International Agency for Research on Cancer

World Health Organization

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024

Introduction

An IARC Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 met in Lyon, France, on 25–27 March 2019. IARC periodically convenes such Advisory Groups to ensure that the *Monographs* evaluations reflect the current state of scientific evidence relevant to carcinogenicity.

Before the meeting, IARC solicited nominations of agents via the website of the *IARC Monographs* programme and the IARC RSS news feed, and through direct contact with the IARC Governing Council and members of the IARC Scientific Council, WHO headquarters and regional offices, and previous participants in the *Monographs* programme. Nominations were also developed by IARC personnel, including the recommended priorities remaining from a similar Advisory Group meeting convened in 2014 (Straif et al., 2014), and the priorities nominated by the Advisory Group.

The list of Advisory Group members and all other meeting participants is provided in Annex 1 (see https://monographs.iarc.fr/wp-content/uploads/2019/02/AGP-ListofParticipants.pdf); the preliminary agenda is provided in Annex 2. Dr Matilde Marques (Portugal) served as Meeting Chair, and Dr Amy Berrington de González (USA) served as Meeting Vice Chair. The Subgroup Chairs were Frederick Beland (USA), Patience Browne (France), Paul Demers (Canada), and Dirk Lachenmeier (Germany).

Meeting preparation and conduct

Relevant background information was distributed before the meeting and through presentations during the meeting. This included introductory material about the *IARC Monographs* evaluation approach, which was recently refined in the Preamble to the *IARC Monographs* (IARC, 2019a).

The Advisory Group considered more than 170 unique candidate agents nominated for consideration. Short draft summaries of each nomination were prepared before the meeting. These drafts summarized the evidence on human exposure (including any evidence of exposure in low- and middle-income countries), cancer epidemiology, cancer bioassays in experimental animals, and carcinogen mechanisms, in line with the evaluation approach that was recently refined in the Preamble to the *IARC Monographs* (IARC, 2019a).

A complementary approach assessed all nominations using a chemoinformatics, text mining, and chemical similarity analysis workflow (Guha et al., 2016) to help reveal coverage and gaps in the extent of evidence across data streams, to support decisions on individual agents and groups of chemically related nominations. In brief, the workflow entailed linking agents to identifiers, performing automated literature searches and queries of relevant online databases supplemented by custom Google searches, and generating chemical similarity maps as well as hierarchical clustering heat maps. The literature search terms used, the chemical similarity maps, and the heat maps are provided in Annex 3.

At the meeting, the Advisory Group reviewed the writing assignments in subgroups organized by evidence stream (i.e. exposure characterization, cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis) and by type of agent (e.g. metals, fibres, chemicals, biological agents, and complex mixtures), to inform the development of recommendations on priorities. The subgroup sessions developed draft indications, for further discussion and adoption in plenary sessions, of which nominations are of highest priority and readiness for future review, on the basis of (i) evidence of human exposure and (ii) evidence or suspicion of carcinogenicity. Agents not meeting these criteria were not recommended for evaluation.

Determining priority

In line with the Preamble to the *IARC Monographs* (IARC, 2019a), priority was assigned for:

(a) A new evaluation of an agent.

(b) An agent reviewed in a previous *Monograph* with new evidence of cancer in humans or in experimental animals or of carcinogen mechanisms, to warrant re-evaluation of the classification.

(c) An agent reviewed in a previous *Monograph* and established to be carcinogenic to humans with new evidence of cancer in humans that indicates a possible causal association with new tumour sites. In the interests of efficiency, the review may focus on these new tumour sites.

Priority was assigned on the basis of (i) evidence of human exposure and (ii) the extent of the available evidence for evaluating carcinogenicity (i.e. the availability of relevant evidence on cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis to support a new or updated evaluation according to the Preamble to the *IARC Monographs*). Any of the three evidence streams could alone support prioritization of agents with no previous evaluation. For previously evaluated agents, the Advisory Group considered the basis of the previous classification as well as the potential impact of the newly available evidence during integration across streams (see Table 4 in the Preamble to the *IARC Monographs*). Agents without evidence of human exposure or evidence for evaluating carcinogenicity were not recommended for further consideration.

Priorities for the *IARC Monographs* during 2020–2024

The types of recommendations encompassed individual agents as well as groups of related agents, taking into account the advice of the Advisory Group. In this regard, the Advisory Group recommended to group some individual nominations, to expand the proposed nomination to encompass related agents meriting evaluation in some cases, and, in other instances, to narrow a group of nominated agents. It was further noted that consideration of information from new approach methods in toxicology, such as ToxCast, Tox21, and quantitative structure–activity relationships as well as read-across from structurally similar compounds, could be particularly informative in some cases. A tabular summary of the evaluations is provided in Annex 4. Summaries of the recommendations are provided in the sections that follow.

The Advisory Group recognized that agents related to the identified priorities may also warrant evaluation. Furthermore, additional agents may merit consideration if new relevant evidence indicating an emerging carcinogenic hazard (e.g. from cancer epidemiology studies, cancer bioassays, and/or studies on key characteristics of carcinogens) becomes available in the next 5 years.

