

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 |
| MONOGRAPH ON HUMAN PAPILLOMAVIRUSES | 45 |
| Human Papillomaviruses | 47 |
| 1. Human Papillomavirus (HPV) Infection..... | 47 |
| 1.1 Evolution, structure and molecular biology | 47 |
| 1.1.1 Introduction | 47 |
| 1.1.2 Structure of the viruses | 48 |
| 1.1.3 Classification of papillomaviruses | 52 |
| 1.1.4 Evolution of papillomaviruses..... | 63 |
| 1.1.5 Function of viral proteins | 66 |
| 1.1.6 Regulation of gene expression..... | 75 |
| 1.1.7 Methylation status of cytosine in CpG sequences in the viral genome | 77 |
| 1.1.8 Replication..... | 78 |
| 1.2 Serological response | 79 |
| 1.2.1 Antigenic properties of HPV virion proteins | 80 |
| 1.2.2 Immune response to papillomavirus infection | 83 |

| | | |
|--------|--|-----|
| 1.3 | Methods for the detection of HPV infection | 87 |
| 1.3.1 | Non-molecular techniques for the detection of genital HPV infection | 87 |
| 1.3.2 | Detection of HPV proteins in infected tissues | 91 |
| 1.3.3 | Detection of HPV nucleic acids | 92 |
| 1.3.4 | Detection of HPV infections and HPV-associated cancers by serological assays | 106 |
| 1.4 | Natural history and epidemiology of HPV infection | 112 |
| 1.4.1 | Introduction | 112 |
| 1.4.2 | Transmission and acquisition..... | 113 |
| 1.4.3 | Prevalence of HPV infection | 117 |
| 1.4.4 | Incidence, persistence and clearance..... | 124 |
| 1.4.5 | Microscopic abnormalities | 128 |
| 1.4.6 | Progression to precancer | 129 |
| 1.4.7 | Progression of lesions | 130 |
| 1.4.8 | Accuracy and reliability of measurements | 132 |
| 1.4.9 | Serology..... | 132 |
| 1.4.10 | Other sites | 132 |
| 1.5 | Pathology of HPV infection of the genital tract and evidence therefrom for progression to malignancy | 136 |
| 1.5.1 | Evolution of concepts and terminology..... | 136 |
| 1.5.2 | Temporal and spatial relationships between precursors of cervical cancer and invasive cancer | 140 |
| 1.5.3 | Histological changes in HPV-related lesions of the lower female genital tract | 142 |
| 1.5.4 | Pathology of cutaneous HPV infection and non-melanoma skin cancer | 148 |
| 1.6 | Non-malignant clinical lesions (other than precursors of cancer) of established HPV etiology | 150 |
| 1.6.1 | Anogenital area | 151 |
| 1.6.2 | Upper respiratory tract..... | 153 |
| 1.6.3 | Oral cavity | 154 |
| 1.6.4 | Conjunctiva | 155 |
| 1.6.5 | Skin | 155 |
| 1.7 | Therapy and vaccination..... | 156 |
| 1.7.1 | Therapy of benign disease..... | 156 |
| 1.7.2 | Therapy of precancerous lesions | 165 |
| 1.7.3 | Therapy of invasive cancer | 167 |
| 1.7.4 | Therapeutic vaccination..... | 173 |
| 1.8 | Prophylaxis | 177 |
| 2. | Studies of Cancer in Humans | 179 |
| 2.1 | Methodological concerns | 179 |
| 2.2 | Cancer of the cervix | 183 |
| 2.2.1 | Historical perspective | 183 |

