

CONTENTS

NOTE TO THE READER	1
--------------------------	---

LIST OF PARTICIPANTS	3
----------------------------	---

PREAMBLE

Background	9
Objective and Scope	9
Selection of Topics for Monographs	10
Data for Monographs	11
The Working Group	11
Working Procedures	11
Exposure Data	12
Studies of Cancer in Humans	14
Studies of Cancer in Experimental Animals	17
Other Data Relevant to an Evaluation of Carcinogenicity and Its Mechanisms	20
Summary of Data Reported	21
Evaluation	23
References	27

THE MONOGRAPHS

Polychlorinated dibenzo-<i>para</i>-dioxins	33
1. Exposure Data	33
1.1 Chemical and physical data	33
1.1.1 Nomenclature and molecular formulae and weights	33
1.1.2 Structural formulae	33
1.1.3 Chemical and physical properties	33
1.1.4 Methods of analysis	37
(a) General considerations	38
(b) Sampling	39
(c) Extraction	41
(d) Clean-up	41
(e) Separation	42
(f) Quantification	43
1.2 Formation and destruction	44
1.2.1 Formation of PCDDs	44
(a) Chemical reactions	44
(b) Thermal reactions	49

(c) Photochemical reactions	52
(d) Biochemical reactions	52
1.2.2 Destruction of PCDDs	52
1.3 Occurrence	53
1.3.1 Occupational and accidental exposures to PCDDs.....	53
(a) Occupational exposures	53
(b) Population exposure due to industrial accident	63
(c) Summary table	65
1.3.2 Environmental occurrence	65
(a) Air	65
(b) Water.....	75
(c) Soil	77
(d) Food	87
(i) Background exposure.....	90
(ii) Foods from contaminated areas	95
(iii) Human intake levels from food.....	96
1.4 Human tissue measurements	98
1.4.1 Blood and tissue samples	98
1.4.2 Human milk	122
1.5 Regulations and guidelines	136
2. Studies of Cancer in Humans	137
2.1 Industrial exposures and industrial accidents	138
2.1.1 Exposure to 2,3,7,8-TCDD and higher chlorinated PCDDs/PCDFs in chemical plants	138
(a) Two United States plants	138
(b) Comprehensive United States study	150
(c) German accident cohort	151
(d) Other German plants	153
(e) British plants	156
(f) Dutch plants	157
(g) IARC multi-country study	158
2.1.2 Population exposure due to industrial accident	161
2.1.3 Industrial exposure to higher chlorinated PCDDs	162
2.2 Herbicide exposures	164
2.2.1 Applicator cohorts	165
(a) Commercial	165
(b) Military	171
2.2.2 Community-based case-control studies	172
(a) Soft-tissue sarcoma	172
(b) Malignant lymphomas	180
(c) Other haematopoietic malignancies	186
(d) Other solid tumours.....	189
2.3 Combined evidence from high-exposure human populations	191

CONTENTS

v

3.	Studies of Cancer in Experimental Animals	195
	<i>2,3,7,8-Tetrachlorodibenzo-para-dioxin</i>	195
3.1	Oral administration	195
3.1.1	Mouse	195
3.1.2	Rat.....	199
3.2	Administration to immature animals	201
3.3	Intraperitoneal or subcutaneous administration	201
3.4	Skin application	202
3.5	Exposure by immersion in water	202
3.6	Administration with known carcinogens and modifying factors.....	202
3.6.1	Skin	207
3.6.2	Lung	208
(a)	Mouse.....	208
(b)	Rat	209
3.6.3	Liver.....	209
(a)	Mouse.....	209
(b)	Rat	209
	<i>Dibenzo-para-dioxin</i>	214
	Oral administration	214
	(a) Mouse.....	214
	(b) Rat	214
	<i>2,7-Dichlorodibenzo-para-dioxin</i>	215
3.1	Oral administration	215
3.1.1	Mouse	215
3.1.2	Rat.....	215
3.2	Administration with known carcinogens	216
	<i>1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin and 1,2,3,7,8,9-hexachloro-dibenzo-para-dioxin (mixture)</i>	216
3.1	Oral administration	216
3.1.1	Mouse	216
3.1.2	Rat.....	217
3.2	Skin application	217
	<i>1,2,3,7,8-Pentachlorodibenzo-para-dioxin</i>	218
	Administration with known carcinogens	218
	<i>1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin</i>	218
	Administration with known carcinogens	218
	<i>Defined mixture of 49 polychlorinated dibenzo-para-dioxins</i>	219
	Administration with known carcinogens	219
4.	Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms ..	219
4.1	Absorption, distribution, metabolism and excretion	219
4.1.1	Humans	219
4.1.2	Experimental systems	221
	(a) Absorption.....	221
	(b) Body distribution	221

(c) Metabolism	223
(d) Excretion	224
(e) Kinetics and toxicity	226
4.2 Toxic effects	227
4.2.1 Humans	227
(a) Chloracne and other effects on the skin	227
(b) Hepatic effects	228
(c) Other gastrointestinal effects	238
(d) Thyroid function	238
(e) Diabetes.....	242
(f) Immunological effects	243
(g) Neurological effects	256
(h) Circulatory system	257
(i) Pulmonary effects	262
(j) Renal effects.....	263
4.2.2 Experimental systems	263
(a) Species comparisons of toxic effects	263
(b) Immunological responses.....	281
4.3 Interactions with receptors and their early molecular consequences and other biochemical responses	295
4.3.1 The Ah receptor	296
4.3.2 Induction of drug-metabolizing enzymes	297
4.3.3 Modulation of growth factors, growth factor receptors, transcription factors, lymphokines and related factors	300
4.3.4 Modulation of thyroid hormones, vitamin A and retinoids	301
4.3.5 Modulation of protein phosphorylation	302
4.3.6 Modulation of biochemical responses associated with glucose metabolism and transport.....	302
4.3.7 Modulation of oestrogenic responses by PCDDs	303
4.3.8 Role of oxidative stress in the toxicity of PCDDs	304
4.3.9 Cell cycle regulation and apoptosis	304
4.4 Reproductive and developmental effects	305
4.4.1 Humans	305
(a) Endocrine and gonadal effects	305
(b) Effects on pregnancy.....	306
4.4.2 Experimental systems	315
(a) Developmental effects	315
(b) Functional developmental toxicity	318
(c) Reproductive effects	321
4.5 Genetic and related effects	324
4.5.1 Humans	324
4.5.2 Experimental systems	324
4.6 Mechanisms of carcinogenicity	330
4.6.1 Introduction.....	330

