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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

REPORT OF THE ADVISORY GROUP TO PLAN VOLUME 100:

A REVIEW OF HUMAN CARCINOGENS

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ADVISORY GROUP TO PLAN VOLUME 100: A REVIEW OF HUMAN CARCINOGENS

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LIST OF PARTICIPANTS[1]

Advisory Group

Valerie Beral, Oxford University, United Kingdom (*Co-Chair*)
Bice Fubini, University of Torino, Italy
Manolis Kogevinas, Barcelona Municipal Institute of Medical Research, Spain
Daniel Krewski, University of Ottawa, Canada
Christopher Portier, National Institute of Environmental Health Sciences, USA
Jerry Rice, Georgetown University, USA[2]
Lesley Rushton, Imperial College London, United Kingdom[3]
Paul Schulte, National Institute for Occupational Safety and Health, USA
Jack Siemiatycki, University of Montreal, Canada
Lorenzo Tomatis, International Agency for Research on Cancer (retired), France (*Chair*)
Hiroyuki Tsuda, Nagoya City University, Japan
Harri Vainio, Finnish Institute of Occupational Health, Finland
Elizabeth Ward, American Cancer Society, USA

Representatives of National and International Health Agencies

Tania Carreon-Valencia, National Institute for Occupational Safety and Health, USA
Christopher De Rosa, Agency for Toxic Substances and Disease Registry, USA
Alicia Huici-Montagud, European Commission: Employment and Social Affairs, Luxembourg
Avima Ruder, National Institute for Occupational Safety and Health, USA

IARC Secretariat

Robert Baan, *IARC Monographs* programme
Paolo Boffetta, Gene-Environment Epidemiology
Peter Boyle, Director
Elisabeth Cardis, Radiation
Vincent Cogliano, *IARC Monographs* programme (*Head of programme*)
Carolyn Dresler, Tobacco and Cancer
Sandrine Égraz, *IARC Monographs* programme
Fatiha El Ghissassi, *IARC Monographs* programme
Silvia Franceschi, Infections and Cancer Epidemiology
Yann Grosse, *IARC Monographs* programme
Mary Heanue, Descriptive Epidemiology
Martine Lézère, *IARC Monographs* programme

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[1] 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 financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. Participants who declared such an interest did not participate in decisions involving agents for which their client or research sponsor had an interest.

[2] Consultant for the American Petrolum Institute, which has interests in benzene. Consultant for Goodell, DeVries, Leech & Dann (a law firm), whose clients have various interests related to the subject of the meeting, including combined estrogen–progestogen menopausal therapy.

[3] Research support from CONCAWE (the European association of oil companies), which has interests in benzene and in benzo[*a*]pyrene, and EUROSIL (the European association of industrial silica producers).

Helene Lorenzen-Augros, *IARC Monographs* programme
Jane Mitchell, *IARC Monographs* programme
Beate Ritz, Visiting Scientist from UCLA, USA
Béatrice Secretan, *IARC Monographs* programme
Kurt Straif, *IARC Monographs* programme
Andreas Ullrich, WHO Programme on Cancer Control, Geneva
Gemma Vestal, WHO Tobacco Free Initiative, Geneva

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

REPORT OF THE ADVISORY GROUP TO PLAN VOLUME 100: A REVIEW OF HUMAN CARCINOGENS

GENERAL COMMENTS OF THE ADVISORY GROUP

The *Monographs* Secretariat presented to the Advisory Group a proposal to mark the 100th volume of the series by creating a special event. The plan that was outlined would consist of an update of the evaluations of all agents that have been judged by previous working groups during Volumes 1 to 99 to be Group 1 carcinogens. In addition, it is intended to expand the evaluations by listing the target organs of each agent. Further, plans were presented to produce complementary volumes that focus on special topics subsequent to the updating process; these were referred to as Annexes.

The Advisory Group considered the proposal from multiple points of view: its potential scientific contribution, its fit within the *Monographs* tradition and its feasibility. In the course of the discussion, the Advisory Group discussed alternative options to mark the milestone. These included but were not limited to: producing a compendium of Group 1 carcinogens with a descriptive presentation of new evidence, but without formally reviewing/reaffirming the evaluations; having authored chapters on the various Group 1 carcinogens without attempting to achieve Working Group consensus and co-authorship; and including estimates of 'threshold limit values' or some other index of potency for each agent.

The following points represent the consensus view of the Advisory Group.

1. The plan outlined by the Secretariat for updating the evaluations of all Group 1 carcinogens would represent a major scientific and public health contribution. Any exercise that would result in anything less than an inclusive listing of Group 1 carcinogens would fall short of this mark. Thus, the alternative proposals raised by Advisory Group members were not deemed to be appropriate for the occasion.

2. The proposal to produce an evaluation by target organ would be a valuable addition to current knowledge.

3. The proposed Annexes should not be seen as integral parts of the main Volume 100, but rather as supplementary endeavours to be carried out after Volume 100. The nature of these supplements falls into the category of 'Lessons Learned' and was supported by the Advisory Group. Several additional ideas were presented by the Advisory Group and are listed in the more detailed comments below.

