
IARC HANDBOOKS
BREAST CANCER SCREENING
VOLUME 15
IARC HANDBOOKS OF CANCER PREVENTION
IARC MONOGRAPHS
SOME ORGANOPHOSPHATE INSECTICIDES AND HERBICIDES
VOLUME 112
IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS
WHO Classification of Head and Neck Tumours
Edited by
Adel K. El-Naggar, John K.C. Chan, Jennifer R. Grandis, Takashi Takata, Pieter J. Slootweg
WHO

Section of Evidence Synthesis and Classification (ESC)

Section head
Dr Kurt Straif

Secretary
Ms Helene Lorenzen-Augros

IARC Monographs Group (IMO)

Group head
Dr Dana Loomis

Scientists
Dr Lamia Benbrahim-Tallaa
Dr Véronique Bouvard
Dr Fatiha El Ghissassi
Dr Yann Grosse
Dr Neela Guha
Dr Kathryn Guyton

Editor
Dr Heidi Mattock
(until December 2016)

Technical assistants
Ms Natacha Blavoyer
(until March 2017)
Ms Sandrine Egraz
Ms Elisabeth Elbers
(until December 2016)
Ms Solène Quennehen
(until December 2016)

Visiting scientists
Dr Robert Baan
(until September 2016)
Dr Christina Bamia
(until February 2017)
Dr Amy Hall
Dr Leslie Stayner
(until April 2017)

Students
Dr Nilmara de Oliveira Alves Brito
(until December 2016)
Dr Manoj Honaryar
(until June 2017)

IARC Handbooks Group (IHB)

Group head
Dr Béatrice Lauby-Secretan

Scientists
Dr Chiara Scoccianti
(until April 2016)
Dr Nadia Vilahur

Technical assistant/secretary
Ms Marieke Dusenberg

WHO/IARC Classification of Tumours Group (WCT)

Group head
Dr Ian A. Cree

Secretary
Ms Anne-Sophie Hameau

Project assistant
Ms Asiedua Asante

IT assistant
Mr Alberto Machado

Visiting scientist
Dr Hiroko Ohgaki

The Section of Evidence Synthesis and Classification (ESC) was created by merging the teams of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* and the *IARC Handbooks of Cancer Prevention* (formerly the Section of IARC Monographs [IMO]) with the team of the *WHO Classification of Tumours* (formerly within the Section of Molecular Pathology [MPA]) to fully benefit from synergies of similar procedures in producing the three flagship publication series, each forming a Group within the new Section. The enhanced structure came into effect on 1 August 2017.

For each volume of the *WHO Classification of Tumours*, the *IARC Monographs*, and the *IARC Handbooks*, IARC convenes international, interdisciplinary Working Groups of expert scientists to systematically review the pertinent scientific literature and to develop consensus evaluations and classifications. IARC selects these experts based on their knowledge and experience and the absence of real or apparent conflicting interests.

The *WHO Classification of Tumours* series provides an evidence-based classification of all cancer types to enable

diagnosis and research worldwide. The definitions are incorporated into the International Classification of Diseases (ICD) codes. They are fundamental to treatment of individual patients, monitoring of global cancer occurrence, and research into all aspects of cancer causation, prevention, and therapy.

The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of cancer. Sometimes called WHO's "Encyclopaedia of Carcinogens", the *IARC Monographs* have reviewed more than 1000 agents and have identified almost 500 known, probable, and possible carcinogens.

The *IARC Handbooks* complement the *IARC Monographs*' evaluations of carcinogenic hazards, providing evidence synthesis and evaluations of the cancer-preventive effects of chemopreventive agents and of primary interventions and cancer screening, using the same rigorous evaluation process as the *IARC Monographs*.

National and international health agencies can then take action to prevent avoidable exposures to known, probable, and possible carcinogens and to implement cancer-preventive strategies. Individuals, too, can use this information to make better choices that will reduce their risk of cancer.

