Biosafety in Industrial Biotechnology

Edited by

P. HAMBLETON, J. MELLING Centre for Applied Microbiology and Research Porton Down Wiltshire UK

and

T.T. SALUSBURY Science and Technology Section British Embassy Japan



BLACKIE ACADEMIC & PROFESSIONAL

An Imprint of Chapman & Hall

London · Glasgow · Weinheim · New York · Tokyo · Melbourne · Madras

Contents

.

1	The development of European legislation on genetically modified organisms A.J. TAYLOR	1
	1.1 Introduction	1
	1.2 The development of the EC directives1.3 The EC Directives on genetic modification	1 2
	1.3.1 Directive 90/219/EEC – Contained use of genetically-modified	
	micro-organisms 1.3.2 Directive 90/220/EEC – Deliberate release of genetically-modified	3
	organisms	5
	1.4 The situation in the twelve Member States (as of February 1993)	8
	1.4.1 United Kingdom 1.4.2 Federal Republic of Germany	8 8 9
	1.4.3 Netherlands	
	1.4.4 France 1.4.5 Denmark	10 10
	1.4.6 Belgium	11
	1.4.7 Remaining EC Member States	11
	 1.5 Situation in the EFTA nations (as of February 1993) 1.6 Europe vs. the USA 	11 12
	Disclaimer	13
	References	13
2	Occupational and environmental safety: the UK legislative	
	framework	14
	A.N. COTTAM	
	2.1 Introduction	14
	2.2 International influences	14
	2.2.1 The UK approach 2.3 Occupational health and safety legislation	15 16
	2.4 The Health and Safety at Work Act	18
	2.4.1 Duties of employers	18
	2.4.2 Duties of employees 2.4.3 Duty not to misuse	19 19
	2.4.4 Duties of manufacturers and suppliers	20
	2.4.5 Management systems	20
	2.5 The Environmental Protection Act 2.6 Specific regulations	21 21
	2.6.1 Control of Substances Hazardous to Health Regulations	21
	1988 (COSHH) 2.6.2 Genetically Modified Organisms (Contained Use) Regulations	21
	i is i separation of i in i is i in i	
	1992 and Genetically Modified Organisms (Contained Use)	
	1992 and Genetically Modified Organisms (Contained Use) Regulations 1993	22
	1992 and Genetically Modified Organisms (Contained Use)	22 23

