APPENDIX N

Integrated Risk Information System
Background Paper

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WATER QUALITY STANDARDS HANDBOOK

SECOND EDITION

IRIS

BACKGROUND PAPER

Integrated Risk Information System

Office of Health and Environmental Assessment

Office of Research and Development

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VERSION 1.0

IRIS Background Paper

On February 25, 1993, a FEDERAL REGISTER notice (58 FR 11490) was published on the Integrated Risk Information System (IRIS). This background paper is a companion piece to that notice.

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Introduction

This background paper provides the history, purposes, and goals of the Integrated Risk Information System (IRIS) and a detailed description of the current processes used by the two Agency scientific work groups responsible for developing the health hazard information in IRIS. This background will help interested persons to better understand the focus and contents of the companion FEDERAL REGISTER notice.

The February 25, 1993 FEDERAL REGISTER notice (58 FR 11490): (1) announces the availability of this paper that describes IRIS, its contents, and the current processes used by the two Agency work groups responsible for developing IRIS information; (2) discusses an Agency activity to review IRIS processes and solicits comments on this review; (3) highlights points in the current process where public input, including information submissions, is encouraged; (4) describes how to access IRIS; and (5) announces a new process to publish regularly a list of the substances scheduled for IRIS work group review and to solicit pertinent data, studies, and comments on these substances.

General Background

IRIS is an EPA data base, updated monthly, containing Agency consensus positions on the potential adverse human health effects of approximately 500 specific substances. It contains summaries of EPA qualitative and quantitative human health information that support two of the four major steps of the risk assessment process outlined in the National Research Council's (NRC) 1983 publication, "*Risk Assessment in the Federal Government: Managing the Process.*"

The risk assessment process described in the 1983 NRC publication consists of four major steps: hazard identification, dose-response evaluation, exposure assessment, and risk characterization. IRIS includes information in support of the first two of those steps, hazard identification and dose-response evaluation. Hazard identification is the qualitative determination of how likely it is that a substance will increase the incidence and/or severity of an adverse health effect. Dose-response evaluation is the quantitative relationship between the magnitude of the effect and the dose inducing such an effect. IRIS information supporting risk characterization consists of brief statements on the quality of data and very general statements on confidence in the dose-response evaluation. IRIS consensus information does not include exposure assessment information. Combined with specific situational exposure assessment information, the summary health hazard information in IRIS may be used as one source in evaluating potential public health risks of or from environmental contaminants.

Many EPA program offices and program support offices, including the Office of Research and Development, both at Headquarters and in EPA's ten Regional offices, are involved in assessment activities in support of various legislative mandates. In the 1980s, as health risk assessment became a more widespread practice across Agency programs, the need became clear for greater consensus and consistency in the areas of hazard identification and dose-response assessment. It was determined that an internal process should be established for reaching an Agency-wide judgment on the potential health effects of substances of common interest to these offices, and a system developed for communicating that Agency judgment to EPA risk assessors and risk managers. These would provide the needed consistency and coordination. In 1986, two EPA work groups with representation from program offices involved in risk assessment were convened to carry out such an internal process to reach consensus Agency positions on a chemical-by-chemical basis. In 1986, the IRIS data base was created for EPA staff as the official repository of that consensus information.

On June 2, 1988, a FEDERAL REGISTER notice (53 FR 20162-20164) of public availability of IRIS was published. That notice described IRIS, the types of risk information it contains, and how to get access to the system. It informed the public about the establishment of the IRIS Information Submission Desk. The submission desk was intended to provide opportunity for public input. The notice explained the procedures for submission of data or comments by interested parties on substances either on IRIS or scheduled for review by the work groups. As stated in the June 1988 notice, a list of the substances scheduled for work group review has been a separate file on IRIS since it became publicly available. It was hoped that users would submit pertinent information to the IRIS Information Submission Desk. In fact, few users have taken advantage of the opportunity to submit data and comments.

Therefore, data submission procedures are reiterated in the FEDERAL REGISTER notice (58 FR 11490) related to this paper and a list of the substances scheduled for review by specific work groups is included. The data submission procedures will be reprinted in the FEDERAL REGISTER every 6 months with a new or revised list of substances scheduled for work group review. For the latest status of the substances scheduled for review, interested persons should first check the IRIS data base itself or contact:

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Data Base Contents

The core of IRIS is the three consensus health hazard information summary sections: the reference dose for noncancer health effects resulting from oral exposure, the reference concentration for noncancer health effects resulting from inhalation exposure, and the carcinogen assessment for both oral and inhalation exposure. All of these terms are commonly used for judging the effects of lifetime exposure to a given substance or mixture. Citations for the scientific methodologies that are the basis for the consensus health hazard sections on IRIS are included on page 10 of this paper.

