

## Contents

### Preface *XIII*

<b>1</b>	<b>Chemicals and Society</b>	<b>1</b>
1.1	Basic Problems	1
1.2	Definition of the Sciences Involved	4
1.3	Trends and Developments over the Years	5
1.4	Legislation	7
1.5	Knowledge about Chemical Hazards	9
1.6	Acceptable Chemical Risks	11
<b>2</b>	<b>The Chemicals of Life and Nature</b>	<b>13</b>
2.1	The Cell	14
2.1.1	Human Cell Types	14
2.1.2	The Basic Components and Functions of a Cell	15
2.2	Chemicals	17
2.2.1	Endogenous vs Exogenous Chemicals	21
2.2.2	Natural vs Synthetic Compounds	22
2.3	Biochemicals	24
2.3.1	Water	24
2.3.2	Carbohydrates	24
2.3.3	Fatty Acids	26
2.3.4	Terpenoids	27
2.3.5	Amino Acids	29
2.3.6	Nucleosides	31
2.4	Biomacromolecules and Cellular Constituents	31
2.4.1	Cell Membranes	31
2.4.2	Proteins	34
2.4.3	Nucleic Acids	35
2.5	Basic Environmental Chemistry	37
2.5.1	The Atmosphere	38
2.5.2	The Hydrosphere	39

2.5.3	The Lithosphere and the Pedosphere	40
2.5.4	The Turnover of Chemicals in and between the Spheres	41
<b>3</b>	<b>Chemical Properties</b>	<b>43</b>
3.1	Critical Chemical Properties	43
3.1.1	Volatility	43
3.1.2	Solubility	47
3.1.3	Adsorption and Absorption	50
3.1.4	Persistence	51
3.1.5	Reactivity	51
3.1.5.1	Explosives	52
3.1.5.2	Acids and Bases	52
3.1.5.3	Reducing and Oxidizing Agents	52
3.1.5.4	Excited Molecules	53
3.1.5.5	Electrophilic Compounds	53
3.1.5.6	Radicals	54
3.1.5.7	Noncovalent Binding	54
3.2	Reactions between Nucleophiles and Electrophiles	55
3.2.1	Nucleophilic Substitutions	55
3.2.2	Nucleophilic Additions	57
3.2.3	The Electrophile	58
3.2.3.1	Strained Cyclic Hydrocarbons and Heterocycles	59
3.2.3.2	Weak Single Bonds between an $sp^3$ Carbon and a Leaving Group	60
3.2.3.3	Polarized Double or Triple Bonds	62
3.2.4	The Nucleophile	64
3.3	Radical Reactions	65
3.4	Factors Modulating Reactivity	65
3.4.1	Electronic Effects	66
3.4.2	Steric Factors	69
3.4.3	Transformations and Conversions that Increase Reactivity	70
<b>4</b>	<b>Uptake, Distribution, and Elimination of Chemicals</b>	<b>71</b>
4.1	Transport through Biological Membranes	71
4.1.1	Diffusion	71
4.1.2	Passive Transport by Proteins	73
4.1.3	Active Transport by Proteins	75
4.1.4	Exocytosis and Endocytosis	76
4.2	Absorption of Chemicals in Man	77
4.2.1	Absorption via the Skin	77
4.2.2	Uptake by the Gastrointestinal Tract	79
4.2.3	Uptake via the Lungs	83
4.2.3.1	Air Contaminants in the Form of Aerosols	84
4.2.3.2	Air Contaminants in the Form of Gases and Vapors	86
4.3	Bioaccumulation	86
4.4	Distribution of Chemicals in Organisms	87

4.4.1	Chemical Properties	87
4.4.2	Biological Barriers	89
4.4.3	Uptake as a Function of Distribution	89
4.5	Excretion of Chemicals from Man	92
4.5.1	Excretion via the Lungs	92
4.5.2	Excretion via the Liver	93
4.5.3	Excretion via the Kidneys	94
<b>5</b>	<b>Metabolism of Exogenous Compounds in Mammals</b>	<b>97</b>
5.1	Overview	98
5.2	Enzymatic Systems Involved in Oxidations	100
5.2.1	Primary and Secondary Metabolism	100
5.2.2	Cytochrome P450	101
5.2.3	Generation of Reactive Oxygen Species	104
5.2.4	Other Oxidative Enzymes	107
5.3	Phase I Conversions	109
5.3.1	Oxidations	110
5.3.1.1	Epoxidations of Carbon–Carbon Multiple Bonds	110
5.3.1.2	Hydroxylations of Saturated Carbon	112
5.3.1.3	Hydroxylation of Amino Groups	116
5.3.1.4	Oxidation of a Single Bond to a Double Bond	116
5.3.1.5	Oxidation of Heteroatoms	117
5.3.1.6	Oxidation of Alcohols and Aldehydes	118
5.3.2	Reductions	118
5.3.3	Hydrolyses	120
5.3.3.1	Hydrolysis of Epoxides	120
5.3.3.2	Hydrolysis of Esters and Amides	123
5.4	Phase II Conversions (Conjugations)	124
5.4.1	Conjugations with Sulfate	124
5.4.2	Conjugations with Glucuronic Acid	125
5.4.3	Conjugations with Amino Acids	127
5.4.4	Conjugations with Glutathione	128
5.4.5	Other Conjugations	132
5.5	Summary of the Major Phase I and Phase II Reactions	133
5.6	Metabolism of Exogenous Compounds in Mammals	134
5.6.1	Metabolism of Hydrocarbons	134
5.6.2	Metabolism of Compounds Containing Nitrogen	140
5.6.3	Metabolism of Compounds Containing Halogen	147
5.6.4	Metabolism of Compounds Containing Sulfur	150
<b>6</b>	<b>Conversions and Transformations in the Environment</b>	<b>153</b>
6.1	Enzymatic Conversions	153
6.1.1	Biodegradation of Saturated Hydrocarbons	155
6.1.2	Biodegradation of Benzene	157
6.1.3	Biodegradation of Alkylbenzenes	157