4.6.2	General issues regarding mechanisms of carcinogenesis	330
(a)	Carcinogenesis is a multistep process	330
(b)	Genotoxicity.....	331
(c)	Ah receptor.....	331
(d)	Effects of 2,3,7,8-TCDD on gene expression	331
(e)	Oxidative damage	331
(f)	Cell transformation	332
(g)	Cell proliferation and tumour promotion	332
(h)	Suppression of immune surveillance	332
4.6.3	Tissue-specific mechanisms of carcinogenicity of 2,3,7,8-TCDD	333
(a)	Liver	333
(b)	Other target tissues	335
4.6.4	Mechanisms for reduced cancer incidence following 2,3,7,8-TCDD exposure.....	335
5.	Summary of Data Reported and Evaluation	335
5.1	Exposure data	335
5.2	Human carcinogenicity data	336
5.3	Animal carcinogenicity data	338
5.4	Other relevant data.....	339
5.5	Evaluation	342
	Polychlorinated dibenzofurans	345
1.	Exposure Data	345
1.1	Chemical and physical data	345
1.1.1	Nomenclature and molecular formulae and weights	345
1.1.2	Structural formulae	346
1.1.3	Chemical and physical properties	346
1.1.4	Methods of analysis	348
1.2	Formation and destruction	348
1.2.1	Formation of PCDFs	348
(a)	Chemical reactions	348
(b)	Thermal reactions.....	352
(c)	Photochemical reactions	357
(d)	Biochemical reactions	357
1.2.2	Destruction of PCDFs	357
1.3	Occurrence	358
1.3.1	Occupational and accidental exposures to PCDFs	358
(a)	Occupational exposures	358
(b)	Accidental exposure	362
(i)	Yusho incident, Japan, 1968	362
(ii)	Yucheng incident, Taiwan, 1979	362
(iii)	PCB explosions and fires	362

1.3.2 Environmental occurrence	364
(a) Air	364
(b) Water	365
(c) Soil	365
(d) Food	366
1.4 Human tissue measurements	367
1.4.1 Blood and tissue samples	380
1.4.2 Human milk	384
1.5 Regulations and guidelines	384
2. Studies of Cancer in Humans	396
2.1 Rice oil contamination incidents	396
2.1.1 Japan	396
2.1.2 Taiwan	397
2.1.3 Comparison of Japan and Taiwan.....	398
2.2 Fish consumption.....	399
2.3 Industrial cohorts	400
3. Studies of Cancer in Experimental Animals	401
3.1 Administration with known carcinogens	401
3.1.1 Mouse skin.....	401
3.1.2 Rat liver	403
4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms ..	404
4.1 Humans	404
4.1.1 Humans	404
4.1.2 Experimental systems	404
(a) Absorption.....	404
(b) Distribution	405
(c) Metabolism	406
(d) Excretion	406
4.2 Toxic effects	408
4.2.1 Humans	408
(a) Non-cancer effects of ingestion of rice oil contaminated with polychlorinated dibenzofurans, quaterphenyls and biphenyls in Japan (<i>yusho</i>) and Taiwan (<i>yucheng</i>)	408
4.2.2 Experimental studies	411
(a) Species comparisons of toxic effects	411
(b) Immunological responses.....	413
(c) Biochemical responses	414
4.3 Interaction with Ah receptor and its early molecular consequences and other biochemical responses	415
4.4 Reproductive and developmental effects	416
4.4.1 Humans	416
4.4.2 Experimental systems	417

4.5 Genetic and related effects	418
4.5.1 Humans	418
4.5.2 Experimental systems	418
5. Summary of Data Reported and Evaluation	420
5.1 Exposure data	420
5.2 Human carcinogenicity data	421
5.3 Animal carcinogenicity data	421
5.4 Other relevant data.....	421
5.5 Evaluation	422
APPENDIX 1. TABLES ON OCCURRENCE (PCDDs)	425
APPENDIX 2. TABLES ON OCCURRENCE (PCDFs)	477
APPENDIX 3. GENETIC AND RELATED EFFECTS	503
A. TEST SYSTEM CODE WORDS FOR GENETIC AND RELATED EFFECTS	505
B. SUMMARY TABLES OF GENETIC AND RELATED EFFECTS	511
C. ACTIVITY PROFILES FOR GENETIC AND RELATED EFFECTS	515
REFERENCES	525
SUMMARY OF FINAL EVALUATIONS	631
ABBREVIATIONS	633
SUPPLEMENTARY CORRIGENDA TO VOLUMES 1–68.....	637
CUMULATIVE INDEX TO THE <i>MONOGRAPHS</i> SERIES.....	639

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean the probability that exposure to an agent will lead to cancer in humans.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Carcinogen Identification and Evaluation, so that corrections can be reported in future volumes.