September 26, 2000

EPA-SAB-EHC-LTR-00-007

Honorable Carol Browner
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Review of the Draft Report to the Congress "Characterization of Data Uncertainty and Variability in IRIS Assessments, Pre-Pilot vs Pilot/post-Pilot"

Dear Ms. Browner:

The Environmental Health Committee (EHC) of the US EPA Science Advisory Board (SAB) met on August 30, 2000, in Washington, DC. The purpose of the meeting was to fulfill a Congressional directive to review (and to provide advice and comment on) the Agency's study of the Integrated Risk Information System (IRIS).

The IRIS data base contains EPA's consensus scientific position on potential adverse human health effects that may result from chronic exposure to specific chemical substances in the environment. First publically available in 1988, the earliest IRIS assessments provided the results of the EPA deliberations culminating in consensus health hazard conclusions. With the passage of time, the assessments gradually included more detailed data and information on the process leading to the reported conclusions. As a consequence of analyzing the IRIS program and responding to comments received about IRIS, the Agency decided to test some improvements through a Pilot Program. The Pilot primarily addressed the assessment, documentation, peer review, and Agency consensus process that precedes IRIS data base entries. EPA developed (or updated, for existing entries) IRIS assessments for ten Pilot substances. The Pilot process consisted of a) a call for technical information on the eleven substances from the public via a Federal Register Notice [April 2, 1996], b) a search of the current literature, c) development of draft IRIS summaries and support documents, d) internal peer review (i.e., within EPA), e) external peer review (outside EPA), f) a new Agency consensus review process, and management approval, g) preparation of final IRIS summaries and support documents, and h) entry of the assessment into the IRIS data base.

In response to the directive in the October 1999 report from Congress (HR 106-379) regarding EPA's appropriations for FY2000, EPA undertook an evaluation of the documentation of

data variability and uncertainty in IRIS assessments developed before, and after, the Pilot program (The specific language in the Congressional report is provided in Enclosure A).

EPA's Office of Research and Development (ORD) National Center for Environmental Assessment (NCEA) consulted with the SAB Executive Committee (EC) on November 29, 1999, about their proposed approach to this study. At this Consultation, individual Members of the EC provided comments, but, following SAB standard procedures, no consensus report was generated. The proposed approach involved assembling a team of independent, qualified individuals, external to EPA, who would evaluate a representative set of IRIS assessments. One particular comment suggested to ORD/NCEA was that it might maximize the number of assessments reviewed in-depth, by limiting the number of independent reviews per assessment to three. In this way, there would still be a range of opinions, given the experts' range of subject area expertise. The study, as ultimately undertaken, reflected the adoption of this, and other, comment(s) received from various EC Members.

The extent of documentation of variability and uncertainty in IRIS assessments was established in two steps, through a stratified random sampling procedure. The first step was to classify a random 10% sample of pre-Pilot IRIS assessments (52 of 522), and all assessments carried out after1995, into 3 categories of documentation: none/minimal, some/moderate, or extensive.

The second step was to select a random sample of IRIS assessments for an in-depth examination of their treatment of variability and uncertainty. The in-depth review then focused on 16 IRIS assessments, subdivided into 8 from the pre-Pilot assessments and 8 from the assessments developed after 1995 ('Pilot/post-Pilot' assessments). Within these 2 subsets the assessments were randomly selected to represent the some/moderate and extensive documentation categories as evenly as possible. ORD/NCEA arranged for a contractor to select this sub-sample.

ORD/NCEA's contractor assembled and coordinated a set of independent experts to carry out the in-depth review. These experts were selected on the basis of their familiarity with EPA's human health risk assessment methodologies, with IRIS, their knowledge of current practices for evaluating and documenting uncertainty and variability in data used in health assessments, and their expertise in how these factors relate to sensitive subpopulations including children. They represent a range of professional affiliations and of health science backgrounds among cancer and non-cancer toxic endpoints. The experts evaluated the documentation of uncertainty and variability in assessments on the basis of the data available at the time each assessment was conducted, focusing on the presentation of available data and variability in that data, discussion of confidence and uncertainty, including any uncertainty factors applied. The final report comprises the individual and collective findings and conclusions of the six evaluators, as well as ORD's summary and conclusions.

The Charge for this review, and the EHC's findings on each element follow below.

The first of the three elements of the Charge asked the Committee to comment on how well the study conformed to the study plan developed after consulting with the SAB EC.