4. The 'updating' aspect of Volume 100 will consist of providing an updated knowledge base and an updated conclusion for those agents that have already been evaluated as Group 1. It does not imply an attempt to evaluate other agents (previously reviewed or not) that might, if the evidence were assessed, be considered to belong to Group 1. The Advisory Group supported using Volumes 97–99 to evaluate some agents that might fall into the latter category. Ideas were presented to the Secretariat on agents to be considered in Volumes 97–99.

5. The Advisory Group firmly believed that Volume 100, as envisioned, should only be undertaken if the high standards of scientific integrity and credibility for which the Programme is justifiably known can be maintained during such an exercise.

6. The plan is bold and innovative, but in the view of the Advisory Group, contains the seeds of potential pitfalls, some of which could compromise the achievement of the objectives and thereby the reputation of the Programme. The Advisory Group had serious doubts about the feasibility of achieving the objective within the time-frame and with the resources apparently available.

7. The Advisory Group believed unanimously that the list of approximately 99 agents could not reasonably be dealt with in the course of one, two or even three meetings. The Advisory Group recommended that the workload of re-evaluating the list of agents be delegated to no fewer than three Working Group meetings on different occasions, each with the authority to make final decisions on the agents on their list. Some Advisory Group members felt that even four meetings would be too few and would impose too great a burden on each Working Group. The Advisory Group encouraged the Secretariat to conduct a careful 'operations plan' to assess the time-frame and the number of meetings that would be needed to achieve the objectives. The results of this 'operations plan' may well indicate that more than four meetings will be needed.

8. The resources currently available to the Programme may not be adequate to deal with this project, especially given the major backlog of work that *Monograph*s programme staff are currently facing. The Advisory Group encouraged the Secretariat to assess the resources needed to achieve the objectives when developing an 'operations plan'.

The Advisory Group expressed concern that Volume 100 may generate a tendency to focus exclusively on agents that are labelled as belonging to Group 1, and therefore reduce concern over probable (Group 2A) and possible (Group 2B) carcinogens. This could lead to a reduction in the value of the 'non- Group 1' carcinogens and reduce the use of precautionary principles to protect public health. As noted by the Agency, "in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans". The Agency should continue to keep a balance between the rigor required for the inclusion of an agent in Group 1 and the need not to overlook probable and possible carcinogens in the principle of primary prevention.

SPECIFIC COMMENTS ON THE DRAFT PLANNING DOCUMENT

[NOTE: Advisory Group comments are in square brackets]

The *IARC Monographs* are a series of scientific reviews that identify the causes of human cancer. They have been published continuously since 1972 and represent a worldwide effort that has involved more than 1000 scientists from 50 countries. The 100th volume of *IARC Monographs* is a historic occasion for the series, and a fitting topic for this volume is a review of the human carcinogens that have been identified to date. The 100th volume is intended to serve as a key reference for scientific information about the agents that are known to cause cancer in humans.

Contents of Volume 100

For each agent that is classified as *carcinogenic to humans* (Group 1),[1] Volume 100 will contain a concise monograph that follows the general structure of others in the series. It will contain fewer details on each agent than are typically found in other volumes, but there will be no reduction in scientific accuracy or quality.

Section 1. General information, occurrence and exposure

This section will identify the agent (e.g. for chemicals CAS Registry Number, important chemical and physical properties, common synonyms) and provide information on occurrence and how people can be exposed. To keep this section short, quantitative information will generally be reported in the aggregate, and details will be provided only when there are substantial time trends or differences among countries or exposure pathways. Other subsections (analysis and detection, production, regulations and guidelines) will generally be omitted.

[The Advisory Group agreed that this particular section can be reduced in size and that the exclusions proposed by the Secretariat seem reasonable. The section should remain authoritative and comprehensive, but it was believed that this can be achieved in a section as short as two pages which may need to be longer for agents such as fibres and exposures to mixtures. The Secretariat was encouraged to generate a few examples that summarize information from existing *Monographs*. In so doing, the Secretariat will gain additional insight into the size of this section and what will be lost by using the approach outlined above. Examples of agents to be considered for sample development would be aflatoxins, hepatitis viruses, vinyl chloride, radon and asbestos.]

Section 2. Cancer in humans

This section will summarize concisely the study design and important results of the epidemiological studies. It will also identify the tumour sites for which there is *sufficient evidence of carcinogenicity*[2] in humans. Studies will be summarized in less detail than in other *Monographs*, but quantitative information will be reported for important design parameters (e.g. cohort size, number of cases and controls) and results (e.g. relative risk, confidence intervals). When numerous studies are available, the less informative studies of poor design quality may be omitted. Presentation of results in tabular form will be encouraged.