	/ committees	24 25
2.7.1 Gu		25
	cal involvement	20 26
	n and enforcement ms of inspection	20
	wers of inspectors	27
	iforcement	28
2.9 The way		29
References		31
3 Regulation	of biotechnology in the United States, Canada,	
and Latin		32
		1
D.T. KIP	NGSBURY	
3.1 Introduc		32
3.2 The Unit		32
	deral regulatory structure	33 36
	ood and Drug Administration	30 43
	nvironmental Protection Agency	45 49
3.2.4 De 3.2.5 Ce	epartment of Agriculture	49 51
	ate regulatory bodies	51
3.3 Canada	are regulatory boules	52
	eterinary biologics	53
	enertically modified plants and micro-organisms	54
	nerica and the Caribbean	54
4 The legal	and regulatory framework for histechnology in	
	and regulatory framework for biotechnology in	57
Japan		57
		57
Japan T. SALU 4.1 An over	USBURY view of the Japanese biotechnology industry	57
Japan T. SALU 4.1 An over 4.2 Govern	USBURY view of the Japanese biotechnology industry ment attitudes to biotechnology	57 57
Japan T. SALU 4.1 An over 4.2 Governu 4.3 The gov	USBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology	57 57 58
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L	VSBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments	57 57 58 58
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M	VISBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments onbusho and STA Guidelines	57 57 58 58 58
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri	VISBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>conbusho</i> and STA Guidelines ial-scale applications of r-DNA technology	57 57 58 58 58 58 61
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 In	VSBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology idustrial uses of r-DNA technology	57 57 58 58 58
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L: 4.3.2 M 4.4 Industri 4.4.1 In 4.4.2 G	VSBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>conbusho</i> and STA Guidelines ial-scale applications of r-DNA technology dustrial uses of r-DNA technology dudance for the use of r-DNA technology in the pharmaceutical	57 57 58 58 58 61 61
Japan T. SALU 4.1 An over 4.2 Governu 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 In 4.4.2 G	VSBURY wiew of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>Jonbusho</i> and STA Guidelines ial-scale applications of r-DNA technology dustrial uses of r-DNA technology juidance for the use of r-DNA technology in the pharmaceutical fector	57 57 58 58 58 61 61
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 In 4.4.2 G sc 4.5 Agricul	VSBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ternment bodies involved in biotechnology aboratory-scale experiments <i>onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology dustrial uses of r-DNA technology industrial content use of r-DNA technology in the pharmaceutical cotor	57 57 58 58 58 61 61
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 Ir 4.4.2 G 5 4.5 Agricul 4.6 Foods a	VISBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology mutuatial uses of r-DNA technology isudance for the use of r-DNA technology in the pharmaceutical ector tural applications of r-DNA technology and food additives	57 57 58 58 58 61 61 61 62 63
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 Ir 4.4.2 G 5 4.5 Agricul 4.6 Foods a	VISBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>(onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology dustrial uses of r-DNA technology isudance for the use of r-DNA technology in the pharmaceutical ector tural applications of r-DNA technology and food additives rate release of genetically-modified micro-organisms	57 57 58 58 58 61 61 61 62 63 64
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 Ir 4.4.1 G 5 S 6 S 4.5 Agricul 4.6 Foods a 4.7 Deliber	VISBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>(onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology dustrial uses of r-DNA technology isudance for the use of r-DNA technology in the pharmaceutical ector tural applications of r-DNA technology and food additives rate release of genetically-modified micro-organisms	57 57 58 58 58 61 61 61 62 63 64 65
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 Ir 4.4.2 G 5 4.5 Agricul 4.6 Foods a 4.7 Deliber Acknowled References	view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology buidance for the use of r-DNA technology in the pharmaceutical ector tural applications of r-DNA technology and food additives rate release of genetically-modified micro-organisms gements	57 57 58 58 58 61 61 62 63 64 65 66
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 In 4.4.2 G 5 4.5 Agricul 4.6 Foods a 4.7 Deliber Acknowled References 5 Biotechno	VISBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology mustrial uses of r-DNA technology industrial uses of r-DNA technology in the pharmaceutical ector tural applications of r-DNA technology and food additives rate release of genetically-modified micro-organisms gements blogy and industrial microbiology regulations	57 57 58 58 58 61 61 61 62 63 64 65 66 66
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 In 4.4.2 G 4.5 Agricul 4.6 Foods a 4.7 Deliber Acknowled References 5 Biotechno in Russia	view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments <i>onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology buidance for the use of r-DNA technology in the pharmaceutical ector tural applications of r-DNA technology and food additives rate release of genetically-modified micro-organisms gements	57 57 58 58 58 61 61 62 63 64 65 66
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 In 4.4.2 G 4.5 Agricul 4.6 Foods a 4.7 Deliber Acknowled References 5 Biotechno in Russia	view of the Japanese biotechnology industry ment attitudes to biotechnology ternment bodies involved in biotechnology aboratory-scale experiments <i>onbusho</i> and STA Guidelines ial-scale applications of r-DNA technology buidance for the use of r-DNA technology industrial uses of r-DNA technology and food additives rate release of genetically-modified micro-organisms gements	57 57 58 58 58 61 61 61 62 63 64 65 66 66
Japan T. SALU 4.1 An over 4.2 Govern 4.3 The gov 4.3.1 L 4.3.2 M 4.4 Industri 4.4.1 Ir 4.4.2 G 5 4.5 Agricul 4.6 Foods a 4.7 Deliber Acknowled References 5 Biotechno in Russia A. RIMM 5.1 Introd	VISBURY view of the Japanese biotechnology industry ment attitudes to biotechnology ernment bodies involved in biotechnology aboratory-scale experiments onbusho and STA Guidelines ial-scale applications of r-DNA technology budance for the use of r-DNA technology in the pharmaceutical ector tural applications of r-DNA technology and food additives rate release of genetically-modified micro-organisms gements blogy and industrial microbiology regulations and the former Soviet republics MINGTON	57 57 58 58 58 61 61 61 62 63 64 65 66 66

