Scientific Evidence of Factual Causation
An Educational Module

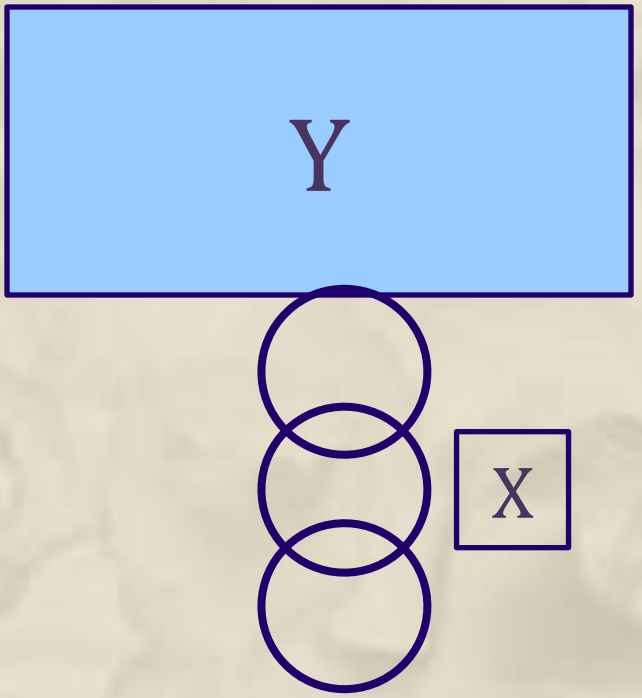
Slides

Steve C. Gold
Professor of Law
Rutgers School of Law-Newark

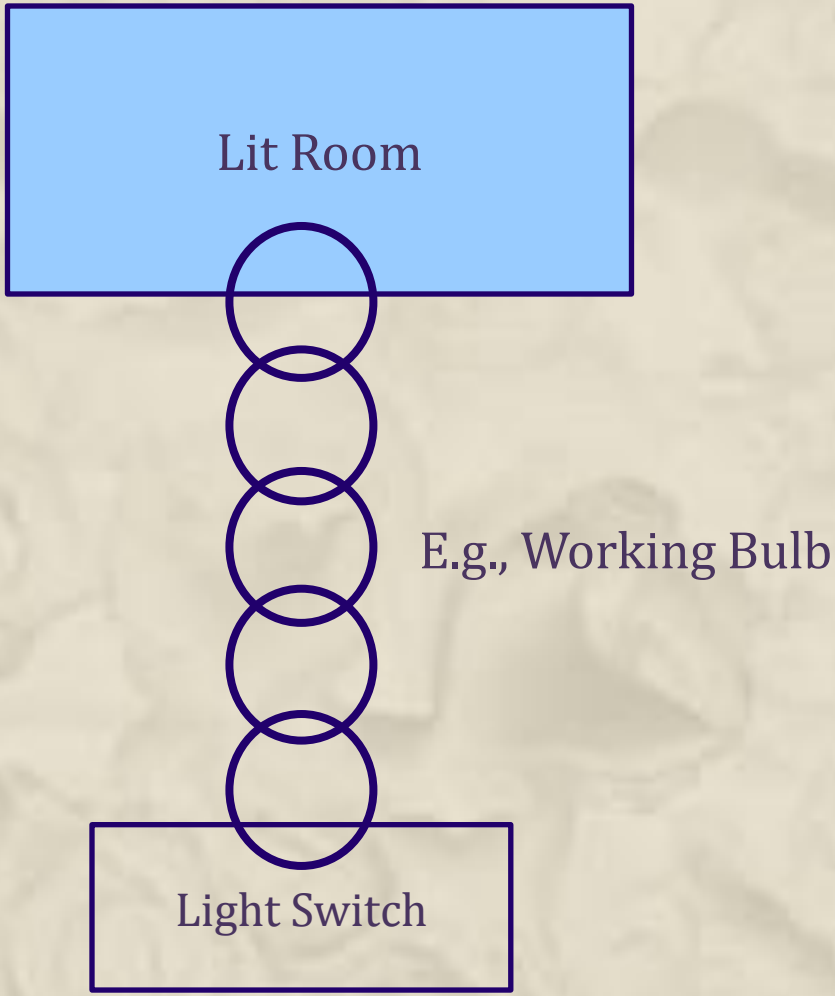
Michael D. Green
Williams Professor of Law
Wake Forest University School of Law

Joseph Sanders
A.A. White Professor of Law
University of Houston Law Center

A "BUT FOR" CAUSE



MULTIPLE BUT-FOR CAUSES (NECESSARY ELEMENT OF A SUFFICIENT SET)

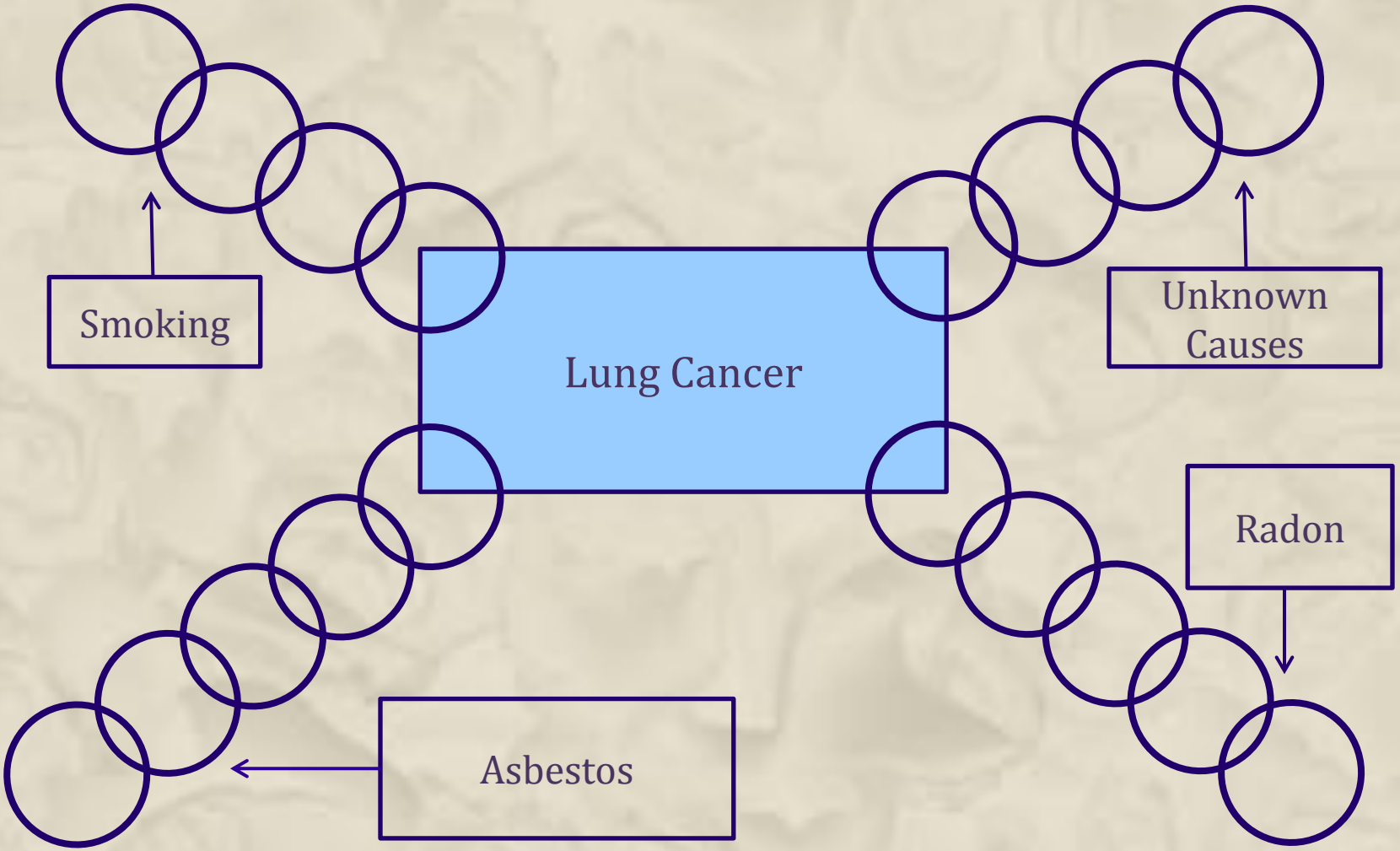


FRAMING THE CAUSAL ISSUE

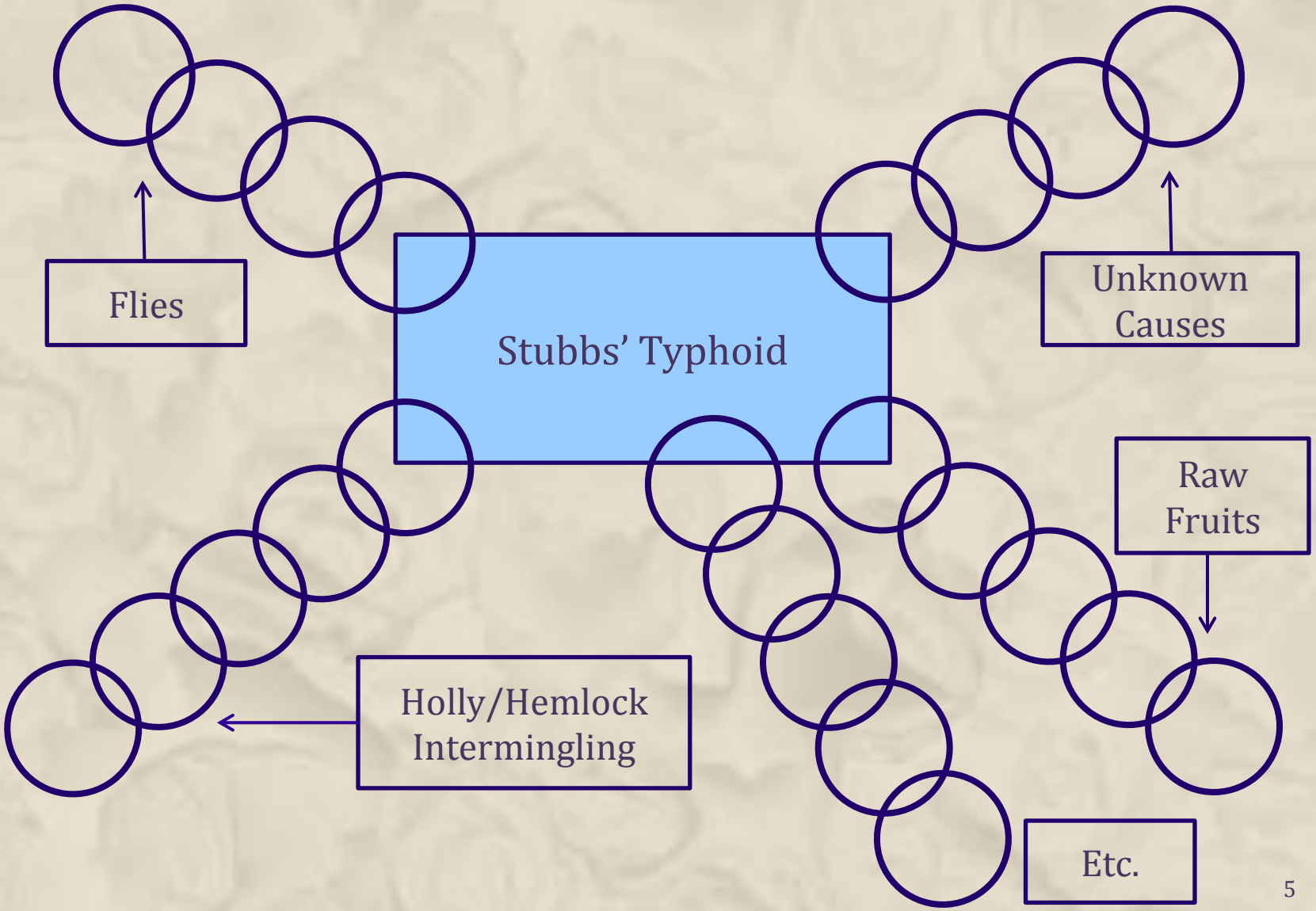
Stubbs' Typhoid
(outcome)

Holly/Hemlock
Intermingling
(Cause)

MULTIPLE COMPETING CAUSES



MULTIPLE COMPETING CAUSES



FRAMING THE CAUSAL ISSUE

Stubbs' Typhoid
(outcome)

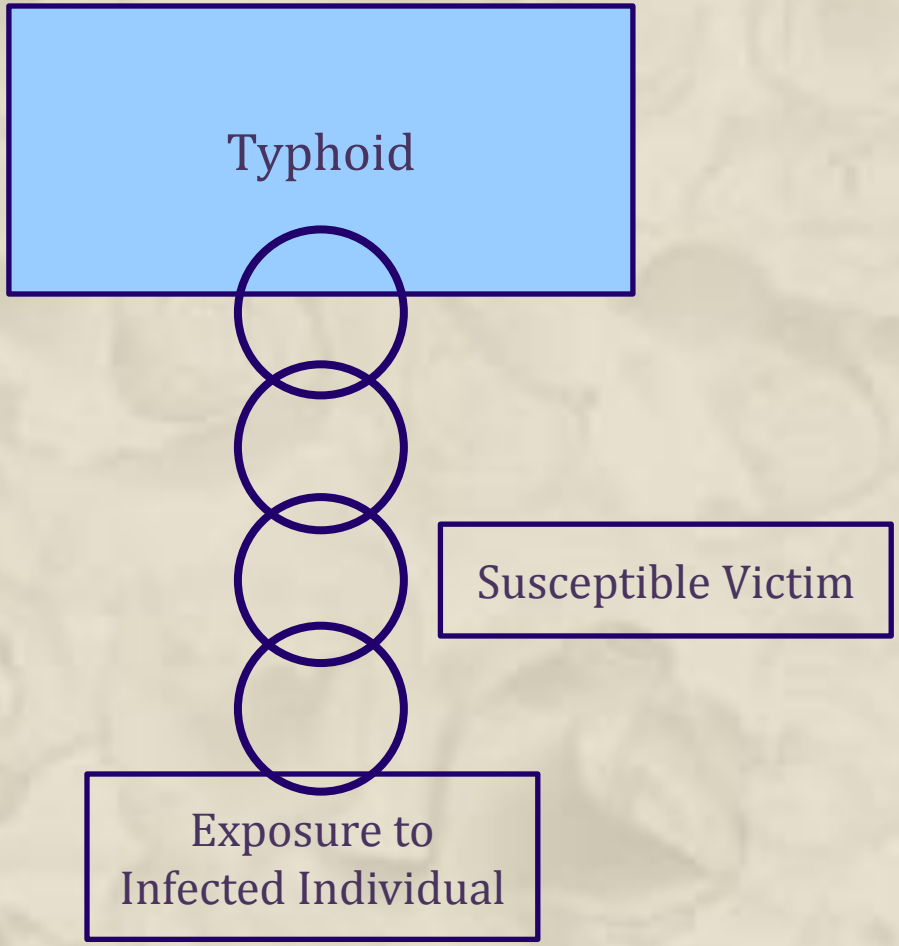
Δ's Negligence in
Holly/Hemlock
Intermingling
(Cause)

FRAMING THE CAUSAL ISSUE

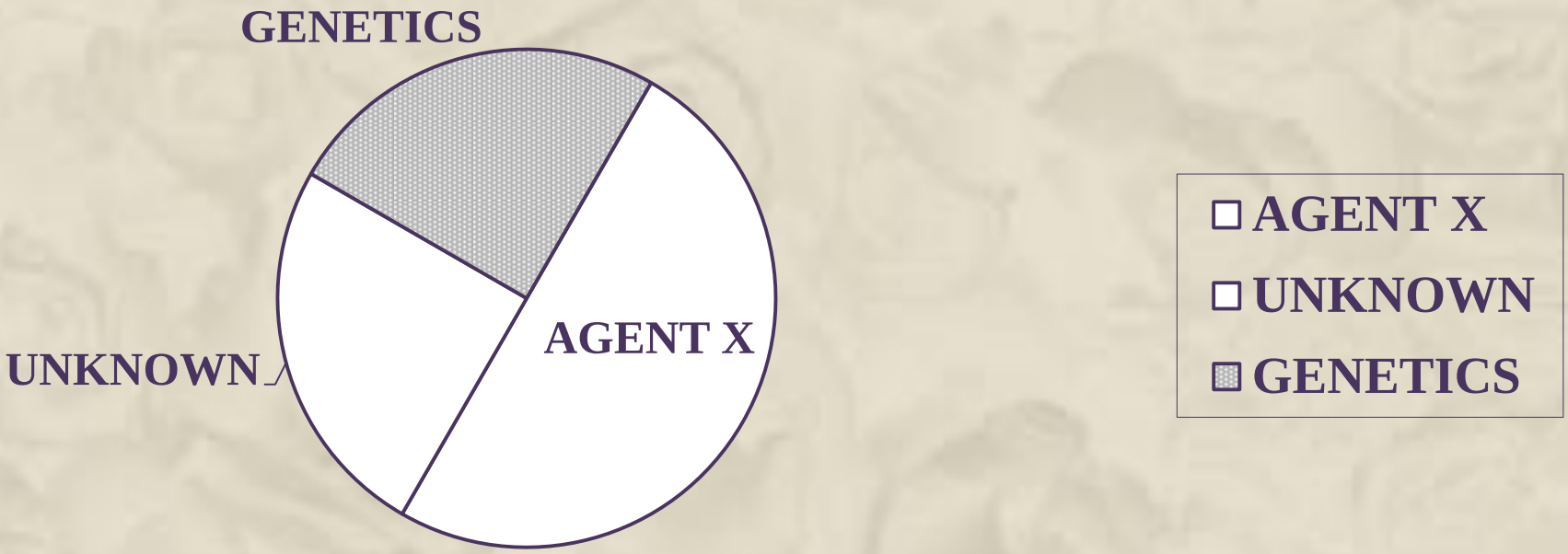
Stubbs' Typhoid
(outcome)

Holly/Hemlock
Intermingling
(Cause)

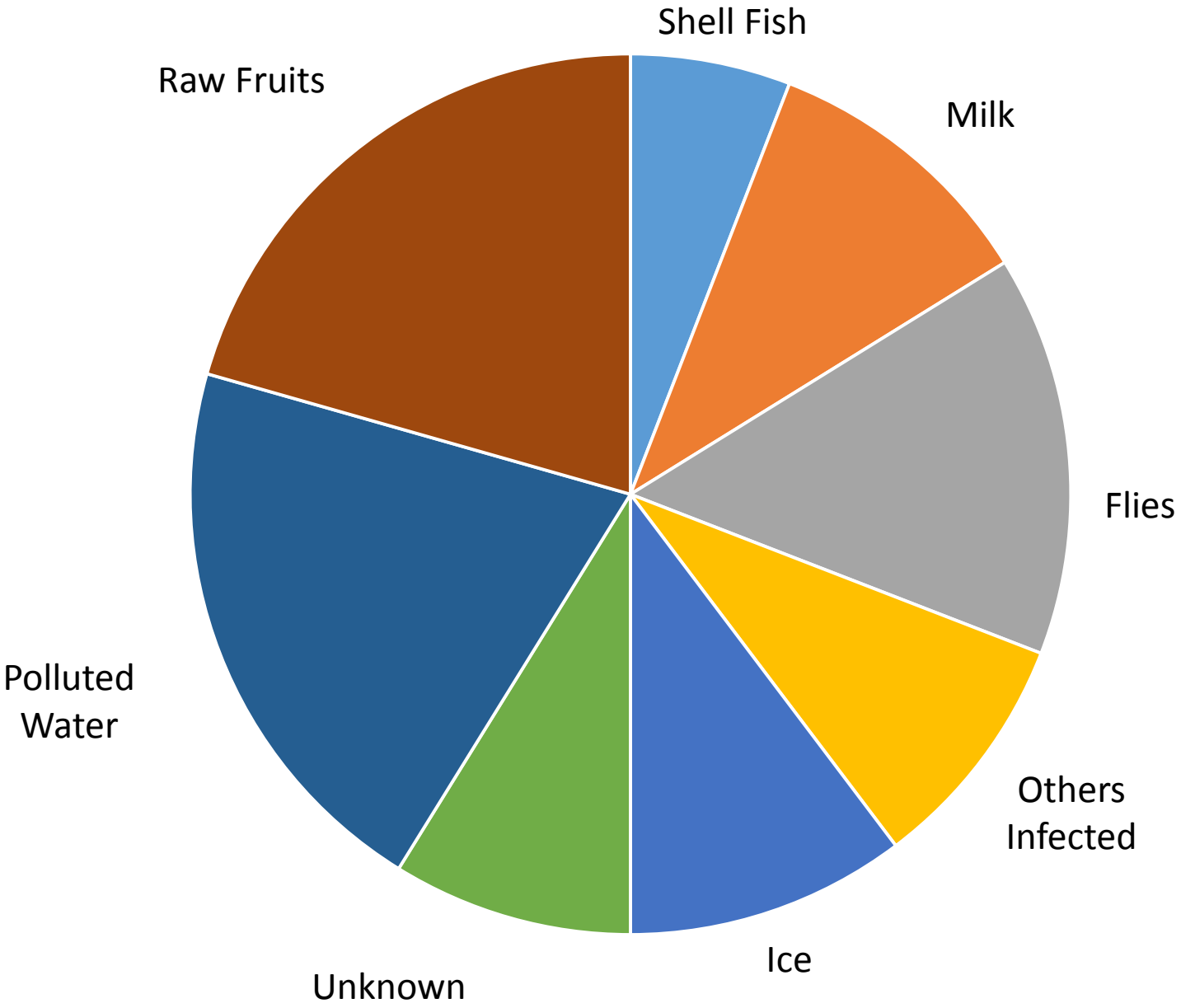
THE CAUSAL ROLE OF SUSCEPTIBILITY



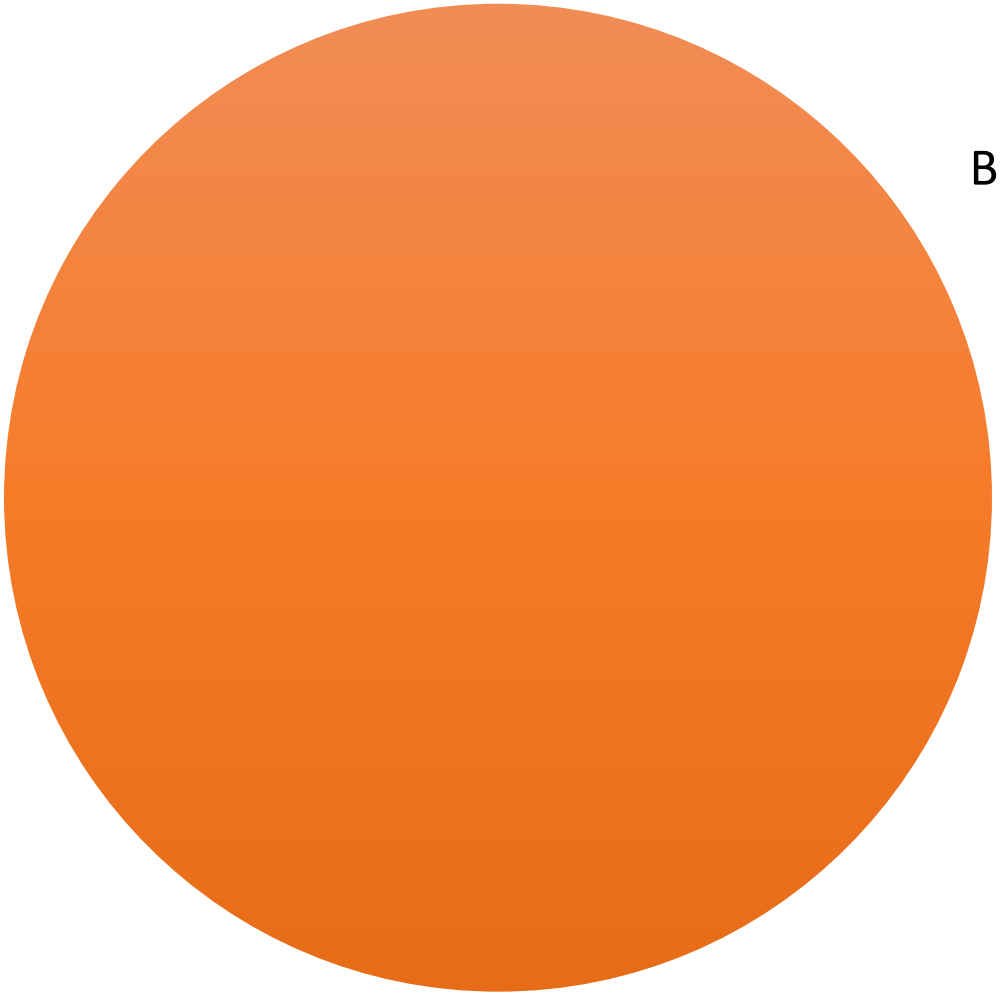
SOURCES OF DISEASE



SOURCES OF TYPHOID



TYPHOID AS A SIGNATURE DISEASE OF BACILLUS SALMONELLA TYPHI



EPIDEMIOLOGY

- **The study, through empirical methodology, of the causes of human disease.**
- **Epidemiology studies disease in groups of human beings.**
- **Epidemiology is not an examination of causation for a single individual.**

GOALS

1) **What is epidemiology?**

2) **What types of epidemiology studies exist? How are they different?**

3) **What are the outputs of an epidemiology study?; What do they mean?**

4) **Why might those outputs be erroneous or invalid?**

5) **When do those outputs support an inference of causation?**

6) **How does epidemiology translate into proving cause in fact in toxic substances cases?**

Epidemiology's Causal Inquiry

Greater Incidence of Disease in a Studied Group Exposed to an Agent

Exposure to the Agent

EXPERIMENTAL STUDY

- **All variables controlled by investigators.**
- **Gold Standard: Randomized; Double Blind; Prospective**
- **Unethical for known or suspected toxic substances.**

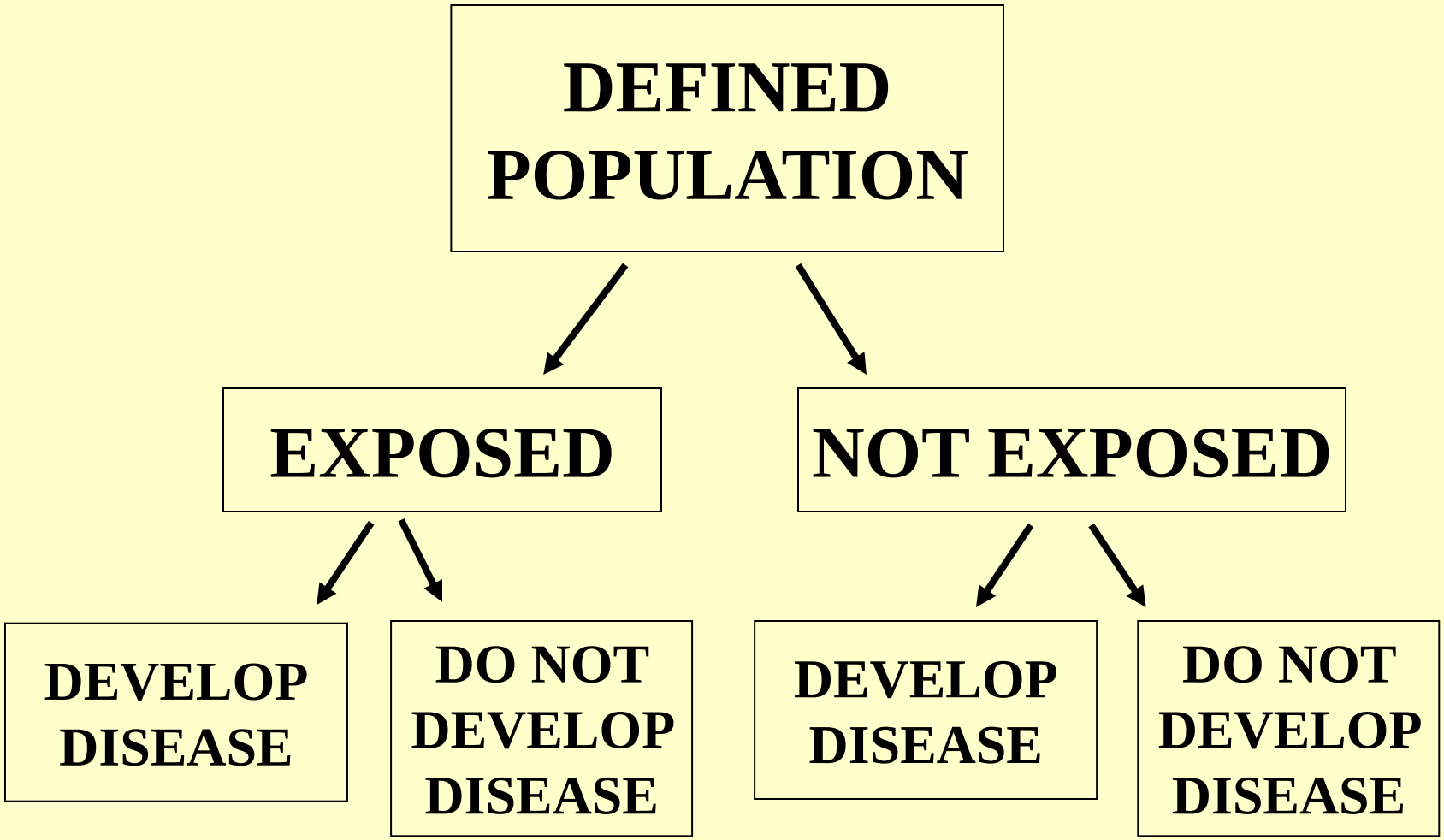
OBSERVATIONAL

- **No control over exposure to agent being studied.**
- **“Observe” those who are exposed to agent.**
- **Compare with control group not exposed.**
- **May be either retrospective or prospective.**

TYPES OF EPI STUDIES

- **Cohort: Comparison of exposed and unexposed populations for disease incidence.**
- **Case-control: Comparison of exposure rate among those with disease and control group without disease.**
- **Cross-sectional: Comparison at single point in time.**
- **Ecological: Population data about exposure and disease, e.g., incidence of colon cancer in the U.S. compared to Italy.**

COHORT STUDY DESIGN



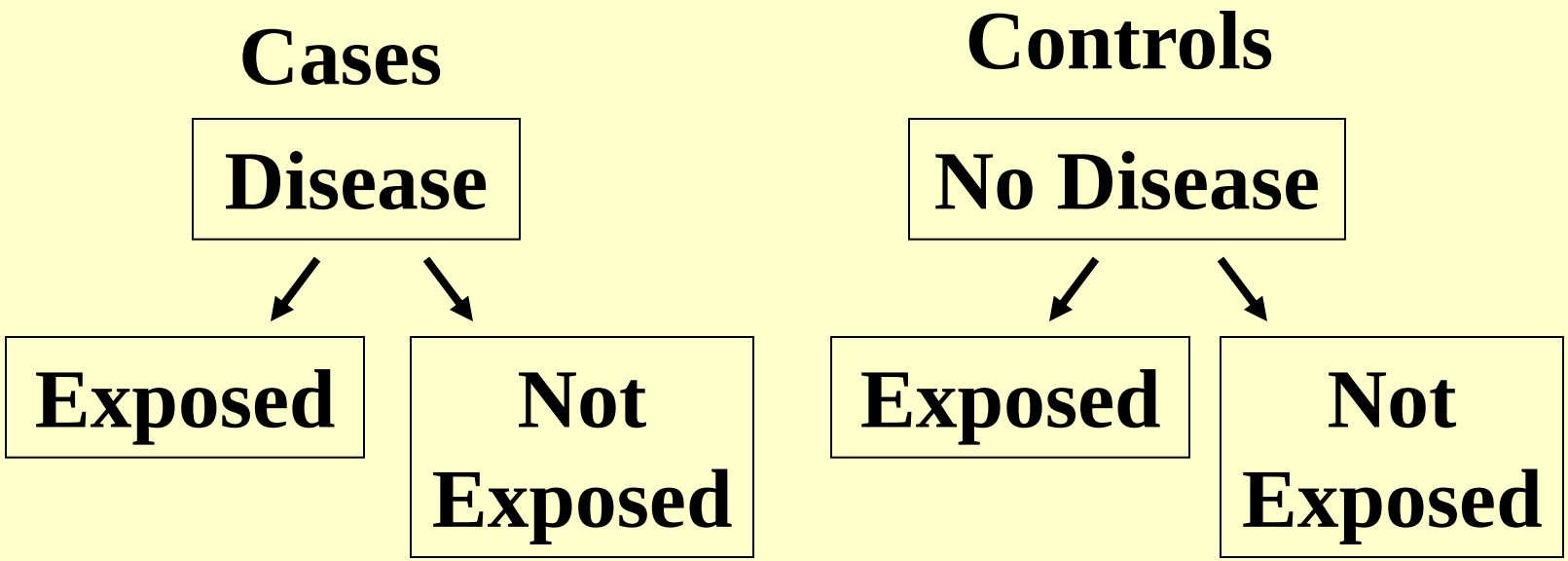
SOURCE: National Research Council. *Reference Manual on Scientific Evidence: Third Edition*. Washington, DC: The National Academies Press, 2011, p. 558. Copyright © 2011 National Academy of Sciences.

Table 1. Cross-Tabulation of Exposure by Disease Status

	No Disease	Disease	Totals	Incidence Rates of Disease
Not Exposed	a	c	a + c	c / (a + c)
Exposed	b	d	b + d	d / (b +d)

SOURCE: National Research Council. *Reference Manual on Scientific Evidence: Third Edition*. Washington, DC: The National Academies Press, 2011, p. 558. Copyright © 2011 National Academy of Sciences.

CASE-CONTROL STUDY DESIGN



SOURCE: Adapted from National Research Council. *Reference Manual on Scientific Evidence: Third Edition*. Washington, DC: The National Academies Press, 2011, p. 560. Copyright © 2011 National Academy of Sciences.

Table 2. Cross-Tabulation of Disease by Exposure Status

	Exposure	No Exposure	Totals	Exposure Odds
Cases	a	c	a + c	a / c
Controls	b	d	c + d	b / d

Deaths and death rates from cholera in London 1854 in households supplied by the Southwark and Vauxhall Water Company and by the Lambeth Water Company

	Houses	Cholera deaths	Deaths per 10,000 houses
Southwark and Vauxhall	40,046	1,263	315
Lambeth Company	26,107	98	37
Rest of London	256,423	1,422	59

ASSOCIATION

- **Exists when there is a difference in the incidence (of disease or exposure) in the two groups being studied.**
- **Suggests, but does not prove, a causal relationship.**

What Does the Existence of an Association Mean?

- **First, and most important, it is not sufficient for an inference of causation.**
- It is necessary for an inference of causation but not sufficient for one.
- Thus, while an association *may* reflect a causal relationship, it may be the result of error:
  - Random error
  - Bias
  - Confounding

RELATIVE RISK

- **Rate of disease in exposed group divided by rate in non-exposed (control) group.**

$$RR = \frac{I_e}{I_c}$$

Table 1. Cross-Tabulation of Exposure by Disease Status				
	No Disease	Disease	Totals	Incidence Rates of Disease
Not Exposed	a	c	a + c	c / (a + c)
Exposed	b	d	b + d	d / (b +d)

$$RR = \frac{I_e}{I_c} = \frac{\frac{d}{b+d}}{\frac{c}{a+c}}$$

EXAMPLE OF RR

EXPOSED GROUP

40 Disease cases per 100 persons per year: $I_e = .4$

CONTROL GROUP

20 Disease cases per 200 persons per year: $I_c = .1$

$$RR = \frac{.4}{.1} = 4.0$$

ODDS RATIO

- **Odds that case (one with the disease) was exposed to the agent divided by the odds that a control (one without the disease) was exposed**

$$OR = \frac{EO_{ca}}{EO_{co}}$$

ca = cases

co = controls

Table 2. Cross-Tabulation of Disease by Exposure Status

	Exposure	No Exposure	Totals	Exposure Odds
Cases	a	c	a + c	a / c
Controls	b	d	c + d	b / d

$$OR = \frac{EO_{ca}}{EO_{co}} = \frac{\frac{d}{b}}{\frac{c}{a}}$$

EXAMPLE OF OR

Cases

40 Cases exposed; 60 unexposed: $EO_{ca} = 40/60 = .67$

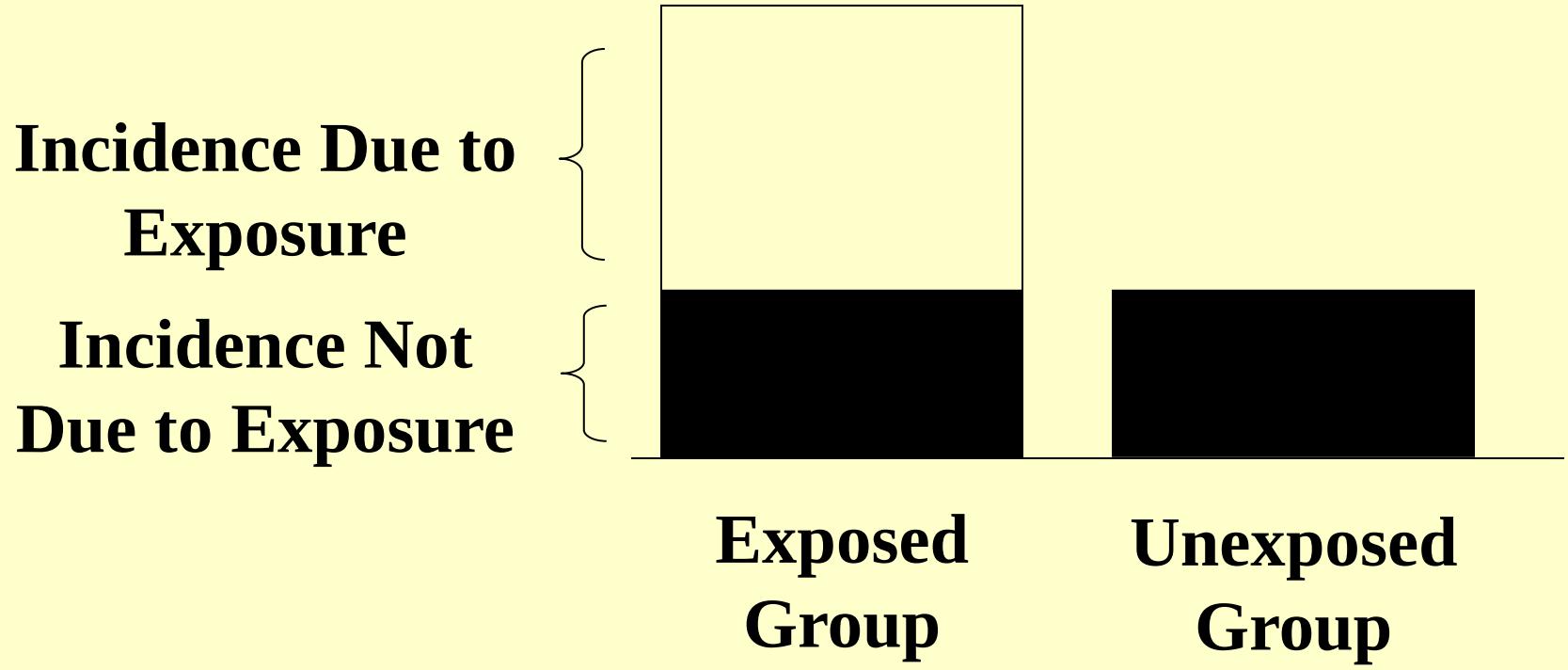
Controls

20 Control exposed; 80 unexposed: $EO_{co} = 20/80 = .25$

$$OR = \frac{.67}{.25} = 2.67$$

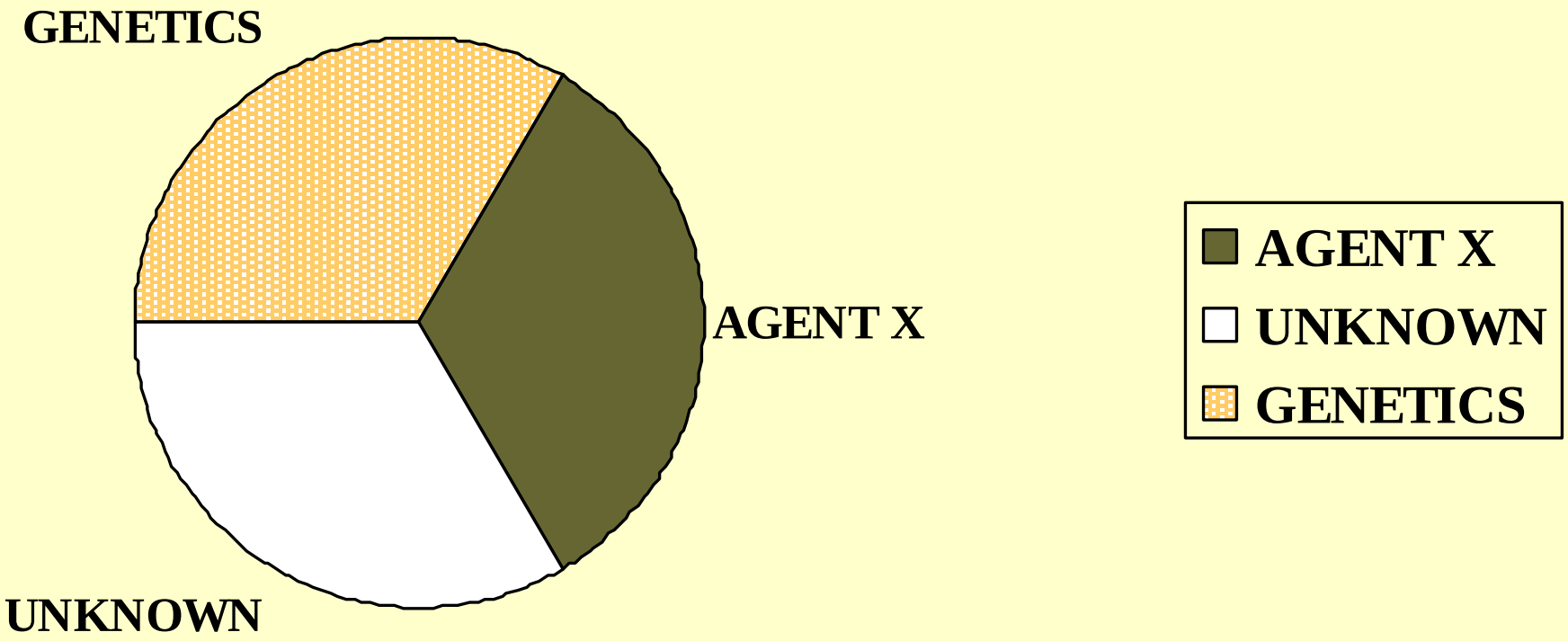
APR CONCEPT

Risks in Exposed and Unexposed Groups



SOURCE: National Research Council. *Reference Manual on Scientific Evidence: Third Edition*. Washington, DC: The National Academies Press, 2011, p. 570. Copyright © 2011 National Academy of Sciences.

SOURCES OF DISEASE



RR For AGENT X

$$RR = \frac{I_e}{I_c} = \frac{\frac{3}{10,000}}{\frac{2}{10,000}} = 1.5$$

APR FORMULA

$$APR = \frac{RR - 1}{RR}$$

EXAMPLE

$$RR = 1.5$$

$$APR = \frac{1.5 - 1}{1.5} = .33$$

AR from RR

- **Rate of disease in exposed group divided by rate in non-exposed (control) group.**

$$AR = \frac{I_e - I_c}{I_e}$$

Adjustment

- Necessary when two study populations have different characteristics that relate to the risk of disease outcome, e.g., age and death.
- Used during data analysis to “tease out” the effect of those different characteristics, such as age.

The Problem Requiring Adjustment

Population 1				
Group	Age (years)	Total Population	Deaths	Death Rate per 100
1	0-24	150	5	3
2	25-49	100	9	9
3	50-74	100	14	14
4	75+	170	24	12
Total		520	52	10

Population 2				
Group	Age (years)	Total Population	Deaths	Death Rate per 100
1	0-24	230	13	6
2	25-49	125	13	10
3	50-74	85	13	15
4	75+	70	13	19
Total		520	52	10

Population 1				
Group	Age (years)	Total Population	Deaths	Death Rate per 100
1	0-24	150	5	3
2	25-49	100	9	9
3	50-74	100	14	14
4	75+	170	24	12
Total		520	52	10

Population 2				
Group	Age (years)	Total Population	Deaths	Death Rate per 100
1	0-24	230	13	6
2	25-49	125	13	10
3	50-74	85	13	15
4	75+	70	13	19
Total		520	52	10

Group	Age	Population age-specific death rate	Population 2 age-specific death rate
1	0-24	3	6
2	25-49	9	10
3	50-74	14	15
4	75+	12	19

Adjustment

- Direct adjustment: Use the two study populations to create a reference/standard population for each that then removes age from consideration. Enables the researcher to determine comparable outcome rates as if age distribution in both populations were the same
- Standard/Reference population can be the two study populations combined or national (U.S.) population

Adjustment

- Indirect Adjustment: Employed when the age distribution of the study population is unknown and employs age specific rates from a standard/reference (e.g., U.S.) population.
- The result is a Standardized Mortality (or Morbidity) Rate, abbreviated SMR that is equivalent to the Relative Risk.

