

CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR PRINCIPLES FOR EVALUATING HEALTH RISKS TO REPRODUCTION ASSOCIATED WITH EXPOSURE TO CHEMICALS

PREAMBLE	ix
ACRONYMS AND ABBREVIATIONS	xx
1. SUMMARY AND RECOMMENDATIONS	1
1.1 Summary	1
1.2 Recommendations	4
2. INTRODUCTION	7
3. PHYSIOLOGY OF HUMAN REPRODUCTION	11
3.1 Introduction	11
3.2 Reproductive endocrinology	11
3.2.1 Gonadal function	11
3.2.2 Basic elements underlying normal development	16
3.3 Female reproductive physiology	17
3.3.1 Ovarian development and oogenesis	17
3.3.2 Functional morphology of the ovary	18
3.3.2.1 Folliculogenesis	19
3.3.2.2 Intraovarian signalling	21
3.3.3 Neuroendocrine regulation of ovarian function and reproductive cycling	24
3.3.3.1 Hypothalamus	24
3.3.3.2 Pituitary	24
3.3.3.3 Patterns of ovarian response	25
3.3.4 Effects of hormones on reproductive tract and breast	25
3.4 Male reproductive physiology	26

3.4.1	Testes	26
3.4.2	Spermatogenesis	27
3.4.3	Intratesticular signalling	29
3.5	Mating behaviour	29
3.6	Gamete transport	31
3.7	Fertilization	32
3.8	<i>In utero</i> development	33
3.8.1	Blastogenesis	33
3.8.2	Implantation	34
3.8.3	Placentation	35
	3.8.3.1 Yolk sac placenta	36
	3.8.3.2 Chorioallantoic placenta	36
	3.8.3.3 Placental steroidogenesis	38
3.9	Embryogenesis	38
3.10	Fetal development	46
3.11	Gestation	49
3.12	Gametogenesis and gonadogenesis	49
	3.12.1 Gamete development	49
	3.12.2 Gonadal and genital development	50
3.13	Parturition	51
3.14	Lactation	51
3.15	Maturation (postnatal)	52
3.16	Reproductive senescence	54
3.17	Summary	54
4.	EVALUATION OF ALTERED SEXUAL FUNCTION AND FERTILITY	56
4.1	Introduction	56
4.2	Experimental data	56
4.2.1	<i>In vivo</i> experimental data	56
	4.2.1.1 Introduction	56
	4.2.1.2 General evaluation of sexual function and fertility	57
	4.2.1.3 Evaluation of male-specific end-points of sexual function and fertility	58
	4.2.1.4 Evaluation of female-specific end-points of sexual function and fertility	64
4.2.2	<i>In vitro</i> experimental data	71

	4.2.2.1	Introduction	71
	4.2.2.2	Cell and tissue culture systems	72
	4.2.2.3	<i>In vitro</i> fertilization studies	72
	4.2.2.4	Other <i>in vitro</i> systems	73
	4.2.3	Structure–activity relationships	73
	4.2.4	Methods to assess endocrine disruption	74
4.3		Human data	74
	4.3.1	Introduction	74
	4.3.2	Fecundity and fertility	74
	4.3.2.1	Male end-points	77
	4.3.2.2	Female end-points	79
4.4		Summary	80
5.		EVALUATION OF DEVELOPMENTAL TOXICITY	81
5.1		Introduction	81
5.2		Background information on abnormal development	82
	5.2.1	Critical periods during development	82
	5.2.1.1	Prenatal toxicity and structural defects	83
	5.2.1.2	Fetal and postnatal developmental defects	84
	5.2.2	Pharmacokinetics and pharmacodynamics	84
	5.2.3	Gene–environment interactions	88
	5.2.4	Site and mechanism of action	89
	5.2.4.1	Mechanisms of developmental toxicity	89
	5.2.4.2	Site of action of developmental toxicants	90
	5.2.5	Nutrition	91
5.3		Experimental data	92
	5.3.1	<i>In vivo</i> experimental data: structural and functional aspects	92
	5.3.1.1	Prenatal observations	92
	5.3.1.2	Postnatal manifestations	94
	5.3.1.3	Male-mediated developmental toxicity and transplacental carcinogenesis	97
	5.3.2	<i>In vitro</i> systems	99
	5.3.2.1	Embryonic stem cell test	100
	5.3.2.2	Whole embryo culture	100

5.3.2.3	Organ culture systems	102
5.3.2.4	Cell and tissue culture	103
5.3.3	Human developmental toxicity studies	103
5.3.3.1	Outcomes measured in the newborn period	104
5.3.3.2	Outcomes measured in infancy and childhood	106
5.3.3.3	Outcomes measured in adulthood	107
5.3.4	Special considerations for developmental toxicity studies in humans	108
5.4	Summary	109
6.	RISK ASSESSMENT STRATEGIES FOR REPRODUCTIVE TOXICITY	110
6.1	Introduction	110
6.2	Testing strategies and protocols	111
6.2.1	Pharmaceutical agents	112
6.2.2	Chemicals	113
6.3	Sources of data on reproductive toxicity	114
6.4	Hazard identification	116
6.5	Human studies	117
6.5.1	Criteria for establishing causality	119
6.5.2	Potential bias in data collection	120
6.5.3	Collection of data on other risk factors, effect modifiers and confounders	121
6.5.4	Examination of clusters, case reports or series	122
6.5.5	Community studies and surveillance programmes	122
6.6	Evaluation of dose–response relationships	124
6.6.1	Quantitative dose–response assessment	126
6.6.2	Determination of the NOAEL, LOAEL, BMD and guidance levels	126
6.6.3	Low-dose estimation/extrapolation	128
6.7	Exposure assessment	129
6.8	Risk characterization	131
6.8.1	Characterization of the database	131
6.8.2	Risk descriptors	134
6.9	Summary	136

REFERENCES	138
APPENDIX: TERMINOLOGY	169
RESUME ET RECOMMANDATIONS	174
RESUMEN Y RECOMENDACIONES	181