WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

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Report of the IARC Advisory Group To Recommend On Quantitative Risk Characterization

18–19 November 2013

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The IARC Advisory Group to Recommend on Quantitative Risk Characterization met in Lyon, France, on 18 and 19 November 2013. The Advisory Group was requested by the *IARC Monographs* Programme (IMO) "*to provide advice to the Programme on the advisability of adding aspects of quantitative risk evaluations to the more qualitative evaluations currently undertaken.*"

Background

The Advisory Group was provided with a range of relevant background information by means of mailings before the meeting and through the three presentations that opened the meeting. The presentations emphasized that *Monographs* are intended for "hazard identification", as specified in the Preamble. However, it was made clear that the Preamble also allows for "quantitative dose–response assessment", but does not define rules under which this is to be accomplished if undertaken. Instances in which quantitative data were notably included in particular Monographs were presented. In addition, instances in which quantitative information from other sources was used to clarify a hazard identified in a Monograph were presented and discussed. It was also noted that the issue of Monographs addressing quantitative risk characterization had received attention in various Advisory Group reports since 2003.

This report does not include a technical discussion or explanations of terms variously used in the Advisory Group discussions. In broad context, the Advisory Group relied upon the typical division of cancer-risk assessment into four distinct steps:

1. *Hazard identification* determines whether exposure to an agent is linked to cancer.
2. *Exposure/dose–response assessment* characterizes the relation between the exposure to/dose of an agent and the incidence/occurrence of cancer.
3. *Exposure assessment* determines the extent of human exposure to an agent.
4. *Risk characterization* combines exposure–response and exposure information to describe the nature and magnitude of risk of cancer in humans, including attendant uncertainty.

The Advisory Group interpreted its terms of reference to involve any data reasonably characterized as relevant to steps 2 to 4 above. The Advisory Group did not proceed on the basis of strict adherence to steps 2 to 4 as specified above, but considered the full scope of quantitative data and analyses as variously available concerning particular types of carcinogen.

During the two days of discussion and deliberation, the Advisory Group developed a number of recommendations for IMO to consider regarding quantitative risk characterization (QRC) activities. During these discussions, members of the Advisory Group stressed the importance and public-health impact of the qualitative hazard identifications that have been the focus of the IMO to date, and expressed the opinion that expansion of the focus of the programme into more quantitative evaluations should not be undertaken at the expense of hazard-identification activities. These recommendations fell into two broad categories: (a) recommendations regarding the development of *Monographs* and the activities of *Monograph* Working Groups; and (b) activities independent of *Monographs* that could be undertaken to strengthen IARC products for use in QRC. These are discussed in detail below. The membership of the Advisory Group is given in Appendix 1; the Charge to the Advisory Group and Preliminary Agenda are given in Appendix 2.

I. Potential activities for *Monograph* Working Groups

Evaluating Existing QRCs

The Advisory Group considered whether *Monograph* Working Groups should be charged with the task of summarizing or evaluating QRCs that have been developed by other national or international health organizations. The Advisory Group judged that this would distract *Monograph* Working Groups from their primary task of compiling, summarizing, and evaluating data on carcinogenicity, and recommended that this activity should not be included in the charge to *Monograph* Working Groups.

Review Burden of Disease and Risk Scenarios

The Advisory Group believed that *Monograph* Working Groups should not routinely be charged with developing new assessments of disease impact or burden. However, there may be estimates of disease impact or burden, or other risk estimates for various exposure scenarios, available to the Working Group before a *Monograph* meeting, specifically through relevant publications in the peer-reviewed literature. The Advisory Group encouraged IARC to identify and include existing literature on the impact or burden of cancer attributable to the agent(s) under review and to summarize this information in the *Monograph*. It is important that any use of this information in the *Monographs* highlights heterogeneity in burden or risk, including the identification of populations with greater burdens of cancer due to high levels of exposure or susceptibility to the agent(s), and including geographical variation in the burden of disease. Where available, the Advisory Group encouraged *Monograph* Working Groups to summarize determinations identified in the literature of impact on population health using measures such as the number of extra cases of cancer per year, or the population attributable fraction for cancers associated with a particular agent(s). Finally, to ensure that the quality of such measures is clear, the Advisory Group advised *Monograph* Working Groups to include an assessment or statement of uncertainty, and to emphasize the difficulty of extrapolation beyond the temporal and population boundaries of the existing evidence.

Exposure-Response Relationships

Data on exposure–response relationships from published epidemiological studies are currently used by *Monograph* Working Groups predominantly for a determination of causal inference. Such data would also be critical for the conduct of QRCs. The Advisory Group indicated that it would be advisable for *Monograph* Working Groups to continue to evaluate these data in support of hazard identification and to also consider their utility for QRC.

