Contents

List of Contributors *XI*
Preface *XIII*

1 Green Chemistry Metrics *1*
David J.C. Constable
1.1 Introduction and General Considerations *1*
1.2 Feedstocks *5*
1.3 Chemicals *6*
1.3.1 Hazard and Risk *6*
1.4 General Chemistry Considerations and Chemistry Metrics *10*
1.5 Evolution of Green Chemistry Metrics *11*
1.6 Andraos: Tree Analysis *14*
1.7 Process Metrics *15*
1.8 Product Metrics *16*
1.9 Sustainability and Green Chemistry *17*
1.10 Making Decisions *18*
References *19*

2 Expanding Rational Molecular Design beyond Pharma: Metrics to Guide Safer Chemical Design *29*
Nicholas D. Anastas, John Leazer, Michael A. Gonzalez, and Stephen C. DeVito
2.1 Introduction to Safer Chemical Design *29*
2.2 Life Cycle Thinking *30*
2.2.1 Sustainability, Green Chemistry, and Green Engineering *30*
2.2.2 Life Cycle Considerations *31*
2.2.3 Life Cycle Assessment *32*
2.2.4 Chemical Process Sustainability Evaluation – Metrics *34*
2.3 Attributes of Chemicals of Good Character *36*
2.4 Tools for Characterizing the Attributes of Chemicals of Good Character *37*
2.4.1 Strive to Reduce or Eliminate the Use of Chemicals *40*
2.4.2 Maximize Biological and Use Potency and Efficacy *40*

2.4.3 Strive for Economic Efficiency *40*
2.4.4 Limited Bioavailability *41*
2.4.5 Limited Environmental Mobility *41*
2.4.6 Design for Selective Reactivity: Toxicity *41*
2.4.7 Minimize the Incorporation of Known Hazardous Functional Groups: Toxicophores and Isosteres *42*
2.4.8 Minimize the Use of Toxic Solvents *42*
2.4.9 Limited Persistence and Bioaccumulation *43*
2.4.10 Quick Transformation to Innocuous Products *44*
2.4.11 Avoid Extremes of pH *44*
2.5 A Decision Framework *44*
2.5.1 A Suggested Protocol for Approaching Safer Chemical Design *45*
2.5.2 Alternatives and Chemical Risk Assessment *45*
2.6 The Road Ahead: Training of a Twenty-First Century Chemist *46*
References *46*

3 Key Metrics to Inform Chemical Synthesis Route Design *49*
John Andraos and Andrei Hent
3.1 Introduction *49*
3.2 Material Efficiency Analysis for Synthesis Plans *50*
3.3 Case Study I: Bortezomib *56*
3.3.1 Millennium Pharmaceuticals' Process *59*
3.3.2 Pharma-Sintez Process *62*
3.3.3 Material Efficiency – Local and Express *64*
3.3.4 Synthesis Strategy for Future Optimization *72*
3.3.5 Summary *73*
3.4 Case Study II: Aspirin *74*
3.4.1 Reaction Network *74*
3.4.2 Material Efficiency *76*
3.4.3 Environmental and Safety–Hazard Impact *78*
3.4.4 Input Energy *84*
3.4.5 Case I *84*
3.4.6 Case II *85*
3.4.7 Case III *85*
3.4.8 Case IV *85*
3.4.9 Case V *86*
3.4.10 Case VI *86*
3.4.11 Concluding Remarks and Outlook for Improvements *88*
References *91*

4 Life Cycle Assessment *95*
Concepción Jiménez-González
4.1 Introduction *95*
4.2 The Evolution of Life Cycle Assessment *96*
4.3 LCA Methodology at a Glance *97*

