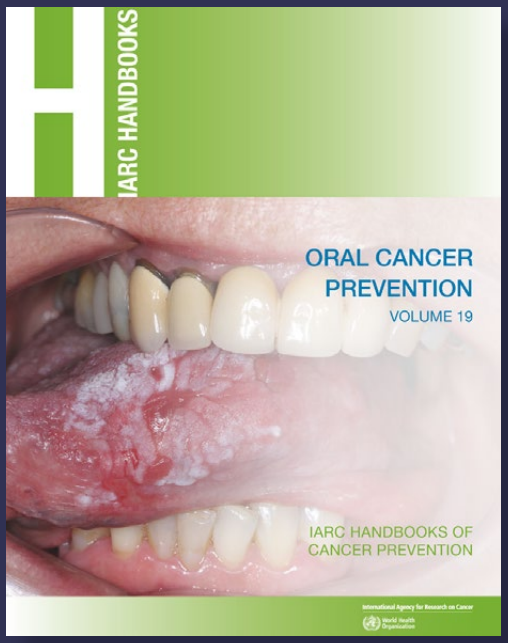
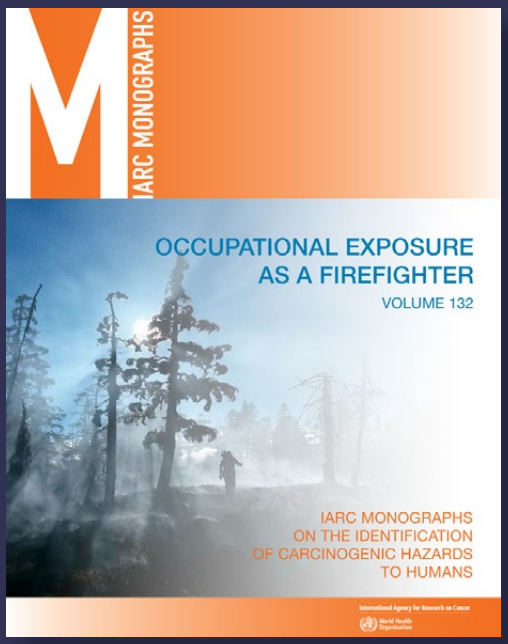
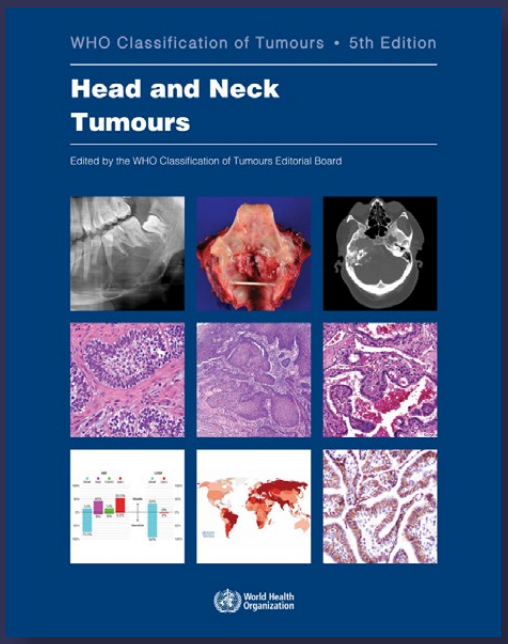

IARC HANDBOOKS
ORAL CANCER PREVENTION
VOLUME 19
IARC HANDBOOKS OF CANCER PREVENTION
International Agency for Research on Cancer
World Health Organization


IARC MONOGRAPHS
OCCUPATIONAL EXPOSURE AS A FIREFIGHTER
VOLUME 132
IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS
International Agency for Research on Cancer
World Health Organization


WHO Classification of Tumours • 5th Edition
Head and Neck Tumours
Edited by the WHO Classification of Tumours Editorial Board
World Health Organization

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The Evidence Synthesis and Classification Branch (ESC) comprises three programmes: the IARC Handbooks Programme, the IARC Monographs Programme, and the WHO Classification of Tumours Programme.