In addition, an IRIS substance file may include supplemental information such as summaries of health advisories, regulatory actions, and physical/chemical properties.

Noncancer Health Effects Information

An oral reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is believed likely to be without an appreciable risk of certain deleterious effects during a lifetime ("Reference Dose [RfD]; Description and Use in Health Risk Assessment" *Regulatory Toxicology and Pharmacology* 8:471-486, 1988). RfDs are developed by an assessment method that assumes that there is a dose threshold below which adverse effects will not occur. An RfD, which is expressed in milligrams per kilogram per day (mg/kg-day), is based on the determination of a critical effect from a review of all toxicity data and a judgment of the necessary uncertainty and modifying factors based on a review of available data. IRIS substance files contain the following information pertaining to the oral RfD: reference dose summary tables, principal and supporting studies, uncertainty and modifying factors used in calculating the RfD, a statement of confidence in the RfD, EPA documentation and review, EPA scientific contacts, and complete bibliographies for references cited.

The inhalation reference concentration (RfC) is analogous to the oral RfD (*Interim Methods for Development of Inhalation Concentrations*, EPA/600/8-90/066A). It is also based on the assumption that thresholds exist for noncancer toxic effects. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extra-respiratory). The inhalation RfC is expressed in milligrams per cubic meter (mg/cu.m). The RfC method departs from that used to determine the oral RfD primarily by the integration of the anatomical and physiological dynamics of the respiratory system (i.e., portal-of-entry) with the physicochemical properties of the substance or substances entering the system. Different dosimetric adjustments are made according to whether the substance is a particle or gas and whether the observed toxicity is respiratory or extra-respiratory. These adjustments scale the concentration of the substance that causes an observed effect in laboratory animals (or in humans, when available from occupational epidemiology studies) to a human equivalent concentration for ambient exposures.

IRIS substance files contain the following inhalation RfC information: reference concentration summary tables, description of dosimetric adjustment, principal and supporting studies, uncertainty and modifying factors used to calculate the RfC, a statement of confidence in the RfC, EPA documentation and review, EPA scientific contacts, and complete bibliographies for references cited.

Cancer Health Effects Information

The carcinogen assessment of an IRIS substance file contains health hazard identification and dose-response assessments developed from procedures outlined in the EPA Guidelines for Carcinogen Risk Assessment (51 FR 33992-43003, September 24, 1986). Each cancer assessment, as a rule, is based on an Agency document that has received external peer review. The hazard identification involves a judgment in the form of a weight-of-evidence classification of the likelihood that the substance is a human carcinogen. It includes the type of data used as the basis of the classification. This judgment is made independently of considerations of the strength of the possible response. The dose-response assessment is a quantitative estimate of the potential activity or magnitude of a substance's carcinogenic effect, usually expressed as a cancer unit risk. A cancer unit risk is an upper-bound estimate on the increased likelihood that an individual will develop cancer when exposed to a substance over a lifetime at a concentration of either 1 microgram per liter (1 μg/L) in drinking water for oral exposure or 1 microgram per cubic meter (1 μg/cu.m) in air for continuous inhalation exposure. Generally, a slope factor for dietary use is also given. It is an upper-bound estimate of cancer risk for humans per milligram of agent per kilogram of body weight per day.

IRIS contains the following information in the cancer assessment section: EPA weight-of-evidence classification and its basis, a summary of human carcinogenicity studies when available, a summary of animal carcinogenicity studies, a summary of other data supporting the classification, oral and/or inhalation quantitative estimates, dose-response data used to derive these estimates and the method of calculation, statements of confidence in magnitude of unit risk, documentation and review, EPA scientific contacts, and complete bibliographies for references cited.

Scientific Contacts

It is important to note that in each of the three sections described above, EPA staff names and telephone numbers are included as scientific contacts for further information. The Agency believes that the inclusion of Agency scientific contacts able to discuss the basis for the Agency's position, has been very valuable. These individuals play a major role in providing public access to IRIS and a conduit for valued public comment.

Bibliographies

IRIS contains full bibliographic citations for each substance file, directing the user to the primary cited studies and pertinent scientific literature. One of the major intents of IRIS was to encourage users to evaluate the primary literature used to develop the IRIS information in light of the assumptions and uncertainties underlying the risk assessment process.