4.3.1 Goal and Scope *98*
4.3.2 Inventory Analysis *98*
4.3.3 Impact Assessment *99*
4.3.4 Interpretation *99*
4.3.5 LCI/A Limitations *100*
4.3.6 Critical Review *101*
4.3.7 Streamlined Life Cycle Assessment *102*
4.4 Measuring Greenness with LCI/A – Applications *103*
4.4.1 Probing Case Studies *103*
4.4.2 Chemical Route Comparison *106*
4.4.3 Material Assessment *109*
4.4.4 Product LCAs *112*
4.4.5 Footprinting *115*
4.5 Final Remarks *117*
References *118*

5 Sustainable Design of Batch Processes *125*
Tânia Pinto-Varela and Ana Isabel Carvalho
5.1 Introduction *125*
5.2 State of the Art *126*
5.2.1 Design and Retrofit of Batch Processes *127*
5.2.2 Sustainability Assessment *131*
5.3 Framework for Design and Retrofitting in Batch Processes *136*
5.3.1 Economic Assessment *138*
5.3.2 Environmental Assessment *139*
5.3.3 Social Assessment *140*
5.3.4 Methodologies *141*
5.4 Case Studies *142*
5.4.1 Retrofit Sustainable Batch Design *142*
5.4.2 Design of Batch Process *147*
5.5 Conclusions *150*
References *152*

6 Green Chemistry Metrics and Life Cycle Assessment for Microflow Continuous Processing *157*
Lihua Zhang, Qi Wang, and Volker Hessel
6.1 Introduction *157*
6.1.1 Green Chemistry and Green Engineering in the Pharmaceutical Industry *157*
6.1.2 Green Metrics and Life Cycle Assessment *158*
6.1.3 Continuous Processing at Small Scale *159*
6.2 Environmental Analysis through Green Chemistry Metrics and Life Cycle Assessment *162*
6.2.1 Green Chemistry Metrics *162*
6.2.2 Life Cycle Assessment (LCA) *163*

6.3 Application of Green Chemistry Metrics and Life Cycle Assessment to Assess Microflow Processing *163*
6.3.1 Use as Benchmarking Tool for Continuous versus Batch; at Lab and Production Scale *164*
6.3.2 Use as Decision Support Tool for Single Innovation Drivers – Choice of Type of Microreactor and Type of a Catalyst (Including Use/Not Use) *167*
6.3.2.1 Reaction Conditions of Batch Process and Continuous Microflow Process *167*
6.3.2.2 SLCA Results *168*
6.3.2.3 Economic Evaluation *170*
6.3.2.4 Conclusions *171*
6.3.3 Use as Decision Support Tool for Single Innovation Drivers – Solvent Choice and Role of Recycling *171*
6.3.4 Use as Decision Support Tool for Bundled Innovation Drivers Such as Multifacetted Process Optimization versus Process Intensification *174*
6.3.4.1 API Production Process at Sanofi *174*
6.3.4.2 Process Alternatives for Optimization and Intensification *174*
6.3.4.3 Ecological Profile Comparison of Crude Batch and Continuous Operation *175*
6.3.4.4 Cost Analysis of Batch and Continuous Operation *178*
6.3.4.5 Conclusions *179*
6.3.5 Cascading Reactions Into a Microreactor Flow Network – Greenness of Multistep Reaction/Separation Integration *179*
6.3.5.1 LCA Study for Single-Step Analyses in Batch and Flow *181*
6.3.5.2 LCA Study for "Two-Reactor Network" Process Designs *184*
6.3.5.3 LCA Study for "Three-Reaction Network" Process Designs *184*
6.3.6 Use as Process-Design Guidance and Benchmarking Tool Against Conventional Processes *186*
6.3.6.1 Process Simulation and CAPEX Cost Study *188*
6.3.6.2 LCA for Continuous Flow Synthesis of ADA *190*
6.3.6.3 LCA for Two-Step Conventional Synthesis of ADA *191*
6.3.6.4 Complete LCA Picture *191*
6.3.6.5 Green Metrics Compared for the Direct Microflow Route and Conventional Two-Step Route *192*
6.3.6.6 Conclusions *194*
6.4 Economic Analysis and Snapshot on Applications with Continuous Microflow Processing *195*
6.4.1 Life Cycle Costing (LCC) *195*
6.4.2 Snapshot on LCC Applications with Continuous Microflow Processing *196*
6.5 Conclusions and Outlook *199*
References *201*

