Contents

Part I Introduction to Risk Analysis

1 Quantitative Risk Assessment Goals and Challenges 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

2 Introduction to Engineering Risk Analysis 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

3 Introduction to Health Risk Analysis 73
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 × 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 5×5 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^{TM} 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® 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^{TM} Qualitative Risk Assessment 353
Limitations of RAMCAP^{TM} 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