CONTENTS

	5.2.1 History	68
	5.2.2 The current guidelines	70
	5.2.3 Regulatory authorities	74
	5.3 Regulations governing labour safety in biotechnology research	
	institutes and the microbiological industry	77
	5.3.1 Labour safety standards	77
	5.3.2 Rules governing the release of micro-organisms into the workplace	78
	5.3.3 Regulations governing the release of micro-organisms into the	70
	environment	79
	5.4 Adherence to regulations governing the containment and safe use of	19
		80
	micro-organisms	• -
	5.4.1 The environment	81
	5.4.2 Waste water	83 84
	5.4.3 Industrial personnel	
	5.5 Conclusions	86
	References	87
6	Physical aspects of the uncontrolled release of material in	
U		00
	biotechnology operations	90
	K.P. NORRIS	
	6.1 Introduction	90
	6.2 The generation of aerosols	92
	6.3 Persistence of aerosols in a closed space	95
	6.4 Persistence of aerosols in the atmosphere	98
	6.5 Retention, clearance and absorption in the respiratory tract	99
	6.6 The biological behaviour of airborne particles	100
	6.6.1 The stability of the organism	100
	6.6.2 Particle size	101
	6.6.3 Relative humidity and temperature	101
	6.6.4 Oxygen	102
	6.6.5 Sunlight	102
	6.6.6 Protecting agents	103
	6.7 Airborne allergens	103
	6.8 Conclusions	104
	References	105
	Kerences	105
7	Health hazards in biotechnology	109
-	A.M. BENNETT	
	A.M. DEMMETT	
	7.1 Introduction	109
	7.2 Health hazards	110
	7.2.1 Laboratory-associated infection	111
	7.2.2 Allergic reactions	112
	7.2.3 Endotoxin reactions	116
	7.2.4 Toxic reactions to products or by-products	118
	7.2.5 Hazards posed by genetic modification	119
	7.2.6 Hazards posed by animal cell culture	120
	7.2.7 Hazards posed by plant cell culture	121
	7.3 Hazards of bioprocessing equipment	122
	7.3.1 Fermentation	122
	7.3.2 Centrifugation	122
	7.3.3 Cell disruption	122
	7.3.4 Filtration	123
	7.3.5 Product handling	123
	7.3.6 Risk assessment	123
	7.3.7 Prevention	124

	Acknowledgements References	124 125
8	Containment of unit processes P. HAMBLETON and J. MELLING	129
	8.1 Introduction	129
	8.2 Unit processes in biotechnology	130 131
	8.3 Categories of containment8.4 Safety cabinets	131
	8.4.1 Classification	132
	8.4.2 Air filtration	134
	8.4.3 Class I cabinets	135 136
	8.4.4 Class II cabinets 8.4.5 Class III cabinets	130
	8.4.6 Laminar flow work stations	137
	8.4.7 Application of Class III cabinets to process containment	137
	8.4.8 Fermentation	137
	8.4.9 Other processes	139 143
	8.4.10 Flexible film isolators 8.5 Design engineering for secondary containment	143
	8.5.1 Fermentation	144
	8.5.2 Other processes	145
	8.6 The cost of containment	146
	8.7 Conclusions	146 147
	References	147
9	Containment in downstream processing J.S. DEANS and I.W. STEWART	149
	9.1 Introduction	149
	9.2 Regulations and guidelines	151
	9.3 Cell separation	152
	9.3.1 Filtration	152 154
	9.3.2 Centrifugation 9.4 Cell disruption	166
	9.4.1 Physical methods	166
	9.4.2 Non-physical techniques	172
	9.5 Fluid handling	173
	9.6 Discussion and conclusions 9.7 Recommendations	174 175
	References	175
10		150
10	Freeze-drying of biohazardous products G.D.J. ADAMS	178
	G.D.J. ADAMS	
	10.1 Introduction	178
	10.2 Principles of the freeze-drying process	178
	10.2.1 Product preparation 10.2.2 Prefreezing	178
	10.2.2 Primary drying	179 179
	10.2.4 Secondary drying	179
	10.2.5 Stoppering and removal	180
	10.2.6 Storage and reconstitution	180
	10.2.7 Technical features of the freeze-drier	180

