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National Toxicology Program Center for the Evaluation of Risks to Human Reproduction: Guidelines for CERHR Expert Panel Members

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INTRODUCTION

The National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) was established at the National Institute of Environmental Health Sciences in 1998. The NTP-CERHR's primary activity is the evaluation of naturally occurring and synthetic chemicals for their potential to adversely affect reproduction and/or development in humans. These evaluations are accomplished through the efforts of independent panels of scientists representing a range of relevant scientific disciplines. Working with NTP-CERHR staff over a period of several weeks, an expert panel prepares a draft report on the subject chemical covering 1) chemistry, usage and exposure, 2) general toxicity, 3) developmental toxicity, and 4) reproductive toxicity. Then, at a public meeting, the expert panel completes the report by reviewing and editing the first four sections and preparing section 5) summaries, conclusions, and critical data needs.

To aid the panels in their evaluations and to help ensure uniformity among reports, the NTP-CERHR developed guidelines for literature evaluation and expert panel report preparation. In developing these guidelines, the NTP-CERHR drew on documents published by three organizations: the Institute for Environmental Health Research (Moore et al., 1995), the International Agency for Research on Cancer (IARC, 1995), and the National Research Council (National Research Council, 2001). The NTP solicited public comments on the draft guidelines (HHS, 2001) and revised the guidelines based on the comments received. The current guidelines reflect additional revisions that have resulted from their use by 6 expert panels and in the preparation of 14 expert panel reports. The guidelines are published here, along with the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Acrylamide, to make them available to a broader scientific audience.

NATIONAL TOXICOLOGY PROGRAM

CENTER FOR THE EVALUATION OF RISKS TO HUMAN REPRODUCTION:

GUIDELINES FOR CERHR EXPERT PANEL MEMBERS

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I. ACTIVITIES OF CERHR EXPERT PANELS

Overview

The primary activity of the CERHR is preparation of reports that provide timely, scientifically rigorous, independent evaluations of the scientific evidence that human exposure to chemicals may result in adverse effects on reproduction including sexual function and fertility (reproductive toxicity) and the normal development of children (developmental toxicity).

Each assessment is carried out by a panel of scientists representing the range of disciplines needed to interpret the scientific literature. The CERHR designates one member of the panel as the panel chair. This person is responsible for coordinating the panel's evaluation activities and for chairing the expert panel meeting. All panel members serve as individual experts in their specific areas of expertise, not as representatives of their employer or other organization, and are required to sign conflict of interest forms before serving on a panel.

The goals of the individual assessments are 1) to produce an objective and scientifically rigorous assessment and interpretation of the scientific evidence that a) a substance constitutes a hazard to human reproduction or development and b) a given exposure circumstance involving the substance poses a potential risk to human reproduction or development, and 2) to identify critical knowledge gaps and data needs to help establish research and testing priorities.

This document is intended to provide expert panel members with guidance on the processes involved in preparation of expert panel reports. The overall process involves three phases: pre-meeting preparation, expert panel meeting, and completion of the panel report. The efficiency and success of this process is highly dependent upon timely and conscientious pre-meeting preparation by panel members.

Pre-meeting Preparation

Each panel member is assigned a topic area of responsibility for the evaluation. Initially, CERHR staff provides each panel member with a bibliography on the chemical(s) to be evaluated, copies of the reprints and reports in their area of responsibility, and summary tables and synopses of the studies deemed most relevant (*having significant and demonstrable bearing on potential reproductive and developmental toxicity*) by the Center staff. The bibliography and available abstracts are available to panel members on restricted pages of the Center's web site (http://cerhr.niehs.nih.gov). Panel members are expected to review the bibliography relevant to their assigned section and provide any additional references relevant to the topic.

The types of documents acceptable for use in preparing panel reports include peer-reviewed papers published or accepted for publication in the open scientific literature and reports or other scientific documents that have been peer-reviewed but may not be published in the open literature. When relevant study reports that have not been peer-reviewed are brought to the attention of the panel members or CERHR staff, they are reviewed for quality and completeness by the expert panel and, if scientifically acceptable, included in the expert panel report. Published abstracts may be discussed and cited to point out the existence of additional information but cannot be used to reach conclusions by the expert panel. Any documents cited in the panel reports that are not available in the open literature will be on file and publicly available from the Center.