IARC Monographs Group (IMO)

The IARC Monographs Group (IMO) is responsible for producing the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. The *IARC Monographs* are fundamental to the Agency's mission of identifying the causes of cancer. Since their inception in 1971, more than 1000 agents have been evaluated for carcinogenicity. This international, interdisciplinary endeavour provides an authoritative reference for researchers, health authorities, and the public. Health agencies worldwide rely on the *Monographs* for scientific support of actions to control exposures and prevent cancer. In addition to producing this important resource, IMO's scientific personnel contribute to the scientific literature on topics related to the *Monographs*' methodology and contents.

Major accomplishments

The Group and its predecessor, the Section of IARC Monographs, organized six Working Group meetings during the 2016–2017 biennium (Figure 1). The agents evaluated at these meetings included 10 that were recommended as high priorities for evaluation and 8 others judged to be medium or medium-to-high priorities by an Advisory Group that met in 2014. The six meetings were the following:

- Volume 115: Some industrial chemicals (2–9 February 2016)
- Volume 116: Coffee, mate, and very hot beverages (24–31 May 2016)
- Volume 117: Pentachlorophenol and some related compounds (4–11 October 2016)
- Volume 118: Welding, welding fumes,

Figure 1. An *IARC Monographs* Working Group in action. © IARC/Roland Dray.

Table 1. Summary of evaluations from the six *Monographs* meetings held in 2016–2017

Agent (Volume)	Evaluation[a]	Tumour site or type in humans with *sufficient evidence* (**bold**) or *limited evidence*	Level of evidence for carcinogenicity in experimental animals	Key characteristics of carcinogens with strong evidence[b]
Some industrial chemicals (Volume 115)				
N,*N*-Dimethylformamide	Group 2A	Testes	*Sufficient*	Multiple (1, 3, 10)
Hydrazine	Group 2A	Lung	*Sufficient*	Multiple (1, 2, 5, 10)
2-Mercaptobenzothiazole	Group 2A	Urinary bladder	*Sufficient*	None
3-Chloro-2-methylpropene	Group 2B		*Sufficient*	2
1-Bromopropane	Group 2B		*Sufficient*	Multiple (1, 5, 6, 7, 10)
N,*N*-Dimethyl-*p*-toluidine	Group 2B		*Sufficient*	None
Tetrabromobisphenol A	Group 2A[c]		*Sufficient*	Multiple (5, 7, 8)
Coffee, mate, and very hot beverages (Volume 116)				
Coffee drinking	Group 3		*Inadequate*	None[d]
Consumption of very hot beverages (> 65 °C)	Group 2A	Oesophagus	*Limited*	None
Pentachlorophenol and some related compounds (Volume 117)				
Pentachlorophenol	Group 1	**Non-Hodgkin lymphoma**	*Sufficient*	Multiple (1, 2, 5, 8, 10)
2,4,6-Trichlorophenol	Group 2B		*Sufficient*	None
Dieldrin, and aldrin metabolized to dieldrin	Group 2A	Breast	*Sufficient*	None
3,3′,4,4′-Tetrachloroazobenzene	Group 2A[c]		*Sufficient*	Multiple (6, 8, 10)
Welding, welding fumes, and some related chemicals (Volume 118)				
Welding fumes	Group 1	**Lung**, kidney	*Limited* (gas metal arc-stainless steel welding fumes)	Multiple (6, 7)
Ultraviolet radiation from welding	Group 1	**Eye (melanoma)**	N/A	None
Indium tin oxide	Group 2B		*Sufficient*	6
Molybdenum trioxide	Group 2B		*Sufficient*	None
Some chemicals that cause tumours of the urinary tract in rodents (Volume 119)				
1-*tert*-Butoxypropan-2-ol	Group 2B		*Sufficient*	None
β-Myrcene	Group 2B		*Sufficient*	None
Furfuryl alcohol	Group 2B		*Sufficient*	1
Melamine	Group 2B		*Sufficient*	6
Pyridine	Group 2B		*Sufficient*	None
Tetrahydrofuran	Group 2B		*Sufficient*	None
Vinylidine chloride	Group 2B		*Sufficient*	None
Benzene (Volume 120)				
Benzene	Group 1	Acute non-lymphocytic leukaemia	*Sufficient*	Multiple (1, 2, 3, 5, 7, 8, 10)

N/A, not applicable.

