

AGENDA
NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

December 13, 1996

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

| | | |
|-------------------|--|--|
| 8:45 - 9:00 a.m. | Report of the Deputy Director, NIEHS & NTP | Dr. S. Wilson, NIEHS |
| 9:00 - 9:15 a.m. | Report of the Director, Environmental Toxicology Program (ETP) | Dr. G. Lucier, NIEHS |
| 9:15 - 9:45 a.m. | Reports of Subcommittee Activities: - Biennial Report on Carcinogens (BRC) - Technical Reports Review Subcommittee | Dr. C. Jameson, NIEHS Dr. J. Bucher, NIEHS |
| 9:45 - 10:00 a.m. | Break | |
| 10:00 - 12 noon | NTP Nomination and Selection Process - Introduction - NIEHS Activities - NTP Participating Agency Contributions - Summary - Questions and Comments | Dr. G. Lucier, NIEHS Dr. H. Matthews, NIEHS Dr. R. Melnick, NIEHS Dr. B. Schwetz, FDA Dr. A. Munson, NIOSH Dr. D. Longfellow, NCI Dr. V. Dellarco, EPA Dr. L. Schuman, OSHA Dr. Lucier |
| Noon - 1:00 p.m. | Lunch | |
| 1:00 - 1:30 p.m. | NTP Nomination and Selection Process - General Discussion | NTP Board |
| 1:30 - 2:30 p.m. | Endocrine Disruptors - Federal Agency Activities | Dr. G. Lucier, NIEHS Dr. R. Chapin, NIEHS Dr. K. Korach, NIEHS Dr. R. Kavlock, EPA Dr. B. Schwetz, FDA |
| 2:30- 2:45 p.m. | Break | |
| 2:45 - 3:30 p.m. | Endocrine Disruptors | |
| 3:30 - 4:15 p.m. | Concept Reviews - Support Contract for the Interagency Center for the Evaluation of Alternative Toxicological Methods - Support for the Preparation of the <i>Biennial Report on Carcinogens</i> | Dr. W. Stokes, NIEHS Dr. C. Jameson, NIEHS |

**NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS**

December 13, 1996

Summary Minutes

**National Toxicology Program
Board of Scientific Counselors
December 13, 1996
Summary Minutes**

| <u>Contents</u> | <u>Page Numbers</u> |
|--|---------------------|
| I. Reports of the Deputy Director, NIEHS and NTP | 1 |
| II. Report of the Director, ETP, NIEHS | 1 |
| III. Biennial Report on Carcinogens Subcommittee Activities | 2 |
| IV. Technical Reports Review Subcommittees Activities | 3 |
| V. NTP Nomination and Selection Process | 3 |
| A. Introduction | 3 |
| B. NIEHS Activities | 4 |
| C. NTP Participating Agency Contributions | 5 |
| • FDA | 5 |
| • NIOSH | 6 |
| • NCI | 6 |
| • EPA | 7 |
| • OSHA | 8 |
| D. Summary | 8 |
| E. Discussion | 9 |
| VI. Concept Review, ETP, DIR, NIEHS | 10 |
| • Support Contract for the Interagency Center for the Evaluation of Alternative Toxicological Methods | 10 |
| • Support for the Preparation of the Biennial Report on Carcinogens | 11 |
| Attachments 1-3 | 14 |

**SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING**

December 13, 1996

The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on December 13, 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 Board are Drs. Kenneth Reuhl (Chairman), Eula Bingham, Elaine Faustman, George Friedman-Jimenez, Carol Henry, David Hoel, Meryl Karol, Claudia Miller, Franklin Mirer, John Mulvihill, and John Stegeman. Expert consultant to the Board is Dr. Hiroshi Yamasaki. All were present except Drs. Hoel, Mulvihill, and Yamasaki.

