

CONTENTS

NOTE TO THE READER	1
LIST OF PARTICIPANTS	3
PREAMBLE	9
A. GENERAL PRINCIPLES AND PROCEDURES	9
1. Background	9
2. Objective and scope	10
3. Selection of agents for review	11
4. Data for the <i>Monographs</i>	11
5. Meeting participants	12
6. Working procedures	13
B. SCIENTIFIC REVIEW AND EVALUATION	14
1. Exposure data	15
2. Studies of cancer in humans	16
3. Studies of cancer in experimental animals	20
4. Mechanistic and other relevant data	23
5. Summary	26
6. Evaluation and rationale	27
References	31
GENERAL REMARKS	33
4-AMINOBIIPHENYL	41
1. Exposure Data	41
1.1 Identification of the agent	41
1.2 Uses	41
1.3 Human exposure	41
2. Cancer in Humans	42
2.1 Descriptive studies	42
2.2 Cohort studies	42
2.3 Synthesis	43
3. Cancer in Experimental Animals	43
4. Other Relevant Data	43

4.1 Aromatic amines: metabolism, genotoxicity, and cancer susceptibility.....	43
4.2 4-Aminobiphenyl.....	49
5. Evaluation.....	50
References.....	50
BENZIDINE.....	53
1. Exposure Data.....	53
1.1 Identification of the agents.....	53
1.2 Uses.....	53
1.3 Human exposure.....	54
2. Cancer in Humans.....	55
3. Cancer in Experimental Animals.....	55
4. Other Relevant Data.....	60
5. Evaluation.....	61
References.....	61
DYES METABOLIZED TO BENZIDINE.....	65
1. Exposure Data.....	65
1.1 Identification of the agents.....	65
1.2 Uses.....	66
1.3 Human exposure.....	66
2. Cancer in Humans.....	68
2.1 Cohort Studies.....	68
2.2 Case-control studies.....	68
2.3 Synthesis.....	68
3. Cancer in Experimental Animals.....	68
4. Other Relevant Data.....	71
5. Evaluation.....	71
References.....	72
4,4'-METHYLENEBIS(2-CHLOROBENZENAMINE).....	73
1. Exposure Data.....	73
1.1 Identification of the agent.....	73
1.2 Uses.....	73
1.3 Human exposure.....	73
2. Cancer in Humans.....	75
3. Cancer in Experimental Animals.....	75
4. Other Relevant Data.....	79
5. Evaluation.....	80
References.....	80
2-NAPHTHYLAMINE.....	83
1. Exposure Data.....	83
1.1 Identification of the agent.....	83
1.2 Uses.....	83
1.3 Human exposure.....	84
2. Cancer in Humans.....	85

3. Cancer in Experimental Animals	86
4. Other Relevant Data	86
5. Evaluation	90
References	90
ortho-TOLUIDINE	93
1. Exposure Data	93
1.1 Identification of the agent.....	93
1.2 Uses.....	93
1.3 Human exposure	93
2. Cancer in Humans.....	94
3. Cancer in Experimental Animals	95
4. Other Relevant Data	98
5. Evaluation	98
References	99
AURAMINE AND AURAMINE PRODUCTION	101
1. Exposure Data	101
1.1 Identification of the agent.....	101
1.2 Manufacture and use.....	101
1.3 Human exposure	102
2. Cancer in Humans.....	102
3. Cancer in Experimental Animals	102
4. Other Relevant Data	102
5. Evaluation	104
References	104
MAGENTA AND MAGENTA PRODUCTION	105
1. Exposure Data	105
1.1 Identification of the agents.....	105
1.2 Manufacturing processes.....	106
1.3 Human exposure	107
2. Cancer in Humans.....	107
3. Cancer in Experimental Animals	107
3.1 Magenta	107
3.2 CI Basic Red 9.....	109
4. Other Relevant Data	109
5. Evaluation	109
References	109
BENZO[a]PYRENE	111
1. Exposure Data	111
1.1 Identification of the agent.....	111
1.2 Occurrence and exposure	111
2. Cancer in Humans.....	112
3. Cancer in Experimental Animals	112
3.1 Skin application.....	113

