January 28, 1998

CANCER GUIDELINES IMPLEMENTATION

SETTING PRIORITIES FOR FUTURE ASSESSMENTS OF CHEMICALS/AGENTS

NOTE: This document is a draft written by the Cancer Guidelines Implementation Workgroup, a workgroup created under the auspices of the U.S. Environmental Protection Agency's (EPA's) Science Policy Council (SPC). This draft does not constitute a final position, and is currently being distributed for input/comments on the directions/ideas presented below.

Overview Statement

The Agency is committed to implement its revised Guidelines for Carcinogen Risk Assessment ("Guidelines") through future reassessment and new assessment activities (subsequently referred to as "assessments") once the Guidelines are issued as final. Each of these activities have implications for the Agency's overall assessment agenda and science consensus process. Therefore, a reasonable and consistent process for priority-setting for assessments of chemicals/agents is necessary.

Discussion

The June 25, 1996 *Federal Register* notice (*FR* 61: 32799-32801, 1996) proposed a process for priority-setting for chemicals/agents assessments once the revised Guidelines for Carcinogen Risk Assessment (*FR* 61: 17960-18011, 1996) are finalized. While the Agency wants to reassess all "old" cancer assessments as well as assess all "new" submissions to the Agency, there are very limited resources and time available to undertake such an effort. Additionally, resources for cancer assessments need to be considered in the context of the broader needs for assessment under the Agency's IRIS (Integrated Risk Information System). Ideally, all assessments would address both cancer and non-cancer effects. However, an examination of each case will be needed to ascertain if it is truly valuable to use limited resources to reassess/assess all information. In some instances, it may be even necessary to examine acute and/or subchronic effects as well or by themselves. In addition, a balance between reassessment of "old" chemicals and new chemicals needs to be established. The assessments priority-setting process should be linked closely with Agency program office and regional priorities. Until a reassessment is complete for "old" chemicals, the existing assessment which applied the 1986 Cancer Guidelines will continue to be scientifically acceptable and available as guidance in Agency decision making.

The Agency's intent is to fully implement the new guidance to the extent that the science allows. A reassessment will not be undertaken solely on the basis of a small arithmetic change either on the Agency's initiative or in response to requests from outside the Agency. "Small changes" are defined as the small (2X - 4X) arithmetic changes in slope factors that result from a new scaling factor, ED's (effective doses), or LED's (lower confidence limit of the effective doses). Those who want changes in a risk assessment need to follow the procedures in the final implementation *FR* and may, under those procedures submit a complete reassessment in accord

with the revised Guidelines. The Agency considered the idea of "easy" wholesale changes to the existing assessments (i.e. small changes), but felt that the approach to examine the whole toxicological picture is the best overall approach based on the science. The rationale is made up of several points:

1) One change e.g., in scaling factor, may reduce a risk number; however, another change e.g., due to model parameters, may result in a small increase -- there will be no selective picking and choosing of specific parts of an assessment; one needs to examine the whole assessment.

2) The arithmetic is not the only pertinent change. The revised Guidelines have important changes such as new criteria for selecting which tumor response or other response to model, and accounting for the influence of mode of action -- on which there may be new and better data now than when the old number was developed.

3) In general, it is not appropriate to ignore the fact that data on a chemical may have changed in important respects since the original assessment was done or the number was developed. Therefore, any reassessment needs to be based on an up-to-date body of literature.

While the reassessment may ultimately change based only upon a "small change" (e.g., scaling factor), it is best that the whole toxicological picture is examined and no other changes are found necessary based on the many new facets of guidance found in the revised Guidelines.

Factors to Consider for Prioritizing Chemicals

In fully implementing the revised Guidelines, the Agency proposed in the 1996 *FR* notice a single criterion to initially screen chemicals/agents for reassessments -- "...provide evidence that application of the revised guidelines is likely to *appreciably* (emphasis added) change the existing cancer assessment." After this criterion is met, the Agency would then apply additional priorities to arrive at a ranked listing of chemicals for assessment (degree of public health protection; protecting the maximum number of people including sensitive subgroups; addressing the public interest; addressing multimedia exposure; addressing agents where there is scientific controversy; and addressing the potential to change a regulation). Commentors to the *FR* notice felt that the single criterion was not adequate and "appreciably" was not well defined. In addition, they thought the other criteria (priorities) should be used in the initial selection. Once the chemicals/agents have been selected and assessed based on the new information, commentors were particularly interested in having the assessments summarized in IRIS.