Supplementary Information

In addition to the RfD, RfC, and carcinogenicity sections, IRIS substance files may contain one or more of three supplementary information sections: a summary of an Office of Water's Drinking Water Health Advisory, a summary of EPA regulatory actions, and a summary of physical/chemical properties. The only purpose of these supplemental sections is to serve as accessory information to the consensus health hazard information. Since the primary intent of the IRIS data base is to communicate EPA consensus health hazard information, these other sections are only included as auxiliary material to provide a broader profile of a substance and are never added until at least one of the consensus health hazard sections described above (namely, the RfD section, RfC section, or carcinogenicity section) is prepared and approved for final inclusion on the data base. These supplemental sections should not be used as the sole or primary source of information on the current status of EPA substance-specific regulations.

Use and Development of Health Hazard Information

The type of substance-specific consensus health hazard information on IRIS may become part of the supporting materials used to develop site-specific EPA health hazard assessments. These assessments may in turn lead to EPA risk management decisions, generally resulting in the formal Agency rulemaking process. This rulemaking process often includes FEDERAL REGISTER publication of a proposed rule where the public is encouraged to comment. These comments may be directed at both the proposed rule and the scientific basis of the decision, including information obtained from IRIS and thus offer a further opportunity for comment on the risk information in the context of its use.

The area of human health risk assessment has evolved over the past several years. As the risk assessment community has grown and the field itself has matured, new approaches to the assessment and use of human health risk information have been developed. The evolving nature of risk assessment has also resulted in changes to IRIS. The development of methodologies such as those for the inhalation RfC determination illustrates the ability of the IRIS information development process to grow with the changing science. Areas of future growth may include less-than-lifetime risk information and developmental toxicity risk information and other endpoint-specific health hazard information. Also, on several occasions, the information in IRIS has

been reevaluated and modified to reflect new information and approaches. New studies on individual substances are continually being conducted by Federal, private, and academic institutions and may have significant impact on IRIS information. In those cases, the IRIS substance information is reevaluated in light of the new data; any changes resulting from that reevaluation are included on the system.

Management of the Data Base

The IRIS data base is managed and maintained by the Office of Health and Environmental Assessment (OHEA), Office of Research and Development (ORD). IRIS is an Agency system primarily funded by OHEA with additional significant support from EPA program offices.

Oversight

Oversight activities for IRIS are conducted by the IRIS Oversight Committee, a subgroup of the Agency's Risk Assessment Council. Committee membership consists of senior Agency risk assessors. The main purpose of the IRIS Oversight Committee is to serve as a forum for discussion and advice on significant scientific or science policy issues involving IRIS. The Council, which is chaired by EPA's Deputy Administrator, receives periodic status reports on IRIS and related work group activities.

Information Development Process

There are two EPA work groups, the Carcinogen Risk Assessment Verification Endeavor (CRAVE) and the Oral Reference Dose/Inhalation Reference Concentration (RfD/RfC) Work Group, that develop consensus health hazard information for IRIS. Each group consists of EPA scientists from a mix of pertinent disciplines and represents intra-Agency membership. The work groups serve as the Agency's final review for EPA risk assessment information. When the work groups reach consensus on the health effects information and the dose-response assessment for a particular substance, the descriptive summary is added to IRIS.

CRAVE: Information Development Procedures

The goals of the CRAVE are to reach Agency consensus on Agency carcinogen risk assessments; to arrive at a unified view on potential cancer risk from exposure to specific substances across Agency programs; and to identify, discuss, and resolve general issues associated with methods used to estimate carcinogenic risks for specific agents. The major outputs of the work group are summaries of risk

information that have been previously developed and documented by scientific experts in Agency program and program support offices, and results of discussions of general issues in carcinogen risk assessment.

Scientists are selected by executive appointment from respective member offices. Membership is open to all major Agency program and regional offices, ORD, and the Office of Policy, Planning, and Evaluation (OPPE). Substances are discussed at the request of Agency offices or regions according to an established timetable. The CRAVE priorities are determined by the member offices. The office requesting review prepares a summary describing both a judgment on the weight-of-evidence for potential health hazard effects and any dose-response information for the substances according to an established format. Literature files on the substances including critical studies, pertinent EPA documents, and other relevant supporting documentation are made available to work group members in advance of the meeting. Generally, the judgment and the dose-response assessment are expected to have appeared in a publicly available document of some sort.

