



## **DIRECTOR'S RESPONSE TO THE SECTIONS OF IARC MONOGRAPHS (IMO) AND MOLECULAR PATHOLOGY (MPA) REVIEWS, HELD AT IARC IN JANUARY 2014**

A number of responses have followed from the peer-review for both the Section of IARC Monographs (IMO) and the Section of Molecular Pathology (MPA). These are detailed below by Section.

### **RESPONSE TO THE REVIEW OF THE SECTION OF IARC MONOGRAPHS (IMO)**

- a) *The Review Panel recommended that IMO maintain its main focus on the Monographs on carcinogens and its current method of expert critical appraisal with strict management of conflict of interest, allowing the production of three Monographs per year. The Panel recommended IMO continue to incorporate methods to increase transparency and efficiency of the evaluations.*

IMO will maintain its focus on carcinogenicity evaluations, producing three Monograph volumes each year. Monograph Working Groups of subject-matter experts are carefully screened to eliminate conflict of interest. A consistent and documented methodology for the selection, review, synthesis and presentation of evidence is followed. The methodology will be enhanced with new procedures and electronic tools to facilitate and promote objectivity in selection of literature, documenting literature searches as well as decisions to include or exclude identified studies.

- b) *The Review Panel strongly encouraged a re-launch of the IARC Handbooks of Cancer Prevention, building on the sound process developed within IMO for the Monographs. However, the Panel emphasized the new programme requires adequate staffing and funding to avoid the diversion of resources from the Monographs.*

Both Scientific and Governing Councils recognized the value of the Handbooks and strongly endorsed their re-launch. However, in line with the advice of the Review Panel, IARC will only do so if additional funding is identified. To this end, the Director and IMO have actively pursued opportunities for voluntary contributions from Participating States and other sources. The first of the re-launched series (Breast Cancer Screening) is partly supported by a grant from INCa, France. In addition, the Director provided support for a Senior Visiting Scientist and additional temporary scientific and technical support staff to enable this first volume in the new series of topics. Otherwise progress in identifying additional resources is limited, but efforts continue.

- c) *The Review Panel suggested that the Monographs and Handbooks may need to articulate or identify the relevance of the work to low- and middle-income countries (LMICs) to fit with the IARC mission going forward.*

The IARC Monographs consider topics for evaluation with worldwide relevance, including instances where exposures occur predominantly in LMICs; the selection of priority agents for evaluation following the Advisory Group Meeting to Recommend Priorities (April 2014) reflects such a strategy. This perspective will be maintained in the selection of agents for evaluation moving forward. The relevance of the Handbooks to LMICs will also be considered. For example, the Breast Cancer Screening Handbook includes breast cancer awareness and early detection and critically reviews and evaluates all options for breast cancer screening, including clinical breast examination and breast self-examination which have more relevance at present for LMICs than mammography. Regarding dissemination see reply to f).

- d) *The Review Panel believes quantitative risk characterization is an important step towards improving risk communication and prioritization in cancer control while recognizing the need for appropriate resources and staffing.*

To better support quantitative analyses, including of disease burden, the methodology for development of Section 1 (exposure information) of the Monographs is being refined. These enhancements will also facilitate analyses of exposure-response information from epidemiological studies. Collaboration with the Section on Cancer Surveillance and targeted analyses of their databases (e.g. GLOBOCAN) will further contribute in this direction.

- e) *The Review Panel recommended IMO to develop a robust and up-to-date framework for the evaluation and incorporation of mechanistic data, which will strengthen the evaluation process and be useful for the scientific community.*

The mechanistic data evaluation methodology is being significantly revised. On-line tools are being implemented to increase the rigor, efficiency and transparency of literature review and mechanistic data capture. Systematic approaches to the use of high-throughput and high-output data are also being pioneered. Additionally, the mechanistic discussion has been restructured to more explicitly analyse evidence for the 10 key characteristics of carcinogens identified during the Volume 100 Workshops. As part of more general strategic considerations in-house, the mechanistic research conducted by the IARC laboratories and the priorities identified in the Monographs are being better aligned through joint discussions on selection of specific agents for analyses.