As a general principle, if resources allow, preparatory work by IARC staff or individual members of the Working Group could be conducted and presented in the Working Group meeting. For example, if the literature were sufficient, a meta-analysis might be conducted to summarize the existing information on exposure–response relationships. Ideally, such determinations would be submitted for peer-reviewed publication.

Mechanistic Data

To assist in hazard identification by the *Monograph* Working Group as well as subsequent evaluation of the dose–response relationship by health agencies, mechanistic events involved in the carcinogenic process should be identified for the agent under discussion. The Advisory Group recommended a systematic review of relevant mechanistic data, including data from in-vitro systems, quantitative structure–activity relationships (QSAR) analyses, studies in experimental animals, and molecular epidemiology, using a list of possible mechanisms and assigning levels of evidence in each case as ‘strong’, ‘moderate’, ‘weak’, or ‘none’. Identifying the extent and quality of the evidence for these evaluations and identifying where gaps in the data exist will clarify the mechanistic evaluation. Following this systematic evaluation, it will be easier to summarize the probable mechanisms and pathways by which the agent causes cancer at different doses and, in

the case of cancers in experimental animals, its relevance to the human population. The Working Group should discuss the uncertainties in the evaluation.

II. The *Monographs* Preamble

In the course of discussion, reference was made by Advisory Group members to the *Monographs* Preamble with respect to the possibility of its revision. The *Monographs* Preamble presently refers to a range of mechanistic issues, including, for example, epigenetic change as contributing to malignant transformation. This section of the Preamble is not comprehensive and should not be caricatured as a "cookbook" for mechanistic information and seen to provide detailed instructions as to how a *Monograph* Working Group should proceed.

These principles acknowledged, the Advisory Group noted two issues that might be addressed in the context of any revision of the Preamble. First, while considering how mechanistic data might contribute to the elucidation of quantitative risk, the manner in which mechanistic data overall are considered in *Monographs* may evolve on the basis of the outcome of deliberations of the Volume 100 Concordance and Mechanisms Working Group. Second, in addressing data pertinent to QRC, conflicting outcomes from meta-analyses or pooled analyses may highlight the need for development and consistent use of criteria to determine where confidence should be placed.

The Advisory Group also noted that other advice provided in this report should be considered if there are revisions to the Preamble.

III. Activities that should be considered for action outside the *Monograph* Working Groups

Storing and Sharing Information

The databases to evaluate concordance and mechanisms, developed by IARC from Working Groups for *Monographs* 100A–F, have demonstrated the utility of capturing key aspects of *Monograph* reviews to gain additional insight. The Advisory Group supported this activity and encouraged IARC to expand upon it. IARC staff should develop, convene a workshop/advisory group, and/or work with others to develop tools that capture study-specific information and retain this information for use in future evaluations by IARC and others. Examples of information to include would be critical information from the study itself (e.g. sample sizes, exposures, species) and comments from the Working Group on study quality and/or utility for hazard identification. In addition, if quantitative study results (e.g. relative risks, tumour counts, means, standard errors) could be captured and appropriately stored in the same database, these could be used to support meta-analyses, dose–response evaluations, and other quantitative exercises that will greatly benefit QRCs.

Estimating the Global Burden of Cancer for Carcinogens

There are generally considerable epidemiological and exposure data associated with a carcinogen that is classified in Group 1. In many cases, the evidence is adequate to estimate the global burden of cancer, but the effort to do this requires substantial additional work beyond that possible in a *Monograph* evaluation. Without estimates of cancer risks related to a specific agent in individual communities, it is difficult to prioritize cancer-prevention efforts and risk-management approaches. The aim of the World Health Organization (WHO) Global Burden of Disease project is estimate the impact of selected diseases on specific populations, sometimes by cause of the disease. The Advisory Group encouraged IARC scientific staff to promote the estimation of global burden of disease for high-priority carcinogens. This activity could be done directly by IARC or in concert with other organizations.

The Advisory Group considered that, in carrying out such estimation of global burden of disease, IARC or other organizations should focus on Group 1 carcinogens (and possibly selected

Group 2 chemicals) for which there is sufficient quantitative information to develop exposure–response relationships, along with widespread exposure and/or high potency in certain populations. Developing estimates of global burden of disease should be considered subsequent to the publication of the *Monograph*, and should involve consultation between *Monograph* staff and any researchers from IARC, WHO, or other agencies that will develop the estimates. It should be recognized that this effort will require a substantial commitment of resources to compile accurate exposure information on a global basis, and to estimate the effect level per unit of exposure (along with evaluation of uncertainty in these parameters). This effort should complement, but not compete with, the *Monographs* Programme for resources, and should include scientific workshops to evaluate the existing methods, clarify their utility for IARC's purposes, and to develop a process to follow in developing estimates of global burden of disease.