I. Report of the Deputy Director, NIEHS & NTP: Dr. Samuel Wilson, Deputy Director, welcomed the members of the Board and briefly described the broad range of scientific programs conducted or supported by the NIEHS, and the concept of how the NTP is integrated with these programs. He said the theme was Good Science for Good Decisions and included extramural grants and centers and intramural research programs that also contributed to the goals of the NTP. Dr. Wilson stated that the NIEHS uses the NIH peer review systems which assures both good science and unbiased interpretations on public health issues. He said that the NIEHS research programs provide the best investment for determining true hazards of environmental agents, and provide for the application of NEW science to environmental health issues. Dr. Wilson noted that the NIEHS funds 500 investigator-initiated grants nationwide, principally RO1s, supports about 40 Centers of Excellence involving about 1,000 principal investigators, and supports 40 doctoral/postdoctoral training programs nationwide. The current budget is \$380 million and under the President's budget would increase by 7.1% in FY 1998. Dr. Wilson reviewed NIEHS funded milestones during recent years including major research discoveries by and Nobel Prizes awarded to staff members or grantees, and milestones in prevention and environmental public health. These milestones included cumulative contributions by the NTP in completion of several hundred 2-year animal studies, and demonstration that many chemicals humans are exposed to are not likely to be carcinogenic. Dr. Wilson concluded by highlighting the biological/pathological events that occur and interact following exposure to an agent, the balance of which determines whether or not the exposure leads to disease. There was some discussion about the roles of genetic and epigenetic influences on etiology of human disease especially those diseases of occupational origin.

II. Report of the Director, Environmental Toxicology Program (ETP), NIEHS: Dr. George Lucier, ETP Director, also welcomed the members and thanked them for giving of their time and expertise to the review of NTP programs and issues. He briefly discussed the agenda topics for the meeting, noting that the Board would be hearing reports from the recent meetings of the two subcommittees. The Biennial Report on Carcinogens Subcommittee at their meeting in November had used for the first time the new criteria for listing or delisting agents in the *Biennial Report on Carcinogens* (BRC). Dr. Lucier said that a major emphasis at this meeting would be a review of the NTP nomination and selection process, a very critical activity for the success of the Program. The Board's input and advice were sought. He said that presentations on Federal agency activities on endocrine disruptors were planned; the NIEHS has had research in this area for many years. Dr. Lucier said that two project concepts would be reviewed by the Board, both

deriving from Congressional mandates, one to prepare a biennial report on carcinogens and the other to develop, validate and gain regulatory acceptance of alternative test methods. Another mandate along with funding has to do with coordinating and conducting research on the possible human health effects of electric and magnetic fields (EMF), which was leading to a series of workshops and a subsequent report by the Director of NTP to Congress on the findings. Dr. Lucier spoke of an October 1996 NTP retreat which included Board members and focused on three issues: (1) how best to establish hazard in the environment - one aim was to develop more hypotheses driven approaches; (2) developing more information from human studies; and (3) putting more emphasis on non-cancer endpoints. Finally, Dr. Lucier discussed recent partnership efforts with other agencies and industry in development, validation and gaining regulatory acceptance of alternative test methods with special emphasis on transgenic rodent models for carcinogenicity, and in establishment of a reproductive toxicology center to provide objective assessments of human risk.

Discussion: Dr. Bingham asked about plans for studying mixtures, alluding to her and Dr. Miller's service on a panel concerned with Gulf War veterans, and stated that there was not much good animal data on toxicity of mixtures. Dr. Lucier responded that the toxicology of mixtures was an issue that the NTP was confronting, and hopefully, would be using tools of molecular biology in a rational way to develop information on mechanisms. A collaborative effort with NIOSH to study mixtures was underway. Dr. Albert Munson, NIOSH, reported that they would be looking at mixtures of occupational importance beginning with studies on asphalt fumes, hoping that these studies will model how to attack other mixtures from standpoints of dose response, interpretation, and engineering issues. Dr. Henry noted that in the list of NTP chemical nomination elements there did not seem to be an entry asking for human exposure information. Dr. Lucier said that would be rectified, and commented on a recent interagency agreement between NIEHS and the Center for Environmental Health of the Centers for Disease Control and Prevention for measuring levels of endocrine disrupting agents in human blood. Dr. Miller commented that one of the best and most widespread examples of complex mixtures could be found in indoor air pollution. Dr. Karol cautioned that the basic design for the studies of human exposure to mixtures should be hypothesis driven.