- f) *The Review Panel emphasized the importance of maximizing dissemination of new information (online, fact sheets, searchable database etc.) and the clarity of communication to different audiences (including the general public) in order to prevent misinterpretation of expert findings. IMO was specifically encouraged to re-examine the terminology of "possibly carcinogenic to humans" in the classification and consider better terminology.*

Dissemination of Monograph findings remains a high priority and IMO works closely with the Media Officer in relation to Monographs and Handbooks to ensure that communication is at the heart of the planning process prior to the meetings. Pre-meeting alerts to WHO, including to LMIC country representatives, has broadened outreach. Following each meeting, a scientific summary of Monograph findings is published rapidly on-line in The Lancet Oncology. Accompanying press releases enhance communication to the general public. The classification terminology will be reconsidered for clarity, and technical terms better communicated through lay language explanations made available on the Monographs website and in press releases. Other recommended avenues of on-line dissemination will also be implemented. Specifically, all Monographs, Advisory Group and Workshop reports are published on-line, with the high volume of downloads documenting substantial general interest. Further, the Monographs are being indexed in the searchable National Library of Medicine database of published books. Launch of the PubCan searchable database of Monograph findings is actively being pursued as an important avenue to further disseminate Monograph findings and additional funds have been assigned to this end.

*g) The Review Panel recognized that the success of the programme depends in part on the special skills of IMO staff. In order to develop and retain high quality staff, the Panel encourages the Agency to enable professional development and/or research activities of IMO staff.*

IMO has demonstrated success in recruiting and retaining high-quality staff, including recently at a senior level. Continued staff professional development is actively encouraged, as is participation of staff in national and international committees (e.g. WHO, French and the US government agencies), scientific publications and/or meeting presentations regarding the Monograph findings, and related scientific topics. The majority of junior (P2) staff recently attended internal training courses (e.g. on effective presentation, epidemiology summer school, etc.) to enhance skill development. IMO is providing expertise to a MCA/MMB project on carcinogen-specific mutation patterns, and is also collaborating with NME/BMA on a chemoinformatics approach to integrate information on chemical structure similarity with systematic, automated text mining of cancer-relevant information in public databases. Further opportunities for research collaboration with other Sections e.g. CSU on population attributable fractions, are being explored.

*h) The Review Panel agrees with the recommendations of the previous Panel that a greater proportion of the staff should be supported from the regular budget to ensure stability of the high-quality staff in this important programme.*

Regular budget funding is highly desirable to promote continuity, and has been achieved over the past years for additional key scientists as well as support personnel. An additional 1.5 posts are envisaged on the regular budget 2016–2017, pending approval by the Governing Council. However, the IARC budget remains inadequate to include all IMO staff costs and the Programme will continue to rely on extra-budgetary funding.

- i) The Review Panel encourages the Director to explore opportunities for special funding from Participating States to develop the future plans and sustainability for this important programme.*

See reply to b) above.

## **RESPONSE TO THE REVIEW OF THE SECTION OF MOLECULAR PATHOLOGY (MPA)**

The MPA Section activities were considered in two parts, first the WHO Classification of Tumours ("Blue Books") and second the research conducted on brain cancer. Responses are also presented separately below.

### **The WHO Classification of Tumours**

#### **General comments:**

- 1. The WHO Classification of Tumours is a very important activity for MPA and for the worldwide reputation of IARC and WHO, and should be continued, with increased resources and staffing.*

A number of increases in resources have been assigned. First, there is an increase in funds assigned from the Governing Council Special Fund (GCSF), including a new Project Assistant post to enable faster publication of Blue Books, from one to two per year. Second, a new senior pathology post in MPA is envisaged on the IARC regular budget 2016–2017, pending decisions by the Governing Council in May 2015.

- 2. The Blue Books series needs to be updated in a timely fashion in order to remain clinically relevant.*

With increased budget and staff, and by outsourcing part of the project (e.g. layout), MPA is now able to carry out work on three to four book projects in parallel. Since each book project takes approximately two years, our goal to publish two books per year will be achieved in 2015/2016.

- 3. Both an eBook and digital online database format are desirable in order for the books to be readily accessible to the broadest readership and useful to the scientific community. The option of commercial print on demand versions should also be considered. Careful consideration needs to be given to development of a viable business plan, particularly with regards to access to the online database.*

IARC Communications Group (COM) has started to prepare eBooks including the WHO Blue Books. The first ebooks of the WHO Classification of Tumours series (Tumours of Female Reproductive Organs 4<sup>th</sup> edition and Tumours of Soft Tissue and Bone 4<sup>th</sup> edition) are expected to be ready in early 2015. Following the new agreement with WHO Press, IARC is the sole distributor of IARC ebooks and other newly created digital format publications; entire sales revenue for digital publications will be returned to the GCSF accordingly. COM is establishing a business plan to ensure sales of the Blue Books continues to enable their timely and efficient production. Distribution contracts with ebook aggregators servicing academic libraries have been established. Workflows and licensing for institutional purchase of ebooks directly through IARC

have been piloted successfully on World Cancer Report 2014. COM is in the process of establishing business processes to support direct electronic sales to individuals, with plans to hire a G-level staff member to assist with the technical aspects. COM is also recruiting for a temporary 1-year P2-level post in order to continue development of PubCan as a database-driven model of distribution for Blue Books content. Print versions of the books will be maintained at least until the completion of the 4<sup>th</sup> edition and will continue to be distributed by WHO Press. These changes also encompass a much more active approach to promoting and marketing the series to enhance ease of access to the books for the cancer community.

