

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS'
BIENNIAL REPORT ON CARCINOGENS SUBCOMMITTEE

May 8, 1996

Summary Minutes

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**SUMMARY MINUTES
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MEETING**

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The National Toxicology Program (NTP) Board of Scientific Counselors' Biennial Report on Carcinogens Subcommittee (the Subcommittee) held its first meeting on May 8, 1996, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (Attachment 1: *Federal Register* meeting announcement; Attachment 2: Agenda and Roster of Members.) Members of the Subcommittee are Drs. Arnold Brown (Chairman), Eula Bingham, Thomas Goldsworthy, Carol Henry, David Hoel, Robert LeBoeuf, Franklin Mirer, Louise Ryan, Frederick Tyson, and Jerrold Ward. Expert Consultant to the Subcommittee is Dr. Hiroshi Yamasaki. All were present except Dr. Hoel.

I. Introduction and Welcome: Dr. Kenneth Olden, Director, NTP and NIEHS, welcomed the Chairman and new Members to this very first meeting of the new subcommittee. He stated that there were four important attributes that the NTP should have. First, was **credibility**. He said the Program has achieved that as exemplified by the thorough, open, and objective process followed in the review of the *Biennial Report on Carcinogens* (BRC). Second, was **leadership**. He commented that the leaders in the NTP are not just passive bystanders but rather are active participants in public health issues. The third was **partnership**. Dr. Olden cited the NTP's interactions with industry, academia, and other groups, most recently in the initiative to develop and validate transgenic animal models for carcinogenicity and toxicity testing. And, the fourth was **change**. He referred to the Advisory Review by the Board in 1992 in which they recommended more extensive use of mechanistic studies, and noted that the NTP was doing this. Dr. Olden concluded by thanking the members of the Subcommittee for their hard work and good advice during the BRC criteria review process that resulted in an excellent document having been sent to the Secretary.

II. Report of the Director, Environmental Toxicology Program (ETP), NIEHS: Dr. George Lucier, Director, ETP, said that when Dr. Olden requested in 1994 a thorough review of all activities related to development of the BRC, our objectives were three-fold: (1) to broaden input into the report at all stages; (2) to strengthen the scientific review regarding listing or delisting a chemical; and (3) to review and possibly revise the criteria for listing or delisting. The criteria review was initiated with the convening in April 1995 of an *Ad Hoc* Working Group of the Board chaired by Dr. Brown which examined whether the criteria should be changed and how, and whether mechanistic considerations should be incorporated into the process. This resulted in proposed revised criteria pending approval by the Secretary that are relatively simple but flexible enough to allow use of all relevant information. Dr. Lucier opined that the revised criteria would increase the need for expert judgment, provision of which would be a role of the Subcommittee. He said that as with the Technical Reports Review Subcommittee, we would actively seek to provide and receive information from the public and sought advice from the Subcommittee as to how to increase public involvement. Since this was a new subcommittee, Dr. Lucier said he would like to give some background on the NTP as framework for the Subcommittees' work. He reviewed the overall NTP goals: - to provide toxicological evaluation on substances of public health

concern, - to develop and validate improved methods that are more sensitive, specific, and faster, - to develop approaches and generate data to strengthen the science base for risk assessments, and - to communicate with all stakeholders. Dr. Lucier spoke of the contributing agencies of the NTP, and described the oversight and review process for the Program with the interagency Executive Committee providing policy oversight and the Board of Scientific Counselors providing scientific oversight. He reported that NTP-related research funded by the NIEHS was allocated as 66% to contracts, 24% to intramural research, and 10% to grants. Dr. Lucier commented that under a recent restructuring of the overall intramural program there were three areas of excellence developed, these being the Environmental Biology Program, the Environmental Diseases and Medicine Program, and the Environmental Toxicology Program (ETP), which provides about 80% of the staff and resources for the NIEHS contribution to the NTP. Using a flow chart, he described the various office and laboratories within the ETP, as well as the various faculties and committees that facilitate coordination and collaboration among the three programs of the Division of Intramural Research. Dr. Lucier concluded by discussing the NTP priorities in 1996, including broadening input into the chemical nomination and selection process, increasing use of mechanism-based toxicology, enhancing NIEHS/NTP integration, refining dose-response models particularly in the low dose range, integrating animal data with findings from human studies supported or managed by the NIEHS, reviewing experimental design and data review strategies, continuing our extensive activity in development and validation of alternative methods, improving the BRC, continuing and expanding research partnerships, and continuing to enhance communications with our many publics.

