

Contents

<i>Preface</i>	xx
<i>Acknowledgments</i>	xxiii
<i>List of Contributors</i>	xxv
1 Introduction	1
<i>Saura C. Sahu</i>	
References	2
2 Environment, Epigenetics, and Diseases	5
<i>Robert Y.S. Cheng and Wan-ye Tang</i>	
2.1 Perceptions of epigenetics	5
2.1.1 Definition of epigenetics	5
2.1.2 DNA methylation	6
2.1.3 Histone modifications and chromatin remodeling	6
2.1.4 Non-coding RNAs	6
2.1.5 Lifetime epigenetics changes	6
2.1.6 Transgenerational inheritance of the epigenome	7
2.1.7 Epigenetic reprogramming and inter-individual variations in human disease risk	7
2.2 Environmental epigenetics and human diseases	8
2.2.1 Chromium (Cr)	9
2.2.2 Cadmium (Cd)	9
2.2.3 Arsenic (As)	10
2.2.4 Nickel (Ni)	10
2.2.5 Lead (Pb)	11
2.2.6 Mercury (Hg)	11
2.2.7 Diethylstilbestrol (DES)	12
2.2.8 Bisphenol A (BPA)	12
2.2.9 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	13
2.2.10 Phthalate ester	13
2.2.11 Polychlorinated biphenyls (PCBs)	14
2.2.12 Disinfection by-products (DBPs)	14
2.2.13 Polycyclic aromatic hydrocarbons (PAHs)	14
2.2.14 Diet or living style	15
2.3 Implications of environmental epigenetics and future prospects	16
2.4 Key questions to be answered	17
Acknowledgments	17
References	17

3	DNA Methylation and Toxicogenomics	25
	<i>Deepti Deobagkar</i>	
3.1	Introduction	25
3.2	Toxicology	26
3.3	Toxicogenomics	27
3.4	Epigenetics	29
3.5	DNA methylation	30
3.6	DNA methyltransferases	34
3.6.1	Techniques of methylation detection	34
3.7	DNA methylation is altered upon exposure to chemicals and toxins	35
3.7.1	Drugs	35
3.7.2	Air pollution	36
3.7.3	Benzene	36
3.7.4	Endocrine-disrupting chemicals and reproductive toxicants	37
3.7.5	Methylmercury	37
3.7.6	Trichloroethylene (TCE), dichloroacetic acid (DCA) and trichloroacetic acid (TCA) and persistent organics pollutants (POP)	38
3.7.7	Metals	38
3.8	Toxicogenomics and epigenetics	40
3.9	Hydroxymethyl cytosine and toxicogenomics	42
3.10	MicroRNAs	42
3.11	DNA methylation in cancer	42
3.12	Bioinformatics approach	44
3.13	Summary	45
	Acknowledgments	46
	References	46
4	Chromatin at the Intersection of Disease and Therapy	51
	<i>Delphine Quénet, Marcin Walkiewicz, and Yamini Dalal</i>	
4.1	Epigenetic marks on chromatin: a complex pathway with high flexibility	51
4.1.1	DNA methylation	52
4.1.2	Post-translational modifications of histones	54
4.1.3	Interconnection between DNA methylation and post-translational modifications of histones	54
4.1.4	Epigenetic modifications and therapeutic strategy	55
4.2	Epigenetic approaches to treatment of cancer	55
4.2.1	HDAC inhibitors	57
4.2.2	DNMT inhibitors	59
4.2.3	Off-target epigenetic effects of commonly used therapeutics	59
4.3	Epigenetic modifications and potential therapy in other diseases	60
4.3.1	Metabolic memory: cause of epigenetic modifications and diabetes	61
4.3.2	Neurodegenerative syndromes and epigenetic modifications	63
4.4	Conclusion	66
	References	66

