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Meeting Report

Quantitative Estimation and Prediction of Risk at the International Agency for Research on Cancer

The identification and quantification of cancer risks are central to the activities of the IARC.[1] In particular, qualitative evaluations are prepared within the IARC Monographs program on the carcinogenicity of a wide variety of agents. The evaluations arrived at in the Monographs are qualitative assessments of the evidence that human exposure to an agent may lead to cancer; they are not quantitative assessments of risk. The evaluations correspond to hazard identification, usually considered to be the first step in risk assessment.

QEP of risk may be done for scientific or for regulatory purposes. Estimates of levels of cancer risk in relation to different levels of exposure to an agent may be used in regulating or in intervening to reduce exposure to the agent. Because QEP entails a large judgemental component and because understanding of the mechanisms of carcinogenesis is still incomplete, QEP has not generally been included in the IARC Monographs.

Outside of that program, however, the Agency has made many contributions to the information necessary for undertaking QEP. These include: the results of long-term experiments in experimental animals; the development of short-term tests for screening for carcinogens; improved methods for measuring exposure; studies of mechanism of action; the results of epidemiological studies of carcinogenic agents that include quantitative measurements of exposure and are analyzed appropriately; and epidemiological studies designed especially for QEP and particularly for quantitative estimation of the effects of low doses.

Because the Agency has been requested repeatedly to become involved in QEP, an Ad-Hoc Working Group[2] was convened in Lyon on October 18–21, 1993, to examine the role that QEP should play in IARC programs and, in particular, in the IARC Monographs. The Group discussed a number of aspects of QEP: its scope and definition, the data used and needed, methodological approaches, and limitations and remaining problems. The group also made a number of recommendations with regard to the involvement of IARC in QEP, both within the Monographs program and in other activities.

Scope and Definitions

Depending on the data available, cancer risk may be quantified at one of three levels of detail: (*a*) point estimates of risk associated with some specified level of exposure; (*b*) analysis of dose-response relationships from the available epidemiological data, which usually covers part of the exposure range of interest; or (*c*) analysis of dose-response relationships across a wider range of exposures, either by extrapolation beyond the range of the epidemiological data or by extrapolation results obtained in experimental animals.

The term "quantitative estimation and prediction" was chosen to describe the topic of the Working Group meeting, inasmuch as it implies a distinction between "estimation" and "prediction." The word "estimate" indicates that the available observations represent only a sample of all observations that could be made; estimates are of varying degrees of precision and accuracy. The term "prediction" was used to infer risk under conditions different from those in which the original data were obtained, and it includes extrapolation outside the range of the original data. Thus, if one has access to dose-response data on cancer in humans, a quantitative estimate of cancer risk can be made at any dose within the range studied. Using the known dose-response data, a prediction can be made of the risk for cancer of humans exposed to doses outside the range studied.

Data Used and Needed for QEP

The group outlined the types of information currently used in QEP and those likely to be needed as the scientific quality of QEP improves, with the addition to the process of more and better data from studies of humans and of experimental animals and from mechanistic studies.

Epidemiological Data. The Group noted that, although cancer epidemiology has evolved from a qualitative field to a more quantitative one, lack of reliable information on exposure is still a frequent reason for rejecting epidemiological data for use in QEP. Improved tools have, however, become available, such as job exposure matrices, expert evaluation of occupational histories, modeling of past exposures, and analysis according to time-related variables. Recently developed biomarkers of exposure could provide a useful adjunct to conventional measures of exposure, once they have been validated with regard to sensitivity, specificity, persistence, and their advantages over conventional tools in epidemiological research.

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[1] The abbreviations used are: IARC, International Agency for Research on Cancer; QEP, quantitative estimation and prediction; PBPK model, physiologically based pharmacokinetic model.

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The problem of individual susceptibility requires examination; most epidemiological studies on which QEP is based involve occupational populations, *i.e.*, mainly healthy adult males. The applicability of their results to more heterogeneous community populations remains to be evaluated.

Data from Studies in Experimental Animals. The group outlined briefly the scope and design requirements of long-term and medium-term bioassays intended to provide dose-response data for QEP. They noted the potential use of transgenic animals to study mechanisms of carcinogenesis, to detect carcinogens and modifiers of carcinogenesis, and to detect mutagenicity *in vivo*. The group also noted the usefulness of obtaining quantitative data on preneoplastic lesions for understanding dose-response relationships, mechanisms of carcinogenesis, and progression. The incorporation of mechanistic information into PBPK models for predicting risk to humans can reduce the degree of uncertainty associated with extrapolations from high to low dose, route to route, species to species, and between dose rates. Considerations of route, level, frequency, and duration of exposure are also involved in such extrapolations.

Comparative Data. Because the activity of many carcinogens varies both qualitatively and quantitatively among species, cross-species extrapolation for QEP may require not only data on humans and experimental animals but also information on relative activity or outcome in humans and animals. The group identified two areas in which comparative data might be particularly useful in QEP: (*a*) differences in metabolic parameters involved in activation and detoxification, including inherited and acquired interindividual variation, are likely to have important implications for QEP; (*b*) the binding of chemicals to DNA, viral induction of tumors, hormone-mediated carcinogenesis, and DNA repair capacity are good instances in which comparative data on mechanisms can be used to support interspecies extrapolation.