SOURCES OF ERROR

- ☹ **Sampling Error**
- ☹ **Bias**
- ☹ **Confounding**

SIGNIFICANCE TESTING

- **Concerned only with random error.**
- **Assesses plausibility the test outcome would occur if no difference exists.**
- **Designed to avoid conclusions that there is a difference when no difference exists (false positives).**

Some Definitional Preliminaries

- False positives
- False negatives
- The “true” or “real” association
- The “study outcome”

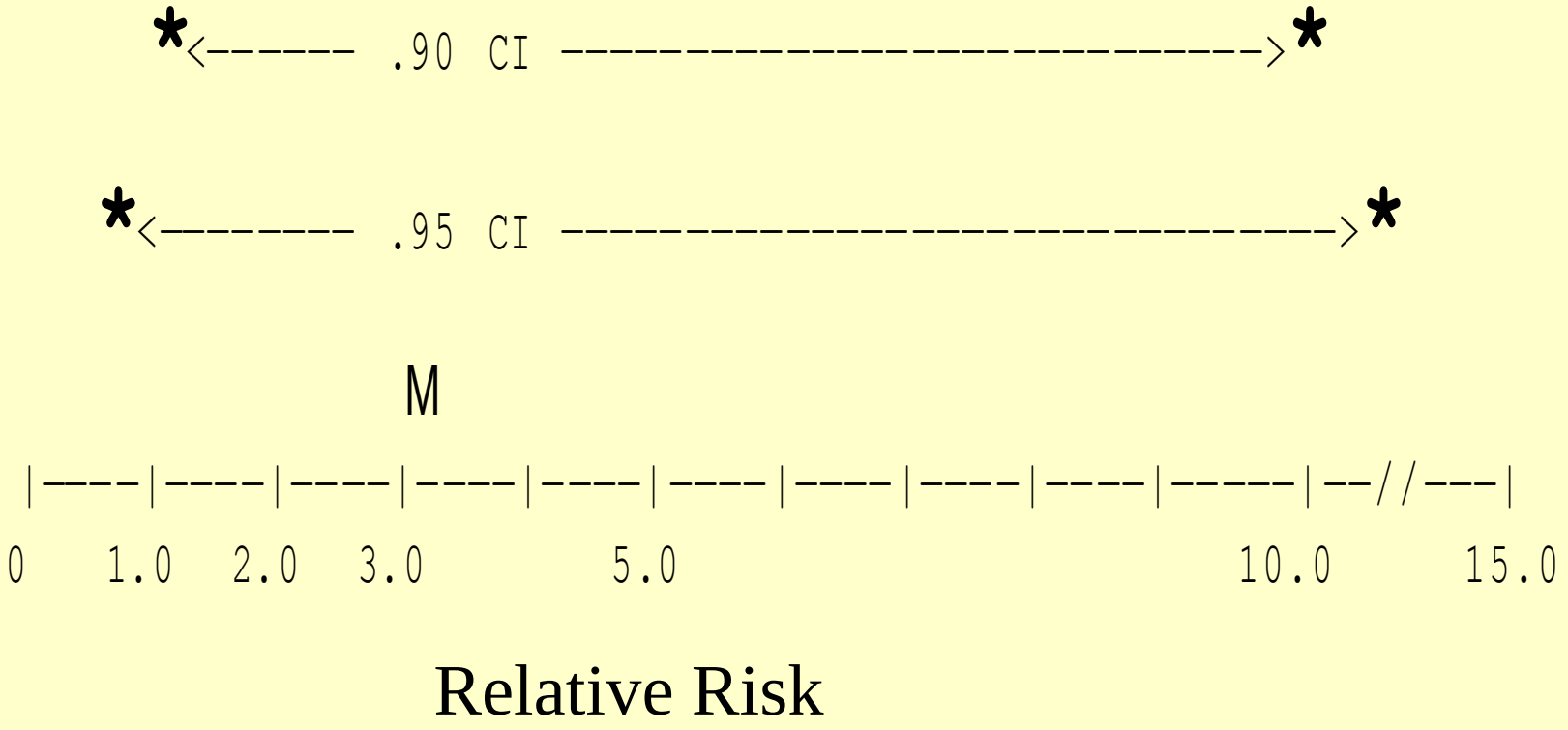
What is p?

P is the probability of finding the study result or a greater one if there is no “true association,” i.e., the true case is that there is a relative risk of 1.0.

The Relationship Between Random Error and Statistical Significance

p ≠ Probability of Random Error

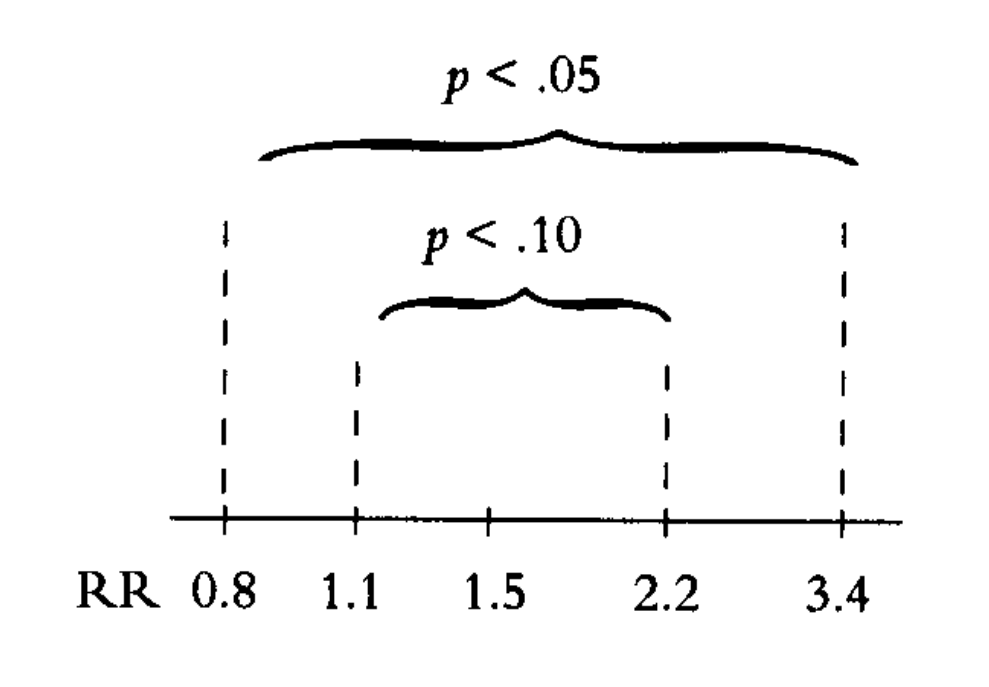
See Ethyl Corp. v. United States Envtl. Protection Agency, 541 F.2d 1, 28 n.58 (D.C. Cir.), *cert. denied*, 426 U.S. 941 (1976); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317 (Fed. Cir. 2006) (contrasting the medical research standard of "very near certainty--perhaps 95% probability" to the standard applied in civil cases, the preponderance standard); Hodges v. Secretary Dep't Health & Human Servs., No. 92-5089, 1993 U.S. App. LEXIS 29590, at *29, 41 (Fed. Cir. Nov. 15, 1993) (Newman, J., dissenting); Almeida v. Secretary, DHHS, No. 96-412V, 1999 U.S. Claims LEXIS 294 (Ct. Fed. Claims Dec. 20, 1999); In re Ephedra Products Liability Litigation, 393 F. Supp. 2d 181 , 192-93 (S.D.N.Y. 2005); Marmo v. IBP, Inc., 360 F. Supp. 2d 1019 (D. Neb. 2005) (expert toxicologist who stated that science requires proof with 95 percent certainty while expressing his understanding that the legal standard to require more probable than not); Liable v. Sec'y of Health & Human Servs., 98-120V, 2000 WL 1517672 (Fed. Cl. Sept. 7, 2000) ("The crucial fact is that the statements were being made in a medical/scientific journal, a context in which attribution of causation is typically not made until a level of very near certainty—perhaps 95% probability—is achieved.16 In this context, the statements are not surprising at all. I certainly do not believe that the available evidence justifies any conclusions about causation—in general or as to specific cases—at anywhere near that 95% level of scientific certainty. But it seems unlikely that the authors of the quoted articles had in mind the lower standard of probability necessary in legal proceedings such as this one—i.e., the requirement that causation be shown to be merely 'more probable than not.'"); Exxon Corp. v. Makofski, 116 S.W.3d 176 (Tex. Ct. App. 2003) (expert testified that while science requires proof to a 95 percent certainty, appropriate standard for testifying in court is 51 percent); RICHARD GOLDBERG, CAUSATION AND RISK IN THE LAW OF TORTS: SCIENTIFIC EVIDENCE AND MEDICINAL PRODUCT LIABILITY 105 (1999); LARRY LAUDAN, TRUTH, ERROR, AND CRIMINAL LAW: AN ESSAY IN LEGAL EPISTEMOLOGY 64-65 (2006); K.S. SHRADER-FRECHETTE, RISK AND RATIONALITY: PHILOSOPHICAL FOUNDATIONS FOR POPULIST REFORMS 132-34 (1991); Ronald J. Allen, *Expertise and the Daubert Decision*, 84 J. CRIM. L. & CRIMINOLOGY 1157 (1994); Margaret A. Berger *What Has a Decade of* Daubert *Wrought?*, 95 AM. J. PUB. HEALTH S59, S62 (2005); Margaret A. Berger & Aaron D. Twerski, *Uncertainty and Informed Choice: Unmasking Daubert*, 104 MICH. L. REV. 257 (2005) ("despite the fact that researchers use a stringent scientific standard of proof that far exceeds the preponderance of the evidence standard that applies in civil litigation"); Neil B. Cohen, *Confidence in Probability: Burdens of Persuasion in a World of Imperfect Knowledge*, 60 N.Y.U. L. REV. 385 (1985); Mark P. Denbeaux & D. Michael Risinger, Kumho Tire *and Expert Reliability: How the Question You Ask Gives the Answer You Get*, 34 SETON HALL L. REV. 15, 46-47 (2003); Edward J. Imwinkelried, *The Admissibility of Expert Testimony in Christophersen v. Allied-Signal Corp.: The Neglected Issue of the Validity of Nonscientific Reasoning by Scientific Witnesses*, 70 DENV. U. L. REV. 473, 478 (1993); Harvey S. Frey, Letter, *When Scientific Data Become Legal Evidence*, 324 SCI. 335 (Apr. 17, 2009); James E. Hulverson, Jr., *Reasonable Degree of Medical Certainty: A Tort et a Travers*, 31 ST. LOUIS U. L.J. 577, 590 (1987); Jeff L. Lewin, *The Genesis and Evolution of Legal Uncertainty about "Reasonable Medical Certainty"*, 57 MD. L. REV. 380, 400 (1998); Andrew A. Marino & Lawrence E. Marino, *The Scientific Basis of Causality in Toxic Tort Cases*, 21 U. DAYTON L. REV. 1, 23-24 & n. 57 (1995); Paul R. Rice, *The Quagmire of Scientific Expert Testimony: Crumping the Supreme Court's Style*, 68 MO. L. REV. 53, 58-60 (2003) ("In fact, most quantitative sciences impose something in the neighborhood of a 95% confidence level. In evidence parlance, this might be the equivalent of establishing . . . admissibility . . . beyond a reasonable doubt."); Wayne Roth-Nelson & Kathey Verdeal, *Risk Evidence in Toxic Torts*, 2 ENVT'L LAW. 405, 415-16 (1996) (authors, two Ph.D. scientists, endorse views of Judge Newman in *Hodges*); Carl Cranor has written an ambitious and illuminating book, *Regulating Toxic Substances: A Philosophy of Science and the Law* (1993); Erica Beecher-Monas, *Blinded by Science: How Judges Avoid the Science in Scientific Evidence*, 71 TEMP. L. REV. 55, 71 n. 110(1998) (citing Carl Cranor for "a discussion of the appropriateness of applying the 95% confidence interval to the regulatory context and tort law"); William M. Sage, *Lessons from Breast Implant Litigation*, 15 HEALTH AFFAIRS 206, 209 (1996) (preponderance of the evidence standard "suggests a *p*-value of roughly 0.49 (or a 51 percent confidence interval)"); Leslie J. Sheffield & Ron Batagol, *The Creation of Therapeutic Orphans–or, What Have We Learned from the Debendox Fiasco*, 143 MED. J. AUSTRALIA 143, 146 (1985); Steven R. Weller, *Book Review: Regulating Toxic Substances: A Philosophy of Science and Law*, 6 HARV. J. L. & TECH. 435, 436, 437-38 (1993)("only when the statistical evidence gathered from studies shows that it is more than ninety-five percent likely that a test substance causes cancer will the substance be characterized scientifically as carcinogenic. . . to determine legal causality, the plaintiff need only establish that the probability with which it is true that the substance in question causes cancer is at least fifty percent, rather than the ninety-five percent to prove scientific causality"); Raymond E. Gangarosa et. al., *Suits by Public Hospitals to Recover Expenditures for the Treatment of Disease, Injury and Disability Caused by Tobacco and Alcohol*, 22 FORDHAM URB. L.J. 81, 139 (1994)("Conversely, the probability that the attributable risk was not obtained by chance alone is 99.9%, which clearly exceeds the >50% "more likely than not" threshold. Thus, in establishing an epidemic, the P-value, and not the attributable risk, is the relevant measure to compare against standards of proof."); SHEILA JASANOFF, SCIENCE AT THE BAR: LAW, SCIENCE, AND TECHNOLOGY IN AMERICA 10 (1995); Cornelia Dean, *When Questions of Science Come to a Courtroom , Truth Has Many Faces*, N.Y. TIMES, Dec. 5, 2006, at § F ("Typically, scientists don't accept a finding unless, statistically, the odds are less than 1 in 20 that it occurred by chance. This standard is higher than the typical standard of proof in civil trials ('preponderance of the evidence') and lower than the standard for criminal trials ('beyond a reasonable doubt')"); William Glaberson, *The Courts vs. Scientific Certainty*, N.Y. TIMES, June 27, 1999, at § 4, p. 5 ("Science, which never stops searching for answers, has a high threshold for reaching scientific conclusions: 95 percent certainty, some scientists say, is necessary to decide that one thing probably caused another. But the law must stop its search at the conclusion of each case. So juries in civil cases are told that a mere preponderance of the evidence–51 percent–is enough certainty to render a verdict."); Michael J. Saks, *Judging Admissibility*, 35 J. CORP. L. 135, 153 (2009) ("Finally, why should studies, or opinions based on them, be admissible only if the studies show differences significant at below some conventional level of probability for research (such as $p<.05$ or $p<.01$) when the ultimate decision in the case is effectively set at a much different level (preponderance of the evidence being akin to $p<.50$)?"). Even the Carnegie Commission has made this error. *See* CARNEGIE COMMISSION ON SCIENCE, TECHNOLOGY, AND GOVERNMENT, SCIENCE AND TECHNOLOGY IN JUDICIAL DECISION MAKING: CREATING OPPORTUNITIES AND MEETING CHALLENGES 28 (1993) ("But judicial decisions that appear to be based on 'bad science' may actually reflect the reality that the law requires a burden of proof or confidence level, other than the 95 percent confidence level that is often used by scientist to reject the possibility that chance alone accounts for observed differences.").


<------ .90 CI ----------->
<------- .95 CI ------------>
M
0 1.0 2.0 3.0 5.0 10.0 15.0
Relative Risk

What is a confidence interval?

- A confidence interval is a range of possible values for the true association calculated from the study results.
- For a 95% confidence interval, the width of the interval reflects the results we would expect to get if we repeated the same study.
- Thus, the width reflects the range of results we would get due to random error in 95% of those repeated studies

Figure III-4. Confidence Intervals



SOURCE: National Research Council. *Reference Manual on Scientific Evidence: Third Edition*. Washington, DC: The National Academies Press, 2011, p. 580. Copyright © 2011 National Academy of Sciences.

POWER

- **Expresses the ability of the study to find a specified relative risk with statistical significance.**
- **For Epidemiologic studies that are not statistically significant, the confidence interval helps reveal whether the study should be interpreted as exonerative or inconclusive based on the role of chance.**

TYPES OF BIASES

- ☹ **Selection Bias: Differences between selected cohorts produce skewed results.**
- ☹ **Information Bias: information about exposure or disease in the study cohorts is inaccurate.**
- ☹ **Conceptual Bias: Study design inadequate to find effect of interest.**
- ☹ **Dozens of other biases have been identified and may exist in an epidemiologic study.**

Agent Orange Potential Control Groups

1) all civilians of a similar age to those in the exposed cohort;

2) all civilian males of a similar age to those in the exposed cohort;

3) all comparable-age males in the military who did not serve in Vietnam when Agent Orange was being sprayed.

For one year, the pesticide malathion was sprayed by helicopter over two counties in the north bay area of California. Concerns were raised about the potential effect on pregnant women that might result in causing birth defects. Several investigators conducted a case-control study. Exposure was determined based on zip codes of residence at the time of birth coordinated with data on where and when spraying occurred with regard to both cases and controls.

CONFOUNDERS

- **Agent being studied and another agent are correlated (e.g., coffee drinking and smoking.**
- **Other agent has the causal relationship, not the studied agent.**
- **Can occur whenever the studied agent is differentially associated with another risk (or protective) factor.**

Evaluating a Suspected Confounding Factor: Smoking in a Study of Alcohol and Emphysema

Table 4. Hypothetical Emphysema Study Data

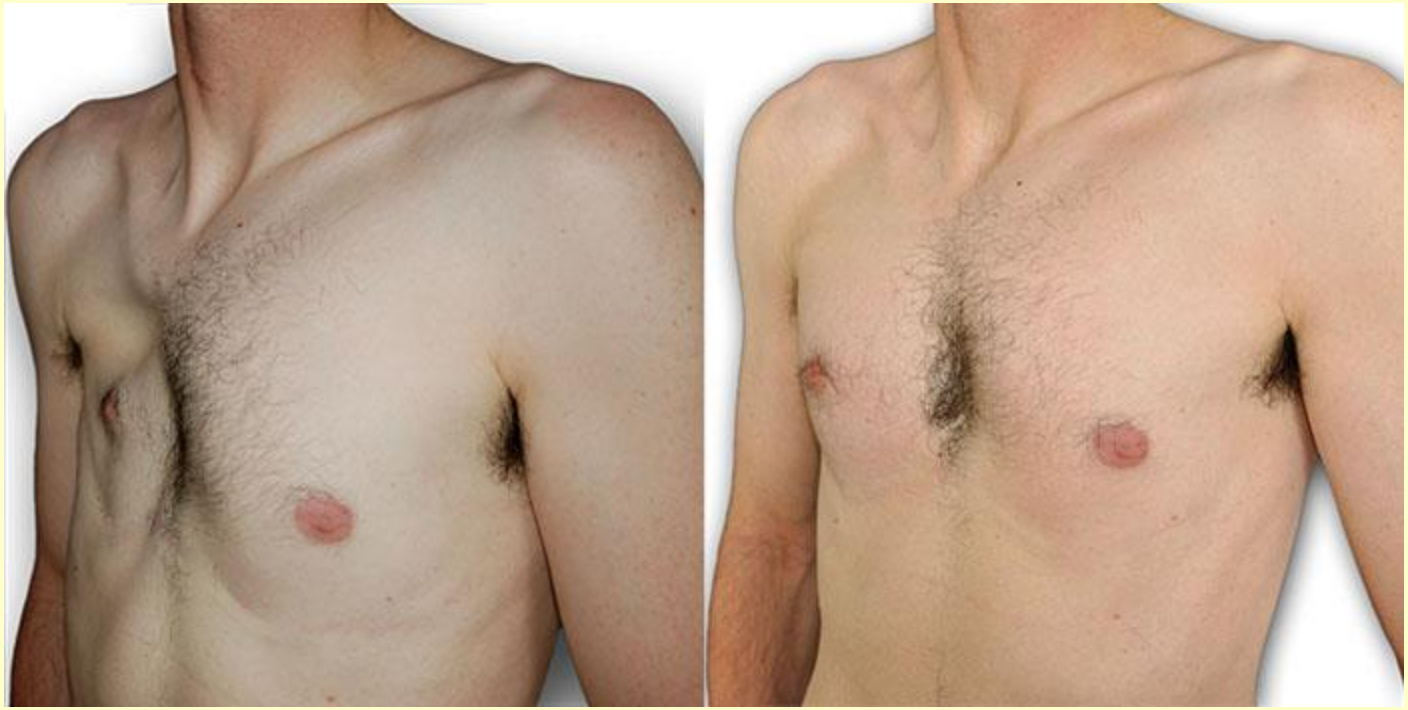
Drinking Status	*Total Cohort*				*Smokers*				*Nonsmokers*			
	Total	Cases	Incidence	RR	Total	Cases	Incidence	RR	Total	Cases	Incidence	RR
Nondrinkers	471	16	0.034	1.0*	111	9	0.081	1.0*	360	7	0.019	1.0*
Drinkers	739	41	0.069	2.0	592	48	0.081	1.0	147	3	0.020	1.0

* "RR" in Table 4 is the relative risk. The relative risk for each of the cohorts is determined based on reference to the risk among nondrinkers, that is, the incidence of disease among drinkers is compared with nondrinkers for each of the three cohorts separately.

HRT and CHD: Study Question

Numerous epidemiologic studies found that women taking hormone replacement therapy ("HRT") had a lower than normal incidence of coronary heart disease ("CHD"), suggesting that HRT had a protective effect for CHD. Yet, randomized clinical trials showed that HRT caused a small increase in risk of CHD for the exposed cohort. Can these results be reconciled? If so, how?

Poland's Syndrome



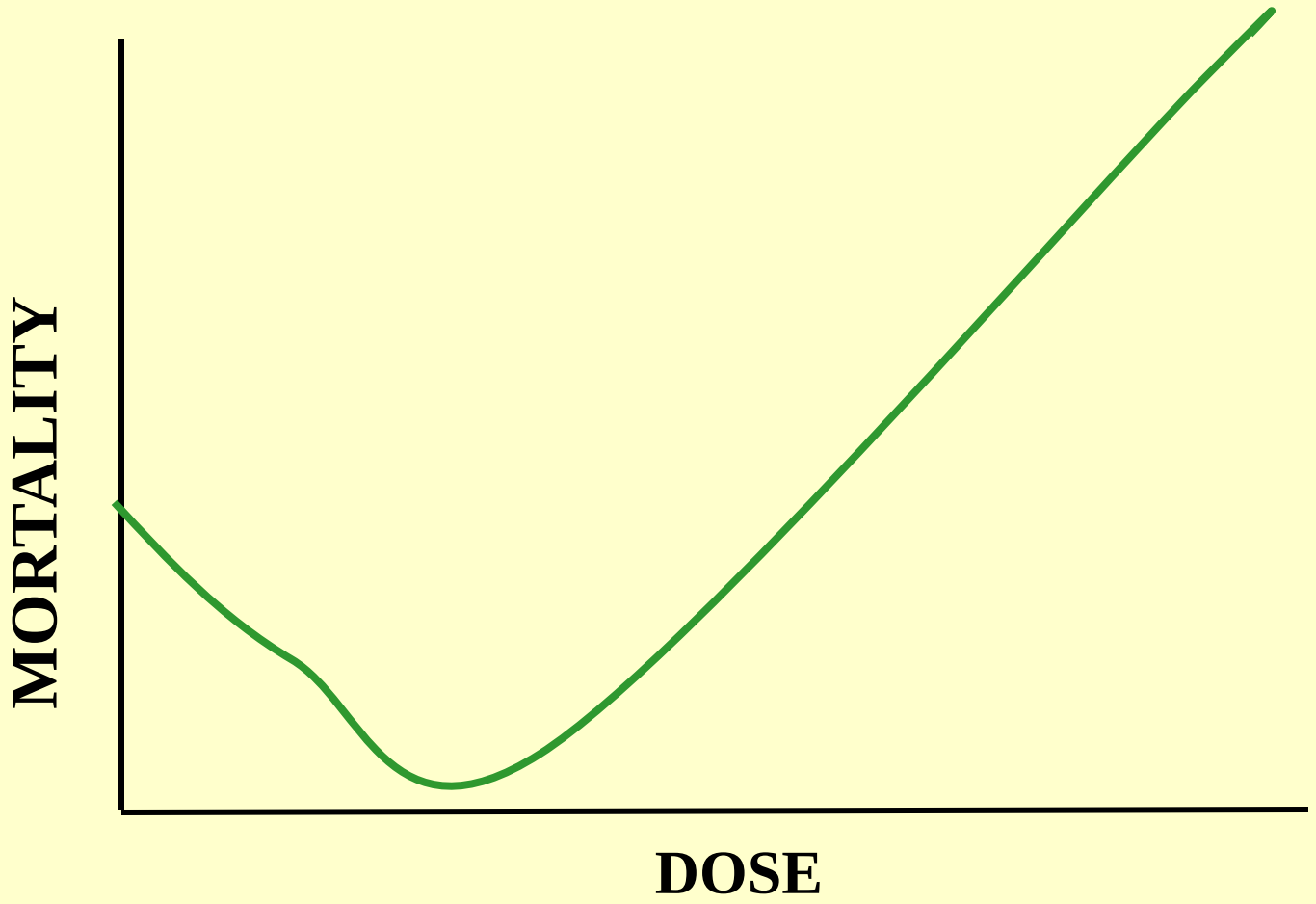
Brock, 874 F.2d at 309:

Ultimately, the “correctness” of our decision that there was insufficient evidence presented by plaintiff on the issue of whether Bendectin caused Rachel Brock's limb reduction defect to enable a jury to draw a reasonable inference may be just a matter of opinion, but hopefully the reasoning below will persuade others of the insights of our perspective.

HILL CRITERIA FOR IMPLYING CAUSATION FROM AN ASSOCIATION

- **Temporal relationship**
- **Strength of association**
- **Dose-response relationship**
- **Consistency of association**
- **Biologic plausibility**
- **Alternative explanations**
- **Specificity of association**
- **Consistency with other information**

RED WINE DOSE-RESPONSE CURVE



RESPONSE ALL EFFECTS

Kutcher et al. Ecological Study on Bendectin and Birth Defects

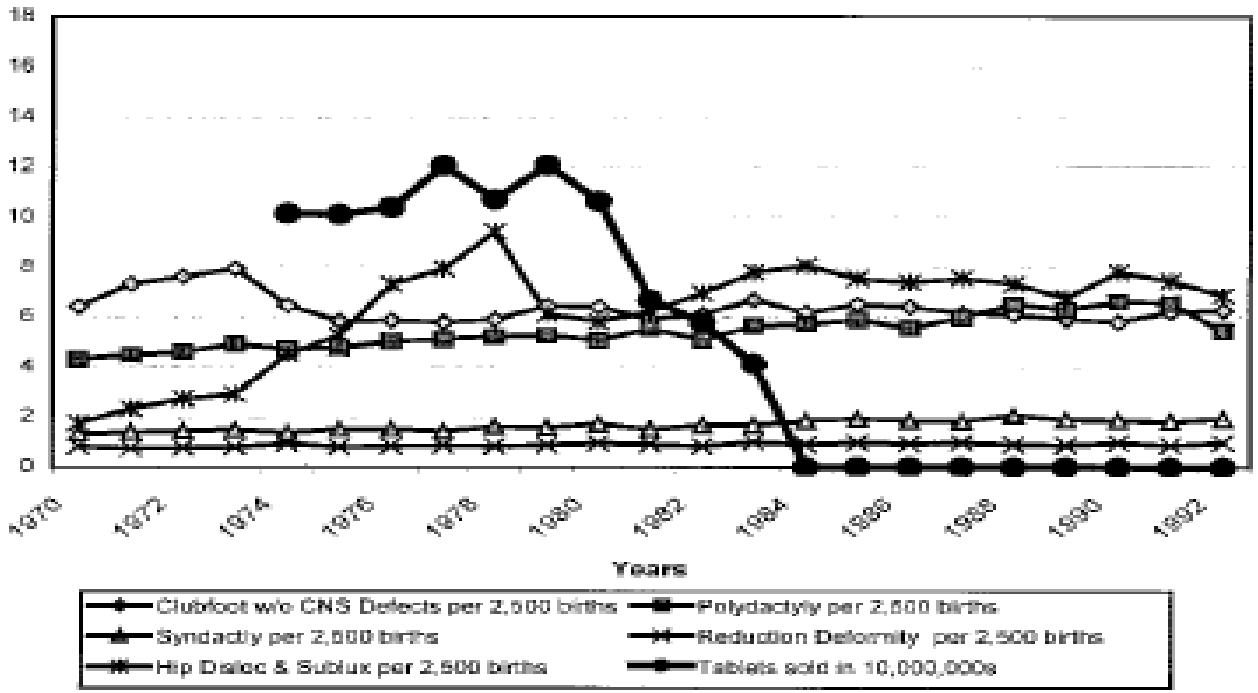


Figure 7. Incidence of limb malformations (BDMP) and Bendectin tablet sales in the United States, 1970–92.

SOURCE: Jeffrey S. Kutcher, "Bendectin and Birth Defects II: Ecological Analyses," 67 *Clin. & Molecular Teratology* 88 (2003). © 2003 Wiley-Liss, Inc.

Li Abstract

European Journal of Endocrinology

Abstract

Objective: Exposure to high levels of air pollutants may be linked to diabetes-associated mortality, but the associations remain unclear. To assess the associations between main air pollutants and diabetes-associated mortality, a systematic review and meta-analysis was performed.

Methods: PubMed, Embase and Web of Science were searched for studies investigating the associations between increments in gaseous (nitrogen dioxide (NO_2), sulphur dioxide, ozone (O_3) and carbon monoxide) and particulate matter (PM; diameter <2.5 μm (PM2.5) or <10 μm (PM10)) air pollutants and diabetes-associated mortality. Using a random-effects model, relative risks (RRs) and 95% CIs were calculated per interquartile range (IQR) increment or per 10 $\mu g/m^3$ increment in pollutant concentrations.

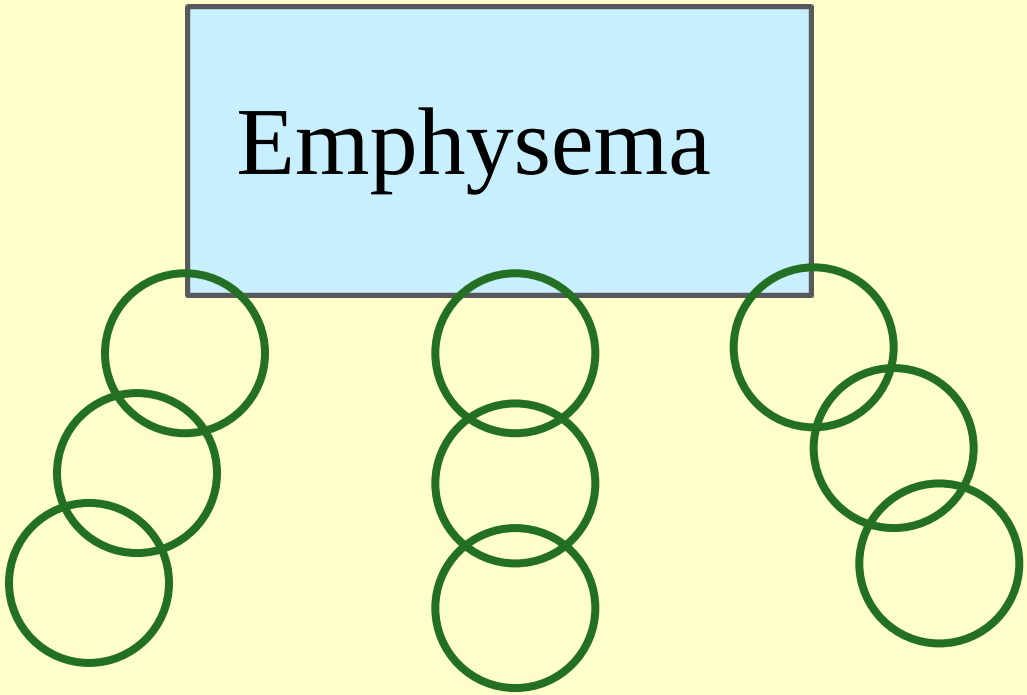
Results: Out of 925 identified articles, 36 were reviewed in depth and 12 studies from 13 articles satisfying the inclusion criteria (five time-series, five case-crossovers and two cohorts) were finally included. Increased risk of diabetes-associated mortality was associated with higher levels of PM2.5 (per 10 $\mu g/m^3$: RR=1.123, 95% CI 1.036–1.217, $P=0.005$, $I^2=96.1\%$), PM10 (per 10 $\mu g/m^3$: RR=1.008, 95% CI 1.004–1.013, $P<0.001$, $I^2=0\%$), NO_2 (per 10 $\mu g/m^3$: RR=1.024, 95% CI 1.007–1.041, $P=0.006$, $I^2=49.7\%$) and O_3 (per IQR increment: RR=1.065, 95% CI 1.017–1.115, $P=0.007$, $I^2=0.0\%$). No obvious risk of publication bias was observed.

Conclusions: Exposure to high levels of air pollutants is significantly associated with an increased risk of diabetes-associated mortality.

SOURCE: Abstract from Chengqian Li et al., *Main air pollutants and diabetes-associated mortality:* a *systematic review and meta-analysis*, 171 Mechanisms in Endrocrinology 183 (2014).

Furthermore, “[s]cientists believe that, in addition to smoke-related processes, there must be other factors that cause emphysema in the general population since only 15 to 20 percent of smokers develop emphysema.”

Lindquist: Other Factors causing emphysema

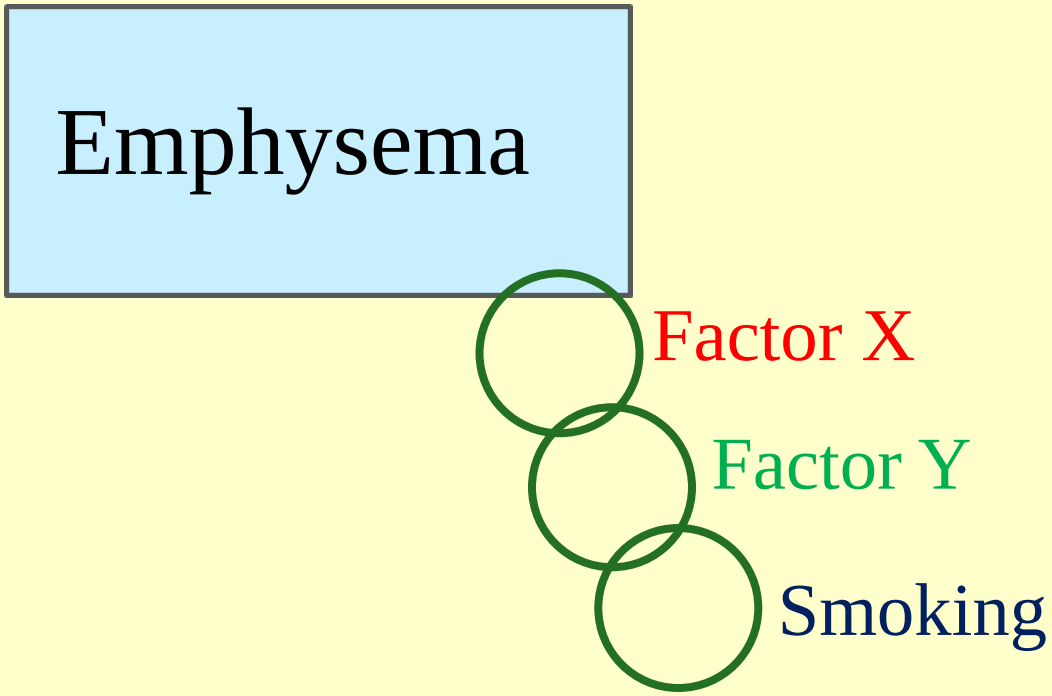


Factor X

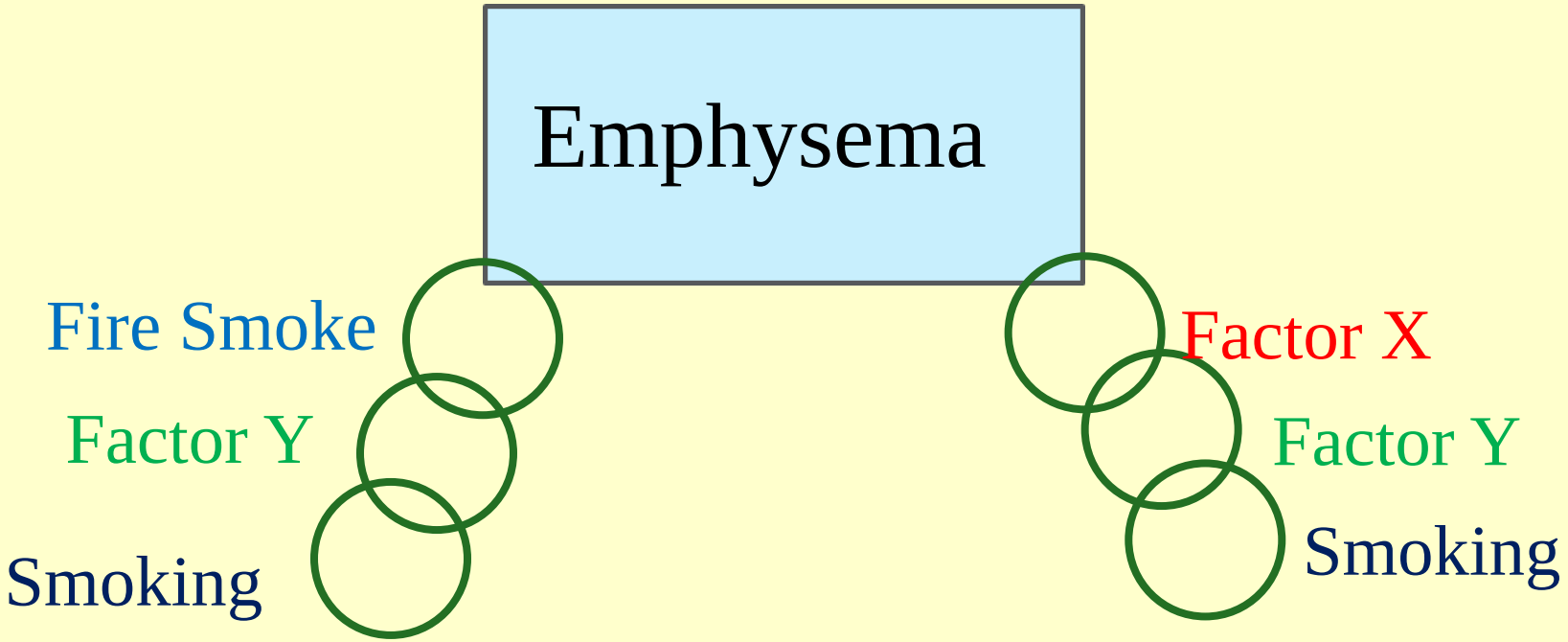
Factor Y

Smoking

Lindquist: Other Factors causing emphysema



Lindquist: How smoke might be a cause of emphysema



Those studies comparing populations of healthy workers, similar in all relevant respects except fire smoke exposure, present the strongest scientific support for the proposition that firefighting is a significant cause of lung disease.

Table 2 Seattle, Portland, and Tacoma firefighter mortality: 1945-89

Cause of death (ICD 9 codes)	*Deaths*	*SMR*	*(95%)*
All causes (001-999)	1169	0·81	(0·77-0·86)
All cancers (140-152-2, 156-9-165-9, 170-175, 179-208)	291	0·95	(0·85-1·07)
Oral and pharyngeal cancers (140-149)	7	0·81	(0·33-1·66)
Oseophageal cancer (150)	6	0·83	(0·30-1·80)
Stomach cancer (151)	16	1·07	(0·61-1·73)
Colon cancer (152, 153)	24	0·85	(0·54-1·26)
Rectal cancer (154)	8	0·95	(0·41-1·87)
Biliary passages and liver cancer (155-0-155-1. 156)	6	1·19	(0·44-2·59)
Pancreatic cancer (157)	14	0·89	(0·49-1·49)
Laryngeal cancer (161)	2	0·47	(0·06-1· 70)
Lung cancer (162)	95	0·96	(0·77-1·17)
Prostate cancer (185)	30	1·34	(0·90-1·91)
Kidney cancer (189-0-189-2)	2	0·27	(0·03-0·97)
Bladder and other urinary cancers (188, 189 3-189-9)	2	0·23	(0·03-0·83)
Skin cancer (172, 173)	6	0·98	(0·36-2·13)
Brain and nervous system tumours (191, 192, 237 5-237-9, 239-6-239-7)	22	2·09	(1·31-3·17)
Brain and nervous system cancers (191, 192)	18	2·07	(1·23-3·28)
Unspecified nervous system tumours (237-5-237-9, 239-6-239 7)	4	2·20	(0·60-5·62)
Lymphatic/haematopoietic cancers (200-208)	37	1·31	(0·92-1·81)
Lymphosarcoma and reticulosarcoma (200)	7	1·42	(0·57-2·93)
Hodgkin's disease (201)	3	1·05	(0·22-3·08)
Leukaemia(204-208)	15	1·27	(0·71-2·09)
Other lymphatic/haematopoietic (202, 203)	12	1·40	(0·72-2·44)
Heart disease (390-398, 402, 404, 410-414, 420-429)	461	0·79	(0·72-0·87)
Ischaemic heart disease (410-414)	394	0·82	(0·74-0·90)
Other circulatory disease (401, 403, 405, 415-417, 430-438, 440-459)	131	0·96	(0·80-1·14)
Cerebrovascular disease (430-438)	79	0·85	(0·67-1·06)
Diseases of arteries, veins and pulmonary circulation (415-417, 440-459)	48	1·24	(0·91-1·64)
Respiratory disease (460-466, 470-478, 480-487, 490-519)	81	0·89	(0·71-1·10)
Acute upper respiratory infection (460-466)	2	3·57	(0·43-12·9)
Pneumonia (480-486)	22	0·67	(0·42-1·01)
Chronic respiratory diseases (470-478, 490-519)	56	1·00	(0·76-1·30)
Emphysema (492)	20	1·19	(0·72-1·83)
Asthma (493)	3	1·05	(0·22-3·08)
COPD and other respiratory disease (470-478, 494-519)	32	0·98	(0·67-1·38)

COPD = Chronic obstructive pulmonary disease.

SOURCE: Paul A. Demers et al., Mortality Among Firefighters from Three Northwestern United States Cities, 49(9) BRITISH J. OF INDUS. MED. 664-670 (1992). Reproduced with permission.