5	Molecular Epigenetic Changes Caused by Environmental Pollutants	73
	<i>Solange S. Lewis, Gregory J. Weber, Jennifer L. Freeman, and Maria S. Sepúlveda</i>	
5.1	Introduction	73
5.2	Mechanisms of molecular epigenetic changes	74
5.2.1	DNA methylation	75
5.2.2	Histone modifications	75
5.2.3	Small non-coding RNAs	76
5.3	Epigenetic assays	76
5.3.1	DNA methylation assays	76
5.3.2	Histone modification assays	77
5.3.3	Detection of microRNAs	78
5.4	Epigenetic changes induced by organic chemicals	78
5.4.1	Bisphenol A (BPA)	78
5.4.2	Dichlorodiphenyltrichloroethane (DDT)	83
5.4.3	Dioxin (TCDD or 2,3,7,8-tetrachlorodibenzo-p-dioxin)	84
5.4.4	17 α -ethinylestradiol (EE2)	85
5.4.5	Hexabromocyclododecane (HBCD)	85
5.4.6	Methoxychlor	86
5.4.7	Mixture of polychlorinated biphenyls, methyl mercury, and organochlorine pesticides	87
5.4.8	Polybrominated diphenyl ethers (PBDEs)	88
5.4.9	Phthalate (di-2-ethylhexyl phthalate or DEHP)	88
5.4.10	Vinclozolin	88
5.5	Epigenetic changes induced by metals	90
5.5.1	Cadmium	90
5.5.2	Chromium	98
5.5.3	Lead	99
5.5.4	Methyl mercury	99
5.5.5	Nickel	100
5.5.6	Heavy metal mixtures – tungsten alloy and its components	101
5.5.7	Zinc	101
5.6	Concluding remarks	101
	References	102
6	Epigenetic Mediation of Environmental Exposures to Polycyclic Aromatic Hydrocarbons	111
	<i>Bekim Sadikovic and David I. Rodenhiser</i>	
6.1	Introduction	111
6.2	Epigenetic modifications: DNA methylation	112
6.3	DNA methylation and cancer	113
6.4	Epigenetic histone modifications	114
6.5	Benzo(a)pyrene – a prototype PAH and environmental carcinogen	115
6.6	Molecular mechanisms of benzopyrene carcinogenicity: geno- and epigeno-toxicity	115
6.7	Epigenetic effects of multiple/synergistic carcinogen exposures	120
6.8	Summary and future considerations	122
	Acknowledgments	123
	References	123

7	Epigenomic Actions of Environmental Arsenicals	129
	<i>Paul L. Severson and Bernard W. Futscher</i>	
7.1	Introduction	129
7.2	Arsenicals in relation to human health	130
7.3	Arsenical mechanisms of action	131
7.3.1	Protein binding	131
7.3.2	Reactive oxygen species (ROS)	132
7.3.3	DNA damage	132
7.3.4	Epigenetic remodeling	132
7.4	Models to study arsenical action	133
7.5	Models used to study epigenetic action	134
7.6	Epigenetic effects of arsenicals	135
7.7	Perspectives	140
7.7.1	Mitochondrial function	140
7.7.2	Reactive oxygen species	140
7.7.3	SAM availability	141
7.7.4	Application	141
	References	141
8	Arsenic-Induced Changes to the Epigenome	149
	<i>Kathryn A. Bailey and Rebecca C. Fry</i>	
8.1	Introduction	149
8.2	Arsenic exposure and DNA methylation	152
8.2.1	Biological significance of DNA methylation	152
8.2.2	DNA methylation mechanisms	153
8.2.3	DNA methylation alterations in cancer	153
8.3	DNA methylation changes associated with arsenic exposure	154
8.3.1	Mechanistic studies: effects of arsenic exposure and metabolism on cofactor availability	154
8.3.2	Mechanistic studies: DNMT inhibition	158
8.3.3	Arsenic-associated alterations in global DNA methylation	159
8.3.4	Arsenic-associated alterations in focal DNA methylation	160
8.3.5	Alterations in DNA methylation patterns associated with arsenic exposure <i>in utero</i>	163
8.4	Histone modifications associated with arsenic exposure	173
8.4.1	Biological significance and mechanisms of histone modification	173
8.4.2	Histone modifications associated with cancer	174
8.4.3	Modifications in histone acetylation, methylation, and phosphorylation associated with arsenic exposure	174
8.5	MicroRNA (miRNA) alterations associated with arsenic exposure	180
8.6	Conclusions and future directions	182
	Acknowledgments	183
	References	183
9	Environmental Epigenetics, Asthma, and Allergy: Our Environment's Molecular Footprints	191
	<i>Stephanie Lovinsky-Desir and Rachel L. Miller</i>	