III. Biennial Report on Carcinogens (BRC) Subcommittee Activities: Dr. Bill Jameson, NIEHS, reported on the BRC Subcommittee meeting held at NIEHS on November 18-19, which was the second meeting of the new subcommittee, and the first meeting where chemicals were reviewed under the revised criteria for possible listing in the BRC. He said there were 15 chemicals reviewed by the Subcommittee, two as *Known to be a Human Carcinogen* and 13 as *Reasonably Anticipated to be a Human Carcinogen*, and he discussed these. Dr. Jameson stated that the structure of the 8th BRC was being revised to make the document more user friendly, and showed examples including header and footer identification on each page which indicates the name of the chemical and when it was first listed in a Report. The chemical structure also will be included for each new entry. Dr. Jameson said there was discussion about the draft Introduction for the 8th BRC which had been updated to reflect new procedures and the recently approved revised criteria. The Program asked for members thoughts on several proposed new appendices. On two proposed appendices, one displaying chemicals evaluated but not listed and a second displaying chemicals nominated but not yet evaluated for listing or delisting, there was a consensus of the Subcommittee that such appendices could be confusing to the reader leading to an impression that the chemicals were being listed in the BRC. A proposal to have an appendix table with chemicals delisted from the BRC was supported. Dr. Jameson

said there was considerable discussion about continued inclusion in the BRC of a reference to certain manufacturing processes, occupations and exposure circumstances classified by IARC as sources which are known to be carcinogenic to humans because of the associated increased incidences of cancer in workers in these settings. The Subcommittee thought these sources should be referenced somewhere in the report but thought that the Program should decide on the most appropriate location. Dr. Lucier noted a consensus that qualifiers needed to be included with these references indicating that some of these processes, occupations and mixtures might not be applicable to current practices in the United States.

Discussion: Dr. Faustman inquired as to what issues or chemicals generated the most discussion at the meeting. Dr. Jameson replied that since this was a learning process for both the staff and the Subcommittee, there was considerable discussion about how the information provided on each chemical could be enhanced. He noted that of the chemicals, Disperse Blue 1 engendered the most discussion as expected since the NIEHS BRC review committee and the NTP Executive Committee BRC Working Group had differed in their recommendations. Dr. Mirer, a member of the Board BRC Subcommittee, reported that there was a consensus on a need for epidemiological expertise. Among other suggestions by Subcommittee members were a need for a staff person to be available to participate in the discussion of individual nominations, a need for some interpretation to give perspective to the genetic toxicology information provided, and a need for reviewers having the full NTP bioassay report available for the review, if there is one. Dr. Reuhl asked whether the criteria for delisting were included in the report. Dr. Jameson said the criteria for listing and delisting are the same and are in the Report.

IV. Technical Reports Review Subcommittee Activities: Dr. John Bucher, NIEHS, reported on the Subcommittee meeting of December 11-12 in which the draft Technical Reports for 10 long-term toxicology and carcinogenesis studies were peer reviewed. He reviewed the findings and public health implications. He said there were presentations and considerable discussion about the NTP position on the impact of infection with *Helicobacter hepaticus* in mice from nine studies started during the late 1980s and early 1990s. Dr. Bucher said the Program believes that liver lesions, particularly in male mice, resulting from the infection may impact on interpretation of carcinogenic effects of chemicals in some of these studies. He provided the Board with a listing of draft Technical Reports tentatively scheduled for review in 1997.

Discussion: Dr. Faustman asked whether further studies were planned with chemicals that were found to be strongly positive for carcinogenic activity, e. g., chloroprene. Dr. Bucher responded that depending on available resources and priorities, such chemicals may be entered into assays that will provide information relating to mechanisms. With regard to chloroprene, the chemical is being evaluated in the p53 transgenic mouse model. Dr. Lucier said there were interdisciplinary faculties within the intramural program that evaluate whether further studies should be done. One of these is the Molecular Oncology faculty.

V. NTP Nomination and Selection Process:

A. Introduction -- Dr. Lucier reiterated his previous statement that the nomination and selection process was critical to Program success for if the wrong chemicals are selected and studied, then the NTP cannot provide the information needed for protection of public health. He noted that the NTP Board supplemented with *ad hoc* experts had reviewed the Program in 1992 and among their major recommendations was one that chemical