Panel members review each publication for their assigned research area and, for each relevant study, summarize the basic facts and findings (see guidelines on the Evaluation of Individual Studies). Individual study summaries will include the reported findings, comments on the strengths and weaknesses of the study, and the utility (*applicability to the purpose of drawing conclusions on whether or not a chemical adversely affects reproduction*) of the data for evaluating reproductive effects. The tables and synopses initially provided by the CERHR staff are intended as a starting point in these efforts.

When a panel member notes missing information in a study or reaches conclusions that differ from the author's, these should be included in square brackets. Examples include:

- key items of information not given in a publication, e.g., **[strain not specified]**.
- substantial limitations noted in a study, e.g., **[only 3 mice were observed in the high dose group, an inadequate number to reach a conclusion]**.
- conclusions other than the author's, e.g., **[significant effects were also observed for the middle dose group]**.

Following completion of the individual study summaries, each panel member is asked to make additions to or deletions from the tables provided by the CERHR staff. Panel members' summaries, any additional references, and the revised table(s) are returned to the CERHR office. CERHR staff integrates expert panel members' submissions into sections 1–4 (see Report Outline below) of the draft expert panel report. The draft report is again sent to each expert panel member for review. Comments and corrections are returned to the CERHR by a predetermined deadline. Based on these comments and corrections, CERHR staff revises the draft report and returns the revised draft to the expert panel. This draft report is announced in the *Federal Register* and made available for public comment through the CERHR office and web site. Written comments submitted by the public are distributed to all expert panel members. Revisions based on public comments may be incorporated prior to or at the public meeting of the expert panel.

Expert Panel Meeting

The most visible activity of the panel is the expert panel meeting. This is the time at which the combined expertise and judgment of the panel are brought to focus on the evaluation. The efficiency and effectiveness of this meeting depend largely on the extent to which each panel member is prepared. Each member is responsible for leading the discussions and deliberations of his/her own sections and participating in the evaluation and integration of all data into a complete report.

At the expert panel meeting, sections 1–4 are reviewed for content and accuracy. The panel openly discusses the

summaries for the individual sections and indicates corrections and clarifications as needed.

When necessary for interpreting individual studies or facilitating comparison among studies, the panel may choose to convert units of exposure, conduct additional statistical analyses, reach its own conclusions on response as a function of exposure, or use the published data to calculate alternative measures such as benchmark doses. All such cases of recalculation or reinterpretation are clearly noted in square brackets, e.g., **[The panel converted the ppm in feed to mg/kg bw/day based on daily food intake]**.

Time is set aside at the beginning of each expert meeting for oral public comments. The panel considers these comments during its deliberations, in revising sections 1–4 and in preparing section 5. Following completion of sections 1–4, the principal activity of the expert panel meeting is drafting and review of the conclusions and the critical data needs. CERHR staff is present to make edits to the draft expert panel report. Workgroup sessions are closed to the public, but findings are reviewed in open plenary session.

The expert panel's goal is to reach consensus on the summaries of sections 3 and 4 and the Summaries, Conclusions, and Critical Data Needs in section 5. In the case that disagreement among members prevents consensus on meaningful statements in any of these areas, the issue is put to a vote by show of hands and majority opinion will prevail. The vote count does not appear in the expert panel report, but is part of the record of the expert panel meeting and is publicly available upon request. Dissenting opinions and the nature of the disagreements may appear in the final expert panel report. The conclusions and the language agreed upon by the panel do not change within the expert panel report after adjournment of the expert panel meeting.

Report Completion

Following the expert panel meeting, CERHR staff prepares a final draft report, assuring that all corrections, revisions, and conclusions agreed to by the expert panel are incorporated. This final draft is sent to panel members to review for completeness and accuracy. According to a predetermined deadline, members' comments are returned to the CERHR and appropriate edits made. The final expert panel report is made available for public comment through a Federal Register Notice and is posted on the CERHR web site. NTP staff reviews the expert panel report and public comments and prepares the NTP Monograph that consists of a NTP brief, the expert panel report, and all public comments on the expert panel report. The NTP brief is written in plain language and includes any new studies pertinent to the conclusions of the panel report. NTP's conclusions regarding the possibility that human development or reproduction might be adversely affected by exposure to the chemical evaluated are noted in this brief. The NTP Monograph is transmitted to the NTP Executive Committee, the NTP Board of Scientific Councilors, and the public.