In line with coordination and communication mechanisms agreed between IARC and WHO headquarters and set out in the interim standard operating procedure (SOP) adopted by the IARC Governing Council (see http://governance.iarc.fr/GC/GC60/En/Docs/GC60_13_CoordinationWHO.pdf), the *IARC Monographs* programme will conduct an evaluation only if IARC and WHO headquarters agree that this does not duplicate work or present a risk of contradictory evaluations across the hazard identification and risk assessment programmes. In keeping with the interim SOP adopted by the IARC Governing Council, IARC will consider this advice when selecting agents for future *Monographs* evaluations according to the Preamble to the *IARC Monographs* (IARC, 2019a, b).

Non-ionizing radiation (radiofrequency) and extremely low-frequency magnetic fields

Radiofrequency electromagnetic fields (RF-EMF) were evaluated by the *IARC Monographs* as *possibly carcinogenic to humans* (Group 2B) (IARC, 2013e), on the basis of limited evidence of an increased risk of glioma. Extremely low-frequency magnetic fields (ELF-MF) were evaluated as *possibly carcinogenic to humans* (Group 2B) (IARC, 2002), on the basis of *limited evidence* of an increased risk of childhood leukaemia.

Exposure Data

Human exposures to RF-EMF can occur from use of personal devices (e.g. cell phones, cordless phones, and Bluetooth) and from environmental sources such as cell phone base stations, broadcast antennas, and medical applications. More than 5 billion people now have access to cell phone devices, and the technology is constantly evolving. Use has also expanded rapidly in low- and middle-income countries, where more than 75% of adults now report owning a cell phone; in high-income countries, the proportion is 96% (Pew Research Center, 2018).

Cancer in Humans

Since the previous *IARC Monographs* evaluation, several new epidemiological studies have been published on the association between RF-EMF and cancer, although the evidence remains mixed. In the Million Women Study cohort, there was no evidence of increased risk of glioma or meningioma, even among long-term users. There was an increased risk of acoustic neuromas with long-term use and a significant dose–response relationship (Benson et al., 2013). Updated follow-up in the Danish nationwide subscribers study did not find increased risks of glioma, meningioma, or vestibular schwannoma, even among those with subscriptions of 10 years or longer (Frei et al., 2011; Schüz et al., 2011). New reports from case–control studies that assessed long-term use also found mixed results; for example, increased risks of glioma and acoustic neuroma were reported by Hardell & Carlberg (2015) and Hardell et al. (2013), but no evidence of increased risks for these tumours were reported by Yoon et al. (2015) and Pettersson et al. (2014). Röösli et al. (2019) recently reviewed these new data. Several large-scale studies are still in progress and should report results within the next few years. Mobi-Kids is a multicentre case–control study of brain tumours in those aged 10–24 years. Cohort Study of Mobile Phone Use and Health (COSMOS) is a new European cohort of adult cell phone users. There will also be updated results from the Million Women Study.

Cancer in Experimental Animals

New data in experimental animals for exposure to RF-EMF have been published since the previous *IARC Monographs* evaluation. The large study by the United States National Toxicology Program found an increased risk of malignant schwannomas of the heart in male rats with high exposure to radiofrequency radiation at frequencies used by cell phones, as well as possible increased risks of certain types of tumours in

the brain and adrenal glands, but no increased risks in mice or female rats (NTP, 2018a, b). Another study in experimental animals also found an increase in schwannomas of the heart in highly exposed male rats and a possible increase in gliomas in female rats (Falcioni et al., 2018).

Mechanistic Evidence

The previous IARC evaluation concluded that there was weak evidence that radiofrequency radiation was genotoxic but that there was no evidence for mutagenicity (IARC, 2013e). Although there have been many new publications from a wide variety of experiments, uncertainty remains about the mechanisms, and there are few systematic reviews of the new data (Kocaman et al., 2018).

Although a future evaluation could be broadened to consider exposure to all non-ionizing radiation (including ELF-MF), ELF-MF were evaluated by IARC as *possibly carcinogenic to humans* (Group 2B), and the Advisory Group did not recommend an update, because of a lack of new informative epidemiological findings, no toxicological evidence, and little supporting mechanistic evidence.

Key References

The following key references were also identified: Coureau et al. (2014); Carlberg & Hardell (2015); Pedersen et al. (2017).

Recommendation for non-ionizing radiation (radiofrequency): High priority (and ready for evaluation within 5 years)

Recommendation for extremely low-frequency magnetic fields: No evaluation

Nuclear industry work

Different types of ionizing radiation have been evaluated repeatedly by the *IARC Monographs* programme (IARC, 2000b, 2012f), and all types have been classified as *carcinogenic to humans* (Group 1); overall evaluations are based on different evidence streams, often including *sufficient evidence* in humans for several cancer sites. New research in recent years has confirmed increased risks per unit of exposure to ionizing radiation for cancer sites and groups of cancer sites that have already been linked with ionizing radiation. No specific evaluation has been made in respect of work in the nuclear industry, which represents a specific exposure condition for agents already classified as *carcinogenic to humans* (Group 1).

Key References

The following key references were identified: Lee et al. (2015c); Leuraud et al. (2015); Richardson et al. (2015); Schubauer-Berigan et al. (2015); Grellier et al. (2017).

Recommendation: No evaluation