

SECTION OF EVIDENCE SYNTHESIS AND CLASSIFICATION (ESC)

Section head

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Secretary

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IARC Monographs Group (IMO)

Group head

Dr Mary Schubauer-Berigan

Scientists

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Ms Jennifer Nicholson

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 (until December 2021)

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Postdoctoral fellow

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 (until August 2021)

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 Ms Samantha Goodman
 (until October 2021)
 Mr Yaqi Liu (until December 2020)
 Ms Samantha Vega
 (until December 2020)

IARC Handbooks Group (IHB)

Group head

Dr Béatrice Lauby-Secretan

Scientist

Dr Véronique Bouvard

Secretary/technical assistant

Ms Marieke Dusenberg

Technical assistants

Ms Niree Kraushaar
 Ms Solène Quennehen

Visiting scientist

Dr Suzanne Nethan

WHO Classification of Tumours Group (WCT)

Group head

Dr Ian A. Cree

Scientists

Dr Iciar Indave (systematic reviewer)
 Dr Valerie White (pathologist)
 (until March 2021)

Secretary

Ms Anne-Sophie Bres

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 (until October 2020)
 Dr Vishal Rao (until July 2021)
 Dr Valerie White

Students

Mr Zi Long Chow
 (until January 2020)
 Mr Ramon Cierco Jiménez

Trainee

Mr Javier Del Aguila

The Section of Evidence Synthesis and Classification (ESC) comprises three Groups: the IARC Monographs Group (IMO), the IARC Handbooks Group (IHB), and the WHO Classification of Tumours Group (WCT). With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, ESC was renamed as the Evidence Synthesis and Classification Branch.

The IARC Monographs Group (IMO) produces the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*, a series of systematic scientific reviews that identify environmental

factors that may cause cancer in humans. IMO also organizes advisory groups and international scientific workshops on key issues pertaining to the assessment of carcinogens and their mechanisms.

The IARC Handbooks Group (IHB) produces the *IARC Handbooks of Cancer Prevention*. This series of systematic scientific reviews identifies interventions and strategies that can reduce the risk of cancer or mortality from cancer.

The WHO Classification of Tumours Group (WCT) produces the *WHO Classification of Tumours* series (also known as the WHO Blue Books). Now in its

fifth edition as a series of 14 volumes, it provides the definitive and internationally accepted standards for the diagnosis of tumours.

For each volume of the *IARC Monographs*, the *IARC Handbooks*, and the *WHO Classification of Tumours*, IARC convenes international, interdisciplinary groups of expert scientists and physicians to systematically review the pertinent scientific literature and develop consensus evaluations and classifications. IARC selects these experts on the basis of their knowledge and experience as well as an absence of conflicting interests.

IARC HANDBOOK ON CERVICAL CANCER SCREENING

At the World Health Assembly in May 2018, WHO Director-General Dr Tedros Adhanom Ghebreyesus made a global call for action towards the elimination of cervical cancer. The *IARC Handbooks* programme responded to this call with the preparation of Volume 18: Cervical Cancer Screening. This volume updates the evaluations of the effectiveness of the current methods of cervical cancer screening and provides statements of the comparative effectiveness of these methods.

This *Handbook* was prepared in close collaboration with WHO headquarters, for the updating of the *WHO Screening and Treatment Recommendations to Prevent Cervical Cancer*. Preliminary steps involved the identification of topics for contribution to the recommendations, harmonization of the protocols for systematic review, and coordination of the calendars so that the two projects would evolve in parallel. The outcome of the collaboration was that the *IARC Handbooks* evaluations of the effectiveness of screening with human papillomavirus (HPV) DNA testing, cytology, and visual inspection with acetic acid (VIA), and the statements of their comparative effectiveness, served as a basis for the WHO recommendations.