The IARC Handbooks Programme produces the *IARC Handbooks of Cancer Prevention*, a series of systematic scientific reviews that identify interventions and strategies that may reduce the risk of cancer or mortality from cancer. The programme also runs collaborative projects on topics related to recent *Handbooks* volumes.

The IARC Monographs Programme 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. The programme also organizes advisory groups and international scientific workshops on key issues pertaining to the assessment of carcinogens and their mechanisms.

The WHO Classification of Tumours Programme 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, this series provides the definitive and internationally accepted standards for the diagnosis of tumours.

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

IARC Monographs Programme (IMO)

The IARC Monographs Programme (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* in 1971, 1046 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, the scientific personnel of IMO contribute to the scientific literature on topics related to the methodology and contents of the *Monographs*.

Major accomplishments

The IARC Monographs Programme organized five Working Group meetings and two Scientific Workshops during the 2022–2023 biennium. The meeting for Volume 131 was held fully remotely, because of the travel restrictions put in place during the COVID-19 pandemic. The other meetings were held as hybrid meetings, incorporating lessons learned from the remote meetings. The agents evaluated at the five Working Group meetings included a range of agents that had been recommended as priorities for evaluation:

- Volume 131: Cobalt, Antimony Compounds, and Weapons-Grade Tungsten Alloy (2–18 March 2022)
- Volume 132: Occupational Exposure as a Firefighter (7–14 June 2022)
- Scientific Workshop on Epidemiological Bias Assessment in Cancer Hazard Identification (17–21 October 2022)
- Volume 133: Anthracene, 2-Bromopropane, Butyl Methacrylate, and Dimethyl Hydrogen Phosphite (28 February–7 March 2023)
- Volume 134: Aspartame, Methyleugenol, and Isoeugenol (6–13 June 2023)
- Scientific Workshop on Key Characteristics-associated End-points for Evaluating Mechanistic Evidence of Carcinogenic Hazards (25–28 July 2023)
- Volume 135: Perfluorooctanoic Acid (PFOA) and Perfluorooctanesulfonic Acid (PFOS) (7–14 November 2023)

The focus and results of these meetings (Table 1) illustrate the unique ability of the *Monographs* to evaluate the carcinogenicity of diverse agents. These agents range from chemicals that have been tested only in animal bioassays to complex exposures, such as occupational exposure as a firefighter, which have been evaluated in epidemiological and mechanistic studies.

The evaluations achieved in these meetings comprised 19 classifications, including 7 agents never before evaluated by IARC, and re-evaluations of 12 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.who.int/).

Table 1. Summary of evaluations from the five *Monographs* meetings held in 2022–2023