II. OUTLINE OF CERHR EXPERT PANEL REPORTS

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1.0. Chemistry, Use, and Human Exposure

The purpose of this section is to present the physical and chemical characteristics of the chemical under evaluation, information on its production and use, evidence for its occurrence in the environment, and levels of human exposure, the sources of that exposure, the people most likely to be exposed, and the factors that contribute to exposure. Direct measurement in human tissues or fluids is particularly important and should be included where possible. In this section, both published and readily available unpublished sources of information such as reports from government committees, may be used. However, each statement of fact should be substantiated by an article or report that is fully referenced and should not reflect general assumptions or personal communications. Any limitation(s) or uncertainties inherent in the reports will be described. Unpublished reports used by the expert panel will be maintained in the files of the CERHR and will be available upon request.

1.1. Chemistry

1.1.1. Nomenclature. The most recent Chemical Abstracts Services Registry Number and Primary Name and other common synonyms from the international literature.

1.1.2. Structural and molecular formulae and relative molecular mass.

1.1.3. Chemical and physical properties of the pure substance. Boiling-point, melting-point, density, solubility, vapor pressure, stability, reactivity

1.1.4. Technical products and impurities. Trade names, specifications, composition, inert ingredients and impurities, manufacturers.

1.2. Use and Human Exposure

1.2.1 Production. Methods of synthesis and production; countries in which the agent is or has been produced; past and present volumes of production and trade.

1.2.2. Use. Information on past and present uses.

1.2.3. Occurrence. Levels reported in occupational environments, air, water, soil, and food including persistence and bioaccumulation when available and any uncertainties about these levels.

1.2.4. Human Exposure. Exposure levels in humans as estimated from levels determined in environmental media or from direct analysis of occurrence in human tissues or body fluids and any uncertainties about these levels. When available, authoritative reviews of other summary documents judged scientifically sound by the panel may be used in preparing this section.

Recognizing that data on human exposure are generally sparse and that such data will differ in type, quantity, and quality for each chemical evaluated, an attempt should be made to summarize these data as to whether or not they are sufficient (*refers to a judgment on a collection of data from multiple studies*) for estimating exposure to the general population, to highly exposed groups, e.g., occupationally exposed, or to potentially high risk groups such as children or pregnant women.

In cases where there are no relevant data or the data are not sufficient to estimate exposures to the general population or to defined populations of concern, it should be stated that there are ***insufficient data*** for use in the CERHR evaluation.

For example, when the available exposure data are from a very limited number of samples or from an unrepresentative population or environmental medium, they may provide some basis for estimating general population exposures or ranges of exposures. However, these should be considered ***limited data*** and may not be sufficient for drawing any conclusions related to human risk.

Available data may permit an estimation of general population exposure or range of exposures with some confidence. Likewise, data may be available to permit such estimates in specific populations such as occupational groups or women of reproductive age. Such ***sufficient data*** may be considered of some use in reaching conclusions regarding potential for risk resulting from the estimated exposures.

Finally, there may be cases in which the available exposure data are sufficient to permit confident estimates of average exposures and exposure ranges in the general population and/or in subpopulations at potentially higher risk. These ***exceptional data*** provide the strongest basis for reaching conclusions regarding potential risk.

1.3. Utility of Exposure Data. A clear statement regarding the nature, extent, strengths and limitations of the exposure data should be included in the report, along with an overall evaluation of the suitability of the data for use in assessing potential human risks.

1.4. Summary of Human Exposure Data. This section provides a summary statement of what can be concluded regarding human exposures to the chemical under evaluation. It should be informative with respect to sources and routes of exposure and known or estimated exposure levels, to include exposures of the general population and subpopulations that may be highly or otherwise uniquely exposed. Further, it should indicate if these exposures are acute, chronic, intermittent, intended, or accidental.