The following criteria have been discussed for the priority-setting process (which is presented here as a one-step process with "two" criteria; this is more in step with the comments from the *FR* notice).

Cancer Implementation Ranking

The Agency has certain regulatory and legal obligations involving cancer risk assessments which must be met from year to year. Therefore, EPA will first address the risk assessment needs for those chemicals that are a part of these obligations. Decisions concerning cancer risk assessment efforts for other chemicals will result from a process that prioritizes the chemical candidates. For those chemicals with existing cancer risk assessments, two broad criteria will be applied to prioritize their reevaluation. These criteria include the analysis of the scientific data using the revised Guidelines and Agency priorities.

1) A determination will be made as to whether the application of the revised Guidelines would appreciably change the existing cancer risk assessment. In general, the Agency will place greater emphasis on those chemicals for which new information addressing scientific uncertainty or controversy has become available. Consistent with the previous discussion, the term "appreciably" is taken to mean more than just a "small change" (e.g., a scaling factor adjustment). Examples of "appreciable" change could include a change in a weight of evidence determination, variations in the cancer risk assessment between route of exposure, or data on mechanism or mode of action that could impact risk estimation up or down.

2) Equally important in prioritizing chemical candidates for reevaluation is whether the cancer risk assessment for a particular chemical meets the Agency's priorities for environmental protection. In determining Agency priorities, office resources will be considered as individual offices will be performing the assessments; during the prioritizing process, specific agents may be a high priority in one office, but less so in another office. Agents that are identified as a priority by more than one office will more likely receive higher priority in the Agency ranking. EPA will also consider priorities from state, local, and community bodies and other stakeholders in the ranking process. In general, higher priority will be given to a chemical if the reevaluation of a cancer risk assessment could affect a regulatory action which results in a significant change in the public health benefit. Similarly, a significant change in the economic benefit will provide a higher priority for reassessment. Furthermore, cases where there are sensitive populations or a large number of people exposed, or multiple sources of exposure (air, food, water or soil) could be considered for a higher Agency priority. In addition, any objectives under the Government Performance and Results Act (GPRA) will be assessed.

As part of the prioritization process, EPA will provide an explanation of the chemical list relative ranking based on the above criteria.

Agency Processes

Responsibility for ensuring the selection and assessment of chemicals must be shared across the Agency. For the reassessment/assessment process to operate realistically, coordinated resources are essential to select the chemicals/agents for reassessment/assessment, conduct or oversee the assessments, insure peer review, facilitate the Agency's internal consensus process, and summarize the assessment for IRIS.

IRIS Process

The Agency is in the process of maintaining the content of its IRIS system, a data base of Agency consensus positions on the chronic human health effects of chemicals/agents found in the environment. Maintenance of IRIS entails assessing and reassessing both cancer and noncancer health effects of agents, summarizing those assessments, and obtaining Agency consensus before loading onto IRIS. It should be noted that the IRIS program utilizes standard formats for assessment summaries and support documents ("Toxicological Reviews") and generally requires that all cancer and noncancer endpoints be addressed. It is therefore recommended that cancer reassessments undertaken under the revised Guidelines be developed in a manner consistent with IRIS if there is an intent to submit the assessment for IRIS candidacy at some later date.

Many of the assessments currently on IRIS need updating to incorporate new scientific information and methodologies; many additional substances are candidates for adding to IRIS. However, due to limited resources in the Agency to address the spectrum of needs, EPA compiles an annual list of priority agents from its Program Offices and Regional Offices. This compilation forms the basis for determining which completed assessments or assessments in progress should be summarized and entered into consensus review for IRIS. The compilation also forms the basis for determining which new assessments to begin. For example, the IRIS agenda for FY 1998 is published in the *Federal Register* (*FR* 63: 75-77, 1998) and lists assessments in progress that will be completed in FY 1998, and new assessments that will be completed between late FY 1998 and early FY 2000.

The IRIS process interfaces with the revised Guidelines implementation process in two ways (see the Cancer Guidelines Implementation Process described below).