Table 3 Seattle, Portland, and Tacoma firefighter mortality compared with police and police mortality compared with United States white male rates: 1945-89

	Firefighters v police			*Police v United States white men*		
Cause of death	*Deaths*	*IDR*	*(95% CI)*	*Deaths*	*SMR*	*(95% CI)*
All causes	1169	0·87	(0·79-0·95)	714	0·87	(0·81-0·93)
All cancers	291	0·97	(0·80-1·17)	169	0·95	(0·81-1·11)
Colon cancer	24	1·58	(0·73-3·3)	8	0·50	(0·22-0·99)
Rectal cancer	8	0·89	(0·30-2·66)	5	1·11	(0·36-2·59)
Biliary passages and liver cancer	6	0·71	(0·19-2·71)	4	1·40	(0·38-3·59)
Trachea, bronchus, and lung cancer	95	0·95	(0·67-1·33)	55	0·92	(0·69-1·19)
Prostate cancer	30	1·43	(0·71-2·85)	11	1·02	(0·51-1·82)
Bladder cancer	2	0·16	(0·02-1·24)	4	0·91	(0·25-2·34)
Emphysema	20	1·45	(0·54-3·88)	5	0·63	(0·20-1·46)
COPD and miscellaneous lung disease	32	0·89	(0·47-1·69)	15	0·83	(0·47-1·37)

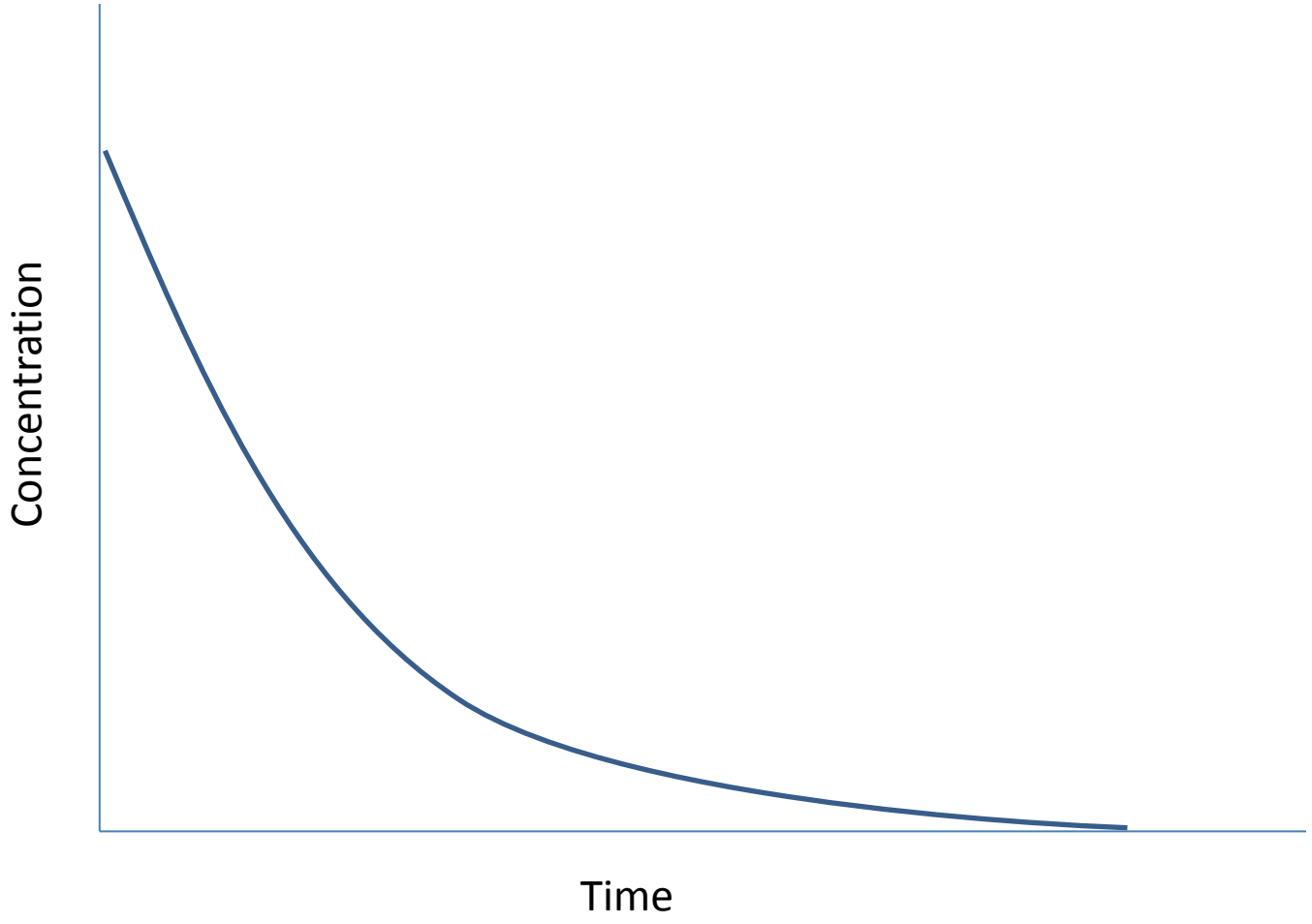
SOURCE: Paul A. Demers et al., Mortality Among Firefighters from Three Northwestern United States Cities, 49(9) BRITISH J. OF INDUS. MED. 664-670 (1992). Reproduced with permission.

Table 4 Seattle, Portland, and Tacoma firefighter mortality by duration of exposed employment: 1945-89

Cause of death	< 10 years			10-19 years			20-29years			≥ 30years		
	Deaths	SMR	(95% CI)	Deaths	SMR	(95% CI)	Deaths	SMR	(95% CI)	Deaths	SMR	(95% CI)
Colon cancer	4	1·40	(0·4-3·6)	2	0·54	(0·1-2·0)	9	0·62	(0·3-1·2)	9	1·21	(0·6-2·3)
Prostate cancer	3	2·42	(0·5-7·1)	2	1·12	(0·1-4·1)	14	1·23	(0·7-2·1)	11	1·36	(0·7-2·4)
Brain and nervous system tumours	5	2·57	(0·8-6·0)	8	3·53	(1·5-7·0)	6	1·24	(0·5-2·7)	3	2·04	(0·4-5·9)
Lymphatic/haematopoietic cancers	4	0·91	(0·2-2·3)	7	1·46	(0·06-3·0)	14	1·06	(0·6-1·8)	12	2·05	(1·1-3·6)
Leukaemia	2	1·13	(0·1-4·1)	2	1·04	(0·1-3·7)	4	0·73	(0·2-1·9)	7	2·60	(1·0-5·4)
Diseases of the arteries, veins, and pulmonary circulation	4	1·36	(0·4-3·5)	4	0·94	(0·3-2·4)	15	0·79	(0·4-1·3)	25	1·99	(1·3-2·9)
Chronic respiratory diseases	2	0·42	(0·1-1·5)	5	0·82	(0·3-1·9)	34	1·15	(0·8-1·6)	15	0·97	(0·5-1·6)
Emphysema	1	0·92	(0·1-5·1)	3	1·83	(0·4-5·3)	12	1·35	(0·7-2·4)	4	0·76	(0·2-1·9)

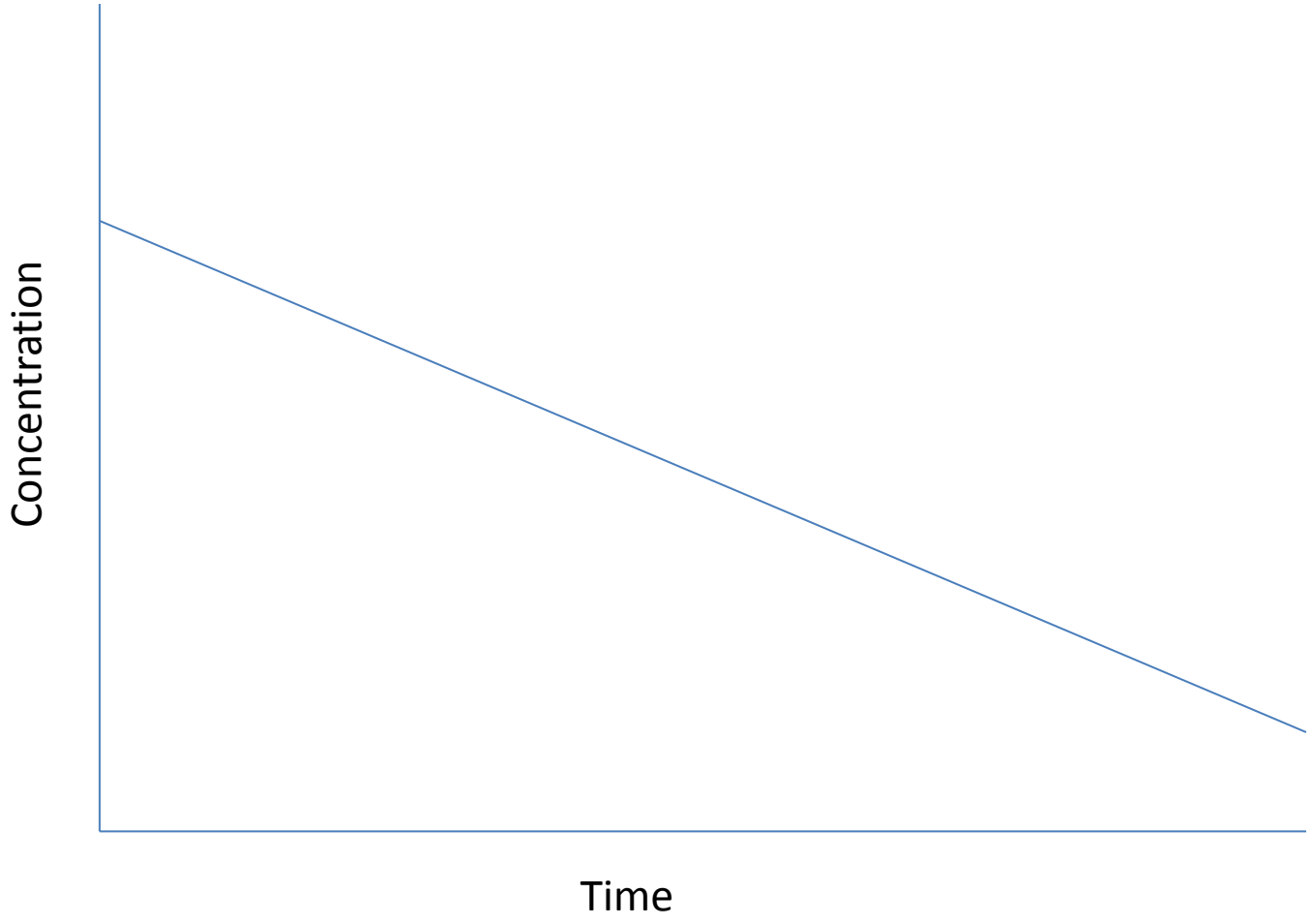
SOURCE: Paul A. Demers et al., Mortality Among Firefighters from Three Northwestern United States Cities, 49(9) BRITISH J. OF INDUS. MED. 664-670 (1992). Reproduced with permission.

Figure IV-1.



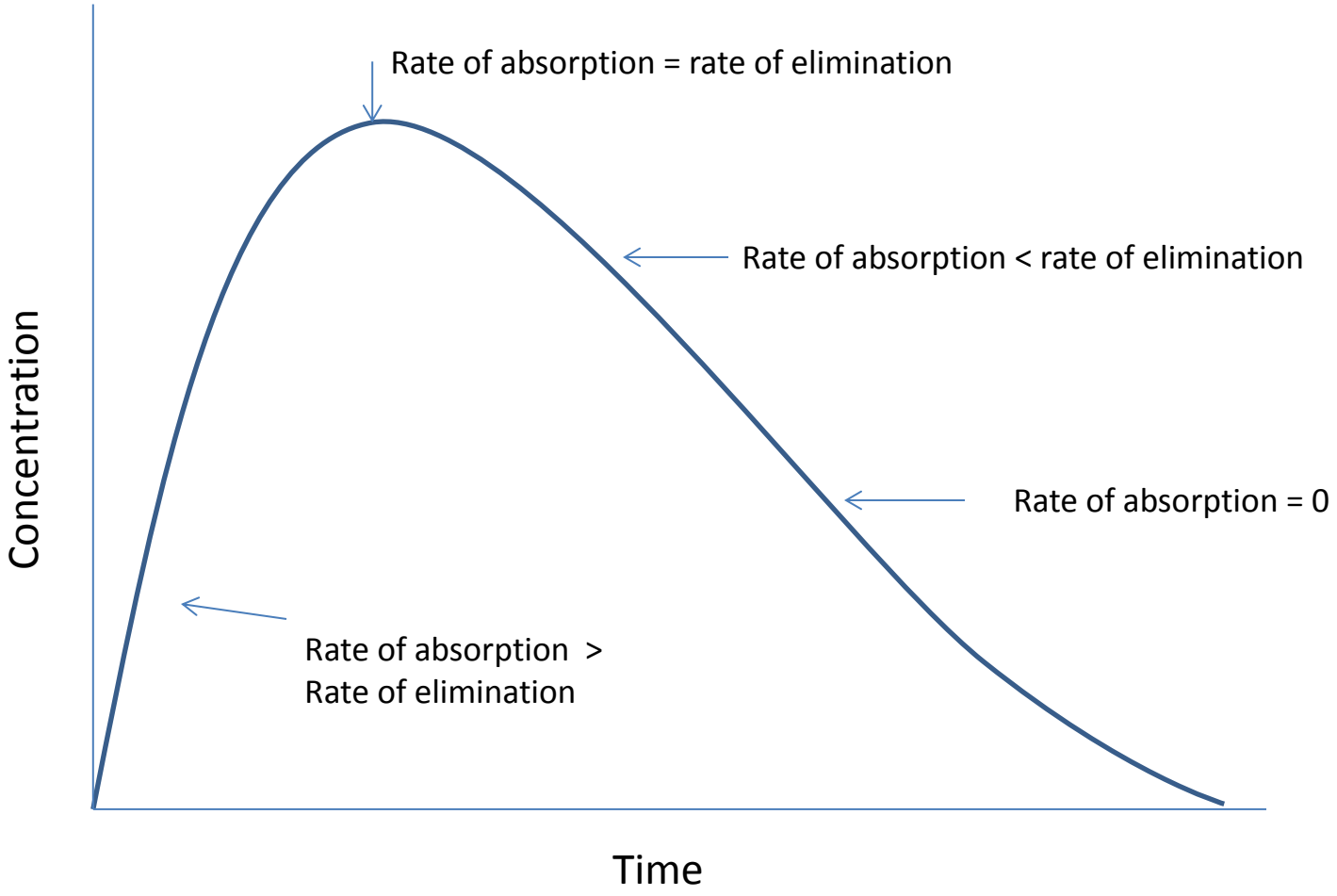
Elimination Rate affected by Concentration

Figure IV-2.



Elimination is a Constant Over Time

Figure IV-3.



Absorption and Elimination of an Oral Dose

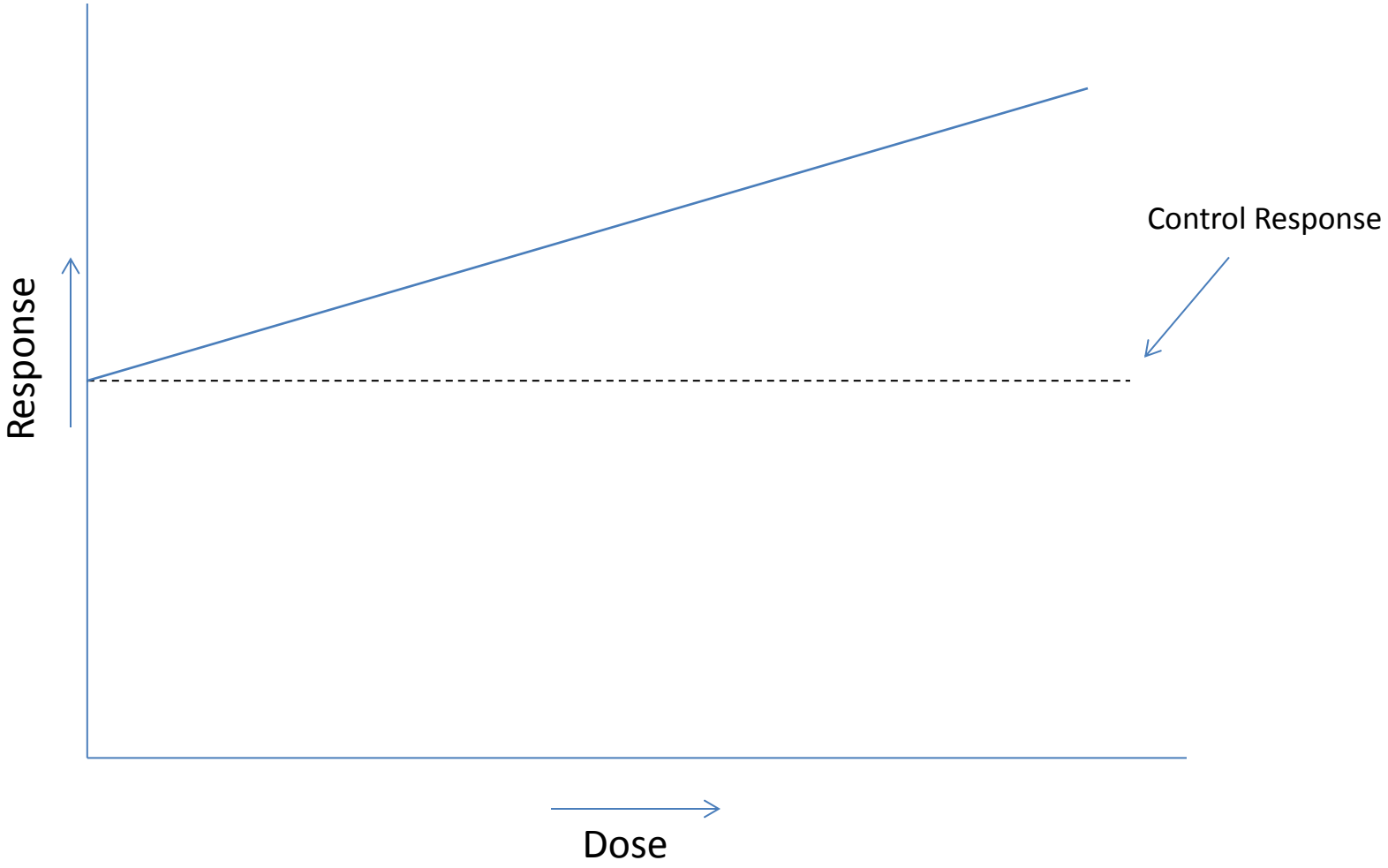
SOURCE: Republished with permission of Taylor and Francis Group LLC Books, from Karen E. Stein and Thomas M. Brown, *Principles of Toxicology*, Third Edition, 2015; permission conveyed through Copyright Clearance Center, Inc.

Table IV-1
Acute Oral LD_{50} In Rats: Various Substances

• Ethanol	7,000	mg/kg
• Sodium chloride	3,000	
• Salt	3,000	
• Aspirin	1,000	
• Caffeine	200	
• Nicotine	50	
• Vitamin D	10	
• Cyanide	10	
• Botulin toxin	0.00001	

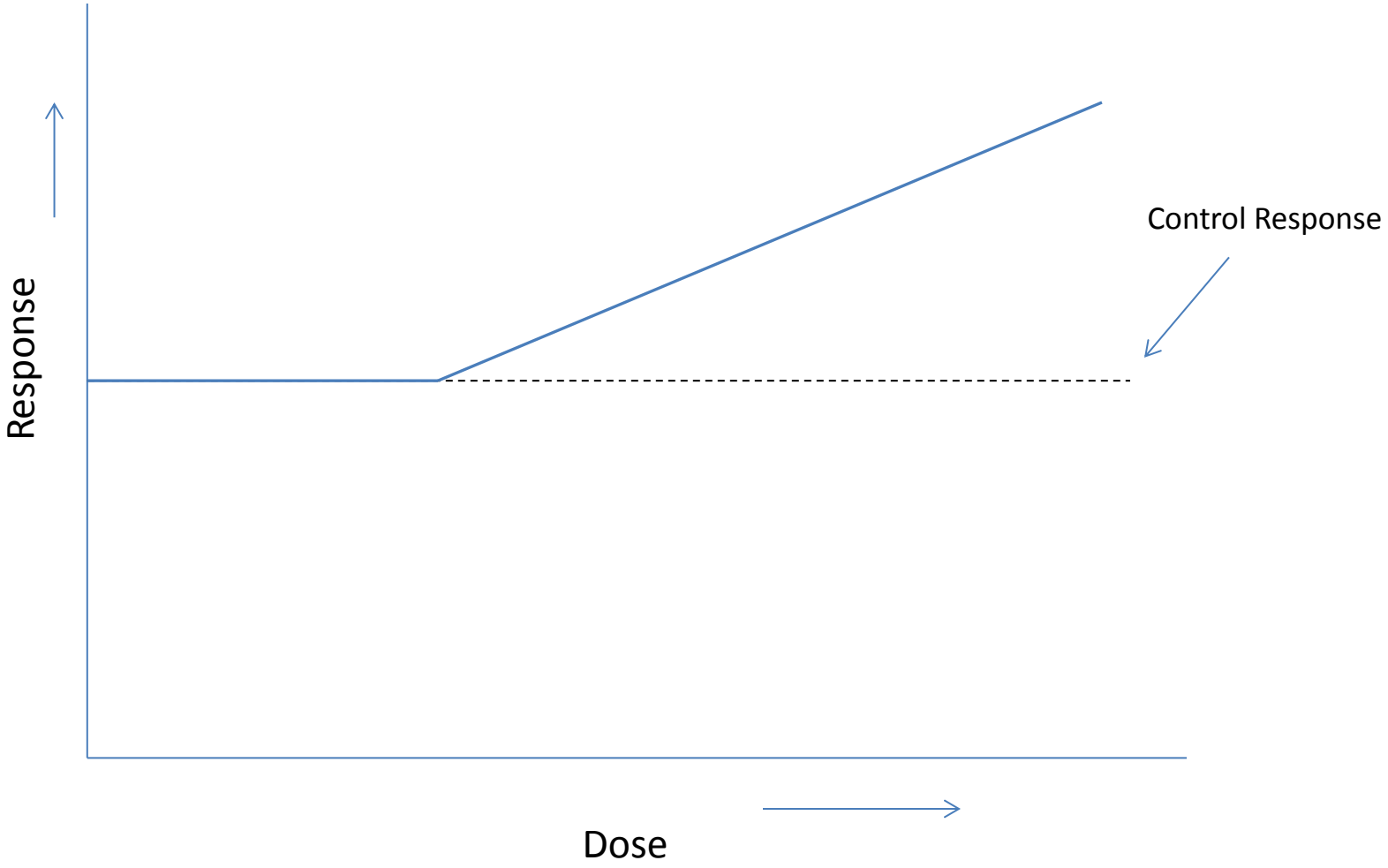
SOURCE: Republished with permission of National Science Teachers Association, from Nancy M. Trautmann, *Assessing Toxic Risk*, Student's Edition, 2001; permission conveyed through Copyright Clearance Center, Inc.

Figure IV-4.



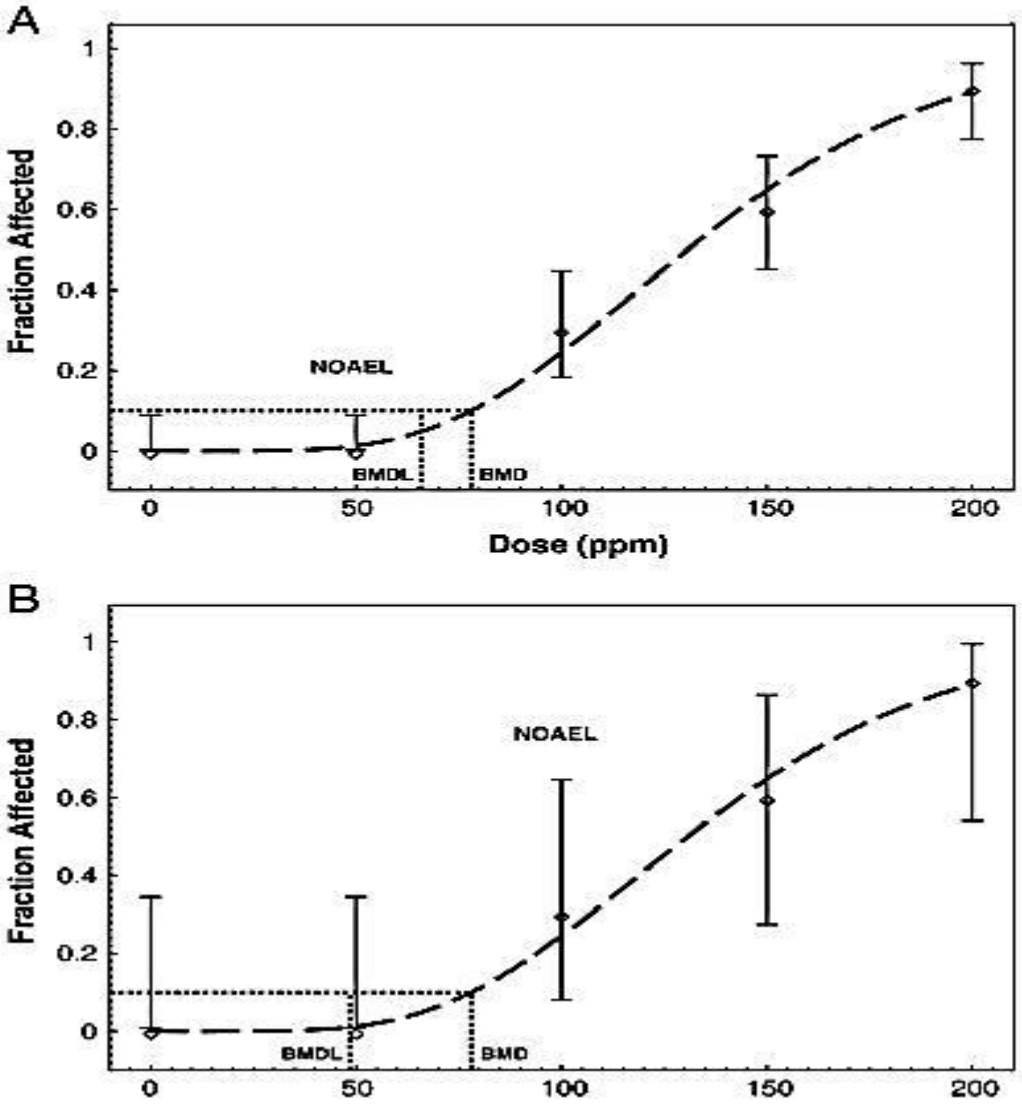
Linear No-threshold (LNT) Model

Figure IV-5.



Linear Threshold Model (LNM)

Figure IV-6.



SOURCE: Reprinted from *Toxicology and Applied Pharmacology* 254(2), J. Allen Davis, Jeffrey S. Gifta, Q. Jay Zhaob, "Introduction to benchmark dose methods and U.S. EPA's benchmark dose software (BMDS) version 2.1.1," pp. 181-91, (2011), with permission from Elsevier.

Table IV-2.

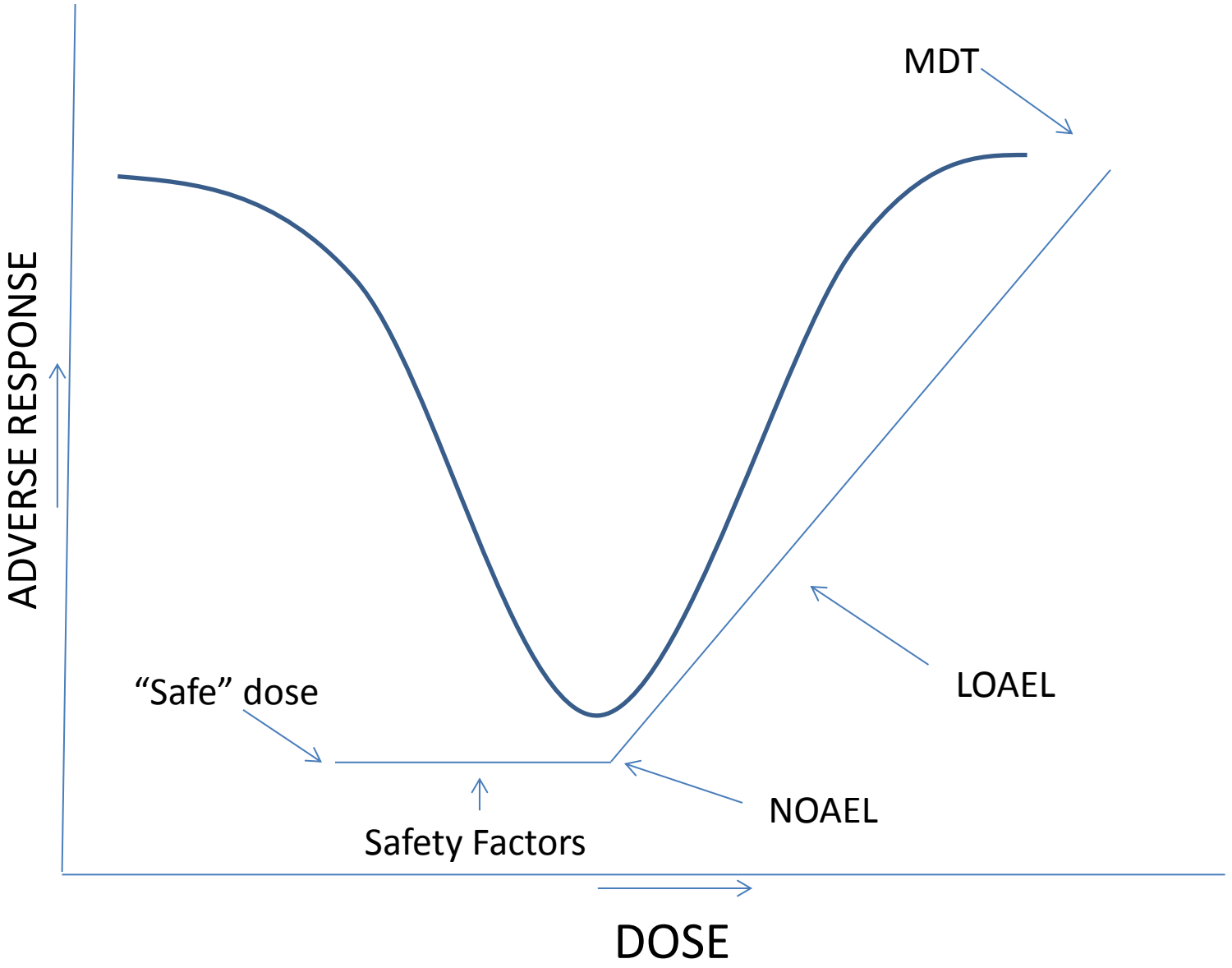
Determination of NOAEL and BMDL dependent on dose group sample size.

Animals per dose group	Dose (ppm)	Incidence	Fisher's exact *p*-value	NOAEL[a]	BMD	BMDL
	0	0	1.00			
	50	0	1.00			
50	100	15	< 0.001	50	78.05	65.85
	150	30	< 0.001			
	200	45	< 0.001			
	0	0	1.00			
	50	0	1.00			
10	100	3	0.105	100	78.05	48.40
	150	6	0.005			
	200	9	< 0.001			

[a]NOAEL determined based on highest dose with Fisher's exact *p*-value of ≤ 0.1.

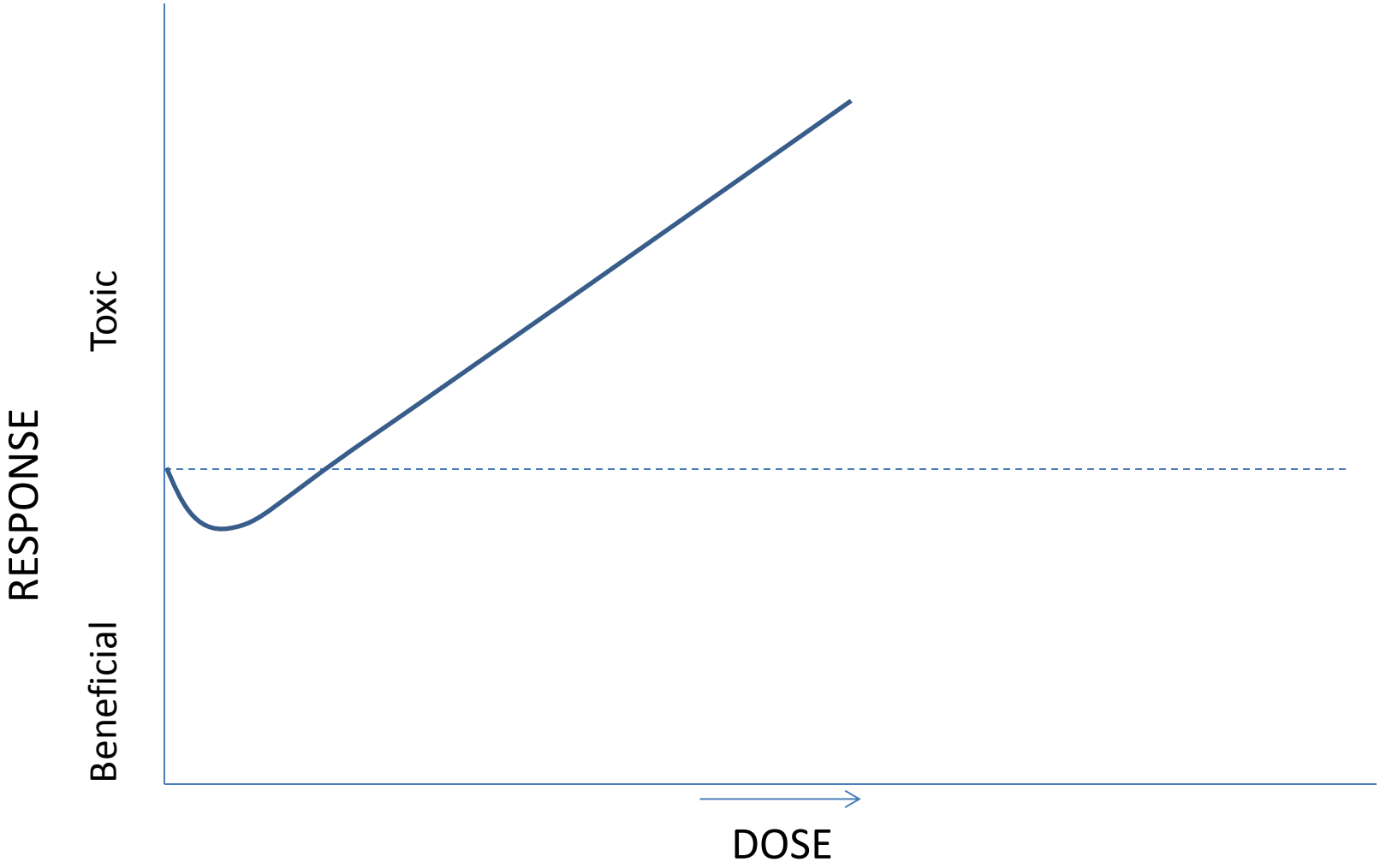
SOURCE: Reprinted from *Toxicology and Applied Pharmacology* 254(2), J. Allen Davis, Jeffrey S. Gifta, Q. Jay Zhaob, "Introduction to benchmark dose methods and U.S. EPA's benchmark dose software (BMDS) version 2.1.1," pp. 181-91, (2011), with permission from Elsevier.

Figure IV-7



SOURCE: Laura N. Vandenberg et al., "Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses," 33(3) *Endocrine Reviews* 378 (2012). Copyright © 2012. The Endocrine Society.

Figure IV-8



Hormesis Effect

SOURCE: Adapted from Edward Calabrese, "Hormesis: Principles & Applications," *Homeopathy* (2015) 104, 69, Figure 1B.

Figure IV-9

Overview of Exposure, Dose, and Injury

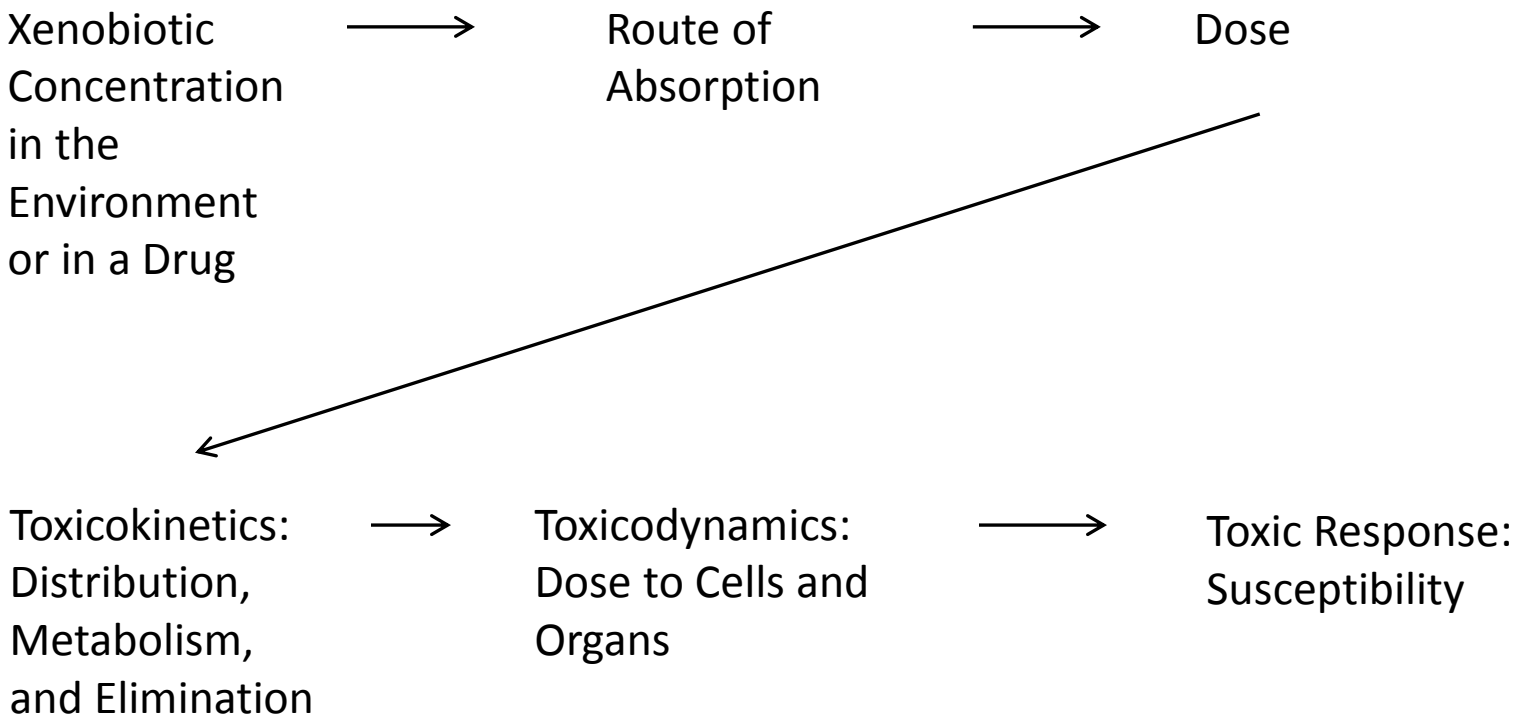
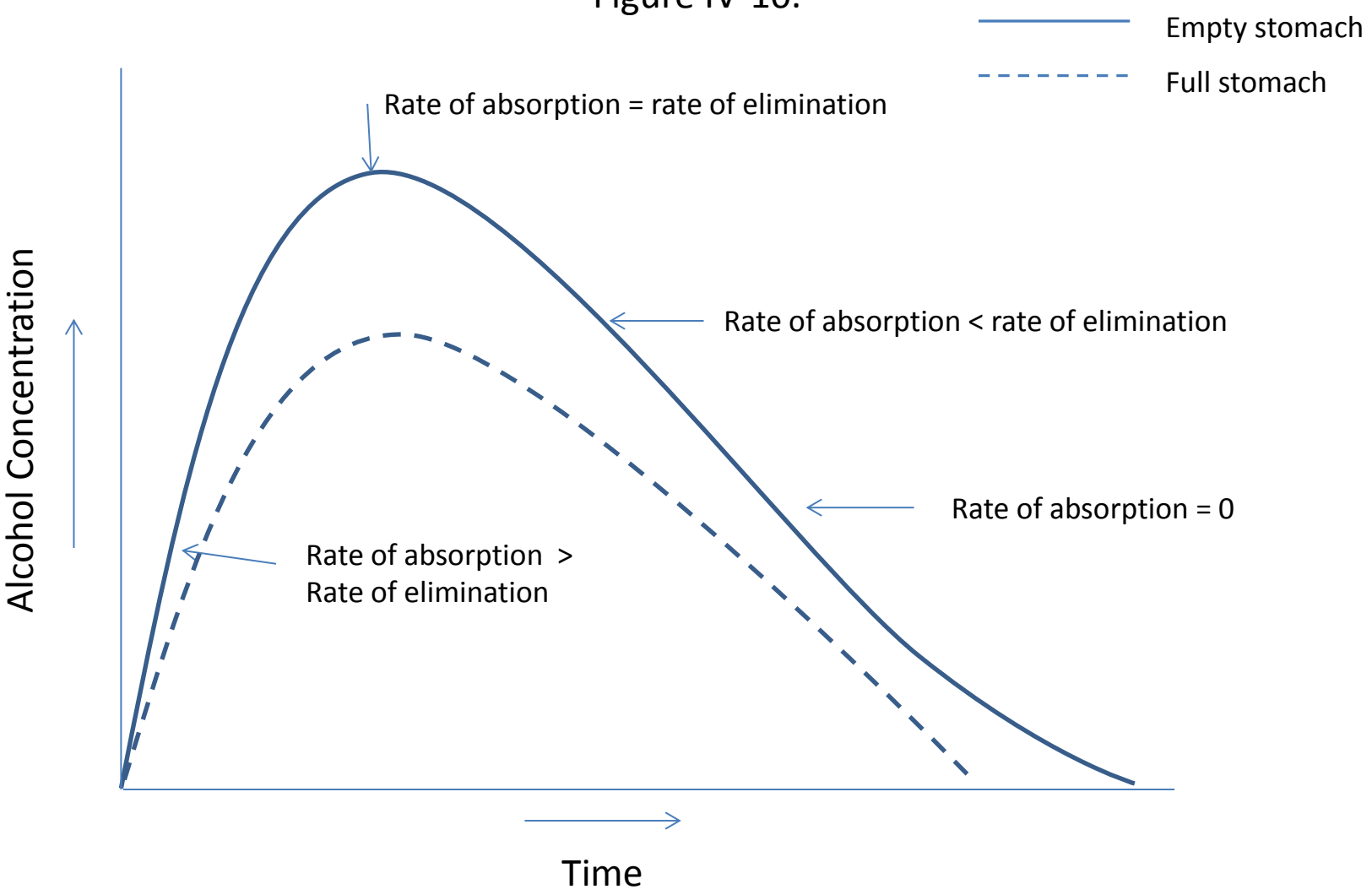


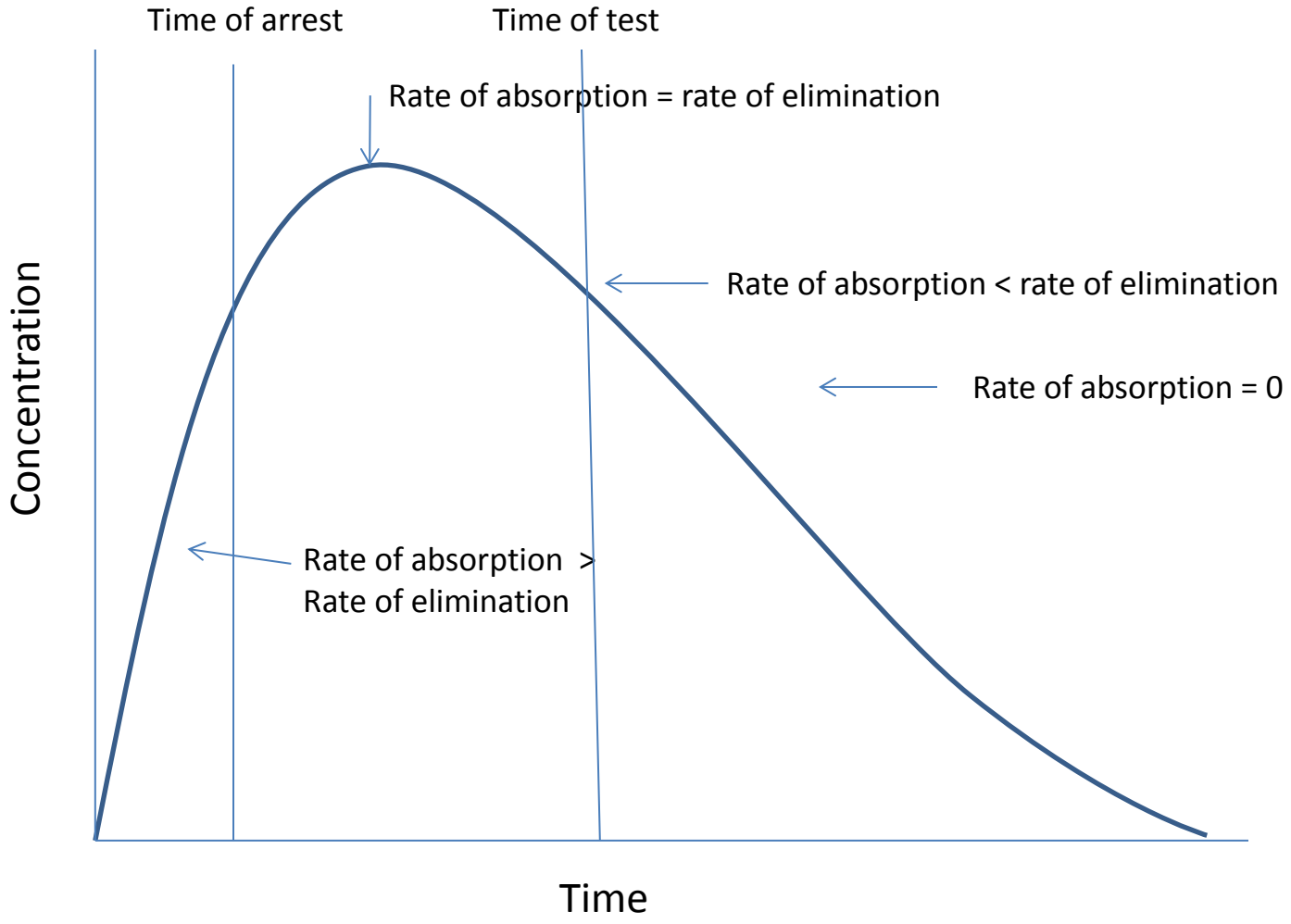
Figure IV-10.



