

WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



***IARC Monographs on the Evaluation of  
Carcinogenic Risks to Humans***

**INTERNAL REPORT 08/001**

**Report of the Advisory Group to  
Recommend Priorities for  
*IARC Monographs* during 2010–2014**

**17–20 June 2008**

**LYON, FRANCE  
2008**

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**REPORT OF THE ADVISORY GROUP TO RECOMMEND PRIORITIES  
FOR *IARC MONOGRAPHS* DURING 2010–2014**

**Lyon, France: 17–20 June 2008**

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***IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*****REPORT OF THE ADVISORY GROUP TO RECOMMEND PRIORITIES  
FOR *IARC MONOGRAPHS* DURING 2010–2014****Lyon, France: 17–20 June 2008****LIST OF PARTICIPANTS****Advisory Group<sup>1</sup>**

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<sup>1</sup> Advisory Group Members serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only. Each participant completed WHO's Declaration of Interests to report employment and consulting activities, individual and institutional research support, and other financial interests. Participants did not take part in decisions involving agents for which their client or research sponsor had an interest.

<sup>2</sup> During 2004-2007 Dr Krewski led a review of aluminium, aluminium oxide, and aluminium hydroxide co-sponsored by the International Aluminium Institute (UK) and the U.S. Environmental Protection Agency.

<sup>3</sup> Dr Rice chairs an advisory panel on benzene research for the American Petroleum Institute and serves as a consultant to Bayer Crop Science and Boehringer-Ingelheim (Germany). On the subject of acrylamide, he works part-time for the U.S. Environmental Protection Agency and consults for several law firms. Recently he has consulted for the Acrylonitrile Group, the American Beverage Association (on artificial sweeteners), Bristol-Meyers Squibb, and Experimental Pathology Laboratories. He also has a partnership in a small vineyard and winery.

<sup>4</sup> Dr Tsuda is a non-industry member of the Board of Trustees of the ILSI Health and Environmental Sciences Institute, whose member companies are drawn from the chemical, agrochemical, petrochemical, pharmaceutical, biotechnology, and consumer products industries.

## **IARC Secretariat**

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**Summary of Advisory Group recommendations**

The Advisory Group (AG) considers the *IARC Monographs* programme to be a cornerstone of the Agency's overall programme. The *Monographs* are highly regarded worldwide and of great value in the evaluation of potential carcinogenic risks to humans.

The *Monographs* programme is predicated on the high quality of the evaluations of agents that are potentially carcinogenic to humans. It is imperative to maintain the accuracy and completeness of the review process in order to maintain the credibility and authoritative nature of the conclusions. To do so will require amelioration of the workload of the current staff. The workload of staff has increased markedly over time, in part because of the growing evidence base, but also because of the uneven quality of input from expert Working Group Members prior to meetings and the loss of several experienced staff. The unusually large scope of Volume 100, which will review and update scientific evidence on all agents categorized into Group 1 (*carcinogenic to humans*), has added and will continue to add considerably to the workload over the next two to three years.

These factors have combined to generate a backlog in the *IARC Monographs* programme, with some recent volumes taking over two years from the time of the Working Group (WG) meeting to finalize. Despite the backlog that has developed recently within the *Monographs* programme, the AG considers the programme to be well managed, and comprised of excellent staff with the expertise needed to deliver the programme.

Current staffing levels have increased on a temporary basis to cope both with a backlog of work and with the demands of producing Volume 100 in a timely fashion. The dedication of the *IARC Monographs* staff in working towards meeting these two challenges is to be commended. Because of the nature of the *IARC Monographs* programme, whose impacts are felt worldwide, the productivity of the programme cannot be measured simply by counting the number of meetings held, or by the number of volumes produced.

The AG acknowledges the efforts of the group but feels there are still insufficient resources to simultaneously finish the *Monographs* remaining in Volumes 92-99 and complete Volume 100. Therefore, it is the view of the AG that in order to maintain quality, the output of the programme needs to be adjusted to take into account the complexity and volume of the material being reviewed. To assist in the efficient development of the *IARC Monographs* programme, the AG has formulated a number of recommendations. The AG's most significant recommendations are summarized below.

- The AG recommends that IARC focus on timely and efficient planning, implementation, and completion of Volume 100. This may include expanding the time between the first three meetings and the second three meetings, and using 2010 to finish Volume 100. Additionally, IARC should use the time through 2010 to finish Volumes 92-99 and plan for Volume 101. The AG recognizes that other high priority cancer risk issues may arise during this period; however, the AG

recommends that addressing these issues be delayed, if at all possible, in order to finish Volume 100.

- The AG recommends that, if necessary, no Working Group meetings be conducted in the year 2010 following the completion of Volume 100, in order to eliminate the backlog in the production of the *IARC Monographs*.
- The AG is concerned that the workload for Volume 100 may exceed the capacity of the *Monographs* programme. The AG recommends that careful consideration be given to both the size (is there a sufficient number of scientists/staff to handle the workload over the next three years?) and the nature of the staff complement within the *Monographs* programme. Of particular concern is that current staff levels are inadequate to meet the volume of work that will be required during the next two years while Volumes 92-99 are finalized and Volume 100 is initiated, developed and finalized.
- The AG strongly supports the preparation of scientific publications focusing on tumour site concordance and mechanisms of carcinogenesis in humans. The AG encourages IARC to explore other opportunities of this type, including a description of exposure levels at which carcinogenic effects are seen in humans and animals. In order to ensure that later *Monographs* are not unavoidably delayed, the AG recommends that the scientific publications regarding issues such as site concordance between humans and rodents, and common mechanistic considerations, be prepared in collaboration with other units at the Agency as well as external collaborators outside the Agency. The AG views these documents as important scientific spinoffs from Volume 100, further enhancing the value of Volume 100.
- The AG recommends against evaluation of carcinogenicity by site in Volume 100 (i.e. giving the weight of evidence for carcinogenicity by specific tumour types); the AG does, however, support the identification of sites affected by individual agents in Volume 100. The sites that are conclusively established as causally related need to be carefully separated from those where the association is plausible yet uncertain.
- The AG recommends that opportunities for efficiencies in production of Volumes 92-99 and Volume 100 be sought, based on the overlapping content of these volumes with respect to Group 1 agents. Checking of individual sections should be done in accordance with the importance of those sections to the overall conclusions.