[a] Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; Group 4, probably not carcinogenic to humans.

[b] Numbers correspond to one or more of the 10 key characteristics of carcinogens, as identified by Smith et al. (2016) and indicated in the *IARC Monographs* Instructions to Authors.

[c] The Group 2A classifications of tetrabromobisphenol A and 3,3′,4,4′-tetrachloroazobenzene are based on *sufficient evidence of carcinogenicity* in experimental animals and strong mechanistic evidence.

[d] Strong evidence for antioxidant effects.

and some related chemicals (21–29 March 2017)
• Volume 119: Some chemicals that cause tumours of the urinary tract in rodents (6–13 June 2017)
• Volume 120: Benzene (10–17 October 2017).

The focus and results of these meetings (Table 1) illustrate the unique ability of the *Monographs* to evaluate the carcinogenicity of diverse agents, ranging from chemicals tested only in animal bioassays to widely consumed beverages with data from hundreds of epidemiological studies.

The 23 evaluations achieved in these meetings included 13 new classifications of agents never before evaluated by IARC and re-evaluations of 10 agents considered previously. All of the re-evaluations except for those of coffee drinking and benzene resulted in a higher classification as a result of evidence accumulated since the agent was last considered. For benzene, three new cancer sites with *limited evidence* of carcinogenicity were identified, and analyses suggesting a linear exposure–response relationship were completed.

A concise summary of each evaluation with the classification, accompanying rationale, and key references is published in *The Lancet Oncology*. Full details and supporting data are provided in the complete *Monograph*, which is expected to be published about a year after the meeting. Both are available for free download on the *Monographs* website (http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php).

Publications

During the 2016–2017 biennium, the following *IARC Monographs* were published:

- Volume 113: 2,4-Dichlorophenoxyacetic acid (2,4-D) and Some Organochlorine Insecticides (Monograph on 2,4-D) (2016)
- Volume 112: Some Organophosphate Insecticides and Herbicides (2017)
- Volume 111: Some Nanomaterials and Some Fibres (2017)
- Volume 110: Some Chemicals Used as Solvents and in Polymer Manufacture (2016)
- Volume 109: Outdoor Air Pollution (2016)
- Volume 108: Some Drugs and Herbal Products (2016)
- Volume 107: Polychlorinated Biphenyls and Polybrominated Biphenyls (2016).

Lessons learned from the glyphosate evaluation

The March 2015 classification of glyphosate as *probably carcinogenic to humans* (Group 2A) has had worldwide impact. IARC has since served as a scientific resource, providing invited presentations to the European Parliament and to national and international health agencies, disseminating scientific references, and accelerating the publication of the *Monograph*. IARC's reach is exemplified by subsequent health agency actions, including California's listing of glyphosate as a carcinogen (https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-tetrachlorvinphos-parathion-malathion-glyphosate; https://oehha.ca.gov/proposition-65/chemicals/glyphosate). IARC's evaluation revealed important data gaps (e.g. on exposure during manufacturing, community spraying operations, and in the general population) and stimulated scientific research publications (https://www.ncbi.nlm.nih.gov/pubmed/?term=glyphosate).

The glyphosate evaluation also triggered orchestrated and unprecedented threats to IARC's scientific independence. The Agency has had positive impacts through its response to these serious challenges. On its website, IARC documented attempts by interested parties to intimidate and harass the glyphosate Working Group, IARC scientists, and the Agency itself. This proved an important resource for IARC's governing and scientific bodies, who were also lobbied by vested interests and worked closely with the Agency in responding. At the same time, IARC has reinforced its strong procedures on conflict of interest disclosure and transparency. IARC collaborated closely with the WHO legal team to protect independent scientists serving future *Monograph* evaluations from harassment. In conducting evaluations, IARC continues to rely on studies in the public domain and available for independent scientific review, a transparent practice being discussed and adopted internationally (http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000526.jsp&mid=WC0b01ac0580789730). Further to its interests in transparency, IARC has pursued full disclosure of conflicts in stakeholder-sponsored publications aimed at discrediting independent science.

