RISK MANAGEMENT

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THE EYES OF THE WORLD WERE UPON US

An inside view of the IARC Monograph Meeting 102: Evaluation of the Carcinogenic Risks of RF-EMF to Humans

"Always speak the truth, think before you speak, and write it down afterwards."
Lewis Carroll

Initiated by Dr. Lorenzo Tomatis, former International Agency for Research on Cancer (IARC) Director, in 1971, IARC has been reviewing agents, occupations and processes (referred to as agents) to identify those that may cause cancer in humans. The Monographs Program[1] has evaluated more than 900 agents and has identified more than 400 as *carcinogenic*, *probably carcinogenic* or *possibly carcinogenic* to humans. For all but one of the remaining agents (caprolactam classified as suggesting a *lack of carcinogenicity*), there was not enough evidence to classify them. But what do these labels mean? Who applies them? How are they used? And what does this mean for cell phones and other devices emitting radiofrequency electric and magnetic fields (RF-EMF)?

The process

An IARC review begins more than one year in advance of the actual meeting. Literature is systematically collected for the agent being studied, and the pool of authors from this literature as well as others with relevant disciplinary expertise become potential candidates for the Working Group (WG). The WG is a multi-disciplinary group of scientists who review the available literature for the target agent, discuss its strengths and weaknesses and, through guidance and the framework provided by the IARC secretariat and the Preamble[2] of the Monographs, evaluate its carcinogenicity. In addition to authors, scientists with general understanding of carcinogenesis who can contribute to the overall evaluation are likely to be considered for the WG. Finally, scientists can apply to be in the WG.

1 http://monographs.iarc.fr/index.php

2 http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

Putting together the right mix of expertise and knowledge for the WG reminds us both of our first chemistry class. If you get the mixture put together correctly, you pass the course; if you fail, the entire thing blows up. IARC considers expertise, demographics, gender, potential for conflicts of interest and the breadth and complexity of the literature to build the WG. There are full voting members who are invited to be on the WG and contribute to the initial drafts that review the available literature. There are also non-voting experts who have some degree of conflict of interest but whose knowledge of the subject is extremely valuable to the WG. Finally, there are representatives from national and international public health institutions interested in the outcome and observers who can represent affected industries and other interested parties and who agreed to respect the Guidelines for Observers in the Preamble. These individuals have no vote with regard to the classification of the agent(s) under consideration.

The IARC WG for RF-EMF consisted of 30 scientists from 15 countries (only 29 were present for the meeting). All WG members were required to declare any conflicts of interest in advance that were reviewed by IARC staff prior to our inclusion. There were medical doctors, epidemiologists, veterinarians, toxicologists, pharmacologists, geneticists, statisticians, engineers and molecular biologists that Dr. Christopher Wild, the IARC Director, referred to as “the world’s leading experts” in RF-EMF health effects. Also present were one non-voting invited specialist who was a member of the WG, five observers, five representatives and 19 people from the IARC secretariat.

The WG began working on the Monograph long before we reached Lyon. Members were given areas of the literature to review and summarize. Other members were asked to review these summaries and provide comments to improve the reviews prior to the meeting. In essence, 90 percent of the document was drafted prior to our arrival in Lyon. These were combined into initial drafts that formed the starting point for our deliberations for the 8-day Monograph meeting.

David L. McCormick (IIT Research Institute, USA), Clemens Dasenbrock (Fraunhofer ITEM, Germany), Tomoyuki Shirai (Nagoya City University, Japan) and Meike Mevissen (University of Bern, Switzerland)

The members of the WG arrived in Lyon on or before May 23, 2011, the day before the meeting began. There was drama just prior to our arrival when Prof. Anders Ahlbom resigned from the WG because of a potential conflict of interest that was not declared in advance. On a less serious note, an author of this report (CP) took a wrong turn at the Lyon airport and ended up on a non-stop train to Paris where he had just changed planes; a 4-hour detour.