## Issues Facing the *Monographs* programme

Dr Vincent Cogliano opened the meeting (see Annex) by identifying the following issues for discussion by the AG.

1. Reducing publication delay
2. Electronic database of *Monograph* results
3. Process changes
  - a. Credit for assistants who write critical reviews for Working Group Members
  - b. Creation of tables by IARC staff before a *Monograph* meeting
  - c. Identification of study sponsors in some situations
4. Volume 100: Steps to make the workload more manageable
5. Volume 100: Terms used to identify occupations evaluated in the *Monographs*
6. Priorities for *Monographs* during 2010–2014
7. Potential expansion of the concept of “agent” in future evaluations

The AG elected Dr Jørgen Olsen (Danish Cancer Society) and Dr Chris Portier (U.S. National Institute of Environmental Health Sciences) as co-chairs of the Advisory Group. Dr Daniel Krewski (University of Ottawa) was elected Rapporteur.

### 1. Reducing publication delay

#### *Background*

- IARC normally hosts three *Monograph* meetings per year and publishes three *Monograph* volumes per year.
- The timeline for Volume 90 (Human papillomaviruses), for example, involved 34 months from the time of the meeting until the volume was published. There was a 21-month delay (due to ongoing checking of previous *Monographs*) between the time of the meeting and the time when checking of the volume began at IARC; checking took place over a period of 6 months.
- *Monograph* volumes have increased from approximately 200 pages in 1987 to approximately 400 pages from 1992 through to 2006, with the notable exceptions of Volume 83 in 2004 (1500 pages) and the three volumes published in 2007 (at an average of over 600 pages each).
- The staff complement has increased by three people from 2003 to 2008. In addition, it was noted that four of the current positions may be time-limited, which may present human resource problems in the future. Newly hired scientific staff restores levels to the 1999 level but does not expand staff to meet current demands.
- IARC has the capacity to check about 1000 pages per year: Page limits may be considered to achieve shorter volumes in the future. [Strict page limits have been established for Volume 100: a maximum of 30 pages of text per agent, with an average of less than 15 pages per agent.]
- The Volume 100 meetings were scheduled so that the meetings that include Group 1 agents from Volumes 92-99 would occur after the checking of those volumes is complete: for example, lifestyle factors (meeting E) and chemical agents (meeting F) are scheduled last. Currently, the checking of all *Monographs* required for the preparation of Volume 100 is planned to be completed by February 2009.

- Two scientific publications (site concordance between animals and humans, and mechanisms involved in human carcinogenesis) will be based on Volume 100 – a four-month break in the production of *Monographs* has been scheduled in each of 2010 and 2011 to allow for the completion of these scientific publications.
- The first meeting (pharmaceuticals) for Volume 100 is scheduled for October 2008; the completion of Volume 100 is anticipated in 2010, with publication in 2011.

The above observations indicate that the *IARC Monographs* programme has faced a steadily increasing workload over the last decade, due to both the increasing volume of scientific literature that needs to be evaluated in individual *Monographs* and the extra demands placed on the programme staff to complete Volume 100 in a timely manner. In considering ways in which these pressures might be addressed, the AG sought options that would ensure that the quality and integrity of the *Monographs* programme be maintained.

### *Discussion*

- The AG noted the need for timeliness in the completion of *IARC Monographs*, as the results of the *Monographs* are widely used in the evaluation of carcinogens worldwide.
- The *Monographs* programme was initiated in 1971 and has been in existence for almost 40 years. Online sources of scientific data are now widely used – can the *Monographs* be developed using a common online document that Working Group Members and IARC staff alike could work on in real time? [For example, SharePoint is a useful software tool for such an application.]
- It was generally felt that to meet current commitments for the completion of past *Monographs*, and to properly prepare for Volume 100, some efficiencies will need to be found. [For example, efforts have been made to shorten Volume 92 on PAHs.]
- Because of the authoritative nature of the *IARC Monographs*, it is important that accuracy not be sacrificed in the interest of speeding up production of the *Monographs*.
- Could the original authors of the reference be asked to check that portion of the *Monograph* relating to that reference? [This would not seem to be generally useful, because of the large number of original authors who would have to be contacted, many of whom might not be able to check the *Monograph* in a timely manner.]
- Could the Working Group Members be asked to conduct the checking on IARC's behalf? [Most Working Group Members have indicated that they do not have time to work on the *Monograph* after the *Monograph* meeting is over.]
- Could some of the checking involved in the backlog be contracted out? [There are three options for additional checking resources: recruit additional staff, contract out the checking, and ask staff to work overtime.]
- Could checking focus primarily on those items that are critical to the classification of the agent under review? [Failing to check the entire *Monograph* could compromise the credibility of the *Monographs* programme.]

- Checking focuses on matters of scientific fact and accuracy; language editing is done by the IARC editor. [Editing normally does not hold up production of a volume.]
- Historically, much of the backlog started with Volume 83 (Tobacco smoke and involuntary smoking), which is approximately 1500 pages.
- Some *Monograph* sections have a large number of references, which need to be reviewed as part of the checking process. [One section of one *Monograph* had over 400 references, all of which had to be ordered from the library for checking.]
- Limiting the number of references that can be included in a *Monograph* could be considered (focusing on the key references needed to support the conclusions drawn).
- IARC may want to consider recruiting an individual to obtain references that need to be checked, and to provide secretarial support to the *Monographs* programme.
- Electronic systems for identifying experts for *Monograph* Working Groups are being considered by IARC; other opportunities to make production more efficient using modern informatics techniques are being considered.
- Electronic publication of unedited/unchecked *Monographs* as prepublication versions might be considered. [This is currently done by the U.S. National Research Council, where prepublication versions of committee reports are often done in advance of the publication of the final version.]
- The *Lancet Oncology* summaries, which appear within eight weeks after a *Monograph* meeting, provide a venue for making the conclusions available in a timely manner; however, IARC still receives many requests for additional information between the time the *Lancet Oncology* article appears and the full volume is published.
- Several groups (IARC, WHO, and the EC) review the same data. (The IARC review should ideally form the foundation on which other evaluations are built.) Prepublication versions of *Monograph* volumes have been provided to these groups upon request.
- Immediate prepublication may not be desirable, in cases where the volume is in only rough form following the *Monograph* meeting.
- Can all of the “production logistics” of the *Monographs* programme be reviewed, in the interest of identifying possible efficiencies in production? [Publication on-demand – using pdf copies that can be accessed online – might be considered as part of this review.]
- Can the *Monographs* be streamlined by relying more on tables (which would be carefully checked), rather than narrative text? [Narrative text might be necessary for key studies.]
- The U.S. Environmental Protection Agency is facing a challenge with the volume of scientific literature on the six “criteria air pollutants” for which national ambient air quality standards are set. (Over 100 000 references have been reviewed in the past; new papers are appearing at a rate of over 1000 per month.) This has led EPA to

focus on the most important studies and to briefly summarize other studies in tabular form.

