

# Contents

## Part I Introduction to Risk Analysis

<b>1 Quantitative Risk Assessment Goals and Challenges</b> .....	3
The Quantitative Risk Assessment (QRA) Paradigm .....	3
Example: A Simple QRA Risk Assessment Model .....	4
Example: Explicit QRA Reasoning Can Be Checked and Debated .....	6
Against QRA: Toward Concern-Driven Risk Management .....	7
Dissatisfactions with QRA .....	7
Example: Use of Incorrect Modeling Assumptions in Antimicrobial Risk Assessment .....	8
Example: Use of Unvalidated Assumptions in a QRA for BSE (“Mad Cow” Disease) .....	9
Toward Less Analytic, More Pluralistic Risk Management .....	11
Alternatives to QRA in Recent Policy Making: Some Practical Examples .....	13
Concern-Driven Risk Management .....	15
Potential Political Advantages of Concern-Driven Regulatory Risk Management .....	16
How Effective Is Judgment-Based Risk Management? .....	18
Example: Expert Judgment vs. QRA for Animal Antibiotics .....	18
Performance of Individual Judgment vs. Simple Quantitative Models .....	19
Performance of Consensus Judgments vs. Simple Quantitative Models .....	26
Example: Resistance of Expert Judgments to Contradictory Data .....	26
Example: Ignoring Disconfirming Data About BSE Prevalence .....	28
Example: Consensus Decision Making Can Waste Valuable Individual Information .....	29
How Effective Can QRA Be? .....	31
Summary and Conclusions .....	32
<b>2 Introduction to Engineering Risk Analysis</b> .....	35
Overview of Risk Analysis for Engineered Systems .....	35
Example: Unreliable Communication with Reliable Components .....	37

Example: Optimal Number of Redundant Components . . . . .	37
Example: Optimal Scheduling of Risky Inspections . . . . .	38
Using Risk Analysis to Improve Decisions . . . . .	39
Hazard Identification: What Should We Worry About? . . . . .	39
Example: Fault Tree Calculations for Car Accidents at an Intersection . . . . .	40
Structuring Risk Quantification and Displaying Results: Models for Accident Probabilities and Consequences . . . . .	41
Example: Bug-Counting Models of Software Reliability . . . . .	42
Example: Risk Management Decision Rules for Dams and Reservoirs . . . . .	43
Example: Different Individual Risks for the Same Exceedance Probability Curve . . . . .	43
Quantifying Model Components and Inputs . . . . .	44
Modeling Interdependent Inputs and Events . . . . .	45
Example: Analysis of Accident Precursors . . . . .	46
Example: Flight-Crew Alertness . . . . .	47
Some Alternatives to Subjective Prior Distributions . . . . .	47
Example: Effects of Exposure to Contaminated Soil . . . . .	49
Example: The “Rule of Three” for Negative Evidence . . . . .	54
Example: A Sharp Transition in a Symmetric Multistage Model of Carcinogenesis . . . . .	55
Dealing with Model Uncertainty: Bayesian Model Averaging (BMA) and Alternatives . . . . .	56
Risk Characterization . . . . .	58
Engineering vs. Financial Characterizations of “Risk”: Why Risk Is Not Variance . . . . .	58
Incompatibility of Two Suggested Principles for Financial Risk Analysis . . . . .	62
Challenges in Communicating the Results of PRAs . . . . .	66
Methods for Risk Management Decision Making . . . . .	67
Example: A Bounded-Regret Strategy for Replacing Unreliable Equipment . . . . .	68
Methods of Risk Management to Avoid . . . . .	69
Game-Theory Models for Risk Management Decision Making . . . . .	70
Game-Theory Models for Security and Infrastructure Protection . . . . .	70
Game-Theory Models of Risk-Informed Regulation . . . . .	71
Conclusions . . . . .	72
<b>3 Introduction to Health Risk Analysis . . . . .</b>	<b>73</b>
Introduction . . . . .	73
Quantitative Definition of Health Risk . . . . .	75
Example: Statistical and Causal Risk Relations May Have Opposite Signs . . . . .	76
A Bayesian Network Framework for Health Risk Assessment . . . . .	77