[The Advisory Group again agreed that the evidence in this section can be presented comprehensively in a more concise fashion than that used currently or by previous working groups. If a comprehensive summary of all 'pertinent' human data (as outlined in the Preamble) is to be included, the Advisory Group felt that a document of 1–20 pages is unlikely to be sufficient and that more pages will be required unless the reporting style is changed. A number of ideas were considered that would help the Secretariat to reduce the size of each 'mini' monograph while maintaining the scientific completeness of the review. One suggestion was that the Secretariat develop a format for summarizing all of the available human data in tabular form, describing the key design aspects of the studies, their

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[1] ***Carcinogenic to humans* (Group 1):** This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity. [Preamble to the *IARC Monographs*, http://monographs.iarc.fr]

[2] ***Sufficient evidence of carcinogenicity* in humans:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. [Preamble to the *IARC Monographs*, http://monographs.iarc.fr]

major results and any major limitations in the use of these findings in the evaluation. In addition, the Advisory Group suggested that the Secretariat consider the use of electronic media (e.g. compact disks and websites) to contain supplementary materials, such as the comprehensive tables described earlier. Finally, the Advisory Group also felt that it would be useful for the Secretariat to create a sample Section 2 from an existing monograph or one currently in development (e.g. alcohol) in order to identify the problems associated with building a succinct Section 2 for Volume 100.

Sufficient evidence of carcinogenicity in humans is almost always based on the observation of an increased risk for cancer at one or more specific organ site and/or tumour site, rather than a general increase in risk for all cancers combined. The Advisory Group agreed that a systematic effort to specify the anatomical sites that are affected by each of the known human carcinogens is a worthwhile exercise. Care should be taken to ensure that this does not create a static list of target sites since carcinogens may, in principle, affect multiple tissues, but not necessarily at identical levels of risk, and may have quite different latency periods. Further studies of a carcinogenic agent may identify additional tumour sites that had not been recognized previously. For example, soluble arsenic salts were originally recognized as being carcinogenic for the skin when given as a medicinal agent (Supplement 7, 1987), and were subsequently recognized as also being an important cause of urinary bladder cancer and lung cancer when present in drinking-water (Volume 84, 2004). Similarly, tobacco smoke was originally recognized as being a carcinogen for the lung, urinary bladder, renal pelvis, lip and oral cavity, pharynx, larynx, oesophagus and pancreas (Supplement 7, 1987). This unusually long list of tobacco-related cancer sites/ types was increased further in 2004 (volume 83) to include the nasal cavities, stomach, liver, kidney cortex, uterine cervix and bone marrow. The identification of cancer sites is thus a dynamic process, rather than a static conclusion. In this volume, the attribution of risk for cancer at certain sites to specific carcinogens should not be viewed as precluding the possibility that additional sites may be added in the future. The Advisory Group also suggested that the Secretariat consider noting cancer sites that are strongly suspected from the literature but have less than sufficient evidence. The Advisory Group strongly suggested that the Secretariat use two terms to describe the sites/types that are associated with a given Group 1 agent and avoid using terms such as ‘sufficient’ and ‘less than sufficient’. Inclusion of tumour sites that are causally linked to the agent and those that are strongly suspected from the literature will help to clarify the dimensions of the carcinogenic hazard and provide important information for the later ‘site concordance’ evaluation. Ionizing radiation and radionuclides created a special concern for the Advisory Group since these agents are broad spectrum carcinogens with the potential to induce tumours at virtually any site in any organ or organ system of the body. The Working Group that will have the task of evaluating these agents should address this issue carefully. Also, the Advisory Group noted that, for radionuclides, the major factor that determines the eventual target site is the location of the exposure rather than the organ itself.]

Section 3. Cancer in experimental animals

This section will summarize concisely the experimental design and important results of carcinogenicity bioassays. It will also identify tumour sites and histological diagnoses for which there is *sufficient evidence of carcinogenicity*[3] in experimental animals. Again, there will be less detail than in other *Monographs* volumes, but quantitative information will be reported for important design parameters (e.g. sample sizes, dose levels) and results (e.g. tumour incidences, *p*-values). When numerous studies are available, the less informative studies of poor design quality may be omitted. Presentation of results in tabular form will be encouraged, and a common format for standard bioassay data will be provided by IARC.

[Comments similar to those for Section 2 are applicable here. Specifically, the review should remain comprehensive, tables should be used to reduce space and summarize information and electronic media should be considered. In addition, since site concordance will be an important aspect of the planned activities associated with Volume 100, the sites with negative results that were evaluated need to be summarized. Similarly to human cancer data, without changing the basic manner in which the conclusions of the Working Group are presented, it is unlikely that the experimental animal data can be presented in 1–5 pages and might require as many as 15 pages for some agents.]

Section 4. Mechanistic and other relevant data

This section will provide a concise description of the toxicokinetics and plausible mechanisms of carcinogenesis of the agent, and potentially susceptible populations. To keep this section short, it will be in the form of a review article that selects and cites representative studies. It will also be noted where there are substantial data gaps or plausible mechanisms that have not received adequate investigation. Information on structure–activity relationships and toxic effects other than cancer will generally be included only when they are important to understanding the mechanisms of carcinogenesis.

