

CONTENTS

NOTE TO THE READER	1
LIST OF PARTICIPANTS	3
PREAMBLE.....	7
1. Background.....	9
2. Objective and Scope	9
3. Selection of Topics for Monographs	10
4. Data for Monographs	11
5. The Working Group	11
6. Working Procedures	11
7. Exposure Data.....	12
8. Studies of Cancer in Humans	14
9. Studies of Cancer in Experimental Animals.....	17
10. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms	20
11. Summary of Data Reported	22
12. Evaluation	23
13. References.....	28
GENERAL REMARKS	33
THE MONOGRAPHS	37
Combined Estrogen–Progestogen Contraceptives	39
1. Exposure Data	41
1.1 Introduction	41
1.2 Historical overview	42
1.3 Preparations of combined hormonal contraceptives.....	44
1.4 Patterns of use	45
1.4.1 Prevalence of use	46
1.4.2 Trends in prevalence	48
2. Studies of Cancer in Humans	50
2.1 Breast cancer	50
2.1.1 Background	50
2.1.2 Use of combined oral contraceptives and detection of breast cancer	50
2.1.3 Cohort studies	53
2.1.4 Case–control studies	55

2.2	Endometrial cancer	60
2.2.1	Descriptive studies.....	61
2.2.2	Cohort studies	61
2.2.3	Case-control studies	63
2.3	Cervical cancer	74
2.3.1	Introduction	74
2.3.2	Meta-analysis.....	76
2.3.3	Methodological considerations	77
2.3.4	Studies of in-situ and invasive cervical cancer in which HPV antibodies were measured.....	78
2.3.5	Studies in which cervical tissue was assayed for HPV DNA	80
2.3.6	Studies conducted to determine whether oral contraceptives alter the risk for progression of cervical lesions	84
2.4	Ovarian cancer	84
2.4.1	Descriptive studies.....	85
2.4.2	Cohort studies	85
2.4.3	Case-control studies	86
2.4.4	Case-control studies among breast cancer gene (<i>BRCA1/2</i>) carriers	94
2.5	Liver cancer	95
2.5.1	Descriptive studies.....	96
2.5.2	Cohort studies	96
2.5.3	Case-control studies	97
2.6	Colorectal cancer	103
2.6.1	Cohort studies	103
2.6.2	Case-control studies	106
2.7	Cutaneous malignant melanoma.....	109
2.7.1	Cohort studies	109
2.7.2	Case-control studies	111
2.7.3	Meta- and pooled analysis.....	120
2.8	Thyroid cancer	120
2.9	Other cancers	122
3.	Studies of Cancer in Experimental Animals	122
3.1	Estrogen-progestogen combinations	122
3.2	Estrogens used in combined oral contraceptives	131
3.2.1	Subcutaneous implantation	134
3.2.2	Subcutaneous injection	136
3.2.3	Oral administration to transgenic mice	137
3.3	Progestogens used in combined oral contraceptives	138
4.	Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms	143
4.1	Absorption, distribution, metabolism and excretion.....	143
4.1.1	Ethinylestradiol and mestranol	144

CONTENTS

vii

4.1.2 Norethisterone	145
4.1.3 Norethisterone acetate, ethynodiol diacetate, norethynodrel and lynestrenol.....	146
4.1.4 Levonorgestrel	146
4.1.5 Desogestrel	148
4.1.6 Gestodene	149
4.1.7 Norgestimate	150
4.1.8 Newly developed progestogens.....	151
4.1.9 Interactions of other drugs with oral contraceptives.....	152
4.2 Receptor-mediated effects.....	153
4.2.1 Combined oral contraceptives	153
4.2.2 Oral contraception and HPV	159
4.2.3 Individual estrogens and progestogens	161
4.3 Genetic and related effects	164
4.3.1 Ethinylestradiol	164
4.3.2 Progestogens	166
5. Summary of Data Reported and Evaluation	168
5.1 Exposure data	168
5.2 Human carcinogenicity data	169
5.3 Animal carcinogenicity data	171
5.4 Other relevant data	174
5.5 Evaluation	175
6. References	176
Combined Estrogen–Progestogen Menopausal Therapy	203
1. Exposure Data	205
1.1 Introduction.....	205
1.2 Historical overview	206
1.3 Preparations of estrogen–progestogen menopausal therapy.....	208
1.4 Patterns of use	210
1.4.1 Patterns of use in 1990–2000	210
1.4.2 Recent trends in hormonal menopausal therapy	215
2. Studies of Cancer in Humans	217
2.1 Breast cancer	217
2.1.1 Background	217
2.1.2 Randomized controlled trials.....	218
2.1.3 Cohort studies	219
2.1.4 Case–control studies	228
2.2 Endometrial cancer	235
2.2.1 Descriptive studies.....	235
2.2.2 Randomized controlled trials.....	235
2.2.3 Cohort studies	235

2.2.4 Case-control studies	240
2.2.5 Overview	245
2.3 Cervical cancer	249
2.3.1 HPV infection	249
2.3.2 Cervical neoplasia	251
2.3.3 Overview	252
2.4 Ovarian cancer	252
2.4.1 Background	252
2.4.2 Randomized controlled trials.....	253
2.4.3 Cohort studies	253
2.4.4 Case-control studies	253
2.5 Liver cancer	255
2.6 Colorectal cancer	256
2.6.1 Background	256
2.6.2 Randomized controlled trials.....	256
2.6.3 Cohort studies	257
2.6.4 Case-control studies	259
2.7 Lung cancer.....	260
2.8 Other cancers	260
3. Studies of Cancer in Experimental Animals	261
3.1 Oral administration	261
3.1.1 Mouse	261
3.1.2 Monkey	261
3.2 Administration with a known carcinogen.....	262
4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms	263
4.1 Absorption, distribution, metabolism and excretion.....	263
4.1.1 Humans	263
4.1.2 Experimental systems	282
4.2 Receptor-mediated effects.....	282
4.2.1 Combined estrogen-progestogen therapy	283
4.2.2 Individual estrogens and progestogens	297
4.3 Side-effects other than genetic or cancer-related effects	300
4.3.1 Cardiovascular effects	300
4.3.2 Other effects.....	311
4.4 Genetic and related effects	317
4.4.1 Humans	325
4.4.2 Experimental systems	325
5. Summary of Data Reported and Evaluation	326
5.1 Exposure data	326
5.2 Human carcinogenicity data	327
5.3 Animal carcinogenicity data	329

CONTENTS

ix

5.4 Other relevant data	329
5.5 Evaluation	332
6. References	332
 ANNEXES	 373
Annex 1. Chemical and Physical Data on Compounds Used in Combined Estrogen-Progestogen Contraceptives and Hormonal Menopausal Therapy	375
1. Estrogens	376
2. Progestogens	395
Annex 2. Composition of Oral and Injectable Estrogen-Progestogen Contraceptives	431
Annex 3. Brands of Estrogen-Progestogen Contraceptives	465
Annex 4. Estrogen-Progestogen Therapies	487
 LIST OF ABBREVIATIONS	 491
 CUMULATIVE INDEX TO THE <i>MONOGRAPHS</i> SERIES	 495

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 under some circumstances. 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.

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 Carcinogen Identification and Evaluation Group, 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 Carcinogen Identification and Evaluation Group, so that corrections can be reported in future volumes.