Dr. Lucier, in Dr. Olden's stead, presented certificates and acknowledged the contributions of retiring members of the Subcommittee: Dr. Brown, Dr. Ryan and Dr. Ward. Besides his service as the first Chair of the Subcommittee and Chair of the *Ad Hoc* Working Group for the BRC, Dr. Brown has served as the Chair of the Technical Reports Review Subcommittee. Dr. Ryan and Dr. Ward have served on the Technical Reports Review Subcommittee as well.

III. Report on the Background History of the *Biennial Report on Carcinogens* (BRC): Dr. Bill Jameson, NIEHS, said a purpose of this first meeting of the Subcommittee was to foster an open discussion between the NTP and the members that would provide input from the Subcommittee on the process of conducting reviews based on the proposed revised criteria. He said the *Annual Report on Carcinogens* (ARC) (the predecessor of the BRC) derived from a Public Health Service Act in 1978 that stipulated that the Secretary DHHS publish an Annual Report which contains: "A list of substances (i) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens, and (ii) to which a significant number of persons residing in the United States are exposed." Dr. Jameson briefly discussed the seven Reports published to date starting with the first ARC in 1980 and ending with the seventh ARC published in 1994, and read the criteria used in selecting substances or industrial processes for inclusion in these first seven Reports. The primary sources of information on the chemicals or processes listed in the first seven Reports were the International Agency for Research on Cancer (IARC) monographs and NTP bioassays, and to a lesser degree the peer-reviewed literature. He said the ARC was geared to identify hazard and alert the public to possible risk but never was considered to constitute a risk assessment. Among early reviews of the process for the preparation of the Reports was a review in 1985 of the 4th ARC by an interagency committee chaired by the Assistant Secretary for Health. This Committee recommended

more opportunity for public input in the process. The NTP held a public meeting in 1987 to discuss the ARC process. Among the major points discussed at this meeting was that the process needed to be more open. As a result the Assistant Secretary chaired a review in 1988 of the process and the selection criteria for the upcoming 5th ARC. Their recommendations included one that the criteria should be reviewed periodically. Dr. Jameson noted controversies had delayed previous ARC publications with one being an actual litigation attempting to prevent listing of *p*-dichlorobenzene in the 5th ARC. In 1993, a petition was filed to delay listing of glasswool in the 7th ARC. In 1994, Dr. Olden asked Dr. Carl Barrett to chair an *ad hoc* committee of NIEHS scientists to examine how the BRC was prepared and make recommendations as to whether and how the process might be improved, considering who should conduct the evaluation for listing, how input from outside sources could be insured, whether there was a need for future review of the criteria and by whom, and what should be the review process for the BRC. Following a presentation by Dr. Barrett about his committee's review, the NTP Board, on April 6, 1994, passed the following resolution: "A new subcommittee of the NTP Board should be created to review the *Biennial Report on Carcinogens*. This subcommittee should include selected members of the NTP Board, *ad hoc* reviewers, and liaison members from the NIEHS and other agencies. A support contract for bibliographic services and draft preparations of nominations is needed. The new subcommittee should begin by convening a working group to review the criteria for listing in the BRC. The NTP Board should approve the work of the subcommittee." Dr. Jameson then went over the new review process for listing and delisting substances in the BRC instituted following the Board's action. This process is as follows: after receipt of a petition of a chemical for listing or delisting, public input is solicited and there is further information gathered, if needed, and a draft summary document containing all relevant information is prepared. The NIEHS Review Group (RG1), comprised of NIEHS scientists, reviews the petition and makes a recommendation. The NTP Executive Committee BRC Review Group (RG2), comprised of members from each of the Executive Committee agencies, then reviews the petition and makes a recommendation. Finally, the NTP Board BRC Subcommittee (RG3) reviews the petition in an open public meeting and makes a recommendation. The separate recommendations of the three groups are presented to the Executive Committee for review and their recommendation is given to Dr. Olden. Dr. Jameson said the objectives for revisions in the selection process for listing were (1) to broaden the input at all stages throughout the process, (2) to broaden the scope of scientific review, and (3) to provide a review of the criteria used for inclusion of substances in the BRC.

