Discussion of Changes in the Draft Preamble

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This paper describes the major changes that appear in the draft Preamble that will be reviewed by an Advisory Group during 5-9 December 2005. Most changes have been made in response to the recommendations of the Advisory Group to recommend updates to the Preamble (May 2005) or in response to comments from recent meeting chairs and subgroup chairs (March-April 2005). These earlier reports are available on the *Monographs* website (http://monographs.iarc.fr).

1. Background

An expanded section describes the programme's origin, historical development, and current role in assisting national and international health agencies to reduce the global burden of cancer. [Advisory Group recommendations 1 and 2a]

2. Objective and scope

New text explains the difference between hazard and risk in the context of the risk assessment paradigm. The *Monographs* are described as an exercise in hazard identification. For several recent *Monographs*, however, the important public health questions have been both qualitative and quantitative. Accordingly, the draft Preamble allows a *Monograph* to address questions of dose-response assessment, in some cases through a subsequent publication prepared by a separate working group with expertise in quantitative dose-response analysis. [Advisory Group recommendation 2b, comments by several recent chairs]

Previously, a carcinogen was defined as an exposure that can increase the incidence of malignant neoplasms. This definition has been expanded to include exposures that can reduce the latency or increase the severity or multiplicity of malignant neoplasms. This is consistent with the current practice of other health agencies. It also makes explicit what is meant in epidemiology by an increase in the age-specific incidence of cancer, a concept that covers a reduction in latency or an increase in the proportion of tumours that are malignant.

This section also explains that IARC can convene international scientific conferences to develop consensus principles on how mechanistic data can be used in an evaluation of human carcinogenicity. The results of these conferences will be reported in IARC Scientific Publications. *Monograph* Working Groups may cite these publications as long as they still reflect the current state of scientific knowledge. [Advisory Group recommendation 12f]

3. Selection of topics for the *Monographs*

New text explains the circumstances under which a *Monograph* would review only the new data published since a prior evaluation. This can be useful for updating a database or identifying new tumour sites associated with a carcinogenic agent. This may become an

important activity in the future, as the programme strives to keep more than 900 past evaluations up to date. [Advisory Group recommendation 3a]

In 1996 IARC stopped producing the directory of agents being tested for carcinogenicity and the directory of on-going research in cancer epidemiology. Accordingly, references to these series have been dropped. [Chair comments]

4. Data for the *Monographs*

This section now explains that the *Monographs* intend to include all pertinent epidemiological studies and cancer bioassays in experimental animals. For mechanistic and other relevant data, however, *Monographs* may cite only those studies that are relevant to an evaluation of carcinogenicity. [Chair comment]

The section also explicitly mentions abstracts and doctoral theses as reports that can be considered in exceptional cases. It is expected that this will happen only when the abstracts or doctoral theses contain detailed information and provide a unique indication of a potential cancer hazard. [Advisory Group recommendation 4b]

5. Meeting participants

This section now includes a discussion of the roles of Working Group Members, Invited Specialists, Representatives of national and international health agencies, Observers, and the IARC Secretariat. Accordingly, the title of the section is being changed to cover all meeting participants, not just the Working Group. The section explains that IARC uses literature searches to identify most experts and gives consideration to the balance of scientific findings and views. [Advisory Group recommendations 5a and 5c and comments by many recent meeting chairs and subgroup chairs]

The section also includes a description of the procedure IARC uses to assess conflicts of interests. It cites the WHO Declaration of Interests, which provides definitions and guidance about what constitutes a real or apparent conflict. IARC now requires all participants to submit their declaration before invitations are extended. The declarations are updated and reviewed again at the opening of a meeting. A participant with a real or apparent conflict of interests may participate only in a limited capacity, and all relevant interests are disclosed at the meeting and in the published *Monograph*. [Advisory Group recommendation 5c and comments from many recent meeting chairs and subgroup chairs]

There is also a description of the recent practice of disclosing the names of participants before each meeting, together with a statement that participants should not be contacted or lobbied. Such information appears on the *Monographs* website (http://monographs.iarc.fr). [Advisory Group recommendation 5a]

IARC is not expanding the role of Invited Specialist to allow them to write text on mechanistic and other relevant data. Strong mechanistic data can sometimes lead to a conclusion that *sufficient evidence* in experimental animals is not relevant to human carcinogenicity. To assure public confidence in the impartiality of such determinations, the mechanistic sections, like the sections on studies in humans and studies in experimental animals, are written by experts with no links to the parties that have a financial interest in the evaluation. [Advisory Group recommendation 5b]

The new practice of issuing a public call for experts is not being incorporated into the Preamble at this time. IARC is currently exploring this on a trial basis. When the draft Preamble is reviewed in December 2005, IARC will report the results of three separate trials for volumes 93, 94, and 95. [Advisory Group recommendation 5e]

Advisory Group recommendation 5d has been addressed by changes to Preamble Section 6 that are described next.