The Committee agreed that the Agency did a good job implementing the study plan laid out in the July 19 NCEA report (National Center for Environmental Assessment Study Plan. Characterization of Data Uncertainty and Variability in IRIS Assessments. 2000. Pre-Pilot vs. Pilot/Post-Pilot. Post-SAB Consultation and Update. Environmental Protection Agency), in terms of the number of reviewers evaluating each IRIS chemical assessment, randomized process for selection of chemicals, number of chemicals evaluated, selection of reviewers and overall scope of the review. The standardized questions asked of the reviewers and the methodology used to evaluate, summarize and report results were consistent with the NCEA study protocol.

One significant deviation from the NCEA plan was in the number of IRIS substances selected with "extensive" and "some" documentation of uncertainty in the "pre-pilot" and "pilot/post-pilot" groups. The Pilot program reviewed ten IRIS substances in order to test improvements in assessment, documentation, peer review, and the Agency consensus process (EPA, 1996). Considerable effort was taken to describe uncertainty in pilot and subsequent IRIS assessments, and, as a result, all but one of the 15 available "pilot/post-pilot" assessments were found in the internal Agency review to have "extensive" documentation of uncertainty. In contrast, only 3 of the 52 selected "pre-pilot" assessments were found to be in this category. According to the NCEA study plan, the 8 pre-pilot and 8 post-pilot assessments chosen for in-depth review were each to have an equal number with "some" and "extensive" documentation of uncertainty. Since this was not possible, the contractor selected all 3 of the 8 pre-pilot assessments, and 7 of the 8 pilot/post-pilot assessments, from the extensive category. The EHC found this to be a reasonable deviation from study plan.

Although the study conformed to the general guidance laid out in the NCEA plan, the Committee would like to highlight a few points regarding its implementation:

a) **The study's definitions of "variability" and "uncertainty."** Although the definition of "uncertainty" used for the study followed that used by the risk assessment community (National Research Council. 1994. Science and Judgment in Risk Assessment. NRC, Committee on Risk Assessment of Hazardous Air Pollutants, National Academy Press, Washington, DC; National Research Council. 1996. Understanding Risk: Informing Decisions in a Democratic Society. NRC Committee on Risk Characterization, National Academy Press, Washington, DC.), the definition of "variability" did not. In a strict sense, uncertainty refers to lack of knowledge, while variability refers to the changeable nature of reality – for example, with time, space, and the perspectives of individuals. Variability as used in the report was seen to encompass "any aspect of the risk assessment process that can have varying results, including the potential

interpretations of the available data, the availability of data collected under different experimental protocols, and the availability of different models and methods" (NCEA Study Plan). Thus variability, as used by the study, covered both uncertainty and what is traditionally covered by variability. The importance of keeping the two terms distinct when assessing and describing risk has been emphasized in a Congressionally mandated review of EPA risk assessment activities conducted by a National Research Council Committee (National Research Council. 1994. Science and Judgment in Risk Assessment. NRC, Committee on Risk Assessment of Hazardous Air Pollutants, National Academy Press, Washington, DC).

Although the definition of variability used in the study may be seen as overly broad, it may have resulted from an interpretation of the Congressional language calling for an evaluation of the IRIS documentation of "the range of uncertainty and variability of the data."

This issue led some SAB Committee Members to express concern that the study did not fully address what may have been (or, to speculate, perhaps should have been) the underlying concern of Congress. Congress asked about "uncertainty and variability of the data." However, since neither the Congress nor the EPA study plan provided a completely satisfactory definition of those terms, EPA chose to interpret the Congressional request to apply mainly to the information underlying the IRIS values, not to the values themselves. An alternative and more salient interpretation would focus on the extent to which the IRIS documentation provides a) a reasonable description of the intrinsic uncertainty in a given human health risk assessments, and b) an estimate of the extent of variability of human risk. For example, it might be possible to state that the IRIS RfD was thought to be below the individual threshold for adverse health effects for 99.99% of the population, and that an RfD ten times higher was thought to be protective for only 99% of the population.

b) **The study's review of IRIS documentation of human variability in response to exposure to the IRIS substance.** Variability in risk, particularly among individuals, is recognized as an important factor to consider in making decisions about risk (see, e.g., the previous NRC references). The study was not implemented to review adequately IRIS qualitative or quantitative descriptions of interindividual differences in susceptibility. Evaluation of IRIS descriptions of individual susceptibility and variability in risk with different life stages would have been consistent with the study plan.

c) **The representativeness of the sample**. The far greater proportion of pilot/post-pilot substances evaluated over pre-pilot substances was appropriate given the underlying study goals of gauging improvements in uncertainty descriptions in IRIS documents, and identifying examples of "good' assessments.