2.0. General Toxicology and Biological Effects

2.1. Toxicokinetics and Metabolism. The purpose of this section is to summarize information on toxicokinetics. Studies summarized should include those that report absorption, distribution, metabolism and excretion, and tissue dosimetry. Concise quantitative information should be given on kinetic factors that may affect a dose-response relationship, such as saturation of uptake, protein binding, metabolic activation and detoxification. Studies of metabolism in vitro may be included when judged relevant. Comparisons of results between animals and humans are considered highly important and should be made when possible. Potential for transplacental transfer or secretion in breast milk is of particular relevance. Authoritative reviews may be employed to prepare this section.

2.2. General Toxicity. The purpose of this section is to summarize information on categories of toxicity other than reproductive or developmental. Studies summarized should include those that report maximum tolerated doses, single and repeated dosing regimens, and effects on specific organs and systems such as the immune, circulatory, nervous, skeletal, and endocrine systems. Although not essential to the assessment of reproductive and developmental effects, such studies can be informative with regard to dose-responses, organs affected, effects of different routes of administration, similarities or differences in effects among species, and the general health status of test animals at doses relevant to interpretation of reproductive or developmental toxicity data. Studies in humans and experimental animals should be included. Authoritative reviews may be employed to prepare this section.

2.3. Genetic Toxicity. The purpose of this section is to summarize information on the genetic effects of the chemical. Chemicals that are mutagenic or exhibit other evidence of genetic toxicity are often observed to adversely affect development and reproduction. Results of both in vitro and in vivo studies, and data from experimental animals or humans, should be summarized. Authoritative reviews may be employed to prepare this section.

2.4. Carcinogenicity. The purpose of this section is to summarize results of studies in which the potential of the chemical to induce cancer has been reported. Studies in both experimental animals and humans should be included. Authoritative reviews may be employed to prepare this section.

2.5. Potentially Sensitive Subpopulations. The purpose of this section is to identify exposure subpopulations with a greater vulnerability for toxicity. This may be the result of physiologic, genetic, or exposure

differences within this population. Authoritative reviews may be employed to prepare this section.

2.6. Summary of General Toxicology and Biological Effects. A summary statement related to each of the four categories in this section should be presented. Each summary statement should state clearly the extent and quality of the data evaluated, e.g., no data available, limited data—not sufficient to reach a conclusion, data sufficient to suggest an effect, or data sufficient to clearly show an effect. Summary statements should state the species, sex, experimental conditions, organs/tissues/cells affected, and the endpoint measured. For genetic toxicity, it should be stated if the effects were observed in in vitro or in vivo systems.

3.0. Developmental Toxicity Data

3.1. Human Data. The purpose of this section is to summarize all studies and reports on developmental effects in humans. All available studies should be summarized including case reports, cohort studies, and case-control studies. When available, information on susceptibility factors, e.g., life stage, diet, genetics, stressors, should be discussed. Because of the paucity and importance of studies in humans, it is important to summarize studies of questionable quality for discussion by the panel, even though they may not contribute to the conclusions.

3.2. Experimental Animal Data. The purpose of this section is to summarize all data relevant to evaluating the developmental effects of the exposure to animals. Studies of doubtful quality should also be summarized for discussion by the panel. In addition to developmental toxicity studies of the chemical under evaluation, the following types of studies should also be summarized: those in which the chemical was administered in conjunction with other toxicants or modifying factors, experiments on the developmental toxicity of known metabolites and derivatives, and studies in which the endpoint was defined or suspected of being an indicator of developmental toxicity. It is particularly important to address mechanism(s) of toxicity whenever the scientific literature permits.

It should be noted that a distinction between developmental and reproductive toxicity studies is not always clear. Developmental toxicity studies may include an evaluation of the reproductive system and the endpoints measured may reflect structural and/or functional effects. When such studies are encountered, they should appear in both the Developmental Toxicity and Reproductive Toxicity sections, with the greatest detail provided in the section deemed by the panel to be the most relevant to the evaluation.

3.3. Utility of Developmental Toxicity Data. A clear statement regarding the nature, amount, strengths and limitations of the developmental toxicity data should be included in the report along with an overall evaluation of the utility of the data for use in assessing potential human risks.