nomination/selection procedures needed to be improved. Although emphasis in today's meeting would be on nomination/selection for the two-year cancer bioassay, other disease endpoints of concern were general toxicology, reproduction and development, immunotoxicology, neurotoxicology, and respiratory toxicology. Selecting chemicals for mechanistic studies and for development of biologically-based models was important also. Among the kinds of substances studied are environmental agents, occupational agents, pharmaceuticals, natural products, physical agents, and mixtures. Dr. Lucier pointed out the ebb and flow of numbers of chemicals started in the bioassay over the past 15 years ranging from 43 study starts in 1982 to four starts in each of 1992, 1994, and 1995. Partly in response to Congressional concerns, there had recently been an upswing in starts to 13 in 1996 and 10 in 1997. He said there was a misperception by some that nearly all chemicals studied by the NTP, and earlier by the NCI, are positive, and this was not so with only about half of 382 bioassay chemicals having been shown to be positive. Dr. Lucier commented that basic and applied research on chemicals is driven by human exposure, toxicological or epidemiological data, or information that key biological molecular processes involved in carcinogenesis may be perturbed by a chemical. He said the data generated feeds into the risk assessment process including hazard identification, exposure assessment, dose-response measurements, species comparisons, and interindividual variation. Dr. Lucier concluded by noting that NTP data is used to alert the public to potential hazards, strengthen the science base for regulatory decisions, and develop research priorities.

B. NIEHS Activities -- Dr. H. B. Matthews, NIEHS, listed the guidelines for what it is that the NTP studies: - - chemicals found in the environment not closely associated with commercial operations; - - biological or physical agents that might not be tested without Federal involvement; - - commercial agents first marketed prior to current testing requirements; - - orphan drugs or chemicals that might not be developed without Federal involvement; - - mixtures of chemicals for which evaluations can not be required of industry; - - chemicals for which testing will enhance knowledge of structure/activity relationships; and - - chemicals involved in emergencies that require immediate government evaluation. Dr. Matthews also described classes or types of chemicals not generally recommended for NTP study including those that have been subjects of previous adequate studies. In looking at high production volume as a possible indicator for study, he noted that two of the highest production volume inorganics have been subjects of two-year studies, - carbon black and titanium dioxide. With regard to organic chemicals, most of those in the top 50 high production volume chemicals have been studied in the *Salmonella* test and rodent bioassays by the NTP, and in many cases have been categorized by IARC. The exceptions are primarily chemicals that would enter into normal intermediary metabolism, e.g., acetic acid. Dr. Matthews went on to say that of the 70 to 75, 000 chemicals currently in commerce about 61,000 predate the Toxic Substances Control Act (TSCA), and of these about half are not suitable for study for various reasons. From estimated unique chemicals reported to the EPA and other chemicals produced and not reported to the EPA, there are about 8,000 remaining to be tested and about 5 to 10% of these are estimated to be human carcinogens. Further, there are an undetermined number of naturally occurring carcinogens.

Dr. Matthews mentioned proactive steps that are being or will be taken to increase the number and improve the quality of nominations received. These steps include: increased communications with the public, Federal and state agencies, labor, industry, and environmental organizations; collaboration with the National Library of Medicine to evaluate 86 different data bases netting about 2,000 unique chemicals; reviewing lists of

chemicals found in human tissues, most of which have been studied; reviewing all chemicals testing positive in the Ames *Salmonella* assay and not studied in a two-year bioassay; and maintaining ongoing review of lists of high production volume chemicals. Dr. Matthews pointed out numbers of nominations by Fiscal Year during the life of the Program, stating there had been a sharp increase in numbers of chemicals nominated over the past three years, and in his opinion, in quality also. He commented on nomination sources since 1980, noting that Federal agencies had contributed the most, led by NCI with 246, while private individuals had provided 125 nominations. Dr. Matthews said that plans to increase the quality and quantity of future nominations included increased collaboration with other Federal and state agencies to review lists of chemicals of mutual concern, increased emphasis on evaluating naturally occurring chemicals and continued and expanded solicitation of nominations and advice from all sectors of society.

Discussion: Dr. Bingham suggested looking at the 10-20 leading chemicals in dump sites and as contaminants of water sources, acknowledging that some of these may have been studied. Dr. Henry cautioned that in winnowing down lists, the emphasis seems to be focused on cancer, and other endpoints, especially reproductive, developmental, and neurotoxic endpoints should not be overlooked. Dr. Lucier commented that of the hundreds of chemicals studied in chronic bioassays perhaps 20-25% also have been studied for some of these other endpoints of toxicity. Dr. Mirer said it would be helpful to have a cumulative list of nominations along with suggested endpoints and status of the nomination.