Announcement of the webinar held on 6 July 2021. Reproduced from <https://www.who.int/news-room/events/detail/2021/07/06/default-calendar/reaching-2030-cervical-cancer-elimination-targets>, Copyright 2021.

The graphic is a teal and red poster for a webinar. It features the WHO logo and the HRP logo (Human Resources for Health Research for Impact). The main title is 'Reaching the 2030 targets for cervical cancer elimination: New WHO recommendations for screening and treatment'. Below the title, it says 'Join the launch of these two new products'. Two dark teal boxes highlight the products: 'WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition' and 'IARC Handbooks of Cancer Prevention Volume 18 – Cervical Cancer Screening'. The time is listed as 'Time: 09:00-10:30 CET, repeated at 14:30-16:00 CET'. It also states 'No registration required' and provides a link to join (bit.ly/cervicalcancerGL) and a password (LAUNCH123). A contact email (corleamy@who.int) is at the bottom right. On the right side, there is a stylized illustration of a woman's head and neck in profile, with a red background behind her neck and shoulders.

Such collaboration represents a major milestone for the *IARC Handbooks* programme, and a similar collaboration is currently under way with the WHO Regional Office for South-East Asia for the preparation of Volume 19: Oral Cancer Prevention.

IARC MONOGRAPHS GROUP (IMO)

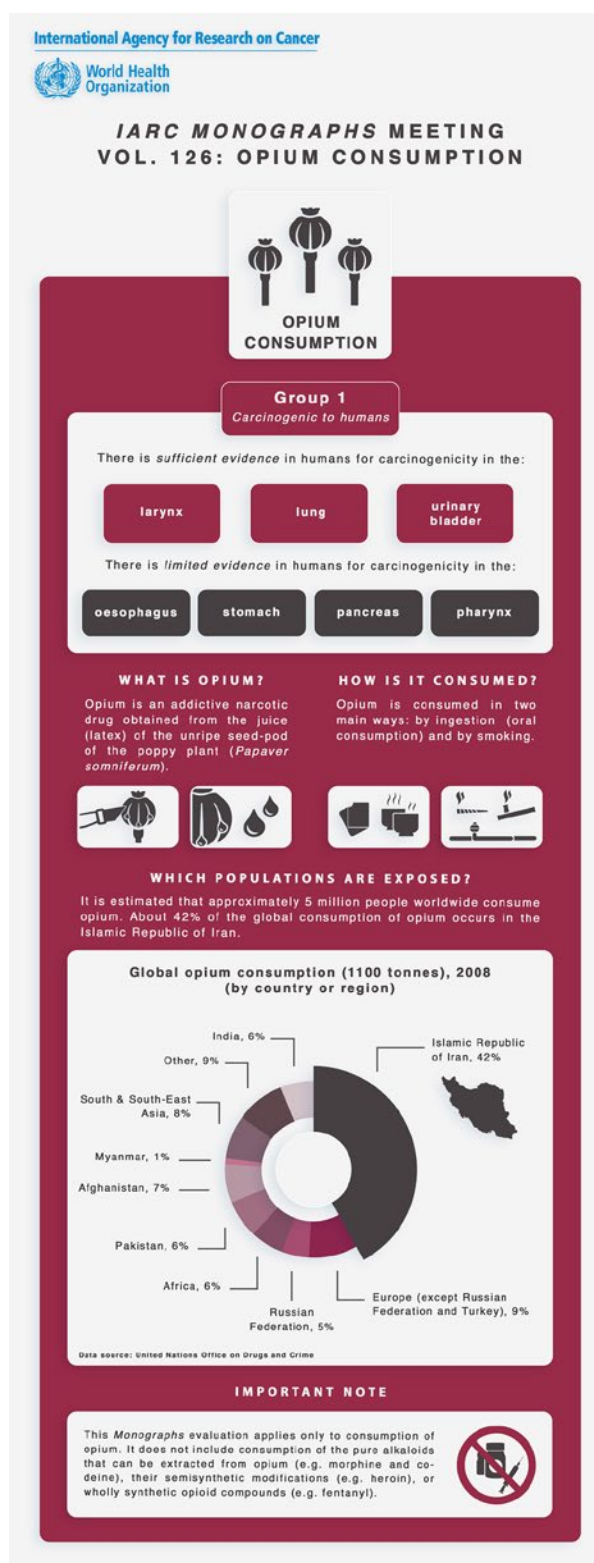
The IARC Monographs Group (IMO) is responsible for producing the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*. The *IARC Monographs* are fundamental to the Agency's mission of identifying the preventable causes of cancer in humans. Since the inception of the *Monographs* programme in 1971, 1032 agents have been evaluated one or more times 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 the scientific support of actions to control exposures and prevent cancer. In addition to producing this important resource, the scientific personnel of IMO contribute to the scientific literature on topics related to the methodology and contents of the *Monographs*.