7 Benchmarking the Sustainability of Biocatalytic Processes *207*
John M. Woodley
7.1 Introduction *207*
7.2 Biocatalytic Processes *207*
7.3 Biocatalytic Process Design and Development *210*
7.4 Sustainability of Biocatalytic Processes *210*
7.5 Quantitative Measuring of the Sustainability of Biocatalytic Processes *212*
7.6 Early Stage Sustainability Assessment *213*
7.6.1 Evaluation of Route Feasibility *214*
7.6.1.1 Atom Economy *214*
7.6.1.2 Carbon Mass Efficiency *214*
7.6.2 Evaluation of Biocatalyst and Reaction Development *215*
7.6.2.1 Process Mass Intensity *215*
7.6.2.2 Solvent Intensity *215*
7.6.2.3 Water Intensity *216*
7.6.2.4 E-factor *216*
7.7 Benchmarking *216*
7.7.1 Route Selection *216*
7.7.2 Biocatalyst and Reaction Development *217*
7.8 Examples *217*
7.8.1 Biocatalytic Route to Atorvastatin *218*
7.8.2 Biocatalytic Route to Sitagliptin *219*
7.9 Future Perspectives *221*
7.9.1 Process Development *221*
7.9.2 Methodology *223*
7.10 Concluding Remarks *224*
References *225*

8 How Chemical Hazard Assessment in Consumer Products Drives Green Chemistry *231*
Lauren Heine and Margaret H. Whittaker
8.1 Introduction *231*
8.2 What Drives Consumer Product Companies to Look for Less Hazardous Chemical Ingredients *232*
8.2.1 Chemical Substitution and Regrettable Substitution *233*
8.2.2 Nonprofit Organization (NPO) Campaigns *235*
8.2.3 Retailer Initiatives *237*
8.2.4 State Initiatives *240*
8.2.5 Consumer Product Sector Leaders: Setting the Example for Others *242*
8.3 What is Chemical Hazard Assessment? *243*
8.3.1 Globally Harmonized System of Classification and Labelling of Chemicals (GHS) *244*
8.3.2 Comprehensive and Abbreviated Forms of CHA *247*

8.3.2.1 GreenScreen for Safer Chemicals *248*
8.3.2.2 Quick Chemical Assessment Tool (QCAT) *252*
8.3.2.3 GreenScreen List Translator (GS LT) *253*
8.4 How Chemical Hazard Assessment is Used *255*
8.4.1 Chemical Footprint Project *255*
8.4.2 Health Product Declaration Version 2.0 (HPD) *259*
8.4.3 Red List – Declare Label *259*
8.4.4 United States Environmental Protection Agency: Safer Choice Program *260*
8.4.5 International Living Future Institute's Living Product Challenges *262*
8.4.6 Cradle to Cradle Certified Product Program *262*
8.4.7 Chemical Alternatives Assessment *263*
8.5 Case Studies Showing How CHA Leads to Safer Consumer Products *264*
8.5.1 Case Study 1. US EPA Safer Choice Product Certification *264*
8.5.2 Case Study 2. Levi Strauss & Co. Screened Chemistry *267*
8.5.3 Case Study 3. Development of an Alternative Food Can Liner *269*
8.6 Challenges: Beyond Chemical Hazard Assessment *271*
8.6.1 Transparency *271*
8.6.2 Filling Data Gaps for Existing and Emerging Hazards: Predictive Toxicology and Tox21 *272*
8.6.3 Integrating CHA into Green Product Design *272*
8.7 Conclusion *274*
References *275*

9 Tying it all together to drive Sustainability in the Chemistry Enterprise *281*
David J.C. Constable and Concepción Jiménez-González
9.1 New Areas of Sustainable and Green Chemistry Metrics Research *286*
References *290*

Index *291*