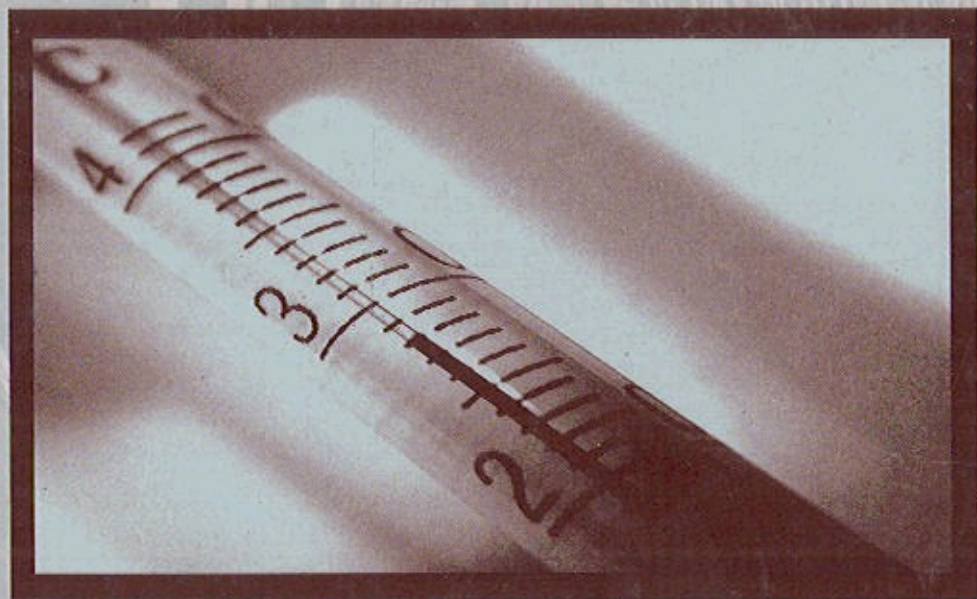


# TEMPERATURE AND TOXICOLOGY

---

An Integrative, Comparative,  
and Environmental Approach



Christopher J. Gordon

 CRC Press  
Taylor & Francis Group

---

# Contents

---

<b>1</b>	<b>Introduction.....</b>	<b>1</b>
1.1	Introduction	1
1.2	The Unique Nature of Thermoregulation	3
1.3	Why Should Toxicologists Study Temperature?	6
1.3.1	Temperature Is a Benchmark of Acute Toxicity in Rodents	6
1.3.2	Temperature Regulation as a Window to Autonomic Physiology	7
1.3.3	Temperature-Dependent Processes	8
1.4	Three Approaches to Studying Temperature and Toxicology	8
1.4.1	Integrative Approach	9
1.4.2	Comparative Approach	10
1.4.3	Environmental Approach	10
1.4.4	Presentation and Breadth of Coverage	11
<b>2</b>	<b>Principles of Temperature Regulation .....</b>	<b>13</b>
2.1	Introduction	13
2.2	Terminology	13
2.3	Heat Balance	15
2.4	The Thermoregulatory System	17
2.4.1	Interspecies Body Temperatures	18
2.4.2	Thermal Homeostasis in the Unrestrained Rat	20
2.5	Mechanisms of Temperature Regulation	22
2.5.1	Temperature Regulation as a Servo Control System	22
2.5.2	Neurophysiological Mechanisms	24
2.5.3	Neurochemical Mechanisms	27
2.6	Set-Point: Regulated Versus Forced Changes in Body Temperature	29
2.7	Thermoeffector Mechanisms and the Thermoneutral Zone	32
2.7.1	Metabolic Thermogenesis	35
2.7.1.1	Shivering Thermogenesis	36
2.7.1.2	Nonshivering Thermogenesis	36