d) **The guiding questions for reviewers**. Although there were differences in the way each reviewer approached the questions asked, there seemed to be reasonable consistency on general points. Defining some of the general terms and providing structure for the reviewers may have resulted in greater consistency in the reviewers' findings on IRIS treatment of uncertainty. Asking reviewers to grade assessments could have reduced the opportunity for misinterpretation of reviewers findings.

e) **Bias**. The contractor reported that a process was followed to ensure that the reviewers were "free of bias or conflicts of interests" (Versar, Inc. 2000. Characterization of Data Uncertainty and Variability in IRIS Assessments. Pre-Pilot vs. Pilot/Post-Pilot. Prepared for EPA National Center for Environmental Assessment. (p. 11)). Although it is possible to avoid conflict of interest, avoidance of bias is probably not possible. All scientists carry bias due, for example, to discipline, affiliation, and experience. Oftentimes discussions of expert committees are initiated with a bias disclosure and discussion. Fuller disclosure of sources of reviewer bias in this study (e.g., beyond Table 2-1 in the contractor's report) would have provided useful information in interpreting study results. In addition, having more reviews would help to insure the balance.

The second element of the Charge inquired as to the whether the EHC concurred with the findings of the external reviewers concerning selected agents incorporated in the IRIS.

The Committee agreed that the reviewers had followed their mandate and reached overall conclusions that were reasonable. The Committee noted that the findings of reviewers on specific points varied, in several cases considerably, even when the discussions of uncertainty were extensive. This was to be expected. There is not currently any scientific consensus on how uncertainty in risk should be described, and practitioners of risk assessment differ on what constitutes a good and adequate discussion of uncertainty. Still, the Committee concurred with the general conclusion that the description of uncertainty could be significantly improved for most pre-pilot chemicals, and that such descriptions have improved significantly since the initiation of the pilot program. The Committee also agreed with general recommendations for improvement of characterizations of uncertainty and variability (see the recommendations addressed in the third element of the Charge, below). Their comments were by and large insightful, and contained several useful suggestions for improvement.

In summarizing the content of the reviews, it should be noted that the reviewers had a number of positive things to say about the IRIS reports, especially those that have been written since 1995. The Committee concurs with the overall summary from the outside reviewers' report that "There is no question that EPA's years of labor in providing biologically-based, consensus IRIS toxicity values to the scientific community has been of inestimable value, at the very least because the process has been instrumental in clarifying issues and suggesting research needs in the developing field of risk assessment. IRIS is indeed a useful tool for public health risk assessment."

The outside reviewers commended the EPA for the improvement in the characterization of uncertainty and variability. They indicated that more recent (i.e., Pilot/Post-pilot) assessments were "distinctly more comprehensive… and included more description and better discussion of data gaps and end points such as reproductive/developmental or neurological effects, as well as physicochemical information relevant to pharmacokinetics and toxicity and more complete synopses of conclusions for each supporting study (p.36)." They considered the Toxicological Review documents that have accompanied the recent IRIS reports to be valuable in that they have provided a more comprehensive discussion of various aspects of studies that bear on variability and uncertainty than was available for older reports.

The last element of the Charge requested that the Committee comment on what further improvements, if any, might the Agency make in IRIS documentation in response to the study results.

In responding, the Committee noted that the draft report does not come to any overall conclusion about the adequacy of uncertainty and variability information in the IRIS documentation. In the pre-pilot sample, half (12 of 24) of the reviewers' ratings of the treatment of uncertainty and variability were judged "negative." One-third (8) were rated as "positive," and the remainder (4) were rated as "mixed." The Committee believes this indicates the IRIS documentation of uncertainty and variability could be significantly improved for the pre-pilot chemicals. The pilot/post pilot results were only somewhat more encouraging (9, 5, and 10 for positive, mixed, and negative, respectively), although the accompanying text suggested that the reviewers may have judged the pre-pilot IRIS documentation less harshly because it often met the standards prevalent at the time it was prepared.

Even in its present form, IRIS could be strengthened in its characterizations of data uncertainty and variability. Therefore, a greater effort needs to be expended in addressing this important issue. Thus, the Committee recommends that EPA should attempt to improve the IRIS database by including more information on uncertainty and variability in every chemical summary that would have been rated less than extensive by the reviewers. Given limited resources for such a task, priority should be given to chemicals for which controversy over the IRIS evaluations is most acute. An examination of the reasons for discrepancies between the EPA evaluators and the expert peer panel evaluations of the study sample might help in refining the protocol.