Absorption and Elimination Curve by food in stomach

SOURCE: Republished with permission of Taylor and Francis Group LLC Books, adapted from Karen E. Stein and Thomas M. Brown, *Principles of Toxicology*, Third Edition, 2015; permission conveyed through Copyright Clearance Center, Inc.

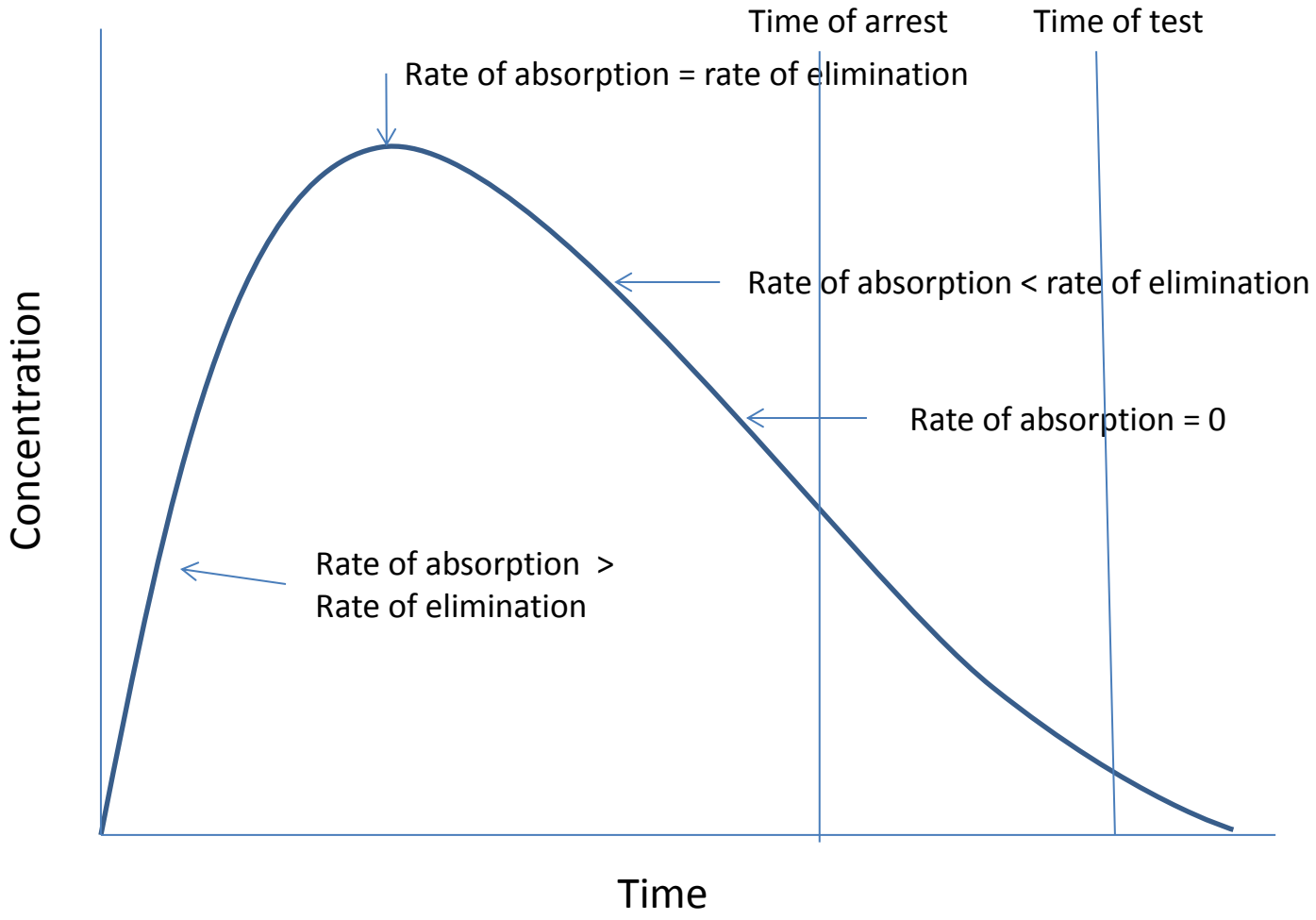
Figure IV-11.



Absorption and Elimination of an Oral Dose

SOURCE: Republished with permission of Taylor and Francis Group LLC Books, adapted from Karen E. Stein and Thomas M. Brown, *Principles of Toxicology*, Third Edition, 2015; permission conveyed through Copyright Clearance Center, Inc.

Figure IV-12.



Absorption and Elimination of an Oral Dose

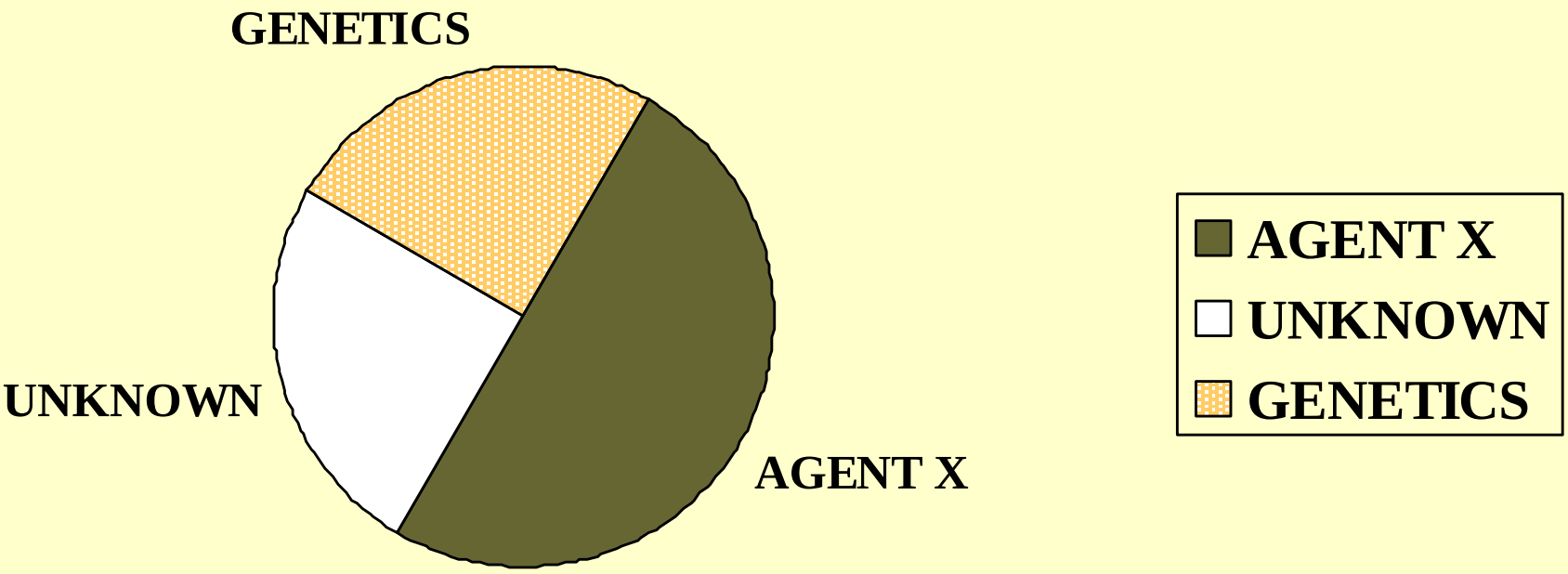
SOURCE: Republished with permission of Taylor and Francis Group LLC Books, adapted from Karen E. Stein and Thomas M. Brown, *Principles of Toxicology*, Third Edition, 2015; permission conveyed through Copyright Clearance Center, Inc.

SPECIFIC CAUSATION: DID IT CAUSE THIS PLAINTIFF'S DISEASE?

- **Remember: Association ≠ Causation. First We Must Decide if Association is Truly Causal.**
- **Converting Relative Risk to Preponderance of the Evidence**
- **External Validity: Is Study Probability (APR) Applicable to Plaintiff?**
- **Assumptions Involved in Converting APR to a a Probability of Specific Causation**
- **Refining the Probability of Causation for a Plaintiff**

APR AS A PROBABILITY

SOURCES OF DISEASE



APR FORMULA

$$APR = \frac{RR - 1}{RR}$$

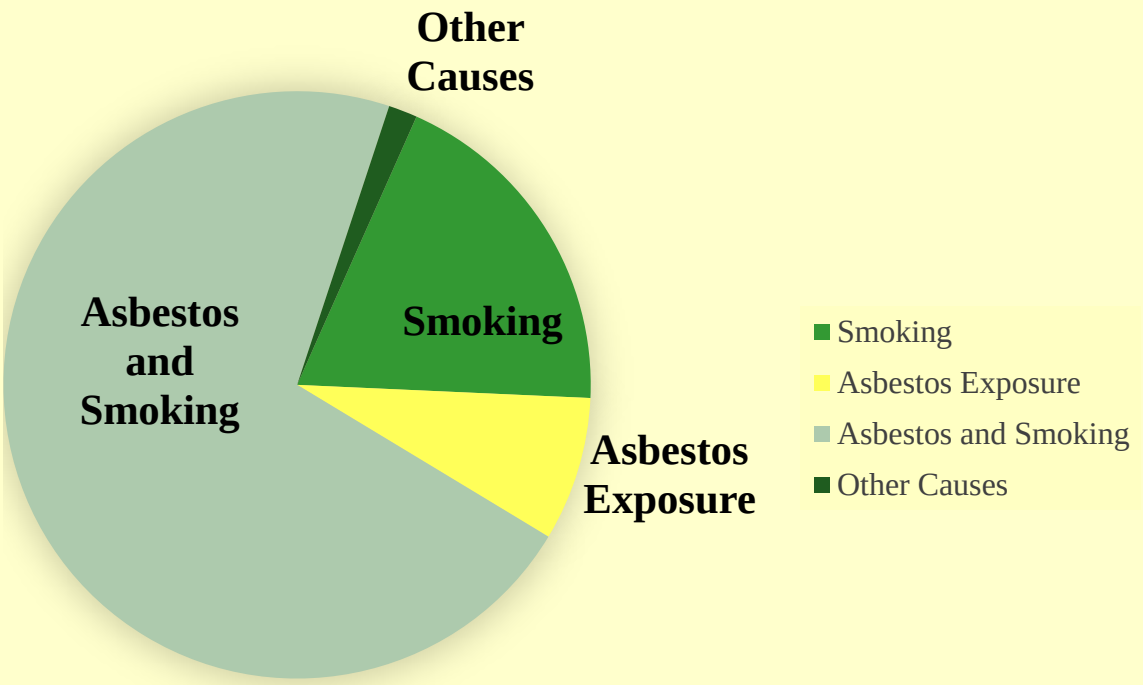
EXAMPLE

$$RR = 2.0$$

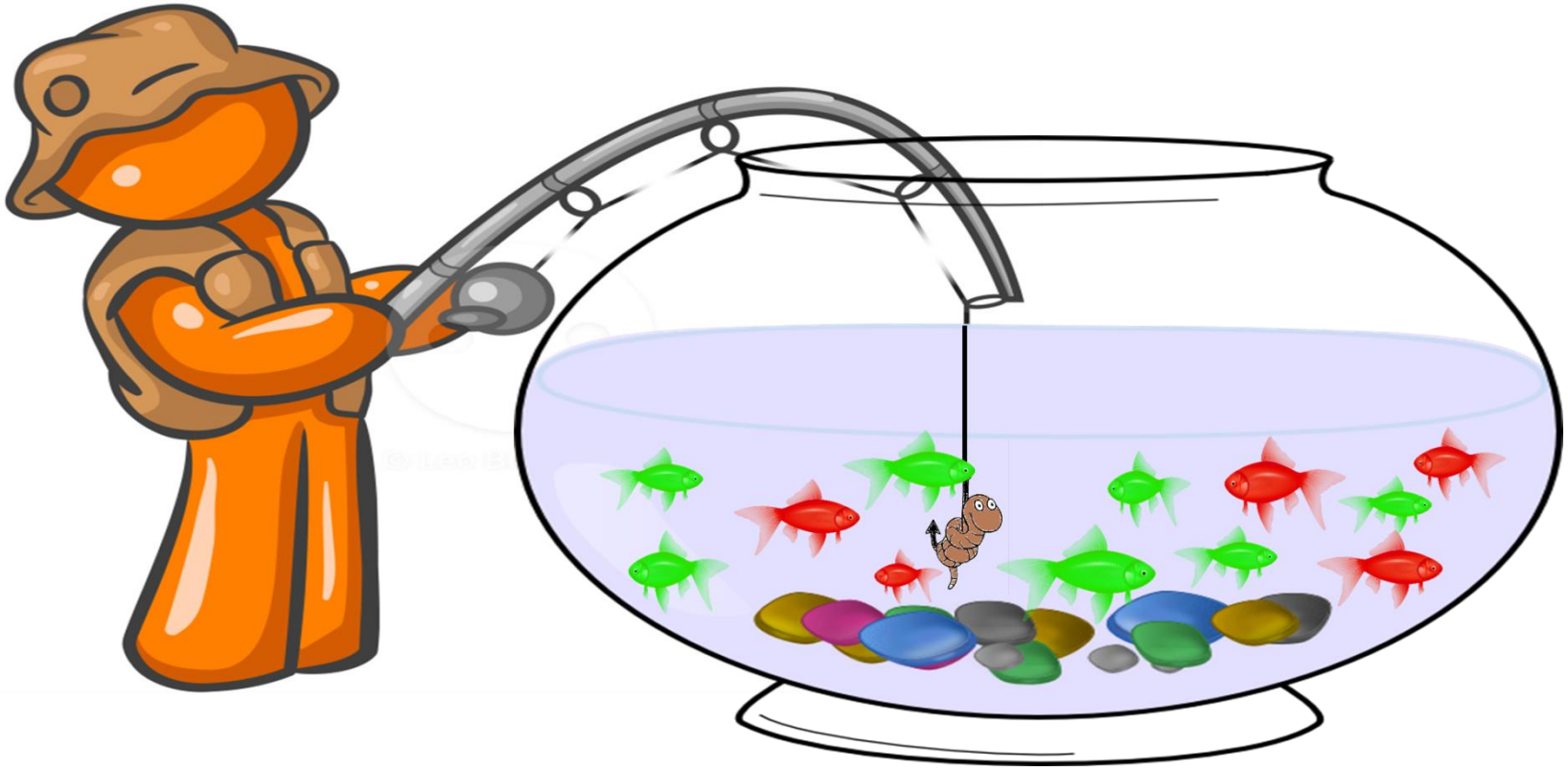
$$APR = \frac{2.0 - 1}{2.0} = .50$$

SYNERGISTIC AGENTS

RISK FACTORS FOR LUNG CANCER

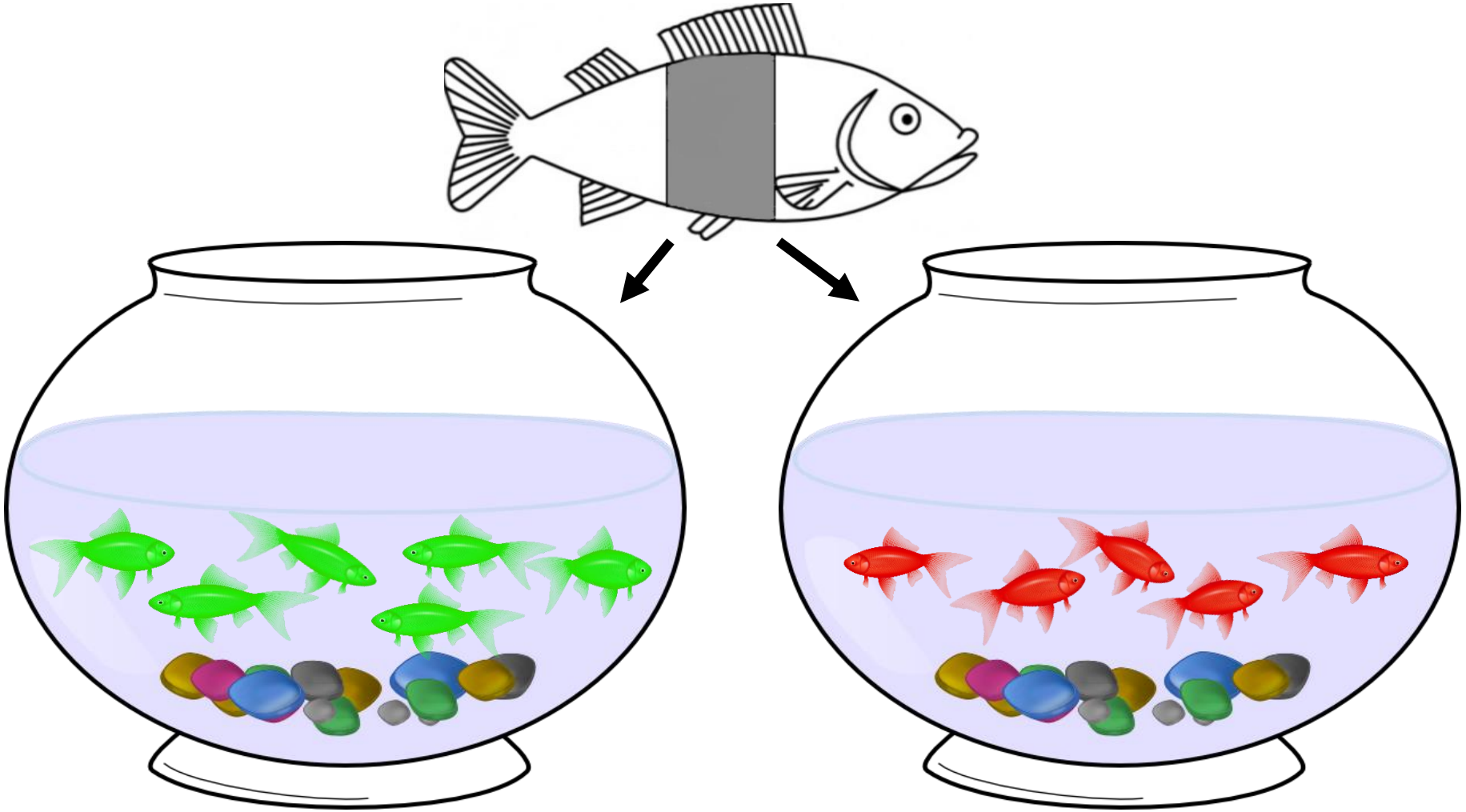


FREQUENTIST PROBABILITY



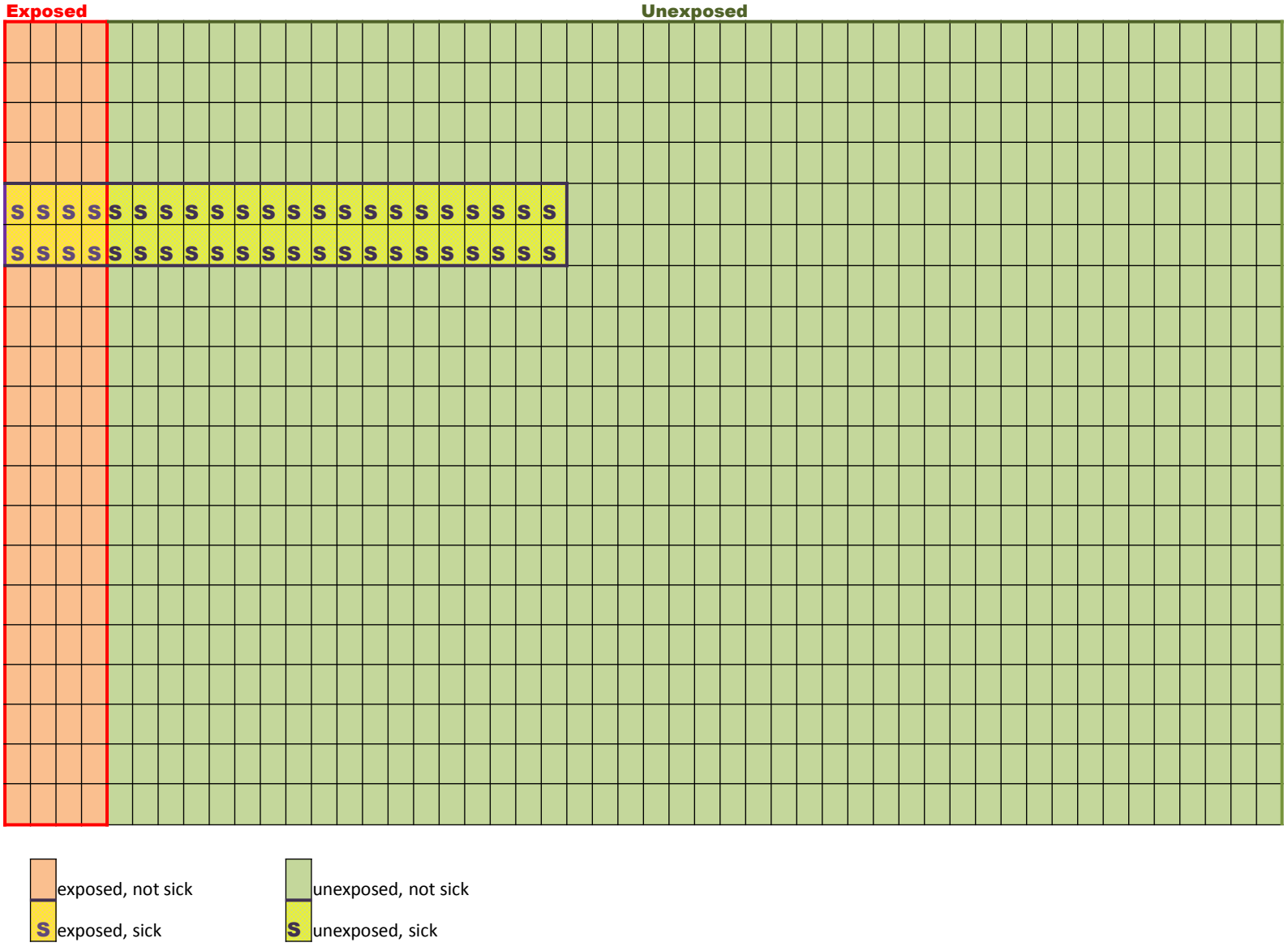
GREEN FISH: CAUSATION EXISTS RED FISH: CAUSATION DOES NOT EXIST

SUBJECTIVIST PROBABILITY

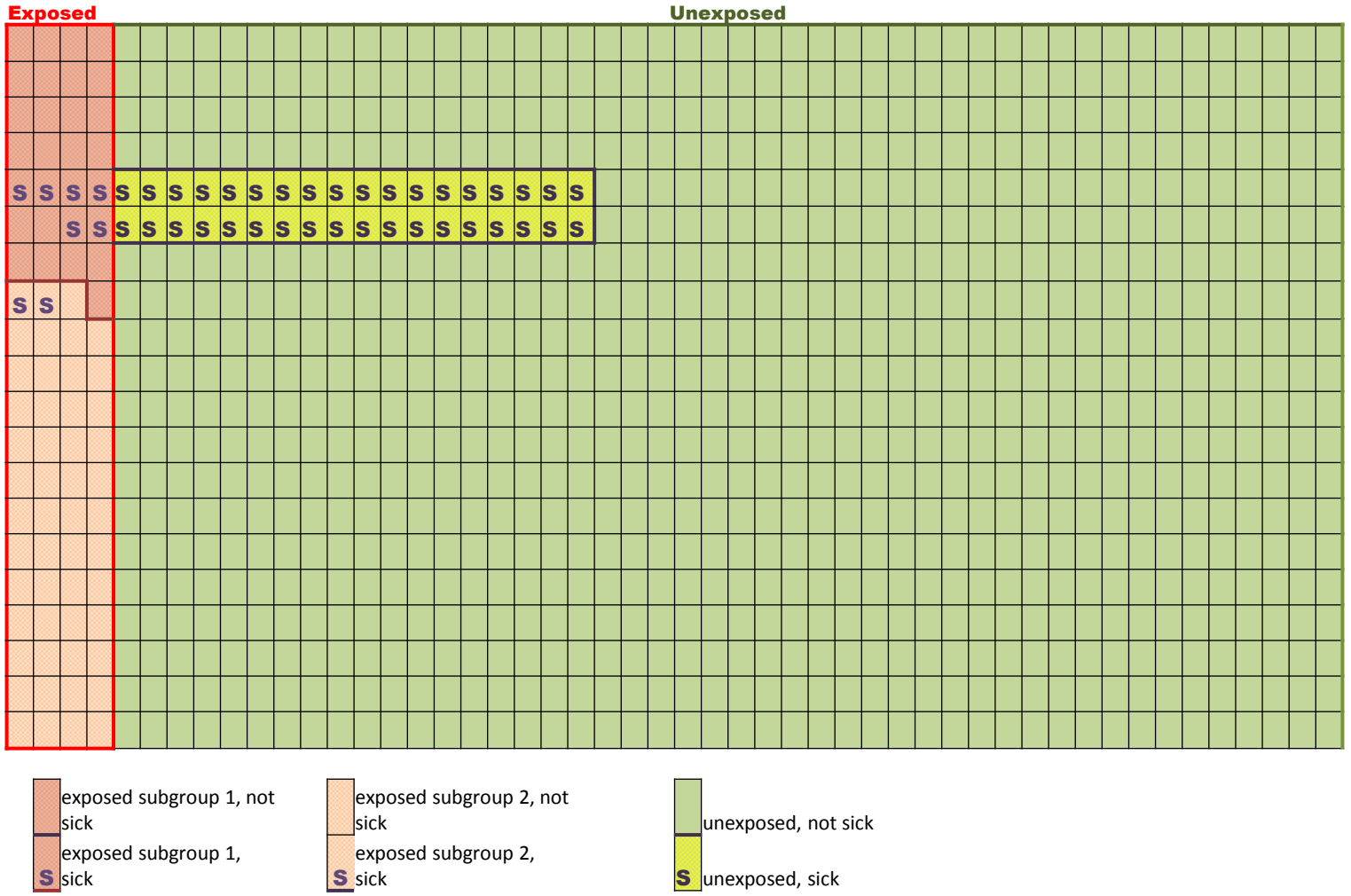


WHICH BOWL DID I COME FROM?

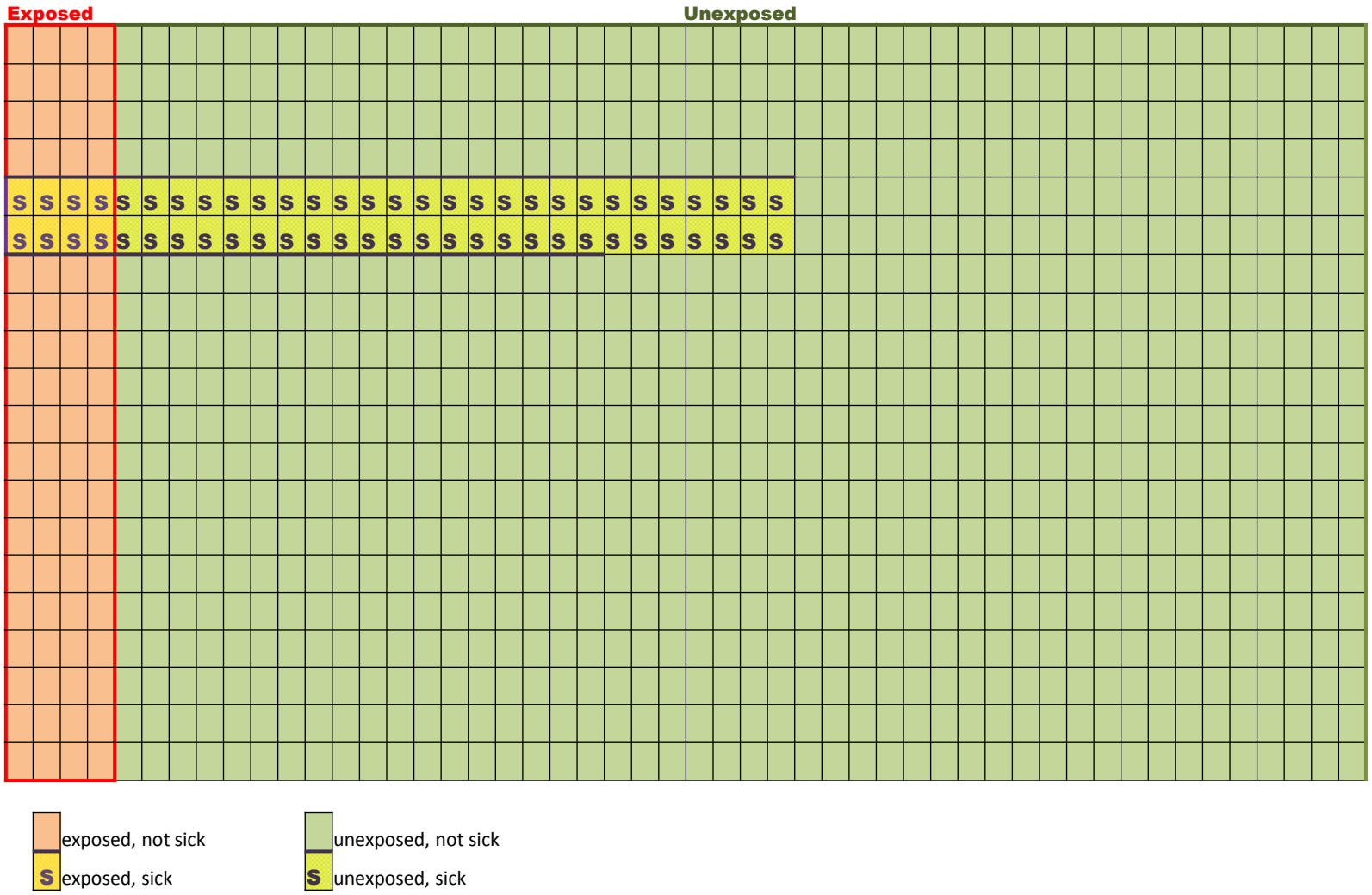
A hypothetical cohort study



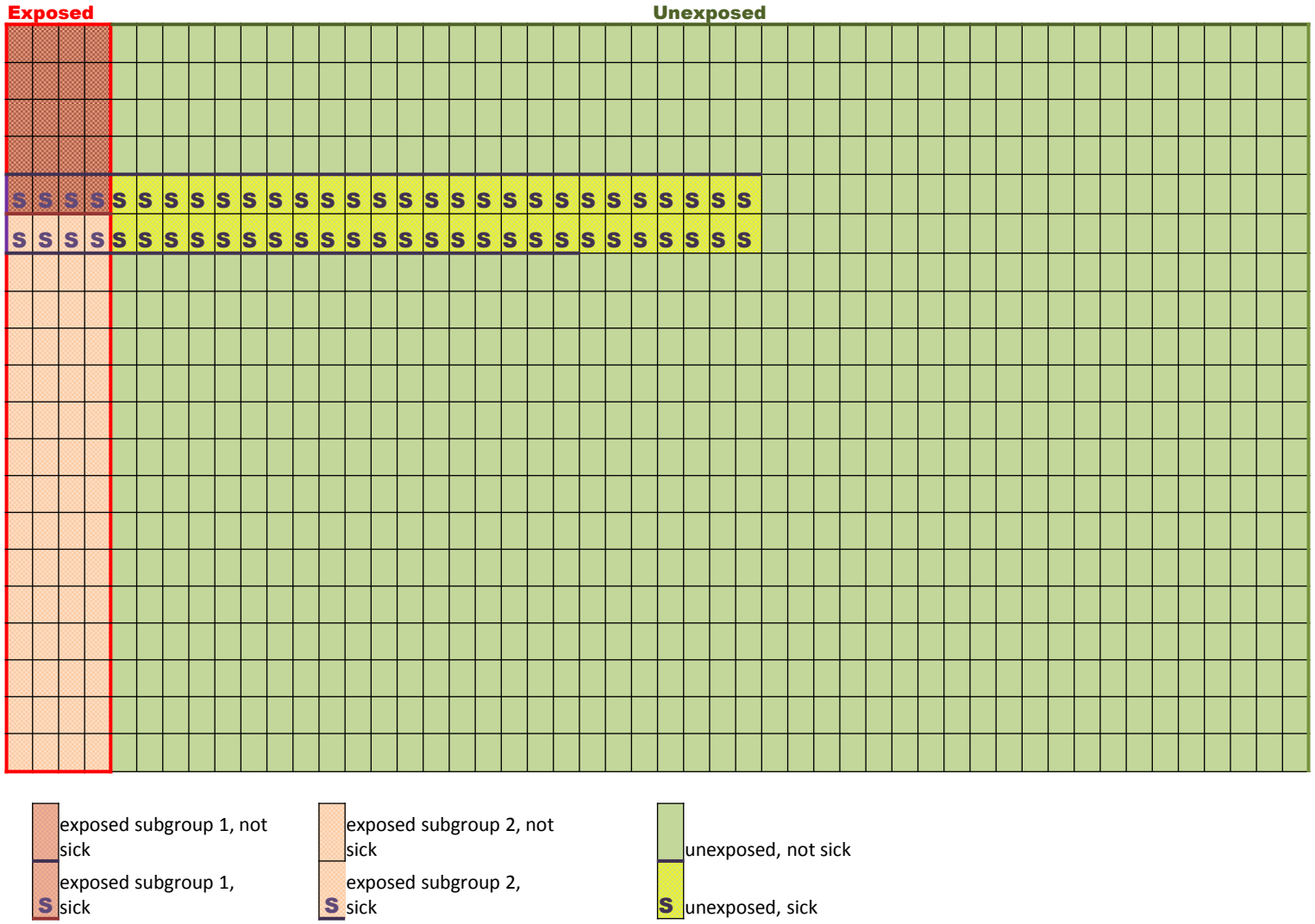
Hypothetical cohort study refined



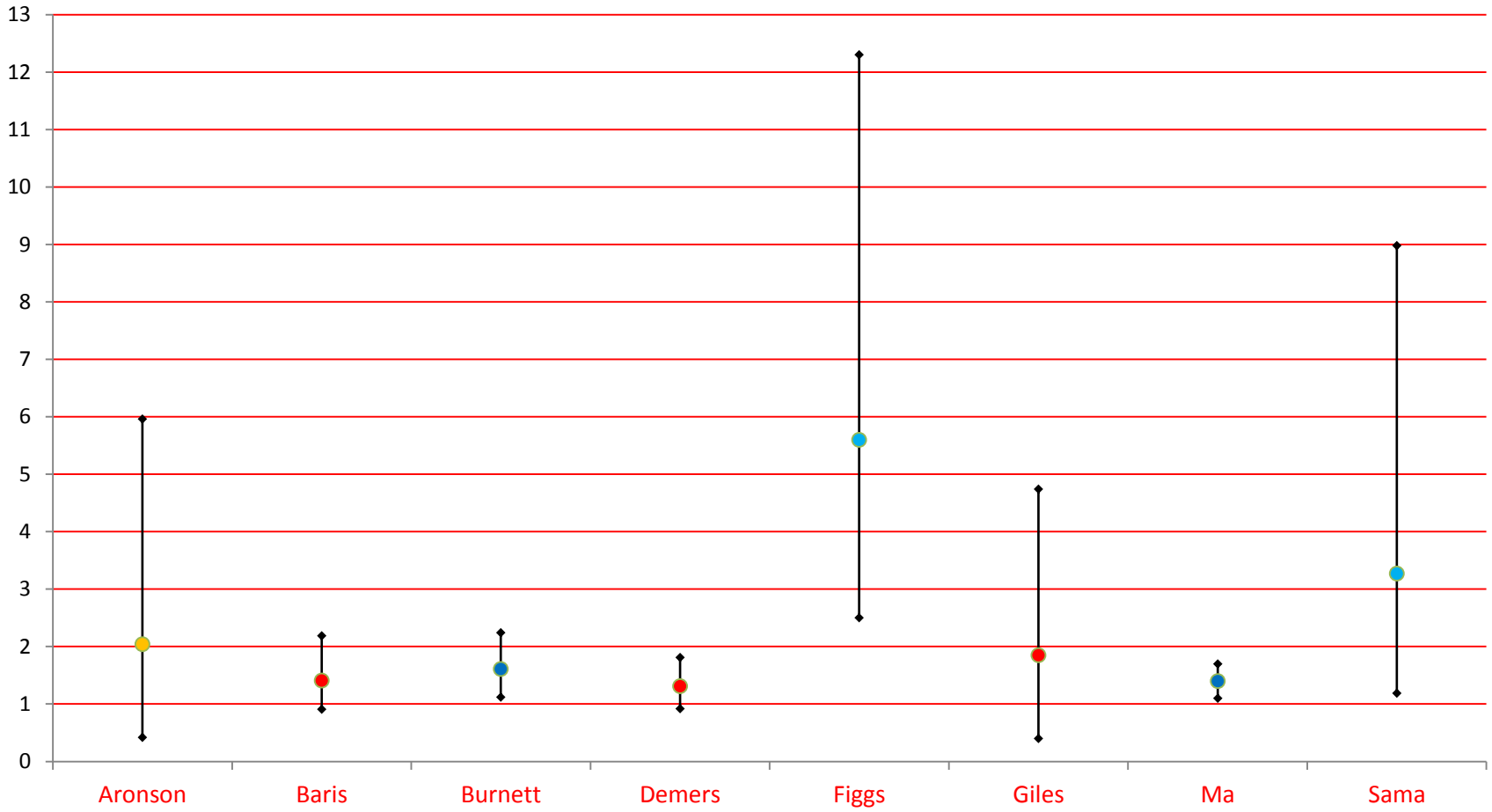
Another cohort study hypothetical



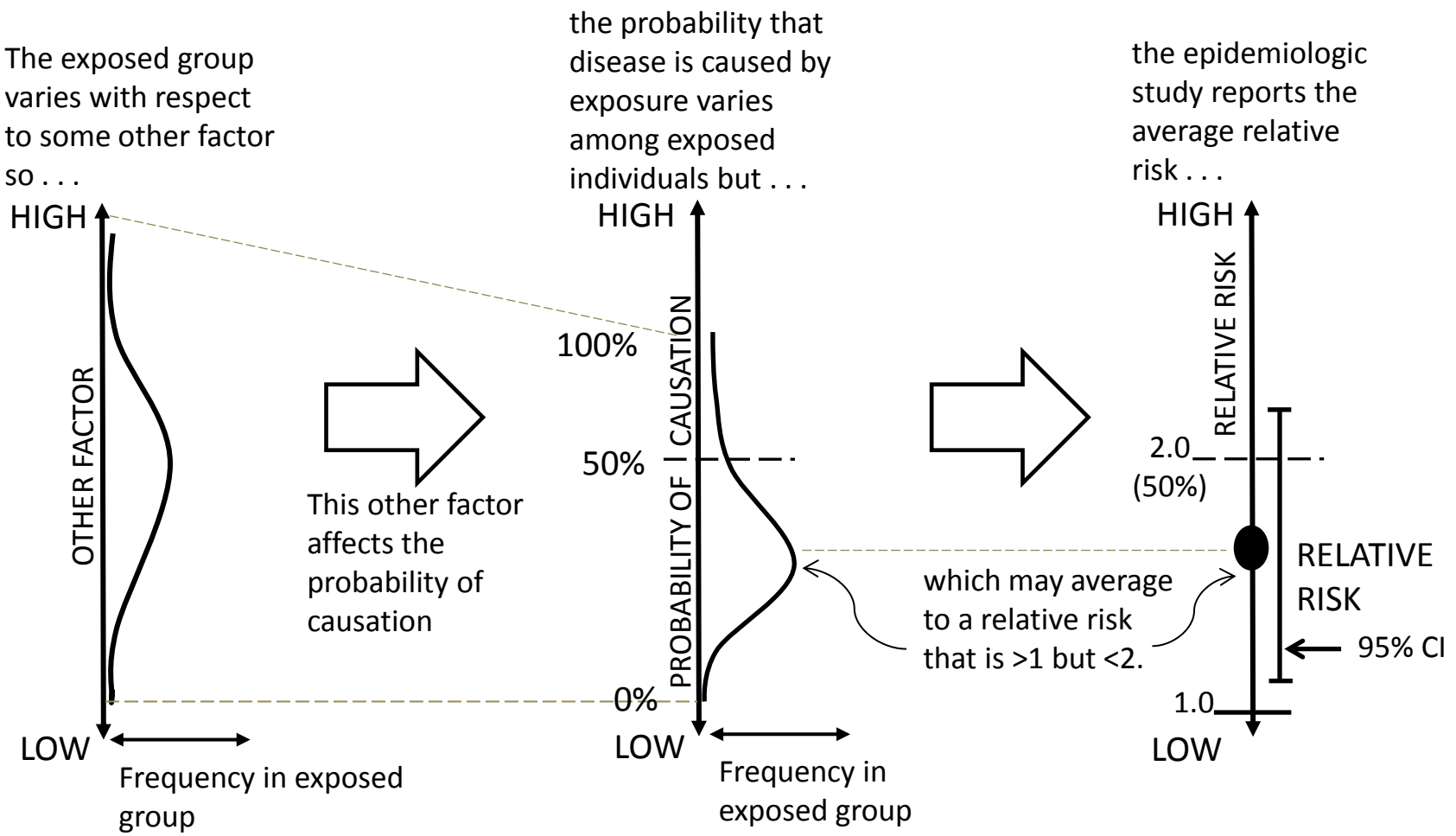
Another hypothetical, refined



Epidemiologic studies of firefighting and NHL in *Estate of George*



The Role of Information About the Individual Plaintiff

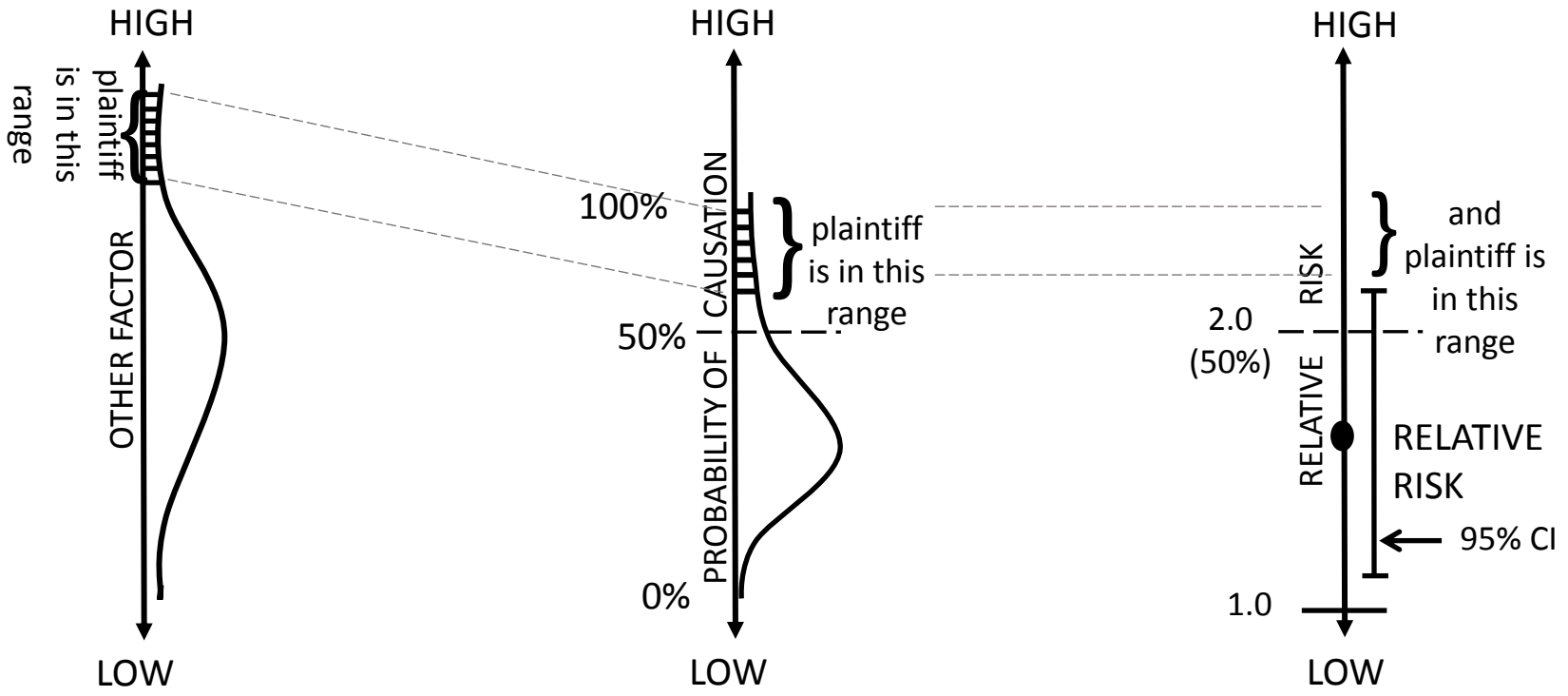


The Role of Information About the Individual Plaintiff (Continued)

The plaintiff is relatively high in the other factor and . . .