Agent (Volume)	Overall classification	Strength of evidence of cancer in humans (tumour type provided for *limited* or *sufficient* evidence)	Strength of evidence of carcinogenicity in experimental animals	Strength of mechanistic evidence (key characteristics of carcinogens with *consistent and coherent* evidence[a])
Cobalt, Antimony Compounds, and Weapons-Grade Tungsten Alloy (Volume 131)				
Cobalt metal without tungsten carbide or other metal alloys	Group 2A	*Inadequate*	*Sufficient*	*Strong* (2, 5, 6, 10)
Soluble cobalt(II) salts	Group 2A	*Inadequate*	*Sufficient*	*Strong* (2, 5, 7, 10)
Cobalt(II) oxide	Group 2B	*Inadequate*	*Sufficient*	
Cobalt(II,III) oxide	Group 3	*Inadequate*	*Inadequate*	
Cobalt(II) sulfide	Group 3	*Inadequate*	*Limited*	
Other cobalt(II) compounds	Group 3	*Inadequate*	*Inadequate*	
Trivalent antimony	Group 2A	*Limited* (lung)	*Sufficient*	*Strong* (2, 5, 6, 10)
Pentavalent antimony	Group 3	*Inadequate*	*Inadequate*	
Weapons-grade tungsten (with nickel and cobalt) alloy	Group 2B	*Inadequate*	*Sufficient*	
Occupational Exposure as a Firefighter (Volume 132)				
Occupational exposure as a firefighter	Group 1	*Sufficient* (mesothelioma, bladder) *Limited* (colon, prostate, testis, melanoma of the skin, non-Hodgkin lymphoma)	*Inadequate*	*Strong* (2, 4, 5, 6, 8)
Anthracene, 2-Bromopropane, Butyl Methacrylate, and Dimethyl Hydrogen Phosphite (Volume 133)				
Anthracene	Group 2B	*Inadequate*	*Sufficient*	
2-Bromopropane	Group 2A	*Inadequate*	*Sufficient*	*Strong* (2, 5, 7)
Butyl methacrylate	Group 2B	*Inadequate*	*Sufficient*	
Dimethyl hydrogen phosphite	Group 2B	*Inadequate*	*Sufficient*	
Aspartame, Methyleugenol, and Isoeugenol (Volume 134)				
Aspartame	Group 2B	*Limited*	*Limited*	(5)
Methyleugenol	Group 2A	*Inadequate*	*Sufficient*	*Strong* (1, 2)
Isoeugenol	Group 2B	*Inadequate*	*Sufficient*	
Perfluorooctanoic Acid (PFOA) and Perfluorooctanesulfonic Acid (PFOS) (Volume 135)				
Perfluorooctanoic acid (PFOA)	Group 1	*Limited* (renal cell carcinoma and testicular cancer)	*Sufficient*	*Strong* (4, 5, 7, 8, 10)
Perfluorooctanesulfonic acid (PFOS)	Group 2B	*Inadequate*	*Limited*	*Strong* (4, 5, 7, 8, 10)

N/A, not applicable.
[a] 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.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/).

A summary of the results of the Scientific Workshop on Epidemiological Bias Assessment in Cancer Hazard Identification was published in the scientific journal *Occupational and Environmental Medicine*, ahead of the publication of a new volume in the IARC Scientific Publications series *Statistical Methods in Cancer Research*. The new volume, expected in the first half of 2024, will summarize methods for bias assessment to support cancer hazard identification, illustrate these methods with examples, and discuss how these methods could also be incorporated into future published studies to better inform cancer hazard and risk assessments.

The discussions during the Scientific Workshop on Key Characteristics-associated End-points for Evaluating Mechanistic Evidence of Carcinogenic Hazards will result in the publication of an *IARC Monographs* Technical Report. The report, expected in the first half of 2024, will provide insights into the mechanistic evaluation of cancer hazards and highlights on the furtherance of the application of the key characteristics of carcinogens. In addition, it is expected that the report will be accompanied by research articles addressing specific topics stemming from the discussions relative to the main themes of the workshop.

Publications

During the 2022–2023 biennium, the following *IARC Monographs* volumes were published:

- Volume 129: Gentian Violet, Leucogentian Violet, Malachite Green, Leucomalachite Green, and CI Direct Blue 218
- Volume 130: 1,1,1-Trichloroethane and Four Other Industrial Chemicals
- Volume 131: Cobalt, Antimony Compounds, and Weapons-Grade Tungsten Alloy
- Volume 132: Occupational Exposure as a Firefighter

IARC Handbooks Programme (IHB)

The IARC Handbooks Programme (IHB) is responsible for producing the *IARC Handbooks of Cancer Prevention*. The *IARC Handbooks* evaluate interventions and strategies for primary and for secondary cancer prevention. Recent volumes have covered screening (for cancers of the cervix and the oral cavity), individual-level and population-level interventions, and preventive strategies.

Major accomplishments

Volume 19: Oral Cancer Prevention (September–December 2021)

This three-in-one *Handbook* of oral cancer prevention provides evaluations of primary and secondary prevention interventions and strategies: (i) the impact of cessation of exposure to the established risk factors (tobacco smoking, alcoholic beverage consumption, smokeless tobacco use, chewing of areca nut with or without tobacco) in reducing oral cancer incidence or mortality; (ii) behavioural and pharmacological interventions aimed at reducing the prevalence of use of smokeless tobacco or areca nut products; and (iii) screening by clinical oral examination (Figure 1).