3.2	Subcutaneous injection.....	113
3.3	Oral administration.....	113
3.4	Intraperitoneal injection.....	130
3.5	Inhalation.....	130
3.6	Intrapulmonary injection.....	130
3.7	Intratracheal administration.....	130
3.8	Buccal pouch application.....	131
3.9	Subcutaneous tracheal grafts transplantation.....	131
3.10	Intramammary administration.....	131
3.11	Intracolonic instillation.....	131
3.12	Intravaginal application.....	131
3.13	Intrafetal injection.....	131
4.	Other Relevant Data.....	131
4.1	Metabolism.....	131
4.2	Diolepoxide mechanism.....	132
4.3	Radical-cation mechanism.....	133
4.4	Other activation mechanisms of benzo[<i>a</i>]pyrene.....	133
4.5	Human exposure to PAH-rich mixtures.....	135
4.6	Synthesis.....	137
5.	Evaluation.....	137
	References.....	138
COAL GASIFICATION.....		145
1.	Exposure Data.....	145
2.	Cancer in Humans.....	146
2.1	Cohort studies of coal-gasification workers.....	146
2.2	Synthesis.....	146
3.	Cancer in Experimental Animals.....	146
4.	Other Relevant Data.....	149
4.1	Mechanistic evidence relevant to the carcinogenic hazards from occupational exposures during coal gasification.....	149
4.2	Synthesis.....	150
5.	Evaluation.....	150
	References.....	150
OCCUPATIONAL EXPOSURES DURING COAL-TAR DISTILLATION.....		153
1.	Exposure Data.....	153
1.1	Manufacturing process.....	153
1.2	Occupational exposure.....	155
2.	Cancer in Humans.....	155
3.	Cancer in Experimental Animals.....	155
4.	Other Relevant Data.....	156
4.1	Mechanistic considerations relevant to the carcinogenic hazards of exposures during coal-tar distillation.....	156
4.2	Synthesis.....	158
5.	Evaluation.....	158
	References.....	159

COAL-TAR PITCH	161
1. Exposure Data	161
1.1 Identification of the agent.....	161
1.2 Human exposure	161
2. Cancer in Humans.....	163
2.1 Cohort Studies	164
3. Cancer in Experimental Animals	164
4. Other Relevant Data	164
4.1 Mechanistic considerations relevant to the cancer hazards from exposure during roofing and paving with coal-tar pitch.....	164
4.2 Synthesis.....	165
5. Evaluation	165
References	165
COKE PRODUCTION	167
1. Exposure Data	167
1.1 Production process.....	167
1.2 Human exposure	169
2. Cancer in Humans.....	169
3. Cancer in Experimental Animals	170
3.1 Skin application.....	170
3.2 Inhalation.....	171
4. Other Relevant Data	172
4.1 Mechanistic evidence relevant to the carcinogenic hazard from occupational exposures during coke production	172
4.2 Synthesis.....	175
5. Evaluation	175
References	175
MINERAL OILS, UNTREATED OR MILDLY TREATED.....	179
1. Exposure Data	179
1.1 Identification of the agent.....	179
1.2 Uses.....	180
1.3 Human exposure	180
2. Cancer in Humans.....	181
2.1 Introduction.....	181
2.2 Cancer of the skin/scrotum.....	181
2.3 Other cancers	182
2.4 Synthesis.....	183
3. Cancer in Experimental Animals	183
3.1 Earlier studies	184
3.2 Studies published since the previous evaluation	191
4. Other relevant data	191
4.1 Humans	191
4.2 Experimental systems.....	192
5. Evaluation	193
References	193