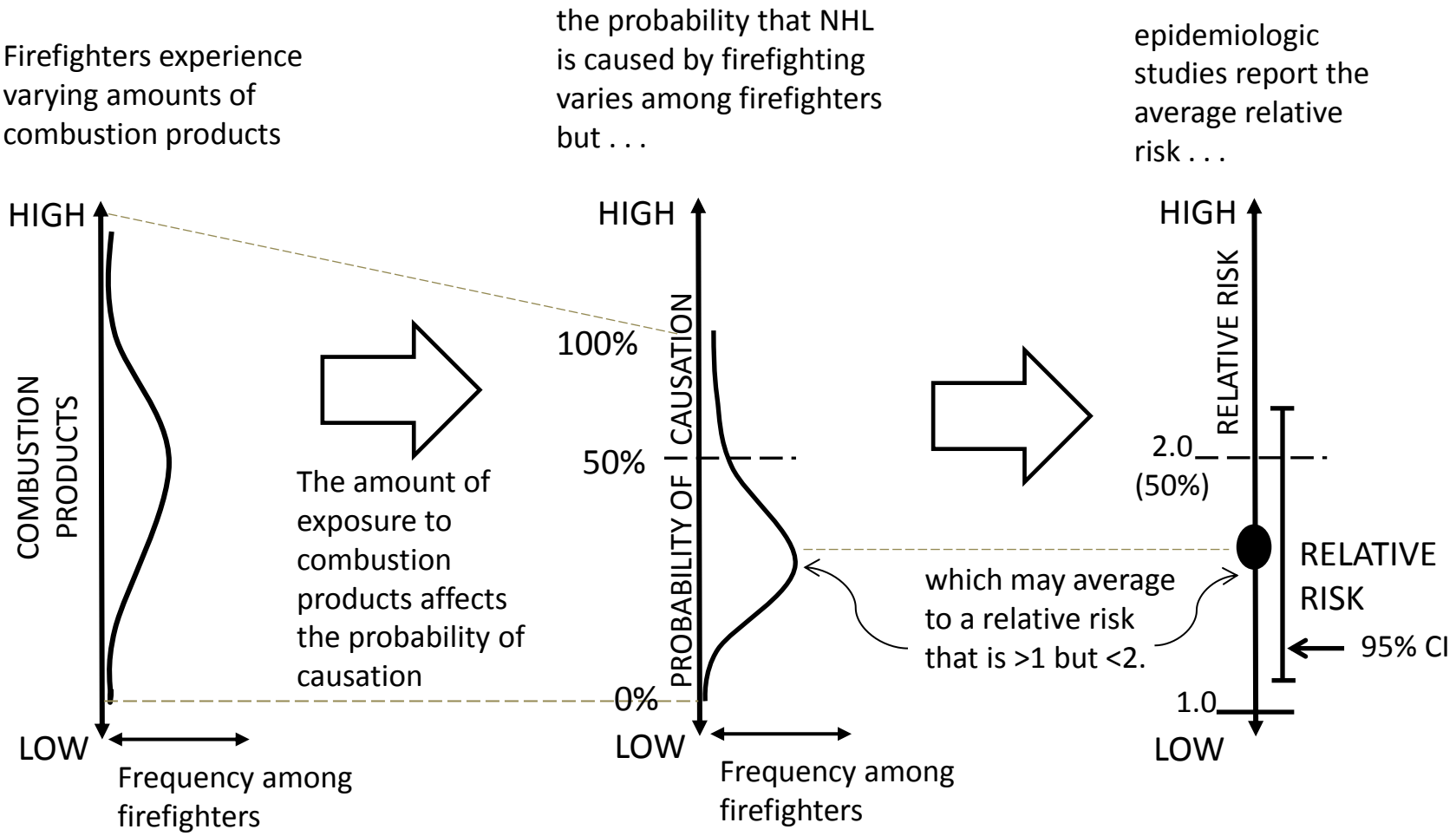
therefore has an above-average probability of causation, so . . .

it can be inferred that exposure more likely than not caused plaintiff's disease even though exposure caused fewer than half the cases in the exposed group.



Individual Information in *Estate of George*

FIREFIGHTING increases risk of NHL

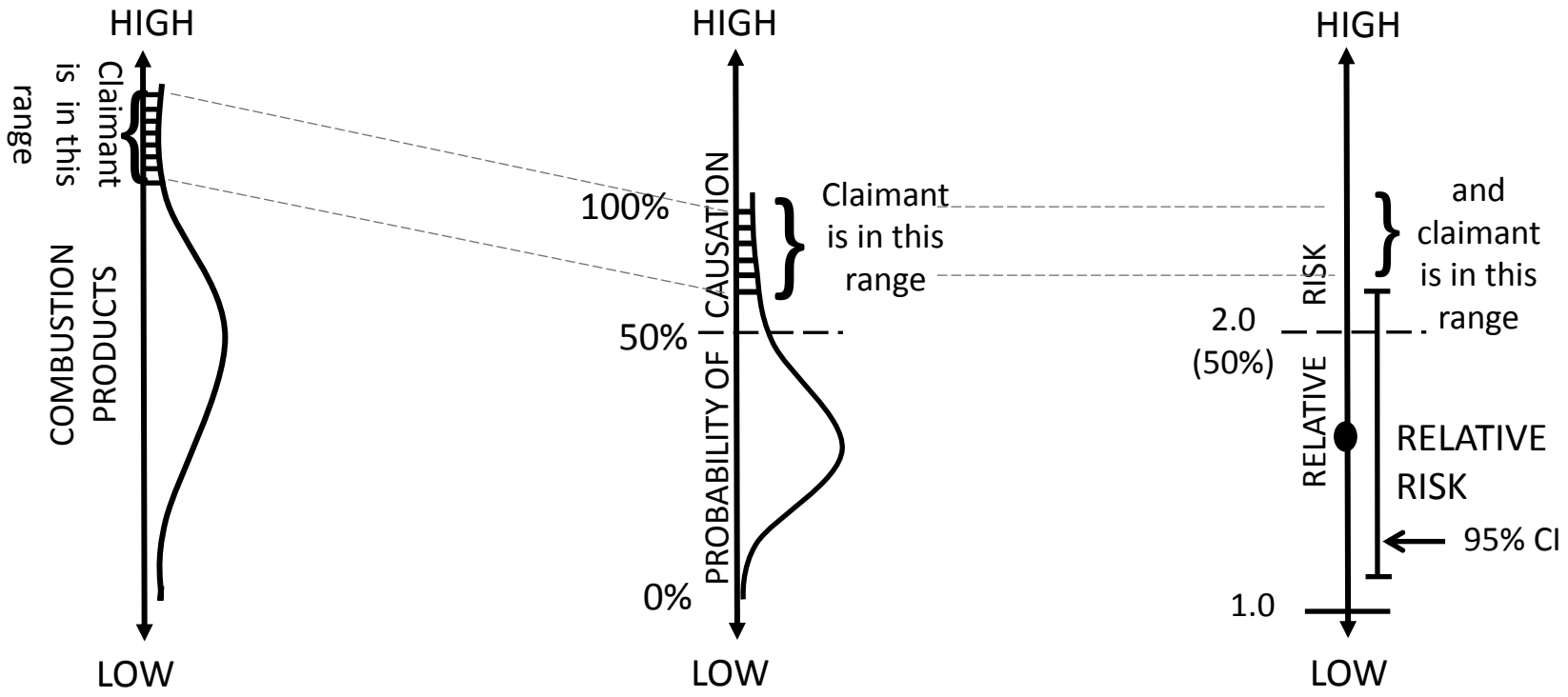


Individual Information in *Estate of George* (Continued)

Mr. George experienced relatively high exposure to combustion products . . .

and therefore had an above-average probability of causation, so . . .

it can be inferred that firefighting more likely than not caused his NHL even if firefighting caused fewer than half of NHL cases in firefighters.



Part of Table III from Baris study.

TABLE III. Observed (Obs) Deaths, Standardized Mortality Ratios (SMR), and 95% Confidence Intervals (CI) Among Philadelphia Firefighters by Duration of Employment as a Firefighter (1925–1986) (N = 7,789)

	Duration of employment								
	≤ 9 years			10–19 years			≥ 20 years		
Cause of death (ICD-9)	**Obs**	**SMR**	**95% CI**	**Obs**	**SMR**	**95% CI**	**Obs**	**SMR**	**95% CI**
All causes (001–999)	586	**0.88**	0.81–0.95	862	**1.07**	1.00–1.14	772	**0.91**	0.85–0.98
All cancers (140–209)	143	**1.26**	1.07–1.49	170	**1.10**	0.94–1.27	187	**0.99**	0.86–1.15
Buccal cavity and pharynx (140–149)	4	**1.15**	0.43–3.07	9	**1.83**	0.95–3.51	6	**1.09**	0.50–2.43
Esophagus (150)	0	—	—	3	**0.82**	0.26–2.52	3	**0.65**	0.21–2.02
Stomach (151)	4	**0.55**	0.21–1.48	14	**1.39**	0.83–2.35	6	**0.65**	0.29–1.44
Colon (153)	18	**1.78**	1.12–2.82	16	**1.11**	0.68–1.81	30	**1.68**	1.17–2.40
Rectum (154)	3	**0.86**	0.28–2.66	6	**1.16**	0.52–2.58	5	**0.92**	0.38–2.22
Liver (155–156)	1	**0.40**	0.06–2.83	3	**0.84**	0.27–2.60	4	**1.09**	0.41–2.91
Pancreas (157)	13	**2.33**	1.36–4.02	5	**0.60**	0.25–1.45	5	**0.49**	0.21–1.19
Larynx (161)	1	**0.66**	0.09–4.59	1	**0.43**	0.06–3.05	3	**1.08**	0.35–3.36
Lung (162)	50	**1.52**	1.16–2.01	56	**1.20**	0.92–1.56	56	**0.89**	0.68–1.15
Skin (172–173)	2	**0.75**	0.19–3.01	5	**1.70**	0.71–4.09	3	**1.05**	0.34–3.26
Prostate (185)	15	**2.36**	1.42–3.91	5	**0.47**	0.19–1.12	11	**0.72**	0.40–1.31
Bladder (188)	4	**1.36**	0.51–3.61	7	**1.48**	0.70–3.09	6	**1.01**	0.45–2.25
Kidney (189)	2	**0.72**	0.18–2.87	0	—	—	10	**2.20**	1.18–4.08
Brain (191–192)	2	**0.47**	0.12–1.89	2	**0.44**	0.11–1.75	4	**0.94**	0.35–2.49
Non-Hodgkin's lymphoma (200,202)	6	**1.47**	0.66–3.26	5	**1.03**	0.43–2.47	9	**1.72**	0.90–3.31
Multiple myeloma (203)	1	**0.73**	0.10–5.17	3	**1.50**	0.48–4.66	6	**2.31**	1.04–5.16
Leukemia (204–207)	5	**0.94**	0.39–2.25	7	**1.14**	0.54-2.38	3	**0.45**	0.15–1.40

SOURCE: Dalsu Baris et al., "Cohort Mortality Study of Philadelphia Firefighters," 39 *Am. J. Indus. Med.* 463, 463 (2001). The article is a U.S. Government work and, as such, is in the public domain in the United States of America.

Part of Table VI from Baris study.

TABLE VI. Observed (Obs) Deaths, Standardized Mortality Ratios (SMR), and 95% Confidence Intervals (CI) Among Philadelphia Firefighters by Cumulative Number of Runs[a] in all Positions (1935–1986) (N = 6,477)

	Low (< 3,323 runs)			Medium (≥ 3,323 & < 5,099 runs)			High (≥ 5,099 runs)		
Cause of death (ICD–9)	**Obs**	**SMR**	**95% CI**	**Obs**	**SMR**	**95% CI**	**Obs**	**SMR**	**95% CI**
All causes (001–999)	644	**0.94**	0.88–1.02	327	**0.93**	0.84–1.04	310	**0.90**	0.81–1.00
All cancers (140–209)	155	**1.14**	0.98–1.34	89	**1.09**	0.88–1.34	96	**1.12**	0.92–1.38
Buccal cavity and pharynx (140–149)	7	**1.72**	0.82–3.61	0	—	—	2	**0.77**	0.19–3.09
Esophagus (150)	2	**0.66**	0.17–2.64	1	**0.50**	0.07–3.54	3	**1.40**	0.45–4.33
Stomach (151)	4	**0.66**	0.25–1.75	1	**0.31**	0.05–2.22	2	**0.66**	0.16–2.63
Colon (153)	23	**1.93**	1.29–2.91	16	**2.22**	1.36–3.62	9	**1.22**	0.64–2.35
Rectum (154)	5	**1.37**	0.51–3.29	1	**0.51**	0.07–3.59	1	**0.54**	0.08–3.85
Liver (155–156)	2	**0.80**	0.20–3.21	1	**0.73**	0.10–5.22	1	**0.76**	0.11–5.38
Pancreas (157)	7	**1.02**	0.48–2.13	5	**1.17**	0.49–2.80	7	**1.61**	0.77–5.74
Larynx cancer (161)	1	**0.53**	0.07–3.76	1	**0.83**	0.11–5.87	1	**0.80**	0.11–5.74
Lung (162)	47	**1.06**	0.79–1.41	30	**1.00**	0.70–1.44	38	**1.18**	0.86–1.63
Skin cancer (172–173)	1	**0.36**	0.05–2.50	5	**3.10**	1.29–7.46	1	**0.52**	0.07–3.75
Prostate (185)	10	**1.33**	0.72–2.48	3	**0.65**	0.21–2.03	6	**1.42**	0.64–3.16
Bladder (188)	4	**1.20**	0.44–3.18	1	**0.50**	0.07–3.56	1	**0.54**	0.08–3.81
Kidney (189)	4	**1.18**	0.44–3.15	4	**1.90**	0.71–5.07	2	**0.89**	0.22–3.55
Brain (191–192)	3	**0.60**	0.19–1.85	2	**0.78**	0.20–3.11	2	**0.73**	0.18–2.93
Non-Hodgkin's lymphoma (200,202)	11	**2.36**	1.31–4.26	4	**1.55**	0.58–4.13	2	**0.73**	0.18–2.94
Multiple myeloma (203)	1	**0.57**	0.88–4.06	3	**2.69**	0.87–8.35	2	**1.73**	0.43–6.90
Leukemia (204–207)	5	**0.84**	0.35–2.02	4	**1.35**	0.51–3.59	4	**1.33**	0.50–3.55

SOURCE: Dalsu Baris et al., "Cohort Mortality Study of Philadelphia Firefighters," 39 *Am. J. Indus. Med.* 463, 463 (2001). The article is a U.S. Government work and, as such, is in the public domain in the United States of America.

Inheritance of ABO Blood Groups: Genotype

	Gene inherited from father			
Gene inherited from mother		A	B	O
	A	AA	AB	AO
	B	BA	BB	BO
	O	OA	OB	OO

Inheritance of ABO Blood Groups: Genotype to Phenotype

If genotype includes:	Phenotype will be:
At least one A, no B	Blood Type A
At least one B, no A	Blood Type B
One A and one B	Blood Type AB
Neither an A nor a B	Blood Type O

		Gene inherited from father		
		A	B	O
Gene inherited from mother	A	Type A	Type AB	Type A
	B	Type AB	Type B	Type B
	O	Type A	Type B	Type O

Penetrance

What if some people with the same genotype had different phenotypes? To put it another way: what if a change (mutation) in a gene only sometimes resulted in a change in the phenotype (e.g. a disease)?

- **Penetrance defined: The Proportion of individuals with a particular allele or genotype who exhibit the associated phenotype of interest**

- **Calculating penetrance:**

$$\frac{\text{\# of individuals with genotype who exhibit phenotype}}{\text{divided by}}$$

Total # of individuals with genotype

Penetrance, illustrated

*	*	*	*	*	*	*	*	*	*
*	*	*	*	*	*	*	*	*	*
@	@	@	@	@	@	@	@	@	@
@	@	@	@	@	@	@	@	@	@
@	@	@	@	@	@	@	@	@	@
@	@	@	@	@	@	@	@	@	@
@	@	@	@	@	@	@	@	@	@
@	@	@	@	@	@	@	@	@	@
@	@	@	@	@	@	@	@	@	@
@	@	@	@	@	@	@	@	@	@

- Most people have the “@” genotype but some have the “*” genotype
- Frequency of the * genotype is 20/100 = 0.2 = 20%
- Everyone with the @ genotype has the beige phenotype
- Some with the * genotype have the purple phenotype
- Penetrance of the * genotype with respect to the purple phenotype is 10/20 = 0.5 = 50%

Cystic Fibrosis: an Example of Varying Penetrance

- The gene *CFTR* codes for a protein involved in transporting molecules across cell membranes
- Thousands of variations of *CFTR* are known
- Some variants produce cystic fibrosis
- Almost all individuals (~ 99%) with certain variations have cystic fibrosis (high penetrance)
- But for other variations, only a small percentage (<0.1%) of individuals have cystic fibrosis (low penetrance)

Why Does Penetrance Vary?

In addition to the polymorphic gene,

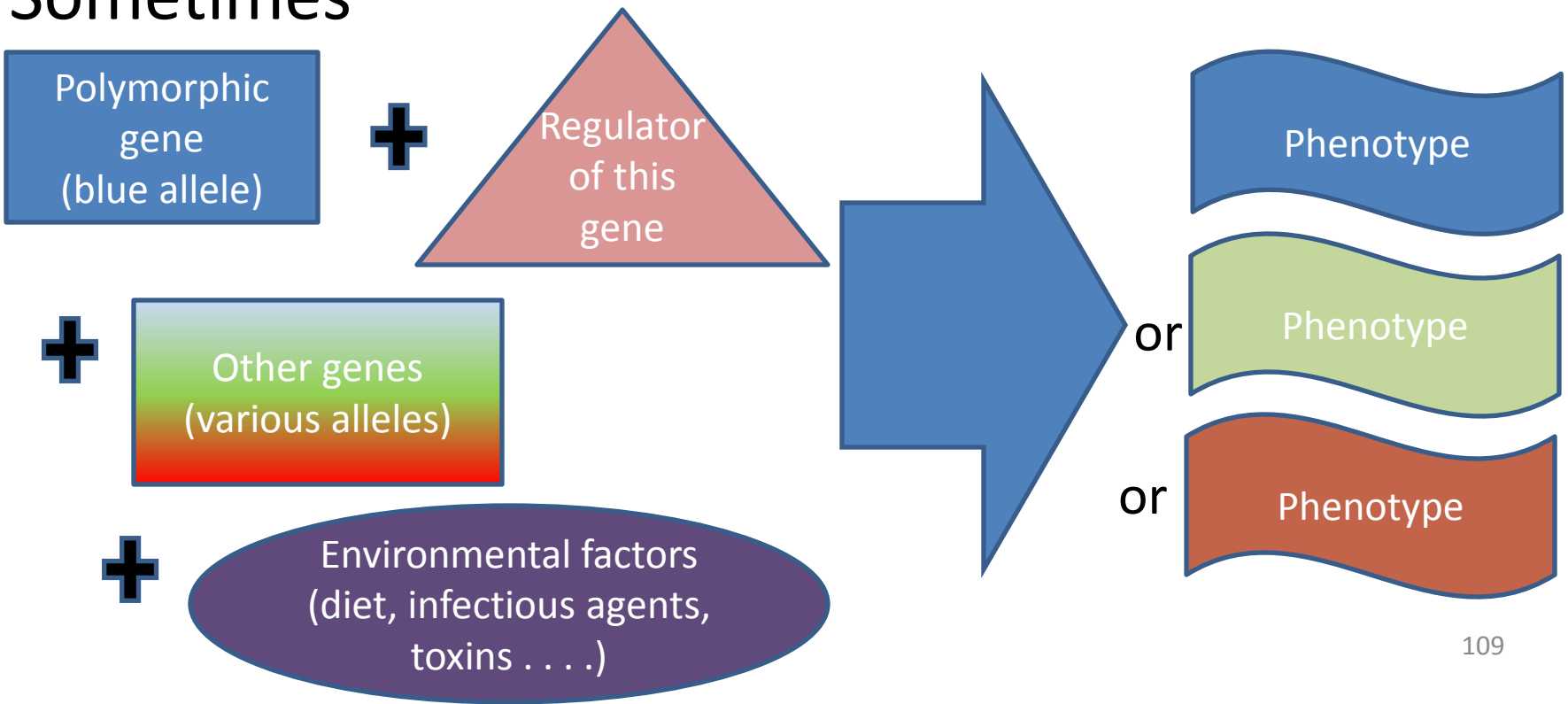
- Regulators of gene expression
- Other genes
- Environmental factors

all may be involved in determining phenotype.

Why Does Penetrance Vary?

Instead of:

Sometimes



Genotype to Phenotype: The Sickle-Cell Trait

Gene: *HBB* – codes for hemoglobin subunit beta

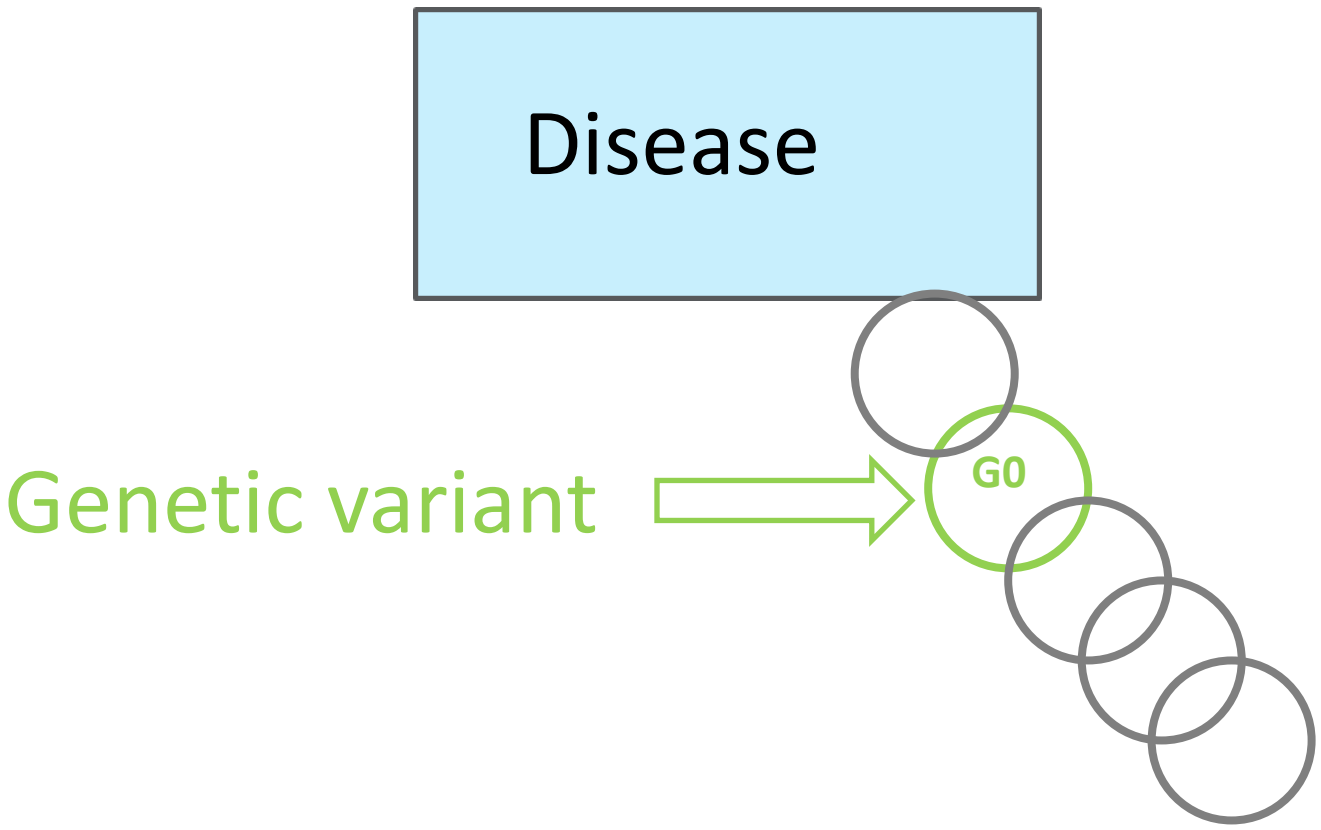
Forms: **A** – typical; **S** – one amino acid changed

Genotype	Phenotype
AA	• Produces typical hemoglobin • Does not have symptoms of anemia • If infected by malaria, is relatively susceptible to dying of it
AS	• Produces both typical and variant hemoglobin • Does not have symptoms of anemia except in some conditions (e.g. high-altitude, low-oxygen environments) • If infected by malaria, is relatively resistant to dying of it
SS	• Produces variant hemoglobin • Has symptoms of anemia • If infected by malaria, is relatively susceptible to dying of it

What role might a genetic variation play in causing disease?

To be a but-for cause of a disease, a genetic variation must be a necessary element of a sufficient set that brings about the disease.

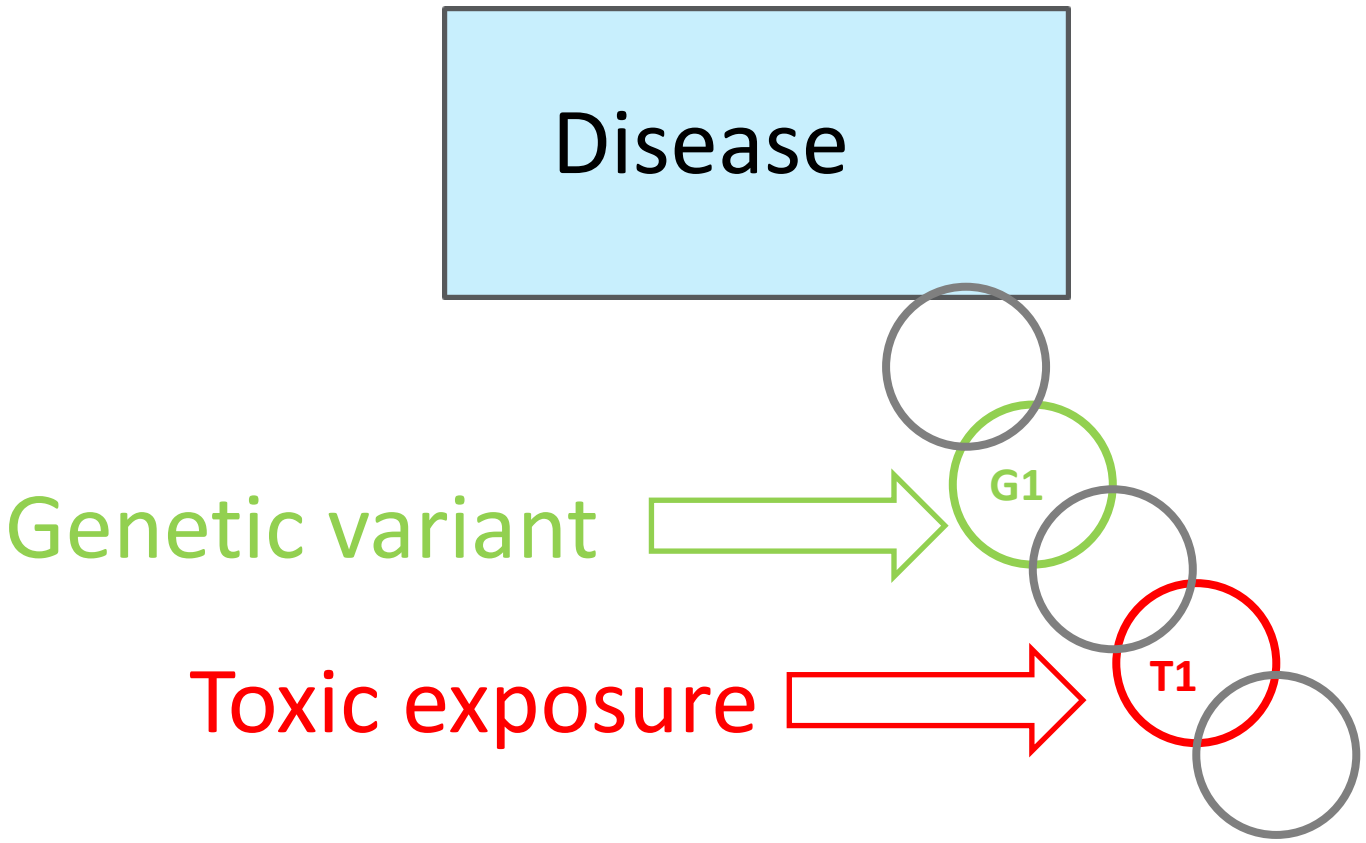
Necessary element of a sufficient set (Link in the chain)



How might the role of a genetic variation in causing disease affect a toxic tort claim?

1) Toxin & Gene are necessary elements of the same sufficient causal set

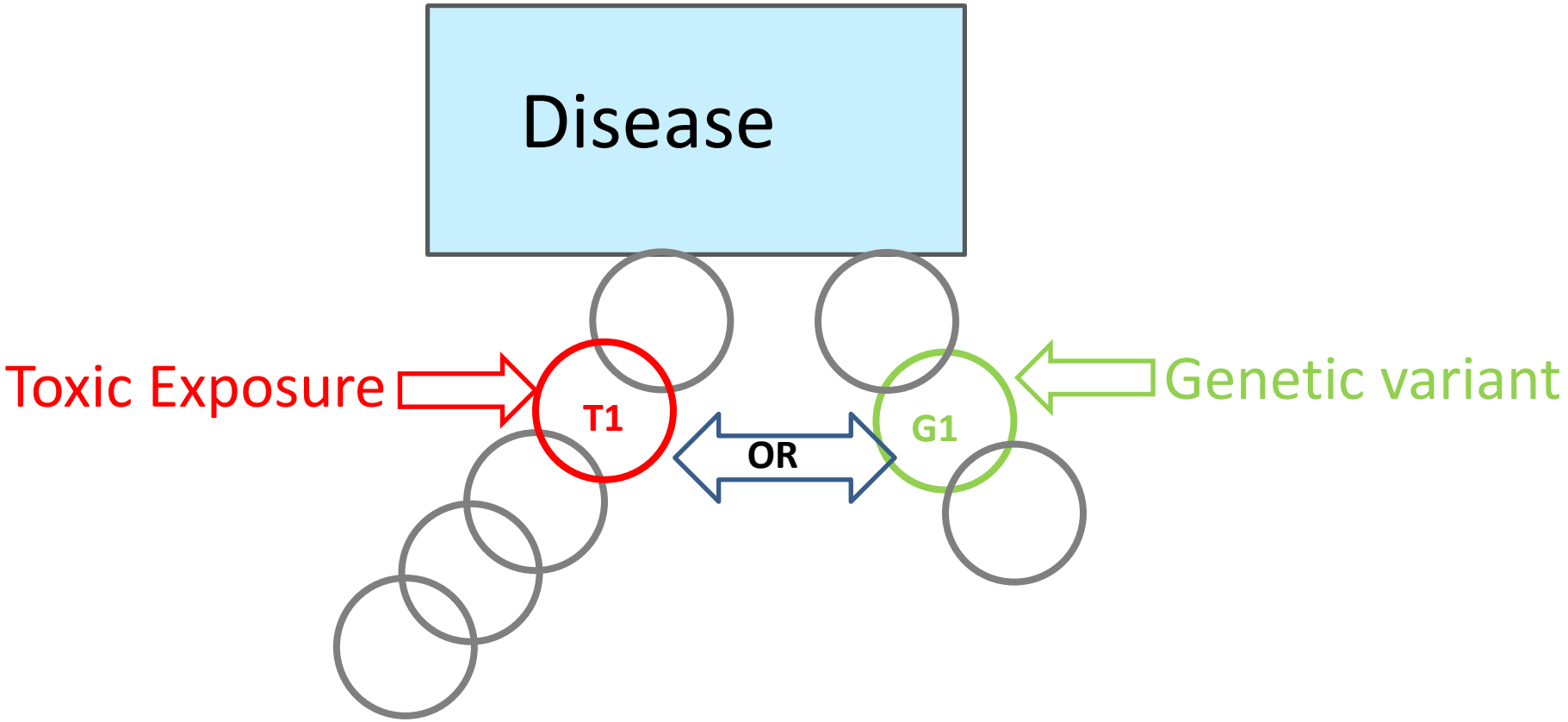
Necessary Elements of the Same Sufficient Causal Set: Concurring Causes



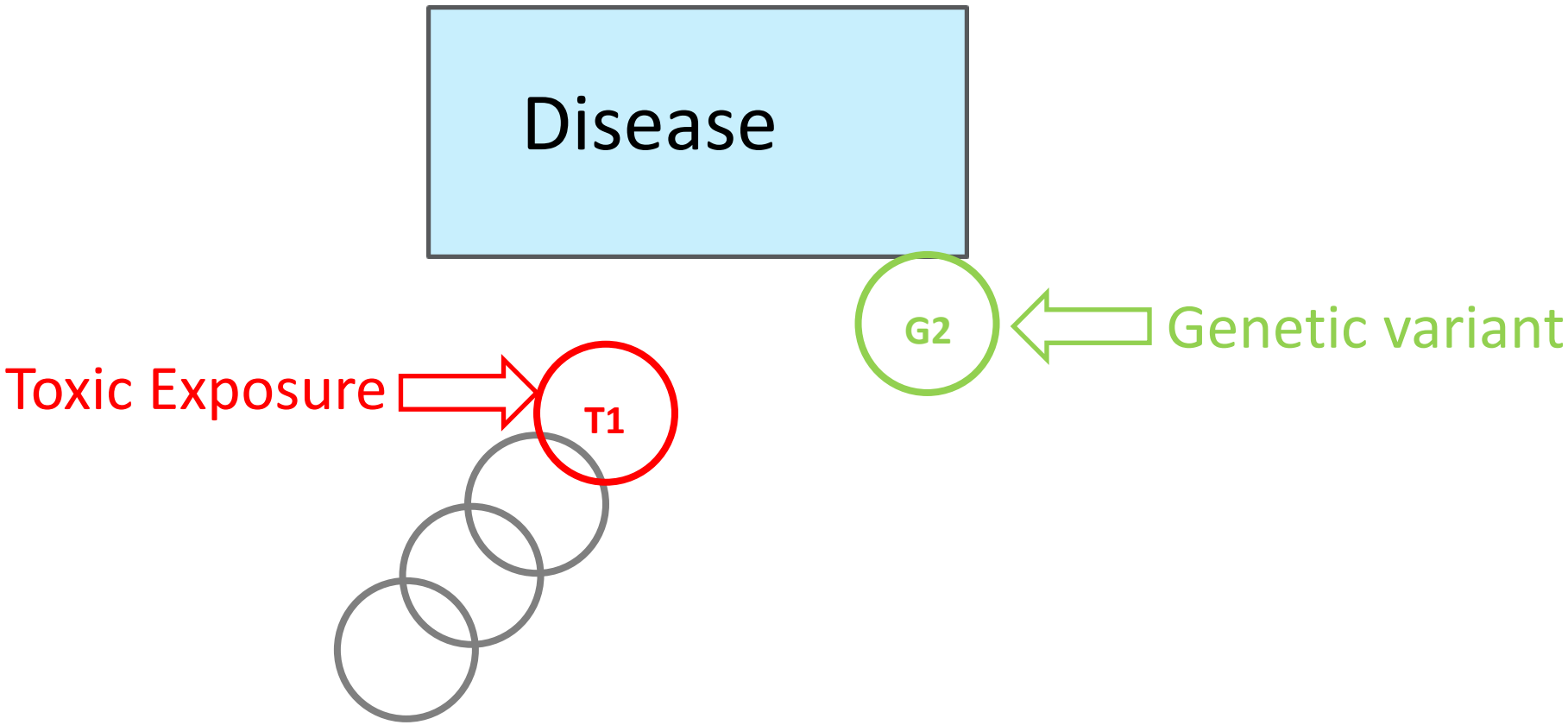
How might the role of a genetic variation in causing disease affect a toxic tort claim?

1) Toxin & Gene are necessary elements of the same sufficient causal set
2) Toxin & Gene are necessary elements of different causal sets

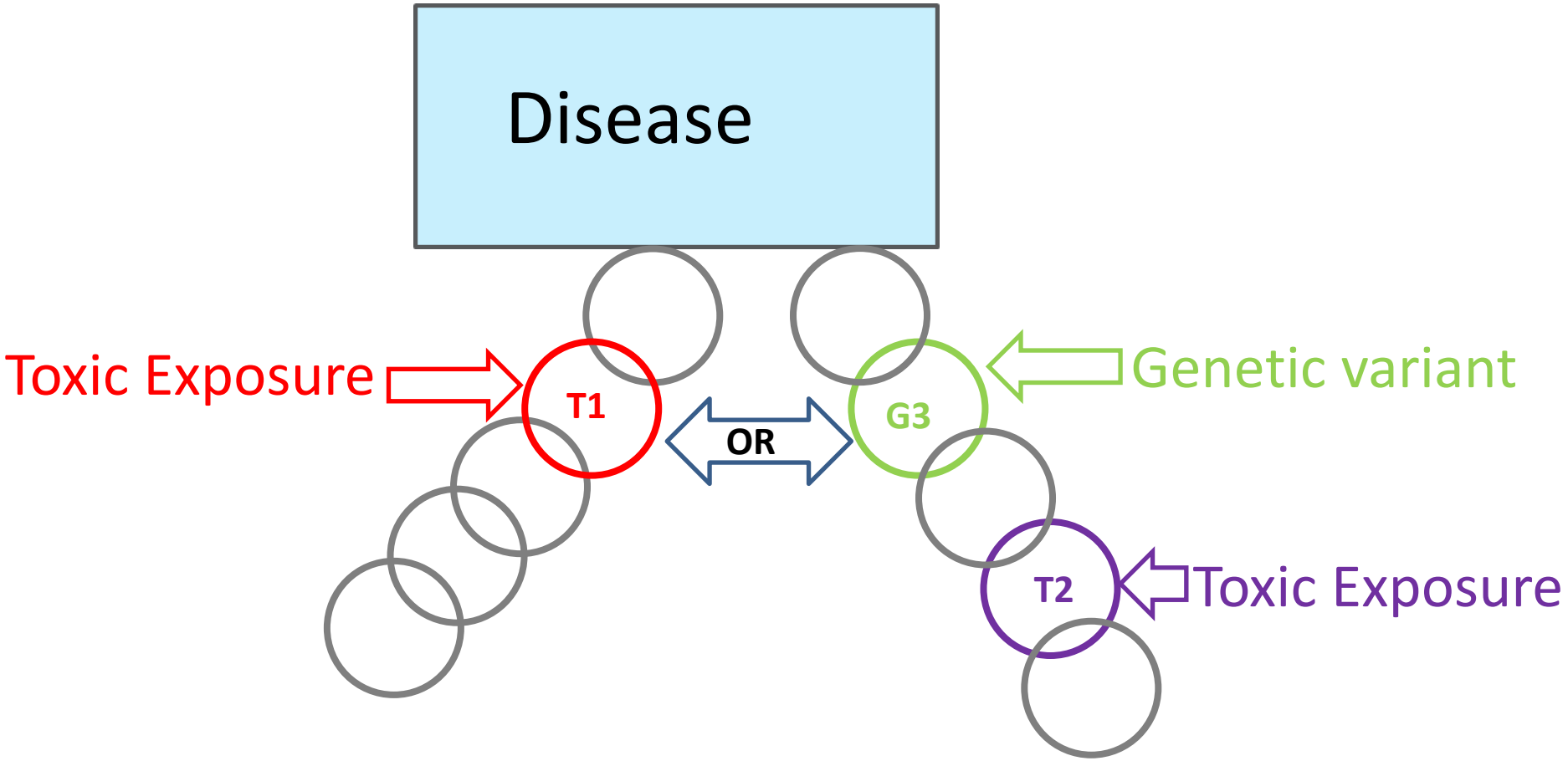
Necessary Elements of Different Sufficient Causal Sets: Competing Causes



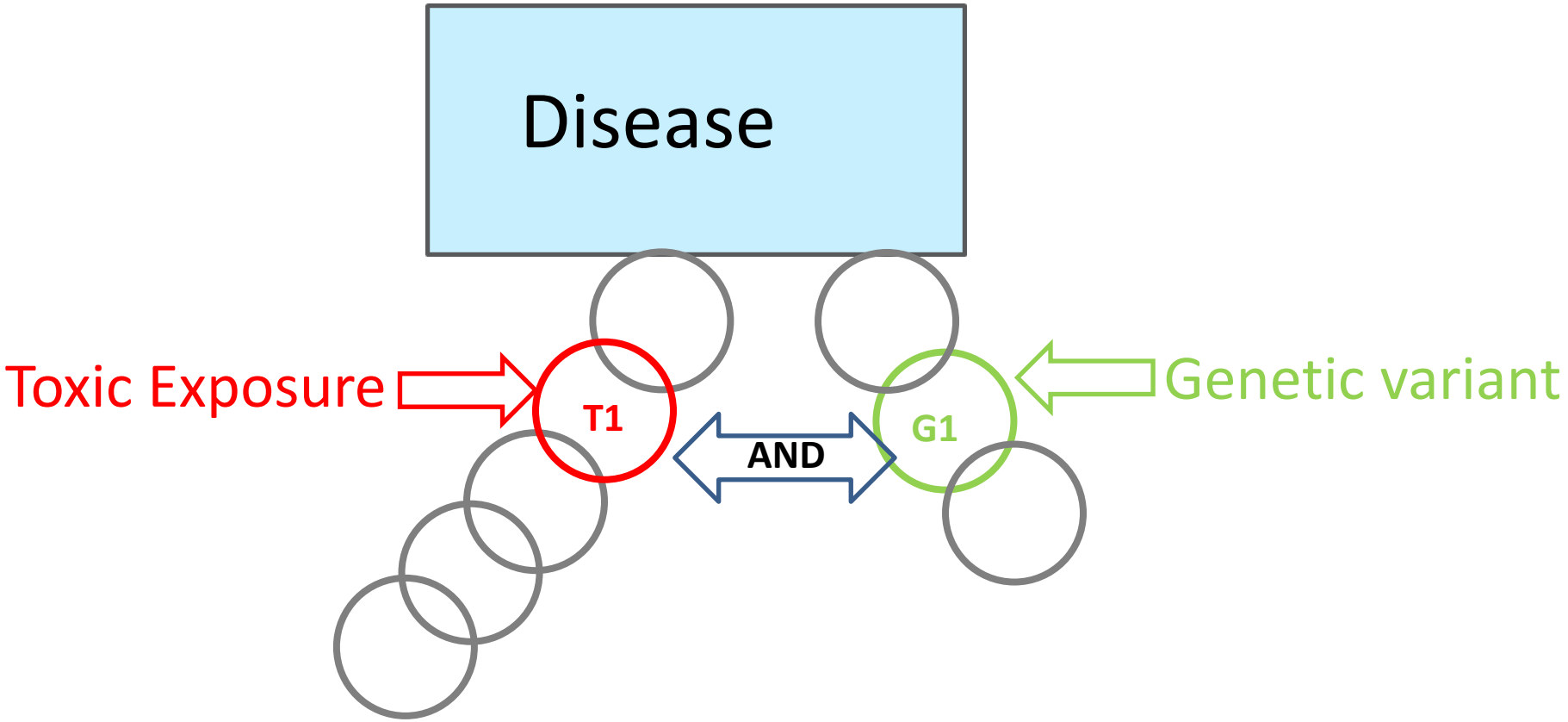
Competing Causes: The Extreme Case of a Genetic Disease



Competing Causes: A More Complex Example (More than One Toxin)