6. Working procedures

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The pre-meeting time schedule has not been changed. Beginning with volume 95, which will meet in October 2006, IARC will generally announce meeting topics 12 months in advance. This information will appear on the *Monographs* website (http://monographs.iarc.fr). The staff thanks the Advisory Group for its insistence on this goal. [Advisory Group recommendation 6a]

In a similar spirit, the post-meeting goal of publishing *Monographs* within 6 months after a meeting has been retained, although the programme does not anticipate being able to return to this schedule in the foreseeable future. There is still a backlog that was created by the 2-year period required to check the large amount of text, tables, and pages for volume 83 on tobacco smoke and involuntary smoking.

This section now describes the division of a *Monograph* meeting into subgroup sessions and plenary sessions and identifies the objectives of each activity. [Chair comment]

No specific restrictions had prevented Working Group Members from drafting and then reviewing text discussing their own work. The staff, however, believes it is a good idea to discourage his practice. Accordingly, some new text in Section 6 states, in a non-restrictive manner, that care is taken to ensure that each study summary is written or reviewed by someone not associated with that study. [Advisory Group recommendation 5d]

7. Exposure data

This section includes several minor changes that reflect the evolution of current practice over the past several years. [Chair comments]

Two new sentences note the availability of exposure data from national agencies and UN agencies. The section encourages future Working Groups to obtain data on exposures in developing countries. [Advisory Group recommendation 7a]

8. Studies of cancer in humans

A new section (labelled 8(c)) was inserted to discuss meta-analyses and pooled analyses of population-based studies. These have been cited or developed for several recent *Monographs*. Such combined analyses can provide a firmer basis than individual studies for drawing conclusions, especially when the individual studies report ambiguous or conflicting results. Some points to consider and limitations of these analyses are listed. [Advisory Group recommendation 8c and comments from recent chairs]

The section on inferences about mechanisms (now 8(d) but formerly 8(c)) was updated to include more detailed guidance on mechanistic biomarkers and the use of molecular epidemiology data on susceptibility. [Advisory Group recommendation 8a and comments from several recent chairs]

There are also some minor wording changes to make the guidance more clear or to reflect prevailing practice. [Comments from several recent chairs]

9. Studies of cancer in experimental animals

Some text was added to include studies of cancer in non-laboratory animals (for example, livestock or companion animals). This reflects current practice for a few viral and chemical agents. [Chair comment]

In Section 9(c) a new paragraph was added to discuss the use of historical control data, which have been considered by several past *Monographs*. Comparisons to historical controls can aid in the interpretation of unusual tumour types, provided careful attention is paid to between-study and within-study variability. [Advisory Group recommendation 12b]

A new paragraph mentions combined analyses of animal studies as an aid in interpreting animal data. [Advisory Group recommendation 9a]

There are also some minor wording changes to make the guidance more clear or to reflect prevailing practice.

10. Mechanistic and other relevant data

The discussion of mechanistic data has been expanded and now appears earlier in the section, immediately after the discussion of toxicokinetics. This gives mechanistic data more prominence and provides a closer link between toxicokinetics and mechanisms. Accordingly, the title of the section is being changed to put mechanisms first. Future Working Groups will attempt to identify the possible mechanisms of carcinogenesis that might be operating, review the data that are consistent or not consistent with each alternative mechanism, and identify significant data gaps and data that may suggest the operation of other mechanisms. Mechanisms can be discussed at several levels, from structural changes at the molecular level to changes at the organism level. [Advisory Group recommendations 10a and 10b, plus comments from many recent chairs]

Future *Monographs* will also include a new section on susceptible individuals, populations, and life-stages. This section builds on the knowledge of toxicokinetics and mechanisms discussed in earlier sections. Several examples of factors that can lead to susceptibility are listed in the draft Preamble. [Advisory Group recommendation 10c]

The draft Preamble does not prescribe a standard outline for *Monograph* Section 4 (which reviews mechanistic and other relevant data), but the order in which topics are discussed suggests the following outline [Advisory Group recommendation 10b]:

4 Mechanistic and other relevant data

4.1 Toxicokinetic data (absorption, distribution, metabolism, excretion)

This section reviews the potential for the agent and its metabolites to be distributed to various organs and tissues.