The opening round

Dr. Wild opened the meeting[3] by saying “The eyes of the world are upon you” as he welcomed us to Lyon and, through his own experiences with other reviews, introduced us to the difficulties and rewards we could expect from a close scientific discussion of such a complex issue. Prof. Jonathan Samet[4] was elected the overall chair of the meeting and took control. Dr. Kurt Straif, Head of the Monograph Program at IARC explained our various roles at the meeting, described how the meeting would proceed, and, most importantly, outlined the guidance established by IARC on evaluating the carcinogenicity of any agents, including RF-EMF.

3 http://www.iarc.fr/en/media-centre/iarcnews/2011/Monographs102.pdf

4 http://www.usc.edu/hsc/info/pr/keckmed/winter09/samet.html

General process

An IARC WG meeting proceeds through four stages. In the first, the drafts are developed prior to the meeting as described above. Once at the meeting, the WG members are divided into four separate groups for evaluating the human epidemiology and cancer in humans, the animal carcinogenicity data, the mechanistic data and the chapter describing the technical details regarding characterizing the agent, how people are exposed and their degree of exposure.

In the second phase of the meeting, the first three subgroups evaluate the literature in their respective areas. IARC has established criteria[5] to guide these various groups as they proceed. In short, the epidemiology and animal carcinogenicity data are evaluated for quality and strength-of-evidence and declared to provide sufficient, limited or inadequate evidence for carcinogenicity. Included in these evaluations are the quality of the studies, the precision of the studies, the magnitude of the data base (numbers and coherence of the study results) and, for animal investigation, the number of independent studies with positive results. The mechanistic evidence is judged as weak, moderate or strong in supporting potential mechanisms that support a carcinogenic finding. There was extensive discussion within the various groups on the strength of evidence in regard to the IARC classification.

The third phase of the review occurs when the subgroups come back together into the full WG for plenary sessions. In these sessions, the wording used by the subgroups in describing the literature is discussed in detail and an overall wording is agreed upon by the entire WG. Then the real "fun" starts. The epidemiology and animal carcinogenicity groups present their suggested ratings for the literature (sufficient, limited or inadequate). There is generally a great deal of debate during these sessions about how these conclusions are reached. In the end, the entire WG votes (if necessary) on the findings in these two areas and a technical definition of the agent is established.

The final phase of the WG meeting is the discussion of the overall evaluation. IARC provides guidance to begin these discussions based upon the ratings from the epidemiology and animal toxicology evaluations. For example, if the human evidence is sufficient, then the recommendation is that the agent be listed as a known human carcinogen; if the human evidence is limited but the animal evidence is sufficient, the recommendation is for a probable human carcinogen; if the human evidence is limited and the animal evidence is less than sufficient, the normal recommendation is for a possible human carcinogen. Then, based upon the mechanistic data and on the overall database, the WG debates a final classification for the agent.