3.4. Summary of Developmental Toxicity Data. This section provides a concise summary of those studies reviewed in sections 3.1 and 3.2 and considered to be of adequate quality for use in making an evaluation of developmental toxicity. Descriptions of studies on which critical comments have been noted in square brackets need not be brought forward to the summary if the study was deemed not of adequate (refers to individual studies) quality or completeness to contribute to the evaluation. Results reported only in abstracts should not contribute to the conclusions.

It is recognized that each chemical evaluated will involve a unique array of data. However, a statement as to whether or not the chemical is considered a developmental hazard is to be presented. The following template provides a general format and guidance on the information that should be included in this statement:

There is (sufficient, insufficient) evidence in (animals and/or humans) that (chemical X) (does or does not) cause developmental toxicity when exposure is (route, dose range, timing, duration). The data are (relevant, assumed relevant, irrelevant) to consideration of human risk.[1]

sufficient/insufficient is a scientific judgment based on the amount, quality, and types of available data.

relevant = human data, or animal data for which pharmacokinetic and mechanism information is adequate to demonstrate a particular similarity to humans.

assumed relevant = no information available to modify the assumption that the data are relevant.

irrelevant = pharmacokinetic or mechanistic features of the animal models are known and demonstrated to be inconsistent with human exposure or response.

4.0. Reproductive Toxicity Data

4.1. Human Data. The purpose of this section is to summarize all studies and reports on reproductive effects in humans. All available studies should be summarized including case reports, cohort studies, and case-control studies. Because of the paucity and importance of studies in humans, it is important to summarize studies of questionable quality for discussion by the panel, even though they may not contribute to the conclusions.

4.2. Experimental Animal Data. The purpose of this section is to summarize all data relevant to evaluating the reproductive effects of exposure to animals. Studies of doubtful quality may also be summarized for discussion by the panel. In addition to reproductive toxicity studies of the chemical under evaluation, the following types of studies should also be summarized: those in which the chemical was administered in conjunction with other toxicants or modifying factors, experiments on the reproductive toxicity of known metabolites and derivatives, and studies in which the endpoint was defined as or suspected of being an indicator of reproductive toxicity. It is particularly important to address mechanism(s) of toxicity whenever the scientific literature permits.

It should be noted that a distinction between reproductive and developmental studies is not always clear. Reproductive toxicity studies may include an evaluation of developmental endpoints that reflect structural and/

[1]This template is taken from the National Research Council Report, Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity. Subcommittee on Reproductive and Developmental Toxicology, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences. Washington, DC: National Academy Press, 2001.

or functional effects. When such studies are encountered, they should appear in both the Developmental Toxicity and Reproductive Toxicity sections, with the greatest detail provided in the section deemed by the panel to be the most relevant to the evaluation. Studies in which effects on reproductive system structure or function are reported following pre- or early postnatal exposure should be included in this section.

4.3. Utility of Reproductive Toxicity Data. A clear statement regarding the nature, volume, strengths, and limitations of the reproductive toxicity data will be included in the report along with an overall evaluation of the utility of the data for use in assessing potential human risks.

4.4. Summary of Reproductive Toxicity Data. This section provides a concise summary of those studies reviewed in sections 4.1 and 4.2 and considered to be of adequate scientific quality for use in making an evaluation of reproductive toxicity. Studies on which critical comments have been noted in square brackets in the text should not be brought forward to the summary if they were not of adequate quality to contribute to the evaluation. Results reported only in abstracts will not contribute to the conclusions.

It is recognized that each chemical evaluated will involve a unique array of data. However, a statement as to whether or not the chemical is considered a reproductive hazard in females or males is to be presented. The following template provides a general format and guidance on the information that should be included in this statement:

There is (sufficient, insufficient) evidence in (animals and/or humans) that (chemical X) (does or does not) cause reproductive toxicity in (females, males) when exposure is (route, dose range, timing, duration). The data are (relevant, assumed relevant, irrelevant) to consideration of human risk.[2]

sufficient/insufficient is a scientific judgment based on the amount, quality, and types of available data.

relevant = human data, or animal data for which pharmacokinetic and mechanism information is adequate to demonstrate a particular similarity to humans.

assumed relevant = no information available to modify the assumption that the data are relevant.

irrelevant = pharmacokinetic or mechanistic features of the animal models are known and demonstrated to be inconsistent with human exposure or response.