[As above, the Advisory Group agreed that this section can be reduced in size through some of the same methods as those discussed for Sections 2 and 3. The old saying that "a picture is worth a thousand words" should be considered here; it may be useful to include an illustration to describe specific mechanisms which are then described succinctly in the text. In a usual monograph, there are five separate sub-sections for this section; the Advisory Group supported maintaining the same sub-sections in Volume 100 but restricting them to relevant topics only (as stated in the Preamble). Since many of the agents in Group 1 will have little or no data in one or more of these sub-sections, the entry would simply be something akin to 'No relevant information'. The number of pages indicated below (1–5) should be adequate in most cases. However, additional pages may be required for agents that have complex mechanisms which are integral to the evaluation.]

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[3] ***Sufficient evidence of carcinogenicity*** **in experimental animals:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*. A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites. [Preamble to the *IARC Monographs*, http://monographs.iarc.fr]

Section 5. Evaluation and rationale

This section will include the standard evaluation statements ("There is *sufficient evidence* . . .") in humans, experimental animals and overall. There will also be a description of the rationale that the Working Group used to reach its evaluation (generally one paragraph, but it may be longer where an evaluation of *carcinogenic to humans* is reached with less than *sufficient evidence* in humans). There will not be a separate 'Summary' section, because sections 1–4 of these monographs will already be concise.

[The Advisory Group discussed this shortened Section 5 and saw no serious difficulties with the approach proposed by the Secretariat. There was some concern over the loss of the 'Summary' section and the Advisory Group suggested that the Secretariat consider removing summaries from each section and only having summaries in Section 5 thus retaining the usual 'Summary' section where it is generally expected. "]

References

This section will list only those studies that are cited in the other sections.

As is standard practice for all volumes of *IARC Monographs*, Volume 100 will be developed from working papers drafted by the Working Group Members. There will be little time at the meeting for extensive revision of sections that are deficient or that do not conform to the *Monographs* style. Consequently, it is imperative that the working papers at the meeting be of high quality. To facilitate a better understanding of what is expected in this special volume, IARC scientists will prepare a sample monograph to serve as a model for the working papers that Working Group Members will be asked to write. This will include standard templates for the tables in which important study details will be summarized.

Length of Volume 100

Volume 100 will contain approximately 100 separate monographs, as there are somewhat more than 100 agents that are classified as *carcinogenic to humans*. The largest volume of *Monographs* produced to date contains approximately 1500 pages. If Volume 100 is to be similar in size, then the 100 monographs of Volume 100 should average less than 20 pages. Some monographs will need to be longer, so this suggests the following page limits.

1. General information, occurrence, and exposure	1–5 pages
2. Cancer in humans	1–20 pages
3. Cancer in experimental animals	1–5 pages
4. Mechanistic and other relevant data	1–5 pages
5. Evaluation and rationale	1 page
References	1–4 pages
Total	6–40 pages

Although it would be possible to include a few monographs of standard length (more than 100 pages each), this would detract from the balanced treatment of all human carcinogens and would make the volume less useful as a reference. Provision for developing a limited number of new or updated full-length monographs is discussed below (see 'Potential for identifying new Group 1 agents').

[The Advisory Group agreed that, in entering into the development of 'mini' monographs for Volume 100, it is both wise and appropriate to set page limits for each section, recognizing that exceptions will be necessary.].

Annexes to Volume 100

After the monographs in Volume 100 have been completed, two additional Working Groups will be convened to develop related scientific publications that build on the data that have been summarized therein . These publications will elaborate analyses that address important questions on risk assessment and will cut across individual agents to discern more general principles. Because the database for each agent that is classified as *carcinogenic to humans* is generally extensive, these analyses should have a high degree of validity. Each scientific publication will be published in a separate book labelled as an Annex to Volume 100.

Annex 1. Tumour-site concordance between humans and experimental animals

This annex will compare the tumour sites observed in humans with those induced in experimental animals. It will explore the circumstances under which it is reasonable to expect analogous tumour sites to occur in different species. Other issues include whether good animal models are available for particular human tumour sites, whether particular tumours in experimental animals have predictive value for human cancer (either at an analogous site or at other sites) and whether tumours at different sites tend to occur simultaneously. The analyses in this Annex may be restricted to subsets of carcinogenic agents (e.g. metals, physical agents, hormonal agents, viruses) or they may be more general in nature.

Annex 2. Mechanisms involved in human carcinogenesis

This annex will compile the mechanisms of carcinogenesis that have been identified in Volume 100. It will be organized by mechanism, not by agent. Joint consideration of multiple agents that act through a similar mechanism could facilitate the development of a more detailed description of that mechanism and its common mechanistic steps. Because susceptibility is often based on a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents that act through each mechanism. This Annex may also identify biomarkers that could be included in future study designs to provide more reliable information on whether a particular mechanism operates in either humans or experimental animals.

[The Advisory Group supported an evaluation of site concordance between humans and experimental animals as well as current evidence on the mechanisms of human carcinogenicity as part of Phase II of the review of the known human carcinogens included in Volume 100. As noted in the introduction, the proposed Annexes should not be seen as integral parts of the main Volume 100, but rather as supplements to be completed after Volume 100 has been compiled and should be published under a different title.