1) EPA's annual internal call for Office/Region IRIS priorities in July of each year will also ask specifically for cancer reassessment priorities (Step 1 of the Cancer Guidelines Implementation Process). The replies will form the basis for assembling the IRIS agenda for the coming fiscal year (i.e., the July 1998 call will form the basis for determining IRIS work to begin in October 1998) as well as the basis for the Agency's discretionary candidate list for cancer reassessments to begin a year hence, following public comment and peer review (e.g., the July 1998 internal call would also ask for candidates for cancer reassessment work to begin in July 1999 -- the actual dates will depend upon the date the candidate selection process is

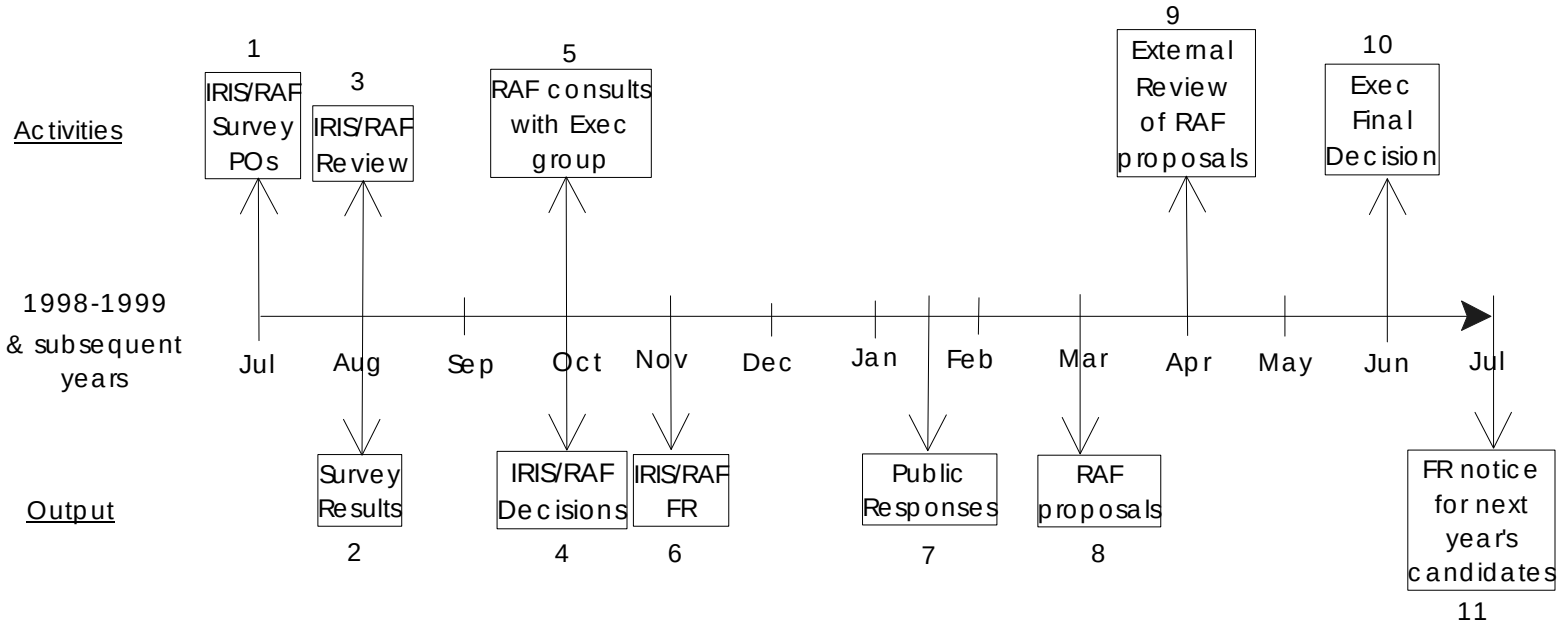
finalized).

2) The reassessments ultimately undertaken under the revised Guidelines may be candidates for the IRIS priority process for the coming fiscal years (i.e., agents selected under the cancer guidelines implementation process by July 1999 could be candidates for the IRIS agenda beginning in October 1999 or October 2000 -- again, actual dates depend upon the date the candidate selection process is finalized). This allows the products of the cancer guideline selection process to feed into the larger universe and work flow of the IRIS program.

Cancer Guidelines Implementation Process (CGIP)

The 1996 *FR* notice of the CGIP proposed publishing a list of Agency selected chemicals and call for additional candidates in the fourth quarter of each fiscal year. This step is now taking place in the first quarter of the fiscal year (Step 6 in Figure 1). As described above, the IRIS process has also been incorporated into the CGIP where appropriate.

Figure 1: Reassessment time line: Starting in FY99 (1998-1999)



Projected Time Line of Reassessment Process

Process begins in July of each year and description below begins in July of calendar year 1 (Y1) and continues to July of calendar year 2 (Y2). Step numbers below correspond to Box numbers in Figure 1.