Hazard Identification . . . . . 80  
 Example: Some Traditional Criteria for Causality Fail to Refute  
 Other Explanations . . . . . 83  
 Exposure Assessment . . . . . 85  
 Example: Simulation of Exposures to Pathogens in Chicken Meat . . . . . 87  
 Example: Mixture Distributions and Unknown Dose-Response  
 Models . . . . . 88  
 Dose-Response Modeling . . . . . 89  
 Example: Apparent Thresholds in Cancer Dose-Response Data . . . . . 90  
 Example: Best-Fitting Parametric Models May Not Fit Adequately . . . . . 91  
 Risk and Uncertainty Characterization for Risk Management . . . . . 93  
 Example: Risk Characterization Outputs . . . . . 93  
 Conclusions . . . . . 96

**Part II Avoiding Bad Risk Analysis**

**4 Limitations of Risk Assessment Using Risk Matrices . . . . . 101**  
 Introductory Concepts and Examples . . . . . 102  
 A Normative Decision-Analytic Framework . . . . . 104  
 Logical Compatibility of Risk Matrices with Quantitative Risks . . . . . 108  
 Definition of Weak Consistency . . . . . 109  
 Discussion of Weak Consistency . . . . . 109  
 Logical Implications of Weak Consistency . . . . . 110  
 The Betweenness Axiom: Motivation and Implications . . . . . 111  
 Consistent Coloring . . . . . 112  
 Implications of the Three Axioms . . . . . 113  
 Example: The Two Possible Colorings of a Standard  
 5 × 5 Risk Matrix . . . . . 113  
 Risk Matrices with Too Many Colors Give Spurious Resolution . . . . . 114  
 Example: A 4 × 4 Matrix for Project Risk Analysis . . . . . 115  
 Risk Ratings Do Not Necessarily Support Good Resource Allocation  
 Decisions . . . . . 117  
 Example: Priorities Based on Risk Matrices Violate  
 Translation Invariance . . . . . 117  
 Example: Priority Ranking Does Not Necessarily Support  
 Good Decisions . . . . . 118  
 Categorization of Uncertain Consequences Is Inherently Subjective . . . . . 119  
 Example: Severity Ratings Depend on Subjective Risk Attitudes . . . . . 119  
 Example: Pragmatic Limitations of Guidance from Standards . . . . . 120  
 Example: Inappropriate Risk Ratings in Enterprise Risk  
 Management (ERM) . . . . . 121  
 Discussion and Conclusions . . . . . 122  
 Appendix A: A Proof of Theorem 1 . . . . . 123

**5 Limitations of Quantitative Risk Assessment Using Aggregate Exposure and Risk Models** . . . . . 125

What Is Frequency? . . . . . 126

    An Example: Comparing Two Risks . . . . . 127

    Event Frequencies in Renewal Processes . . . . . 127

    Example: Average Annual Frequency for Exponentially Distributed Lifetimes . . . . . 128

    The “Frequency” Concept for Nonexponential Failure Times . . . . . 128

    Example: Average Annual Frequency for Uniformly Distributed Lifetimes . . . . . 128

    Conflicts Among Different Criteria for Comparing Failure Time Distributions . . . . . 129

    Do These Distinctions Really Matter? . . . . . 130

    Summary of Limitations of the “Frequency” Concept . . . . . 132

Limitations of Aggregate Exposure Metrics . . . . . 133

    Use of Aggregate Exposure Metrics in Risk Assessment . . . . . 134

    Aggregate Exposure Information May Not Support Improved Decisions . . . . . 134

    Example: How Aggregate Exposure Information Can Be Worse Than Useless . . . . . 135

    Multicollinearity and Aggregate Exposure Data . . . . . 137

    Example: Multicollinearity Can Prevent Effective Extrapolation of Risk . . . . . 137

    A Practical Example: Different Predictions of Asbestos Risks at El Dorado Hills, CA . . . . . 138

    Summary of Limitations of Risk Assessments Based on Aggregate Exposure Metrics . . . . . 140

Limitations of Aggregate Exposure-Response Models: An Antimicrobial Risk Assessment Case Study . . . . . 141

    Statistical vs. Causal Relations . . . . . 142

    Example: Significant Positive K for Statistically Independent Risk and Exposure . . . . . 142

    Example: A Positive K Does Not Imply That Risk Increases with Exposure . . . . . 143

    Example: Statistical Relations Do Not Predict Effects of Changes . . . . . 143

    Prevalence vs. Microbial Load as Exposure Metrics . . . . . 144

    Attribution vs. Causation . . . . . 145

    Human Harm from Resistant vs. Susceptible Illnesses . . . . . 147

    Summary of Limitations of Aggregate Exposure-Response Model,  $Risk = K \times Exposure$  . . . . . 148