The Advisory Group suggested that consideration be given to lessons learned from an examination of other topics including: (1) the types of evidence that have been used to reach a determination of human carcinogenicity and the types of evidence that would be ideal for making such determinations; (2) the extent to which human carcinogens may differ with respect to their potency (when data on potency are available); (3) variation in exposure to known human carcinogens in different populations around the world; (4) characteristics of human carcinogens (e.g. site specificity or aspecificity for chemical carcinogens and radiation, respectively); (5) the impact of improved industrial hygiene and changing industrial processes on occupational cancer; (6) the role of immunosuppression and immuno-enhancement in the modification of cancer risk; and (7) the identification of susceptible populations based on genetic, social and other factors that can modulate cancer risk. It would be impossible to cover all of these topics in the same format as the Annnexes and the Advisory Group suggested that other outlets be used, such as scientific publications and workshops.]

Special considerations

Publication cut-off date. Approximately 100 different agents will be considered in Volume 100, and each has an extensive database. Volume 100 will review the current scientific literature for each of these agents. Consequently, it will be necessary to impose a publication cut-off date for studies to be considered. This date will be around 15 September 2007, approximately one month before the first meeting for Volume 100 (see 'Chronological list of meetings' below). Notice of this cut-off date will be posted on the *Monographs* Programme website approximately 12 months in advance.

[The Advisory Group agreed that there needs to be a cut-off date for publications that will be considered in Volume 100. The proposal by the Secretariat was that the cut-off date be 30 days prior to the first meeting for each chemical in Volume 100. Hence, if there were two preliminary meetings with half of the Group 1 agents reviewed in each preliminary meeting, there would be two separate cut-off dates. Recognizing that there may be a considerable delay between this initial meeting and the final meeting for Volume 100, the Secretariat was encouraged to keep abreast of the literature published during this period and, in consultation with the Chair(s) of the Volume 100 Working Group(s), exceptionally consider these for inclusion. Note that the Advisory Group suggested an alternative format in a later comment that alleviates this problem.]

Peer review. To promote working papers that are comprehensive and of high quality, a round of peer reviews will take place before the Working Group convenes. Working Group Members will be expected to send preliminary working papers to IARC at least 5 months before the first meeting. IARC will send these papers to other Working Group Members for comment, and the original writer will incorporate these comments and send a revised working paper to IARC at least 1 month before the meeting. This review before the Working Group convenes is intended to ensure that the text receives more attention than can be given during the meeting. The peer reviewers will also be asked to identify key issues so that the meeting can be planned to allow adequate time for each discussion.

[The Secretariat was encouraged to alter the terminology used here to reflect that the monograph is a peer-review of the available evidence and a consensus of the meaning of these data; what was proposed is more akin to a 'pre-meeting review'. The Advisory Group supported shifting the deadline for working papers to an earlier time-point to provide additional thoughtful reflection by the Volume 100 Working Group Members before the meeting. Having a round of discussions of a draft before the meeting could only improve the scientific quality of the initial documents at the start of the meeting.]

Evaluations of occupational exposures. More than 10 occupations have been classified as *carcinogenic to humans* and will be considered in Volume 100. Two issues that involve occupational exposures will need special attention. First, important changes in processes or measures for worker protection may have been introduced, so that the workplace being evaluated in Volume 100 may differ from that which was reviewed in earlier *Monographs*. In these cases, it is not clear how to handle the previous evaluation, which may still be applicable to workplaces that have not adopted modern processes or measures for worker protection. Second, more detailed data on occupational exposures may enable the attribution of a cancer hazard to specific substances rather than to the workplace in general. In these cases, it may be more informative to classify the specific substance as being carcinogenic, but this may involve a previously unevaluated agent that should be reviewed in a full-length monograph. Advice will be sought from several experts at the special planning meeting (see below).

[The Advisory Group noted that changes in occupational environments could impact on the risk for occupational cancer, either through changes in industrial processes or reductions in exposure to certain specific carcinogens that are present in the occupational environment. However, it was not clear to the Working Group whether this has occurred within the occupations that have been evaluated to date as Group 1. The Advisory Group noted that

the reduction in exposures that may have occurred in certain industrial processes in industrialized countries may not have occurred in those industries within developing countries.

The Advisory Group also noted that while it is desirable to seek the identification of specific agents that are responsible for increased cancer risk in occupational environments, the multiple exposures experienced in such environments make this difficult, particularly in the absence of data that show a reduction in risk following removal of a specific agent from a given occupational setting.

The Advisory Group further noted that a substantial amount of new information has become available for several occupations, including painting, boot and shoe manufacture and repair, welding and furniture and cabinet making. These agents could be evaluated in a future monograph, some of them before the preparation of Monograph 100.]

Evaluations for new groups of agents. The Preamble states that "when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative." There are a few chemical compounds that IARC has classified as carcinogenic to humans (e.g. benzidine, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin) for which there are mechanistic data that have led national health agencies to extend this classification to a broader group (e.g. dyes that are metabolized to benzidine, polychlorodibenzodioxins). It would be inappropriate to ignore these mechanistic data, but they may lead to the classification of a broader group of agents than before. Advice will be sought from several experts at the special planning meeting (see below).