MAJOR ACCOMPLISHMENTS

IMO organized five Working Group meetings during the 2020–2021 biennium. Because of the travel restrictions put in place during the COVID-19 pandemic, all of the meetings were held fully remotely, and they were extended beyond 8 days to accommodate the time zones associated with global remote participation. The agents evaluated at the five Working Group meetings included several that had been recommended as priorities for evaluation:

- Volume 127: Some Aromatic Amines and Related Compounds (25 May–12 June 2020)
- Volume 126: Opium Consumption (11–20 September 2020)
- Volume 128: Acrolein, Crotonaldehyde, and Arecoline (29 October–13 November 2020)
- Volume 129: Gentian Violet, Leucogentian Violet, Malachite Green, Leucomalachite Green, and CI Direct Blue 218 (22 February–5 March 2021)

Figure 1. *IARC Monographs Volume 126: Opium Consumption*. © IARC.



• Volume 130: 1,1,1-Trichloroethane and Four Other Industrial Chemicals (7–22 October 2021).

Table 1 presents the results of these meetings, highlighting the important contribution of the *Monographs* in evaluating the carcinogenicity of diverse agents. These agents range from chemicals tested only in animal bioassays to complex exposures that have been evaluated in epidemiological and mechanistic studies, such as opium consumption (Figure 1).

The evaluations reached in these meetings included 20 classifications, comprising 14

agents never before evaluated by IARC and re-evaluations of 6 agents considered previously.

A concise summary of each evaluation with the classification, accompanying rationale, and key references is published in *The Lancet Oncology* within several weeks of each meeting. Full details and supporting data are provided in the complete *Monographs* volume, which is expected to be published about a year after each meeting. Both are available to download for free from the IARC Publications website (<https://publications.iarc.fr/>).

PUBLICATIONS

During the 2020–2021 biennium, the following *IARC Monographs* volumes were published:

Volume 128: Acrolein, Crotonaldehyde, and Arecoline (2021)

Volume 127: Some Aromatic Amines and Related Compounds (2021)

Volume 126: Opium Consumption (2021)

Volume 125: Some Industrial Chemical Intermediates and Solvents (2020)

Volume 124: Night Shift Work (2020)

Volume 123: Some Nitrobenzenes and Other Industrial Chemicals (2020).

Table 1. Summary of evaluations from the five *Monographs* meetings held in 2020–2021