IARC Handbooks Group (IHB)

The IARC Handbooks Group (IHB) is responsible for producing the *IARC Handbooks of Cancer Prevention*. The *IARC Handbooks* programme was initiated in 1995 to complement the *IARC Monographs* by providing evaluations of interventions and strategies to cancer prevention. The same rigorous procedures of critical review and evaluation as for the *IARC Monographs* are used. *Handbook* evaluations have included chemopreventive agents, preventive actions, effectiveness of screening, and effectiveness of tobacco control.

Volume 16: Body fatness (5–12 April 2016)

The topic of this *Handbook* was selected in relation to the United Nations/WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases to reduce obesity worldwide.

Evidence has accumulated to show that obesity is a risk factor for several cancers in addition to those identified in a previous *Handbook* (Volume 6). A Working Group of 20 international experts met in Lyon and reviewed data from more than 1000 studies to evaluate (i) the association between various anthropometric

measures of body fatness and some 25 cancer sites or types, (ii) the impact of overweight/obesity at different ages on cancer risk, including the impact on cancer risk of weight change during early life or young adulthood, and (iii) the effect in cancer patients of overweight/obesity and of weight loss on cancer recurrence or cancer-related survival.

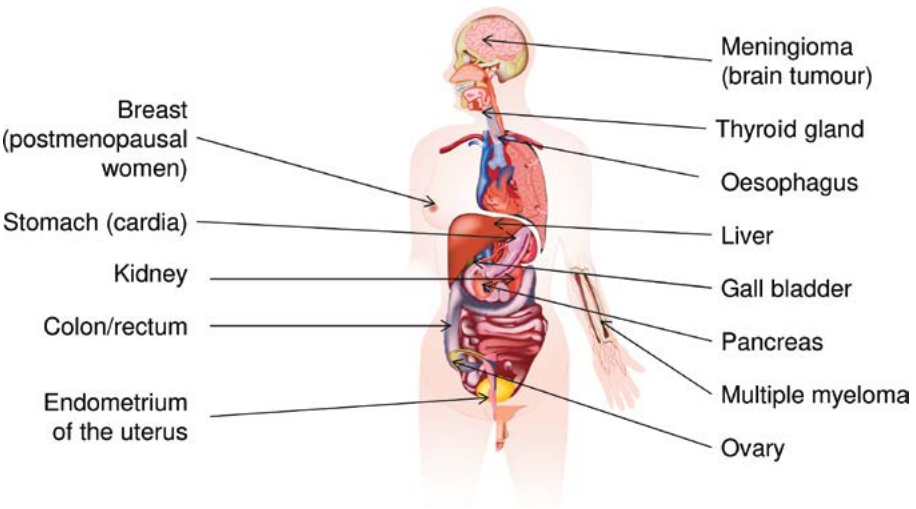
The Working Group concluded that there is *sufficient evidence* in humans for the cancer-preventive effect of absence of excess body fatness. Absence of excess body fatness reduces the risk of cancers of the colon and rectum, pancreas, gall bladder, oesophagus (adenocarcinoma), gastric cardia, liver (hepatocellular carcinoma), kidney (renal cell carcinoma), ovary, endometrium of the uterus, breast in postmenopausal women, and thyroid, and of meningioma and multiple myeloma. In addition, it may reduce the risk of fatal prostate cancer, diffuse large B-cell lymphoma, and breast cancer in men. Results of studies in experimental animals concur with those in humans. There is *sufficient evidence* in experimental animals for a cancer-preventive effect of limitation of body weight gain by dietary restriction, for cancers of the mammary gland, colon, liver, pancreas, skin, and pituitary gland. In addition, an association between limitation of body weight gain by dietary restriction and reduced cancer occurrence was observed for cancer of the prostate and for lymphoma and leukaemia. Several mechanisms linking excess body fatness with carcinogenesis were identified, including chronic inflammation and dysregulation of the metabolism of sex hormones. These results provide further scientific evidence that absence of excess body fatness can reduce the risk of many cancers, and highlight eight additional cancer sites that have now also been linked with overweight/obesity (Figure 2).