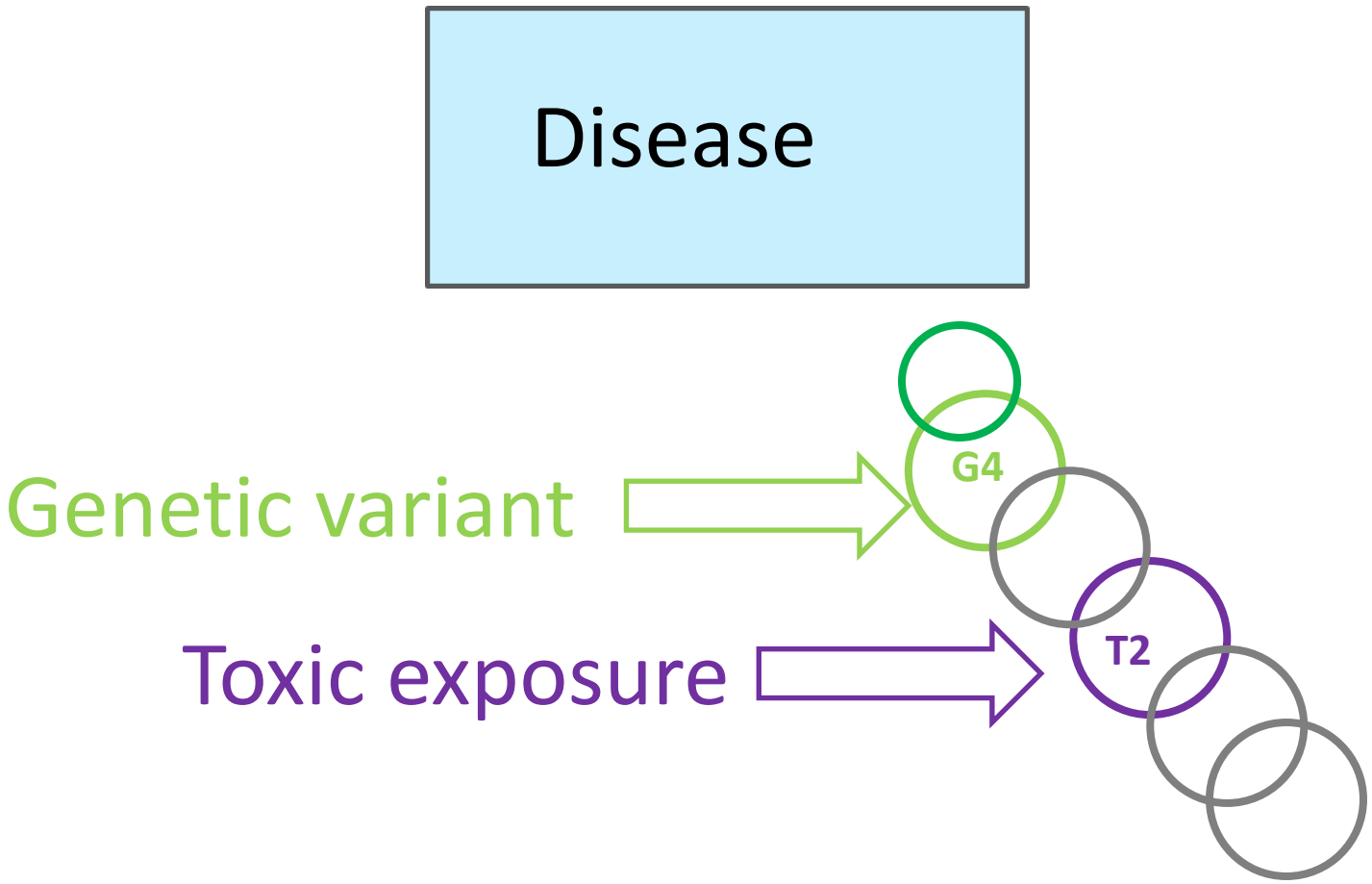
Necessary Elements of Different Sufficient Causal Sets: Multiple Sufficient Causes



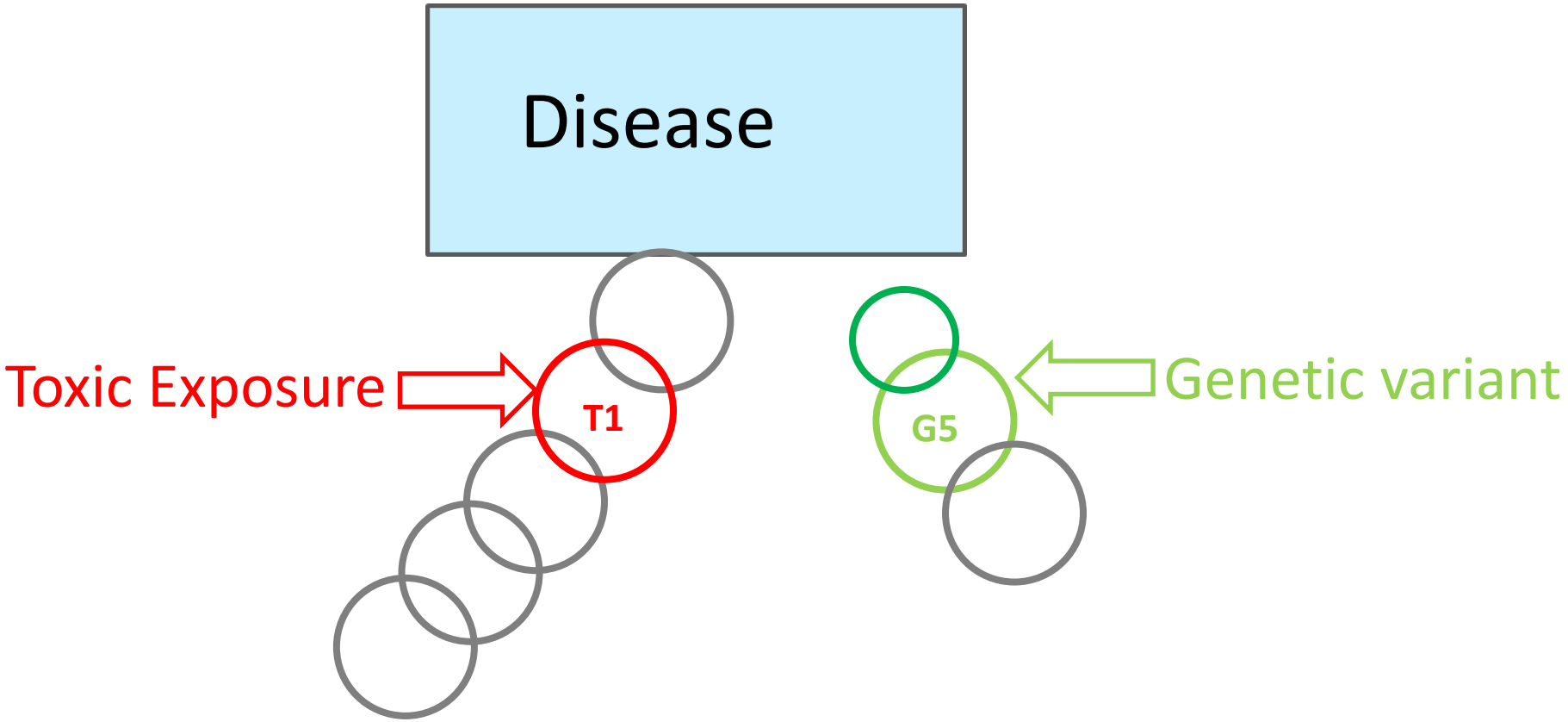
How might the role of a genetic variation in causing disease affect a toxic tort claim?

1) Toxin & Gene are necessary elements of the same sufficient causal set
2) Toxin & Gene are necessary elements of different causal sets
3) Protective effect: Causal set including toxic exposure

Protective Effect Against Causal Set that Includes a Toxic Exposure



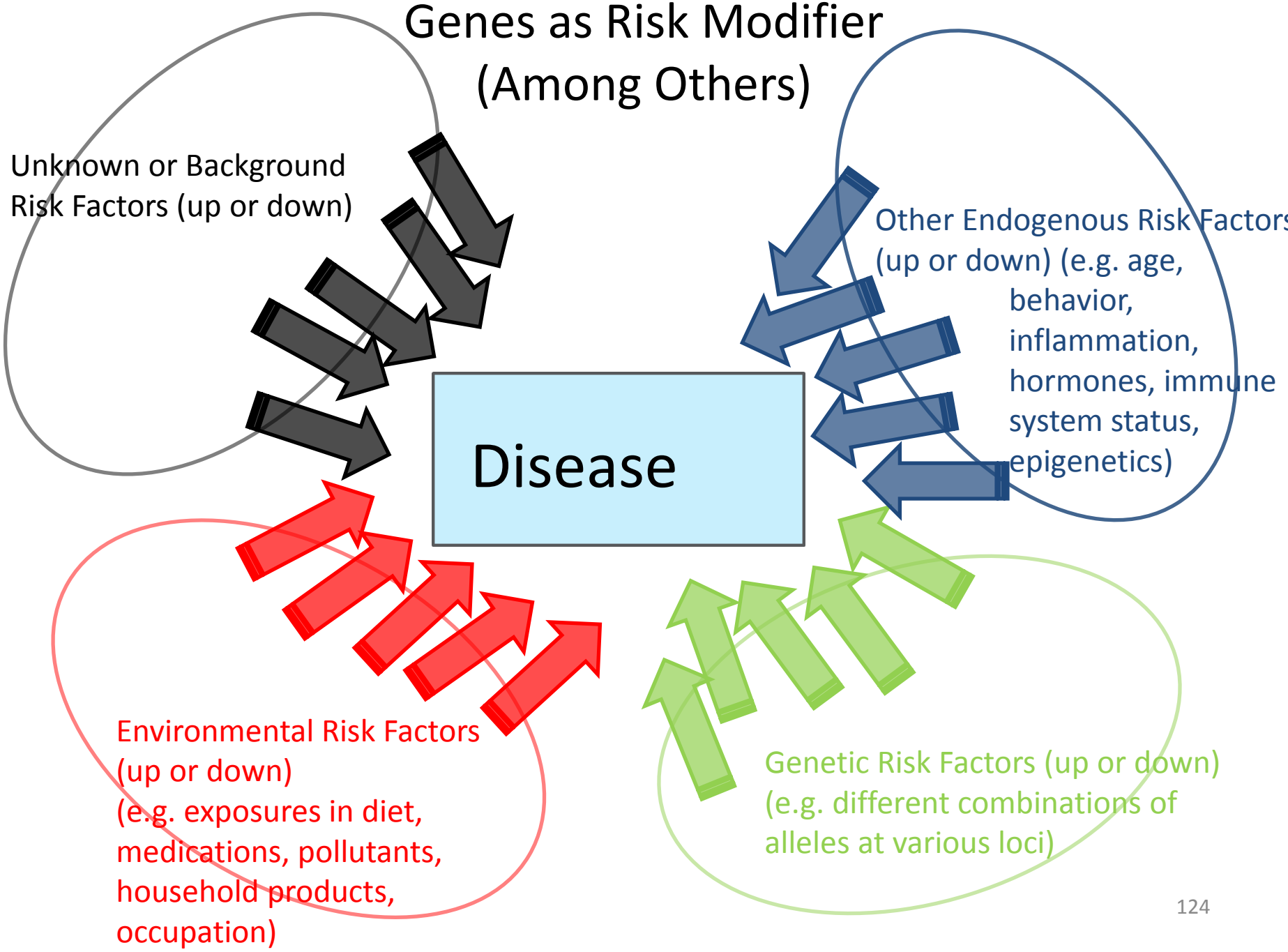
Protective Effect Against Causal Set Competing with Toxic Exposure



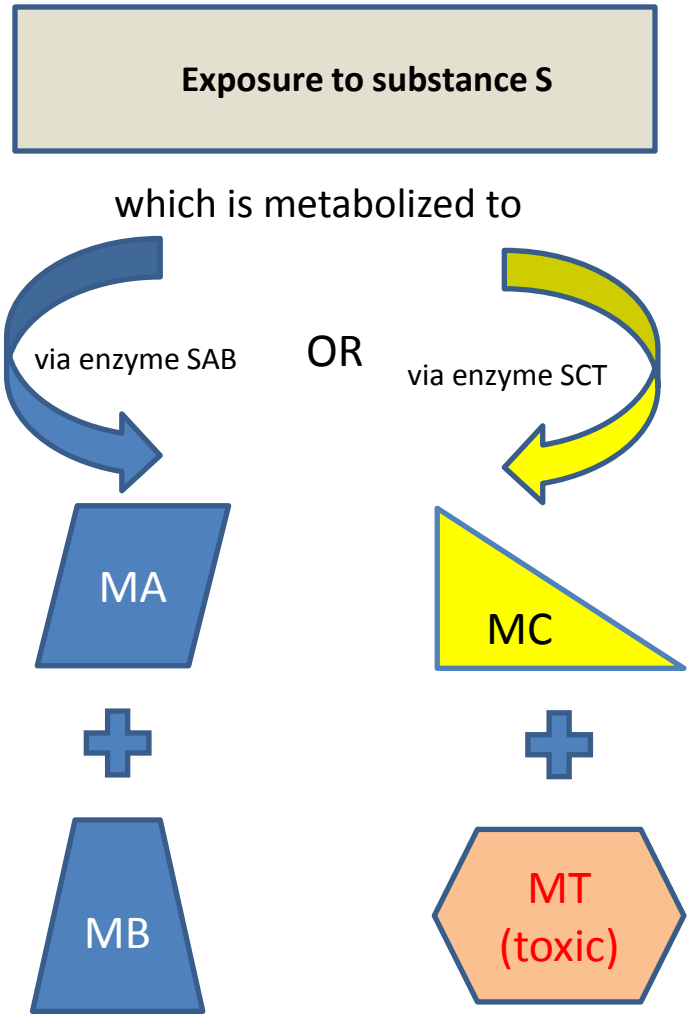
How might the role of a genetic variation in causing disease affect a toxic tort claim?

1) Toxin & Gene are necessary elements of the same sufficient causal set
2) Toxin & Gene are necessary elements of different causal sets
3) Protective effect: Causal set including toxic exposure
4) Risk modifier (causal or protective)

Genes as Risk Modifier (Among Others)



One Way Genes Can Affect Toxic Response

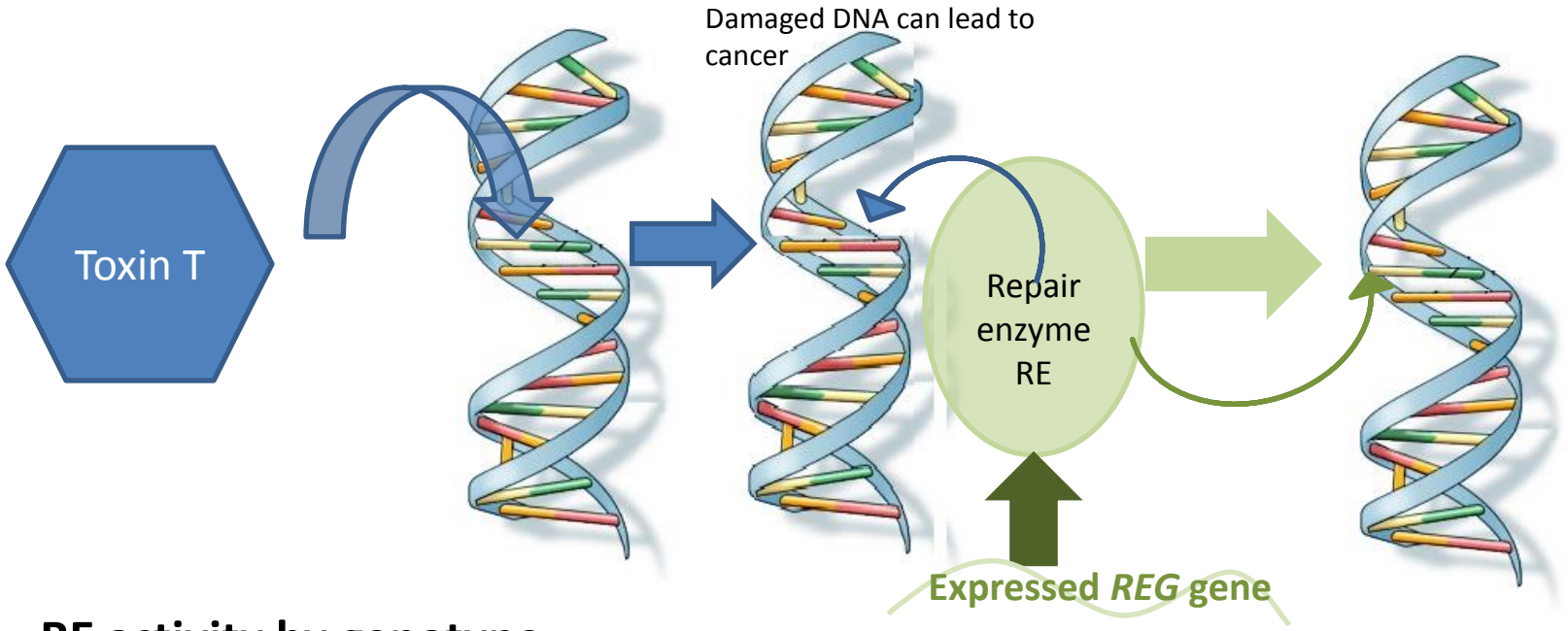


Two Alleles for the *SCT* gene produce three genotypes		
	High	Low
High	High-High	High-Low
Low	High-Low	Low-Low

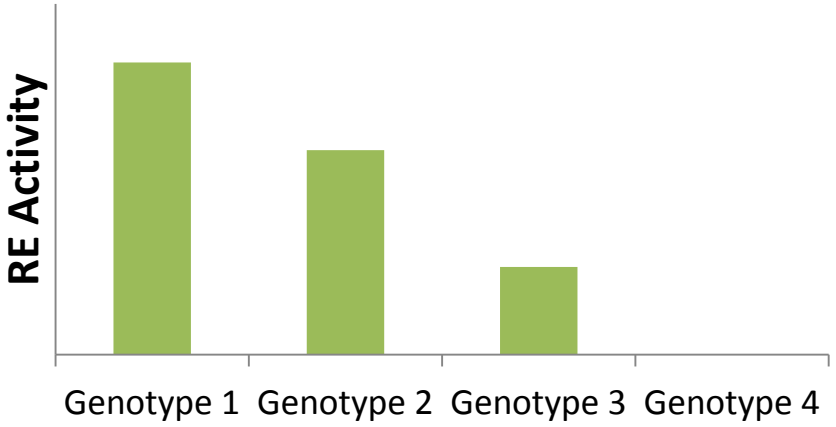
Which result in three phenotypes		
High-High	High-Low	Low-Low
High SCT activity	Medium SCT activity	Low SCT activity

And different effects of the same exposure to S		
High SCT activity	Medium SCT activity	Low SCT activity
High MT level	Medium MT level	Low MT level
High likelihood of toxic effect	Moderate likelihood of toxic effect	Low likelihood of toxic effect

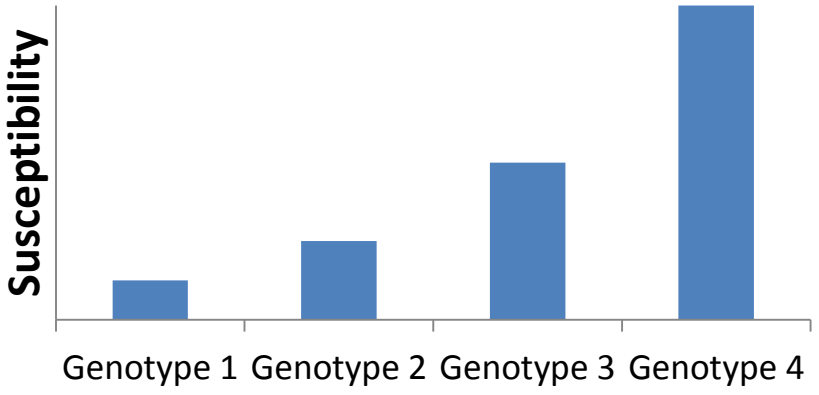
Another Way Genes Can Affect Toxic Response



RE activity by genotype



Susceptibility to T-caused Cancer



SOURCE: Image of DNA Molecule courtesy U.S. National Library of Medicine. Image in the public domain. The remaining material in the slide is courtesy of the authors.

Studies in Expert Report of T. Toxicologist

Gene	High-risk genotype	Increased Risk	Plaintiff's Genotype	Expert's conclusion
NQO1	One-base substitution makes detoxifying protein inactive	2.4x if 2 copies of variant allele	1 copy of variant allele	"no increased risk benzene hematotoxicity"
NQO1	Same	2.82x (Odds Ratio) if 2 copies of variant allele	1 copy of variant allele	"no increased risk for benzene poisoning"
GSTT1	"Null" genotype (no functional alleles)	1.91x (Odds Ratio)	Non-null	Same
NQO1, GSTT1, & GSTM1	Same variant Null genotype Null genotype	20.41x (Odds Ratio) if all 3 variations	1 copy Non-null Non-null	Same
MPO	Variant allele causes reduced expression & possibly less production of carcinogenic metabolites	1) No effect on benzene poisoning 2) Increased WBC with 1 or 2 copies 3) No effect on chromosome breakage	1 copy variant allele	"indicates reduced risk to catalyze benzene into toxic metabolites"

This slide was prepared by the authors. The sources of the data summarized in the slide are the Len van Zyl report and references cited therein, as follows:

Rothman, N. et al. "Benzene Poisoning, a Risk Factor for Hematological Malignancy, Is Associated with the NQO1 ^{609}C->T Mutation and Rapid Fractional Excretion of Chlorzoxazone." 57 *Cancer Research* 2839-2842 (1997), p. 2841 Table 3; Chen, Y. et al. "Genetic polymorphisms involved in toxicant-metabolizing enzymes and the risk of chronic benzene poisoning in Chinese occupationally exposed populations." 37 *Xenobiotica* 103-112 (2007), p. 103 (abstract); Wan, J. et al. "Association of Genetic Polymorphisms in CYP2E1, MPO, NQO1, GSTM1, and GSTT1 Genes with Benzene Poisoning." 110 *Envtl. Health Perspectives* 1213-1218 (2002), p. 1216 Table 4; Lan, Q. et al. "Hematotoxicity in Workers Exposed to Low Levels of Benzene." 306 *Science* 1774-1776, p. 1775; and Garte, S. et al. "Genetic Susceptibility to Benzene Toxicity in Humans." 71 *J. Toxicology Envtl. Health Part A* 1482-1489 (2008), p. 1485.

Effect of *NQO1* Genotype on risk for Benzene Poisoning in Shanghai, China, 1992

Attribute	**Number (%) of Cases (workers exposed to benzene with benzene poisoning)**	**Number (%) of Controls (workers not exposed to benzene without benzene poisoning)**	**Odds Ratio (95% Confidence Interval)**
Two copies of variant *NQO1* allele	20 (41%)	11 (23%)	2.4 (1.0 – 5.7)
One or no copy of variant *NQO1* allele	29 (59%)	37 (77%)	1.0

SOURCE: Courtesy of the authors based upon data from Nathaniel Rothman et al., "Benzene Poisoning, a Risk Factor for Hematological Malignancy, Is Associated with the NQO1 $^{609}C \rightarrow T$ Mutation and Rapid Fractional Excretion of Chlorzoxazone," 57 *Cancer Research* 2839, 2841 Table 2 (1997).

Effect of Genetic Polymorphisms on the Risk of Chronic Benzene Poisoning

Polymorphism	No. (%) Cases (benzene exposure + poisoning)	No. (%) controls (benzene exposure, no poisoning)	Adjusted Odds Ratio (95% confidence interval)
NQO1 **no variant allele**	22 (22.00%)	25 (27.78%)	1.00
NQO1 **1 variant allele**	40(40.00%)	49 (54.44%)	1.00 (0.48 – 2.09)
NQO1 **2 variant alleles**	38 (38.00%)	16 (17.78%)	2.94 (1.25 – 6.90)*
GSTT1 **non-null**	45 (45.00%)	53 (58.89%)	1.00
GSTT1 **null**	55 (55.00%)	37 (41.11/5)	1.91 (1.05 – 3.45)*
GSTM1 **non-null**	37 (37.00%)	43 (47.78%)	1.00
GSTM1 **null**	63 (63.00%)	47 (52.23%)	1.67 (0.92 – 3.05)

Red print with * indicates statistically significant results.

SOURCE: Y. Chen et al., "Genetic Polymorphisms Involved in Toxicant-Metabolizing Enzymes and the Risk of Chronic Benzene Poisoning in Chinese Occupationally Exposed Populations," 37 *Xenobiotica* 103, 108 Table III (2007). Reprinted by permission of Taylor & Francis Ltd, www.tandfonline.com.

NQO1, GSTT1, GSTM1 and Genetic Susceptibility to Chronic Benzene Poisoning

Genotype	No. Cases (benzene exposure + poisoning)	No. (%) controls (benzene exposure, no poisoning)	Adjusted Odds Ratio (95% confidence interval)
NQO1 **no or 1 variant allele +** ***GSTT1*** **non-null +** ***GSTM1*** **non-null**	11	21	1.00
NQO1 **2 variant alleles + GSTT1 null + GSTM1 null**	17	2	20.41 (3.79 – 111.11)*

Red print with * indicates statistically significant results.

SOURCE: Y. Chen et al., "Genetic Polymorphisms Involved inToxicant-Metabolizing Enzymes and the Risk of Chronic Benzene Poisoning in Chinese Occupationally Exposed Populations," 37 *Xenobiotica* 103, 109 Table V (2007). Reprinted by permission of Taylor & Francis Ltd, www.tandfonline.com.

Effect of Genetic Polymorphisms on the Risk of Chronic Benzene Poisoning

Polymorphism	Adjusted Odds Ratio (95% confidence interval)
NQO1 2 variant alleles (compared to 1 or none)	2.94 (1.25 – 6.90)*
GSTT1 null (compared to non-null)	1.91 (1.05 – 3.45)*
GSSTM1 null (compared to non-null)	1.67 (0.92 – 3.05) (not sig.)
NQO1 2 variant alleles + *GSTT1* null + *GSTM1* null (compared to 1 or non, non-null, and non-null)	**20.41 (3.79 – 111.11)***

Red print with * indicates statistically significant results.

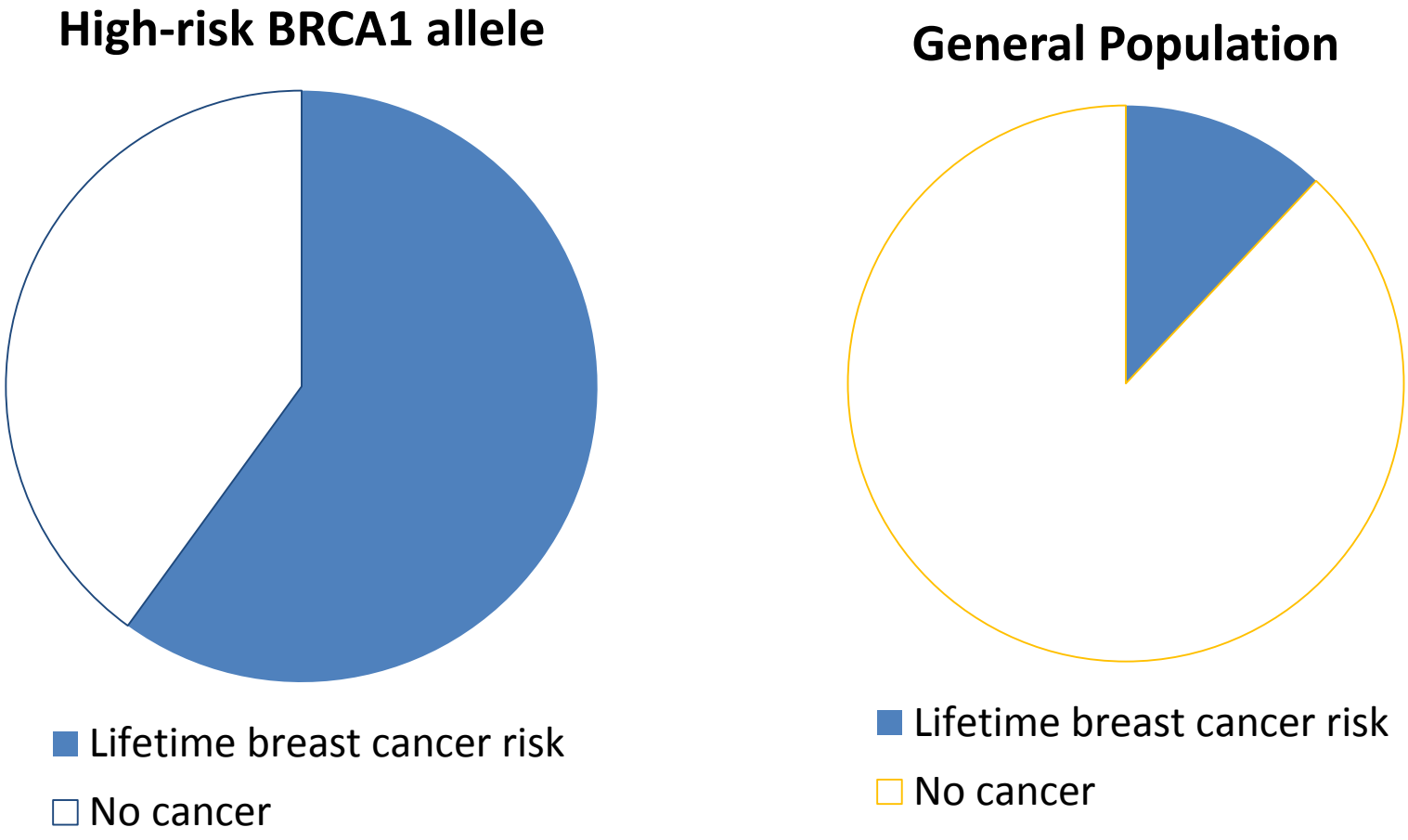
SOURCE: Y. Chen et al., "Genetic Polymorphisms Involved inToxicant-Metabolizing Enzymes and the Risk of Chronic Benzene Poisoning in Chinese Occupationally Exposed Populations," 37 *Xenobiotica* 103, 109 Table V (2007). Reprinted by permission of Taylor & Francis Ltd, www.tandfonline.com.

Summary of Three Studies on *MPO* and Benzene Toxicity

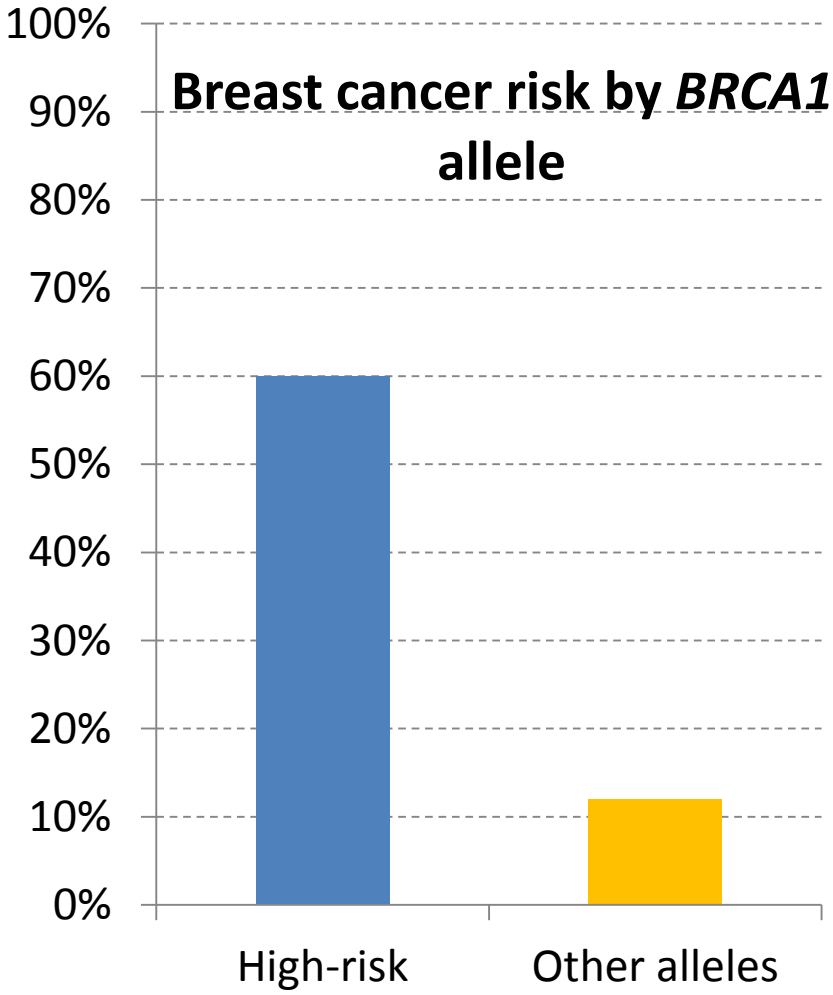
Study	Variant Studied	Endpoint Studied	Result
Wan 2002	Substitution of 1 base at a particular point in *MPO* (which reduces *MPO* activity & therefore may reduce benzene toxicity)	Benzene Poisoning	No association found: adjusted odds ratio 1.09 (95% CI 0.60 – 1.97)
Lan 2004	Same as Wan 2002	White Blood Cell (WBC) Count (reduced by benzene exposure)	Subjects with 1 or 2 variant alleles had reduced gene expression & smaller decrease in WBC count after exposure (P=0.04)
Garte 2008	Same as Wan 2002	Single-strand DNA breaks	No effect observed

SOURCE: Courtesy of the authors based upon information from Junxiang Wan et al., "Association of Genetic Polymorphisms in CYP2E1, MPO, NQO1, GSTM1, and GSTT1 Genes with Benzene Poisoning," 110 *Envtl. Health Persp.* 1213 (2002); Q. Lan et al., "Hematotoxicity in Workers Exposed to Low Levels of Benzene," 306 *Sci.* 1774 (2004); and S. Garte et al., "Genetic Susceptibility to Benzene Toxicity in Humans," 71 J. *Toxicology Envtl. Health A.* 1482 (2008).

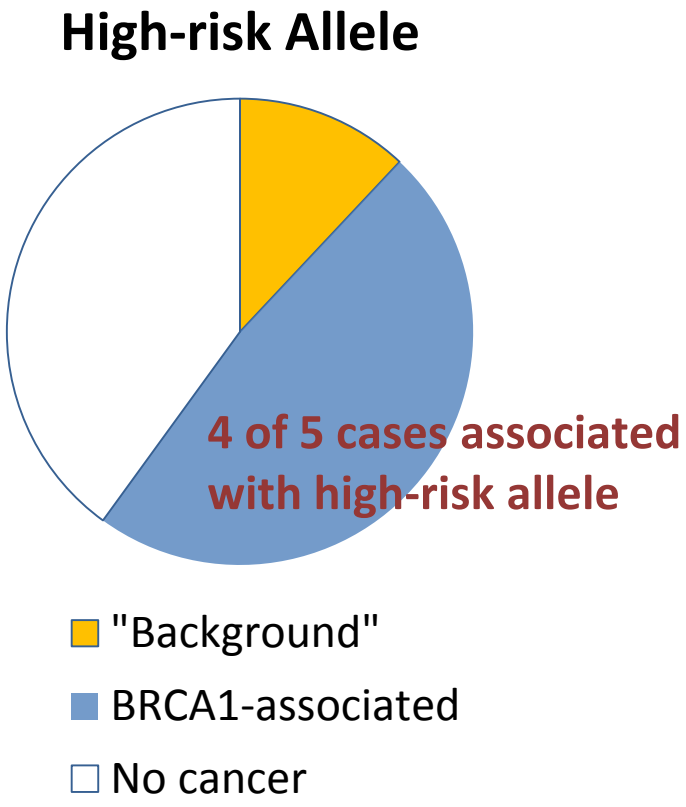
Lifetime Breast Cancer Risk: *BRCA1* High-risk Allele vs. General Population



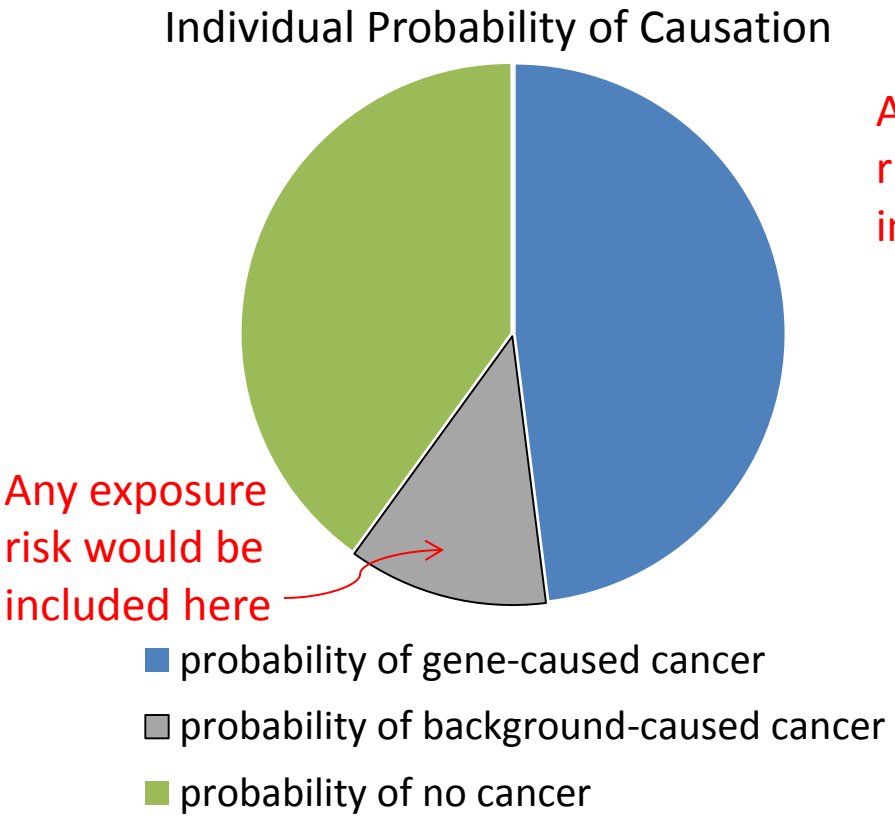
BRCA1 High-risk Allele vs Other Alleles: Relative Risk

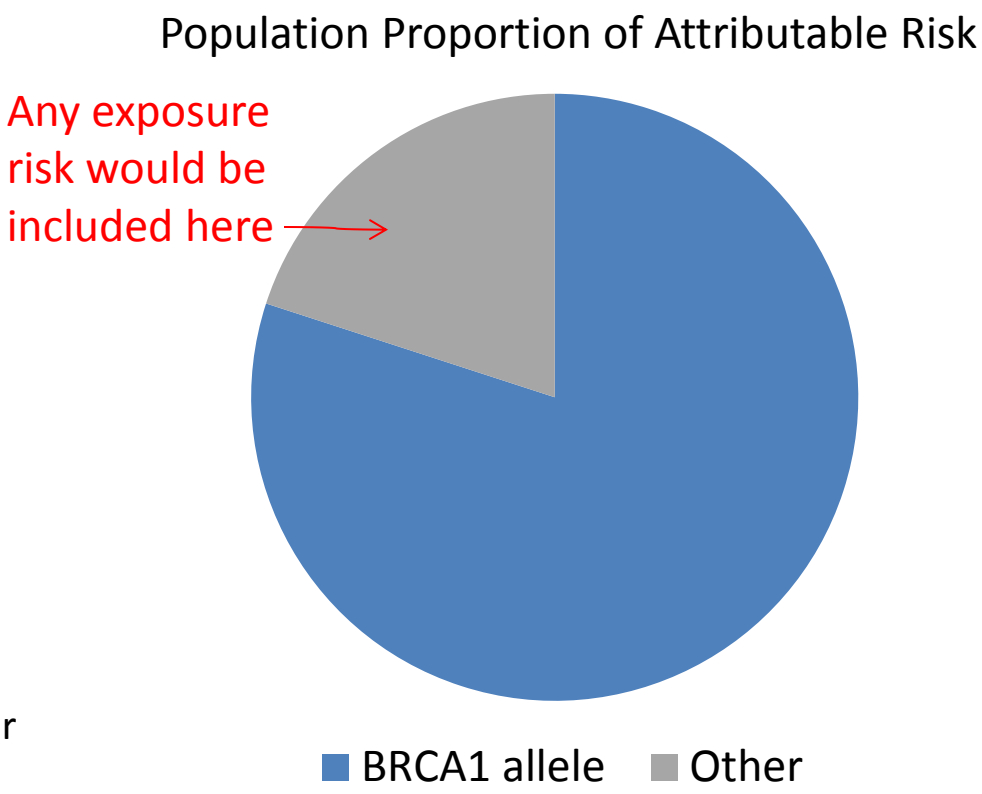


RELATIVE RISK = 60% / 12% = 5.0

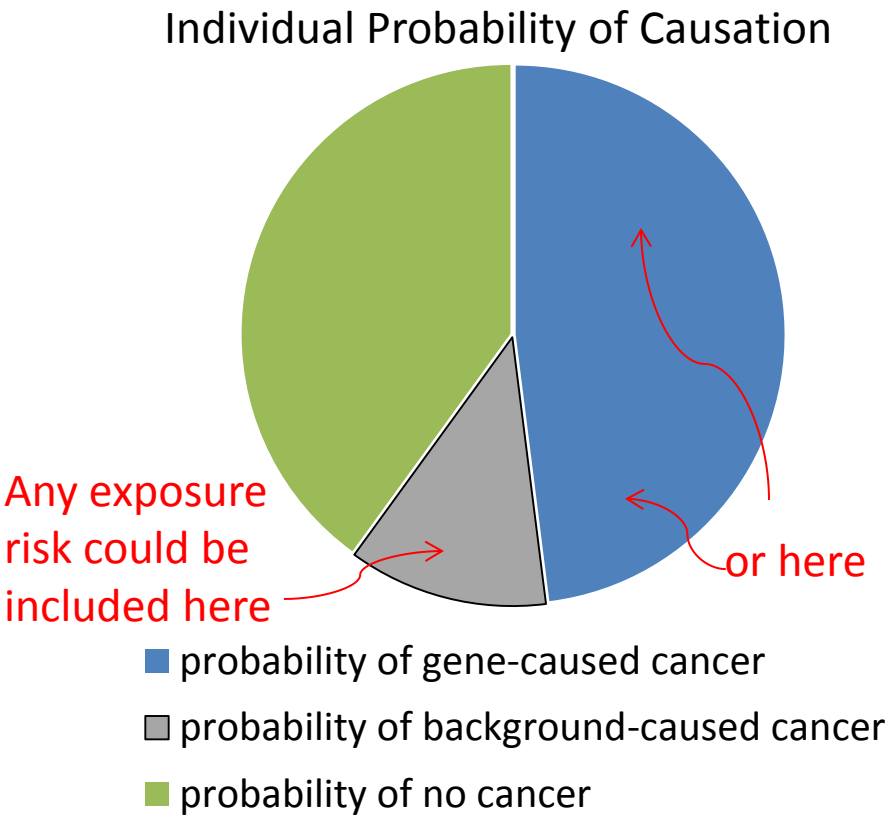


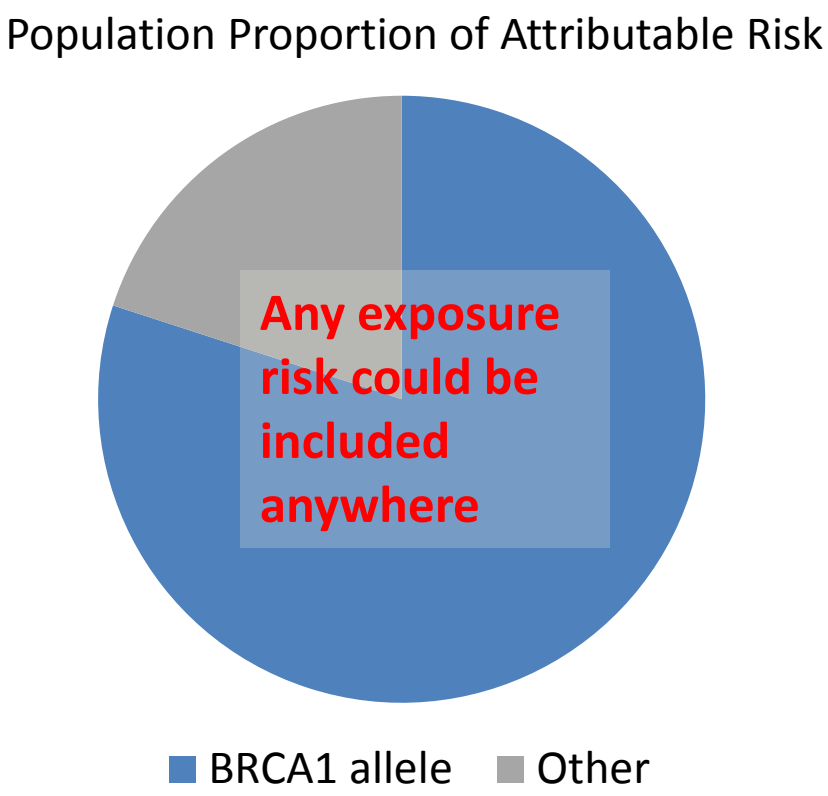
High-risk *BRCA1* allele & toxic exposure: assumption of independent, additive risk increments