The CRAVE usually meets bimonthly for two days. Work group members normally receive draft summaries for pre-meeting review at least one week prior to the scheduled meeting. At the meeting, data and documentation are examined, and there is discussion of the basis for the risk information and the methods by which it was derived. In addition, the nature and extent of previous internal and external peer review, including the comments received, are reviewed by the work group. The summary is revised by the office originating the review to reflect the meeting discussion and accurately express the consensus view of the work group. After the process of revision is completed, the summary is circulated again to the work group for final approval prior to its inclusion on IRIS.

Consensus means that no member office is aware either of information that would conflict with the final carcinogenicity summary, or of analyses that would suggest that a different view is more credible. Such assurance rests on the capabilities of the individuals who represent their offices; thus, every effort is made to seek scientists who are both expert in the area of human health assessment and who can represent their office.

Peer review has generally been part of the IRIS information development processes from the beginning of the system. In the preparation of summaries, emphasis has been placed on the use of peer-reviewed EPA assessments. These have included Office of Pesticide Programs assessments that have received both program office peer review and Science Advisory Panel review. Other EPA documentation includes assessments prepared by OHEA such as Health Assessment Documents, Health and Environmental Effects Documents, and Health Effects Assessments. These documents receive OHEA review and program office review and some receive Science Advisory Board (SAB) or other external review. Assessments developed by or for the Office of Ground Water and Drinking Water and incorporated

in either Drinking Water or Ambient Water Criteria Documents, or in Drinking Water Health Advisories generally receive extensive Agency review and SAB review prior to discussion by CRAVE.

On occasion, risk assessments that were contained in draft documents have been discussed by CRAVE. In these instances, results of the work group deliberations have been incorporated into the document development process at the program office or program support office level. Loading of the information on IRIS is delayed pending completion of the document.

If consensus is not reached at the meeting it is generally because an issue is raised that requires resolution. Work group deliberations continue until consensus is achieved. In the case of substance-specific issues, the substance is referred back to the member office that initiated the review for more information and clarification. In some instances, it has been necessary for more than one program office to engage in a dialogue to resolve the issue.

For general issues, CRAVE practice has been to form a subcommittee to prepare an issue paper that is subsequently discussed at a special meeting. As examples of this process, issue papers have been developed for (1) issues relating to accuracy and precision of quantitative dose-response information, (2) factors involving confidence in quantitative estimates, and (3) use of split classifications and combining estimates.

When consensus is not achieved on a particular substance at a meeting of the CRAVE, it is considered to have "under review" status. If after three months, there is no further activity to bring the substance back to the work group for additional review, the substance loses its "under review" status. The substance is then dropped from the work group review list after notifying the responsible office. Any office may resubmit the substance for further discussion at any time.

Reference Dose (RfD)/Reference Concentration (RfC): Information Development Procedures

The purpose of the RfD/RfC Work Group is to reach consensus on oral RfDs and inhalation RfCs for noncancer chronic human health effects developed by or in support of program offices and the regions. The work group also works to resolve inconsistent RfDs or RfCs among program offices and to identify, discuss, and resolve generic issues associated with methods used to estimate RfDs and RfCs.

Scientists are selected by executive appointment from respective member offices. Membership is open to all major Agency program and regional offices. There are two work group co-chairs. In addition, scientists from the Agency for Toxic Substances and Disease Registry and the Food and Drug Administration are invited to work group meetings as observers to assist the Agency in the information gathering process. Their

involvement fosters better communication and coordination among federal agencies regarding assessment approaches and data evaluation. Members reflect a variety of pertinent scientific disciplines including expertise in the fields of general and inhalation human toxicology.

Member offices schedule substances for discussion through the work group co-chairs for specific meetings, usually one or two months in advance. Regional requests for specific substance discussions are routed through the co-chairs, who then either schedule these substances in the usual manner or, if the region has not prepared a file, requests an appropriate office to undertake that task.

The RfD/RfC Work Group usually meets once a month for two days. Substances are discussed at the request of any Agency office or region. The requesting office generally prepares a file that consists of a summary sheet, a copy of the critical study and supporting documentation, and distributes these to work group members prior to the meeting.

Consensus generally means that no member office is aware either of information that would conflict with the RfD or RfC, or of analyses that would suggest a different value that is more credible. Such assurance rests on the capabilities of the individuals who represent their offices; thus, a large effort is conducted biannually to seek scientists who are both expert in this area of assessment and can represent their offices.