Dr. Jameson moved to a discussion of the criteria review process. This began with convening of an *Ad Hoc* Working Group of the Board on April 24-25, 1995, in public session in Washington, D.C. Besides NTP Board members, the Working Group had a diverse composition of representatives from academia, industry, labor, public/environmental organizations, State and local health departments, international experts on carcinogenesis, and NTP Executive Committee agencies. The format included having plenary sessions at beginning and end of the meeting while in between, three breakout groups dealt with the issues to be addressed. The issues were (1) the adequacy of existing criteria for listing substances in future Reports, and (2) the incorporation of mechanistic data as part of the criteria for listing substances in future Reports which may include the consideration of sensitive sub-populations as well as procedures to upgrade or downgrade the evaluation of the results of animal bioassay or epidemiology studies. The products

sought were to define the areas of consensus, the areas of debate over the criteria, and the knowledge gaps that create this debate. Public comments were received and ranged from - 'current criteria should be retained with no changes', to -- 'there should be minor revision of existing criteria to incorporate mechanistic information', or 'there should be major revision of existing criteria to incorporate all available mechanistic data'. In the breakout groups, the main discussion concerned the degree of prescription. A majority of the members of the *ad hoc* Working Group thought the criteria: (1) should be revised, (2) should include mechanistic information, (3) should not be overly prescriptive, (4) should not add additional categories, and (5) should not substitute for expert judgment. Based on the recommendations of the *ad hoc* Working Group, the NTP drafted proposed revised criteria for the BRC and presented them to the NTP Board at its meeting on June 29, 1995. The Board passed several resolutions at this meeting, which included: (1) the current criteria should be revised, (2) mechanistic information should be used, (3) the number of categories should remain the same, (4) there should be a formal mechanism for delisting, (5) the proposed explanatory paragraph should be revised, and (6) they are aware that incorporation of mechanisms will require an expansion of resources. Dr. Jameson reported that the Board's recommendations and comments were incorporated into the proposed revised criteria and were subsequently reviewed by the NTP Executive Committee Working Group (RG2), the PHS' Environmental Health Policy Committee, and several times by the NTP Executive Committee, the last time being January 26, 1996. The comments and recommendations from these reviews were incorporated into the proposed revised criteria and a report of the criteria review and the final recommendations for the BRC criteria for listing and delisting of substances were submitted to the Secretary in February 1996.

Dr. Jameson proceeded to compare the existing BRC criteria with the final proposed revised criteria. He pointed out modest revisions to category 1, these being to add clarifying words (**shown in bold face**) as follows: "1. Known To Be **Human** Carcinogens: There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between **exposure to the agent, substance or mixture** and human cancer." With regard to category 2 ("Reasonably Anticipated To Be **Human** Carcinogens"), in 2.a., there were no changes between current and revised criteria, except to remove the 'a.' reflecting Executive Committee discussion that 'a' and 'b' inferred a ranking. Thus, with regard to category 2.b., the 'b' was removed. A number of changes in this subcategory were made by the Board and the Executive Committee. Word, phrases, or sentences removed are underlined in the existing criteria as follows: "There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure. In the proposed revised BRC criteria, wording added is shown in **bold face**: "There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant **and/or combined benign and malignant** tumors: (a) in multiple species **or at multiple tissue sites, or (b) by multiple routes or exposures, or** (c) to an unusual degree with regard to incidence,

site or type of tumor, or age at onset; **or**". Dr. Jameson reported that a third paragraph or subcategory was added to cover agents supported with mechanistic data as follows: **There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous *Annual or Biennial Report on Carcinogens* as either a known to be human carcinogen, or reasonably anticipated to be a human carcinogen or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans."** Dr. Jameson then read a final paragraph which applies to all the criteria and discusses the role of scientific judgment, and other relevant information: **"Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose-response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore reasonably be anticipated not to cause cancer in humans."**

Discussion: In a general comment, Dr. Henry said she saw the Subcommittee as a vehicle for public comments. Dr. Lucier agreed but added that there were other means for this including public announcements of petitions and requests for public comment in the *Federal Register* and the NTP Liaison Office newsletter.