To undertake that task most effectively, EPA should first develop a detailed protocol of steps for completing an adequate documentation of uncertainty and variability and then rigorously train the managers of IRIS assessments in that protocol. The protocol should indicate what aspects of uncertainty and variability should, at a minimum, be discussed (e.g., interspecies and intraspecies differences in susceptibility; uncertainties introduced by using predictive models rather than clearly applicable human data). The protocol should also present criteria for deciding whether any meaningful discussion of uncertainty is possible with the available data(e.g., are results in at least two species of

laboratory animals via relevant exposure routes needed to characterize the uncertainties due to interspecies variability?).

The Agency should also develop a strategy for *reducing* uncertainties where these severely compromise the utility of IRIS evaluations. Although it may be beyond the IRIS mandate to recommend the development of entirely new datasets, it may be possible to improve the precision and accuracy of its toxicity numbers by more insightful use of existing information, for example by:

a) Continuing the development of ways to use data-driven uncertainty factors rather than default values

b) Refining methods for examining curvilinearity and/or thresholds in dose-response relationships

c) Integrating information from multiple relevant studies of adequate quality, rather than using only one study as the basis for the toxicity numbers

d) Performing a balanced assessment of known human variability in susceptibility to various classes of chemical compounds, and using the results to improve the discussions of human variability for other chemicals within those classes

More broadly, the Committee recommends that EPA should investigate the feasibility of providing more information that can help answer the underlying question about the uncertainties and variabilities in human health risk assessments based on the IRIS toxicity numbers. One proposal suggested by some reviewers is to characterize the toxicity of chemicals through distributional analyses of toxicity, as well as of exposure, in human health risk assessments. In essence, good environmental policy should be able to answer the questions "How many people might be harmed by current patterns of exposure?," and "What are reasonable limits on this estimate?" Whether the toxicity numbers should be replaced by uncertainty/variability distributions, confidence limits on the point estimates now presented, or simply enhanced by presentation of quantitative or qualitative discussions of uncertainty and variability is not as yet clear.

The request from the Congress indicates that it is driven by "...concern about the accuracy of information in the IRIS data base..." It is recognized both within and outside of the Agency that the major problem with IRIS is that most evaluations are at least 10 years old and that they fail to reflect more recent improvements and Agency practices in risk assessment. The evaluation of the adequacy of the uncertainty and/or variability analysis for representative agents responds to the specific language in the congressional request but it does not fully address the more important quality issue. In order for IRIS to be of greatest value to the Agency, the database must be current, and there should be a mechanism for the IRIS data to be subjected to external scientific and independent peer review and capable of timely and continuous revision. Another criticism of IRIS is that is does not include data for

many of the agents for which information is needed within the Agency offices. The mandate for adding new agents, plus the need to revise the documentation on the current agents, exceeds the resources allocated by the EPA to this task. Because the IRIS database is critical to the Agency and extremely important to outside stakeholders, the Congress should consider allocating resources which are earmarked for this specific purpose. In the interim, the Agency should consider collaborative efforts with outside institutions, such as the National Academy of Sciences to expedite the generation of IRIS files. To facilitate this, EPA could provide Internet as well as the Federal Register listings of the current status of updates and prioritization information.

Many of the pre-pilot IRIS documents provide information on the specific toxicological and/or epidemiological studies that support the IRIS recommendations, whereas most of the post pilot agents have more extensive toxicologic reviews. The reviews cover the issues of ancillary studies, transparency and uncertainty/variability evaluation in more detail and they are scientifically more informative. There is considerable overlap between IRIS toxicology review and the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicology Profiles, the International Agency for Research on Cancer (IARC) cancer documents, the EPA's Acute Exposure Guideline Level program documentation, the documentation for national and international occupational exposure levels, and the World Health Organization and the Organization for European Community Development databases as well as those created and maintained by state governments, environmental groups, industry, and other list generating groups. The IRIS staff should make the best possible use of the IARC, ATSDR, and other documents so as to avoid duplication of effort and make their own reviews easier to conduct, and should also seek to cross-reference these other reviews. In this way, EPA could focus on improving the quality of input data, eliminating redundant compilations of the same data and developing single "gold standard" evaluations for all important compounds. This long term goal may be difficult to achieve. In the near term, efforts should emphasize the development of IRIS documents on chemicals with significant environmental exposures that are not currently on IRIS, or for which the IRIS is believed to be inaccurate, out-of-date, or non-informative.

IRIS could provide an evaluation of the epidemiologic and toxicologic data, and these evaluations could be used by all stakeholders as the basis for their recommendations for regulatory, occupational, or environmental levels. One suggestion to enhance the quality of the toxicologic evaluations is to make the IRIS process open to public stakeholder review in a more formal manner. This could be similar to the process the EPA OPP Special Review and Registration Division and the USDA Office of Pest Management follows for re-registration of pesticides in which an open meeting is held to discuss the risk assessment documents. The purpose of such a meeting is to make sure that key information and data that impact the final risk assessment are available to EPA. Non-profit organizations such as ILSI or Toxicology Excellence for Risk Assessment could be involved in organizing the panels to debate and uncover the range of scientific opinion and critical data that impact the risk assessment. The EPA SAB or NAS/NRC could provide peer review.