Agent (Volume)	Evaluation ^a	Strength of evidence of cancer in humans (tumour type provided for <i>limited or sufficient</i> evidence)	Strength of evidence for carcinogenicity in experimental animals	Key characteristics of carcinogens with strong evidence ^b
<i>Opium Consumption (Volume 126)</i>				
Opium consumption	Group 1	<i>Sufficient</i> (larynx, lung, urinary bladder) <i>Limited</i> (oesophagus, stomach, pancreas, pharynx)	<i>Sufficient</i>	2
<i>Some Aromatic Amines and Related Compounds (Volume 127)</i>				
Aniline ^c	Group 2A	<i>Inadequate</i>	<i>Sufficient</i>	Multiple (1, 2, 5, 10)
Aniline hydrochloride ^c	Group 2A	<i>Inadequate</i>	<i>Sufficient</i>	Multiple (1, 2, 5, 10)
<i>ortho</i> -Anisidine ^c	Group 2A	<i>Inadequate</i>	<i>Sufficient</i>	Multiple (1, 2, 10)
<i>ortho</i> -Anisidine ^c hydrochloride	Group 2A	<i>Inadequate</i>		Multiple (1, 2, 10)
<i>ortho</i> -Nitroanisole ^c	Group 2A	<i>Inadequate</i>	<i>Sufficient</i>	Multiple (1, 2, 10)
Cupferron	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	2
<i>Acrolein, Crotonaldehyde, and Arecoline (Volume 128)</i>				
Acrolein	Group 2A	<i>Inadequate</i>	<i>Sufficient</i>	Multiple (1, 2, 3, 5, 6, 7, 10)
Crotonaldehyde	Group 2B	<i>Inadequate</i>	<i>Limited</i>	Multiple (1, 2, 5, 6)
Arecoline	Group 2B	<i>Inadequate</i>	<i>Limited</i>	Multiple (1, 2, 3, 5)
<i>Gentian Violet, Leucogentian Violet, Malachite Green, Leucomalachite Green, and CI Direct Blue 218 (Volume 129)</i>				
Gentian Violet	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	None
Leucogentian Violet	Group 3	<i>Inadequate</i>	<i>Inadequate</i>	None
Malachite Green	Group 3	<i>Inadequate</i>	<i>Limited</i>	None
Leucomalachite Green	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	None
CI Direct Blue 218	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	None
<i>1,1,1-Trichloroethane and Four Other Industrial Chemicals (Volume 130)</i>				
1,1,1-Trichloroethane	Group 2A	<i>Limited</i>	<i>Sufficient</i>	None
Hydrazobenzene	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	None
<i>N</i> -Methylolacrylamide	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	None
Diphenylamine	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	None
Isophorone	Group 2B	<i>Inadequate</i>	<i>Sufficient</i>	None

^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.

^b Numbers correspond to one or more of the 10 key characteristics of carcinogens, as identified by Smith et al. (2016; <https://www.ncbi.nlm.nih.gov/pubmed/?term=26600562>) and described in the Preamble to the *IARC Monographs* (<https://monographs.iarc.fr/preamble-to-the-iarc-monographs/>).

^c This agent was determined to belong to a class of aromatic amines for which several members (including *ortho*-toluidine, 2-naphthylamine, and 4-aminobiphenyl) have been classified as *carcinogenic to humans* (Group 1).

IARC HANDBOOKS GROUP (IHB)

The IARC Handbooks Group (IHB) is responsible for producing the *IARC Handbooks of Cancer Prevention*. The objective of the *IARC Handbooks* is to publish critical reviews and evaluations of interventions and strategies that can reduce the burden of cancer. The principles of systematic review are applied to the identification, screening, synthesis, and evaluation of the evidence. Interventions or strategies are selected for evaluation on the basis of published scientific evidence of preventive effects and potential public health relevance. *Handbook* evaluations have included chemopreventive agents, preventive actions, effectiveness of screening, and effectiveness of tobacco control measures. The *Handbooks* are used worldwide by public health representatives to set guidelines and recommendations for cancer prevention.

MAJOR ACCOMPLISHMENTS

IHB organized two meetings during the 2020–2021 biennium: the Working Group meetings for *IARC Handbooks* Volume 18 (Cervical Cancer Screening) and Volume 19 (Oral Cancer Prevention). Because of the COVID-19 pandemic, both meetings were held fully remotely.