Dr. Ronald Melnick, NIEHS, said he would talk about NTP activities that benefit the risk assessment process. As done by regulatory agencies, more emphasis is being given to descriptions of the uncertainties and to descriptions of the evidence for toxicity or carcinogenicity. Applications of mechanistic information should help reduce uncertainties and facilitate the process of extrapolation from animals to humans or from laboratory to human exposures. He said that NIEHS and NTP scientists have participated with EPA in the updating of EPA's risk assessment guidelines for cancer, neurotoxicity and reproductive and developmental toxicity. Because these new guidelines have implications for how mechanistic information will be used in the risk assessment process, the NIEHS and EPA held a workshop in April 1996 where they discussed research priorities related to the new guidelines. Dr. Melnick discussed some of the conclusions. Among applications of NIEHS research useful for determining hazard and dose-response assessments with respect to cancer were animal bioassay data, toxicokinetic data, historical control data, estimation of structure-activity-relationships (QSAR), use of transgenic and knock-out animals, biomarkers of exposure and effects, mechanistic modeling, and use of "mode-of-action" information. He illustrated how SAR and dose-response information on 1,3-butadiene led to selection of the analogs, isoprene and chloroprene for study. Dr. Melnick also described some of the risk assessment related research at NIEHS in neurotoxicology and in reproductive and developmental toxicology. Dr. Melnick concluded his presentation by discussing a large class of chemicals selected for possible studies because of their presence in water as chlorination byproducts including trihalomethanes, haloacetic acids, haloacetonitriles, and cyanogen halides. Some of the trihalomethanes have been shown to be colon carcinogens. Alternative test methods are being considered for some of these compounds.

C. NTP Participating Agency Contributions -- FDA: Dr. Bernard Schwetz, Director of NCTR and Associate Commissioner for Science at FDA, pointed out the broad range of chemicals, agents and non-chemical items that fall under the purview and regulatory

responsibilities of the FDA, including foods, food additives, drugs, biologics including vaccines, veterinary products, and various kinds of devices. He said the FDA has a Chemical Selection Working Group (CSWG) that meets at least twice a year and evaluates nominations for NTP study of agents submitted by the various centers and offices. The CSWG selects priorities among chemicals/agents and considers benefit, since unlike environmental pollutants, many agents under FDA purview may have beneficial effects, e.g., cancer chemotherapeutics. From this process, FDA priority chemicals are brought forth to be considered for study by the NTP. Dr. Schwetz discussed the rationale for study and status of NTP studies on D & C Yellow No. 11, *t*-butylhydroquinone, polyvinyl alcohol, cinnamaldehyde, and ethoxyquin. He noted the development of an interagency agreement in 1992 between FDA and NIEHS to enable the FDA to conduct applied and mechanistic studies on more recent priority chemicals at NCTR. Dr. Schwetz gave brief descriptions of the rationale for study of chloral hydrate, fumonisin B1, malachite green and urethane/ethanol under the agreement.

NIOSH: Dr. Albert Munson, Director, Health Effects Research Laboratory Division, NIOSH, said he was the new NIOSH-NTP liaison. He said the current procedures for obtaining nominations were to solicit recommendations from researchers and policy staff. Any recommendations were reviewed by an internal working group and nominations made to the NTP through the Director, NIOSH. To enhance this process, a large amount of data on about 600 chemicals in the NIOSH database is being reviewed and updated to determine if there may be some candidates for study. A quantitative risk assessment activity is ongoing that should aid the NTP as well as NIOSH. Under a new interagency agreement with NIEHS, complex occupational and industrial exposures will be evaluated. The first of these is asphalt fumes for which there is already much data including exposure data and some human blood level data. Studies on three or four other compounds or mixtures will follow. Dr. Munson reported that there is a concerted effort under the direction of Dr. Douglas Sharpnack to evaluate the NIOSH list of occupational carcinogens and compare this list with that in the *Biennial Report on Carcinogens*, and this may result in some good nominations. Dr. Munson, noting that his primary expertise was in immunotoxicology, commented on the development and validation of an immunotoxicity assay battery by NIEHS researchers in the early 1980s progressing to human studies of immune system effects in occupational settings by NIOSH under an interagency agreement with NIEHS/NTP