The Committee noted also that the quality of the EPA's interpretation of the weight of evidence, and the use of this information to select appropriate uncertainty parameters or quantitative risk assessment approaches, are critical to the success of the IRIS database in aiding regulators and industry in adequately protecting the public. However, these factors are very difficult to measure, and they were not the primary focus of the IRIS study. Instead, the emphasis was on documentation of the scientific evidence supporting the decisions that were made. The IRIS Study is indeed an important step forward in making the process more transparent. SAB agrees with the reviewers that, in general, pilot/post-pilot IRIS assessments were more detailed and provided more chemical-specific information. However, there were several cases in which individual reviewers from the IRIS study as well as SAB Members were aware of critical data that were not included in the IRIS risk assessment discussion. It is not the expectation that every reference associated with the chemical should be cited in order for the IRIS database to be considered complete. It is also understandable that the budget and time constraints make it difficult to thoroughly evaluate the large amount of published data often available on each chemical. However, key studies of high quality that have impact on interpretation of the weight of evidence and risk assessment need to be discussed and considered.

Finally, the Committee noted that the reviewers only occasionally discussed whether or not the IRIS files cited children as a subpopulation that might be more sensitive than the general population, and that the ORD/NCEA summary did not mention this issue at all. This issue is central to whether or not the uncertainty factors assigned for intraspecies (human) variability are sufficient to cover such potential childhood sensitivity. EPA should relatively quickly decide how it will deal with the concern that children might be at greater risk from certain environmental chemicals than adults. Pesticide risk assessments are required by law to include an "extra" uncertainty/safety factor of three to ten-fold whenever there are toxicological concerns or when data on the safety of a pesticide for children are lacking. Some observers believe that a similar factor should be included in every IRIS assessment lacking childhood-specific data, whereas others believe that the current uncertainty factor for intraspecies (human) variability is adequate. The correct answer is undoubtedly chemical-specific, and the Agency needs to decide whether, and if so, how, to modify IRIS toxicity numbers for potential childhood sensitivity.

Although not part of the formal Charge, the Committee wished to comment on several other issues. First, the Committee is of the opinion that the report should be prefaced by some statements that will assist the reader in understanding the IRIS review process, and it should also cite the SAB's report on the extent to which these assessments document the range of uncertainty and the variability of the data.

Lastly, we recommend that EPA establish protocols for the whole IRIS process, not just the uncertainty and variability parts noted above. Having such protocols would contribute to three important goals EPA should work towards:

a) making the total process by which all the available information is integrated to arrive at the toxicity numbers presented in IRIS more transparent, e.g., why certain studies were selected for inclusion over others

b) instituting a standardized approach to determining what information will be considered in the IRIS evaluations (e.g., the inclusion of unpublished studies or studies not fully conforming to good laboratory practice in addition to those that fully meet current criteria)

c) developing a standardized process to determine which agents should be added to the IRIS database, perhaps using some of the following criteria:

1) likelihood that a large population is exposed
2) high likelihood that a large population of children is exposed
3) judgment that the agent is hazardous at low doses
4) judgment that the agent is not being considered by other public health entities
5) pertinent to the agency's overall mission in that significant exposures are likely to occur via environmental routes
6) extant toxicity findings in two or more animal species
7) extant clinical or epidemiology studies of sufficient power and quality showing a trend in toxicity

We appreciate the opportunity to review these issues, and look forward to your response.

Sincerely,

Dr. Morton Lippmann, Interim Chair
Science Advisory Board

Dr. Mark Utell, Chair
Environmental Health Committee
Science Advisory Board

ENCLOSURE A

Report Language from the Senate Appropriations Committee accompanying the EPA budget for FY 2000:

"The Committee is concerned about the accuracy of information contained in the Integrated Risk Information system [IRIS] data base which contains health effects information on more than 500 chemicals. The Committee directs the Agency to consult with the Science Advisory Board (SAB) on the design of a study that will a) examine a representative sample of IRIS health assessments completed before the IRIS Pilot Project, as well as a representative sample of assessments completed under the project and b) assess the extent to which these assessments document the range of uncertainty and variability of the data. The results of that study will be reviewed by the SAB and a copy of the study and the SAB's report on the study sent to the Congress within one year of enactment of this Act."

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Integrated Risk Information System (IRIS) Review
August 30, 2000

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