VOLUME 18: CERVICAL CANCER SCREENING (JUNE–OCTOBER 2020)

Cervical cancer screening was re-evaluated by the *IARC Handbooks*. The Working Group considered new screening technologies, including human papillomavirus (HPV) testing, and provided statements of the comparative effectiveness of established screening methods (Figure 2). This *Handbook* was published in response to the WHO Cervical Cancer Elimination Initiative, which was launched after the WHO Director-General's call for action at the World Health Assembly in May 2018. This was the first close collaboration between the *Handbooks* programme and WHO headquarters, and it enabled the development and updating of WHO recommendations.

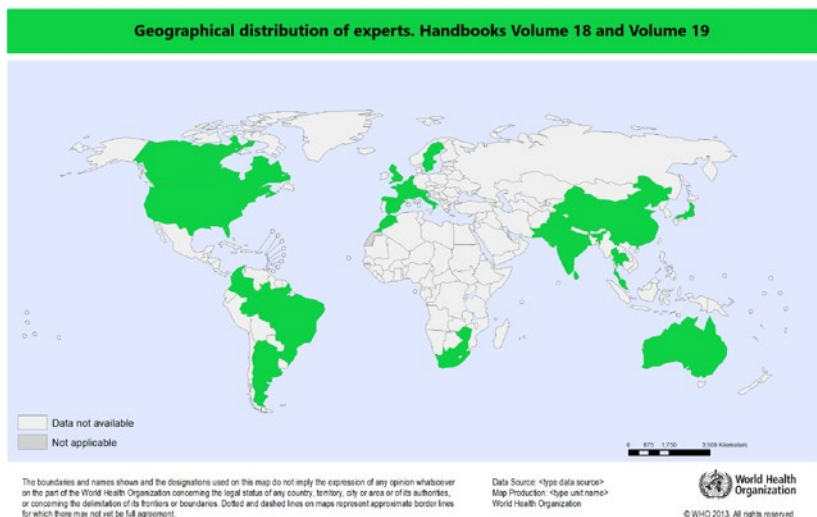
A summary of the outcome of the meeting, which took place remotely between June and October 2020, was published in *The New England Journal of Medicine* in November 2021 (Bouvard et al., 2021).

VOLUME 19: ORAL CANCER PREVENTION (SEPTEMBER–DECEMBER 2021)

This *Handbook* is a first-time evaluation of all approaches to oral cancer prevention, with a special emphasis on low- and middle-income countries and on oral cancer associated with the use of smokeless tobacco and products derived from the areca nut. This *Handbook* will cover primary prevention through the evaluation of whether reduction of exposure to the established (IARC Group 1) risk factors leads to reduced incidence or mortality, primary prevention through interventions aiming to reduce exposure to smokeless tobacco or products derived from the areca nut, and secondary prevention through screening.

A scoping meeting for Volume 19 took place in February 2021, and the meeting took place fully remotely between September and December, first in subgroups and then in plenary sessions. The evaluations reached at this *Handbooks* meeting will lead to the development of tools and recommendations for the implementation of prevention measures in those countries most in need.

Figure 2. The Working Group for IARC Handbooks Volume 18: Cervical Cancer Screening, the geographical distribution of the participants, and the summarized outcomes of the meeting. All © IARC.



International Agency for Research on Cancer
 World Health Organization

IARC Handbooks Volume 18: Cervical Cancer Screening

Estimated age-standardized incidence rates (World) in 2020, cervix uteri, all ages

EVALUATIONS OF SCREENING METHODS

Conventional cytology	Liquid-based cytology	HPV nucleic acid testing	Visual inspection with acetic acid (VIA)	Cytology based on Romanowsky-Giemsa staining
Group A	Group A	Group A	Group A/B	Group C
Benefits outweigh the harms for women aged 30 years and older. There is less certainty for women younger than 30 years and for women older than 65 years.	Benefits outweigh the harms for women aged 30 years and older. Benefits and harms are very similar to those of conventional cytology, owing to a reduced proportion of inadequate results but slightly higher referral rates.	Benefits outweigh the harms for women aged 30 years and older. There is less certainty for women younger than 30 years, especially when triage testing of HPV-positive women is not in place.	Benefits may outweigh harms, but only in VIA screening programmes implemented by well-trained providers, with quality assurance and with appropriate treatment of lesions and follow-up care.	No comparative study on accuracy, efficacy, and effectiveness of the technique in cervical cancer screening was available to the Working Group.