NCI: Dr. David Longfellow, Chief, Chemical and Physical Carcinogenesis Branch, Division of Cancer Biology, NCI, said that the Environmental Cancer Program had as part of its mission to identify potential chemical carcinogenic hazards. He said the primary body within the NCI charged with evaluating and recommending chemicals for study by the NTP was the NCI Chemical Selection Working Group (CSWG) comprised of representatives from 14 Federal agencies. Dr. Longfellow commented that the focus of the members of the CSWG was to evaluate the chemicals under evaluation strictly from a scientific perspective while focus of the members of the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) was also to bring their agency needs to the evaluation process. Historically, carcinogenesis studies at NCI began in the early 1960s with a basic research program to address mechanisms of carcinogenesis under the direction of John and Elizabeth Weisburger. In the late 1960s to the late 1970s, carcinogenesis testing (bioassays) became a major part of the program with impetus in 1971 from the War on Cancer. Then, the Bioassay Program was transferred by the Secretary of DHHS to the NIEHS in 1981. Dr. Longfellow said the NCI chemical selection process is based on a need for a systematic approach to selection and testing of chemicals,

with selection criteria including significant human exposure, suspicion of carcinogenicity, and a need for data to characterize carcinogenicity of chemicals, and especially chemical classes. If there is insufficient data, e.g., *Salmonella* results, there is a contractor who can help fill in the gaps. He said that among sources of nominations from the 'universe of chemicals' are various class studies based on structure or use, nominations from Federal agency staff, and screening of the literature for chemicals with potential for increased usage or of current national interest and substitutes for toxic chemicals. The screening serves to provide information for the PHS 149 document series, *Survey of Compounds Tested for Carcinogenicity*, and for the CCRIS data base through the NLM. Dr. Longfellow listed some class studies by structure, e.g., aromatic amines, alkyl halides, and by use category, e.g., solvents, dyes and pigments, and sunscreens. He noted that chemicals recommended to NTP are an eclectic mix but often of significance as regards human exposure, e.g., methyl isocyanate, phenolphthalein, and pyridostigmine bromide. Among the uses of test results beyond the obvious to identify carcinogenic hazards are those to stimulate new research and help validate short-term assays. Dr. Longfellow spoke of the impact of the NCI studies process on the NTP by noting that NCI nominations accounted for 36% of nominations to NTP from 1980 to 1996, 58% of chemicals currently in NTP prechronic studies, and 73% of chemicals currently in the chronic studies process. He concluded his presentation by stating that there were two points to consider: (1) agencies could make more meaningful nominations for testing priorities if NTP would identify the types of assays it is willing to consider running; and (2) NTP should enter chemical data packages into an electronic database that is searchable by the public.

EPA: Dr. Victoria Dellarco, EPA, said her agency thinks the nomination/selection process has improved over the past few years, and in particular with the development of an NTP/EPA Federal Testing Policy Framework, which provides guidance on how to coordinate testing between the EPA and NTP. The Framework embodies the policy that manufacturers of chemicals should provide toxicity data on their chemicals, and it recognizes the balance needed between traditional testing and mechanistic considerations. She pointed out EPA testing authorities, one being FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act), and a second being TSCA (Toxic Substances Control Act) which covers a broader range of substances. Dr. Dellarco said that TSCA is currently being used to collect data on 21 air pollutants leading to a test rule and including studies of reproductive and developmental toxicity and neurotoxicity, and perhaps development of pharmacokinetic data by industry. She mentioned the Interagency Testing Committee (ITC) formed under TSCA which recommends a priority testing list of chemicals to the EPA Administrator. The ITC has members from 16 agencies including NTP. The EPA is also involved with 18 countries in the Organization for Economic Cooperation and Development (OECD), where under the SIDS (Screening Information Data Set) program minimum data sets to aid in further testing decisions are being developed on about 300 chemicals. So why does EPA need the NTP, Dr. Dellarco asked? There are many times when the statutory testing authorities under TSCA or FIFRA can't be used or do not meet timeliness of the data needs. A recent example was the need for studies on water chlorination disinfection byproducts. The NTP can help meet EPA's needs for data to conduct risk assessments by linking their research to the risk assessment process through studies defining dose-response relationships, through mechanistic research on generic or cross-cutting issues, and through developing and validating new approaches, e.g., transgenic rodent models for carcinogenesis. Dr. Dellarco noted that NTP has interacted with EPA on high profile risk assessments, e.g., dioxin, and has led the organization of workshops on risk assessment issues. She noted some recent trends in health risk assessment including more emphasis on mechanistic studies, greater attention to risk to sensitive subpopulations such as

children, integrative health risk assessments for cancer and noncancer risks, and shifting emphasis from single chemical exposures to studying multiple chemical exposures via multiple pathways. Dr. Dellarco concluded with a graphical presentation of data and extrapolation using modeling in the observed range of effects, use of benchmark dose or point of departure for extrapolation, and margin of exposure.