9.1	Introduction	191
9.2	Asthma environmental toxicants associated with epigenetic regulation	193
9.2.1	Dietary folic acid	193
9.2.2	Environmental tobacco smoke	195
9.2.3	Particulate matter	196
9.2.4	Diesel exhaust particles	196
9.2.5	Polycyclic aromatic hydrocarbons	197
9.3	Epigenetic changes and asthma phenotype	197
9.3.1	Molecular phenotypes	197
9.3.2	Clinical phenotypes	199
9.4	'Pharmacoeugenetics'	200
9.5	Conclusion	200
	References	201
10	miRNAs in Human Prostate Cancer	205
	<i>Ernest K. Amankwah and Jong Y. Park</i>	
10.1	Introduction	205
10.2	Biogenesis, function, and target of miRNA	206
10.3	miRNA and human cancer	208
10.4	miRNAs as oncogenes and tumor suppressors	209
10.5	Expression profile of miRNA in prostate cancer	210
10.6	miRNA as therapeutic targets for prostate cancer	213
10.7	Conclusion and future directions	213
	References	213
11	Environment, Epigenetics, and Cardiovascular Health	219
	<i>Sanjukta Ghosh and Andrea Baccarelli</i>	
11.1	Introduction	219
11.2	Epidemiological evidence of environmental factors affecting cardiovascular health	220
11.2.1	PM, ozone, and ambient air pollution	220
11.2.2	Tobacco smoke	221
11.2.3	Metallic contaminants and industrial environment	221
11.2.4	Metallic contaminants in soil and water – lead, arsenic, and cadmium	221
11.2.5	Organic chemicals	221
11.2.6	Social and emotional	222
11.3	Cause and effect relation between environmental exposure and cardiovascular diseases	222
11.3.1	Inflammation and oxidative stress relate toxic exposure to atherosclerosis and CVD: cellular and molecular candidates of toxicogenomic effect	222
11.3.2	Epigenetic regulation of DNA and chromatin in atherosclerosis and vascular dysfunction	224
11.3.3	MicroRNA mediated epigenetic regulation of cardiovascular diseases	228

11.4	Cardiovascular epigenetic signatures as risk factors and biomarkers for environmental exposure	232
11.5	Conclusion	233
	References	233
12	Toxicology, Epigenetics, and Autoimmunity	241
	<i>Craig A. Cooney and Kathleen M. Gilbert</i>	
12.1	Introduction	241
12.2	Drugs and toxicants in epigenetics	243
12.2.1	Inhibitors of the enzymes of epigenetic regulation	243
12.2.2	Cell signaling and epigenetics	244
12.3	Metabolic requirements for epigenetics	244
12.4	Autoimmunity and epigenetics	245
12.4.1	Drugs, epigenetics, and SLE	246
12.4.2	Environmental pollutants and autoimmunity	248
12.4.3	The age of toxicant exposure affects outcome	249
12.4.4	Environmental immunotoxicants and epigenetic alterations	249
12.4.5	Exogenous and endogenous retroviruses in autoimmunity	250
12.5	Conclusion	251
	References	252
13	Toxicoepigenomics in Lupus	261
	<i>Donna Ray and Bruce C. Richardson</i>	
13.1	Introduction	261
13.2	Etiology of lupus	262
13.2.1	Genetic and environmental contributions are required	262
13.2.2	Aging and lupus	262
13.3	Epigenetics and lupus	264
13.3.1	Epigenetics, chromatin structure, and gene expression	264
13.3.2	DNA methylation	264
13.3.3	T cells, DNA methylation, and lupus	265
13.4	Environmental contributions to lupus	267
13.4.1	Drugs	268
13.4.2	UV light, silica, infections, and oxidative stress	268
13.4.3	Diet	269
13.5	Summary	270
	References	270
14	Ocular Epigenomics: Potential Sites of Environmental Impact in Development and Disease	275
	<i>Kenneth P. Mitton</i>	
14.1	Introduction	275
14.2	Gene expression in ocular development	277
14.3	Epigenetic regulation in ocular development	280
14.3.1	DNA-methylation and histone-acetylation crosstalk	280
14.3.2	Epigenetic regulation in retinal development	281