Some Limitations of Risk Priority-Scoring Methods . . . . . 149

    Motivating Examples . . . . . 149

    Example: Scoring Information Technology Vulnerabilities . . . . . 150

    Example: Scoring Consumer Credit Risks . . . . . 150

    Example: Scoring Superfund Sites to Determine Funding Priorities . . . . . 151

Example: Priority Scoring of Bioterrorism Agents . . . . . 151

Example: Threat-Vulnerability-Consequence (TVC) Risk Scores  
and Risk Matrices . . . . . 152

Priorities for Known Risk Reductions . . . . . 152

Priorities for Independent, Normally Distributed Risk Reductions . . . . . 153

Priority Ratings Yield Poor Risk Management Strategies  
for Correlated Risks . . . . . 155

Example: Priority Rules Overlook Opportunities  
for Risk-Free Gains . . . . . 155

Example: Priority Setting Can Recommend the Worst  
Possible Resource Allocation . . . . . 156

Example: Priority Setting Ignores Opportunities for Coordinated  
Defenses . . . . . 157

Priority Rules Ignore Aversion to Large-Scale Uncertainties . . . . . 158

Discussion and Conclusions on Risk Priority-Scoring Systems . . . . . 159

Conclusions . . . . . 160

**Part III Principles for Doing Better**

**6 Identifying Nonlinear Causal Relations in Large Data Sets . . . . . 165**

Nonlinear Exposure-Response Relations . . . . . 166

Entropy, Mutual Information, and Conditional Independence . . . . . 168

Classification Trees and Causal Graphs via Information Theory . . . . . 170

Illustration for the Campylobacteriosis Case Control Data . . . . . 173

Conclusions . . . . . 177

**7 Overcoming Preconceptions and Confirmation Biases Using Data Mining . . . . . 179**

Confirmation Bias in Causal Inferences . . . . . 180

Example: The Wason Selection Task . . . . . 180

Example: Attributing Antibiotic Resistance to Specific Causes . . . . . 181

Study Design: Hospitalization Might Explain Observed  
Resistance Data . . . . . 183

Choice of Endpoints . . . . . 185

Quantitative Statistical Methods and Analysis . . . . . 185

Results of Quantitative Risk Assessment Modeling for vatE  
Resistance Determinant . . . . . 193

Results for Inducible Resistance . . . . . 197

Discussion and Implications for Previous Conclusions . . . . . 198

Summary and Conclusions . . . . . 200

Appendix A: Computing Adjusted Ratios of Medians  
and their Confidence Limits . . . . . 201

**8 Estimating the Fraction of Disease Caused by One Component of a Complex Mixture: Bounds for Lung Cancer** . . . . . 203

Motivation: Estimating Fractions of Illnesses Preventable by Removing Specific Exposures . . . . . 203

Why Not Use Population Attributable Fractions? . . . . . 204

    Example: Attribution of Risk to Consequences Instead of Causes . . . . . 204

    Example: Positive Attributable Risk is Compatible with Negative Causation . . . . . 205

Theory: Paths, Event Probabilities, Bounds on Causation . . . . . 206

    A Bayesian Motivation for the Attributable Fraction Formula . . . . . 208

The Smoking-PAH-BPDE-p53-Lung Cancer Causal Pathway . . . . . 210

Applying the Theory: Quantifying the Contribution of the Smoking-PAH-BPDE-p53 Pathway to Lung Cancer Risk . . . . . 212

    A Simple Theoretical Calculation Using Causal Fractions . . . . . 212

    Step 1: Replace Causal Fractions with Fractions Based on Occurrence Rates . . . . . 213

    Step 2: Quantify Occurrence Rates Using Molecular-Level Data . . . . . 216

    Step 3: Combine Upper-Bound Surrogate Fractions for Events in a Path Set . . . . . 218

Uncertainties and Sensitivities . . . . . 219

Discussion . . . . . 220

Conclusions . . . . . 221

**9 Bounding Resistance Risks for Penicillin** . . . . . 223

Background, Hazard Identification and Scope: Reducing Ampicillin-Resistant *E. faecium* (AREF) Infections in ICU Patients . . . . . 223

Methods and Data: Upper Bounds for Preventable Mortalities . . . . . 225

    Estimated Number of ICU Infections per Year . . . . . 226

    Fraction of ICU Infections Caused by *E. faecium* . . . . . 227

    Fraction of ICU *E. faecium* Infections That Are Ampicillin-Resistant and Exogenous (Nonnosocomial) . . . . . 227