10.3 Risk assessment	181
10.3.1 Potential hazards	181
10.3.2 Processing biohazardous materials	181
10.3.3 Liquid and particulate aerosols	182
10.4 Hazards associated with product dispensing and handling finished	
materials	183
10.4.1 Dispensing pumps	183
10.4.2 Dispensing needles	183
10.4.3 Filling reservoirs	184
10.4.4 Tray dispensing	184
10.4.5 Ampoules	184
10.4.6 Vials	185
10.4.7 Container breakage	185
10.4.8 Spillages	185
10.4.9 Stoppering	186
10.4.10 Product removal	186
10.4.11 Container sealing	186
10.4.12 Product storage	186
10.4.13 Container leakage during storage	187
10.4.14 Leak testing of sealed vials and ampoules	187
10.4.15 Reconstitution	188
10.5 Formulation	188
10.5.1 General concepts	188
10.5.2 Prefreezing	189
10.5.3 Freeze-drying	189
10.5.4 Freeze-drying excipients	189
10.5.5 Container breakage and miscellaneous consequences of product	
freezing	190
10.5.6 Storage	190
10.5.7 Comparison of protection during aerosolation or freeze-drying	191
10.6 Ablation	191
10.6.1 Loss of contents	191
10.6.2 Influence of product formulation on ablation	191
10.6.3 Ablation and spillage	192
10.6.4 Ablation and back-migration of vacuum pump oil	192
10.7 Practical aspects of the design and operation of freeze-driers and	
associated equipment	192
10.7.1 Freeze-drier design	193
10.7.2 Freeze-drier fabrication	194
10.7.3 Chamber/condenser geometry	194
10.7.4 Protective devices	195
10.7.5 Electrostatic precipitation and ultraviolet irradiators	195
10.7.6 Incineration	195
10.7.7 Filtration	196
10.7.8 Selection and position of filters	196
10.7.9 Decontamination of the interior of the freeze-drier	199
10.7.10 Biocides and sanitising agents	199
10.7.11 Sterilisation by gaseous biocides	200
10.7.12 Dry heat	204
10.7.13 Atmospheric pressure steam (live steam)	204
10.7.14 Pressurised steam	204
10.7.15 Integrated approach to safe freeze-drying of biohazardous materials	206
10.7.16 Factors affecting operational safety	206
10.7.17 Dispensing product	207
10.8 Conclusions	207
Acknowledgement	209
References	209

11	Interpretation of regulatory requirements to large scale biosafety – the role of the Industrial Biosafety Project G. LEAVER	213
	11.1 Introduction	213 213
	11.2 Regulatory issues 11.3 Risk assessment	213
	11.4 Human health and safety	215
	11.4.1 Estimation of GMO hazard	215
	11.4.2 Elaboration of containment principles	217
	11.4.3 Equipment containment design principles	218
	11.4.4 Measuring and monitoring containment	228 232
	11.4.5 Maintenance and training 11.5 Environmental safety	232
	11.5 Environmental safety	235
	Acknowledgements	236
	References	236
12	Managing the effluent from bio-industrial processes J.R. COURT	240
		240
	12.1 Introduction	240 241
	12.2 Regulatory background 12.3 Assessment of risk and appropriate action	241
	12.4 Categories of waste	242
	12.5 Liquid effluent	242
	12.6 Choice of treatment method	244
	12.7 Containment considerations	244
	12.7.1 Multiplicity of containment devices	245 246
	12.7.2 'Dead legs' and crevice avoidance 12.7.3 Leak testing	240
	12.7.4 Standard operating procedure (SOPs) and process records	247
	12.7.5 Planned preventative maintenance (PPM) schedule	248
	12.7.6 Commissioning and validation	248
	12.8 Practical treatment methods	248
	12.8.1 Filtration	248 249
	12.8.2 Disinfection using chemical agents	249 250
	12.8.3 Heat treatment using steam 12.9 Testing effluent for sterility	250
	12.10 Design and qualification of a heat treatment effluent plant	252
	12.10.1 Design considerations	252
	12.10.2 Qualification of effluent treatment plant	256
	12.11 The approach to effluent at CAMR References	257 266
13	Sampling methods for testing and monitoring biosafety of	
	biotechnology equipment and activities	268
	J.E. BENBOUGH	
	13.1 Introduction	268
	13.2 Sampling microbial aerosols	269
	13.3 Sampling methods	270
	13.4 Air sampling devices 13.4.1 Inertial collectors	272 273
	13.4.2 Air centrifuges	280

284
286
286
286
288
291

Index

293