COMPARATIVE EFFECTIVENESS OF SCREENING METHODS

HPV DNA testing versus VIA	HPV DNA testing versus cytology	HPV DNA testing alone versus co-testing
HPV DNA testing showed higher reduction in cervical cancer incidence and mortality than VIA, which outweighed the potential increase in positive tests and colposcopy referrals.	HPV DNA testing showed higher reduction in cervical cancer incidence and mortality than cytology, which outweighed the increase in positive tests and colposcopy referrals, and potential increase in psychological harms.	Compared with HPV DNA testing, co-testing (HPV DNA + cytology) showed minimal increase in sensitivity and lower specificity for precancerous lesions, resulting in increased colposcopy referrals and decreased positive predictive value.

<https://handbooks.iarc.fr>

WHO CLASSIFICATION OF TUMOURS GROUP (WCT)

The work of the WHO Classification of Tumours Group (WCT) encompasses the *WHO Classification of Tumours* series (also known as the WHO Blue Books), the IARC histopathology laboratory, and the International Collaboration for Cancer Classification and Research (IC³R).

WHO BLUE BOOKS

Tumour classification is a major scientific endeavour of considerable importance, underpinning the diagnosis of all cancer worldwide. In recent years, the series' adoption of a relational database approach and a hierarchical classification according to Linnaean principles has vastly improved the standardization of tumour classification across anatomical sites, requiring authors to consider all

characteristics of each tumour and highlighting the increasingly multidisciplinary nature of cancer diagnosis.

During the 2020–2021 biennium, the following volumes were published:

- *Soft Tissue and Bone Tumours*, fifth edition (2020)
- *Female Genital Tumours*, fifth edition (2020)
- *Thoracic Tumours*, fifth edition (2021).

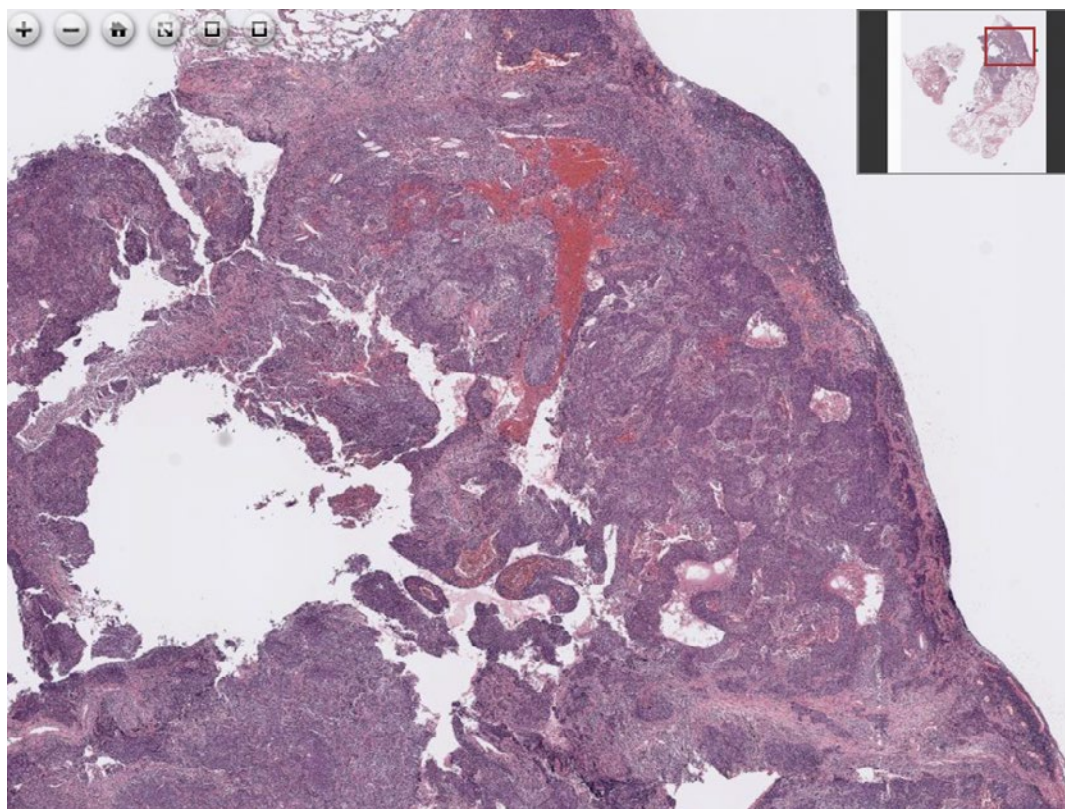
A fourth volume (*Central Nervous System Tumours*, fifth edition) is almost complete. The 14-volume fifth edition of the *WHO Classification of Tumours* series is well under way, with a further five volumes in various stages of production. The books and the accompanying website (WHO Classification of Tumours Online; <https://tumourclassification.iarc.who.int/>) have both been very well received, and