14.3.3	Epigenetic regulation in lens development	283
14.4	DNA-methylation changes in ocular disease	283
14.4.1	Vision and toxicology of UV and blue light	283
14.4.2	Cancer: uveal melanoma	285
14.4.3	Pterygia	286
14.5	Inherited and age-related diseases of the eye	286
14.5.1	Genetic diseases	286
14.5.2	Diabetes: metabolic memory	287
14.5.3	Spinocerebellar ataxia type 7 (SCA7): histone acetylation	287
14.6	Pharmacological effects on retinal function	287
14.7	Future research	289
	References	289
15	Nuclear RNA Silencing and Related Phenomena in Animals	297
	<i>Radek Malik and Petr Svoboda</i>	
15.1	Introduction	297
15.1.1	miRNA and RNAi pathways	298
15.1.2	piRNA pathway	302
15.1.3	Repeat-induced gene silencing (RIGS)	303
15.1.4	Meiotic silencing of unpaired DNA (MSUD)	304
15.1.5	Artificially induced transcriptional regulation by siRNAs	304
15.2	Conclusion	310
	Acknowledgments	310
	References	310
16	Epigenetic Biomarkers in Cancer Detection and Diagnosis	317
	<i>Ashley G. Rivenbark and William B. Coleman</i>	
16.1	DNA methylation	317
16.1.1	CpG islands	317
16.1.2	DNA methyltransferases	318
16.1.3	DNA methylation-mediated regulation of transcription	318
16.2	Epigenetics of cancer	319
16.2.1	DNA methylation and gene silencing in cancer	319
16.2.2	DNA hypomethylation and hypermethylation in cancer	320
16.3	Epigenetic biomarkers for cancer diagnostics: DNA methylation	320
16.3.1	Sources of DNA for evaluation of epigenetic biomarkers	322
16.3.2	Methods for analyzing DNA methylation of epigenetic biomarkers	322
16.3.3	Identification of methylation-sensitive cancer biomarkers	323
16.4	Application of aberrant DNA methylation to cancer diagnostics	323
16.5	Epigenetic biomarkers in breast cancer	323
16.6	Epigenetic biomarkers in prostate cancer	324
16.7	Epigenetic biomarkers in lung cancer	325
16.8	Epigenetic biomarkers in colorectal cancer	326
16.9	Epigenetic biomarkers in liver cancer	328
16.10	Cancer detection and diagnosis	330
	References	332

17	Epigenetic Histone Changes in the Toxicologic Mode of Action of Arsenic	339
	<i>John F. Reichard and Alvaro Puga</i>	
17.1	Introduction	339
17.2	Epigenetics and cancer	340
17.3	Epigenetics effects of arsenic	341
17.3.1	Arsenic and DNA methylation	341
17.3.2	Arsenic and histone modification	342
17.3.3	Arsenic and acetylation at lysine 16 of histone H4 (H4K16ac)	343
17.3.4	Arsenic and histone methylation	347
17.4	Conclusions	348
	References	350
18	Irreversible Effects of Diethylstilbestrol on Reproductive Organs and a Current Approach for Epigenetic Effects of Endocrine Disrupting Chemicals	357
	<i>Shinichi Miyagawa, Ryohei Yatsu, Tamotsu Sudo, Katsuhide Igarashi, Jun Kanno, and Taisen Iguchi</i>	
18.1	Introduction	357
18.2	Adverse effects of perinatally-exposed DES on the mouse vagina	358
18.3	MeDIP-ChIP	359
18.4	Future research needs	362
	Acknowledgments	363
	References	363
19	Epigenomics – Impact for Drug Safety Sciences	365
	<i>Harri Lempiäinen, Raphaëlle Luisier, Arne Müller, Philippe Marc, David Heard, Federico Bolognani, Pierre Moulin, Philippe Couttet, Olivier Grenet, Jennifer Marlowe, Jonathan Moggs, and Rémi Terranova</i>	
19.1	Introduction – the dynamic epigenome and perturbations in disease	365
19.2	Relevance of epigenetics for toxicology	370
19.3	Towards identifying epigenetic biomarkers of drug-induced toxicity	371
19.4	Challenges of integrating epigenetic analysis into toxicity testing	373
19.5	Practical considerations	374
19.6	Bioinformatics and modeling of epigenomic data	376
19.7	Case study: identification of early mechanism and biomarkers for non-genotoxic carcinogenesis (NGC)	378
19.8	Conclusions	379
	Acknowledgments	380
	References	380
20	Archival Toxicoeugenetics: Molecular Analysis of Modified DNA from Preserved Tissues in Toxicology Studies	387
	<i>B. Alex Merrick</i>	
20.1	Introduction	387
20.2	Preservation of tissue: effects on protein and nucleic acids	388
20.3	Extraction of nucleic acids from fixed or embedded tissues	391
20.4	Analysis of methylated DNA for epigenetics	394