[The Advisory Group felt that it would be unacceptable to restrain the Volume 100 Working Group from altering the presentation of their scientific evidence. That said, the Advisory Group felt that the Working Group should be cautious in taking the step to create new groupings unless they are certain that they have seen all of the available evidence and that the usual scientific rigor of an IARC review is maintained. Since many of the groupings that might occur involve mechanistic or metabolic linkages, it is critical that these issues be discussed and evaluated fully before the grouping is accepted.]

Evaluations for new mixtures of agents. There are two cases in which the US National Toxicology Program Report on Carcinogens has classified a mixture of agents as 'known to be a human carcinogen' while IARC has evaluated only individual components as being probably carcinogenic to humans: analgesic mixtures containing phenacetin; and broad-spectrum ultraviolet radiation. Advice will be sought at the special planning meeting about whether IARC should evaluate these mixtures as well as their components.

[The Advisory Group again felt that it would be unacceptable to restrain the Volume 100 Working Group from determining their presentation of the scientific evidence.]

Nomenclature of previously evaluated agents. It has been standard practice for Working Groups to agree on the best name to describe an agent, which can evolve when it is re-evaluated. For example, 'oestrogen–progestin replacement therapy' from Supplement 7 became 'post-menopausal oestrogen–progestogen therapy' in Volume 72 and 'combined estrogen–progestogen menopausal therapy' in Volume 91. The Working Group for Volume 100 will have the same leeway to modify the name of an agent when appropriate.

[The Advisory Group recommended generally maintaining the nomenclature for previously evaluated agents, yet allowing the Working Group for Volume 100 the flexibility to propose more precise terminology in specific cases or to propose more standardized terminology (e.g. for related agents such as occupational exposures, where a common term like 'production' or 'manufacture' might be employed).]

Potential for identifying new Group 1 agents

Recent working groups have identified several new Group 1 agents, and there are probably others that would be classified in Group 1 if a new review of the current scientific literature were undertaken. It would be valuable to include the most important of these agents in Volume 100 so that there are no prominent, avoidable omissions.

One source of potential new Group 1 agents would be the re-evaluation, before the publication of Volume 100, of all agents that are currently in Group 2A, on the premise that these most probably have new data that could warrant classification in Group 1. Approximately 40 were upgraded from Group 2B based on supporting mechanistic and other relevant data; at least 30 of these were upgraded more than 10 years ago when mechanistic data were sparser than today and a smaller data set was considered adequate for an upgrade. A focus on Group 2A would also miss other agents that more probably warrant classification in Group 1. Among recently identified Group 1 agents, combined estrogen–progestogen menopausal therapy and the tobacco-specific nitrosamines, *N*'-nitrosonornicotine (NNN) and 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) were previously classified in Group 2B, betel quid without tobacco was classified in Group 3 and areca nut had not been evaluated previously.

A new classification in Group 1 should generally follow from a review of a full-length monograph with ample time for discussion. In addition, any new classification in Group 1 would need to be documented thoroughly, and the 20-page target for Volume 100 that was discussed earlier would be highly restrictive. Moreover, the meeting time required to discuss new evaluations thoroughly would subtract from the time available to discuss the more than 100 agents already in Group 1.

For these reasons, a different approach is being followed. IARC will consult with several experts (see 'Special planning meeting' below) to identify those agents that (a) represent a significant human exposure and (b) for which there are new data that are likely to result in a Group 1 classification. A few of the most important of these may be recommended for urgent evaluation before Volume 100 is prepared. These would not be limited to agents that are already in Group 2A and could include other agents for which significant new studies are available, agents that national health agencies have classified as carcinogenic after the previous IARC evaluation or agents for which there may be new tumour sites with *sufficient evidence* in humans.

To provide an opportunity for these evaluations, the scheduled meetings for Volume 97 (June 2007) and Volume 99 (October 2008) will be available for developing full-length monographs on the agents recommended in September 2006 at the special planning meeting (see 'Chronological list of meetings' below). A separate Working Group with expertise on these agents will be selected for each volume. These working groups will classify each agent according to the criteria in the Preamble; this may or may not result in new Group 1 classifications. Short summaries for the agents that are classified in Group 1 will be included in Volume 100.

A more opportune time for *Monographs* meetings that focus especially on the current Group 2A agents may be after Annex 2 has been developed. The compendium of mechanisms involved in human carcinogenesis in Annex 2 may lead to a more informed determination of whether these agents should remain in Group 2A or be re-classified in a higher or lower category. In addition, the identification of biomarkers in Annex 2 would give epidemiological investigators some guidance on which markers to include in their studies, which would provide critical information on whether an agent has the capacity to act through mechanisms known to induce human carcinogenesis.

[The Advisory Group spent a considerable amount of time and effort going through the list of 99 agents that are currently classified as Group 1 as well as a number of agents in Group 2A. The purpose of this review was to determine which agents will probably require

the most time for re-review because of a large accumulation of new knowledge or recent research that might engender substantial discussion. It was felt that IARC should draw candidates for review in Volumes 97 and 99 from these lists of agents. Thus, while it was felt to be important to review several Group 2A/B agents that might move into Group 1, it was felt to be equally important to clarify the listing for several Group 1 agents that might prove to pose a problem during an expedited review. The Advisory Group suggested that six items be considered as a priority for review but cautioned the Secretariat that, while the discussions on these choices were extensive, they were by no means comprehensive.

