
CONTENTS

ENVIRONMENTAL HEALTH CRITERIA ON PRINCIPLES FOR EVALUATING HEALTH RISKS IN CHILDREN ASSOCIATED WITH EXPOSURE TO CHEMICALS

PREAMBLE	xi
PREFACE	xvii
ACRONYMS AND ABBREVIATIONS	xix
1. SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS	1
1.1 Summary	1
1.2 Conclusions and recommendations	4
2. INTRODUCTION AND BACKGROUND	7
2.1 Introduction	7
2.2 Purpose and scope of document	9
2.3 Global burden of disease in children	12
2.4 Major environmental threats to children	14
2.4.1 Economic and nutritional factors	15
2.4.2 Social, cultural, demographic, and lifestyle factors	16
2.4.3 Chemical hazards	17
2.5 Intrinsic factors	19
2.6 The significance of a developmental stage approach	20
2.7 Summary and conclusions	21
3. UNIQUE BIOLOGICAL CHARACTERISTICS OF CHILDREN	22
3.1 General physical growth of children	22
3.1.1 Body weight and height	22
3.1.2 Organ weights/volumes	23
3.1.3 Skin	25
3.2 Anatomical and functional characteristics	25
3.3 Physiological characteristics	26

3.3.1	Breathing rate	26
3.3.2	Cardiac output	26
3.3.3	Blood flow to organs	27
3.3.4	Body composition	28
3.3.5	Tissue composition	29
3.3.6	Bone growth and composition	29
3.4	Metabolic characteristics	29
3.5	Toxicokinetics	31
3.5.1	Absorption, distribution, metabolism, and elimination	31
3.5.2	Physiological changes in mothers and their influence on toxicokinetics	33
3.5.2.1	Pregnancy	33
3.5.2.2	Lactation and breast milk	35
3.5.3	Dose to target	36
3.6	Normal development	39
3.6.1	Basic principles of normal development	39
3.6.2	Nervous system	40
3.6.3	Reproductive system	42
3.6.4	Endocrine system	44
3.6.4.1	Hypothalamic–pituitary axis	44
3.6.4.2	Thyroid gland	46
3.6.4.3	Adrenal glands	47
3.6.4.4	Gonads	48
3.6.4.5	Somatotropin (growth hormone), calcium homeostasis, and bone development	48
3.6.4.6	Pancreas	48
3.6.5	Cardiovascular system	49
3.6.6	Immune system	49
3.6.7	Respiratory system	50
3.6.8	Kidney	52
3.7	Summary and conclusions	53
4.	DEVELOPMENTAL STAGE–SPECIFIC SUSCEPTIBILITIES AND OUTCOMES IN CHILDREN	55
4.1	Introduction	55
4.2	Mortality, growth restriction, and birth defects	60
4.2.1	Mortality	60
4.2.2	Growth restriction	63
4.2.3	Birth defects (structural malformations)	64

	4.2.3.1 Etiology	66
	4.2.3.2 Functional developmental toxicity	67
4.3	Specific organ systems	68
	4.3.1 Nervous system	68
	4.3.1.1 Periods of susceptibility and consequences of exposures	69
	4.3.1.2 Specific examples	72
	4.3.2 Reproductive system	78
	4.3.2.1 Periods of susceptibility	79
	4.3.2.2 Consequences of exposures	80
	4.3.3 Endocrine system	85
	4.3.3.1 Periods of susceptibility	85
	4.3.3.2 Consequences of exposures	92
	4.3.4 Cardiovascular system	95
	4.3.4.1 Periods of susceptibility	96
	4.3.4.2 Consequences of exposures	96
	4.3.5 Immune system	97
	4.3.5.1 Periods of susceptibility	98
	4.3.5.2 Consequences of exposures	101
	4.3.6 Respiratory system	105
	4.3.6.1 Periods of susceptibility	105
	4.3.6.2 Consequences of exposures	106
	4.3.7 Kidney	113
	4.3.7.1 Periods of susceptibility	113
	4.3.7.2 Consequences of exposures	114
4.4	Cancer	115
	4.4.1 Childhood cancers that may have environmental causes	116
	4.4.1.1 Lymphoid tissues	116
	4.4.1.2 Liver	118
	4.4.1.3 Thyroid	118
	4.4.1.4 Brain and nervous system	119
	4.4.1.5 Other organ sites	119
	4.4.2 Adult cancers related to childhood exposures	120
	4.4.2.1 Brain and nervous system	120
	4.4.2.2 Thyroid	121
	4.4.2.3 Female breast	122
	4.4.2.4 Female reproductive tract	122
	4.4.2.5 Integument	122
	4.4.2.6 Other organ sites	123

