Risk in the Law of* Torts, *supra* note 2 at 43 n 242).

167 See Katherine Grevling, Book Review of *Interpreting Scientific Evidence: Evaluating Forensic Science in the Courtroom* by Bernard Robertson & GA Vignaux, (1996) 112 LQR 509 at 510.

168 Stephen E Fienberg & Mark J Schervish, "The Relevance of Bayesian Inference for the Presentation of Statistical Evidence and for Legal Decisionmaking" (1986) 66:4 BUL Rev 771 at 772, 782, 794.

169 See also A Philip Dawid, "The Role of Scientific and Statistical Evidence in Assessing Causality" in Richard Goldberg, ed, *Perspectives on Causation* (Oxford: Hart, 2011) 133 at 140–45.

cause of disease in an individual claim that is based on epidemiological evidence.

Support for the refining and personalizing of epidemiological evidence in cases of individual causation involving medicinal products is now gaining traction in courts. One relevant recent case is *Andersen v. St Jude*, a Canadian trial on the merits of a class claim concerning the "safety of the mechanical prosthetic heart valves and annuloplasty rings with Silzone that were designed and manufactured by the defendants and approved for sale in Canada in the late 1990s."[170] In *Andersen*, the Ontario Superior Court recognized that the doubling of risk standard is merely a presumptive threshold, so that a negative finding on causation could be rebutted using probative individualized evidence in a subsequent individual trial.[171]

Silzone was a proprietary term for a coating comprising layers of titanium, pallodium, and an outer layer of metallic silver, which was applied to a polyester sewing cuff that surgeons used to attach a prosthetic heart valve to heart tissue. Silver is known as an antimicrobial, and the Silzone coating was designed to inhibit the growth of bacteria that could cause endocarditis, an infection of the lining of the heart that is a potential serious complication of heart valve surgery. Other than the application of the coating to the sewing cuff, "the Silzone valves were of the same design as conventional mechanical valves that the defendants had manufactured for many years."[172] Following a randomized clinical trial called AVERT, which had "revealed a small, but statistically significant increase in explants due to a medical complication known as paravalvular leak (PVL) in patients who had received a Silzone implant," the defendants in *Andersen* issued a worldwide recall of all Silzone-coated products in early 2000.[173] A class action against St. Jude Medical was commenced in 2001. At its core was a claim in negligence, which focused on the breach of St. Jude's duty of care to patient class members and questions of general causation.[174]

> The plaintiffs advanced the theory that Silzone [was] a toxic substance that interfere[d] with the cells involved in tissue healing and impair[ed] the body's ability to properly incorporate the Silzone device into the heart, thereby causing or contributing to a variety of serious medical complications for Silzone patients. As medical complications can occur with all prosthetic heart valves, a key inquiry in

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[170] *Andersen*, *supra* note 18 at para 1.

[171] *Ibid* at para 1.

[172] *Ibid* at para 2.

[173] *Ibid* at para 1.

[174] *Ibid* at para 4.

> this trial was whether Silzone ... *materially increased* [the] *risk* of [patients] experiencing one or more of these complications.[175]

While the couching of this inquiry in terms of "material increase in risk" may seem peculiar,[176] the issue being addressed was whether the plaintiffs could prove that the Silzone valve caused a true excess risk of the medical complications—above the risk caused by the conventional valves. In essence, the Ontario Superior Court was adopting the same approach to the issue as the English High Court in *XYZ v. Schering Health Care Ltd.*[177]

Notwithstanding that Justice Lax found that the defendants did not breach any duty of care in the pre-market design, manufacture, and testing, or in the post-market surveillance, warning, and recall of Silzone-coated products,[178] she proceeded to determine the common issues of causation had the court found differently on the breach of duty issue. She explained that

> statistical epidemiological evidence ha[d] been presented to aid [her] in determining whether or not Silzone valve patients experience a higher risk of medical complications than conventional valve patients. In other words, the purpose of this evidence [was] to determine the risk of medical complications posed by the Silzone valve *relative* to the risk posed by the conventional valve.[179]

This introduced the concept of relative risk, which was "a numerical expression of the risk of medical complications for one class of patients relative to another."[180] While recognizing the limitations of epidemiological evidence, in that it ought not to be considered determinative of individual causation,[181] Justice Lax used simple arithmetic, the application of the "but for" test, and the balance of probabilities standard to conclude that for the purposes of issues of *general* causation in a class action trial, a doubling of risk standard should be adopted. A product (here the Silzone valve) thereby creates a material risk of an adverse event where the risk

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[175] *Ibid* at para 5.

[176] The reason for the use of the word "material", which was formulated by Justice Cullity in his certification decision (*ibid* at paras 5, 520), was "to ensure that findings with respect to whether Silzone increases the risk of complications would be sufficiently meaningful that they would be indicative of something more than a remote possibility of causation" (*ibid* at para 528).

[177] *XYZ*, *supra* note 40 at paras 20–21.

[178] See *Andersen*, *supra* note 18 at paras 6, 182–83, 214.