SHALE OILS.....	197
1. Exposure Data	197
1.1 Identification of the agent.....	197
1.2 Uses.....	197
1.3 Human exposure	198
2. Cancer in Humans.....	198
3. Cancer in Experimental Animals	199
3.1 Raw and spent oil-shale.....	199
3.2 Crude shale oils from low-temperature retorting	202
3.3 Crude shale oils from high-temperature retorting	202
3.4 Shale-oil fractions	202
3.5 Shale-oil distillates, blends and other commercial products	203
3.6 Synthesis.....	203
4. Other Relevant Data	203
4.1 Humans	203
4.2 Experimental systems.....	204
4.3 Synthesis.....	204
5. Evaluation	204
References.....	205
SOOT, AS FOUND IN OCCUPATIONAL EXPOSURE OF CHIMNEY SWEEPS	209
1. Exposure Data	209
2. Cancer in Humans.....	211
3. Cancer in Experimental Animals	212
4. Other Relevant Data	212
4.1 Mechanistic evidence relevant to the carcinogenic hazards from occupational exposure as a chimney sweep.....	212
4.2 Synthesis.....	213
5. Evaluation	213
References.....	214
OCCUPATIONAL EXPOSURES DURING ALUMINIUM PRODUCTION	215
1. Exposure Data	215
1.1 Natural occurrence	215
1.2 Manufacturing processes.....	215
1.3 Human exposure	217
2. Cancer in Humans.....	217
2.1 Cancer of the urinary bladder.....	219
2.3 Synthesis.....	219
3. Cancer in Experimental Animals	219
4. Other Relevant Data	220
4.1 Mechanistic evidence relevant to the carcinogenic hazard from occupational exposures during aluminium production.....	220
4.2 Synthesis.....	221
5. Evaluation	221
References.....	222

AFLATOXINS.....	225
1. Exposure Data	225
1.1 Identification of the agents.....	225
1.2 Sources and uses	226
1.3 Human exposure	227
2. Cancer in Humans.....	229
2.1 Hepatocellular carcinoma	229
2.2 Synthesis.....	230
3. Cancer in Experimental Animals	230
3.1 Previous evaluations	230
3.2 Aflatoxin B1.....	235
3.3 Aflatoxin G1	235
3.4 Synthesis.....	235
4. Other Relevant Data	236
4.1 Toxicokinetics	236
4.2 Metabolism.....	237
4.3 Aflatoxin–albumin adducts	239
4.4 Aflatoxin–DNA adducts.....	240
4.5 Mutagenicity	241
4.6 Molecular lesions	241
4.7 Synthesis.....	243
5. Evaluation	243
References	244
BENZENE.....	249
1. Exposure Data	249
1.1 Identification of the agent.....	249
1.2 Uses.....	249
1.3 Human exposure	250
2. Cancer in Humans.....	257
2.1 Leukemias and lymphomas	258
2.2 Cancer of the lung	261
2.3 Cancer of the kidney	262
2.4 Other cancers	262
3. Cancer in Experimental Animals	262
4. Other Relevant Data	276
4.1 Genetic and related effects.....	276
4.2 Leukaemogenic potential of benzene	276
5. Evaluation	285
References	285
BIS(CHLOROMETHYL) ETHER AND CHLOROMETHYL METHYL ETHER	295
1. Exposure Data	295
1.1 Identification of the agents.....	295
1.2 Uses.....	295
1.3 Human exposure	296