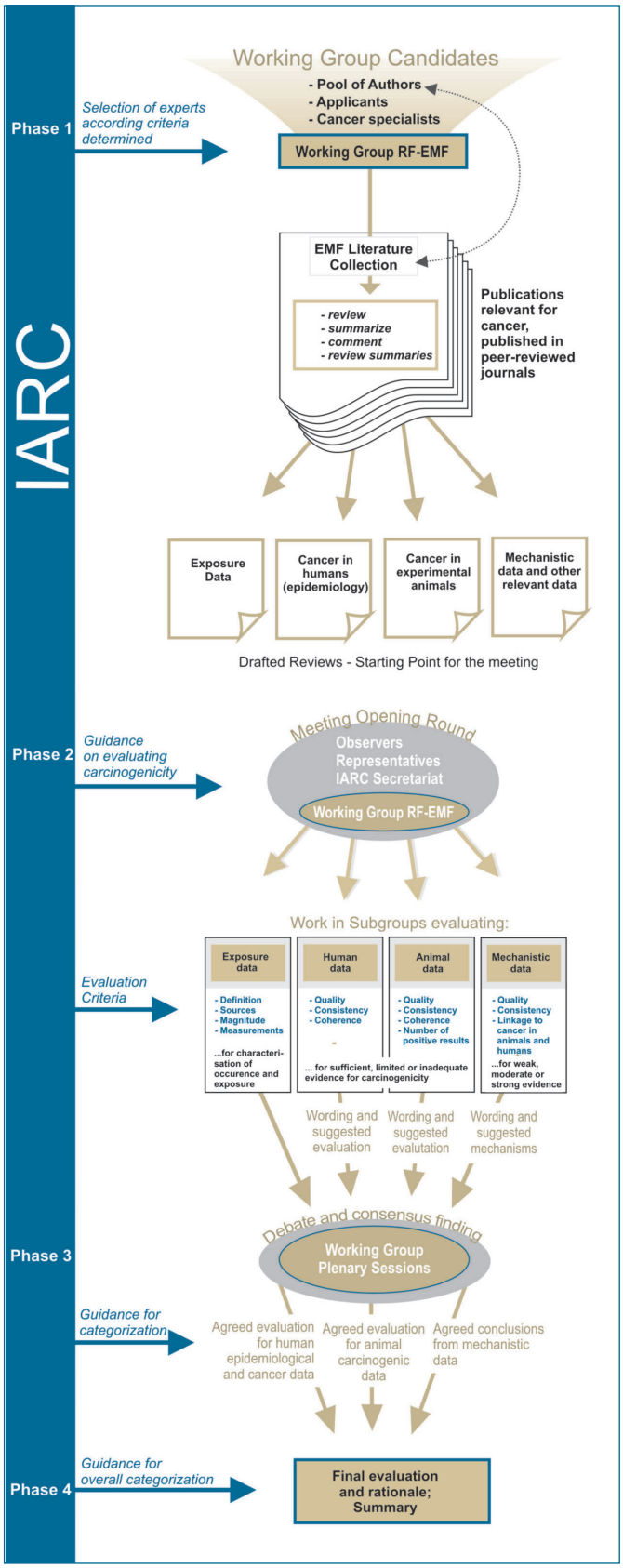

Diagram illustrating the four phases and most important steps of an IARC Monograph Meeting.

5 http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

Birds of a feather flock together

Following the RF-EMF WG opening session, the participants spent most of the first five days in the subgroups, going over the initial drafts, modifying them and drawing their conclusions from the literature. The initial drafts were significantly changed in all of the subgroups. For the initial drafters, it was akin to the most intensive peer-review of your writing you will ever experience. In some cases, whole sections of the draft chapters were completely rewritten to take into account the changes proposed. When multiple participants had different views regarding what needed to be said, they were teamed together to reach a compromise wording that the entire group could agree to. We had copies of all of the papers available to us during the meeting and many of them were reread and discussed in great detail.

The debate raged in the subgroup working rooms, the morning and afternoon breaks, over breakfast, lunch and dinner, and in hotel rooms. All of the subgroups began at least one of the days very early in order to be finished on time and most worked until early evening before breaking for dinner. The epidemiology group worked through dinner one evening. Many of the participants had plans for the weekend such as touring, but that changed; we all worked on Saturday and many of us on Sunday as well. We are certain that, at some point, participants asked themselves the same question, “Why did I agree to this torture?”.

As a note, we had to be self-reliant; IARC strongly discourages outside influences during the WG meeting. The logic behind this is simple; the final report is that of the participants who have declared all conflicts of interest. Scientists outside of the WG who are allowed to address questions posed by the WG could have unknown, but important, biases that would go undetected.

Flying fur

There is an old saying that, when two cats come together for the first time, the fur will fly. In this case, it was 29 cats. Following the subgroup meetings, we spent the remaining time in Lyon in plenary. After several days, Prof. Jonathan Samet had to face the challenge of herding these cats through the last two phases of the review. There were clearly tensions in the room. Prof. Samet did a remarkable job and started this phase of the evaluation reminding us that we are seeking a “broad consensus” on the overall findings. As we discussed the individual chapters,

Kurt Straif (Head IARC Monographs Section), Christopher Wild (Director IARC), and Laurent Galichet (Technical Editor IARC)

The IARC Working Group for Radiofrequency Electromagnetic Fields

some of the arguments in the subgroups resurfaced and the entire WG debated issues from the subgroups once again. After finally agreeing on the text regarding the individual studies, we had to agree on the epidemiology and animal carcinogenesis evaluations.