6.1.4	Biodegradation of Fused-Ring Aromatic Compounds	157
6.1.5	Biodegradation of Halogenated Aromatic Compounds	160
6.2	Chemical Transformations	161
6.2.1	Oxidations	162
6.2.2	Hydrolyses	163
6.2.3	Substitutions, Eliminations, and Additions	166
6.3	Transformations Induced by Radiation	168
6.3.1	Photolysis	168
6.3.2	Isomerization/Rearrangement	170
6.3.3	Additions/Eliminations	170
6.3.4	Photoionization	171
6.3.5	Electron Transfer	171
6.3.6	Sensitization	171
<b>7</b>	<b>Toxic Effects of Chemicals</b>	<b>175</b>
7.1	Toxicological Concepts	175
7.1.1	The Toxicity of Different Chemicals	176
7.1.2	Toxicological Concepts	178
7.1.2.1	Acute and Chronic Effects	178
7.1.2.2	Reversible and Irreversible Effects	178
7.1.2.3	Local and Systemic Effects—Target Organs	179
7.1.2.4	Independent, Additive, Synergistic, and Antagonistic Effects	179
7.1.2.5	Tolerance	180
7.1.3	Factors Modulating Toxicity	180
7.1.3.1	The Purity and Physical State of the Toxicant	180
7.1.3.2	The Exposure	181
7.1.3.3	The Victim	183
7.1.4	Acute Toxicity	185
7.1.4.1	Measures for Acute Toxicity	185
7.1.4.2	Specific and Nonspecific Toxicity	186
7.1.4.3	Selective and Nonselective Toxicity	188
7.1.5	Interpretation of Results from Toxicological Testing	189
7.2	General Toxic Effects	191
7.2.1	Nonspecific Effects of Lipophilic and Amphipathic Compounds	191
7.2.2	Lipid Peroxidation	191
7.2.3	Acidosis	196
7.2.4	Oxygen Deficiency Due to Effects on the Blood	200
7.2.4.1	Carbon Monoxide	200
7.2.4.2	Methemoglobinemia	203
7.2.5	ATP Deficiency Due to Inhibition of the Primary Metabolism	204
7.2.5.1	Inhibition of the Citric Acid Cycle	205
7.2.5.2	Inhibition of the Respiratory Chain	206
7.2.5.3	Uncoupling of the Oxidative Phosphorylation	208
7.3	Specific Toxic Effects to Organs (or Equivalents)	209
7.3.1	Effects on the Blood	209

7.3.2	Effects on the Nervous System	209
7.3.3	Effects on the Liver	214
7.3.4	Effects on the Kidneys	215
7.3.5	Effects on the Respiratory System	216
7.3.6	Effects on the Skin	217
7.4	Chemical Allergens	218
7.4.1	Immediate Hypersensitivity	221
7.4.2	Delayed-Type Hypersensitivity	223
7.5	Chemical Teratogenicity	223
7.6	Endocrine Disruptors	227
<b>8</b>	<b>The Molecular Basis for Genotoxicity and Carcinogenicity</b>	<b>233</b>
8.1	Chromosomes, Genes, and Mutations	233
8.2	DNA as a Molecular Target	236
8.3	Chemical Effects on DNA and DNA-Handling Systems	237
8.3.1	Modification of the DNA Bases	237
8.3.2	Intercalation	240
8.3.3	Loss of Modified Bases	241
8.3.4	Modification of other Macromolecules	241
8.4	Different Types of Mutations	243
8.4.1	Point Mutations	243
8.4.1.1	Base-Pair Substitution Mutations	243
8.4.1.2	Frame Shift Mutations	243
8.4.2	Chromosome Aberrations	244
8.5	Chemical Mutagenesis	245
8.6	Effects of Mutations	248
8.6.1	Effects of Mutations in Germ Cells	249
8.6.2	Effects of Mutations in Embryo Cells	249
8.6.3	Effects of Mutations in Somatic Cells	249
8.6.4	Which Mutation is the Most Serious?	250
8.7	Chemical Carcinogenesis	250
8.7.1	Reactive or Pre-reactive Chemical Carcinogens that Act on DNA	251
8.7.1.1	Electrophiles	252
8.7.1.2	Radicals or Reactive Products Formed after Radical Reactions	252
8.7.1.3	Metal Ions	252
8.7.2	Chemical Carcinogens Affecting DNA by Indirect Mechanisms	252
8.7.2.1	Chemicals Acting on the Components of DNA Metabolism	253
8.7.2.2	Alteration of Gene Expression	253
8.7.2.3	Mitogenic Chemicals	253
8.7.2.4	Cocarcinogens and Promoters	254
8.7.2.5	Immunosuppressive Agents	255
8.7.2.6	Hormones	256
8.8	Oncogenes, Proto-oncogenes and Anti-oncogenes	256
8.9	Techniques to Establish Carcinogenicity	259
8.9.1	Epidemiological Investigations	260