5.0. Summaries, Conclusions, and Critical Data Needs

5.1. Developmental Toxicity. This section of the expert panel report provides a brief synopsis of the summaries presented in section 3. It should state whether or not the scientific data reviewed has led the panel to conclude that the chemical assessed is likely or is not likely to be a potential developmental hazard to humans. When data are not sufficient to reach such a conclusion, this should be clearly stated. This evaluation should be made without consideration of human exposure levels or the numbers or subpopulations of people who may be exposed.

5.2. Reproductive Toxicity. This section of the expert panel report provides a brief synopsis of the summaries presented in section 4. It should state whether or not the scientific data reviewed has led the panel to conclude that the chemical assessed is likely or is not likely to be a potential reproductive hazard to humans. When data are not sufficient to reach such a conclusion, this should be clearly stated. This evaluation should be made without consideration of human exposure levels or the numbers or subpopulations of people who may be exposed.

5.3. Summary of Human Exposures. This section of the expert panel report presents a synopsis of the information available on human exposures as reviewed and summarized in section 1. The sufficiency of the data should be stated and, when possible, exposure estimates included for the general population as well as for any highly exposed groups, e.g., occupationally exposed, or for potentially high risk groups such as children or pregnant women.

5.4. Conclusions. This section is based on an integration of the toxicity and exposure data and, when possible, evidence on the mechanism of action. Conclusions are presented in narrative form and present the panel's best scientific judgment on the likelihood that adverse reproductive and/or developmental effects may occur under the exposure circumstances specified, i.e., a qualitative statement of potential risk. If the panel concludes that adverse effects may result, the conclusions should specify the population subgroup (e.g., occupational group), sex or life stage in which such exposures may result in adverse reproductive or developmental effects. The rationale of the panel in reaching this conclusion should be clearly described.

Although strict categories of potential risk are not prescribed for use by the panels, the narrative conclusions should qualify the likelihood of an adverse effect under specified exposure conditions. Previous panel reports can serve as examples for the wording of such conclusions.

5.5. Critical Data Needs. As a result of conducting the evaluation, the panel is asked to identify critical data gaps, i.e., tests or experiments that could provide information to substantially improve an assessment of human reproductive risks. Inclusion of these critical research and testing needs in the report will provide a basis for government agencies to set research and testing priorities. It is important that the data needs identified are critical to improved risk evaluations. Data needs that are simply desirable or generally informative can be presented but should be clearly distinguished from critical needs.

6.0. References

The bibliography for each report will be prepared and maintained by the CERHR staff. Panel members should provide the staff with complete citation or source information on publications they feel should be added. When possible, reprints should be provided.

[2]This template is taken from the National Research Council Report, Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity. Subcommittee on Reproductive and Developmental Toxicology, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences. Washington, DC: National Academy Press, 2001.

7.0. Data Tables

Data tables will be prepared and provided by the staff of the CERHR. Panel members are expected to review the tables for completeness and accuracy.

III. GUIDELINES FOR THE EVALUATION OF INDIVIDUAL STUDIES

Evaluation of Studies in Humans

(applies to sections 2, 3, and 4 of the expert panel report)

Studies should be organized by type, e.g., case reports, descriptive studies, cohort studies, case-control studies. A brief, factual synopsis of each study, to include the information listed below, should be provided.

Case Reports. A brief narrative summary of the report.

Descriptive Studies. A brief narrative summary of the report.