    Fraction of Vancomycin-Susceptible Cases . . . . . 228

    Fraction of Exogenous Cases Potentially from Food Animals . . . . . 229

    Penicillin Allergies . . . . . 230

    Excess Mortalities . . . . . 231

Results Summary, Sensitivity, and Uncertainty Analysis . . . . . 232

Summary and Conclusions . . . . . 234

**10 Confronting Uncertain Causal Mechanisms – Portfolios of Possibilities** . . . . . 237

Background: Cadmium and Smoking Risk . . . . . 238

Previous Cadmium-Lung Cancer Risk Studies . . . . . 239

    Cadmium Compounds are Rat Lung Carcinogens . . . . . 239

    Epidemiological Data are Inconclusive . . . . . 240

Pharmacokinetic Data Show That Smoking Increases Cadmium Levels in the Human Lung . . . . . 240

Biological Mechanisms of Cadmium Lung Carcinogenesis . . . . . 242

    A Transition Model Simplifies the Description of Cadmium-Induced Lung Carcinogenesis . . . . . 242

    Cadmium Can Affect Lung Carcinogenesis via Multiple Mechanisms . . . . . 244

    Smoking and Cd Exposures Stimulate Reactive Oxygen Species (ROS) Production . . . . . 245

    Cadmium Inhibits DNA Repair and Is a Co-Carcinogen for PAHs . . . . . 248

Quantifying Potential Cadmium Effects on Lung Cancer Risk . . . . . 251

    Polymorphism Evidence on Lung Cancer Risks from Different Mechanisms . . . . . 252

    Quasi-Steady-State Analysis . . . . . 252

    A Portfolio Approach to Estimating the Preventable Fraction of Risk for Cd . . . . . 256

Discussion and Conclusions . . . . . 257

Appendix A: Relative Risk Framework . . . . . 258

**11 Determining What Can Be Predicted: Identifiability . . . . . 261**

    Identifiability . . . . . 262

        Example 1: A Simple Example of Nonidentifiability . . . . . 262

        Example 2: Unique Identifiability in a Two-Stage Clonal Expansion Model . . . . . 262

    Multistage Clonal Expansion (MSCE) Models of Carcinogenesis . . . . . 266

    Nonunique Identifiability of Multistage Models from Input-Output Data . . . . . 270

        Example 3: Counting  $5 \times 5$  Matrices with Sign Restrictions . . . . . 270

        Example 4: Two Equally Likely Effects of Reducing a Transition Rate . . . . . 271

    Discussion and Conclusions . . . . . 275

    Appendix A: Proof of Theorem 1 . . . . . 277

    Appendix B: Listing of ITHINK™ Model Equations for the Example in Figure 11.3 . . . . . 279

**Part IV Applications and Extensions**

**12 Predicting the Effects of Changes: Could Removing Arsenic from Tobacco Smoke Significantly Reduce Smoker Risks of Lung Cancer? . . . . . 283**

    Biologically Based Risk Assessment Modeling . . . . . 283

    Arsenic as a Potential Human Lung Carcinogen . . . . . 284

    Data, Methods, and Models . . . . . 287

A Multistage Clonal Expansion (MSCE) Framework for Lung Field  
 Cancerization . . . . . 287  
 A Mathematical Model of Field Carcinogenesis . . . . . 291  
 Modeling the Effects on Lung Cancer Risk of Reductions  
 in Carcinogenic Constituents . . . . . 293  
 Linking Biomarker Data to Model Transition Parameters . . . . . 295  
 Results . . . . . 296  
 Limitations of Modeling Assumptions and Calculations . . . . . 298  
 Sensitivities, Uncertainties, Implications, and Conclusions . . . . . 298  
 Appendix A: Listing for TSCE Model of Smoking and Lung Cancer . . . . . 300  
 Appendix B: Listing for MSCE Lung Cancer Model with Field  
 Carcinogenesis . . . . . 301

**13 Simplifying Complex Dynamic Networks: A Model of Protease  
 Imbalance and COPD Dynamic Dose-Response . . . . . 303**  
 Background on COPD . . . . . 304  
 A Flow Process Network Model of Protease-Antiprotease  
 Imbalance in COPD . . . . . 305  
 Mathematical Analysis of the Protease-Antiprotease Network . . . . . 308  
 Some Possible Implications for Experimental and Clinical COPD . . . . . 313  
 Is the Model Consistent with Available Human Data? . . . . . 314  
 Summary and Conclusions . . . . . 316  
 Appendix A: Equilibrium in Networks of Homeostatic Processes . . . . . 317  
 Representing Biological Knowledge by Networks of Flow Processes . . . 317  
 Example: ODE and ITHINK<sup>®</sup> Representations  
 of a Single Process . . . . . 319  
 Reducing Chains of Coupled Processes to Simpler Equivalents . . . . . 320