- The AG considered the possibility of not preparing Volume 100 as currently envisaged, and continuing with the development of *Monographs* on new agents, as in the past. The AG considered Volume 100 and the two related scientific publications on tumour site concordance and mechanisms of carcinogenesis to be important contributions to the field of cancer risk assessment and did not recommend that Volume 100 be abandoned.

### *Origin of the Backlog*

Beginning with the production of an unusually large volume (1500 pages) on tobacco smoke and involuntary smoking in 2002 (published two years later in 2004), a backlog in the completion of *IARC Monographs* has developed. The tendency towards larger and more complex *Monographs* (as a consequence of the increasing volume of literature that is emerging on agents evaluated within the *Monographs* programme) has also contributed to this backlog. With the increasing demands on people's time, Working Group Members may be relying more on IARC staff in the preparation of current *Monographs* than in the past. The production of Volume 100, a monumental and resource-intensive undertaking that will update the information on Group 1 carcinogens considered in Volumes 1-99, will add considerably to the workload of the *Monographs* programme staff.

### *Recommendations*

#### **Volumes 92-99**

- The AG considered it inadvisable to reduce the level of checking of Volumes 92-99 in a way that would compromise the quality and integrity that the *Monographs* programme has historically enjoyed. However, as discussed below, the AG has suggested several opportunities for achieving some increases in efficiency that could be considered.
- The checking of Volumes 92-99 is targeted for completion by February 2009. (Volumes 92 and 97 have been checked.) To ensure that this goal is achieved, additional resources will need to be dedicated to checking these volumes. (These additional resources need not be new full-time staff, but could come from short-term secondments, or staff from the sponsoring organizations.)
- The unchecked versions of Volumes 92-99 that pertain to Group 1 carcinogens could be shared immediately with the Working Groups for Volume 100, asking them to correct any discrepancies they see in the tables or text. However, this is unlikely to significantly reduce staff workload, unless the Volume 100 experts check these tables and text to the same standard currently applied by IARC staff.
- The AG recommends that opportunities for efficiencies in production of Volumes 92-99 and Volume 100 be sought, based on the overlapping content of these volumes with respect to Group 1 agents. Checking of individual sections should be done in accordance with the importance of those sections to the overall conclusions.
- To allow proper completion of Volumes 92-99 prior to the preparation of Volume 100, the production of Volume 100 could be delayed. Alternatively, the latter three meetings could be delayed.

**Volume 100**

- The AG discussed the possibility of recommending to delay the initial meeting for Volume 100, or cancellation of Volume 100, as a means of reducing the backlog in finalizing *Monographs* 92-99. However, given the scientific value of Volume 100 as currently envisaged, the AG did not see the delay of the initial meeting or cancellation of Volume 100 in the interests of workload management as a desirable option.
- If necessary, the AG recommends that the later meetings scheduled for Volume 100 be delayed to allow the Agency to manage its workload in a manner that will ensure that the quality and integrity of the *Monographs* are maintained.
- The AG is concerned that the workload for Volume 100 may exceed the capacity of the *Monographs* programme. The AG recommends that careful consideration be given to both the size and composition of the staff complement within the *Monographs* programme. Of particular concern is the volume of work that will be required of support staff (e.g. reference librarians, technical typists) during the next two years while Volumes 92-99 are finalized and Volume 100 is initiated, developed and finalized.
- The AG discussed the possibility that extending the timeframe for Volume 100 could seriously delay the evaluation of the carcinogenic potential of novel exposures (e.g. radiofrequency EMF). The AG believes that Volume 100 is an important scientific contribution and warrants the time, effort and resources being employed in its development.
- Dedicated “fact checkers” could be used for Volume 100 to ensure the accuracy of information copied from the scientific literature before, during, and after the *Monograph* meetings (verifying discrepancies between what is stated at the meeting and what appeared in the original scientific publication). If resources permit, these “fact checkers” could be recommended by Working Group Members (e.g. post-docs, junior faculty) and used as “fact checkers” on the draft.
- The AG recommends that opportunities for efficiencies in production of Volumes 92-99 and Volume 100 be sought, based on the overlapping content of these volumes with respect to Group 1 agents. Checking of individual sections should be done in accordance with the importance of those sections to the overall conclusions.

**Future volumes**

- The AG recommends that IARC focus on timely and efficient planning, implementation, and completion of Volume 100. This may include expanding the time between the first three meetings and the second three meetings, and using 2010 to finish Volume 100. Additionally, IARC should use the time through 2010 to finish Volumes 92-99 and planning for Volume 101. The AG recognizes that other high priority cancer risk issues may arise during this period; however, the AG recommends that addressing these issues be delayed, if at all possible, in order to finish Volume 100.
- The AG recommends that, if necessary, no *Monograph* meetings be conducted in the year 2010 following the completion of Volume 100, in order to eliminate the backlog in production.