20.5	Survey of epigenetic studies using formalin preserved tissues	395
20.6	Prospects for toxicoepigenetics in preserved tissues	401
20.7	Conclusion	402
	References	403
21	Nanoparticles and Toxicoepigenomics	409
	<i>Manasi P. Jain, Angela O. Choi, and Dusica Maysinger</i>	
21.1	Nanoparticles	409
21.2	Particles and the environment	410
21.2.1	Natural nanostructures and synthetic nanoparticles	410
21.2.2	Nanotoxicity and the environment	411
21.3	Nanoparticles in soil	412
21.4	Nanoparticles in water	412
21.5	Nanoparticles in air	413
21.6	Nanoparticles in medicine	414
21.7	Nanotoxicology	414
21.8	Nanotoxicology in humans and experimental animals	414
21.8.1	Titanium dioxide nanoparticles	415
21.8.2	Carbon nanotubes	415
21.8.3	Quantum dots	416
21.9	Complications with nanotoxicological studies	416
21.10	Molecular mechanisms of nanoparticle toxicity and cellular defense mechanisms	417
21.11	Molecular mechanisms of nanoparticle-induced cytotoxicity	418
21.12	Nano-epigenomics and epigenetics	419
21.13	Conclusion	421
	References	422
22	Methods of Global Epigenomic Profiling	427
	<i>Michael W.Y. Chan, Zhengang Peng, Jennifer Chao Weber, Ying-Wei Li, Matthew T. Zuzolo, and Huey-Jen L. Lin</i>	
22.1	Introduction	427
22.2	DNA methylation	428
22.2.1	Aberrant DNA methylation captured by genomic profiling	428
22.2.2	Assessment of DNA methylation by using restriction endonucleases	428
22.2.3	Hybridization-based gene chips and bisulfite conversion	429
22.2.4	Genome-wide methylation profiling by high throughput global DNA sequencing technology NGS	430
22.3	Histone modifications and chromatin remodeling	435
22.3.1	ChIP	436
22.3.2	ChIP-chip	436
22.3.3	ChIP-seq	437
22.3.4	ChIP-seq deciphers chromatin remodeling	437
22.4	Noncoding RNA	439
22.5	Summary and discussion	440
	Acknowledgments	440
	References	440

23	Transcriptomics: Applications in Epigenetic Toxicology	445
	<i>Pius Joseph</i>	
23.1	Introduction	445
23.2	Microarray analysis of gene expression profiles	446
23.2.1	Microarray study design	447
23.2.2	RNA isolation	449
23.2.3	cDNA synthesis	449
23.2.4	Target synthesis	450
23.2.5	Hybridization	450
23.2.6	Washing	450
23.2.7	Image acquisition	451
23.2.8	Data generation and analysis	451
23.2.9	Confirmation of microarray data	451
23.2.10	Bioinformatics analysis of differentially expressed genes	452
23.2.11	Functional analysis of differentially expressed genes	452
23.3	Gene expression studies – challenges	453
23.3.1	Confirmation of microarray data	453
23.3.2	Comparability of transcriptomics data	453
23.3.3	Establishing standards in acquiring and processing transcriptomics data	455
23.3.4	Translation of transcriptomics data from experimental models to human	456
23.4	Conclusions	456
	Acknowledgments	456
	Disclaimer	457
	References	457
24	Carcinogenic Metals Alter Histone Tail Modifications	459
	<i>Yana Chervona and Max Costa</i>	
24.1	Introduction	459
24.2	Epigenetics and histone tail modifications	460
24.3	Arsenic	462
24.4	Nickel	463
24.5	Hexavalent chromium (Cr [VI])	466
24.6	Cadmium	468
24.7	Summary	470
	References	470
25	Prediction of Epigenetic and Stochastic Gene Expression Profiles of Late Effects after Radiation Exposure	475
	<i>Yoko Hirabayashi and Tohru Inoue</i>	
25.1	Introduction – pathological profiling (diagnostic endpoint) and toxicological profiling (probabilistic endpoint)	475
25.2	Radiation exposure and dosimetric quantum biology	477
25.2.1	Dose of ionizing radiation	477
25.2.2	Probability of stochastic gene expression	477
25.2.3	Probability of common gene expression	478