The six priority choices for review are painters, asbestos, 1,3-butadiene, tri- and tetrachloroethylene, diesel engine exhausts and human herpesvirus 8 (HHV8). For painters, the actual chemical composition of paints, at least in developed countries, has changed and it is time to assess whether current painters face the same carcinogenic hazards as those in the past. For asbestos, there has been a tremendous increase in the available literature since this was last reviewed 33 years ago and it is not clear that the format for Volume 100 will provide sufficient time for a detailed review of all of this literature. The chemicals, 1,3-butadiene and tri- and tetrachloroethylene are currently Group 2A agents. New human studies, new laboratory data and, in the case of trichloroethylene, a recent review by the US National Academy of Sciences have increased concern about their hazards. For diesel engine exhausts, recent literature has clarified many aspects of the exposure to this mixture and provides stronger data on human responses and better laboratory data. Finally, it was felt that HHV8, although a Group 2A agent, should be considered for an immediate upgrade to Group 1. The Advisory Group felt that HHV8 could be reviewed during the Volume 100 meeting, but that it should be the only Group 2A agent to be considered.

The other agents considered for review prior to the Volume 100 monograph meetings included dyes that are metabolized to benzidine and chloroprene and other epoxide-forming compounds.

Monographs **meetings for Volume 100** (see also ‘Chronological list of meetings’)

The list of agents that are classified as being *carcinogenic to humans* is broad and diverse, and each agent generally has an extensive database. Consequently, it will be a monumental effort to develop and produce Volume 100. A large Working Group will be required, and it would be prudent to split the development of Volume 100 into several meetings.

Three meetings will be dedicated to the development of Volume 100. The first meeting (October 2007) will review chemical agents and the occupational exposures that involve these agents. The second meeting (February 2008) will review physical agents, biological agents and lifestyle factors, plus occupational and other exposures related to these agents. A few closely associated chemical agents will also be reviewed with the second group, for example, the tobacco-specific nitrosamines NNN and NNK will be reviewed together with smokeless tobacco. As with most *Monographs* meetings, about half of the time will be devoted to subgroup work (exposure, cancer in humans, cancer in experimental animals and mechanistic and other relevant data) and half of the time will spent in plenary sessions.

The third meeting (December 2008) will initially be reserved for a final reading and approval of the *Monographs* developed during the first two meetings. This is intended to allow time for some items to be carried over from the first two meetings, if the Working Group decides that they warrant additional time for further reflection and review. Because the draft *Monographs* will have been developed earlier during the first two meetings, most of the third meeting will take place in plenary session.

A triage will be performed on the agents to be considered during the first two meetings. Agents that have received a full *Monographs* review during the past few years will generally

need little updating. Accordingly, the text for these can be taken from the recent *Monographs* to the extent possible, and their discussion is expected to take only a few minutes at the meeting. This will allow more time to be devoted to updating and discussing the agents for which substantial new information is available, especially those that have not been reviewed in many years.

In addition, Volume 97 (June 2007) and Volume 99 (October 2008) will be reserved for agents for which new data are available that may result in a Group 1 classification. They may also be used for re-evaluating a small number of related agents for which the literature update will be particularly extensive or for which several new tumour sites might be considered to have *sufficient evidence of carcinogenicity*.

Volume 98 (June 2008) is currently reserved for a review of portable telephones, but could be used in a similar way if there is no urgent need to evaluate these commodities. This would occur only if the INTERPHONE studies and IARC's combined analyses thereof are mutually consistent in not showing a positive association at any level of exposure, in which case portable telephones would be evaluated soon after Volume 100.

A special planning meeting in September 2006 (see below) will recommend agents to be considered in these volumes. The agents that are ultimately selected for Volume 97 will be announced at that time (in September 2006, approximately 9 months before the meeting for Volume 97). The decision to evaluate portable telephones in Volume 98 or to review other agents will be announced in June 2007 (approximately 12 months before). Agents selected for Volume 99 may also include chemical agents that were not completed during the October 2007 meeting and will be announced at that time (approximately 12 months before).

[The Advisory Group generally felt that this time-frame was overly ambitious and impractical with regard to the amount of work to be covered. It recommended that the Secretariat should NOT attempt to use this schedule, should not use this number of meetings and should change the overall format. In addition, the Advisory Group was concerned that staffing levels are insufficient in this time-frame to edit and complete existing documents that are currently in abeyance, to continue the pace of current reviews and to address the needs of Volume 100. The Secretariat should consider the use of other WHO and international/ national agencies and academic institutions as partners in staffing this activity while adhering to the strict guidelines on conflict of interest in the Preamble.