- Consideration could be given to initiating Volume 101, the next volume that would address a new high priority agent potentially carcinogenic to humans, before Volume 100 is published in final form.
- IARC can check about 1000 pages per year with the regular complement. The AG recommends that the number of volumes produced each year be tied to this page limit, in order not to compromise the quality and integrity of the *Monographs*.
- To avoid future backlogs in production, more concise approaches to presenting the scientific data on the agents of interest should be considered. In particular, more reliance may be placed on short narrative summaries and tabular, rather than textual, summaries of data, using narrative summaries primarily for key studies and knowledge integration. The use of web annexes, a now common practice with many scientific journals, might be considered as a way of shortening *Monographs*. (A web annex might be used, for example, to list studies that were considered, but not used, in the evaluation.)
- The AG strongly supports the preparation of scientific publications focusing on tumour site concordance between animals and humans and mechanisms of carcinogenesis in humans. The AG encourages IARC to explore other opportunities of this type, including a description of exposure levels at which carcinogenic effects are seen in humans and animals and implications for more quantitative assessments of carcinogenic risks to humans. In order to ensure that later *Monographs* are not unavoidably delayed, the AG recommends that the scientific publications regarding issues such as site concordance and mechanisms of carcinogenesis be prepared in collaboration with other units at the Agency as well as external collaborators outside the Agency. The AG views these documents as important scientific spinoffs from Volume 100, further enhancing the value of Volume 100.
- As recommended for Volume 100, an ongoing pool of “fact checkers” could be established to assist in the checking of future *Monographs*. Training of the fact checkers could be provided (possibly via the Internet). The AG noted that compensation for time spent on fact checking may need to be provided by IARC, or its sponsors.
- The AG suggests the expanded use of project management techniques, such as Gantt charts, to assist in the timely production of future *Monographs*.
- Modern informatics tools (e.g. heat maps, text mining of scientific manuscripts), should be explored as a way to present large amounts of information in future *Monographs*.

## **2. Electronic database of *Monograph* results**

### *Discussion*

The IARC staff suggested that it would be useful to create an electronic database of *Monograph* results, and that Volume 100 provides an excellent opportunity to build such a database. The AG discussed this concept, and made several recommendations in this regard.

### *Recommendations*

- The AG recommends that IARC pursue the development of an advanced database for use within the *Monographs* programme. The creation of such a database has the potential to provide IARC with the capacity to handle information related to the *Monographs* more efficiently, and to make this information available to others in an easy-to-use form.
- IARC staff presented a list of potential data elements that could be included in such a database; the AG agreed with all of the proposed data elements.
- The AG also discussed additional data elements, including a descriptor of the nature of the exposure (e.g. pharmaceutical agent, environmental pollutant), an indication of the nature of the dose–response relationship, and information on the mechanisms of carcinogenesis of the agent.
- The AG felt that a comparatively advanced database structure should be implemented (such as ACCESS rather than EXCEL), in order to provide IARC with the capacity to extract and summarize information from the database in the most informative manner possible.
- The AG recommends that IARC evaluate the experience of other organizations, such as the U.S. National Cancer Institute, in moving forward with the development of the database. Tumour nomenclature algorithms already in use by other organizations (such as the U.S. NCI) may also be useful in this regard.

The AG noted that the creation of a sophisticated computerized database on carcinogenic agents as described here will require specialized informatics expertise to implement and maintain. If such a database is pursued, it may be necessary to recruit additional specialists. A web-based version of Volume 100 could be maintained as a living, regularly updated volume on the Internet, supplemented with short updates (20-30 pages) as new Group 1 agents are identified and as existing Group 1 agents are re-evaluated. As resources become available, a web-based version of *Monographs* for agents falling outside of Group 1 would also be valuable.

### **3. Process changes**

#### **a. Credit for assistants who prepare critical reviews for Working Group Members**

##### *Discussion*

- IARC staff noted that, on occasion, draft documents for *Monograph* meetings have been written by individuals other than Working Group Members. The AG acknowledged the need for individuals who have contributed to a *Monograph* to be recognized. At the same time, the AG pointed out that Working Group Members assume responsibility for the written material submitted to IARC.
- The AG observed that the use of assistants by Working Group Members in preparing their submissions to IARC may actually be beneficial to the *Monographs* programme, as a consequence of the additional resources that are contributed to the programme.

*Recommendation*

- The AG acknowledges that Working Group Members may receive assistance from others in the assembling of materials submitted to the *Monographs* programme. While Working Group Members may make use of such assistance in gathering information that they may include in their submissions, Working Group Members should draft the text and tables that are submitted to IARC. Ultimately, Working Group Members assume full responsibility for the material they provide to IARC.

**b. Creation of tables by IARC staff before a *Monograph* meeting***Discussion*

- The AG recognized that the creation of the tables by IARC staff in advance of a *Monograph* meeting would improve the quality of the information available for discussion at the meeting, reduce the time needed during the meeting for tasks that are not central to discussing the overall conclusions, and speed up checking the *Monograph* following the meeting.

*Recommendations*

- The AG does not support the preparation of tables by IARC staff prior to a *Monograph* meeting at this time. The AG feels that immediately implementing this policy could lead to less involvement of the Working Group Members in preparing the material for which they are responsible and inefficiencies in the use of staff and scientists in preparing the *Monographs*. The AG recommends that IARC selectively implement creating tables in advance of a *Monograph* meeting to assess whether this approach will lead to greater efficiency and overall quality.
- The AG recommends that IARC investigate the use of electronic questionnaires and query tools that allow the capture of information from Working Group Members regarding relevant studies that can then be automatically formatted into a table for use in a *Monograph*.

**c. Identification of study sponsors in some situations***Discussion*

- IARC staff noted that many scientific journals require authors to acknowledge sponsorship. There have been some cases in the literature where the results of a scientific publication reflect, explicitly or implicitly, the perspective of the (private or public sector) sponsor.

*Recommendation*

- The AG did not feel it necessary to draw attention to the sponsorship of specific research studies; rather, it is the responsibility of the Working Group to evaluate each study on its own merits, and to determine the integrity of the results obtained before they are included in a *Monograph*.

#### 4. Volume 100: Steps to make the workload more manageable

##### *Discussion*

- The value of Volume 100 will be to update the scientific literature and provide a summary of the overall literature as of this point in time. Volume 100 will also be useful in identifying specific tumour sites that are affected by Group 1 carcinogens. The two scientific publications (tumour site concordance and mechanisms of human carcinogenesis) will be valuable follow-on products from Volume 100.

##### *Recommendations*

The AG offered the following observations on the steps proposed by IARC to make the production of Volume 100 more manageable.

- a. Each agent and section (exposure data, cancer in humans, cancer in experimental animals, mechanistic and other relevant data) will have strict page limits. The longest *Monographs* (for example, tobacco smoke or asbestos) will not exceed 30 pages of text. The average *Monograph* should be less than half of this upper limit.