Cohort Studies. To the extent possible, a summary of each study should include information on:

- size, sex, race, and other descriptions of the original cohort
- nature of the health outcome studied and how the outcome was ascertained
- geographical location of the study
- dates of study cohort participation start and finish
- exposure studied, how measured, duration, and level of exposure
- possible confounding exposures and how measured
- criteria for inclusion/exclusion
- response and follow-up rates
- size of final cohort
- basis for risk estimation
- method of analysis
- power of study
- overall quality of the study and potential for bias, e.g., selection, recall, etc., of any type in the results
- estimates of risk and associated measures of uncertainty, e.g., 95% confidence intervals or standard errors

Case-Control Studies. To the extent possible, a summary of each study should include information on:

- population base
- geographical location of the study
- source of case ascertainment and how endpoints were measured
- time period covered
- selection and number of controls
- source of information on exposures and how measured
- response rates of cases and controls
- method of controlling for potential confounders and how measured
- power of study
- overall quality of the study and potential for bias, e.g., selection, recall, etc., of any type in the results
- estimates of risk and associated measures of uncertainty, e.g., 95% confidence intervals or standard errors

Comments on the quality of the study (design, execution, analysis, and interpretation) should include the following factors:

- is the adverse health outcome well defined and appropriately measured?
- is the exposure well defined and appropriately measured?
- are the controls appropriate?
- are potential confounding factors identified?
- what were the confounding variables and were they measured and controlled for appropriately?
- was there evidence of a dose-effect relationship?
- is the interval between time of exposure and time of observation appropriate?
- are statistical methods clear and appropriate?
- was the power of the study adequate to detect an association of the size expected?
- what were the potential effect modifiers and were they measured and analyzed appropriately?

Evaluation of Studies in Experimental Animals

(applies to sections 2, 3, and 4 of the panel report)

Experiments should be organized by animal species and route of administration. A brief, factual summary of each study should be provided, which includes the following information:

- numbers of animals in each treated and control group
- species, strain, and sex
- age at beginning and end of treatment
- route of administration
- purity of substance
- solvent or vehicle
- controls (untreated, solvent, positive)
- doses
- dosing schedule
- basis for dose selection
- duration of treatment
- endpoints observed
- method of examination
- age at observation
- number of animals and/or litters observed
- statistical methods utilized
- statistical significance
- author's conclusions supported by the data
- GLP study

Whenever these items of information are not given in a publication, this fact should be noted in square brackets, e.g., **[strain not specified]**. Likewise, when a limitation is noted in a study, this should also be noted in square brackets, e.g., **[only 3 mice were observed in the high dose group, an inadequate number to reach a conclusion]**. Conclusions other than the author's may be reached by the panel but must be clearly identified as the panel's, explained, and included in **square brackets**.

When necessary to help interpret individual studies or facilitate comparison among studies, the panel may choose to convert units of exposure, conduct additional statistical analyses, reach its own conclusions on effect as a function of exposure, or use the published data to

calculate summary measures such as benchmark doses. All such cases of recalculation or reinterpretation must be clearly noted in square brackets, e.g., **[The panel converted the ppm in feed to mg/kg bw/day based on daily food intake]**.

Comments on the quality of a study (design, execution, analysis, and interpretation) should take into consideration the following factors:

- was an appropriate number of animals used?
- were they randomly assigned to experimental groups?
- was the test chemical defined, source and purity stated?
- was there chemical verification of dosing preparations?
- were age of animals and duration of exposure appropriate?
- were appropriate endpoints observed?
- were endpoints observed at appropriate life stages?
- were data reported in appropriate detail?
- were appropriate statistics employed?

REFERENCES

HHS. 2001. Department of Health and Human Services (HHS). Public Health Service. National Toxicology Program. National Institute of Environmental Health Sciences; Center for the Evaluation of Risks to Human Reproduction (CERHR) solicits public comments on Draft Guidelines for CERHR Expert Panel Members. Fed Regist 66:20823–20824.

IARC. 1995. International Agency for Research on Cancer (IARC) monographs programme on the evaluation of carcinogenic risks to humans: preamble and instruction for authors. http://www-cie.iarc.fr/monoeval/preamble.html

Moore JA, Daston GP, Golub M, Hart WL, Hughes, C Jr., Kimmel CA, Lamb JC IV, Schwetz BA, Scialli AS. 1995. An evaluative process for assessing human reproductive and developmental toxicity of agents. Reprod Toxicol 9:61–95.

National Research Council. 2001. Evaluating chemical and other agent exposures for reproductive and developmental toxicity. National Research Council. Washington, DC: National Academy Press. p 24–80.