IV. Presentation and Discussion of the Process for Listing or Delisting Substances in the BRC: Dr. Jameson said that when petitions of chemicals for listing or delisting are received, there is an information gathering phase followed by preparation of a draft summary document. The petition is first reviewed by the NIEHS Review Group (RG1), then by the NTP Executive Committee BRC Review Group (RG2), next by the NTP Board's BRC Subcommittee (RG3), and finally by the NTP Executive Committee. He then took the Subcommittee step-by-step through the process from receipt of petitions to submission to the Secretary. Petitions: Petitions are submitted to the NTP and must contain a rationale for listing or delisting, and should contain appropriate background information and relevant data. Action Taken Upon Receipt of a Petition: The receipt will be announced in the *Federal Register* and other media and comments solicited. An initial discussion of the petition and any public comments will be conducted by RG1 and a decision made that the petition merits formal consideration or does not merit formal consideration. If the latter, a public announcement of this action is made, the petitioner is informed and given the opportunity to add information and resubmit. If the petition is determined to merit formal consideration, a Draft Summary Document will be prepared. Draft Document Format: Included will be all or some of the following -- 1.0 - Introduction, 2.0 - Exposure Assessment, 3.0 - Human Studies, 4.0 - Animal Carcinogenicity Studies, 5.0 - Genotoxicity, and 6.0 - Mechanistic and Other Relevant Studies. In discussion, Dr. Bingham opined that Exposure Assessment implies risk assessment and suggested retitling this section as 'Potential Human Exposure'. Dr. Jameson agreed. There was some concern expressed by members that the document received by them contain economic and other nonscientific information to give perspective from a standpoint of possible public health significance. Review of Petitions by RG1: Primary and secondary reviewers are assigned, there is an

initial consideration of the petition and any public comments followed by search of pertinent data bases leading to preparation of the draft summary document. The RG1 formally considers the petition and makes recommendations, which are either to go forward or not go forward with the petition. In discussion, Dr. Mirer stated that the petitioner for a petition rejected by RG1 for further consideration should have the option of insisting it go forward anyway. Dr. Jameson noted that the NTP has to notify RG2, RG3, the Executive Committee, and the Board of such a recommendation, and any of these groups may request that the rejected petition go forward in the process. Review of Petitions by RG2: Upon receipt of a petition, a primary reviewer is assigned who leads consideration of the petition and supporting information concluding with a formal recommendation by RG2. Public Notification of RG1 and RG2 Action on Petition: The recommendations are published in the *Federal Register* and other media and public comment is solicited. As well, announcement also is made of an open public meeting of RG3 to consider the petition and receive public input. Draft Procedures for Review of Petitions by the BRC Subcommittee (RG3): Although to be determined by the Subcommittee, this step could involve assignment of primary and secondary reviewers, formal consideration of the petition and all public comments, and a recommendation. Public Notification Action on Petition: Following RG3 action, their recommendations are published in the *Federal Register* and elsewhere and solicitation made of final public comments. NTP Executive Committee's Review of Petitions: Independent recommendations of RG1, RG2, and RG3 and all public comments on the petition are presented for review and recommendation. Final Action on Petitions: Based on the independent recommendations from the four groups, the Director, NTP, makes the final decision to submit the BRC (petitions) to the Office of the Secretary, DHHS, with a recommendation to forward the Report to Congress. Upon review and approval of the BRC by the Secretary and submission of the Report to Congress, a final public notification, indicating all newly listed or delisted substances, will be published in appropriate publications.

Discussion: Dr. Brown set the tone by noting that the Subcommittee's task today was to determine how they would conduct their part of the review process. Dr. Mirer said the likely review process by the Subcommittee seemed to be analogous to that for the Technical Reports Review Subcommittee. Dr. LeBoeuf commented that unlike the review of bioassay reports where the criteria are clear-cut, the criteria here are not and this leads to a more judgmental process for the reviewers. Dr. Lucier agreed that the processes were similar but with the use of mechanistic data expert judgment comes more into play than with the Technical Reports. Dr. Bingham saw the role of the Subcommittee as being larger than that of RG1 or RG2 in that this was the only avenue for public comment. She asked for a definition of what constitutes 'public comment'. Dr. Lucier replied that this could cover a spectrum from opinions to peer reviewed papers and it was the Subcommittee's role to evaluate the credibility. Dr. Brown stated that it would be preferable that public comments be received in writing prior to the meeting. Finally, there was a consensus expressed among the Subcommittee members that something akin to 'external peer review' was preferable to the RG3 designation.