Methodological Approaches to QEP

Quantification of cancer risks due to exposure to agents in the environment and in the occupational setting involves five basic steps: (*a*) collection of data; (*b*) formulation of models on the basis of current understanding of the carcinogenic process; (*c*) choice and use of data for estimating the parameters of the model; (*d*) use of the model for QEP; and (*e*) assessment of the overall uncertainty in estimated risks. Precautions to be taken in each of these aspects were outlined.

Empirical methods are available for modeling epidemiological data, which include risk regression models. They should include consideration of potential interactions. Biologically based models can also be applied to the analysis of epidemiological data.

Data from carcinogenicity studies in experimental animals fall into two broad categories: that in which the results can be summarized in terms of the percentage of animals that develop tumours during the experiment; and that which includes age-dependent observations of tumor prevalence and age at death with a tumor. The analyses applied to these two categories are different and vary in the degree to which they can be interpreted for QEP. Methods for analysis of the first category include statistical models of dose-response relationships and biologically based models of carcinogenesis such as the multistage model and the two-stage clonal expansion model. Methods for analysis of the second category include statistical methods based on assumptions of incidental tumors, lethal tumors, or knowledge on intermediate events or in which simple adjustments are made to age-specific rates; they also include many biologically based multistage models of carcinogenesis which were developed to analyze data on age-specific rates of tumor onset.

PBPK models, for determining the amount of reactive metabolite that reaches the target tissues, are potentially of great value for QEP. The use of tissue dose rather than external exposure level in modeling dose-response relationships would lead to more accurate predictions of risk, although many assumptions are involved.

Methods for extrapolating between species were also discussed. These include use of an interspecies scaling factor, which is usually based on body weight, although basal metabolism, oxygen consumption, cardiac output, and several other rate parameters can be scaled roughly with surface area or body weight.

Because all models are abstractions of perceived reality, studies should be designed to validate the resulting estimates and predictions. Ways in which this could be done are being developed and include collection of biological samples for validating the predictions of PBPK models, use of case-control studies to test extrapolations from occupational situations to population settings, testing the goodness of fit of dose-response models, and use of novel experimental protocols different from those used originally to characterize the model.

In general, it should be recognized that information on mechanism of action does not necessarily predict dose-response relationships and that carcinogens may act by multiple mechanisms. Furthermore, QEP must be based on sound statistical procedures, and the effect of untested assumptions on estimated and predicted risks must be assessed.

In order to undertake comprehensive modeling, all of the data available must be included. Scientific QEP will require a wider analysis of these data, showing exactly how they fit together. Currently available methods allow qualitative linkage of the results of PBPK modeling to biochemical models and to progression to malignancy or augmentation from one form of modeling to the next level by using summary measures. Considerable effort will be required to develop these models further.

Limitations and Problems

The group identified specific areas in the accuracy of QEP that should be improved.

In epidemiological studies, the main problems areas identified were: measurement of exposure; the validity of extrapolations from study participants to the general population; limited statistical power to detect and estimate low levels of risk; the accuracy of diagnosis and of cancer registration; and the potential for confounding and other biases inherent in observational studies.

The main problems identified with regard to experimental data were: the limited numbers of animals and dose levels used in conventional bioassays; inadequate provision in the design of studies for obtaining information on mechanisms of action; and the validity of extrapolations between species and from high to low doses.

General uncertainties also exist with regard to how to integrate different types and levels of information from relevant disciplines into QEP. The limitations of statistical methods and the effect of choice of method were also identified as persistent problems in QEP.

Activities Related to QEP within IARC Programs

The task of the Ad-Hoc Working Group was to consider whether it is appropriate for IARC to expand its activities in QEP as part of its evaluation of scientific risks. The group first considered whether QEP should be included within the IARC Monographs program and made the following recommendations: IARC should preserve the primary function of the Monographs program, namely, to identify carcinogenic hazards to humans; although the Monographs should not include QEP, presentation of quantitative data on exposure to and the effects of carcinogens should be enhanced; the information that would

be useful in subsequent attempts to characterize carcinogenic risk would include that on: (*a*) dose-response relationships for cancer in humans and in nonhuman test species; (*b*) levels of human exposure, including variation in exposure among individuals and population subgroups; and (*c*) toxicokinetic and mechanistic information on, *e.g.*, metabolism, genetic polymorphism, mutation, and cell proliferation, which may be helpful in interpreting dose-response relationships and in extrapolating carcinogenic effects between species.

The Group identified a number of activities that the Agency could conduct in the area of QEP, within the fields of analysis, research, education and training: (*a*) QEPs of cancer risk could be performed for important carcinogens about which extensive data are available. Documents developed in the course of such assessments could be published as individual IARC Scientific Publications; (*b*) exposure measures in epidemiological studies, including biological markers, could be improved; (*c*) measurements relevant to mechanisms of carcinogenesis could be incorporated into both epidemiological and experimental studies; (*d*) studies could be designed and conducted for estimating risks to humans of exposures at low levels; (*e*) the Agency could conduct research to develop further the various mathematical and statistical methods that have been used for QEP of cancer risks, some of which are based on current knowledge of mechanisms of carcinogenesis; (*f*) the Agency could provide guidance, education, and training on the use of scientific methods in QEP; (*g*) the Agency might hold scientific meetings on critical issues in QEP and to review existing QEPs. Under appropriate circumstances, the results of such meetings could be published in the IARC Scientific Publications series.

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