High-risk *BRCA1* allele & toxic exposure: assumption of interacting risk factors

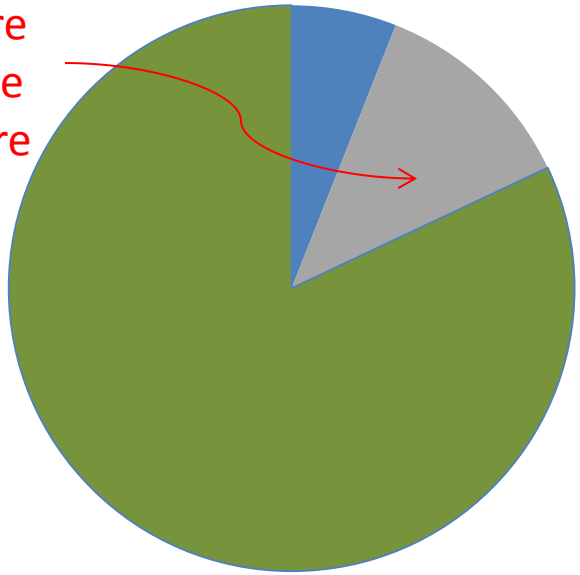




Variant *FGFR2* allele & toxic exposure: assumption of independent, additive risk increments

Individual Probability of Causation
(RR=1.5 for 2 copies of variant allele)

Any exposure risk would be included here



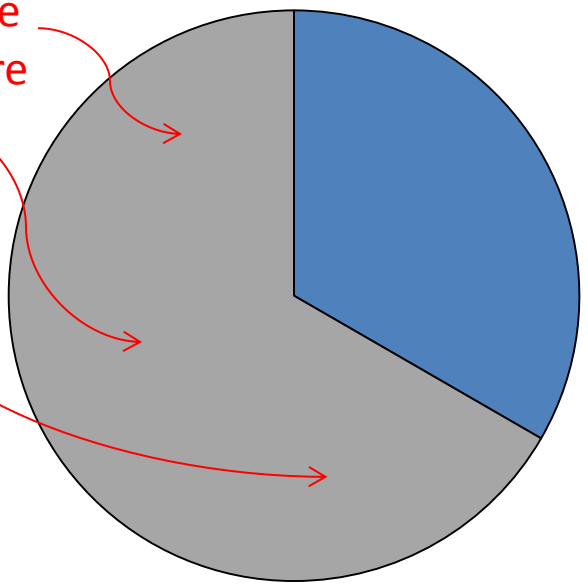
probability of gene-caused cancer

probability of background-caused cancer

probability of no cancer

Population Proportion of Attributable Risk

Any exposure risk would be included here



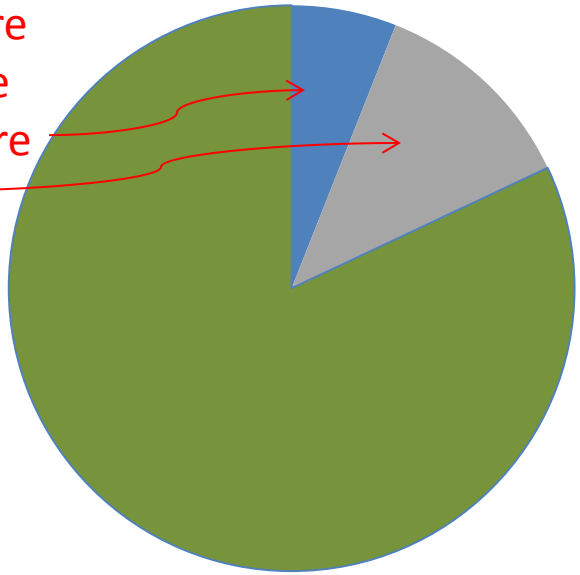
FGFR2 genotype

Background

Variant *FGFR2* allele & toxic exposure: assumption of interacting risk factors

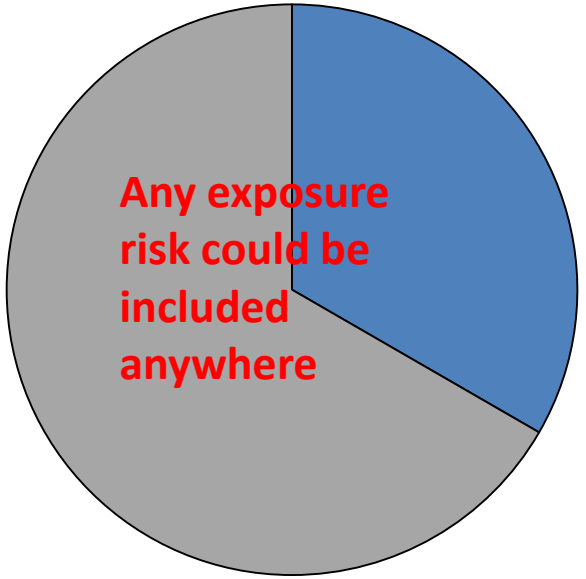
Individual Probability of Causation
(RR=1.5 for 2 copies of variant allele)

Any exposure risk could be included here or here



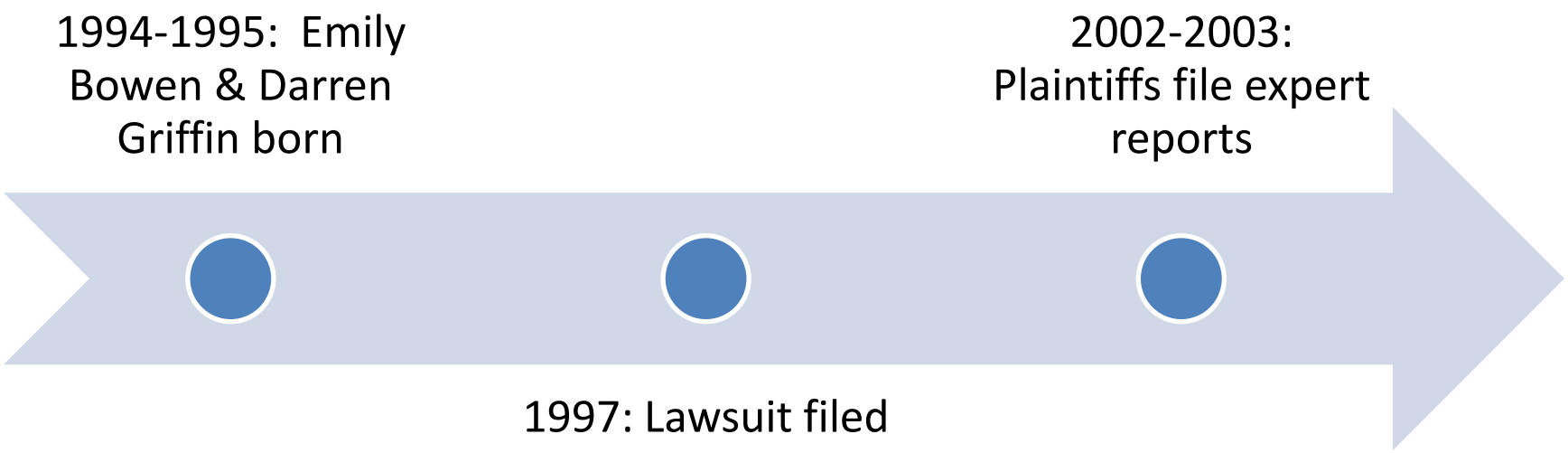
probability of gene-caused cancer
probability of background-caused cancer
probability of no cancer

Population Proportion of Attributable Risk

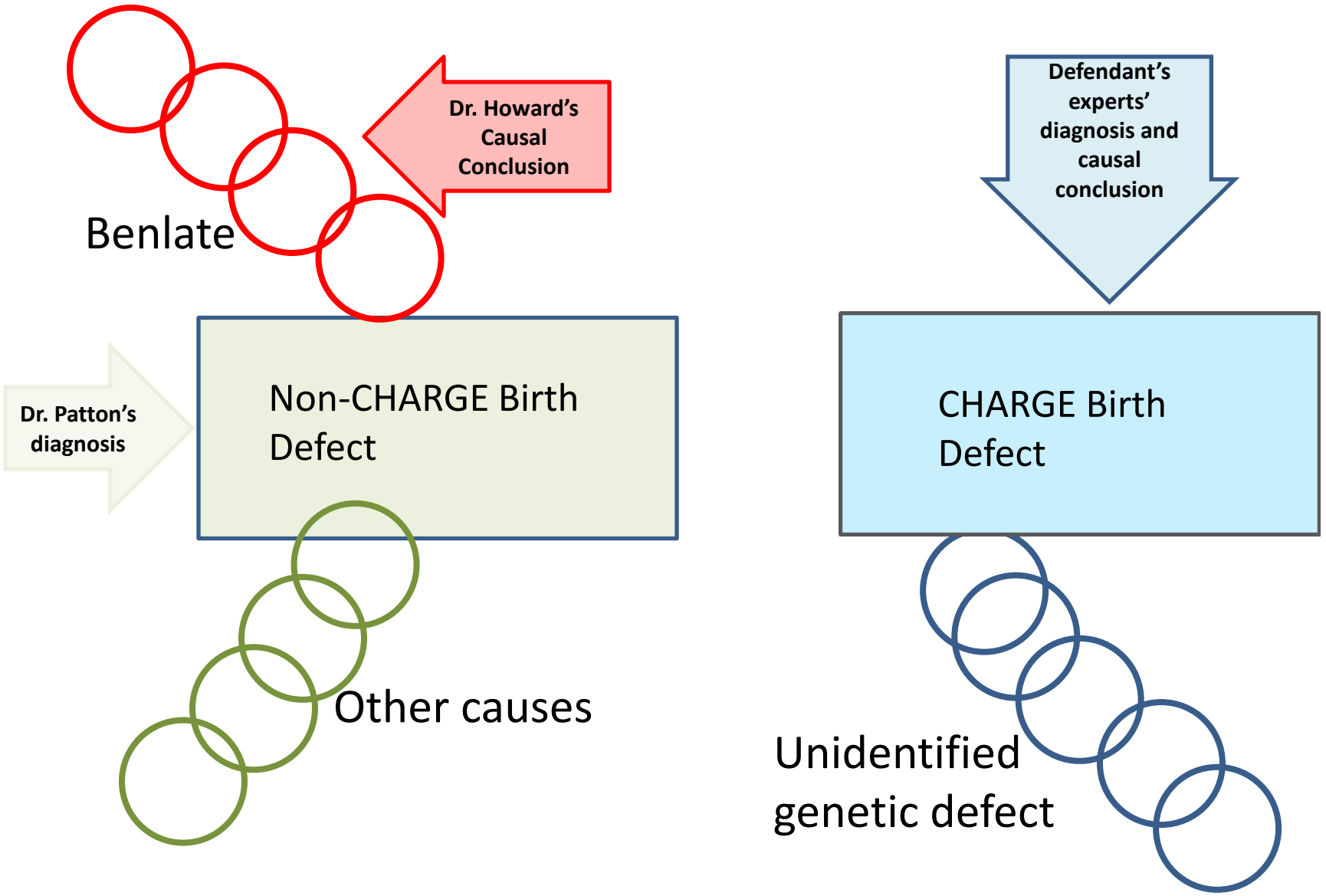


FGFR2 genotype
Background

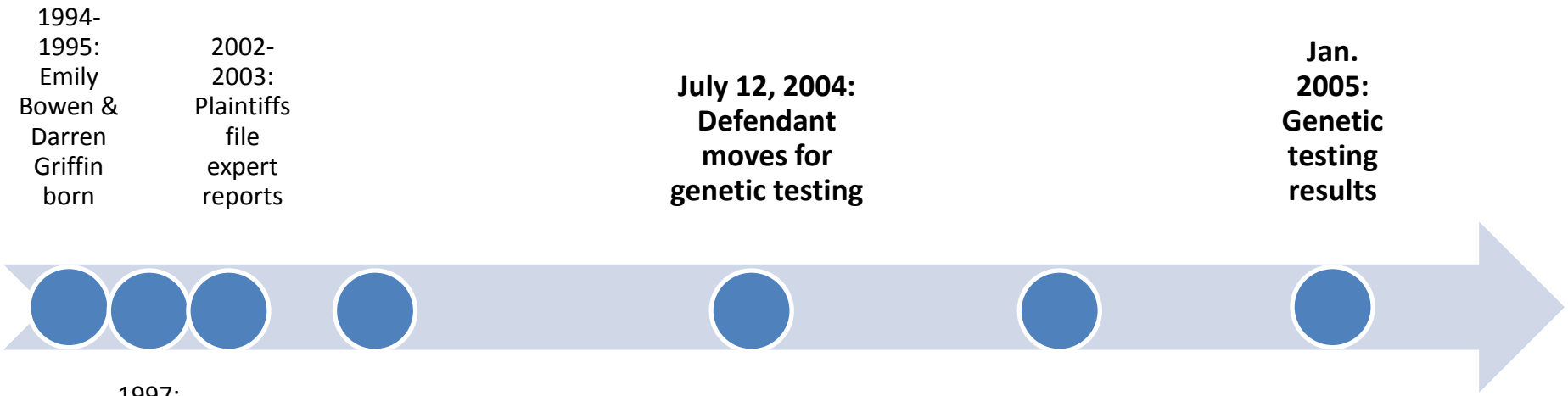
Bowen time line



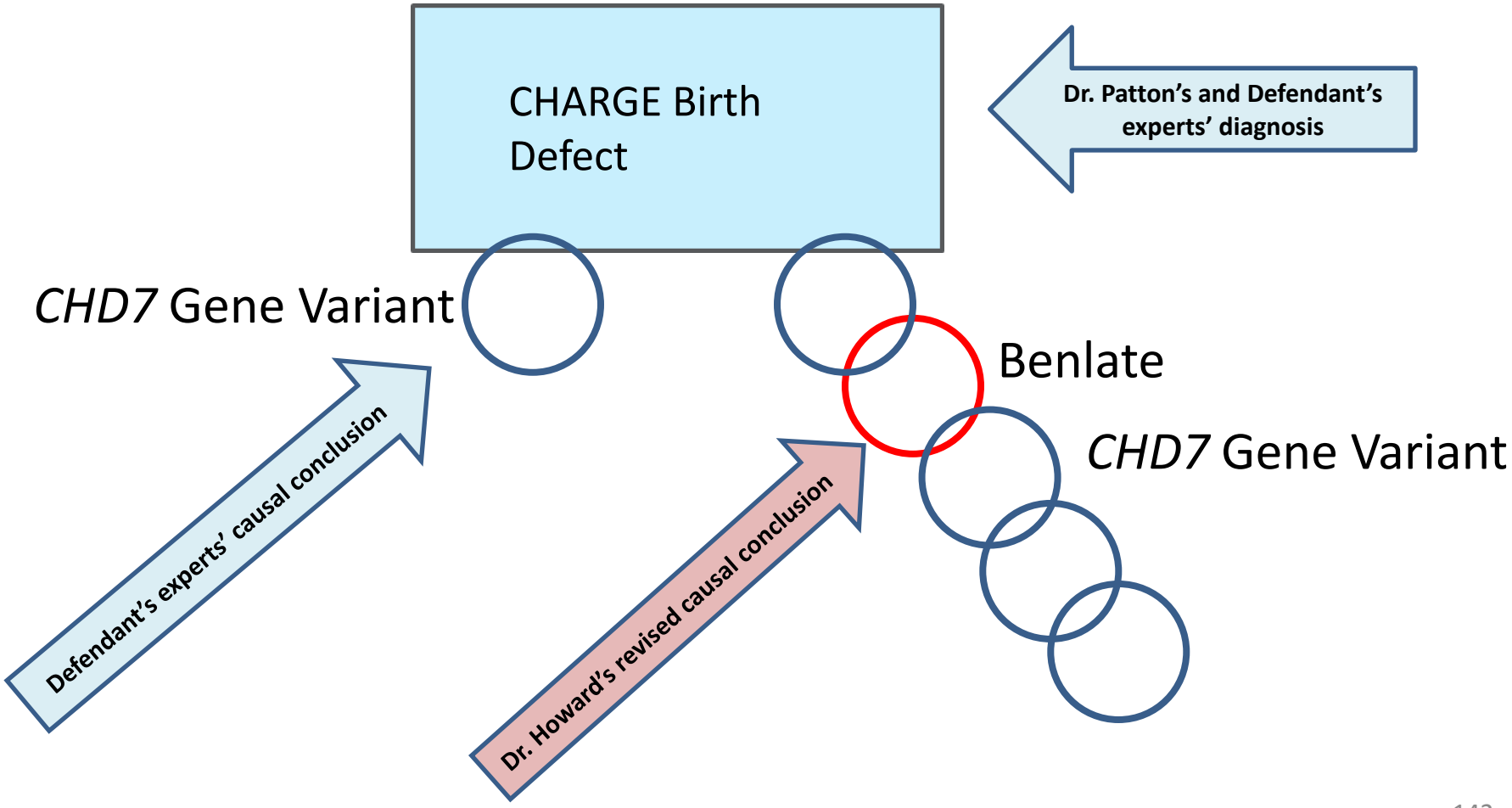
Bowen to 2003



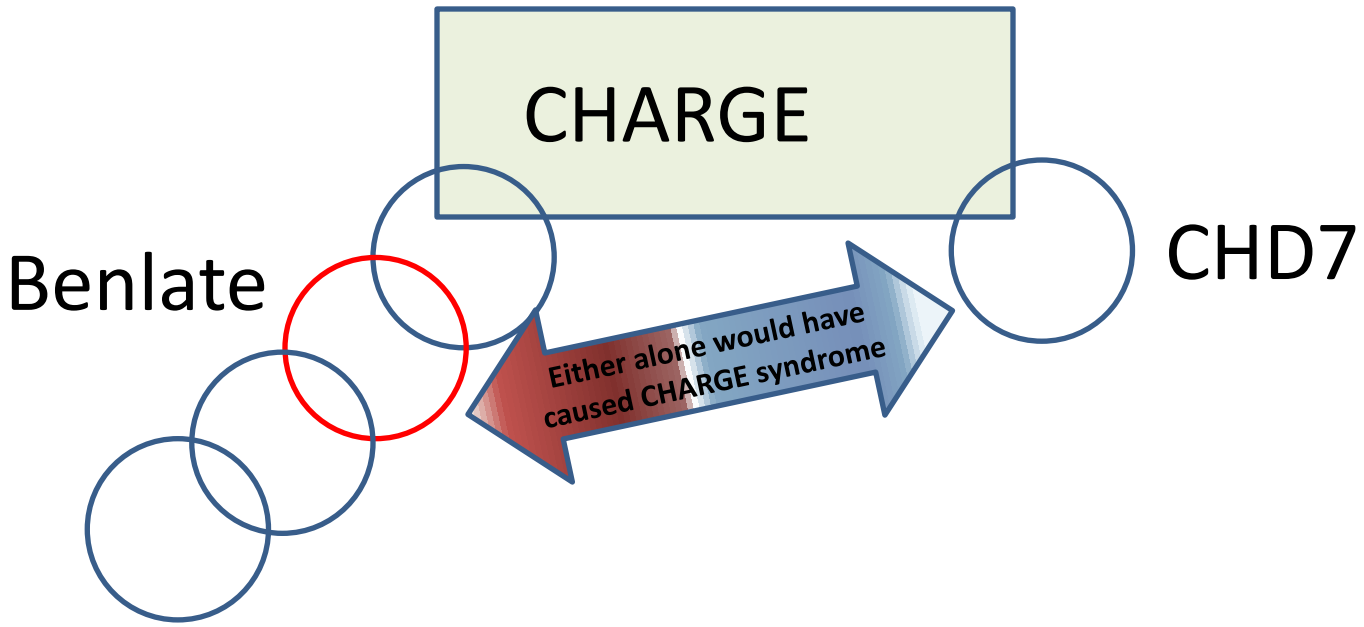
Bowen time line



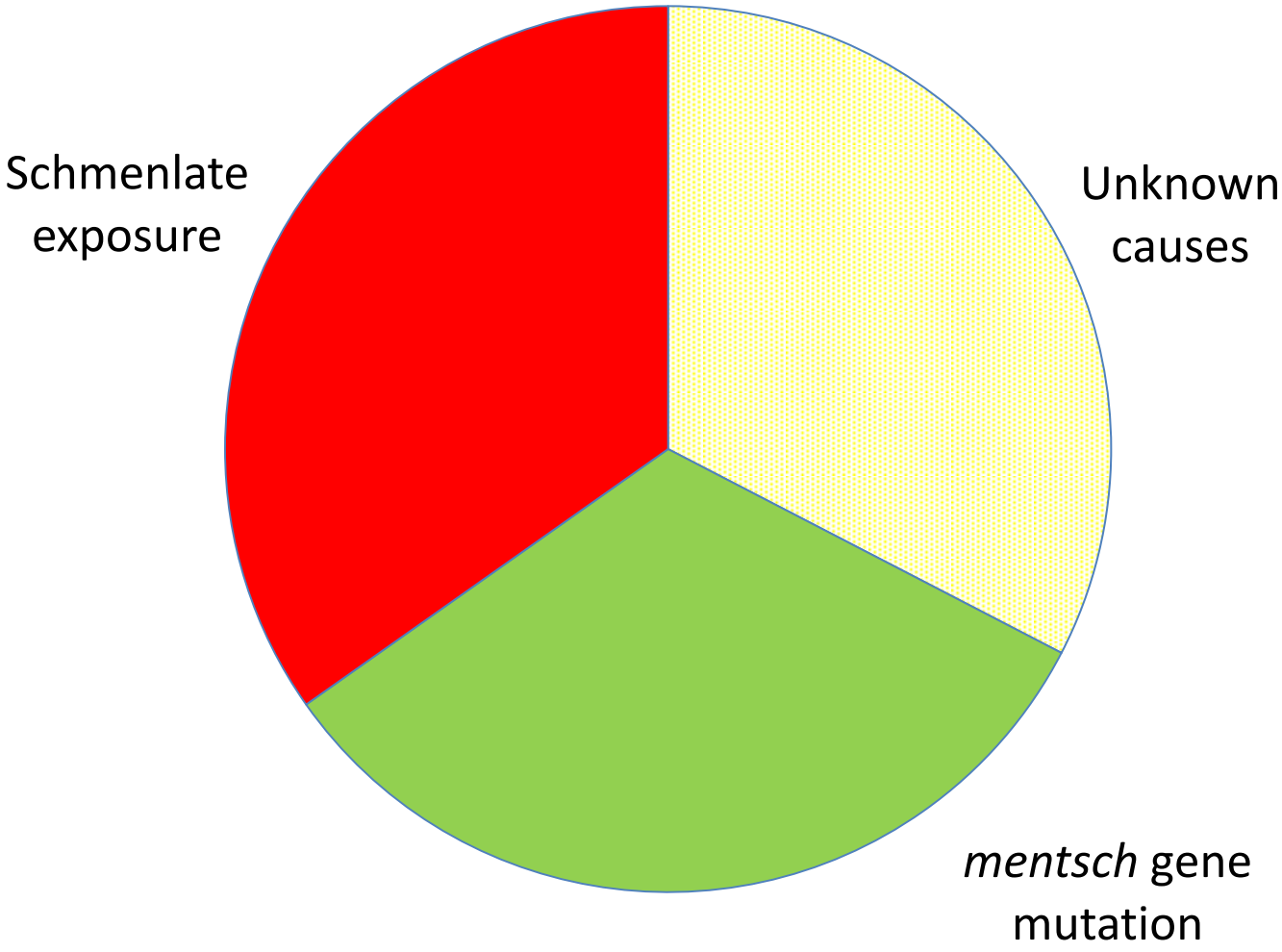
Bowen After Genetic Testing Reveals Emily Bowen's *CHD7* Mutation



Another View of Dr. Howard's Amended Opinion: Multiple Sufficient Causes



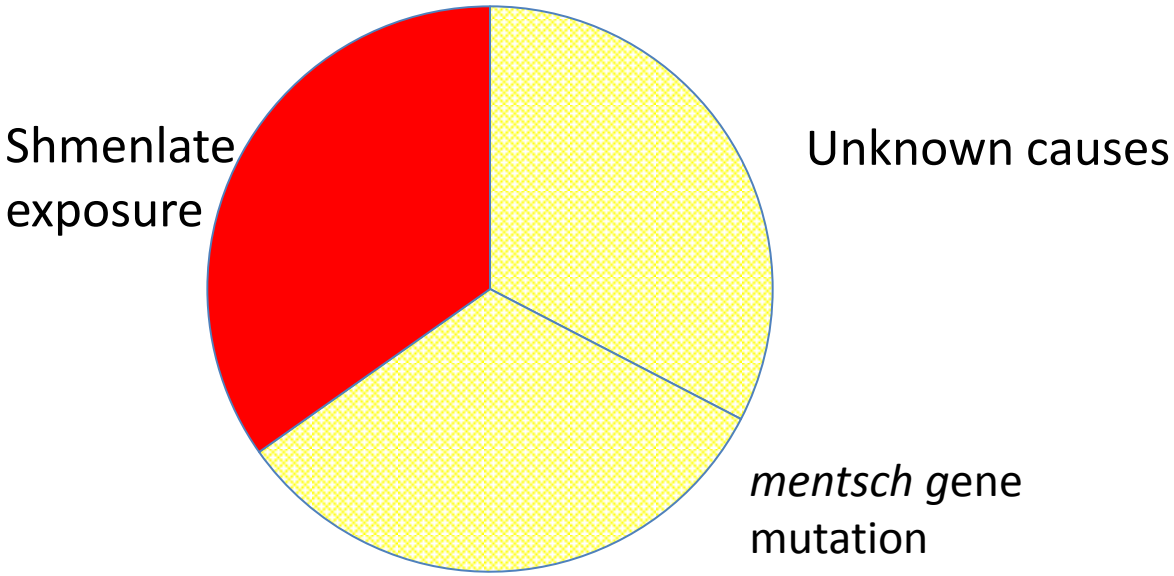
Exercise: Sources of a Birth Defect



Refining the probability of causation for subgroups

Plaintiff exposed to Shmenlate,

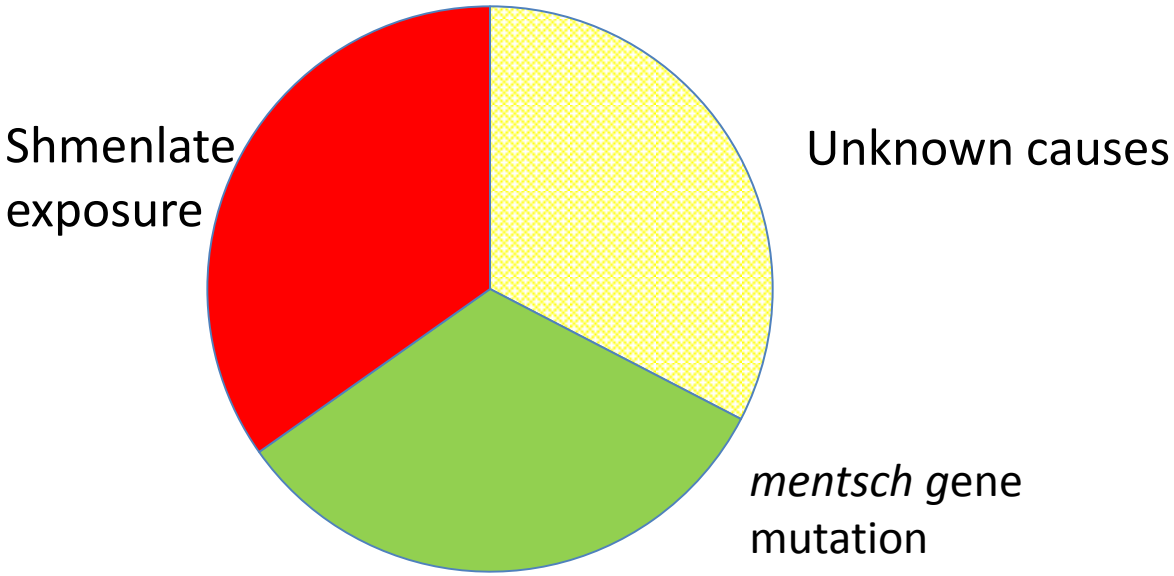
mentsch Genotype Unknown



APR = .33, so apparent probability of specific causation is 33%

Refining the probability of causation for subgroups

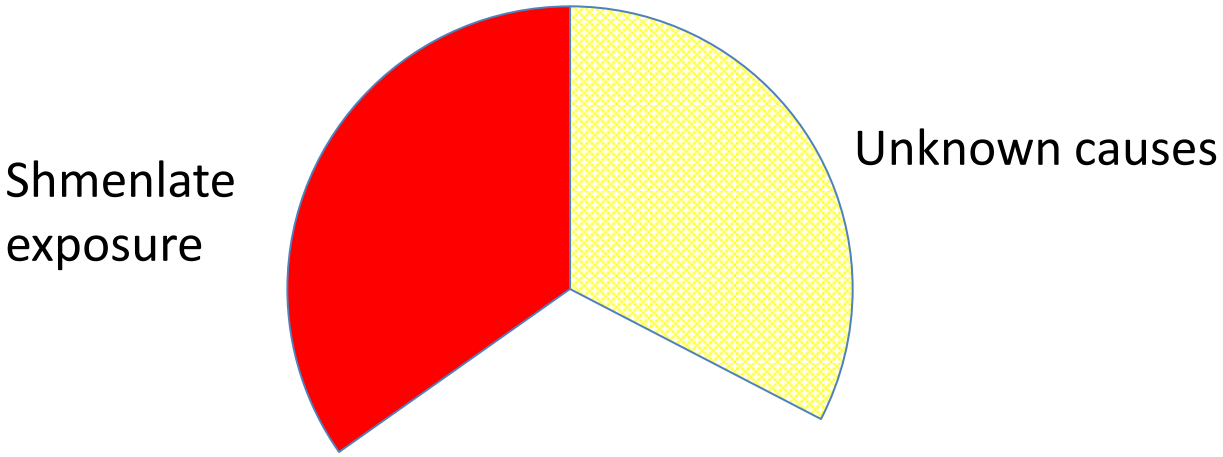
Plaintiff exposed to Shmenlate has *mentsch* Gene Mutation



APR = .33, so apparent probability of specific causation is 33%

Refining the probability of causation for subgroups

Plaintiff exposed to Shmenlate does not have *mentsch* gene mutation

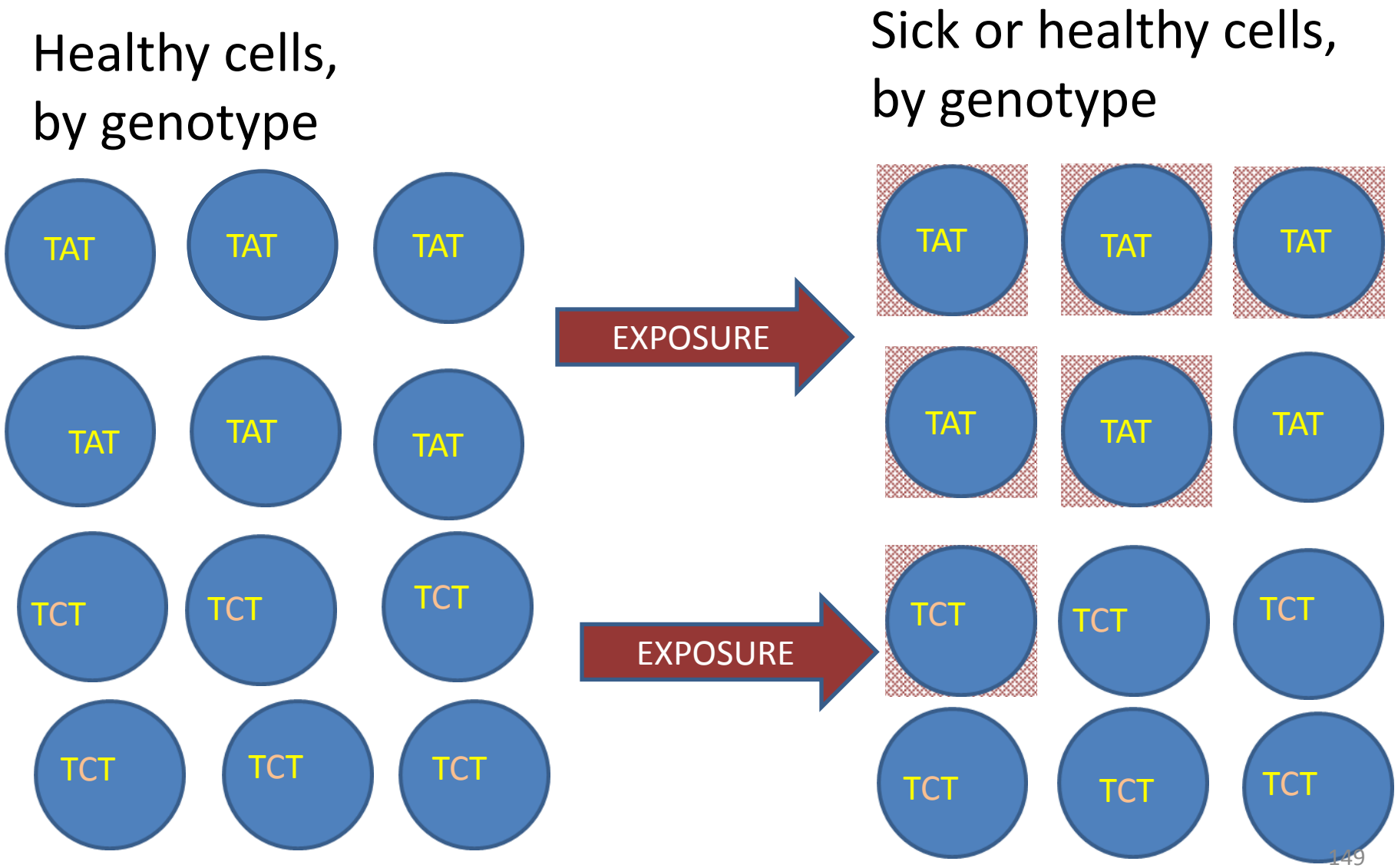


APR = .50, so apparent probability of specific causation is 50%

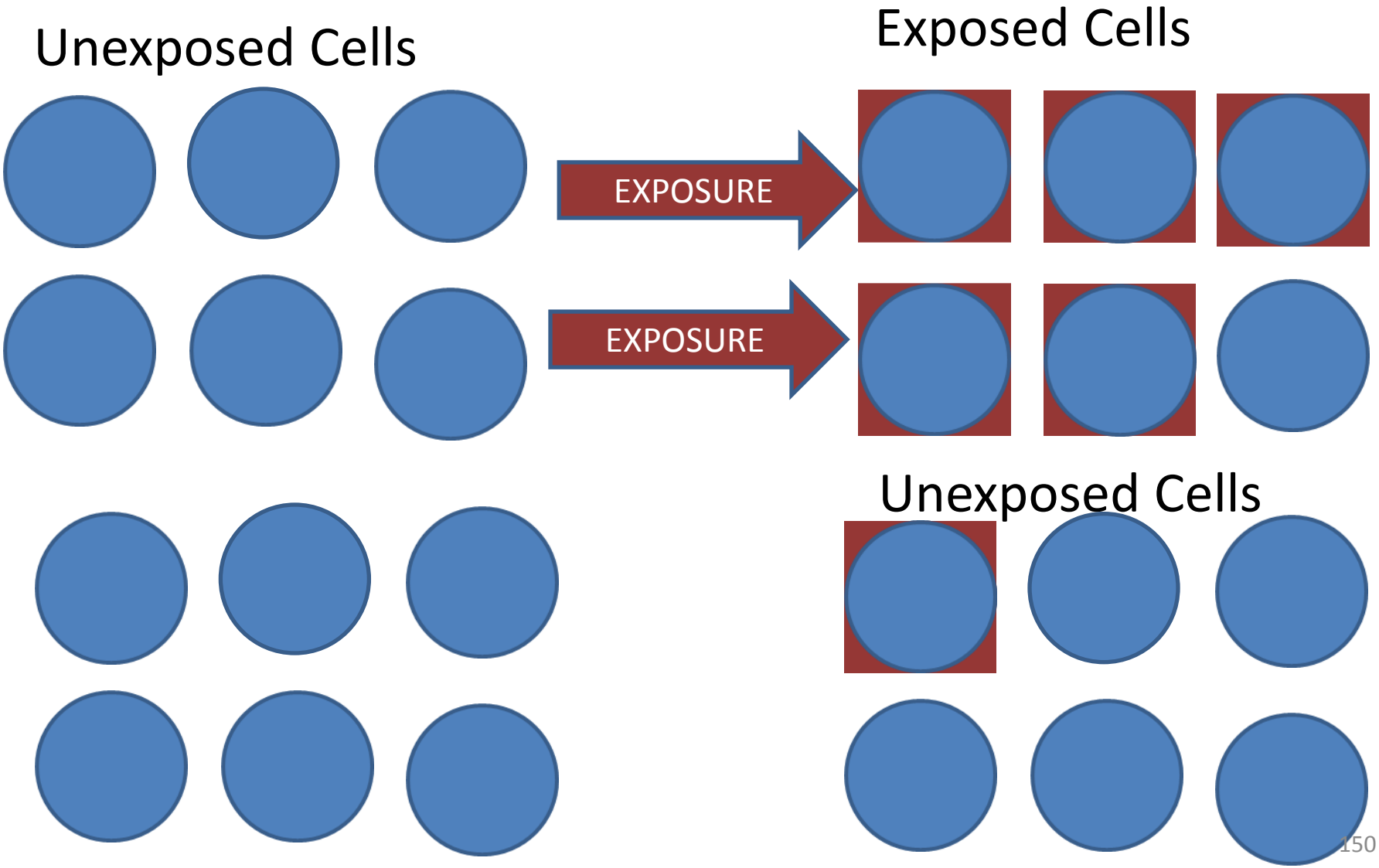
Biomarker

An observable biological change that is associated with a characteristic of interest.

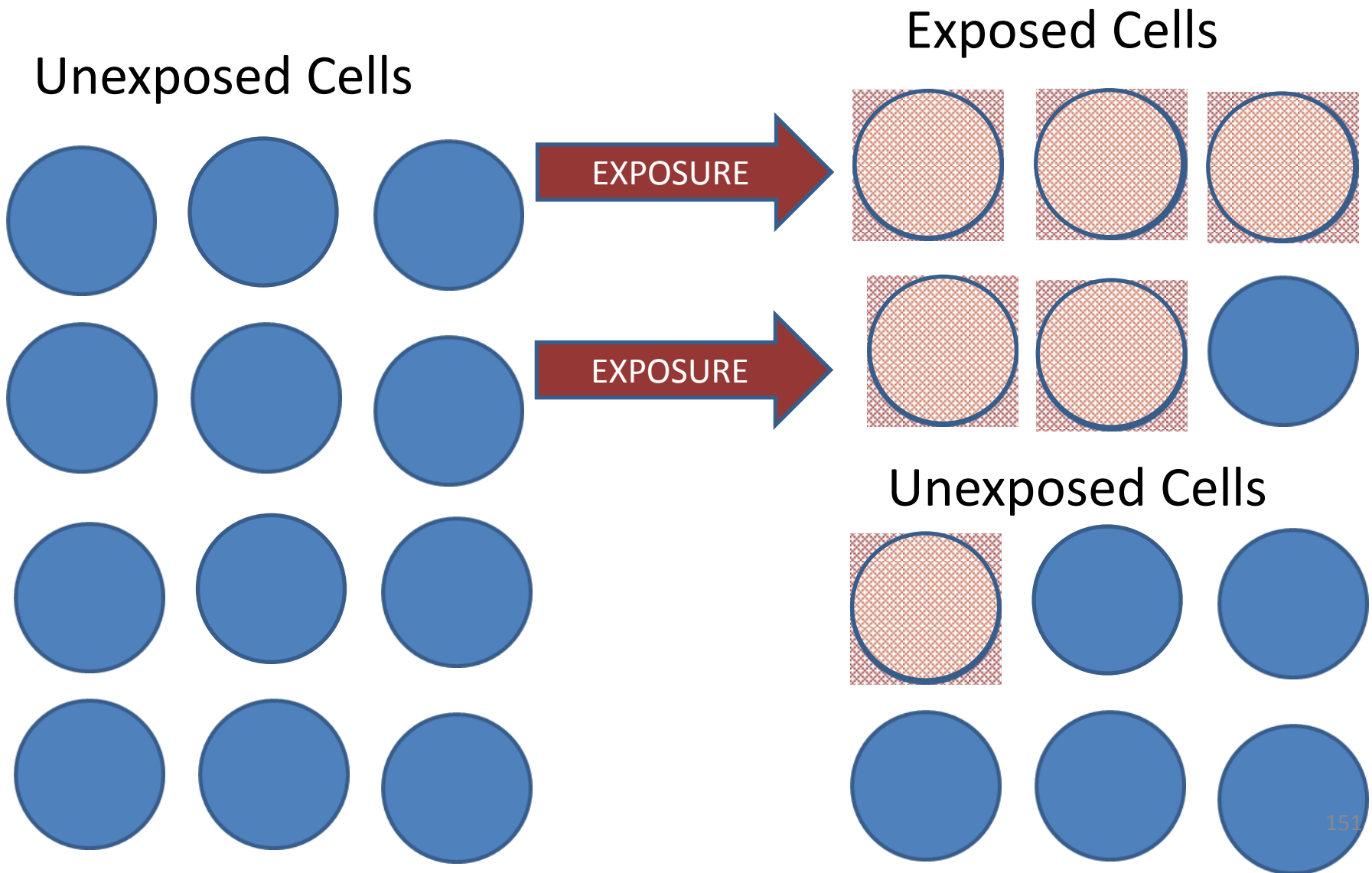
Biomarker of Susceptibility



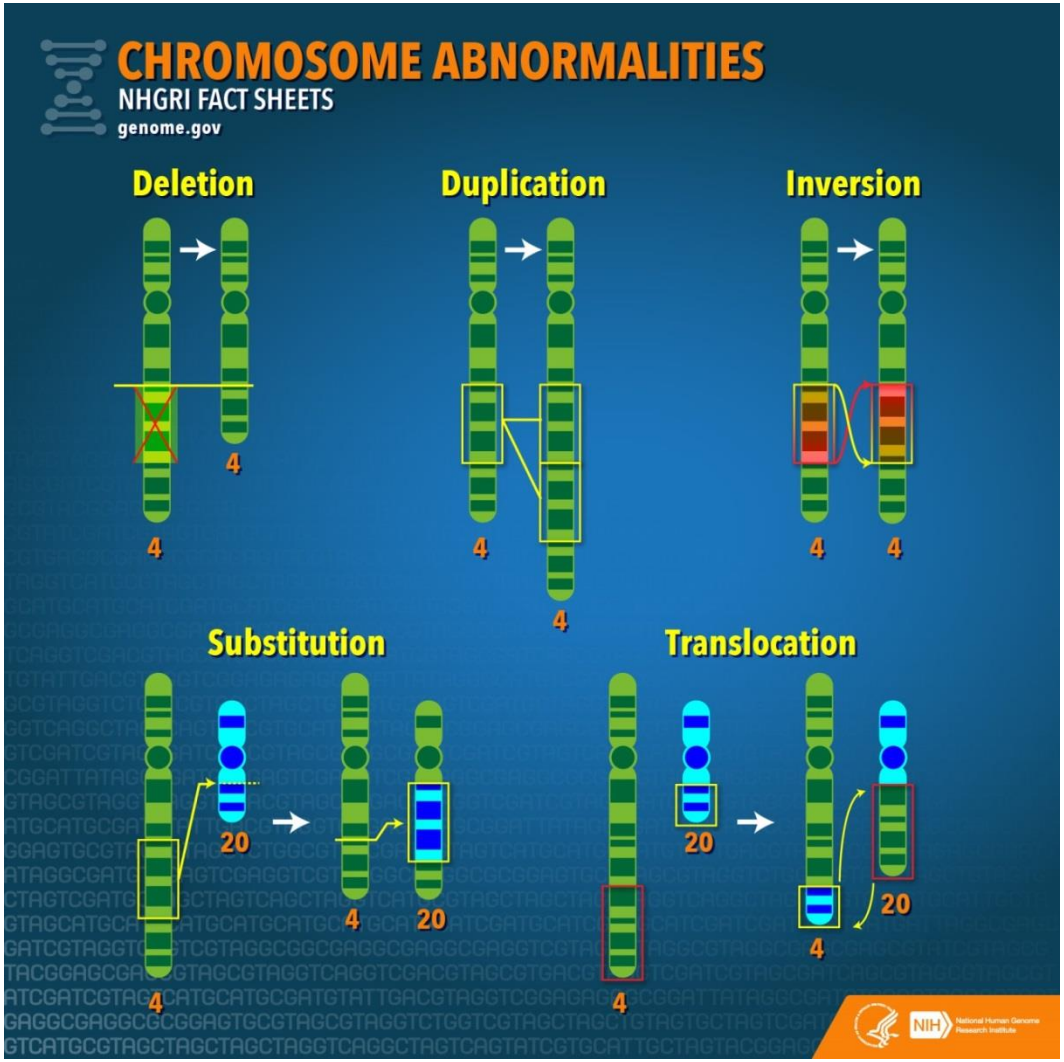
Biomarker of Exposure



Biomarker of Effect



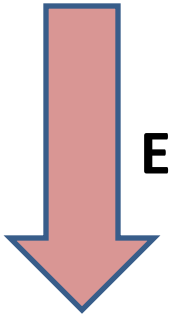
Potential biomarkers of exposure or effect: chromosome abnormalities



SOURCE: Image courtesy National Human Genome Institute, www.genome.gov. Image in the public domain.