V. Report from the NIEHS/NTP BRC Review Group (Review Group 1): Dr. John Bucher, NIEHS, listed the members of Review Group 1 (RG1) along with their expertise and noting that Dr. Jameson is Chair. He said the intent is to add an epidemiologist as well as *ad hoc* primary reviewers when needed; these could be the study scientist for a chemical on which the Technical Report of an NTP bioassay was supporting evidence. Dr. Bucher said the

RG1's work could be divided into early, intermediate, and later functions. Initially, petitions for listing or delisting would be received along with public comments that had been solicited and primary and secondary reviewers would be assigned. The NIEHS petitions would be formulated drawing on NTP Technical Reports, IARC documents, the literature and other sources. The primary and secondary reviewers then would be responsible for determining the adequacy of the petitions and rationale for listing as "known" or "reasonably anticipated", and bringing their recommendations to a meeting of the full RG1. At this point, if the petition is accepted, a literature survey will be undertaken. If the petition is deemed to be of merit but unsupported, a literature search may be initiated to fill in the gaps. If the petition is considered unjustified or frivolous, it will be returned to the petitioner with a reason for the decision and/or request for more information. Dr. Bucher said these intermediate functions are very critical. Next, in concert with a support contractor, the reviewers determine a literature search strategy and review the selection of papers to aid them in putting together an annotated bibliography. The review group evaluates the bibliography and papers as needed to assist the support contractor in orientation of the draft BRC text. The text is reviewed and modified by the reviewers and along with public comments is presented to the full RG1 for debate, following which the text is revised reflecting the debate and serves as a working document. to send on to the RG2. Dr. Bucher said we would like to streamline the final BRC document. Full documentation for inclusion of a substance in the Report and a description of the literature search would be provided to RG2 and subsequent review groups. The types of mechanistic information examined would be listed and the thinking associated with acceptance or rejection of mechanistic data as influencing the decision to list or delist would be described, and brief descriptions of this would be included in the BRC. The later functions of RG1 are to (1) forward the draft BRC report text, documentation and recommendation to list or delist to the NTP Executive Committee Working Group for the BRC (RG2), (2) forward decisions to deny petitions along with all documentation to RG2 and the NTP Board's BRC Subcommittee, and (3) publish lists of petitions that were not accepted for listing or delisting in the *Federal Register*, the NTP Newsletter, trade journals and in subsequent editions of the BRC. Dr. Mirer asked whether the NTP would revisit previously listed chemicals in light of the revised criteria. Dr. Bucher said this would be done only in response to a petition.

VI. Report from the NTP Executive Committee Working Group for the BRC (Review Group 2): Dr. Marilyn Wind, CPSC, a Member of RG2, outlined the listing of members who represent the regulatory and research agencies on the NTP Executive Committee. She said she would discuss how RG2 has operated and how she sees its role in the future. The Working Group serves two purposes and she saw this continuing. Once chemicals have been identified as candidates for listing by RG1, the Working Group members play an active role in exposure assessment. Second, the members are asked to search their individual agency databases for any information on the chemical, and further to determine whether there are any regulations pertaining to the chemical. An ongoing role of the members is to assess what measures have been taken to reduce exposure to a chemical, information that can be incorporated in a subsequent volume of the BRC. Prior to a Working Group meeting, a primary reviewer is assigned. At the meeting, the reviewer presents the chemical and a rationale for listing or not listing which is voted on by the members present. In the case of a high volume chemical for which there was considerable outside interest, the Working Group might meet more than once. A final report with recommendations was then submitted to the Executive Committee for action. Dr. Wind did not see the process changing much other than the addition of the new review group. Based

on previous listings in the ARCs, there are only about 2% that are controversial. She said that while examination of mechanistic information was not precluded in the past, more emphasis will be given to seeking and evaluating such information in the future.

Discussion: In view of the increased emphasis on mechanistic information, Dr. LeBoeuf wondered whether the NTP Executive Committee Working Group would need supplementary expertise. Dr. Wind thought there was sufficient expertise among the membership. Additionally, the Working Group benefits from the expertise of RG1 members in the documents sent to them by RG1. Dr. Goldsworthy predicted the number of controversial petitions would increase. Dr. William Eastin, NIEHS, noted that RG2 members have the option of drawing on expertise within their own agencies and this can be quite valuable. Dr. Mirer commented on the lack of clinical/human studies expertise on RG1. Dr. Bucher responded that the intent is to add an epidemiologist.