*Recommendation:* In order to keep Volume 100 to be of manageable size, the AG supported the page limits proposed by IARC (recognizing that exceptions may be necessary in some cases).

- b. For epidemiological studies and cancer bioassays, all information on study design and results will be summarized in tables and these details will not be repeated in the text. There will be no page limits for tables. Nonetheless, for clearly established associations such as tobacco smoke and human lung cancer, HPV-16 and cervical cancer, or benzo[a]pyrene and lung cancer or skin cancer in experimental animals, individual Working Groups may decide to limit tables to a small number of the most informative studies (that is, those that provide significant or new information) and the rationale for study inclusion and exclusion will be explained in the *Monograph*.

*Recommendation:* The AG agreed with the intent to limit tables to the most informative studies. The amount of text in the *Monograph* will also be reduced through greater reliance on tabular summaries of pertinent studies.

- c. Tables may be taken from any authoritative source: earlier *Monographs*, background documents for the NTP Report on Carcinogens, or assessment documents prepared by national health agencies such as the U.S. EPA. These tables will be electronically imported or manually typed into Volume 100 and credited and referenced appropriately. To lessen the pre-meeting efforts of the six Working Groups, their writing assignments will be (1) to update these tables by including studies published after the earlier tables had been prepared and (2) to write a text summary of the studies as a whole. To save time in the post-meeting verification of the tables, the *Monographs* programme staff will verify only those studies that were added for Volume 100, not the information that appeared in the earlier authoritative source.

*Recommendation:* The AG supported the reliance on existing tables from earlier *Monographs* and limiting verification to studies that were added to these tables by the Working Groups for Volume 100. The AG did not support the direct use of tables from other sources.

*Recommendation:* The AG also suggested that it may be helpful to move away from the traditional concept of tables towards the more general concept of structures; this would permit the storage of relevant scientific data in a structured database that could be easily searched, and used to generate tables that would summarize the relevant information in an appropriate form.

- d. Mechanistic studies and other relevant data will be discussed in a section that resembles a review article. Individual study design information will generally not be reported. Mechanistic sections will be limited to approximately 20-50 references that provide a representative but not exhaustive review of these studies.

*Recommendation:* The AG concurred that an accurate description of mechanisms of carcinogenesis could be accomplished with a limited bibliography and supports the proposed practice of limiting the number of references in the section on mechanistic and other relevant data.

- e. To ensure that Volume 100 will be of high quality, IARC will coordinate a review of working papers before each *Monograph* meeting. Working Group Members have been asked to send their preliminary working papers and reference lists to IARC five to six months before each meeting, IARC will then send these papers to other Working Group Members for comment, and the original writer will address the comments in a revised working paper due two to three months before the meeting. This pre-meeting review will ensure that each section receives more attention than can be given during the meeting. Pre-meeting reviewers will also be asked to identify key issues so that the meeting can be planned to allow adequate time for each discussion.

*Recommendation:* The AG felt that the timetable proposed for developing the individual working papers in Volume 100 was reasonable and appropriate, although this timetable does represent a significant challenge. (The AG felt that having *Monograph* materials several months ahead of the meeting would greatly facilitate the completion of Volume 100 in a timely manner.)

## **5. Volume 100: Terms used to identify occupations evaluated in the *Monographs***

The following terms have been used to describe jobs and occupations in previous *IARC Monographs*:

- Boot and shoe manufacture and repair (vol 25, sup 7)
- Furniture and cabinet making (vol 25, sup 7)
- Haematite mining (underground) with exposure to radon (vol 1, sup 7)
- Coal gasification, occupational exposures during (vol 92)
- Paving and roofing with coal-tar pitch, occupational exposures during (vol 92)
- Coal-tar distillation, occupational exposures during (vol 92)
- Coke production, occupational exposures during (vol 92)
- Chimney sweep, occupational exposure as a (vol 92)
- Aluminium production (vol 34, sup 7, vol 92)
- Auramine production (vol 99)
- Iron and steel founding (vol 34, sup 7)
- Isopropyl alcohol manufacture (strong-acid process) (sup 7)
- Magenta production (vol 99)
- Painter (occupational exposure as a) (vol 98)
- Rubber industry (vol 28, sup 7)
- Strong-inorganic-acid mists containing sulfuric acid (occupational exposure) (vol 54)

*Recommendations*

- The AG recommends that IARC provide guidance to the Working Groups on terminology to be used to characterize occupational exposures, although the final determination of the terminology to be used in this regard remains the responsibility of each Working Group.
- Ideally, it would be desirable to focus on the specific agents found in occupational environments that are responsible for increased cancer risk. However, when this is not possible, the occupational circumstances associated with increased cancer risk should be described as precisely as possible.
- The influence of occupation on cancer risk may well change over time. As industrial processes evolve and enhanced hygiene measures are implemented, it may be appropriate to review the manner in which such occupational circumstances are described. At the same time, it is recognized that such modernization is not likely to occur uniformly throughout the world.
- The AG also recognizes that these issues may apply beyond occupational exposures and they should use the same guidance there.

**6. Should genetics be treated as a main effect or as a modifying factor for human cancer?**

Evaluating genetic susceptibility (polymorphisms and somatic mutations) is a complex issue. Should genetic variation be addressed in some way by IARC, for example, as the main topic within a *Monograph* focusing on risk factors for human cancer?

*Recommendation*

- Genetic factors (polymorphisms or somatic mutations) are intrinsic to the human organism and essentially non-modifiable at this point in time. With the large number of genetic risk factors linked to human cancer, the evaluation of genetic risk factors for human cancer will be complex. It is recommended that genetic factors be treated as modifying factors within the *Monographs* programme, and discussed in the 'mechanisms' section of the *Monographs*.

## Priorities for *Monographs* during 2010–2014

In February 2008, the *Monographs* programme widely distributed a notice requesting nominations for agents or exposures to be evaluated during 2010–2014. The AG reviewed the nominated agents and exposures, added several new ones, and discussed the priority for each. The agents with highest priority are described below and the remaining agents are listed as medium or low priorities. The AG emphasizes that placement of an agent in the medium- or low-priority categories does not necessarily reflect the AG's long-term concerns about the agent. Rather, rankings reflect a variety of factors considered, including how recently the agent was reviewed by IARC, availability of new data, and ongoing assessments by other organizations that may shed light onto the state of the science.