Exposure-Response Relationships

To further support quantitative estimates of exposure–response relationships, the Advisory Group encouraged IARC to evaluate and improve methods for combining epidemiology data to better characterize response, as measured by risk, and include qualitative or quantitative measures of one or more factors affecting that response. Activities that would strengthen the use of these methods for QRC include scientific workshops, scientific publications, guidelines, and case studies, all of which would be conducted outside of *Monograph* Meetings.

IV. Resources

In anticipating implementation of recommendations made in this report, the Advisory Group recognized that it would be necessary to accord additional resources and time to IMO. For example, implementing the recommendation on global burden of disease would require a scientist with expertise in quantitative-risk estimation to develop and oversee contributions from IARC; assigning existing staff to devote time to this activity would have a serious impact on the *Monograph* activities. Also, adding reviews of quantitative information and the development of databases may require that fewer agents be evaluated in each *Monograph*, reducing output or require more experts to accommodate the added material.

In this context, the Advisory Group was not aware of any general modifications that would allow efforts presently expended on *Monograph* preparation to be reduced without compromising the quality of the Monographs. The Advisory Group therefore recommended that provision be made for additional resources to be allocated to IMO if the recommendations of the Advisory Group are to be implemented.

Summary

The Advisory Group considered that IMO is doing an excellent job with the *Monographs* Programme and efficiently using resources to successfully achieve its mission, which has important public health impacts globally. While the Advisory Group was able to make suggestions for modifications to the *Monographs* Programme that would be likely to result in contributions to QRC, they felt that charging a *Monograph* Working Group to address broader issues of QRC would divert the Working Group from its established main purpose and reduce the effectiveness of the current *Monographs* Programme.

There is clearly a need for better information on the global burden of cancer, and for information that would be useful in developing and monitoring interventions to reduce this burden. If IARC wishes to pursue QRC to the point of developing risk estimates, combining these risks with exposures and predicting cancer burden, additional resources will need to be committed by the Agency to accomplish this goal. Establishing partnerships with other groups with expertise in QRC would also help in achieving this goal. The Advisory Group encourages IARC to consider

this new activity, and take advantage of the broader community involved in noncommunicable disease that has been grappling with QRC problems and solutions.

Appendix 1: Advisory Group Participants

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[1] Working Group Members and Invited Specialists 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. Invited specialists are marked by an asterisk.

Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US $1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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[2] Daniel Krewski holds a Research Chair in Risk Science, funded by the Natural Sciences and Engineering Council of Canada (NSERC) Industrial, at the University of Ottawa. This is a peer-reviewed NSERC programme under which industry contributions to the Chair are matched on a one-for-one basis. Industry contributions include funds from the Exxon Mobil Research Foundation.
[3] Lesley Rushton has a research grant from The European Chemical Industry Council (CEFIC) to compare NOAELs from animal data with those from human data.
[4] Martyn Smith receives payment for consulting and testimony for various law firms in the USA, including one on risk assessment for acrylamide.

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Appendix 2: Charge to the Advisory Group and Preliminary Agenda

Advisory Group Meeting to Recommend on Quantitative Risk Characterization for the *IARC Monographs* Programme

Since 1971, more than 950 agents have been evaluated for carcinogenicity by the IARC Monographs Programme (the Programme) in 109 monographs. These evaluations have focused on the identification of classifications for the carcinogenicity of an agent with over 400 classified as either carcinogenic, probably carcinogenic or possibly carcinogenic to humans. Several times within the history of the Programme, IARC has convened Advisory Groups to provide advice on the direction of the Programme and the scientific approaches being used. This Advisory Group is being convened to provide advice to the Programme on the advisability of adding aspects of quantitative risk evaluations to the more qualitative evaluations currently undertaken.

Quantitative risk assessment takes many forms in the various countries and municipalities around the globe and no single agency can provide every country with all of its needs in this area. However, most countries share a common general paradigm which can be divided into three specific parts.

Review: The scientific literature relating to the toxicity of any agent is likely to be diverse and derived from numerous scientific fields. In most countries, all epidemiological and toxicological literature is reviewed for its quality and the clarity of exposures as a precursor to developing quantitative risk estimates. In some countries, mechanistic information is also reviewed for its ability to enhance any quantitative estimates. One possible role for the IARC is the review of the literature for adequate quantitative information to include in a risk assessment.