| | | |
|-------|--|-----|
| 2.2.2 | Data on pooled HPV types | 184 |
| 2.2.3 | Data on type-specific HPV | 192 |
| 2.3 | Cancer at other anogenital sites | 209 |
| 2.3.1 | Cancer of the vulva | 209 |
| 2.3.2 | Cancer of the vagina | 213 |
| 2.3.3 | Cancer of the penis | 215 |
| 2.3.4 | Cancer of the anus | 215 |
| 2.4 | Cancer of the upper aerodigestive tract | 222 |
| 2.4.1 | Cancer of the oral cavity | 222 |
| 2.4.2 | Cancer of the oropharynx and tonsil | 230 |
| 2.4.3 | Cancer of the oesophagus | 235 |
| 2.4.4 | Cancer of the larynx | 239 |
| 2.5 | Cancer of the skin and conjunctiva..... | 245 |
| 2.5.1 | Cancer of the skin | 245 |
| 2.5.2 | Cancer of the eye and conjunctiva | 259 |
| 2.6 | Cancer at other sites | 260 |
| 2.6.1 | Cancer of the nose and nasal sinuses | 260 |
| 2.6.2 | Cancer of the lung | 261 |
| 2.6.3 | Cancer of the colon and the rectum..... | 267 |
| 2.6.4 | Cancer of the breast..... | 268 |
| 2.6.5 | Cancer of the ovary | 269 |
| 2.6.6 | Cancer of the prostate | 269 |
| 2.6.7 | Cancer of the urinary bladder and urethra..... | 270 |
| 2.7 | Co-factors of HPV in cervical cancer..... | 278 |
| 2.7.1 | Non-infectious co-factors for cervical cancer | 278 |
| 2.7.2 | Infectious co-factors | 313 |
| 2.8 | Special populations | 327 |
| 2.8.1 | Skin cancer in patients with epidermodysplasia verruciformis (EV) and HPV infection | 327 |
| 2.8.2 | Studies of the incidence of HPV-associated neoplasia in transplant patients | 332 |
| 2.8.3 | Studies in human immunodeficiency virus (HIV)-infected persons | 355 |
| 3. | Studies of Animal Papillomaviruses | 412 |
| 3.1 | Non-human primate papillomaviruses | 412 |
| 3.2 | Bovine papillomavirus (BPV) | 414 |
| 3.2.1 | Heterogeneity of BPV | 414 |
| 3.2.2 | BPV 1..... | 416 |
| 3.2.3 | BPV 2..... | 417 |
| 3.2.4 | BPV 3..... | 420 |
| 3.2.5 | BPV 4..... | 420 |
| 3.2.6 | BPV 5 and BPV 6 | 422 |
| 3.2.7 | Unknown BPV types that cause cancer in cattle..... | 422 |
| 3.2.8 | BPV in equine sarcoids | 423 |

| | | |
|-------|---|-----|
| 3.3 | Equine papillomavirus (EqPV)..... | 425 |
| 3.4 | Papillomavirus in cervidae | 425 |
| 3.5 | Cottontail rabbit papillomavirus (CRPV)..... | 425 |
| 3.5.1 | Species specificity | 426 |
| 3.5.2 | Viral multiplication and tumour induction | 426 |
| 3.5.3 | Co-factors for tumour induction and progression | 426 |
| 3.5.4 | Latency of CRPV | 427 |
| 3.5.5 | CRPV in transgenic rabbits | 427 |
| 3.6 | Domestic rabbit oral papillomavirus (ROPV) | 428 |
| 3.7 | Ovine papillomatosis (OPV)..... | 428 |
| 3.8 | <i>Mastomys natalensis</i> papillomavirus (MnPV) | 430 |
| 3.9 | Mouse papillomavirus (MmPV)..... | 431 |
| 3.10 | Canine oral papillomavirus (COPV)..... | 431 |
| 3.11 | Feline papillomas | 431 |
| 3.12 | Avian papillomavirus | 432 |
| 4. | Molecular Mechanisms of HPV-induced Carcinogenesis..... | 432 |
| 4.1 | Experimental data that support the carcinogenicity of specific HPV genotypes and analyse the mechanism of HPV-linked carcinogenesis | 432 |
| 4.1.1 | Transforming capacity of HPV | 432 |
| 4.1.2 | Biochemical properties of HPV proteins..... | 435 |
| 4.1.3 | Biological properties of HPV proteins | 437 |
| 4.1.4 | Experimental evidence for a role of mucosal high-risk HPV in malignant conversion and in human cervical cancer | 440 |
| 4.1.5 | Interactions between HPV and environmental agents..... | 446 |
| 4.1.6 | Transgenic models for HPV-associated cancers | 457 |
| 4.2 | Immune mechanisms and HPV-associated neoplasia..... | 460 |
| 4.2.1 | Immunosuppression..... | 460 |
| 4.2.2 | Histological studies | 460 |
| 4.2.3 | Cell-mediated immunity | 461 |
| 4.2.4 | Major histocompatibility complex (MHC) | 463 |
| 4.2.5 | Modulation of innate immune responses by HPV | 464 |
| 5. | Summary of Data Reported and Evaluation | 465 |
| 5.1 | Human papillomavirus (HPV) infection..... | 465 |
| 5.2 | Human carcinogenicity data | 468 |
| 5.3 | Animal carcinogenicity data | 473 |
| 5.4 | Other relevant data | 474 |
| 5.5 | Evaluation | 476 |
| 6. | References | 477 |
| | LIST OF ABBREVIATIONS..... | 633 |
| | CUMULATIVE INDEX TO THE <i>MONOGRAPHS</i> SERIES | 637 |

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.