The AG wished to note that some of these high-priority agents and exposures appear to be more pressing than others. Included in this list are the radiofrequency electric and magnetic fields, motor vehicle exhausts, polyomaviruses, bitumen, and acrylamide.

### High Priorities

**Acetaldehyde:** Acetaldehyde is toxic, mutagenic, and carcinogenic in rodent models. It is an important factor in alcohol-associated carcinogenesis of the upper aerodigestive tract. Polymorphism or mutation in genes coding for acetaldehyde generation from alcohol or in detoxification enzymes are associated with an increased cancer risk of the upper aerodigestive tract in humans. Individuals carrying the acetaldehyde dehydrogenase 2\*2 (ALDH2\*2) allele have a significantly increased cancer risk when they consume alcohol. The alcohol dehydrogenase 1\*1 (ADH1C\*1) allele encodes for an alcohol dehydrogenase (ADH) isoenzyme that produces 2.5 times more acetaldehyde than the corresponding allele ADH1C\*2 and is associated with an increased risk of alcohol-related cancer. People are also exposed to acetaldehyde itself, not only through the metabolism of ethanol, and many alcoholic beverages (for example, Calvados) contain considerable amounts of acetaldehyde.

**Acrylamide and Furan:** Both compounds have previously been evaluated as industrial chemicals. Both are now recognized to be dietary contaminants as well, being produced in certain foods cooked at high temperatures. Human exposure is very widespread as a result, and new bioassays and mechanistic studies of acrylamide have been completed. JECFA and U.S. EPA reviews are expected during 2009.

**Asphalt and Bitumen:** Both materials are processed from residues of petroleum refining and liberate fumes when heated for use as paving materials. Exposure is primarily occupational and is widespread.

**Carbon-based nanoparticles:** The new nanotechnologies have produced carbon-based nanomaterials with exceptional properties. Carbon nanotubes (CNT) are the most relevant ones and have already been proposed for a large variety of products and applications, including within the biomedical field (e.g. imaging, drug delivery). Therefore, an increasing number of workers and users will be exposed to them. Carbon-based nanomaterials include single wall (SWCNT) and multiwall (MWCNT) carbon nanotubes, fullerenes (C<sub>60</sub>, C<sub>70-100</sub>), carbon particles and dusts from various sources, some carbon fibres. Animal studies report that exposure to MWCNT by intratracheal instillation induces inflammation and irreversible lung fibrosis that could lead to cancer. In one study, introduction of CNT in the peritoneal cavity induced mesotheliomas in mice. There is a rising concern that, in spite of the differences in chemistry, because of their needle-like fibre shape, they might act like asbestos. A recently published exposure

study shows that it is possible to generate high CNT airborne concentrations during processes such as blending. Fullerenes, which are also used in various applications in different fields, have already shown toxic effects in several studies.

**Crystalline fibres other than asbestos:** Beside the six recognized forms of asbestos, several asbestiform minerals (crystalline and in fibrous habit) appear locally, which may be as harmful as asbestos. Only erionite (Group 1) has been so far considered by IARC. A cluster of mesotheliomas among people never exposed to asbestos in a rural area in Sicily (Biancavilla, Italy), has led to the identification of a new fibre, fluoroedenite, very abundant in the material extracted locally from the rocks and widely used for whitewashing. The vermiculite in Libby, Montana (USA) appears contaminated by fibres that have seriously affected the local population. There is concern that a similar situation might be found in other similar sites. Several unclassified asbestiform minerals often associated with chrysotile asbestos occur naturally as outcrops in certain serpentine rocks (e.g. Western Italian Alps), which could increase the hazard associated with land work. Some artificial ceramic fibres change from amorphous to crystalline upon heating when in use and may become hazardous when disposed of. Although the studies appear limited, in view of the discovery of future sources of carcinogenic fibres, it could be useful to examine together all data on these kinds of materials.

**Growth hormone:** Growth hormone (GH) is a pituitary hormone involved in mammalian growth. It is used in medicine to treat hypopituitarism. It has been used by athletes to increase muscle mass. In dairy cows bovine growth hormones are administered to increase milk production. Administration of GH increases mammary density in macaque monkeys and causes prostate hypertrophy.

**Iron and Iron Oxides:** Tens of millions of workers worldwide are exposed to iron fumes. Most are exposed by inhaling welding fumes whose main component is iron. Exposure to iron fumes is also extensive in steel mills and iron/steel foundries. Epidemiological studies have suggested an elevated risk of lung cancer among mild steel welders, stainless steel welders, and foundry workers. Some studies have associated this risk with iron fumes, which is a common component of these complex fumes. Due to various potential confounding exposures, such as chromium VI, nickel compounds, polycyclic aromatic hydrocarbons, crystalline silica, asbestos, and smoking, the causative factor is difficult to identify. Because of potentially substantial health impacts and suggestive evidence from epidemiological studies, the carcinogenicity of iron fumes, mild steel welding fumes, and stainless steel welding fumes should be evaluated separately, if possible.

**Malaria:** Malaria has been associated with Burkitt lymphoma among children in Africa, with other non-Hodgkin lymphomas, and also as a co-factor in the aetiology of Kaposi sarcoma (although this latter case is less certain).

**Motor vehicle exhaust emissions:** Motor vehicle exhaust emissions, particularly related to transportation, are a significant worldwide public health problem. Exposures are widespread and include a number of known and likely carcinogens. New health data are also available. Ideally, the carcinogenic potential of emissions from various engines and fuel types would be considered together in a comparative manner; however, the magnitude of this task will likely require a more sequential approach. Nominated categories are diesel, gasoline and biofuel exhaust emissions.

**Nucleoside analogue antiviral drugs:** Nucleoside analogues include drugs active against HIV or HBV. Some are known to be carcinogenic in animals but only a few have previously been evaluated. Human exposure is widespread owing to the high

prevalence of HIV and HBV infections. Some but not all are incorporated into nuclear DNA and are genotoxic.