4.2 Mechanistic data

This section identifies the possible mechanisms of carcinogenesis that might be operating, reviews the data that are consistent or not consistent with each alternative mechanism, and identifies significant data gaps and data that may suggest the operation of other mechanisms.

4.3 Susceptible individuals, populations, and life-stages

This section builds on the knowledge of toxicokinetics and mechanisms to identify those who might be more susceptible. This includes, for example, susceptibility that arises from polymorphisms of metabolism, from the presence of disease, from exposure to the agent at a critical period of development (for example, infancy, puberty, or old age), and from exposure to other agents that can alter the kinetics or dynamics of the agent being evaluated.

4.4 Other forms of toxicity that are relevant to carcinogenicity

This section reviews toxicological effects that are relevant to the evaluation, including developmental and reproductive toxicity. It is not an encyclopaedia of chronic toxic effects, but should focus on, for example, toxic effects that confirm distribution and biological effects at the sites of tumour development, or toxicity that alters physiology in a way that could lead to tumour development.

4.5 Additional relevant data

This section reviews structure-activity relationships, the toxicological implications of physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

11. Summary and integration

Future *Monographs* will include an integration section that presents and discusses the reasoning the Working Group used to reach its evaluation. This new section is a significant addition to the *Monographs*, because it is the only place that the Working Group can explain the full logic of how it weighed data and drew conclusions. (The critical reviews in *Monograph* Sections 1-4 and the summaries in *Monograph* Sections 5.1-5.4 are factual reviews with minimal interpretation, and the evaluations in *Monograph* Section 5.6 can be as short as three simple sentences that state the standard categories chosen to describe the evidence of cancer in humans, in experimental animals, and the overall evaluation.) IARC receives many requests for information about how a Working Group reached its evaluations, and the *Monographs* will be improved by including this explanation of the Working Group's deliberations. Accordingly, the title of the section is being changed to include the word "integration." [Advisory Group recommendations 11a and 12g, plus comments from several recent chairs]

The integration section will be the place to report minority views. This new practice should not be abused to discuss every conceivable interpretation of the data. It will be reserved for cases where the Working Group tried but could not reach consensus, and the minority strongly believes that their differing views should be presented. [Advisory Group recommendations 12g and 12h, plus comments from several recent chairs]

The Advisory Group suggested several alternative locations for the new integration section. The draft Preamble places the integration section after the separate summaries (*Monograph* Sections 5.1-5.4) and before the evaluations (to become *Monograph* Section 5.6). This ordering best reflects the sequence in which these items emerge during a *Monograph* meeting. The new Section 5.5 will integrate the separate lines of evidence that are summarized in Sections 5.1-5.4 and discuss the reasoning that leads to the evaluations that are stated in Section 5.6. Thus, the draft Preamble implicitly suggests the following outline for *Monograph* Section 5:

5 Summary, integration, and evaluation [new title]
5.1 Exposure data
5.2 Human carcinogenicity data
5.3 Animal carcinogenicity data
5.4 Mechanistic and other relevant data
5.5 Integration [new section]
5.6 Evaluation [formerly Section 5.5]

Because *Monograph* summaries should not introduce data that were not discussed earlier, most of the detailed text on mechanistic data that previously appeared in Preamble Section 11 has been updated and moved to an expanded Preamble Section 10.

There are also some wording changes to make the guidance more clear or to reflect prevailing practice. [Comments from several recent chairs]

12. Evaluation

The general philosophy in making changes in this section was to maintain stability in the evaluation criteria whenever this is consistent with the current state of the science. Accordingly, substantive changes were made only when recommended by the Advisory Group. Comments from recent meeting chairs and subgroup chairs were incorporated where they would clarify the Preamble to better reflect prevailing practice or to reduce the possibility of misinterpretations that had occurred in the past. Other comments that would have substantively altered the evaluation criteria were not incorporated, as the intent of the Preamble amendment process is not to toughen or relax the evaluation criteria.