2. Cancer in Humans.....	296
3. Cancer in Experimental Animals	297
3.1 BCME	297
3.2 CMME	305
4. Other Relevant Data	305
4.1 Toxicokinetics and toxicity	305
4.2 Genetic and related effects	305
4.3 Mechanistic considerations	306
4.4 Synthesis.....	306
5. Evaluation	306
References	306
1,3-BUTADIENE	309
1. Exposure Data	309
1.1 Identification of the agent.....	309
1.2 Use.....	309
1.3 Human exposure	309
2. Cancer in Humans.....	311
3. Cancer in Experimental Animals	313
3.1 1,3-Butadiene	313
3.2 Diepoxybutane	313
4. Other Relevant Data	327
4.1 Metabolism of butadiene.....	327
4.2 Haemoglobin adducts	329
4.3 DNA adducts	330
4.4 Mutagenicity of butadiene and butadiene metabolites	331
4.5 Synthesis.....	332
5. Evaluation	333
References	333
2,3,7,8-TETRACHLORODIBENZO-<i>para</i>-DIOXIN, 2,3,4,7,8-PENTACHLORODIBENZOFURAN, AND 3,3',4,4',5-PENTACHLOROBIPHENYL.....	339
1. Exposure Data	339
1.1 Identification of the agents.....	339
1.2 Occurrence and use	340
1.3 Human exposure	341
2. Cancer in Humans.....	344
2.1 Description of the most informative studies.....	345
2.2 All cancers combined	347
2.3 Cancer of the lung	347
2.4 Soft-tissue sarcoma.....	348
2.5 Non-Hodgkin lymphoma.....	348
2.6 Other cancers	348
2.7 Synthesis.....	348
3. Cancer in Experimental Animals	349
3.1 2,3,7,8-Tetrachlorodibenzo- <i>para</i> -dioxin.....	349

3.2 Dioxin-like compounds	365
4. Other Relevant Data	365
4.1 AhR activation.....	365
4.2 Mechanisms of carcinogenicity.....	366
4.3 Dioxin-like compounds	367
4.4 Synthesis.....	369
5. Evaluation	370
References	371
ETHYLENE OXIDE	379
1. Exposure Data	379
1.1 Identification of the agent.....	379
1.2 Uses.....	379
1.3 Human exposure	380
2. Cancer in Humans.....	382
2.1 Lympho-haematopoietic malignancies	382
2.2 Cancer of the breast.....	384
2.3 Other cancers	384
2.4 Synthesis.....	384
3. Cancer in Experimental Animals	384
3.1 Inhalation exposure	384
3.2 Other routes of exposure.....	388
4. Other Relevant Data	388
4.1 Absorption, distribution, metabolism, and excretion.....	388
4.2 Genetic and related effects.....	389
5. Evaluation	395
References	396
FORMALDEHYDE.....	401
1 Exposure Data	401
1.1 Identification of the agent.....	401
1.2 Use.....	401
1.3 Occurrence and exposure	402
2. Cancer in Humans.....	404
2.1 Cancer of the nasopharynx.....	404
2.2 Leukaemia	406
2.3 Cancer of the nasal sinuses.....	408
2.4 Other cancers	409
2.5 Synthesis.....	409
3. Cancer in Experimental Animals	410
3.1 Inhalation	410
3.2 Oral administration (drinking-water)	410
3.3 Skin application.....	410
4. Other Relevant Data	417
4.1 Absorption, distribution, metabolism, and excretion.....	417
4.2 Toxic effects	419

4.3 Genetic and related effects.....	419
4.4 Mechanistic considerations	427
4.5 Synthesis.....	430
5. Evaluation	430
References.....	430
SULFUR MUSTARD.....	437
1. Exposure Data	437
1.1 Identification of the agent.....	437
1.2 Uses.....	437
1.3 Human exposure	438
2. Cancer in Humans.....	438
3. Cancer in Experimental Animals	440
4. Other Relevant Data	442
4.1 Absorption, distribution, metabolism, and excretion.....	442
4.2 Genetic and related effects.....	443
4.3 Synthesis.....	446
5. Evaluation	446
References.....	446
VINYL CHLORIDE.....	451
1. Exposure Data	451
1.1 Identification of the agent.....	451
1.2 Uses.....	451
1.3 Human exposure	451
2. Cancer in Humans.....	454
2.1 Angiosarcoma of the liver	455
2.2 Hepatocellular carcinoma	455
2.3 Cancer of the lung.....	456
2.4 Malignant neoplasms of connective and soft tissue.....	456
2.5 Other cancers	457
2.6 Synthesis.....	457
3. Cancer in Experimental Animals	457
3.1 Inhalation exposure	458
3.2 Oral administration.....	458
3.3 Subcutaneous and intraperitoneal injection.....	458
3.4 Transplacental administration and perinatal exposure.....	458
3.5 Carcinogenicity of metabolites	467
4. Other Relevant Data	467
4.1 Kinetics and metabolism – studies in humans.....	467
4.2 Kinetics and metabolism – studies in animals.....	469
4.3 Reaction with cellular macromolecules	470
4.4 Synthesis.....	472
5. Evaluation	473
References.....	473