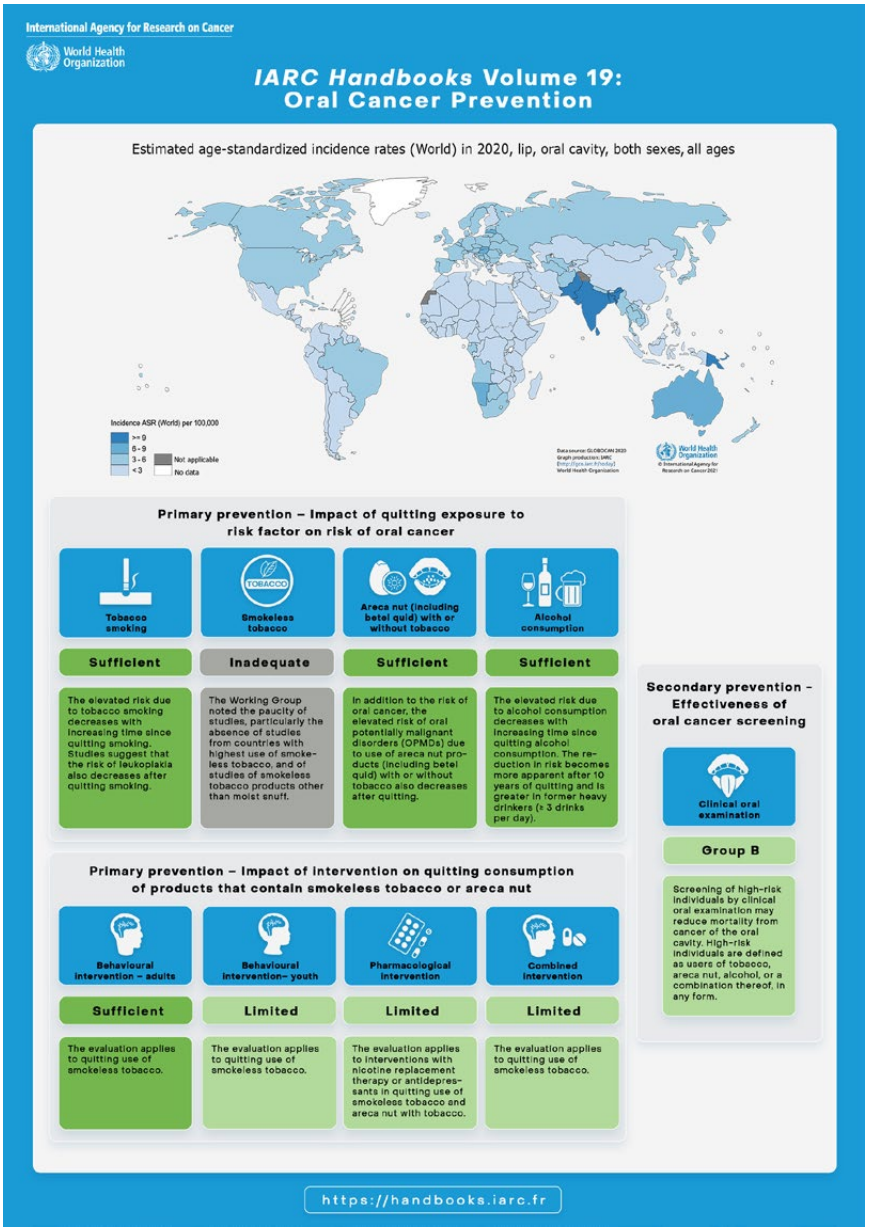
Volumes 20A and 20B: Alcohol Control

Alcoholic beverages have been classified by the *IARC Monographs* as carcinogenic to humans (Group 1), causing cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum, and female breast. At the World Health Assembly in 2010, Resolution WHA63.13 was adopted, on a global strategy to reduce the harmful use of alcohol. Therefore, similar to the series on tobacco control (Volumes 11–14), the *IARC Handbooks* Programme is currently developing a two-part volume on alcohol control.