**Specific suggestions:**

*Provide a stable budget that is independent of fluctuations in book sales revenue.*

Three staff and most of the non-staff budget for the WHO Classification of Tumours series is supported with funds from the GCSF, which is constituted of revenue from book sales. This sales revenue has thus far been very stable and it is not considered by IARC management as a less secure source of support than the regular budget. As mentioned above the Agency is involved in a major piece of work to plan for future revenue streams from electronic versions of the Blue Books.

*Add a senior pathologist to assist the Section Head with the Blue Book efforts and provide continuity during transition to the 5<sup>th</sup> edition series.*

A senior pathologist position will be advertised in 2015 and recruited in early 2016, to assist the Section Head with the Blue Book projects and to provide continuity during the transition to eBook/digital format publications and the 5<sup>th</sup> edition.

*Efforts should be made to ensure that a higher proportion of Blue Book revenues go to IARC, and within IARC to the Blue Book effort.*

Renegotiation of our dissemination contract with WHO Press Geneva, to have sole rights to distribution of eBooks and digital publications, ensures a higher proportion of Blue Book revenues return to IARC. Following the Review Panel the Director made a request to the Governing Council to lift the ceiling of revenue returned to the publication programme from book sales and this was approved under Resolution GC/56/R12. The major proportion of revenues to the GCSF generated predominantly through sales of Blue Books is assigned to the Blue Book activities. However, it is also important to use this income to support other IARC publications which are valuable to the international cancer community but which generate less income.

*Encourage volume editors to consider how to most effectively incorporate the input of clinicians and molecular biologists into future editions.*

MPA will ensure that volume editors are instructed to include clinicians and molecular biologists as authors and also as Working Group members of the Consensus and Editorial conferences.

*Emphasize to the WHO leadership the importance of these classifications for all aspects of global cancer care, research and epidemiology, as well as the negative consequences should the series fail.*

This is a crucial project not only for pathology communities and clinicians, but also for cancer registries, clinical trials and epidemiology studies. The Director will raise this issue at the highest level in future meetings with senior colleagues at WHO.

*Evaluate whether retention of the name "PubCan" is appropriate in association with online WHO Blue Book efforts.*

This has been considered following the Review Panel and the name will be changed from "PubCan" to "WHO Classification of Tumours".

### **Brain tumour research programme**

- 1) *Continue cohort-based approach, focusing on issues which build on their historical expertise in molecular markers and intra-tumoural heterogeneity.*

Given the limited resources available to the Section, MPA will focus on a number of key areas where it can make a unique contribution. The Section will continue, therefore, population-based studies on gliomas in the Canton of Zurich, Switzerland. A large number of glioma tissues was collected from 2005–2009, with detailed data including clinical history, treatment, survival, pathology, and genetics. MPA plans to carry out a new study in the same population between 2010 and 2014 to provide information on the effects of new treatment protocols on patients' survival. These studies will permit a correlation between histopathology and genetic/epigenetic/expression profiles of brain tumours, in order to identify novel molecular markers for diagnosis that will be essential for their future molecular classification. As advised by the Review Panel, the Section will also prioritize work on intra-tumoural genetic heterogeneity in brain tumours.

- 2) *Increase computing and bioinformatics capacity to allow for cutting edge molecular research, possibly through greater interaction with local groups.*

MPA has expanded collaborations with bioinformaticians in IARC, in the Genetic Susceptibility Group (GCS), and with external collaborators (INSERM, Lyon, France; German Cancer Research Center (DKFZ), Heidelberg, Germany).

- 3) *Consider expanding international outreach and examination of molecular alterations in geographically distinct populations, particularly in countries without such expertise.*

MPA has previously carried out genetic analyses in glioblastomas in Japanese patients and compared them to those in European patients. Genetic profiles were remarkably similar in the two patient populations. Genome wide genetic profiling in glioblastomas from other regions will be considered if extra-budgetary funds become available; new collaborative opportunities may arise through the links the IARC Biobank is making with pathology departments in LMICs.

- 4) *Fully staff the research effort, including an additional full time scientist, to facilitate increased speed and scope of the planned technically challenging studies.*

One junior scientist position in MPA has been frozen due to IARC budget constraints. One postdoctoral position has been provided to compensate for this situation.