VII. Discussion of the BRC Process by the Subcommittee: Dr. Brown proposed that there be a primary and secondary reviewer from the Subcommittee for each chemical and they would evaluate the available information and give their recommendations on the conclusions. There seemed to be a consensus for this approach. Dr. Mirer asked that the group be provided a generic listing of key parts of the nomination package that the NTP wanted feedback on. Dr. Bucher agreed. Dr. Henry expressed concerns as to whether there was adequate expertise among the members. Dr. Ryan inquired whether one could draw on the expertise of colleagues. Dr. Bucher agreed noting that the staff had considered providing *ad hoc* experts when needed. Dr. Brown suggested that the Subcommittee be willing to listen to a summary from the staff for each petition, perhaps analogous to the presentation by the study scientist at report review meetings. There was some discussion as to whether the staff presenter should be the primary reviewer of the petition from RG1 or RG2, or rather, a staff person involved in the BRC process. Dr. Mirer argued for the former. Drs. Goldsworthy and LeBoeuf stated it would be helpful to have a primary reviewer from RG1 or RG2 present as a resource person. Dr. Bucher commented that a principal reviewer from RG1 or RG2 usually would not have a depth of expertise concerning a chemical analogous to that of a study scientist presenting a bioassay report. Dr. LeBoeuf said this person could be an *ad hoc* expert. Dr. Brown asked for input on how far ahead of the meeting was the review package needed by the members. Dr. Henry opined that the package should be received no later than one month before the meeting. Dr. Bingham said that the amount of time needed by a reviewer will in part depend on the mix of data available for a petition, e.g., if primarily mechanistic type data, this may be more difficult to evaluate than standard bioassay data. Also, if there was disagreement between RG1 and RG2 that could add an element of difficulty. Dr. Wind commented that the data summary prepared for chemicals being considered for selection by the NTP would be a good model. Dr. Brown concluded that there may need to be some changes in the process after the first review meeting of the Subcommittee but for now there seemed to be agreement that receipt by the members of the data package a month in advance of the meeting was a good starting point.

VIII. Presentation of Select Chemicals Proposed for Upcoming BRCs to Compare Application of Proposed Revised Criteria with Previous Selection Criteria and Discussion by the Subcommittee of BRC Review Responsibilities: Dr. Jameson said that he would display the data derived from a literature search on three chemicals previously approved for listing in the 8th or 9th BRC to provide some idea of the amount of literature and other data that the reviewers might have to deal with. He described the search strategy which was to

begin with examination of recent review articles and very recent primary journal papers. In addition, strategy formulation and selection for retrieval will be done in conjunction with advisors from RG1. Ordinarily, if an IARC monograph or another authoritative review has been published, literature searches will be generally restricted from the year before publication to the current year. Citations obtained will be used by the RG1 reviewers in preparation of the draft document. Dr. Jameson asked for Subcommittee feedback and alternative suggestions. Dr. Bingham cautioned that some of these searches don't go back very far in time and there was a danger of overlooking pertinent older literature. Dr. Jameson said there were about 21-22 databases used and of these the five or six most productive were searched first.

Dr. Jameson then turned to a discussion of the draft document format which he had outlined earlier in the meeting. He said the data for these categories should come from publicly available peer-reviewed literature. Dr. LeBoeuf said he could be comfortable using data coming into a regulatory agency even though it might not be peer reviewed. Dr. Ward said this could open the door to all kinds of non-peer reviewed studies, e.g., carcinogenicity studies by industry that are never published in the literature. Dr. Brown asked for a definition of peer review. Dr. Jameson responded that NTP would consider IARC Monographs, NTP Technical Reports, and articles in peer reviewed journals including those in press to fulfill the requirement for peer review. Proceedings published in peer reviewed journals, such as *Environmental Health Perspectives* Supplements would be acceptable. Dr. Henry thought excluding data submitted to and accepted by a regulatory agency would restrict which chemicals could be considered. Dr. Goldsworthy said the NTP should stick with peer reviewed data, and work with others to encourage industry to publish their data. Dr. Bucher said an alternative source of data that RG1 will accept is industry data that has not been published in the peer reviewed literature but which the company has had peer reviewed by qualified reviewers from academia and elsewhere, and is willing to make publicly available. Dr. Henry suggested that review criteria acceptable to RG1 in their evaluations be acceptable to the BRC Subcommittee. Dr. Brown summarized the discussion by stating that the Subcommittee would consider data acceptable that was peer reviewed in the conventional sense, and publicly available, as well as data not peer reviewed in the conventional sense as described by Dr. Bucher. RG1 serves as the initial review group and data they consider acceptable would be acceptable to the Subcommittee. Further, there was consensus that members must have the data package at least one month prior to the review meeting. Dr. LeBoeuf asked for clarification again as to whether data submitted and accepted in the regulatory review process but not published could be considered. Dr. Brown said that it could but doesn't have to be used.