[179] See *ibid* at para 384.

[180] *Ibid*.

[181] See *ibid* at para 395.

is at least twice the risk of the adverse effect occurring in the absence of the product's use (namely, when using the conventional valve).[182]

However, in an important development which may help to constrain the emergence of overly optimistic emphasis on doubling of risk as some magic formula with which to prevent cases from going forward to trial in the future, Justice Lax explained that the establishment of material risk and the application of the doubling of risk standard were not determinative of individual causation. Instead, for the purpose of individual class member claims, the application of the doubling of risk standard is merely a *presumptiv*e as opposed to a prescriptive threshold, so that a negative finding on causation (where the relative risk is below two) could be rebutted using probative individualized evidence in a subsequent individual trial.[183] Justice Lax added that if she had found the defendants to be negligent, she would have presumptively applied the doubling of risk standard for materiality.[184] Accordingly, patients who suffered complications for which the increase in risk was not material (i.e., where the relative risk was below two) or even not statistically significant would still be able to recover at the individual stage of those proceedings, provided they presented sufficient individualized evidence to rebut the presumption of a lack of causation flowing from a relative risk below two, and that they were able to persuade their trier of fact that Silzone was the "but for" cause of their complications.[185] The benefit of adopting this approach is that "it does not shut the door on individual class members solely on the basis of evidence regarding group risk."[186] As Justice Lax explained, the adoption of a presumptive approach to materiality, permitting negative findings on causation to be rebutted by individualized evidence, allowed her to advance the litigation and to outline how a trier of fact at the individual stage of similar proceedings could properly utilize relative risk as ascertained by epidemiological data.[187]

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[182] See *ibid* at paras 532–38. The arithmetical explanation for adopting the "doubling of risk" rule (*ibid* at paras 532–34) is almost identical to that provided in *XYZ*, *supra* note 40 at para 21.

[183] *Andersen, supra* note 18 at paras 542, 544, 555, 558–59.

[184] "Materiality" means determining whether the Silzone valve materially increased the risk of a particular medical complication (*ibid* at para 427).

[185] *Ibid* at para 559.

[186] *Ibid* at para 560.

[187] *Ibid* at para 562.

Conclusion

We can make the following observations about recent cases from the United Kingdom that examine the role of epidemiological evidence in assessing causation in medicinal product liability claims.

There remain considerable difficulties in reconciling standards of proof in law and in science. Despite the trenchant criticisms of the doubling of risk theory in the United States, the theory appears to be gaining ground in the United Kingdom. However, the majority of the UK Supreme Court in *Sienkiewicz* appears to be sceptical of introducing a threshold for the use of epidemiological evidence and remain of the view that such evidence can be useful but must be viewed with caution. Without further non-statistical evidence, there is reluctance for courts to proceed to find the existence of a causal relationship. The danger otherwise is that counsel, in assessing the chances of success of "no win, no fee" multi-party product liability litigation, especially that which involves medicinal products, may regard this doubling of risk theory as the sole basis on which to allow or prevent cases from going forward to trial, even where epidemiological evidence is lacking. This could potentially prejudice access to justice in future cases. If the doubling of risk approach is to be embraced by UK courts, it should be treated as it was in the Canadian decision of *Andersen*, where the standard operated as merely a *presumptive* as opposed to a prescriptive threshold, so that a negative finding on causation (where the relative risk is below two) could be rebutted using probative individualized evidence in a subsequent individual trial. In such cases where there is a dearth of epidemiological evidence, courts and, for that matter, funding bodies should learn from the US experience and should avoid insisting on epidemiological studies which have a relative risk of greater than two, allowing all evidence which falls "within a zone of reasonable [scientific] disagreement"[188] to be considered.

While it seems the United Kingdom is becoming more receptive to the need for epidemiologists to come to court to speak to their evidence and for it to be taught to the fact finder, courts have nonetheless recently developed an overly cautious approach to the use of epidemiological evidence, particularly in Scots law. We have seen two main reasons for judicial scepticism about epidemiological evidence emerging from the case law, namely the propriety of drawing causal inferences from observed associations (a general causation issue) and the propriety of drawing causal

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[188] Cranor, *supra* note 37 at 366; see also *ibid* at 289–90, 335. Courts should not exclude causal opinions based on non-epidemiological evidence where a body of epidemiological data does not exist (David L Faigman et al, "How Good is Good Enough?: Expert Evidence Under *Daubert* and *Kumho*" (2000) 50:3 Case W Res L Rev 645 at 663).

inferences in individual cases from concededly causal associations observed in samples of populations (a specific causation issue). The concern with taking such a cautious approach to epidemiological evidence is that it may make it harder to discern that there is *any* reconciliation of the legal standard of proof on a balance of probabilities with the scientific standard of statistical significance. Moreover, there is also concern that placing an obligation on a plaintiff to teach epidemiological analysis to a court suggests that the court can remain passive in this process. This is surely an unhelpful approach in cases such as *McTear*, where there is a clear societal expectation that a judge will resolve these matters to the satisfaction of both parties. Had the pursuer explained the epidemiological evidence properly, and had Lord Nimmo Smith been more receptive to evidence of relative risk, taken a more active role in forcing the pursuer to present her evidence effectively, and given adequate weight to the generally accepted scientific evidence that cigarette smoking can cause lung cancer, general causation could have been established in this case.