Specific recommendations were as follows:

1. Use more working groups to consider fewer Group 1 agents at each meeting. This will reduce a number of concerns discussed by the Advisory Group, which include (a) having too few reviewers for each agent, (b) limiting the potential for bias that could be introduced by a single Working Group scientist pushing to change a listing substantially and not having sufficient expertise to evaluate the proposal carefully, (c) having too little time for in-depth discussion of each agent and (d) the risk of complications regarding the identification of tumour sites (as noted above). The experience of the Secretariat in managing Working Group meetings and from other similar endeavours by other WHO agencies (such as IPCS) and international/national agencies could help to inform this decision.
2. Consider not to hold a final meeting that would include all of the individual Working Groups but instead focus on completing a set of agents at each meeting. This will reduce the problems associated with a long period between the publication cut-off date and the final decisions of the Working Group.
3. Increase the lead time for each review for the development of drafts, calling for papers and identifying experts. This will reduce the risk of receiving inaccurate and incomplete drafts to be made available to the Working Group before their arrival at the meeting. In addition, when inviting experts for the Working Group meeting(s), it is

recommended that the Secretariat carefully outline the responsibilities, duties and level of work expected from each Working Group Member.

4. Increase the use of a number of effective pre-meeting activities such as conference calls, short subgroup meetings and shared drafts. This will also improve the quality of the drafts available to the Working Group before the meeting. In addition, improved access to electronic journals and electronic databases will substantially reduce the time needed to obtain copies of all of the critical scientific publications.
5. Use scientific groupings that will effectively improve the scientific expertise needed in the review. For example, the first meeting could group chemical agents, polyaromatic hydrocarbons and occupational exposures to chemical agents, basically grouping all of the individual chemicals (excluding metals).
6. Consider issues that could affect consistency. If these recommendations are accepted, Volume 100 will be a collection of documents from several separate Working Group meetings. The Secretariat needs to be diligent in evaluating formats for each of the multiple Working Groups to ensure they are consistent.
7. Review carefully the staffing needed to develop this monograph.]

Working Group for Volume 100

The effort to produce Volume 100 calls for a larger-than-normal Working Group. Because most agents that are *carcinogenic to humans* have an extensive database of epidemiological studies, the Working Group will include a large number of epidemiologists. Instead of the typical Working Group of 20–25 scientists, there should be about 40 scientists for each of first two meetings, with approximately five to write the exposure sections, 20 to write the epidemiology sections, five to write-up the experimental animal bioassays and 10 to write-up mechanistic and other relevant data. These Working Group Members will generally be senior-level scientists of worldwide renown. All will be invited to participate in the third meeting, which will culminate in the completion of Volume 100.

Two additional Working Groups will be convened later to develop the Annexes. The membership of these Working Groups will be tailored to their more specialized tasks and may include some scientists who participated in the development of Volume 100.

The three Working Groups for Volumes 97, 98 and 99 will be selected in the usual manner, independent of the Volume 100 effort, and will be tailored to the agents selected for review in these volumes.

[The Advisory Group agreed with the Secretariat that there needs to be some careful discussion and determination of the membership of the Working Group and some guidance on how they will be selected. The Advisory Group wished to reaffirm its support of the rules and policies outlined in the current Preamble regarding the Working Group, especially those that relate to conflict of interest, the role of observers and the designation of Secretariat Staff. The Advisory group recommended that the Secretariat develops an alternative time schedule that takes into account the proposal for at least three independent Volume 100 working group meetings, and no final meeting to read the summaries.]

Chronological list of meetings

September 2006	Advisory Group on Planning Volume 100
October 2006	Volume 95: Household combustion and heating has been announced as the subject
February 2007	Volume 96: Alcoholic beverage consumption has been announced as the subject
June 2007	Volume 97: Agents that need extensive updating or in-depth review; to be announced 9 months before, in September 2006, after the special planning meeting
October 2007	**Volume 100, first meeting: Chemical agents**
February 2008	**Volume 100, second meeting: Physical agents, biological agents, and lifestyle factors**
June 2008	Volume 98: Reserved for portable telephones, decision to be announced in June 2007
October 2008	Volume 99: Agents that need extensive updating or in-depth review; to be announced in October 2007 after the first meeting on chemical agents
December 2008	**Volume 100, third meeting: Final reading and approval of all summaries**
February 2009	**Annex 1: Tumour site concordance**
June 2009	**Annex 2: Mechanisms involved in human carcinogenesis**
October 2009	Resume normal schedule with Volume 101

Schedule for Volume 100 Working Group activities

October 2006	Preliminary invitations and initial Declaration of Interests
December 2006	Working Group selected and writing assignments sent
May 2007	Preliminary working papers due from Working Group Members
June 2007	Peer review comments due from reviewers in the Working Group
September 2007	Publication cut-off date for studies to be considered
September 2007	Revised working papers due from Working Group Members
October 2007	First meeting (chemical agents)
February 2008	Second meeting (physical agents, biological agents, lifestyle factors)
September 2008	Draft final *Monographs* for all agents sent to Working Group
November 2008	Draft final *Monographs* for agents in Volume 99 (Oct 2008) sent to Working Group
December 2008	Third meeting (final reading and approval for all agents)

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