2.7.2	Peripheral Vasomotor Tone	39
2.7.3	Evaporation	42
2.7.3.1	Sweating	43
2.7.3.2	Panting	43
2.7.3.3	Saliva Grooming	44
2.7.4	Behavioral Thermoregulatory Effectors	44
2.7.5	Motor Activity: A Thermoeffector?	48
2.8	Poikilotherms	49
<b>3</b>	<b>Acute Toxic Thermoregulatory Responses .....</b>	<b>51</b>
3.1	Introduction	51
3.2	General Mechanisms	52
3.3	Methods for Monitoring Body Temperature	54
3.4	Hypothermia: A Common Response in Rodents	54
3.5	Thermoregulatory Response to Toxicants	56
3.5.1	Anticholinesterase Agents	57
3.5.1.1	Correlation between Hypothermia and Cholinesterase Inhibition	58
3.5.1.2	Integrated Thermoregulatory Responses	62
3.5.1.3	CNS Mechanisms	69
3.5.2	Chlordecone	71
3.5.2.1	CNS Mechanisms	72
3.5.3	Airborne Toxicants	73
3.5.3.1	Ozone	74
3.5.3.2	Carbon Monoxide	76
3.5.3.3	Particulate Matter	77
3.5.4	Metals	77
3.5.4.1	Body Temperature and Metabolic Rate	77
3.5.4.2	Brown Adipose Tissue	79
3.5.4.3	Autonomic and Behavioral Effects	81
3.5.4.4	Primate and Human Studies	83
3.5.4.5	Neural Mechanisms	84
3.5.4.6	Organotins	86
3.5.5	Alcohols	87
3.5.6	Mechanisms	88
3.5.6.1	Human Responses	88
3.5.7	Organic Solvents	89
3.5.8	Formamidines	90
3.6	Toxicants Eliciting Hyperthermia	91
3.6.1	DDT	91
3.6.2	Uncouplers of Oxidative Phosphorylation	93
3.6.2.1	Thermogenesis	93
3.6.2.2	Behavior	94
3.6.3	Pyrethroids	95
3.7	Pre-Natal and Post-Natal Effects	95
3.7.1	Dioxin and PCBs	97

3.7.2 Anticholinesterase Agents	98
3.7.3 Alcohol	100
3.8 Chronic, Subchronic, and Repeated Dosing	101
<b>4 Temperature Effects on Chemical Toxicity .....</b>	<b>107</b>
4.1 Introduction	107
4.2 Systemic, Whole-Animal Toxicity	108
4.2.1 Temperature Coefficient and $Q_{10}$	108
4.2.2 Magnitude Versus Duration	109
4.2.3 Lethality	111
4.2.4 Patterns of Toxicity as a Function of Temperature	113
4.2.5 Nonlethal End Points	115
4.2.6 Nervous System	115
4.2.7 Cardiovascular System	116
4.2.8 Liver and Kidney	118
4.3 Cellular and Molecular Mechanisms of Toxicity	120
4.3.1 Temperature and Cell Death	120
4.3.2 Chemotherapy	122
4.3.3 Membrane Fluidity and Toxicity	123
4.3.4 Toxic Mechanisms Attenuated by Hypothermia	124
4.3.4.1 Reactive Oxygen Species	126
4.3.5 Toxicant Mechanisms Exacerbated by Hypothermia	127
4.4 Physiologically Based Pharmacokinetic Models	130
4.4.1 Pulmonary Uptake	130
4.4.2 Hepatic Metabolism	132
4.5 Temperature Acclimation	133
4.5.1 Terminology	134
4.5.2 Lethality	134
4.5.3 Renal Toxicity and Temperature Acclimation	135
4.5.4 Anticholinesterase Agents	137
4.5.5 Lead Poisoning	138
4.5.6 Ethanol and Cold Acclimation	140
4.5.7 Chemical Carcinogens	141
<b>5 Regulated Hypothermia: An Adaptive Response to Toxic Insult .....</b>	<b>145</b>
5.1 Introduction	145
5.2 Fever Versus Hypothermia as Adaptations	145
5.3 Behavioral Thermoregulation: A Tool for Studying Regulated Versus Forced Hypothermia	146
5.3.1 Defining the Limits of Normothermia in Toxicant-Exposed Subjects	147
5.4 Thermoregulatory Response to Toxicants: Relationship to Other Pathological Insults	149
5.4.1 Hypoxia	150
5.4.2 Endotoxemia	152