There also remains a lack of clarity on the extent to which generalized epidemiological evidence can be useful in determining individual, or specific, causation. Accordingly, this paper supports the use of logistic regression techniques and other forms of statistical refining mechanisms using specific risk factors to give quantitative or quasi-quantitative expression to conclusions about the cause of disease in an individual drug product liability claim that is based on epidemiological evidence. Logistic regression is also closely linked to other forms of statistical refining such as Bayes' theorem. We have seen that while Bayes' theorem can modify evaluations of probability based on initial assumptions in light of more data using specific factors embodied in the likelihood ratio, implementation of the theorem, in practice, is likely to be difficult. It is important to stress that Bayes' theorem is not necessarily the answer to the problem of establishing specific causation in the context of epidemiological evidence. However, the crucial point is that statistical refining mechanisms using specific risk factors can assist courts in determining specific causation in drug product liability cases when the dominating evidence is epidemiological in nature. This is likely to be increasingly true, as the quality of scientific evidence increases with time.[189]

It has been suggested that this approach could have been adopted with the specific case information available in *Peterson*, instead of the plaintiff's personal circumstances being blindly treated as diminishing the

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[189] For support for a probabilistic model of specific causation in toxic torts, when the dominating evidence comprises population-based data of the toxic effect, see especially Gold, "Certainty Dissolves", *supra* note 130 at 281, 303–04, 338–39.

strength of the epidemiological evidence.[190] Indeed, the interdisciplinary Vaccine Safety Committee of the Institute of Medicine adopted such an "informal Bayesian approach" to assessing case reports in its review of scientific and medical literature on specific risks to children associated with vaccines.[191] Courts could use this information to refine generalized statistics to produce as accurate a posterior probability as possible, especially in the pharmaceutical field. This, however, would require epidemiologists and physicians to assist courts in such an exercise, and clearly, without courts having access to existing prior probabilities and the ability to quantify likelihood ratios, the utility of the process would be limited.[192]

Notwithstanding the scepticism of the majority of the UK Supreme Court in *Sienkiewicz*, there is little doubt that the use of epidemiological evidence in medicinal product liability cases, especially where non-numerical solutions are elusive, has now come of age. Albeit with caution, courts are recognizing the importance of such evidence. The challenge is now for lawyers and epidemiologists to come to some consensus as to what amounts to a suitable use of epidemiological evidence in such cases when establishing proof on a balance of probabilities. It is arguable that the so-called doubling of risk approach mooted in *Sienkiewicz* is overly simplistic. In particular, doubling of risk does not consider absolute risk (that is, the risk of something occurring without any context)[193] and the severity of

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[190] *Peterson*, *supra* note 17.

[191] See Kathleen R Stratton, Cynthia J Howe & Richard B Johnston, Jr, eds, *Adverse Events Associated with Childhood Vaccines: Evidence bearing on Causality* (Washington, DC: Division of Health Promotion and Disease Prevention, Institute of Medicine, National Academy Press, 1994) at 25.

[192] See Cranor, *supra* note 37 at 256–59. For further discussion of the National Childhood Vaccine Injury Compensation Program, see Goldberg, *Causation and Risk in the Law of Torts*, *supra* note 2 at 163–70.

[193] Feldschreiber, Mulcahy, and Day provide a good illustration of the failure to take account of absolute risk: "If there is an incidence of disease in an unexposed population of one in a million cases and in an exposed population of two in a million cases, the RR is two but the absolute risk is very low" (Feldschreiber, Mulcahy & Day, *supra* note 19 at 188). The Federal Full Court of Australia observe in *Peterson* that "[d]oubling a very low absolute risk of an adverse result may produce an absolute risk which itself remains so low that a positive finding of causation on the balance of probabilities would itself be an affront to common sense" (*supra* note 17 at para 119). However, I respectfully submit that as a matter of statistics, this observation is incorrect. If one accepts the premise of this paper that population-based estimates are relevant to causal conclusions in individual cases, then doubling of risk is doubling of risk, irrespective of absolute risk. One can concede the intuitive appeal of the court's statement. Thus, if in a population of 100 million unexposed individuals, only one case of disease were expected, who could submit that finding two cases represented anything other than a fluke? However, that intuition is merely an illustration of the difficulty in obtaining statistically significant results in the epidemiological investigation of rare conditions. If there were a way of designing an epidemiological study of sufficient quality, capable of identi-

the outcome. Any attempt to reach a consensus in the future must address these, and related, difficult issues.

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fying an association that truly exists (i.e., one with sufficient power), it could be said with great confidence that the exposure (generally) causes the disease. I am grateful to an anonymous reviewer for this point.