**Perfluorooctanoic acid (PFOA) (include broader group of perfluorinated compounds):**

PFOA is used to make fluorocarbons used in the manufacture of non-stick cookware and breathable, all-weather or stain-resistant clothing. PFOA is persistent in the environment and is found in low levels in blood in the U.S. population. PFOA has been associated with increased incidence of liver, Leydig cell and pancreatic acinar-cell tumours in rodent bioassays. It is currently being tested in two-year bioassays by the NTP.

**Polyomaviruses (SV40, BK, JC, Merkel cell virus):** There is a growing literature on the possible role of polyomaviruses in the aetiology of human cancer. There has been particular concern in relation to infection with Simian Virus 40 (SV40), following recognition that it was a contaminant of poliovirus vaccines that had been used to inoculate more than 100 million people in the USA alone and countless more elsewhere in the world. A carcinogenic role for SV40 has been suggested in relation to mesothelioma, brain cancer and haematological malignancies (among others) and remains a controversial area in cancer research. Similarly, BK virus has been linked in some studies (but not others) with cancers of the urogenital tract, and JC virus with colorectal cancer. All three viruses have transforming potential in in-vitro and animal studies. In addition, a newly discovered polyomavirus has been linked to Merkel cell carcinoma in humans.

**Radiofrequency electric and magnetic fields:** The rapid expansion of communication and other emerging technologies has resulted in widespread exposure of the general public and many workers. Uncertainties in the science and its interpretation in relation to possible adverse effects on health have led to different conclusions among the scientific community and attendant public and media concerns, particularly about a possible risk of cancer.

**Sedentary work:** There are established linkages among energy balance, obesity, and various cancers. Obesity is a global public health problem. IARC should explore these topics and consider what aspect would be most important to address. Since many people are involved in sedentary work, this aspect might be the focus of a *Monograph*.

**Statins:** Statins (HMG-CoA reductase inhibitors) have become the most popular drugs used for treating high cholesterol. Randomized controlled trials have shown that statins improve the blood lipid profile and may decrease a number of cardiovascular diseases and mortality from coronary heart disease. They inhibit the mevalonate pathway that leads to critical changes in cell function. Cancer-preventive as well as cancer-causative effects have been reported in animal models with some statins. Statins can possess antiproliferative, proapoptotic and radiosensitizing properties. Cancer effects may also be associated with mutations of activated RAS-proteins. Several meta-analyses have been published on the effects of statins on cancer incidence or mortality, with somewhat discrepant results.

**Stress:** Stress has been associated with cancer and there is a relatively large literature available on the topic. Stress-producing conditions are widespread. There is a growing literature on the measurement of stress and the effect of interventions such as modification of the organization of work for preventing or controlling stress. Due to the complexity of the topic, the AG recommends a specific advisory group on this topic before IARC proceeds to develop a *Monograph*.

**Testosterone (broader category of androgenic steroids):** Testosterone is commonly prescribed to older men with low testosterone levels and is also prescribed for women with symptoms of decreased libido. Anabolic (androgenic) steroids are widely abused among athletes and others. Since 1987, when testosterone was last evaluated, there has been increasing knowledge of how androgens act and may affect carcinogenesis, including epidemiological studies of the association between circulating androgenic hormone levels and cancer risk in humans, carcinogen bioassays and mechanistic studies.

**Ultrafine Particles:** Ultrafine particles are a common component of combustion products, some manufacturing, volcanic emissions and a natural result of vapour solidification. As a consequence, exposures are widespread. Carcinogenic concerns relate both to the particles themselves as well as chemicals that adhere to the surface of the particles. Ultrafine particles share difficult scientific issues, such as complex physical chemistry and dosimetry. The complexity of these issues warrants an integrated review of this topic. Ultrafine particles could be considered independently, or as a component of fuel combustion products, air pollution, or in conjunction with engineered nanoparticles.

**Welding:** The IARC has previously evaluated welding in Group 2B. New epidemiological data on welders corroborate earlier findings on the increased risk of lung cancer among welders. There is a dose relationship among stainless steel (but not mild steel) welders. Furthermore, observations have been published on excess uveal cancer among welders, as well as case reports on skin cancer.

**Agents recently tested in experimental animals:** There are several chemical agents for which toxicological data would suggest they are possibly carcinogenic to humans. The AG recommends the IARC review the chemicals listed below and others to develop a volume on "Some chemical agents shown to increase carcinogenicity in experimental studies". Descriptions of these chemicals come from the Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. Additional *Monographs* on lower priority agents with positive bioassay results could be added to make a volume of reasonable size.

**2-Aminoanthraquinone:** 2-Aminoanthraquinone is used as an intermediate in the industrial synthesis of anthraquinone dyes. It is the precursor of five dyes and one pigment: Colour Index Vat Blues 4, 6, 12, and 24; Vat Yellow 1; and Pigment Blue 22. When administered in the diet, 2-aminoanthraquinone increased the incidences of hepatocellular carcinomas and neoplastic nodules in male rats, hepatocellular carcinomas in mice of both sexes, and lymphomas in female mice.

**1-Amino-2,4-debromoanthraquinone (ADBAQ):** ADBAQ and other aminoanthraquinones are key intermediates for the production of almost all anthraquinone dyes. Anthraquinones, including ADBAQ, are widely used as starting materials for the manufacture of vat dyes. Orally administered ADBAQ significantly increased the incidences of benign and/or malignant tumours at multiple tissue sites in two species of animals. ADBAQ caused benign and malignant liver tumours in rats and mice of both sexes; tumours of the large intestine, kidney, and urinary bladder in male and female rats; and tumours of the forestomach and lung in male and female mice.

**1-Amino-2-methylantraquinone:** 1-Amino-2-methylantraquinone is used almost exclusively as a dye and dye intermediate for the production of a variety of anthraquinone dyes. It was used as a dye for synthetic fibres, furs, and thermoplastic resins. Technical grade 1-amino-2-methylantraquinone, administered in the feed, induced hepatocellular carcinomas in rats of both sexes,

and kidney carcinomas in males. The compound induced an increased combined incidence of hepatocellular carcinomas and neoplastic nodules in female mice

**Bromochloroacetic acid and dibromoacetonitrile:** Bromochloroacetic acid is a water disinfection by-product. Dibromoacetonitrile is formed as a result of the reaction of chlorine oxidizing compounds (e.g., chlorine gas, hypochlorous acid, and hypochlorite) with natural organic matter, particularly nitrogen-containing organic compounds, in water containing bromine; it is also a by-product of ozone disinfection. Draft NTP Technical Reports 549 and 544 indicate increased incidences of tumours at several sites in rats and mice.