8.9.2	Animal Experiments	262
8.9.3	Assays with Mammalian Cells	262
8.9.4	Assays with Bacteria	263
<b>9</b>	<b>Hazardous Chemicals</b>	<b>265</b>
9.1	Fuels, Exhausts, and Other Air Pollutants	266
9.1.1	Biogas	267
9.1.2	Natural Gas	267
9.1.3	Petrol	268
9.1.4	Diesel	268
9.1.5	Oil and Coal	269
9.1.6	Ethanol	269
9.1.7	Polycyclic Aromatic Hydrocarbons	270
9.1.8	Carbon Dioxide	272
9.1.9	Methane	273
9.1.10	Ozone	274
9.1.11	Nitrogen and Sulfur Oxides	275
9.1.12	Summary	275
9.2	Pesticides and Chemical Warfare Agents	275
9.2.1	Naphthalene (in Mothballs)	276
9.2.2	DDT	277
9.2.3	Aldrin and Dieldrin	280
9.2.4	Hexachlorobenzene	281
9.2.5	1,2-Dibromoethane and 1,2-Dichloroethane	282
9.2.6	The Phenoxy Acids	283
9.2.7	Tributyltin Oxide	285
9.2.8	Carbaryl	286
9.2.9	Glyphosate	287
9.2.10	Dinoseb	288
9.2.11	Chemical Warfare Agents Containing Sulfur	289
9.2.12	Chemical Warfare Agents Containing Phosphorus	291
9.2.13	Summary	293
9.3	Food, Pharmaceuticals, and Natural Products	293
9.3.1	Safrole, Myristicin, Elemicin and Estragole	294
9.3.2	Nitrite	294
9.3.3	Polycyclic Aromatic Hydrocarbons and Heterocyclic Aromatic Compounds	297
9.3.4	Food Colorants	298
9.3.5	Penicillin	300
9.3.6	Acetaminophen	301
9.3.7	Thalidomide	303
9.3.8	Chemotherapy	305
9.3.9	The Botulinum Toxins	307
9.3.10	The Tetanus Toxins	308

9.3.11	Aflatoxins	309
9.3.12	The Ergot Alkaloids	310
9.3.13	Muscarine	311
9.3.14	Summary	312
9.4	Polymers, Adhesives, and Other Materials	313
9.4.1	Vinyl Chloride	313
9.4.2	Acrylamide	314
9.4.3	Dialkyl Phthalates	316
9.4.4	Brominated Flame Retardants	317
9.4.5	Cyanoacrylates (Superglue)	319
9.4.6	Asbestos	320
9.4.7	Dental Amalgam	321
9.4.8	Concrete Containing Radon	322
9.4.9	Summary	324
9.5	Legal and Illegal Chemical Pleasures	324
9.5.1	Caffeine	324
9.5.2	Tobacco Smoke	326
9.5.3	Ethanol	328
9.5.4	Amphetamines and Ecstasy	330
9.5.5	Cannabis	332
9.5.6	GHB	333
9.5.7	LSD	333
9.5.8	Opium, Morphine, and Heroin	334
9.5.9	Summary	335
<b>10</b>	<b>Environmental Effects of Chemicals</b>	<b>337</b>
10.1	Natural Emission of Chemicals	337
10.1.1	Inorganic Chemicals	337
10.1.2	Organic Chemicals	338
10.1.2.1	Hydrocarbons	339
10.1.2.2	Sulfur Compounds	339
10.1.2.3	Halogenated Compounds	340
10.2	Smog and other Air Pollution	340
10.2.1	Degradation of Trace Gases in the Troposphere	341
10.2.2	Photochemical Oxidants	341
10.3	Acid Pollution	343
10.4	Depletion of Stratospheric Ozone	345
10.5	Greenhouse Effect	348
10.6	Pollution by Halogenated Hydrocarbons	352
10.6.1	Dioxins	352
10.6.2	PCB	354
10.7	Pollution by Metals	355
10.7.1	Arsenic (As)	356
10.7.2	Cadmium (Cd)	357

**XII** | *Contents*

10.7.3 Chromium (Cr) 358

10.7.4 Copper (Cu) 359

10.7.5 Lead (Pb) 360

10.7.6 Mercury (Hg) 361

10.7.7 Tin (Sn) 362

**Glossary** 365

**Index** 389