25.3	Common gene expression profiles after subacute and prolonged effects after radiation exposure	478
25.4	Stochastic expression gene profiles after radiation exposure	483
25.4.1	Repertoires of stochastic expression genes (SEGs)	484
25.4.2	Biological relevance of stochastic gene repertoires of oxidative-stress-related genes	485
25.4.3	Example of signaling networks	489
25.5	Conclusions	492
	Appendix A	494
	Appendix B	495
	Appendix C	496
	References	509
26	Modulation of Developmentally Regulated Gene Expression Programs through Targeting of Polycomb and Trithorax Group Proteins	511
	<i>Marjorie Brand and F.J. Dilworth</i>	
26.1	Introduction	511
26.2	Polycomb group (PcG) proteins	512
26.2.1	PRC2 complex	512
26.2.2	PRC1 complex	515
26.3	Trithorax group genes	516
26.3.1	Histone H3 lysine 4 methyltransferase complexes	516
26.3.2	Subunits that are specifically associated to MLL1 or MLL2 complexes (trx-like complexes)	519
26.3.3	Subunits that are specifically associated to MLL3 or MLL4 complexes (trr-like complexes)	521
26.3.4	Subunits that are specifically associated with Set1A and Set1B complexes (dSet1-like complexes)	523
26.3.5	ATP-dependent chromatin remodeling complexes (SWI/SNF)	523
26.4	Model for the transcriptional regulation of developmentally regulated genes by PcG and TrxG	526
26.5	PcG and TrxG proteins in disease	527
26.6	Targeting PcG and TrxG proteins in disease	528
	References	529
27	Chromatin Insulators and Epigenetic Inheritance in Health and Disease	539
	<i>Jingping Yang and Victor G. Corces</i>	
27.1	Introduction	539
27.2	Structure and organization of insulators	540
27.3	Insulators and chromatin architecture	543
27.3.1	Genome-wide distribution of insulator proteins	543
27.3.2	Intra-chromosomal interactions and insulator function in <i>Drosophila</i>	545
27.3.3	Intra-chromosomal interactions and insulator function in vertebrates	545
27.3.4	Insulator-mediated inter-chromosomal interactions	549
27.3.5	Insulators and the nuclear matrix	551

27.4	Regulation of insulator function	552
27.5	Insulators and the external/internal cellular environment	555
27.5.1	Response to hormones	555
27.5.2	Insulators and viral expression	556
27.6	Insulators and disease	557
27.6.1	Neurological diseases caused by alteration of CTCF function	557
27.6.2	Imprinting-related diseases caused by changes in CTCF function	558
27.6.3	Alteration of CTCF function results in cancer	558
27.6.4	Other mechanism that alter CTCF function also lead to disease states	559
27.7	Concluding remarks	560
	Acknowledgments	561
	References	561
28	Bioinformatics for High-Throughput Toxico-Epigenomics Studies	569
	<i>Maureen A. Sartor, Dana C. Dolinoy, Laura S. Rozek, and Gilbert S. Omenn</i>	
28.1	Introduction	569
28.2	Evaluating environmental influences on the epigenome	570
28.3	Establishment of the field of environmental epigenomics	570
28.4	An evolutionary perspective: the case of genomic imprinting	571
28.5	Transitioning from epigenetics to epigenomics and related bioinformatics	572
28.5.1	DNA methylation approaches	572
28.5.2	Histone modifications	575
28.6	Observational studies in epigenomics	576
28.7	Integrative analyses with epigenomics data	577
28.8	Gene set enrichment and concept tools for pathway analyses	578
28.8.1	ConceptGen and LRpath	578
28.8.2	Enrichment testing with epigenomic deep sequencing data	579
28.8.3	Commercial pathway analysis tools	580
28.9	Databases and resources	580
28.10	Illustrative applications from environmental exposures/perturbations	581
28.10.1	From mice to men: BPA epigenomics across dose	581
28.10.2	Epigenetic mechanisms in head and neck squamous cell carcinomas	582
28.11	University of Michigan NIEHS center approach to Lifestage Exposures and Adult Disease (LEAD)	583
28.11.1	Lifespan analyses	583
28.12	Future directions	584
	Acknowledgments	584
	References	584
29	Computational Methods in Toxicoeigenomics	589
	<i>Joo Chuan Tong</i>	
29.1	Introduction	589
29.2	Data sources	589