**Cumene:** Cumene is the principal chemical used in the production of phenol and its co-product, acetone, via the chemical intermediate cumene hydroperoxide. It is also used as a starting material in the production of acetophenone, alpha-methylstyrene, diisopropylbenzene, and dicumylperoxide. Minor uses of cumene include as a thinner for paints, enamels, and lacquers; as a constituent of some petroleum-based solvents, such as naphtha; in gasoline blending, diesel fuel, and high-octane aviation fuel; and as a raw material for peroxides and oxidation catalysts such as polymerization catalysts for acrylic- and polyester-type resins. It is also a good solvent for fats and resins and, as such, has been suggested as a replacement for benzene in many of its industrial applications. Draft NTP Technical Report 542 indicates that when administered by inhalation, there is clear evidence of carcinogenicity in male rats and in mice of both sexes, and some evidence in female rats.

**Methyleugenol:** Methyleugenol is used as a flavouring agent in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, pudding, relish, and ice cream. Methyleugenol has been used as an anaesthetic in rodents. It also is used as an insect attractant in combination with insecticides. In animal studies, methyleugenol given orally to rats induced liver and stomach tumours in both sexes and kidney, mammary-gland, and skin tumours in males. Methyleugenol given orally to mice induced benign and malignant tumours of the liver. Tumours of the stomach in male mice also were considered related to exposure to methyleugenol.

***ortho*-Nitrotoluenes and other nitrotoluenes:** *ortho*-Nitrotoluene is a chemical intermediate used in the synthesis of azo dyes. It is also used (either directly or as an intermediate) in the production of other dyes, agricultural chemicals, rubber chemicals, pesticides, petrochemicals, pharmaceuticals, and explosives. When administered in the diet, *ortho*-nitrotoluene induced subcutaneous skin neoplasia and mammary-gland fibroadenoma in both sexes of rats, malignant mesothelioma and liver tumours in male rats, haemangiosarcoma in both sexes of mice, carcinoma of the large intestine (cecum) in male mice, and hepatocellular tumours in female mice.

The Advisory Group noted that air pollution (including sulfur oxides, nitrogen oxides, ozone, and dusts) was already a high priority and would be treated in the series of *Monographs* on air pollution. They also noted that coke oven emissions and hexavalent chromium would be covered in Volume 100 and that occupational exposures for truck drivers and railroad personnel were likely to be covered in the high-priority volume on motor vehicle exhaust emissions.

### **Medium priorities**

Artificial sweeteners: aspartame, sucralose, acesulfame potassium  
Atrazine

Dyes metabolized to 3,3'-dimethylbenzidine  
Dyes metabolized to 3,3'-dimethoxybenzidine  
Herbs and other alternative medicines  
2-Mercaptobenzothiazole  
Metalworking fluids and lubricants  
Methotrexate and anti-TNF antibody therapy  
MTBE (methyl *tert*-butyl ether) and other fuel additives  
*N*-Nitroso compounds with widespread occupational and environmental exposure (e.g. *N*-nitroso-*n*-propylamine)  
Polybrominated biphenyls (PBBs)  
Polybrominated diphenyl ethers (PBDEs)  
Polychlorinated biphenyls (PCBs)  
Primidone  
Salicylazosulfapyridine  
Some phthalates (e.g. bis(2-ethylhexyl)phthalate, diisononyl phthalate)  
Styrene  
Trichloroethylene (TCE) and other chlorinated solvents  
Ultraviolet radiation, broad-spectrum UV radiation, sunlamps and sunbeds

### **Low priorities**

2-Acetylaminofluorene  
Amitrole  
Bisphenol A  
Celecoxib  
Chlorine  
Chlorine dioxide  
2-Chloroacetaldehyde  
3-Chloro-2-methylpropene  
Cupferron  
2,4-D  
DDT  
Diazoaminobenzene  
Dichlorvos  
Diepoxybutane  
1,2-Diphenylhydrazine  
Effects of climate change (e.g. via nutrition)  
Ethyl acrylate  
Ethylene bisdithiocarbamates  
Ethylenethiourea  
Fibres, regardless of composition  
Genistein  
Glass wool  
Hydrazobenzene  
4-Hydroxyphenylretinamide, other retinoids  
Indole-3-carbinol  
Iron, iron oxides  
Isothiocyanates: benzyl, phenyl, phenethyl, phenylpropyl, phenylbutyl, phenylhexyl  
Leaded and unleaded gasoline  
Metallic nickel  
3-Monochloropropane-1,2-diol (3-MCPD)  
Organic fibres: *para*-aramid, cellulose, polyvinyl alcohol  
Ptaquiloside and bracken fern  
Reserpine

Selenium sulfide

Siloxanes

Sodium hypochlorite

*tert*-Butyl alcohol

Thiourea

Treatment regimens related to acid peptic disease

2,4,6-Trichlorophenol

## **Annex: Agenda for the Advisory Group meeting**

### **Tuesday, 17 June**

- 9.00 – 13.00      Opening session  
                            Welcome, participant introductions  
                            Presentation of proposed agenda by *Monographs* programme staff  
                            Discussion of issues facing the *Monographs* programme
- 14.00 – 18.00      Discussion of issues facing the *Monographs* programme  
                            Discussion of working papers written for Volume 100

### **Wednesday, 18 June**

- 9.00 – 13.00      Closed-session discussion for Advisory Group members only
- 14.00 – 18.00      Recommendations on issues facing the *Monographs* programme  
                            Recommendations on Volume 100

### **Thursday, 19 June**

- 9.00 – 13.00      Discussion of priorities for *Monographs* during 2010–2014
- 14.00 – 18.00      Discussion of priorities for *Monographs* during 2010–2014

### **Friday, 20 June**

- 9.00 – 13.00      Recommendations on priorities for *Monographs* during 2010–2014
- 14.00 – 18.00      Completion of the Advisory Group's report  
18.00                  Adjourn