Jul/Y1 1) Start IRIS/Agency's Risk Assessment Forum (RAF) identification of Agency candidates
- a) IRIS/RAF survey offices/regions to determine their priorities for reassessment (new data, new agenda, new issue)

Aug/Y1 2) Survey results come in

3) IRIS/RAF review of survey results
- a) RAF subgroup focuses on scientific aspects, i.e. new data; reevaluations based on new scientific considerations, e.g. route specific information, mode of action reconsideration
- b) IRIS central unit identify updates, maintenance items, reassessment priorities for IRIS database
- c) Synthesis of last year's non-selected candidates and this year's survey results into one list

Oct/Y1 4) IRIS/RAF decisions on recommended lists of chemicals, including:
- a) IRIS "must do" list (subsequently designated as "IRIS list"), including chemicals legally and/or legislatively mandated, already in queue for assessment, and already being assessed
- b) The rest of the candidates that are offered for public consideration during the open period calling for public candidates -- in step 6 below (subsequently designated as "discretionary list")

5) IRIS/RAF consults with Executive Oversight Group
- a) Executive Oversight Group (composed of senior Agency program managers) meets to bring in program and management priorities to reshape candidate lists; considering GPRA objectives
- b) Begin determination of potential resources from the program offices, Office of Research and Development (ORD), and IRIS central unit to address candidates for reassessment; this also provides a preliminary commitment by the offices, ORD and IRIS central unit to perform the reassessments
- c) Executive Oversight Group then makes final determination on both the IRIS list and discretionary list for publication in an *FR* notice
- d) Help finalize the *FR* notice

Nov/Y1 6) IRIS/RAF *FR* notice

a) *FR* notice announces Agency final decisions on the IRIS list, and requests public comments and/or new proposals for any candidates on the discretionary list; both of these lists will be presented with the rationale for their selection. Note: In the very first year of this implementation process, a 90 day open period for commentators to respond will be provided; in subsequent years, since the process will be known to all, the open period will be 30 days

b) The Agency's IRIS list of chemicals is announced, with the IRIS agenda, similar to the announcement in FY 1998 (*FR* 63: 75-77, 1998) which listed assessments in progress that will be completed in FY 1998, and new assessments that will be completed between late FY 1998 and early FY 2000

c) Establish clearly that any new proposed public candidates (subsequently referred to as the "public list") to be considered with the agency discretionary list need to use the same ranking criteria as Agency used to identify the Agency discretionary candidates

d) A public administrative record will be established for notices and comments; RAF staff to have record oversight

Mid-Jan/Y2 7) Public Responses -- RAF consider and incorporate public responses

Mar/Y2 8) RAF proposals of revised list of chemicals, mainly pooling the discretionary list with the public list into a single revised "proposed RAF list", including all chemicals from these two lists ranked by the established criteria

Apr/Y2 9) External review of RAF proposals

a) As judged by the selection criteria, a single ranked list is proposed by combining the Agency discretionary list with the proposed public candidates. This combined "proposed RAF list" does not include the IRIS list

b) Agency presents the proposed RAF list for External review; the External review group will provide recommendations for the rankings in the combined "proposed RAF list"; the IRIS list will also be presented to the External review group as FYI only

c) The RAF takes the recommendations of the review and develops one ranked "RAF consensus list"

Jun/Y2 10) RAF presents the resulting RAF consensus list (from the External review group) to the Executive Oversight Group; Executive Oversight Group provides final approval of selections and commits resources for upcoming year

a) A recommendation for a final ranked RAF consensus list (from

External review group) is provided to the Executive Oversight Group

b) The Executive Oversight Group endorses (or changes and endorses) the final list for reassessments and resources are committed to the reassessments to be performed

c) As many reassessments as resources allow will be committed to

d) After approval, need to put commitment into the operating plan and have the Deputy Administrator endorse this on a yearly basis

Jul/Y2 11) Issue *FR* notice

a) *FR* notice announces selected candidates and resources commitment from Program Offices

b) Explains selections

c) Need to explain that all assessments will not neatly be finished within a one year time frame and that some assessments will be multiple year commitments

d) Also, explain why remaining candidates from RAF consensus list are not selected

Restart at 1) Restart yearly cycle of prioritization of chemicals, with remaining candidates from step 11-d) included at start of cycle

Summary of the various lists:

IRIS list:	list of Agency "must do" chemicals
Discretionary list:	list of proposed Agency candidates beyond the IRIS list
Public list:	list of candidates proposed by the public
RAF proposed list:	combined list of discretionary and public candidates
RAF consensus list:	ranked RAF list after peer review