Volume 20A: Reduction or Cessation of Alcoholic Beverage Consumption (February 2023–May 2023)

The *IARC Handbooks* Programme reviewed and evaluated evidence from epidemiological and mechanistic studies on cessation or reduction of alcoholic beverage consumption. Overall, there is *sufficient evidence* that reduction or cessation of alcoholic beverage consumption reduces alcohol-associated risk of oral cancer and oesophageal cancer, *limited evidence* for laryngeal cancer, colorectal cancer, and breast cancer, and *inadequate evidence* for pharyngeal cancer and liver cancer. Moreover, there

Figure 1. *IARC Handbooks* Volume 19: Oral Cancer Prevention. © IARC.



is *sufficient evidence* that cessation of alcoholic beverage consumption reduces alcohol-related carcinogenesis, based on *strong evidence* for three mechanisms: (i) cessation results in the elimination of alcohol-related local exposure of the upper aerodigestive tract and colon to acetaldehyde; (ii) in the context of chronic heavy alcohol consumption, cessation leads to a decrease in DNA chromosomal aberrations and micronuclei in peripheral blood mononuclear cells within a few months to several years, and in a rapid reduction or elimination of acetaldehyde–DNA adduct formation in cells of the oral cavity; and (iii) among individuals with alcohol use disorders, cessation reverses increased intestinal permeability and microbial translocation.

Volume 20B: Alcohol Control Policies

This volume, prepared in close collaboration with the WHO Regional Office for Europe, aims to evaluate how individual-level and population-level interventions may reduce the prevalence of alcohol consumption. A scoping meeting for Volume 20B took place in November 2023, to identify scientific priority areas for review, define the relevant experts to invite, and discuss the outline of the book. Subgroup sessions are planned in June 2024 (remotely), and plenary sessions will be held in October 2024 (in person).

Publications

- *IARC Handbooks* Volume 18: Cervical Cancer Screening was published online in May 2022 and in print in October 2022.
- *IARC Handbooks* Volume 19: Oral Cancer Prevention was published online in November 2023.

WHO Classification of Tumours Programme (WCT)

The work of the WHO Classification of Tumours Programme (WCT) encompasses the *WHO Classification of Tumours* series (also known as the WHO Blue Books), the *IAC-IARC-WHO Cytology Reporting Systems* series, the IARC histopathology laboratory, and the International Collaboration for Cancer Classification and Research (IC^3R) including the Evidence Gap Map project, which is funded by a European Union Horizon grant (grant number HORIZON-HLTH-2021-CARE05 PROJECT 101057127).

WHO Classification of Tumours series

Tumour classification is a major scientific endeavour of considerable importance, underpinning the diagnosis of all cancers worldwide. In recent years, the adoption of a relational database approach for the series and a hierarchical classification format 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 2022–2023 biennium, the following volumes were published in print (these are also available on the WHO Classification of Tumours Online website; https://tumourclassification.iarc.who.int/):

- *Central Nervous System Tumours*, fifth edition (2022)
- *Urinary and Male Genital Tumours*, fifth edition (2022)
- *Paediatric Tumours*, fifth edition (2023) (Figure 2).

The following volumes were made available on the WHO Classification of Tumours Online website as beta versions:

- *Head and Neck Tumours*, fifth edition
- *Endocrine Tumours*, fifth edition
- *Haematolymphoid Tumours*, fifth edition
- *Skin Tumours*, fifth edition
- *Eye and Orbit Tumours*, fifth edition
- *Genetic Tumour Syndromes*, fifth edition

These six web-based volumes are in various stages of print production. *Head and Neck Tumours* and *Haematolymphoid Tumours* are intended to be produced by early 2024 and the rest during 2024. The books and the accompanying website have both been very well received, and use of the classification is expanding in the wider biomedical community (e.g. among epidemiologists, radiologists, researchers, oncologists, molecular pathologists, and geneticists). Production of the *WHO Classification of Tumours* series continues to be funded by book sales and website subscriptions alone. Special discounts are provided for readers in low- and middle-income settings and for trainees.