**14 Value of Information (VOI) in Risk Management Policies  
 for Tracking and Testing Imported Cattle for BSE . . . . . 325**  
 Testing Canadian Cattle for Bovine Spongiform Encephalitis (BSE) . . . . . 327  
 Methods and Data . . . . . 330  
 Formulation of the Risk Management Decision Problem  
 as a Decision Tree . . . . . 330  
 Estimated Economic Consequences of Detecting Additional  
 BSE Cases . . . . . 333  
 Scenario Probabilities . . . . . 339  
 Solution Algorithms . . . . . 342  
 Results . . . . . 343  
 Optimal Decision Rule for the Base Case . . . . . 343  
 Sensitivity Analysis Results . . . . . 343  
 Discussion . . . . . 346  
 Epilogue and Conclusions . . . . . 347  
 Appendix: Market Impact Assumptions and Calculations . . . . . 349



**15 Improving Antiterrorism Risk Analysis** . . . . . 351

    The *Risk = Threat × Vulnerability × Consequence* Framework . . . . . 351

    RAMCAP™ Qualitative Risk Assessment . . . . . 353

    Limitations of RAMCAP™ for Quantitative Risk Assessment . . . . . 354

        Example: Distortions Due to Use of Arithmetic Averages  
        on Logarithmic Scales . . . . . 355

        Example: Limited Resolution . . . . . 355

        Example: Manipulating Vulnerability Estimates by Aggregating  
        Attack Scenarios . . . . . 355

        Example: Nonadditive Vulnerabilities . . . . . 356

        Example: Product of Expected Values Not Equal to Expected  
        Value of Product . . . . . 356

    Risk Rankings Are Not Adequate for Resource Allocation . . . . . 357

        Example: Priority Ranking May Not Support Effective Resource  
        Allocation . . . . . 358

    Some Fundamental Limitations of *Risk = Threat ×*  
    *Vulnerability × Consequence* . . . . . 358

        “Threat” Is Not Necessarily Well Defined . . . . . 359

        “Vulnerability” Can Be Ambiguous and Difficult to Calculate  
        via Event Trees . . . . . 360

        “Consequence” Can Be Ambiguous and/or Subjective . . . . . 367

    Discussion and Conclusions . . . . . 367

**16 Designing Resilient Telecommunications Networks** . . . . . 371

    Introduction: Designing Telecommunications Infrastructure Networks  
    to Survive Intelligent Attacks . . . . . 372

    Background: Diverse Routing, Protection Paths, and Protection  
    Switching . . . . . 372

        Automated Protection Switching (APS) for Packets and Light Paths . . . 373

        Demands Consist of Origins, Destinations, and Bandwidth  
        Requirements . . . . . 373

        Multiple Levels of Protection for Demands . . . . . 374

    A Simple Two-Stage Attacker-Defender Model . . . . . 376

    Results for Networks with Dedicated Routes (“Circuit-Switched”  
    Networks) . . . . . 377

        Designing Networks to Withstand a Single ( $k = 1$ ) Link Cut . . . . . 377

        Designing Networks to Withstand  $k = 2$  Link Cuts . . . . . 380

        Results for the General Case of  $k$  Cuts . . . . . 380

    Statistical Risk Models and Results for Scale-Free Packet Networks . . . . 381

    Real-World Implementation Challenges: Incentives to Invest  
    in Protection . . . . . 384

        Example: An N-Person Prisoner’s Dilemma for Network  
        Maintenance . . . . . 385

        Example: Nash Equilibrium Can Be Inadequate for Predicting  
        Investments . . . . . 386

Example: A Network Collusion Game with an Empty Core ..... 387

Example: A Tipping Point ..... 388

Summary ..... 388

Epilogue ..... 389

**References** ..... 391

**Index** ..... 423



<http://www.springer.com/978-0-387-89013-5>

Risk Analysis of Complex and Uncertain Systems

Cox Jr., L.A.

2009, XXVIII, 436 p., Hardcover

ISBN: 978-0-387-89013-5