Starting with the animal findings, the subgroup recommended limited evidence noting that they were sitting right on the fence between limited and inadequate. There was tremendous debate regarding this initial recommendation with WG participants ranging from sufficient to inadequate in their view of the evidence. After several presentations by the subgroup explaining the positive key studies and a review of IARC's guidance, the overall WG concluded the evidence was limited based upon no positive tumor site in any of the seven chronic carcinogenicity studies and positive results in seven other types of studies (tumor-prone animals, initiation-promotion and co-carcinogenesis studies) that had limitations with regard to scientific quality and clarity. There were interesting differences in approaching the interpretation of the evidence on the parts of the experimentalists and the epidemiologists.

The discussions surrounding the human evidence were more contentious. Even though there were a fairly large number of studies, the debate centered around the findings of two groups; the large, multi-nation study coordinated by the IARC and supported by several funding groups known as the INTERPHONE Study and several linked studies conducted in Sweden. Both groups conducted case-control studies that were construed as "positive" for glioma and acoustic neuroma and "negative" for meningioma. While the results of the Swedish studies showed a clear statistically significant relationship, the findings of the INTERPHONE study were more complex and affected by incompletely controlled bias. The subgroup recommended limited evidence, but there were a few participants in the subgroup that strongly held the opinion that the data were inadequate. The main arguments for inadequate focused on the INTERPHONE study showing weak results and that an effect of the magnitude estimated by the results from the Swedish studies should have resulted in observable changes in the brain tumor incidence in national statistics. For limited evidence, the majority felt the studies, when combined, showed a reasonable effect and that the null findings for meningioma suggested that recall or selection bias could not explain the overall findings. This conclusion does not reflect the belief that the association is causal, but instead that although chance and bias cannot be ruled out, a causal interpretation is possible. The discussions that ensued were heated and passionate. The studies by both groups were discussed in intimate detail and finally, a large majority felt the data were limited for carcinogenicity. We agreed to include a minority opinion and moved on.

The final decisison

So, with limited human evidence and limited animal carcinogenicity evidence, we started the final debate on the overall decision with RF-EMF being a possible human carcinogen. This is where the mechanistic data could play an important role. But in this case, there was only weak evidence to support most mechanisms that had been proposed for why RF-EMF causes cancer. Additionally, fundamental considerations related to the physical interactions of the RF-EMF with cells did not point to any specific potential mechanism, other than warming. Hence, by an almost unanimous decision, RF-EMF was declared to be a possible human carcinogen.

Epilogue

> *"Sometimes I've believed as many as six impossible things before breakfast".*
>
> Lewis Carrol

We both came to the IARC meeting with opinions of where the evidence would take us, as we expect did most of the other participants. However, when faced with the entire range of data and our colleagues' arguments, many of us were no longer able to stick with those opinions. Many times, we thought we understood the implications of a particular set of studies only to learn something new that changed "things we believed". In the end, the IARC evaluation was a positive experience for both of us. Colleagues became friends and we gained newfound respect for their ability to support and defend their arguments.

There is no doubt that research is still needed on the possibilities of health effects from RF-EMF. But we also believe this decision is based in sound science and reasonable public health practice. The "eyes of the world were upon us" and we believe we rose to the challenge. For scientists who are offered the opportunity to be a member of an IARC WG in the future, we strongly encourage you to participate. Both of us have been included in other reviews and we look forward to doing it again, despite the hard work and the long hours.

A more scholarly report on the WG meeting is available from *The Lancet Oncology* (Volume 12(6), pages 624-626, 2011).

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