RfD or RfC summaries are not always based on existing EPA assessment documents but may be based on assessments prepared specifically for the work group. This is a fundamental difference between the usual processes of the RfD/RfC Work Group and those of CRAVE. As stated previously, the general rule has been that for a substance to be brought to the CRAVE Work Group for review there should be an existing peer-reviewed Agency health effects document. However, for RfDs there may or may not be an existing EPA document on which to base work group deliberations and in the case of RfCs, there have not, to date, been any existing peer-reviewed EPA documents. Thus, RfC deliberations are based on extensive assessment summaries prepared expressly for the work group. Therefore, when an Agency peer-reviewed document is not available, as with RfCs and some RfDs, extensive assessment summaries are included on IRIS once the work group has completed verification and reached consensus.

The work group co-chairs assure that the final summary accurately expresses the consensus view of the group at the meeting as specified in the meeting notes. Once unanimous consensus is reached, the substance-specific summary for either an RfD or RfC is prepared for inclusion on IRIS. In some cases, the work group agrees that adequate information is not available to derive an RfD or RfC. A message is then put on IRIS to that effect and the reasons for the "not verifiable" status. In most cases the message states that the health effects data for a specific substance were reviewed by the work group and determined to be inadequate for derivation of an RfD or RfC.

Conflicts that arise during a meeting regarding a given RfD or RfC generally are resolved outside the meeting by scientists from the appropriate offices, and then brought back to the work group for clarification and subsequent consensus. Conflicts that arise regarding the methods by which RfDs or RfCs are estimated, or the incorporation of new methods, are generally taken up at separately scheduled meetings of the work group, for which the sponsoring office prepares the appropriate material for review.

While, as discussed above, the RfD/RfC Work Group process is somewhat different from that of the CRAVE, they both use generally the same consensus procedures. Other procedural similarities are discussed in the following paragraphs.

On occasion, scientific issues on individual substances, methods, or on a general question cannot be resolved at the work group level. In the event that an issue is unresolvable in the work group processes, the issue is referred to the Risk Assessment Council. In some cases, the issue is brought to the IRIS Oversight Subcommittee for review and discussion, prior to consideration by the full Council. If an issue is raised to the Council, it may be referred by the Council to the Risk Assessment Forum for consultation.

Both the CRAVE and RfD/RfC Work Groups, through the IRIS Information Submission Desk, discussed in the companion FEDERAL REGISTER notice, have received comments and studies from interested parties outside of the Agency that were either pertinent to the work group's initial review or resulted in reconsideration of a particular substance assessment. Further, the work groups often contact the authors of a primary study if clarifications are necessary, and consult with outside experts on scientific issues that require expertise that is not present in the work group. Also, through professional societies and other private sector organizations, the work groups have fostered discussions and exchanges regarding new and innovative approaches to human health assessment methodologies.

Methods and Guidelines

Both Agency work groups responsible for the development of the health hazard information on IRIS use Agency scientific methods documents and EPA's risk assessment guidelines as the basis for their work. These guidelines and methodologies used to develop the RfD or RfC have been peer reviewed by the SAB.

Summaries of methods used for development of oral RfDs and carcinogenicity information on IRIS are contained in IRIS background documents that are available on the system. A paper copy of the oral RfD and CRAVE background documents, "Reference Dose (RfD); Description and Use in Health Risk Assessment" (*Regulatory Toxicology and Pharmacology* 8:471-486, 1988) and *The U.S. EPA Approach for Assessing the Risks Associated with Chronic Exposures to Carcinogens*, respectively, is also available from IRIS User Support by calling: (513) 569-7254.

The draft methods document, *Interim Methods for Development of Inhalation Concentrations* (EPA/600/8-90/066A), is the basis for the inhalation RfCs. A copy of the document is available from the Center for Environmental Research Information (CERI) by calling: (513) 569-7562. Please cite the EPA document number (EPA/600/8-90/066A) when requesting a copy. A revised RfC methodology document based on SAB peer-review comments will undergo a second SAB review and will be available later this year.

The CRAVE background document is based on EPA's 1986 Guidelines for Carcinogen Risk Assessment (51 FR 33992-34003). A copy of the EPA risk assessment guidelines (EPA/600/8-87/045) is also available by calling CERI.

Public Involvement

The section in the companion FEDERAL REGISTER notice (February 25, 1993, 58 FR 11490) on **Current Opportunities for Public Involvement in the IRIS Process** elaborates on opportunities for public input and dialogue.