

TABLE OF CONTENTS

FOREWORD	1
1. EXECUTIVE SUMMARY	4
2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES	6
3. ANALYTICAL METHODS	7
3.1 Environmental monitoring	7
3.2 Biological monitoring	8
4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE	9
4.1 Natural sources	9
4.2 Anthropogenic sources	9
4.3 Production and use	9
5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION	9
5.1 Environmental releases	9
5.2 Environmental partitioning	10
5.3 Bioaccumulation	11
5.4 Environmental degradation	12
5.4.1 Atmospheric degradation	12
5.4.2 Aquatic degradation and biodegradation	13
5.5 Contribution to photochemical ozone production and ozone depletion	16
6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE	16
6.1 Environmental levels	16
6.1.1 Ambient air	16
6.1.2 Indoor air	17
6.1.3 Drinking-water	17
6.1.4 Surface water	17
6.1.5 Groundwater	18
6.1.6 Sediment and soil	18
6.1.7 Sewage and municipal wastewater	18
6.1.8 Food	18
6.2 Human exposure: environmental	19
6.3 Human exposure: occupational	19
7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS	20
7.1 Absorption	20
7.2 Distribution	21
7.3 Biotransformation	22
7.4 Excretion	25
7.5 Biological monitoring	26
7.6 Physiologically based pharmacokinetic models	26

8.	EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS	27
8.1	Single exposure	27
8.1.1	Inhalation	27
8.1.2	Oral	28
8.1.3	Dermal	28
8.2	Short-term and medium-term exposure	28
8.2.1	Inhalation	28
8.2.2	Oral	32
8.3	Long-term exposure and carcinogenicity	34
8.3.1	Inhalation	34
8.3.2	Oral	35
8.3.3	Dermal	36
8.3.4	Injection	36
8.3.5	Initiation/promotion studies	36
8.4	Genotoxicity and related end-points	37
8.4.1	In vivo studies	37
8.4.2	In vitro studies	37
8.5	Reproductive toxicity	38
8.5.1	Effects on fertility	38
8.5.2	Developmental toxicity	39
8.6	Other toxicity	40
8.7	Mode of action	40
9.	EFFECTS ON HUMANS	42
9.1	Local effects (irritation and sensitization)	42
9.2	General systemic effects	42
9.3	Carcinogenicity	43
9.4	Genotoxicity	51
9.5	Reproductive and developmental toxicity	51
9.6	Nephrotoxicity	53
9.7	Hepatotoxicity	54
9.8	Neurotoxicity	55
9.8.1	Studies on volunteers	55
9.8.2	Studies on occupational and residential exposure	56
9.9	Cardiotoxicity	59
10.	EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD	59
10.1	Aquatic environment	59
10.1.1	Aquatic microorganisms	59
10.1.2	Aquatic plants (algae)	60
10.1.3	Aquatic invertebrates	60
10.1.4	Field study data	60
10.1.5	Fish	60
10.2	Terrestrial environment	61
10.2.1	Terrestrial mammals	61
10.2.2	Terrestrial invertebrates	61
10.2.3	Soil-dwelling bacteria	62
10.2.4	Terrestrial plants	62
11.	EFFECTS EVALUATION	64
11.1	Evaluation of health effects	64

11.1.1	Hazard identification and dose-response assessment	65
11.1.2	Criteria for setting tolerable intakes and concentrations	68
11.1.3	Sample risk characterization	69
11.1.4	Uncertainties in the evaluation of health risks	69
11.2	Evaluation of environmental effects	70
11.2.1	Assessment end-points	70
11.2.2	Sample environmental risk characterization	70
11.2.3	Uncertainties in the environmental risk assessment	74
12.	PREVIOUS EVALUATIONS BY IOMC BODIES	74
	REFERENCES	75
	APPENDIX 1 — ACRONYMS AND ABBREVIATIONS	93
	APPENDIX 2 — SOURCE DOCUMENTS	94
	APPENDIX 3 — CICAD PEER REVIEW	97
	APPENDIX 4 — 12TH CICAD FINAL REVIEW BOARD	98
	APPENDIX 5 — CONSULTATIVE GROUP	99
	APPENDIX 6 — 13TH CICAD FINAL REVIEW BOARD	99
	APPENDIX 7 — CALCULATION OF BMC AND BMCL	100
	APPENDIX 8 — DERIVATION OF AN ORAL DOSE EQUIVALENT TO INHALATION TOLERABLE CONCENTRATION BY PBPK MODELLING	104
	INTERNATIONAL CHEMICAL SAFETY CARD	106
	RÉSUMÉ D'ORIENTATION	108
	RESUMEN DE ORIENTACIÓN	112