IAC-IARC-WHO Cytopathology Reporting Systems series

Cytopathology is important as a discipline for early cancer detection or diagnosis, especially in low- and middle-income settings. It also provides a pathway to molecular and cellular diagnosis. In keeping with the IARC objective of promoting international collaboration in cancer research, WCT initiated a dialogue with the International Academy of Cytology (IAC) in 2019, to develop IAC-IARC-WHO reporting systems for cytopathology. The aim of this series is to harmonize cytopathology reporting across different body sites at a global level. The first two volumes – for lung cytopathology and pancreaticobiliary cytopathology – have been published. These will be followed by reporting systems for lymph node, spleen, and thymus cytopathology and soft tissue cytopathology. In 2023, work started on the upcoming volumes for breast cytopathology, liver cytopathology, and kidney and adrenal cytopathology. After all major sites have been covered, the reporting

Figure 2. *Paediatric Tumours*, fifth edition, Part A. © IARC.

systems will be revised regularly with new and emerging research evidence. These new reporting systems are designed to be a helpful addition to the *WHO Classification of Tumours* series.

During the 2022–2023 biennium, the following volumes were published in print (these are also available on the WHO Classification of Tumours Online website; https://tumourclassification.iarc.who.int/):

- *WHO Reporting System for Lung Cytopathology*, first edition (2023)
- *WHO Reporting System for Pancreaticobiliary Cytopathology*, first edition (2023)

Histopathology laboratory

The histopathology laboratory provides pathology expertise and support across the Agency through four WCT pathologists and a research assistant. It also provides a histopathology service to other IARC groups, including providing whole slide images for the WHO Blue Books. The histopathology imaging needs of the WHO Blue Books are critical to their future success, and close links with pathology provision within IARC are facilitated by WCT's leadership of the histopathology laboratory. This is also an essential service to the laboratory groups and others engaged in studies involving human tissue.

The histopathology laboratory has modernized its equipment, with a corresponding increase in capacity and capability. The laboratory is increasingly involved in all aspects of digital and computational pathology. Its capacity to produce high-quality immunohistochemistry for research projects has been enhanced by the acquisition of an automated immunostainer and a cryostat, which is used to produce slides and frozen sections. It is now a state-of-the-art research laboratory located within the new IARC building. Collaborations conducted with Centre Léon Bérard and other institutions worldwide continue to expand.

International Collaboration for Cancer Classification and Research (IC^{3}R)

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.

The International Collaboration for Cancer Classification and Research (IC^{3}R; https://ic3r.iarc.who.int/) was established by WCT to bring cancer research institutions together to improve research quality and to meet the need for evaluation and synthesis of research findings. Currently, 22 institutions are involved in IC^{3}R, and it is funded by membership dues. IC^{3}R aims to promote evidence-based practice in pathology and to set standards for tumour classification and cancer research harmonization to underpin successful translation of cancer pathology research into tumour classifications and clinical practice. The formation of inter-professional research teams, including pathologists, epidemiologists, systematic reviewers, and cancer researchers, under the IC^{3}R umbrella was further enhanced by securing a large innovative European Union Horizon grant for the WCT Evidence Gap Map project in 2022.

Evidence Gap Map (EVI MAP) project

Mapping the Evidence for the WHO Classification of Tumours: a Living Evidence Gap Map by Tumour Type (EVI MAP) includes an international consortium of five European institutions and one additional international partner, coordinated by WCT. The initiative will enable the identification of evidence gaps, strengths, and weaknesses in the entire spectrum of human tumour classifications, to build a solid framework for future evidence-based pathology practice and research on tumour classification. It aims to inform the WCT editorial process for the upcoming editions of the WHO Blue Books, by creating dynamic interactive evidence maps for human tumours. A sample evidence gap map is shown in Figure 3.

Figure 3. A sample evidence gap map from the EVI MAP project. Generated using v.2.0.1 of the EPPI-Mapper, powered by EPPI Reviewer and created with the Digital Solution Foundry team. Digital Solution Foundry and EPPI Centre (2023), EPPI-Mapper, Version 2.2.4. EPPI Centre, UCL Social Research Institute, University College London.