5.5	Extrapolation from Rodent to Human	155
5.5.1	Principles of Allometric Scaling	155
5.5.2	Thermal Conductance and Toxicant-Induced Hypothermia	158
5.6	Human Versus Rodent	159
5.7	Relevance of Regulated Hypothermia in Toxicology	160
5.7.1	Assessment of Risk	161
5.7.2	Hypothermia as Therapy in Poisonings	162
5.7.2.1	Changing the Set-Point to Treat Poisonings	163
5.7.3	Evolution of Homeothermy and Resistance to Toxicants	166
<b>6</b>	<b>Fever and Hyperthermia .....</b>	<b>169</b>
6.1	Introduction	169
6.2	Mechanism of Fever	170
6.2.1	Rodents as a Model for Fever and Toxicology Studies	171
6.3	Fever and Cholinesterase-Inhibiting Insecticides	172
6.3.1	Fever Versus Hyperthermia	174
6.3.2	Evidence That Anti-ChE Hyperthermia Is a Fever	175
6.3.3	Manifestation of Fever: Day Versus Night	179
6.4	Fever and Hyperthermic Responses in Humans	180
6.4.1	Responses to Anti-ChEs	180
6.4.2	Response to Other Toxicants	184
6.4.2.1	Chlorinated Hydrocarbons	184
6.4.2.2	Oxidative Phosphorylation Uncouplers	184
6.4.2.3	Arsenic	185
6.4.2.4	Turpentine	186
6.5	Alcohol: Rebound Hyperthermia or Fever?	187
6.6	Carbon Monoxide: Toxicant and Endogenous Mediator of Fever	189
6.7	Metal Fume Fever	190
6.8	Inflammation, Fever, and the P-450 Pathway	192
6.9	Is Toxic-Induced Fever Adaptive?	194
<b>7</b>	<b>Environmental Stress.....</b>	<b>195</b>
7.1	Introduction	195
7.2	Role of Environmental Physiology in Toxicology: A Brief History	196
7.3	The Physical Environment	196
7.3.1	Selecting an Appropriate Laboratory Test Environment	199
7.4	Temperature and Work: Their Impact on a Toxic Response	200
7.4.1	Thermal Stress and Entry of Toxicants into the Body	200
7.4.2	Sweating and Absorption of Toxicants	202
7.4.3	Sweating and Toxicant Excretion	205
7.5	Interaction between Heat Stress, Work, and Toxicant Exposure	206
7.5.1	Carbon Monoxide	206
7.5.2	Cholinesterase Inhibitors	208
7.5.2.1	Animal Studies	208
7.5.2.2	Human Studies	209
7.6	Agricultural Workers and Pesticide Exposure	210
7.7	Trained Versus Sedentary Models of Toxicant Susceptibility	212
7.8	Stress and Modulation of Thermoregulatory Response	215

7.8.1 Psychological Stress	215
7.8.2 Restraint and Handling Stress	218
7.8.2.1 Thermoregulation and Restraint	218
7.8.2.2 Restraint and Response to Drugs and Toxicants	219
7.8.3 Metallothionein Induction and Stress	222
7.9 Gulf War Syndrome	223
7.10 Meteorological Conditions and Environmental Toxicology	224
7.11 Arsenic, Cold Stress, and Raynaud's Disease	225
7.12 Ambient Temperature, Pollution, and Human Mortality	226
7.12.1 Greenhouse Effect and Thermoregulation	229
<b>8 Comparative Physiological Responses .....</b>	<b>233</b>
8.1 Introduction	233
8.2 Ecotoxicology	234
8.3 Effects of Temperature on Toxicity in Aquatic Organisms	235
8.3.1 Critical Thermal Maximum and Minimum	238
8.4 Fish Behavioral Thermoregulation	240
8.4.1 Endogenous Ethanol and Hypothermia	246
8.4.2 Relationship between Behavior and Temperature-Dependent Lethality	248
8.5 Amphibians	252
8.6 Insects	253
8.7 Unicellular Organisms	256
8.8 Responses to Wildlife	257
8.8.1 Birds	258
8.8.2 Mammals	261
<b>9 Genetic Variability and Molecular Markers .....</b>	<b>265</b>
9.1 Introduction	265
9.2 Genetic Strain Variation	265
9.2.1 Intraspecies Variation	266
9.2.2 Selective Breeding	268
9.2.3 Genetic Markers: Quantitative Trait Loci	270
9.3 Heat Shock Proteins	270
9.3.1 Endotoxin and Heat Shock	273
9.3.2 <i>In Vivo</i> Xenobiotic Studies	274
<b>10 Natural Toxins and Venoms .....</b>	<b>279</b>
10.1 Introduction	279
10.2 Fescue Toxicosis	280
10.3 Wildlife and Toxins	283
10.4 Algal Toxins	285
10.5 Venoms	289
<b>References .....</b>	<b>295</b>
<b>Index .....</b>	<b>329</b>