Dr. Jameson returned to the two preliminary draft reports for furan and o-nitroanisole that had been included in the Subcommittee package. He asked whether the data tables, including carcinogenicity and genetic toxicity, were helpful. There seemed to be general agreement that the tables were helpful. Dr. Bingham asked that synonyms for chemical names and structural formulas be added. Dr. Jameson said the NTP would like input on the format for the BRC itself, as the staff doesn't think it to be very 'user friendly'. Dr. Bucher commented that future volumes would better explain the rationale for listing and the category chosen. Dr. Mirer requested that new entries be highlighted in some fashion. Dr. Bucher agreed, particularly since new entries henceforth will have been judged by the revised criteria. Dr. Jameson next spoke to an issue that he had referred to earlier having to do with inclusion in the Introduction of the 7th ARC of 10 manufacturing processes, occupations, or mixtures of chemicals. These entries had been included in the regular

listings as 'Known to be Human Carcinogens' until the 5th ARC when they were placed in the Introduction for unclear reasons. He stated that the NTP proposes to bring them back to all three review groups with the intent of returning the 10 entries to the regular listings. Dr. Jameson said we would update the status of these entries before bringing them back to RG1, RG2 and the Subcommittee.

There ensued discussion around the use of dose-response information. It was noted by Dr. Wind that the BRC is intended as a document providing hazard identification and not risk assessment. There was agreement that under the proposed revised criteria, emphasis is given to considering all relevant information in determining whether an agent, substance or mixture might be reasonably anticipated to be a human carcinogen. This certainly would include dose-response data when available. Dr. Ryan inquired as to how the categories for the BRC relate or correspond to the levels of evidence used in evaluating carcinogenicity in NTP long-term rodent studies. Dr. Bucher said we will have to see how this works, although a level of evidence considered positive, **some evidence of carcinogenic activity**, in the bioassay would likely translate to **reasonably anticipated to be human carcinogens** in the BRC. Dr. Brown inquired as to what kind of 'product' was expected from the primary and secondary reviewers. Dr. Lucier replied that he envisioned a written format analogous to that used by principal reviewers for the draft Technical Reports. This would lead to a vote by the entire Subcommittee. Following the meeting, the staff would write up the final conclusions on each petition and transmit this to the reviewers for comments and approval. This could include not only the reviewers comments but the essence of the discussion leading to the recommendation. Dr. LeBoeuf suggested that a draft review form be sent to the members for comment.

IX. Draft Approach to Evaluating Epidemiology Studies -- Discussion: Dr. Mirer said the treatment of epidemiology data could be improved with development of decision rules that help define what constitutes a positive or a negative study. As a point of reference, he noted that 50 to 55 mortality studies had been conducted among United Auto Worker (UAW) members. These had motivated him to design decision criteria which had been sent as part of a discussion paper to Subcommittee members ahead of the meeting. The paper proposes and explains terminology to be applied to the interpretation of individual human mortality studies for cancer and other health effects. The goal of the proposal is to provide consistent interpretation of findings of such studies for use in risk assessments and other applications. The "levels of evidence" applied by the NTP to individual bioassay results are the model for this practice. Dr. Mirer said his scheme may be helpful in dealing with 'hard calls'. He suggested that the RG1 and RG2 consider such a scheme in aiding interpretation of human mortality studies for cancer. In discussion, Dr. Yamasaki said that the scheme appears similar to what IARC has been doing, and wondered if there was just one level of evidence. Dr. Mirer said that inadequate analysis of individual studies leads to lack of clarity in the interpretation of cumulative studies. Dr. Bucher said a problem is going to reside in the fact that we probably would be dealing with published epidemiology studies where the data is not as complete as in our bioassay studies.

[*Federal Register*: April 19, 1996 (61 FR 17314)]
[Billing Code 4140-01-P]
Public Health Service
National Toxicology Program

National Toxicology Program (NTP) Board of Scientific Counselors' Biennial Report on Carcinogens (BRC) Subcommittee Meeting

Pursuant to Public Law 92-463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors' Biennial Report on Carcinogens (BRC) Subcommittee, U.S. Public Health Service, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 Alexander Drive, Research Triangle Park, North Carolina, on May 8, 1996.