The evaluation criteria for human data (Section 12(a)) now instruct Working Groups to identify the target organ(s) or tissue(s) where there is *sufficient evidence of carcinogenicity* in humans. This reflects the prevailing practice over the past several years. [Advisory Group recommendation 12e and chair comments]

Clarifying text has been added to reiterate (from Section 8) the characteristics of epidemiological study results that would lead to a finding of *evidence suggesting lack of carcinogenicity* in humans. [Chair comment]

The evaluation criteria for animal data (Section 12(b)) have been changed to reflect the Good Laboratory Practices (GLP) that emerged after the original text was written. As discussed in both the Advisory Group report and the chair comments, considerable confidence can be placed in findings of clear evidence from GLP studies, such as those conducted by the US National Toxicology Program. As recommended by the Advisory

Group, the draft Preamble now states that positive results in both sexes of a single species in a GLP study can provide *sufficient evidence of carcinogenicity*. In addition, "strong findings of tumours at multiple sites" was added to the list of results in a single study that might be considered to provide *sufficient evidence*. "Exceptionally" was removed from the "single study" sentence in response to the Advisory Group's recommendation that the phrase "to an unusual degree" was already sufficiently restrictive in limiting the use of single-study findings. [Advisory Group recommendation 12a]

"Age at exposure" is now mentioned in the list of conditions that limit a conclusion of *evidence suggesting lack of carcinogenicity* in animals. "Conditions of exposure" was also added to cover other factors such as exposure route. [Advisory Group recommendation 12c]

The evaluation criteria for mechanistic and other relevant data (Section 12(c)) discuss several factors that may strengthen a conclusion that a particular mechanism is operating in experimental animals. There was some discussion at the May 2005 Advisory Group meeting about replacing the term "mechanism" by "mode of action" and citing the IPCS framework for considering mode of action. The Advisory Group did not support this, calling "mechanism" the scientific term that is appropriate for *Monograph* evaluations while recognizing that national regulatory agencies may prefer to use the less specific concept of mode of action to make pragmatic decisions. Accordingly, the term "mechanism" has been retained in the Preamble and some key relevant concepts of the IPCS framework are discussed. The draft Preamble stresses the importance of considering the possibility that multiple mechanisms might contribute to tumour development, a key concept of the IPCS framework.

There is also a reiteration of the Preamble's intent that the conclusion that a mechanism does not operate in humans is not based on exposure or risk levels. *Monograph* evaluations are a determination of hazard, not risk.

The expert workshop that developed IARC Scientific Publication 146 recommended in their consensus report that, in the absence of cancer bioassays in experimental animals, strong mechanistic data could be used in an evaluation. This reflects the increasing ability of mechanistic data to provide an indication of carcinogenic potential. Accordingly, the Advisory Group recommended that an agent can be characterized as *possibly carcinogenic to humans* based solely on strong mechanistic data. The overall evaluation criteria (Section 12(d)) have been updated to follow this advice. [Advisory Group recommendation 12d]

Clarifying text has been added to explain that the terms "*probably carcinogenic*" and "*possibly carcinogenic*" have no mathematical significance. [Chair comment]

Some commercial entities have claimed that classification of their product in Group 3 was a determination of safety by IARC. A statement has been added to discourage this erroneous interpretation. [Advisory Group recommendation 12i]

Advisory Group recommendations 12b, 12g, and 12h were addressed by changes to other sections of the Preamble, as described above.

Other changes

The title *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is not being changed to substitute the word "hazard" for "risk." Several reasons are discussed in the Advisory Group report. A discussion of "hazard" versus "risk" now appears in Preamble Section 2, with specific mention of how this relates to the title. [Advisory Group recommendation 13a]

The Advisory Group discussed the terms "weight of evidence" and "strength of evidence." The draft Preamble continues the previous use of "strength of evidence" as a matter of historical continuity. It should be understood that *Monograph* evaluations have always considered both studies that support the finding of a carcinogenic hazard and those that do not. [Advisory Group recommendation 13b]

The term "chemical compound" has been replaced by "agent" to reflect the broader scope of the programme. [Advisory Group recommendation 13b and chair comments]