Point-of-Departure (POD): Once a country has decided upon the literature that is adequate for developing a quantitative risk assessment, most then develop a POD from which to develop a standard. This can vary considerably across different countries, but most either use a no-observed-adverse-effect-level (NOAEL)/lowest-observed-adverse-effect-level (LOAEL) or the benchmark dose (BD) as their POD. The NOAEL/LOAEL approaches identify an exposure from one or more studies which suggests no appreciable risk to the studied population usually because of a non-statistically significant risk and scientific judgment. The BD approach uses modeling approaches to identify an exposure associated with a specific risk then use some statistic associated with that exposure (e.g. 95% lower confidence bound) as the POD. In most countries, the interpretation of a POD is the lower end of the scientific data that supports little or no risk from exposures in the evaluated population. One possible role for the IARC would be the development of a scientifically-based POD for agents that fall into a carcinogenic classification.

Extrapolation: Moving from the "range" of the scientific evidence into an area where a standard can be employed usually requires a number of adjustments from the POD. These adjustments can be done through modification factors that address uncertainty (e.g. going from adults to children, laboratory animals to humans), factors that address risk (e.g. drawing a straight line from a benchmark dose to 0 risk and finding an exposure associated with 10^{-6} risk, safety factors), and factors that address study quality. Not all countries use all of these approaches and many use a combination depending upon additional information such as the mechanism by which agents cause cancer. One potential role for the IARC would be the review of the underlying mechanisms to guide countries in making their decisions on how to extrapolate from the POD.

In order to provide guidance to the Programme on a possible role for IARC in quantification of risks, we have developed a series of questions we would like the Advisory Group to address. These are given below.

- Should the IARC begin to address the scientific aspects of quantitative risk assessment for agents it has reviewed in the Monographs Programme?

- If yes, what triggers (e.g. only known human carcinogens, only agents with strong exposure information) should be used to decide on when to engage in addressing quantitative issues? Logistically, should this be part of a Monograph meeting or a separate meeting following the Monograph meeting? Who should attend?

- It is unlikely the IARC will develop full quantitative risk assessments for many agents, but what guidance can you give to guide the IARC on how far this effort should go? For example, should they only review the literature for inclusion in risk assessments or go all the way to developing a POD? How much effort should be spent on using the mechanistic data to guide risk assessments? How should this be done?

- In the Monographs, the IARC has more recently focused on describing effects related to the potential carcinogenicity. Should IARC do the same thing when addressing quantitative issues?

- If quantitative risk characterization is recommended by the Advisory Group additional resources are needed. Should resources for quantitative risk characterization be integrated into the next grant proposal (next five-year proposal to NCI due in summer 2014) or which other funding sources would be suggested?

The format of the meeting will be designed to have substantive discussion of IARC's potential role in addressing the more detailed scientific issues associated with quantitative risk assessment (question 3) before a general discussion on the broader issues (questions 1, 2 and 4).

We propose the attached tentative agenda.

Advisory Group to Recommend on Quantitative Risk Characterization for the *IARC Monographs*
Lyon, 18 and 19 November, 2013

PRELIMINARY AGENDA

Monday, 18 November

08:30-09:00	Registration	
09:00-10:30	Opening session	
	Welcome, introductions	
	Presentation of proposed agenda by *Monographs* programme staff	
	The IARC Monographs programme: Issues related to quantification of risk	K. Straif
	Overview on approaches to quantification of risks	C. Portier
	Approaches to risk assessments by WHO programmes	A. Tritscher
10:30-11:00	Group photo followed by coffee break	
11:00-13:00	General discussion and delineation of questions for subgroup discussion	
13:00-14:00	Lunch, IARC cafeteria	
14:00-17:00	Subgroup discussion on risk quantification	
	Subgroup 1: Exposure and human cancer data	
	Subgroup 2: Cancer bioassays and other relevant data	
15:45-16:15	Payment of *per diem* & dinner reservation (Lobby, during coffee break)	
16:15-17:00	Continuation of subgroup discussion	
17:00-18:00	Presentation of subgroup discussions to plenary	
20:00	Group dinner, Café Comptoir Abel	

Tuesday, 19 November

09:00-10:30	Plenary discussion to develop recommendations on quantitative risk characterization
10:30-11:00	Coffee break
11:00-13:00	Plenary discussion to develop recommendations on quantitative risk characterization
13:00-14:00	Lunch, IARC cafeteria
14:00-15:45	AG's recommendations on quantitative risk characterization for the IARC Monographs Programme
15:45-16:15	Coffee break
16:15-18:00	AG's recommendations on quantitative risk characterization for the IARC Monographs Programme
18:00	Adjourn and farewell cocktail for participants and their guests (12^{th} floor)