The primary agenda topic will be concerned with the discussion of the process for listing or delisting substances in the *Biennial Report on Carcinogens* (BRC) (formerly *Annual Report on Carcinogens* (ARC)).

The preliminary agenda topics with approximate times are as follows:

8:30 a.m. - 8:45 a.m. --	Report of the Director, NTP
8:45 a.m. - 9:00 a.m. --	Report of the Director, Environmental Toxicology Program (ETP)
9:00 a.m. - 10:00 a.m. --	Report on the background history of the BRC
10:15 a.m. - 11:15 a.m. --	Presentation and discussion of the process for listing or delisting substances in the BRC
11:15 a.m. - 11:35 a.m. --	Report from the NIEHS/NTP BRC Review Group
11: 35 a.m. - 12:00 p.m. --	Report from the NTP Executive Committee Working Group for the BRC
1:00 p.m. - 2:00 p.m. --	Subcommittee discussion of BRC presentations
2:00 p.m. - 3:00 p.m. --	Presentation of select chemicals previously approved for listing in the 8th and 9th BRC to compare application of proposed BRC criteria with previous ARC selection criteria
3:15 p.m. - 4:30 p.m. --	Subcommittee discussion of BRC review responsibilities

Adjournment

Public Comments Encouraged

The meeting is open to the public. A brief summary of the review of the BRC criteria for listing or delisting substances is available on request from the NTP Liaison Office, P.O. Box 12233, MD B3-01, Research Triangle Park, NC 27709, phone: (919) 541-0530, FAX: (919) 541-0295. Brief public oral comments will be allowed at appropriate times during the meeting. Registration to attend is not required; however, to ensure adequate seating, we ask that those planning to attend let us know. To register, receive information on the agenda, or be put on the mailing list for summary minutes subsequent to the meeting, please contact: **Dr. L. G. Hart, P.O. Box 12233, Research Triangle Park, NC 27709; telephone: (919) 541-3971; FAX: (919) 541-0719.**

Dated : April 12, 1996

Kenneth Olden, Ph.D., Director, National Toxicology Program

AGENDA
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS'

BIENNIAL REPORT ON CARCINOGENS SUBCOMMITTEE MEETING

May 8, 1996

Conference Center, Building 101, South Campus
National Institute of Environmental Health Sciences (NIEHS)
Research Triangle Park, North Carolina

8:45 - 9:15 a.m.	Report of the Director, Environmental Toxicology Program (ETP)	Dr. G. Lucier, NIEHS
9:15 - 10:15 a.m.	Report on the Background History of the <i>Biennial Report on Carcinogens</i> (BRC)	Dr. C. Jameson, NIEHS
10:15 - 10:35 a.m.	<i>Break</i>	
10:35 - 11:35 a.m.	Presentation and Discussion of the Process for Listing or Delisting Substances in the BRC	Dr. C. Jameson Dr. G. Lucier
11:35 - 12:00 p.m.	Report from the NIEHS/NTP BRC Review Group (Review Group 1)	Dr. J. Bucher, NIEHS
12:00 - 1:00 p.m.	<i>Lunch Break</i>	
1:00 - 1:20 p.m.	Report from the NTP Executive Committee Working Group for the BRC (Review Group 2)	Dr. M. Wind, CPSC
1:20 - 2:20 p.m.	Discussion of the BRC Process	Dr. A. Brown, Chair Subcommittee
2:20 - 2:35 p.m.	<i>Break</i>	
2:35 - 3:35 p.m.	Presentation of Select Chemicals Proposed for Upcoming BRCs to Compare Application of Proposed BRC Criteria with Previous Selection Criteria	NTP Staff
3:35 - 4:35 p.m.	Subcommittee (Review Group 3) Discussion of BRC Review Responsibilities	Dr. A. Brown Subcommittee
4:35 - 4:45 p.m.	Draft Approach to Evaluating Epidemiology Studies — Discussion	Dr. F. Mirer, Member

Adjournment

**National Toxicology Program
Board of Scientific Counselors'
Biennial Report on Carcinogens Subcommittee**

May 8, 1996

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National Toxicology Program
Board of Scientific Counselors'
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National Institute of Environmental Health Sciences
South Campus
Conference Center, Building 101
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