4.4.3	Chemical exposures of special concern	123
4.5	Summary and conclusions	126
5.	EXPOSURE ASSESSMENT OF CHILDREN	129
5.1	Introduction	129
5.2	General principles of exposure assessments	129
5.3	Methods for conducting exposure assessments	133
5.3.1	Direct methods	133
5.3.2	Biomarkers of exposure	136
5.3.3	Modelling	137
5.4	Unique characteristics of children that affect exposure	139
5.5	Exposure as it relates to children around the world	144
5.5.1	Sources/geographical location	144
5.5.2	Pathways of exposure	145
5.5.2.1	Ambient air exposure pathway	145
5.5.2.2	Indoor exposure pathways	150
5.5.2.3	Water exposure pathway	152
5.5.2.4	Soil exposure pathway	153
5.5.2.5	Food-chain exposure pathway	154
5.5.2.6	Human to human exposure pathways	155
5.5.3	Settings/microenvironments	156
5.5.3.1	Residential	157
5.5.3.2	School	157
5.5.3.3	Child-care centres	157
5.5.3.4	Recreational	158
5.5.3.5	Special settings	159
5.5.4	Environmental equity factors (vulnerable communities)	161
5.6	Special considerations for children's exposure: case-studies	162
5.6.1	Influence of activities	162
5.6.1.1	Arsenic	162
5.6.1.2	Insecticides	162
5.6.1.3	Environmental tobacco smoke (ETS)	162
5.6.1.4	Lead	163
5.6.2	Hazardous waste sites	163
5.6.3	Aggregate exposure	164
5.6.3.1	Chlorpyrifos	164

5.6.3.2	Smelter areas	165
5.6.3.3	Malarious areas	165
5.6.4	Cumulative exposure	165
5.7	Summary and conclusions	166
6.	METHODOLOGIES TO ASSESS HEALTH OUTCOMES IN CHILDREN	168
6.1	Introduction	168
6.1.1	Methodological approaches for children's health studies	168
6.1.1.1	Epidemiological methods	171
6.1.1.2	Comparison of study designs	171
6.1.1.3	Descriptive designs	176
6.1.1.4	Analytic designs	178
6.1.1.5	Unique methodological considerations	180
6.1.2	Methodological approaches for animal studies	181
6.1.2.1	Developmental stage susceptibility, dosing periods, and assessment of effects	184
6.1.2.2	Dosing of fetuses and pups	190
6.2	Growth and development	190
6.2.1	Human studies	190
6.2.1.1	Puberty	194
6.2.1.2	Birth defects	195
6.2.2	Animal studies	195
6.2.2.1	Body weight and postnatal growth	195
6.2.2.2	Pre-, peri-, and postnatal death	196
6.2.2.3	Physical and functional developmental landmarks	196
6.2.2.4	Birth defects and malformations	198
6.3	Reproductive development and function	198
6.3.1	Human studies	198
6.3.2	Animal studies	202
6.3.2.1	Malformations of reproductive organs	202
6.3.2.2	Anogenital distance	203
6.3.2.3	Nipple/areola retention	204
6.3.2.4	Sexual maturation and puberty	204

6.3.2.5	Fertility	204
6.3.2.6	Histopathology of reproductive organs	206
6.3.2.7	Sperm quality and estrous cyclicity	207
6.4	Neurological and behavioural effects	207
6.4.1	Human studies	207
6.4.2	Animal studies	208
6.4.2.1	Motor activity	208
6.4.2.2	Motor and sensory functions	209
6.4.2.3	Learning and memory	209
6.4.2.4	Evaluation of effects	210
6.5	Cancer	211
6.5.1	Human studies	211
6.5.2	Animal studies	212
6.6	Immune system effects	212
6.6.1	Human studies	212
6.6.2	Animal studies	213
6.7	Respiratory system effects	213
6.7.1	Human studies	213
6.7.2	Animal studies	213
6.8	Haematopoietic/cardiovascular, hepatic/renal, skin/musculoskeletal, and metabolic/endocrine system effects	214
6.8.1	Human studies	214
6.8.2	Animal studies	214
6.9	Summary and conclusions	214
7.	IMPLICATIONS AND STRATEGIES FOR RISK ASSESSMENT FOR CHILDREN	217
7.1	Introduction	217
7.2	Problem formulation	220
7.3	Hazard identification	221
7.3.1	End-points and critical periods of exposure	223
7.3.2	Human studies	224
7.3.3	Relevance of animal studies for assessing potential hazards to children	225
7.3.4	Reversibility and latency	229
7.3.5	Characterization of the health-related database	230
7.4	Dose-response assessment	230
7.4.1	Application of health outcome data	232

7.4.2	Quantitative evaluation	233
7.4.2.1	Tolerable daily intake (TDI) and reference dose (RfD)/reference concentration (RfC) approaches	233
7.4.2.2	Benchmark dose (BMD)/benchmark concentration (BMC) approach	236
7.4.2.3	Biologically based dose–response models	236
7.4.2.4	Duration adjustment	237
7.4.2.5	Toxicokinetics	237
7.5	Exposure assessment	238
7.5.1	Age-specific exposures	238
7.5.2	Assessment methods	240
7.6	Risk characterization	242
7.7	Summary and conclusions	244
REFERENCES		247
ANNEX 1: WORKING DEFINITIONS OF KEY TERMS		310
RESUME, CONCLUSIONS ET RECOMMANDATIONS		315
RESUMEN, CONCLUSIONES Y RECOMENDACIONES		323