29.3	Computational tools	591
29.4	Conclusion	592
	References	592
30	Databases and Tools for Computational Epigenomics	595
	<i>V. Umashankar and S. Gurunathan</i>	
30.1	Introduction	595
30.2	Epigenetics and computational epigenetics	596
30.3	Epigenomics and computational epigenomics	596
30.4	Human epigenome project (HEP)	596
30.5	Epigenome prediction mechanism	597
	30.5.1 DNA methylation prediction	598
	30.5.2 Promoter prediction	599
	30.5.3 CpG island prediction	599
	30.5.4 Prediction of nucleosome positioning	599
30.6	Epigenomics databases	599
	30.6.1 Generalized databases	600
	30.6.2 Specialized databases	601
30.7	Tools employed in computational epigenomics	606
	30.7.1 Basic tools	606
	30.7.2 Advanced and specific epigenomic tools	607
30.8	Sophisticated algorithms	611
30.9	Conclusion	612
	References	613
	Website references	613
31	Interface of Epigenetics and Carcinogenic Risk Assessment	615
	<i>Paul Nioi</i>	
31.1	Introduction	615
31.2	Key epigenetic changes implicated in carcinogenesis	616
31.3	DNA methylation changes in chemical carcinogenesis	617
	31.3.1 DNA methylation changes in human leukemias associated with exposure to cancer chemotherapeutic agents	618
	31.3.2 Alterations in the liver genomic methylome by the non-genotoxic carcinogen phenobarbital	619
	31.3.3 Altered DNA methylation within the endometrium following exposure to carcinogenic agents acting via the estrogen receptor	621
31.4	Methods of detecting alterations in the genomic methylome	623
	31.4.1 Bisulfite DNA treatment and pyrosequencing	623
	31.4.2 Methylated DNA immunoprecipitation	623
31.5	Conclusions	624
	31.5.1 Integration of DNA methylation analyses with carcinogenic risk assessment	624
	31.5.2 Future perspectives	625
	References	627

32 Epigenetic Modifications in Chemical Carcinogenesis	631
<i>Igor P. Pogribny, Igor Koturbash, and Frederick A. Beland</i>	
32.1 Introduction	631
32.2 Epigenetic alterations in cancer cells	632
32.3 Role of epigenetic alterations in chemical carcinogenesis	634
32.3.1 Tobacco smoke	634
32.3.2 Arsenic	635
32.3.3 Pharmaceuticals	636
32.3.4 Mycotoxins	637
32.4 Future perspectives: epigenetic alterations and cancer risk assessment	638
References	638
33 Application of Cancer Toxicoepigenomics in Identifying High-Risk Populations	645
<i>Mukesh Verma and Krishna K. Banaudha</i>	
33.1 Introduction: epigenetic mechanisms and cancer	645
33.2 Toxicity and cancer epigenetics	646
33.2.1 Arsenic	648
33.2.2 Benzene	648
33.2.3 Cadmium	648
33.2.4 Chromium	649
33.2.5 Nickel	649
33.2.6 Perfluorooctane sulfonate (PFOS)	649
33.2.7 Uranium	649
33.3 Advantages of using a cohort consortia approach to studying toxicoepigenomics in cancer	649
33.4 Data integration	650
33.5 Challenges and future directions	650
References	651
Author Index	653
Subject Index	655