Volume 17: Colorectal cancer screening (14–21 November 2017)

In November 2017, the *IARC Handbooks* evaluated the published scientific evidence on the benefits and harms of colorectal cancer screening. This evaluation was timely because of the increasing incidence of colorectal cancer worldwide, including in low- and middle-income countries, and because several countries have set up screening programmes with different procedures and strategies. A Working Group of 23 international experts met at IARC. The Working Group reviewed the available data for endoscopic methods (colonoscopy and flexible sigmoidoscopy), stool-based tests for blood (guaiac-based and immunochemical tests), computed tomography colonography, and other emerging tests. The beneficial effects of colorectal cancer screening were evaluated in terms of reduction in incidence, reduction in mortality, and benefit-to-harm ratio.

The systematic review of the scientific literature and the Working Group's conclusions can support the development of guidelines by WHO and the implementation of organized screening programmes by health care systems. The outcome of the meeting will be published in the *New England Journal of Medicine* in early 2018.

Figure 2. Absence of excess body fatness reduces the risk of these types of cancer (*IARC Handbooks* Volume 16). © IARC.



WHO/IARC Classification of Tumours Group (WCT)

The WHO/IARC Classification of Tumours Group (WCT) is a new Group within the new Section of Evidence Synthesis and Classification (ESC), established on 1 August 2017. WCT has taken over responsibility for production of the *WHO Classification of Tumours* series (WHO Blue Books) from the former Section of Molecular Pathology (MPA). Dr Hiroko Ohgaki, who retired in July 2017, provided the leadership to the Blue Books volumes during the majority of the biennium covered in this report.

The information and cases illustrated within the WHO Blue Books provide the standards against which cancers are classified and diagnosed worldwide. The diagnosis and classification of individual cancers underpins research into cancer causation, prevention, diagnosis, and treatment. Now in its fourth edition, the WHO Blue Books series has become an essential resource for diagnosis by histopathologists and an important reference for all involved in cancer research.

During the 2016–2017 biennium, the following volumes were published:

- *WHO Classification of Tumours of the Urinary System and Male Genital Organs*, 4th edition (2016)
- *WHO Classification of Tumours of the Central Nervous System*, revised 4th edition (2016)
- *WHO Classification of Head and Neck Tumours*, 4th edition (2017)
- *WHO Classification of Tumours of Endocrine Organs*, 4th edition (2017)
- *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, revised 4th edition (2017).

Pathology is currently undergoing a more rapid transformation than at any time during the past 30 years, as a result of the introduction of new technologies. Whereas cancer classification has previously been based on consensus of histopathological opinion, the understanding of cancer at a molecular level is now at a point where it needs to be integrated into diagnosis. In addition, digital pathology and image analysis are producing new insights, and providing quantitative justification of many existing diagnostic criteria, while challenging others. Finally, the pace of improvement in computer technology, including artificial intelligence, is already producing clinically applicable aids to diagnosis, and this trend is likely to accelerate. There is an urgent need to integrate these facets of diagnosis into cancer classification.

WCT is taking a leading role in cancer classification and pathology internationally, and in the next year will be responsible for the publication of the two remaining volumes of the fourth edition. *WHO Classification of Skin Tumours* is being prepared by four volume editors (Dr David E. Elder, Dr Daniela Massi, Dr Richard Scolyer, and Dr Rein Willemze) and 178 contributors from 25 countries. The consensus and editorial meeting was held at IARC on 24–26 September 2017, and the volume is scheduled to be published in spring 2018. *WHO Classification of Tumours of the Eye*, the last volume of the fourth edition, is being prepared by three volume editors (Dr Hans Grossniklaus, Dr Charles Eberhart, and Dr Tero Kivelä) and 61 contributors from 21 countries. The consensus and editorial meeting will be held at IARC on 11–13 January 2018. The volume is scheduled to be published in autumn 2018.

Planning for the fifth edition is at an advanced stage. This will incorporate new information and electronic content, based on expert consensus review of reproducible peer-reviewed published evidence. It will define the requirements for diagnosis, applicable to patients living in high-, middle-, or low-income countries. The major pathology organizations worldwide are nominating members of a new Editorial Board, which will be tasked with improving the timeliness and quality of the WHO Blue Books.