Potential biomarkers of exposure or effect: DNA sequence changes

TTTTCCCAAAGTAGCATAGCCGGAAGAAACCCG



EXPOSURE

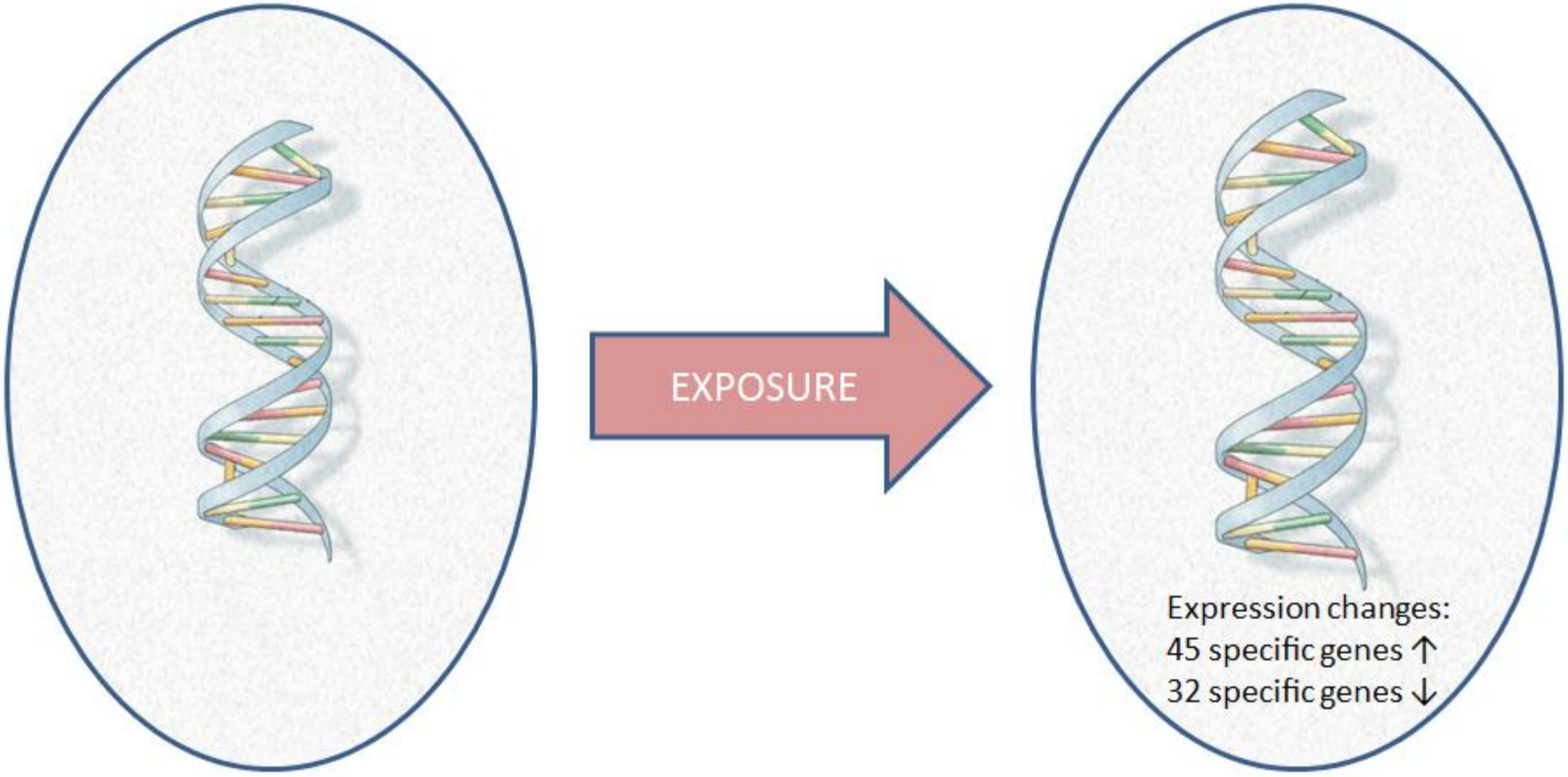
TTTTCCCAATGAAGCATAGCCGGAAGAACCCCG

e.g.,

Inversion: AGT becomes TGA

Substitution: AAC becomes ACC

Potential biomarkers of exposure or effect: gene expression pattern changes

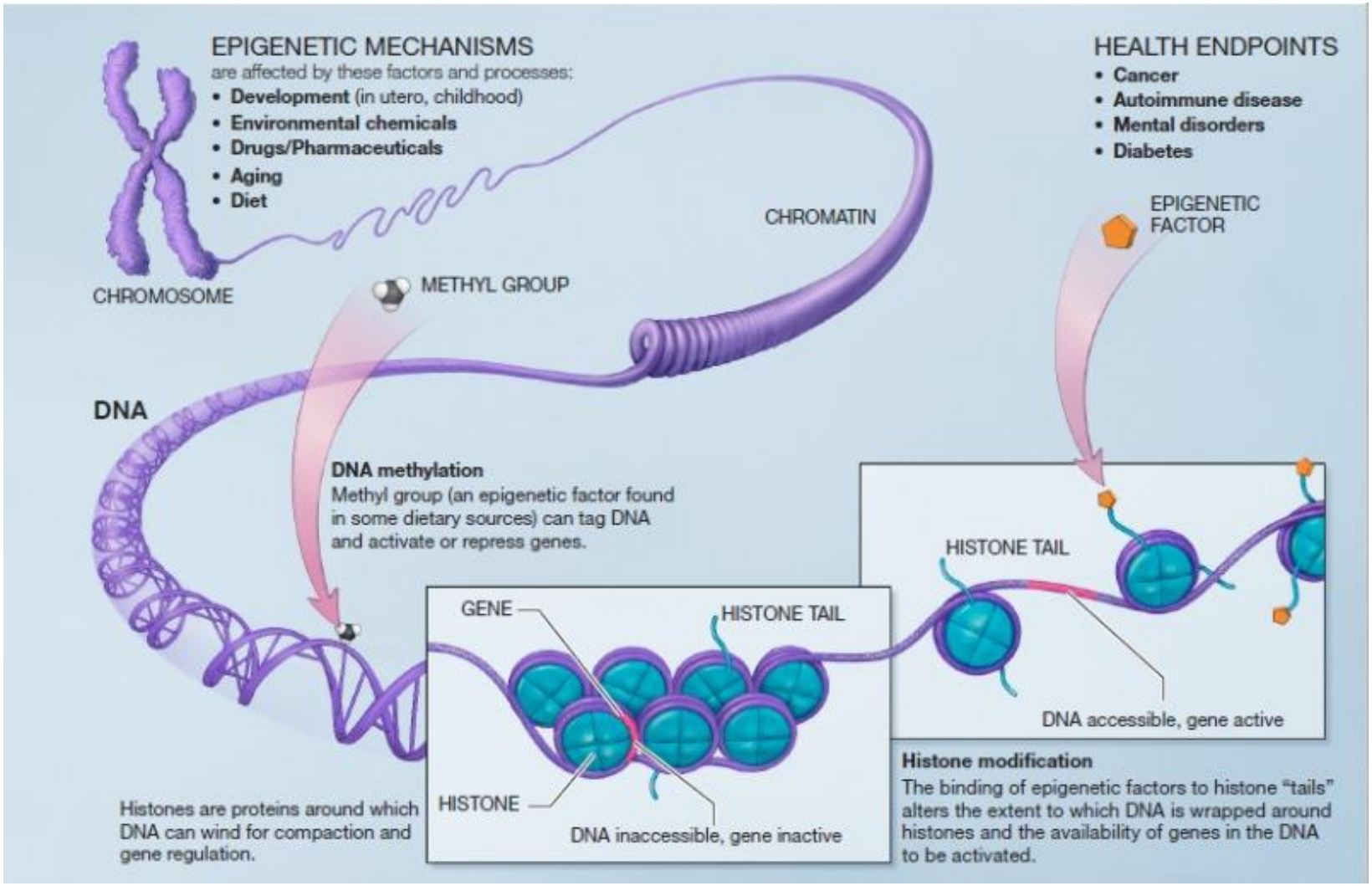


1000s of genes expressed to varying degrees

1000s of genes expressed to varying degrees

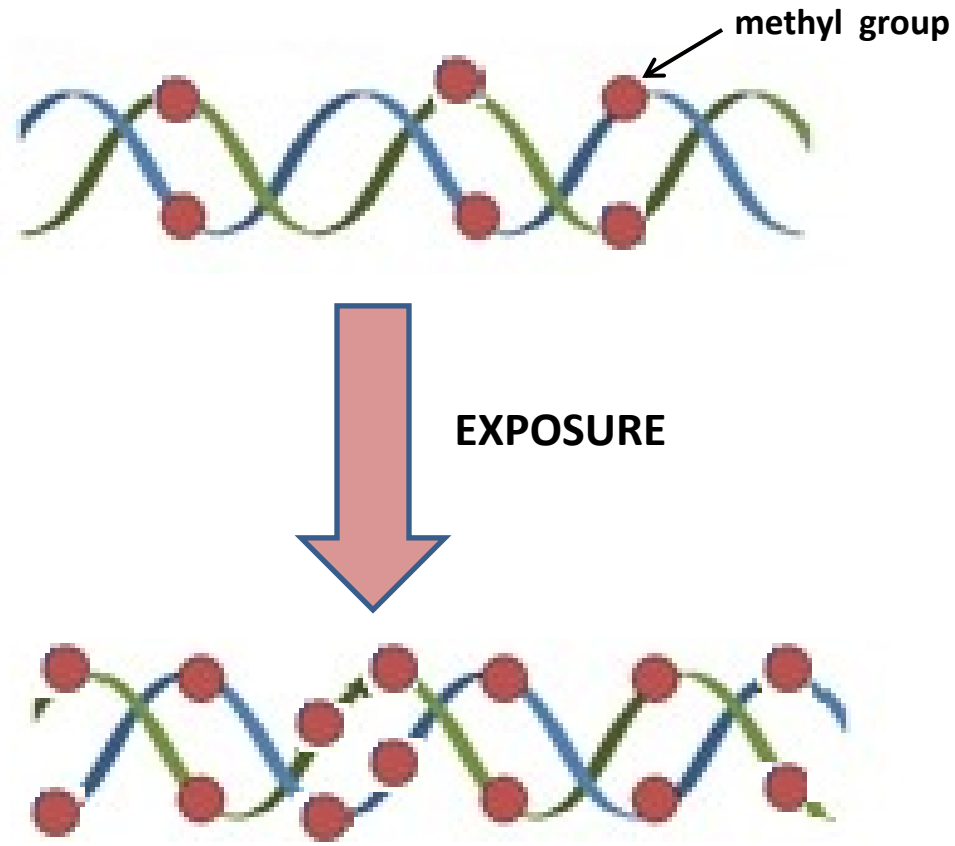
SOURCE: Image of DNA Molecule courtesy U.S. National Library of Medicine, http://ghr.nlm.nih.gov/handbook/basics/dna. Image in the public domain. The remaining material in the slide is courtesy of the authors.

Potential biomarkers of exposure or effect: epigenetic changes



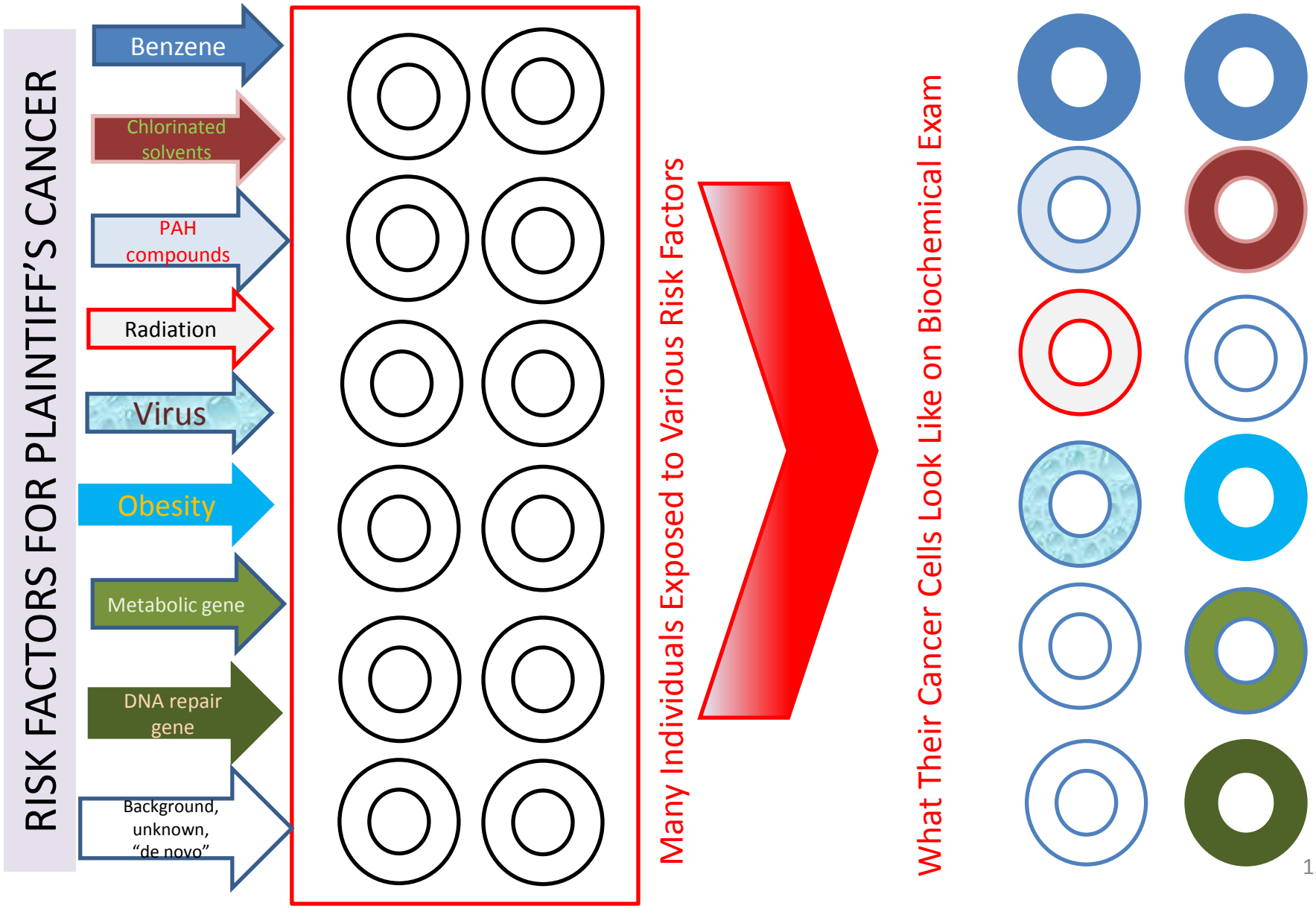
SOURCE: Image courtesy National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, www.ncbi.nlm.nih.gov. Image in public domain.

Example of an epigenetic change: altered methylation

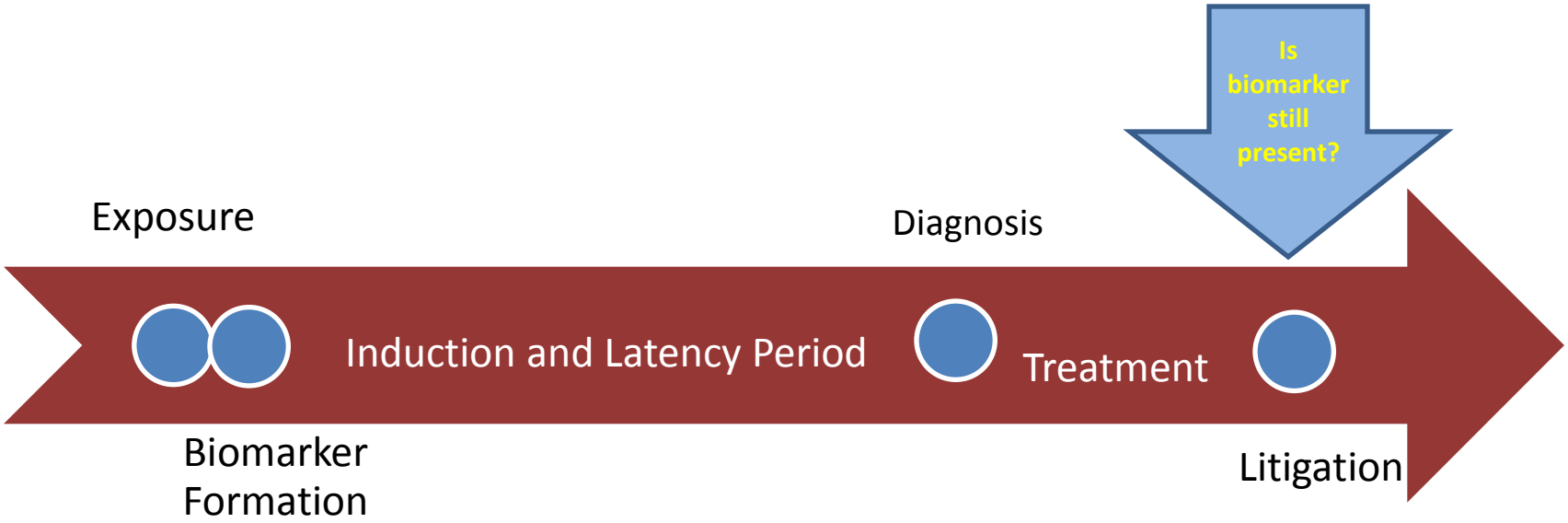


SOURCE: Portions of adapted image courtesy National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, www.ncbi.nlm.nih.gov. Image in public domain.

The Idealized Potential of Biomarkers

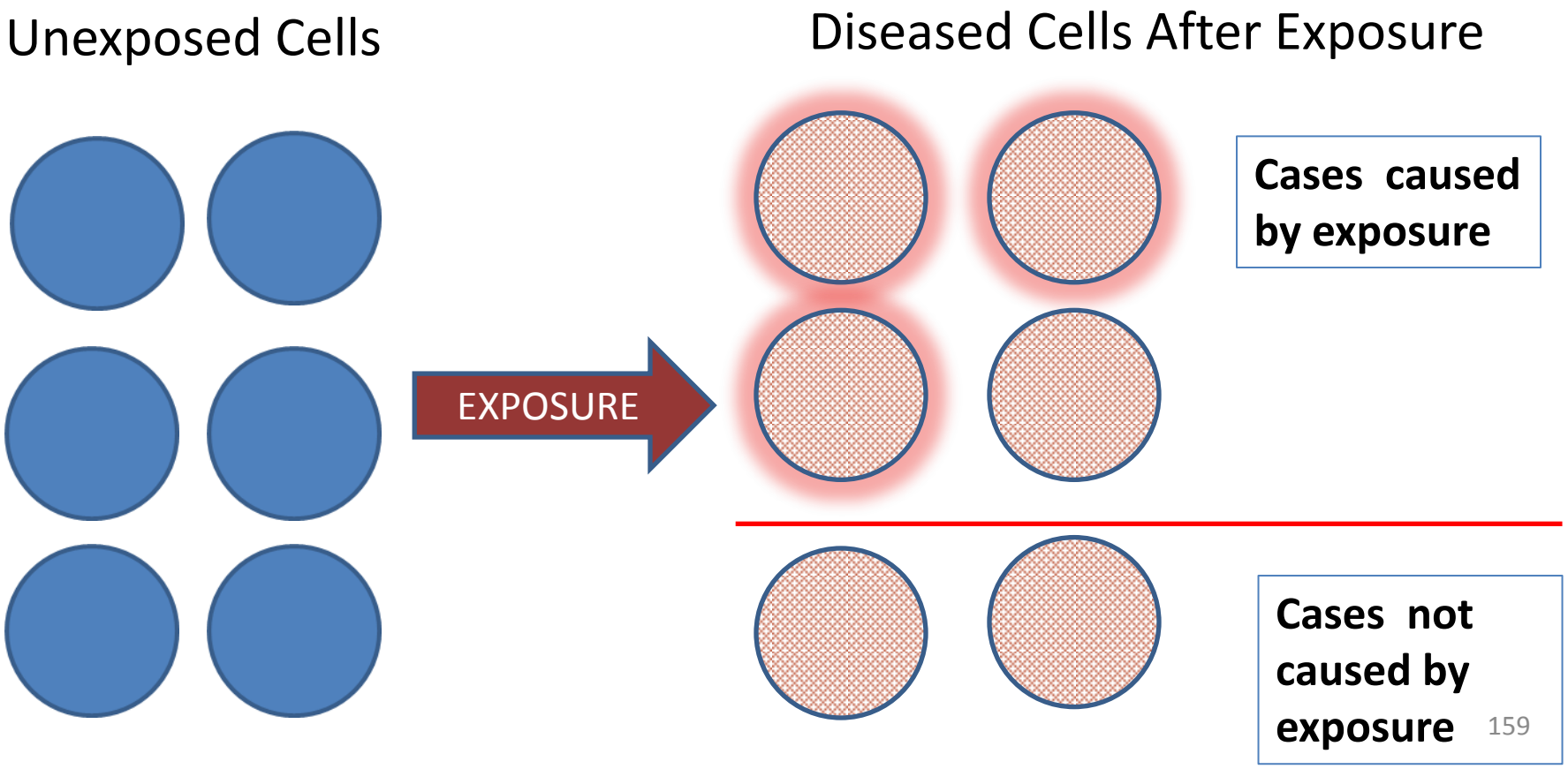


Biomarker Persistence and Toxic Tort Litigation



Biomarkers of Effect (Causation): Specificity

A perfectly specific biomarker of causation would only appear if causation is true.



Computing biomarker specificity

SPECIFICITY

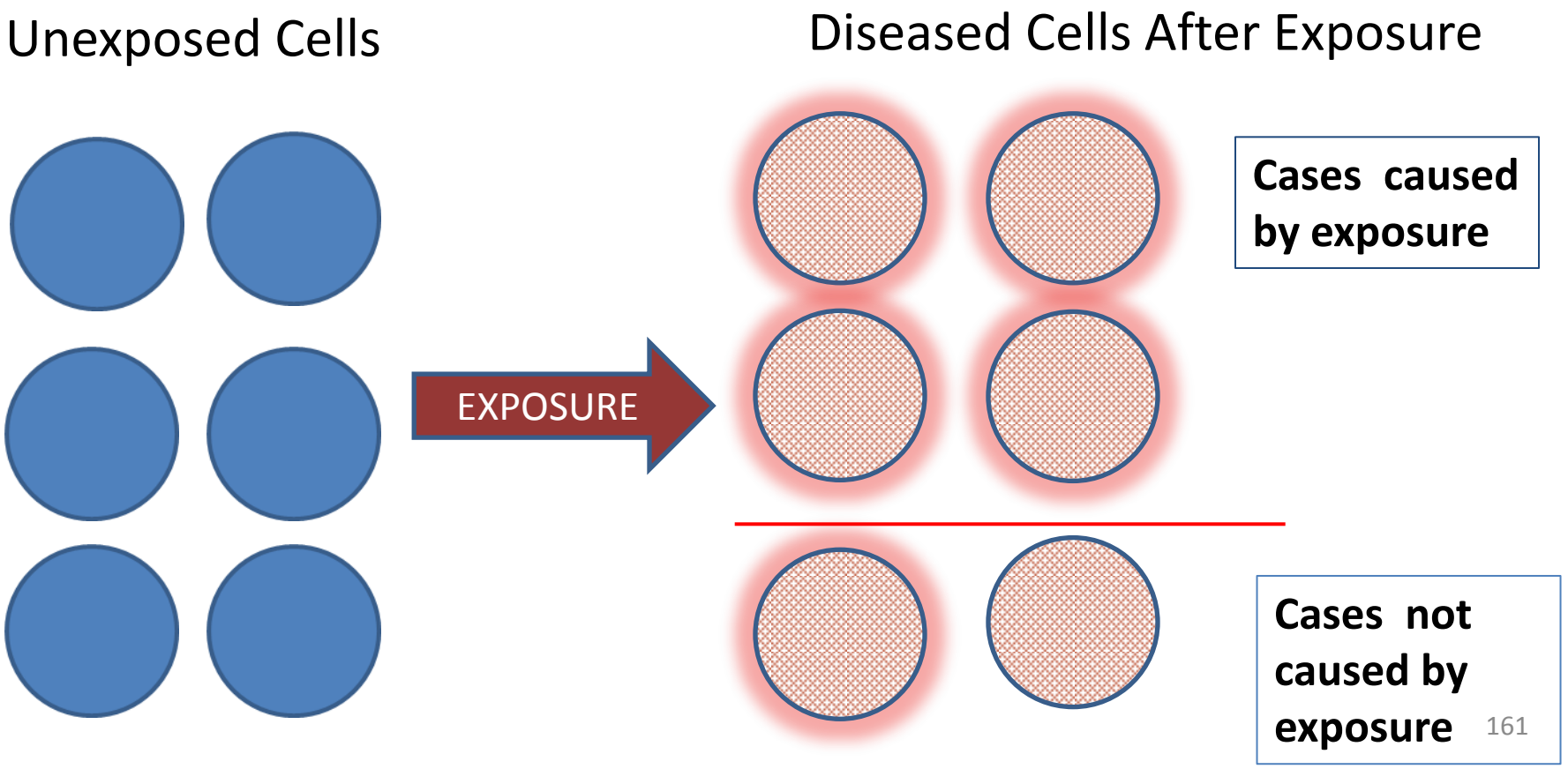
measures how well the biomarker avoids misidentifying negative cases.

	Cases Caused by Exposure	Cases Not Caused by Exposure
Biomarker Present	**TRUE POSITIVES**	**FALSE POSITIVES**
Biomarker Absent	**FALSE NEGATIVES**	**TRUE NEGATIVES**

$$\text{SPECIFICITY} = \frac{\text{TRUE NEGATIVES}}{(\text{TRUE NEGATIVES} + \text{FALSE POSITIVES})}$$

Biomarkers of Effect (Causation): Sensitivity

A perfectly sensitive biomarker of causation would always appear if causation is true.



Computing biomarker sensitivity

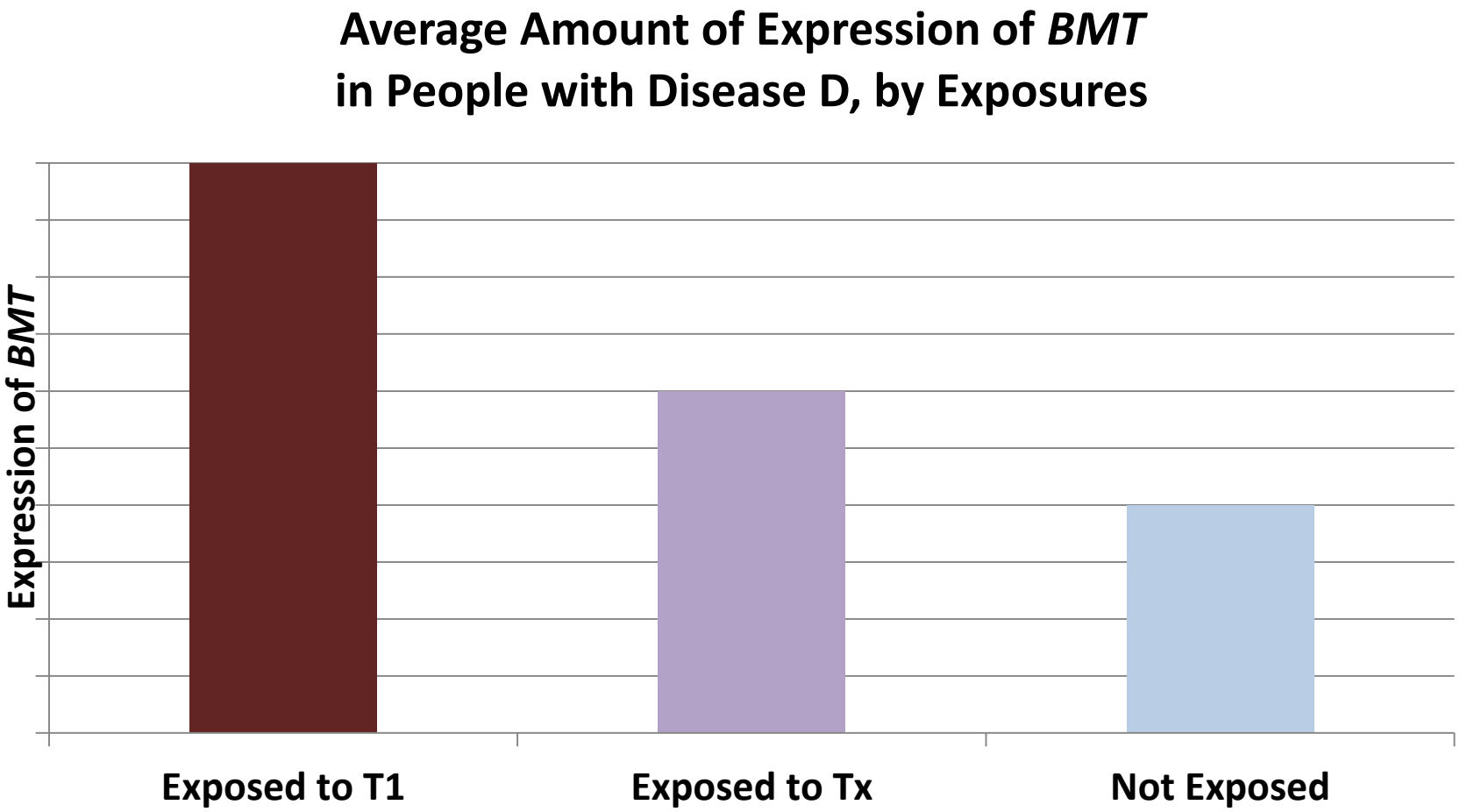
SENSITIVITY

measures how well the biomarker avoids misidentifying negative cases.

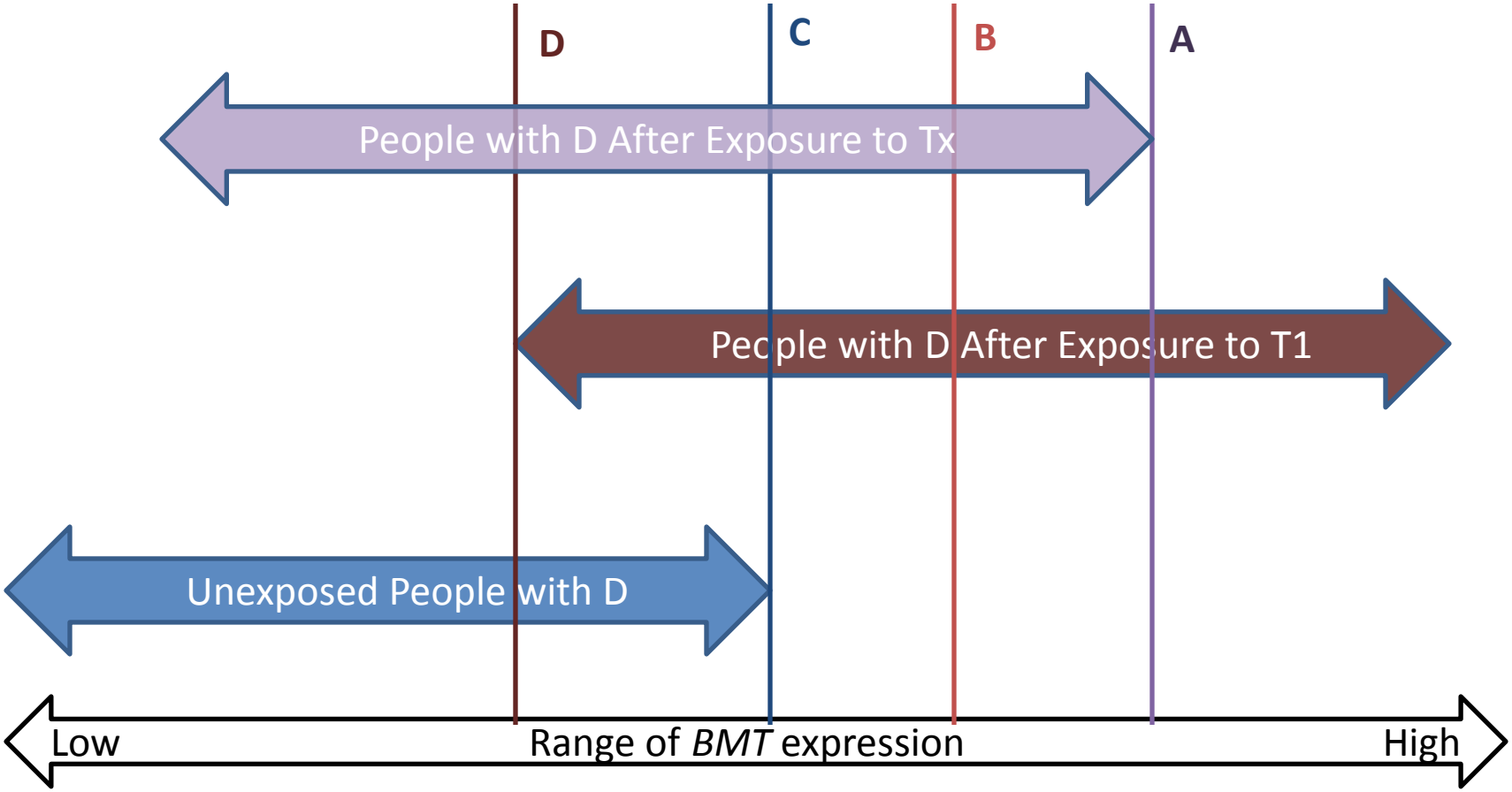
	Cases Caused by Exposure	Cases Not Caused by Exposure
Biomarker Present	**TRUE POSITIVES**	**FALSE POSITIVES**
Biomarker Absent	**FALSE NEGATIVES**	**TRUE NEGATIVES**

$$\text{SENSITIVITY} = \frac{\text{TRUE POSITIVES}}{(\text{TRUE POSITIVES} + \text{FALSE NEGATIVES})}$$

Specificity-Sensitivity Tradeoff: *BMT* expression hypothetical



Specificity-Sensitivity Tradeoff: Four Possible Biomarkers for T1 Exposure or Effect



Defendant's Biomarker Testimony in *Henricksen v. ConocoPhillips*

	"Secondary" AML	*"De Novo"* AML
Chromosome Aberrations Present	**90% of Secondary AML cases**	**50% of *De Novo* AML CASES**
Chromosome Aberrations Absent	**10% of Secondary AML cases**	**50% of *De Novo* AML cases**

SPECIFICITY of biomarker for secondary AML = 0.50

50% *de novo* w/o aberrations
divided by
(50% *de novo* w/o aberrations
+
50% *de novo* w/ aberrations)

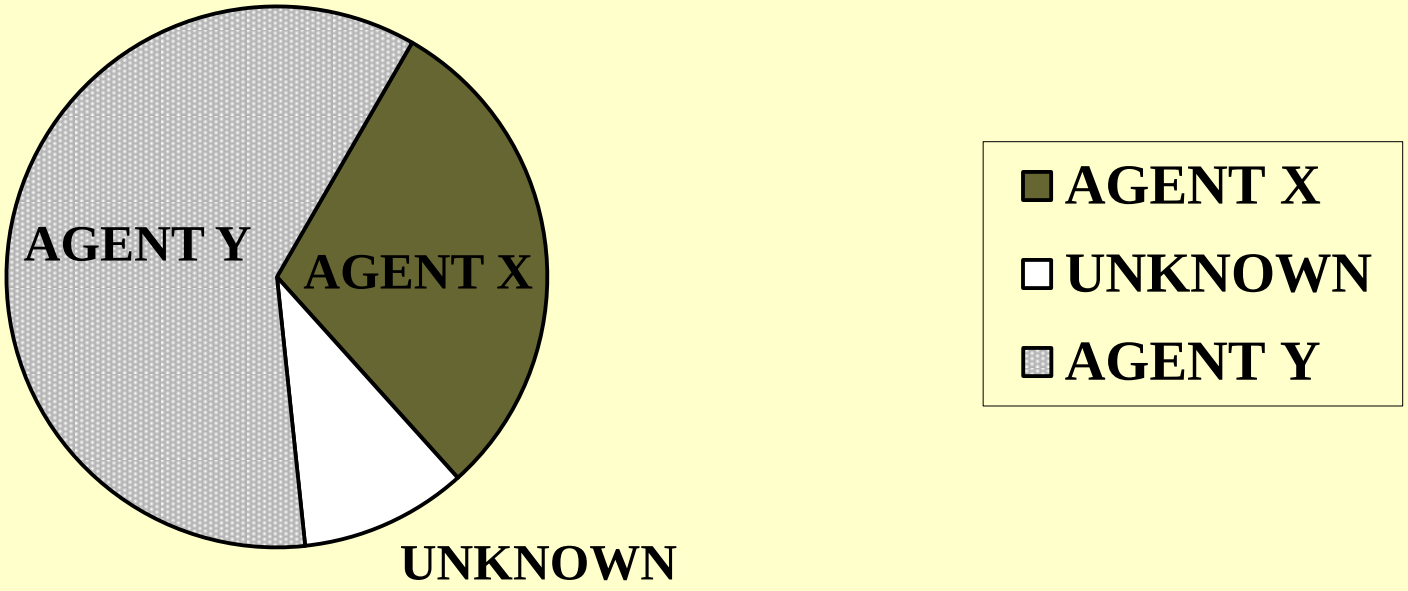
SENSITIVITY of biomarker for secondary AML = 0.90

90% secondary w/ aberrations
divided by
(90% secondary w/ aberrations
+
10% secondary w/o aberrations)

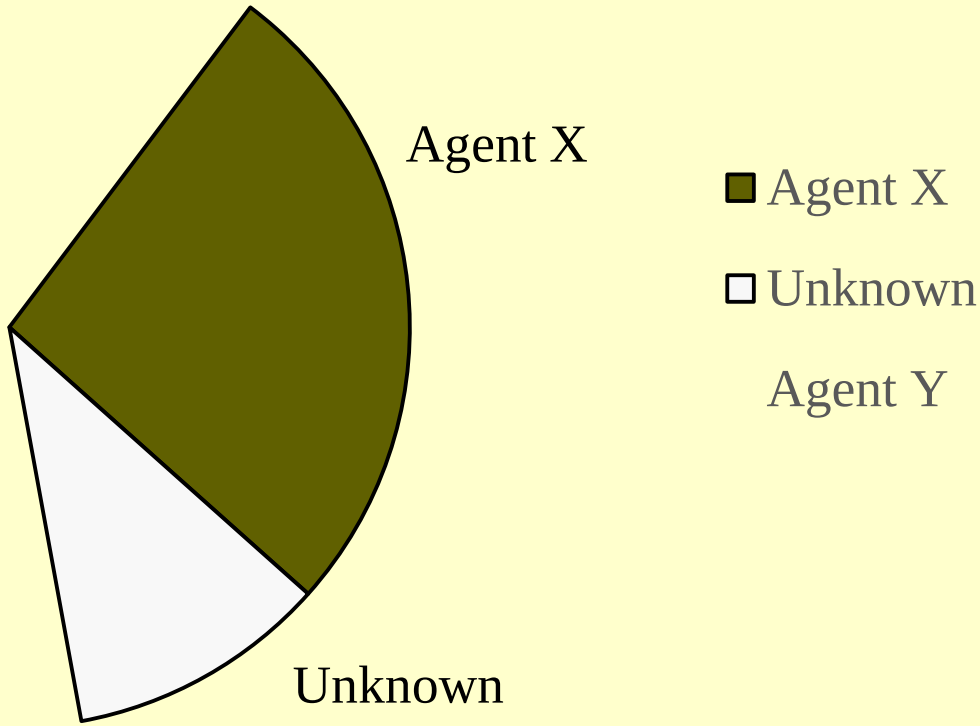
RELATIVE RISKS < 2.0

RELATIVE RISKS < 2.0

SOURCES OF DISEASE

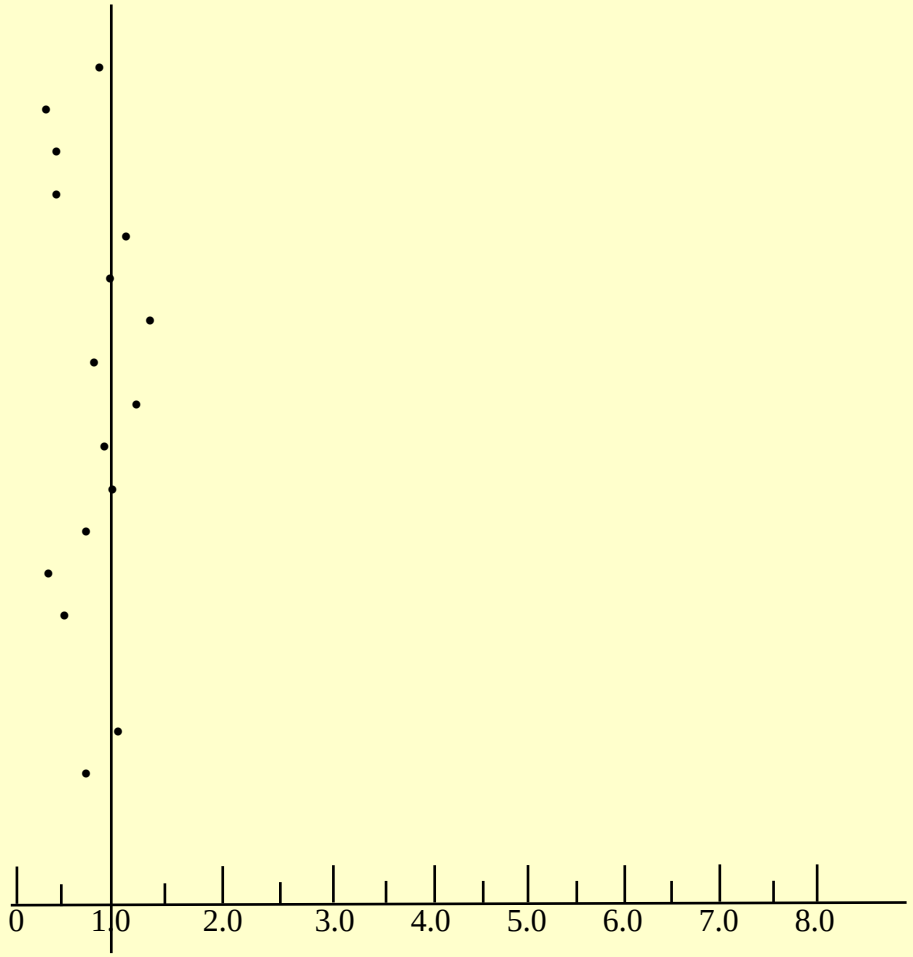


Revised Probability after Differential Etiology



Adjusted Relative Risk Estimates for Definite CTDs Combined

Study	Estimated RR
Burns	0.95
Dugowson	0.41
Englert	0.52
Goldman	0.52
Hennekens	1.24
Hochberg	1.07
Lacey	1.48
Teel	0.90
Wolfe	1.35
Edworthy	1.00
Gabriel	1.10
Nyren	0.80
Park	0.42
Sanchez-Guerrero	0.60
All Studies	1.14
exclude Hennekens	0.80



SOURCE: Michael D. Green, *The Future of Proportional Liability*, in "Exploring Tort Law," Stuart Madden, ed. (Cambridge: Cambridge University Press, 2005). Reproduced courtesy of the author.