use of the classification is expanding in the wider biomedical community (e.g. among radiologists). Production of the *WHO Classification of Tumours* series continues to be funded by book sales and website subscriptions alone.

HISTOPATHOLOGY LABORATORY

During this biennium, thanks to the IARC Scientific Council and Governing Council Special Funds (2021), the histopathology laboratory has modernized its equipment, with a corresponding increase in capacity and capability. It continues to operate with a single scientist but provides technical support to a wide range of projects across the Agency, including providing whole slide images for the WHO Blue Books (Figure 3). The laboratory is increasingly involved in

Figure 3. A lymphoepithelial carcinoma of the lung showing a syncytial growth pattern of tumour cells with large vesicular nuclei (whole slide image). © IARC.



all aspects of digital and computational pathology, including artificial intelligence and machine learning projects. Its capacity to produce high-quality immunohistochemistry for research projects has been enhanced by the acquisition of an automated immunostainer, and older equipment used to produce slides and frozen sections is being updated. All of the laboratory's equipment will eventually be moved to the Nouveau Centre building, which will have a dedicated histopathology laboratory similar to the one currently in use. Collaborations with Centre Léon Bérard and other institutions continue to expand.

INTERNATIONAL COLLABORATION FOR CANCER CLASSIFICATION AND RESEARCH (IC³R)

The translation of research findings into practice is never easy, and the sheer volume of information produced each year can be daunting for those involved. Crucially, scientific information must be of high quality to be of use. Unlike in other branches of medicine, the translation of cancer research into diagnostic practice is largely in the hands of its users, through incorporation into the WHO Classification of Tumours (with the exception of health technology assess-

ment, which is the remit of health-care services within individual countries).

The International Collaboration for Cancer Classification and Research (IC³R; <https://ic3r.iarc.who.int/>) was established to bring cancer research institutions together to improve research quality and to meet the need for evaluation and synthesis of research findings (Figure 4). Currently, 22 institutions are involved in IC³R, and it is funded by membership dues.

Figure 4. The WHO Classification of Tumours (WCT) is run by an Editorial Board composed of standing members nominated by major societies, and expert members selected for each volume. The International Collaboration for Cancer Classification and Research (IC³R) has been formed to bring together cancer research institutes around the world interested in diagnosis to improve the evidence base for the classification. The classification can also be used to identify gaps and priorities for future research. © IARC.