ISOPROPYL ALCOHOL MANUFACTURE BY THE STRONG-ACID PROCESS	479
1. Exposure Data	479
1.1 Manufacturing processes.....	479
1.2 Human exposure	479
2. Cancer in Humans.....	480
2.1 Cohort studies	480
2.2 Case–Control Studies	481
3. Cancer in Experimental Animals	481
4. Other Relevant Data	481
4.1 Absorption, distribution, metabolism, and excretion.....	481
4.2 Genetic and related effects.....	483
4.3 Toxicity relevant to carcinogenicity	483
4.4 Synthesis.....	483
5. Evaluation	484
References	484
MISTS FROM STRONG INORGANIC ACIDS	487
1. Exposure Data	487
1.1 Manufacturing processes.....	487
1.2 Human exposure	487
2. Cancer in Humans.....	489
2.1 Cohort studies	489
2.2 Case–control studies.....	491
3. Cancer in Experimental Animals	493
4. Other Relevant Data	493
5. Evaluation	493
References	493
OCCUPATIONAL EXPOSURES DURING IRON AND STEEL FOUNDING	497
1. Exposure Data	497
1.1 Manufacturing process	497
1.2 Human exposures	497
2. Cancer in Humans.....	504
2.1 Cohort studies	504
2.2 Case–control studies.....	504
2.3 Synthesis.....	505
3. Cancer in Experimental Animals	505
4. Other Relevant Data	505
4.1 Mechanistic evidence relevant to the carcinogenic hazards from occupational exposures during iron and steel founding.....	505
4.2 Synthesis.....	505
5. Evaluation	505
References	506

OCCUPATIONAL EXPOSURE AS A PAINTER	509
1. Exposure Data	509
1.1 Description of paint products.....	509
1.2 Human exposure	518
2. Cancer in Humans.....	519
2.1 Cancer of the lung.....	519
2.2 Mesothelioma.....	521
2.3 Cancer of the urinary bladder.....	521
2.4 Childhood leukaemia	522
2.5 Lympho-haematopoietic cancers	523
2.6 Other cancers	523
2.7 Synthesis.....	523
3. Cancer in Experimental Animals	524
4. Other Relevant Data	524
4.1 Toxicokinetics and metabolism.....	524
4.2 Genetics and related effects.....	526
4.3 Susceptible populations.....	530
4.4 Synthesis.....	531
5. Evaluation	531
References	531
OCCUPATIONAL EXPOSURES IN THE RUBBER-MANUFACTURING INDUSTRY	541
1. Exposure Data	541
1.1 Manufacturing process	541
1.2 Chemicals used in the rubber-production process	542
1.3 Human exposure	543
2. Cancer in Humans.....	546
2.1 Cancer of the bladder.....	546
2.2 Leukaemia.....	547
2.3 Malignant lymphoma including multiple myeloma and other lymphopoietic cancers.....	548
2.4 Cancer of the lung.....	549
2.5 Cancer of the larynx.....	550
2.6 Cancer of the stomach.....	550
2.7 Cancer of the oesophagus.....	551
2.8 Cancer of the prostate	552
2.9 Other cancers	552
3. Cancer in Experimental Animals	552
4. Other Relevant Data	552
5. Evaluation	559
References	559
LIST OF ABBREVIATIONS	563
CUMULATIVE CROSS INDEX TO IARC MONOGRAPHS	567

NOTE TO THE READER

The term ‘carcinogenic risk’ in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word ‘risks’ in the title.

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. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

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 Section of IARC Monographs, 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 Section of IARC Monographs, so that corrections can be reported in future volumes.