OSHA: Dr. Loretta Schuman, OSHA (Occupational Safety and Health Administration), Department of Labor, stated that Congress created OSHA through the Occupational Safety and Health Act in 1970 to assure so far as possible every working man and woman in the Nation safe and healthful working conditions. NIOSH was created under the same act to do research and develop criteria documents to assist OSHA in setting workplace standards. Dr. Schuman said she would discuss how NTP testing data is used in setting OSHA standards. The standards promulgation process derives from the OSHA act. However, the act does not specifically define how the standards are to be set. She said that the major driving forces for OSHA regulations are: (1) EPA under TSCA Section 9 (a) can refer substances to OSHA for regulation if occupational exposure would be the primary problem, e.g., methylene chloride and glycol ethers; (2) The primary driving forces are petitions by trade unions or various public interest groups, e. g., cadmium and chromium. Before regulation can be carried out, OSHA has to perform a risk assessment. The best type of data are from a good epidemiological study; however, without this animal studies must be used, and these should have used several appropriate dose levels with one at a maximum tolerated dose, and for an appropriate exposure period which for cancer assessment should be two years. Dr. Schuman said that in an ideal world, OSHA would anticipate potential hazards years in advance and be able to nominate the chemical to the NTP, have a bioassay conducted and peer reviewed, and then do a risk assessment. However, in the real world, OSHA is forced by a petition or law suit to promulgate a standard and have a risk assessment completed within a year. Many OSHA risk assessments use NTP bioassays as they may be the best data available for a number of reasons including being the best designed and conducted, multiple dose levels, adequate exposure period which is usually two years, and finally, NTP is viewed as an "honest broker". Examples are 1,3-butadiene, and, currently, methylene chloride. Dr. Schuman concluded by expressing concerns about the increasing emphasis on studies of "mechanism of action" drawing resources from conduct of two-year bioassays. This was of concern to OSHA because NTP two-year bioassays are essential for risk assessment and signalling potential human health hazards, and she noted that the need for studies of "mechanism of action" has been used by industry as rationale to delay standard setting. Dr. Schuman stated that studies of "mechanism of action" did not provide data useful for risk assessment and setting of standards.

D. Summary -- Dr. Lucier said that in lieu of a formal summary, he would respond to questions that had been raised. He said that Dr. Henry had inquired about a possible 'White Paper' on nomination/selection, and commented that a paper discussing how the NTP goes about the process both for carcinogenicity studies as well as for other endpoints was in preparation and would be submitted to a peer reviewed journal. With regard to the two-year bioassay, the NTP commitment will continue until appropriate alternatives are accepted by the regulatory community. Dr. Lucier said that we would like to accompany findings from the bioassays with mechanistic and other data to help regulators in the risk assessment process. In response to Dr. Longfellow, he commented that putting together a 'menu' of assays that the NTP had available and could perform was a good idea, and perhaps, merited another 'white paper'. Dr. Lucier said that many NTP/NIEHS databases were on the World Wide Web, and asked Dr. William Eastin, NIEHS, to speak to this. Dr. Eastin said we hoped to put CSWG packages on the Web in the near future, and currently,

health and safety packages for all chemicals that NTP studies are on the Web, and much in demand.

E. Discussion -- Dr. Miller asked for comment on mixtures and neurobehavioral studies and how they fit into the NTP mission. With regard to mixtures, Dr. Lucier said one problem was tractability with engineering and molecular systems needing to be developed. He said studies were in protocol development for Stoddard solvent and mixtures of water disinfection byproducts. Dr. Michael Shelby, NIEHS, commented that there were a number of neurobehavioral assays being used and others being developed. He noted two current studies in collaboration with EPA, one with mercury by inhalation, and the other on water disinfection byproducts. Dr. Lucier reported that about 70 agents had been tested for neurobehavioral effects. Dr. Stegeman observed from Dr. Longfellow's presentation that there appeared to be considerable rationality in selection of chemicals for cancer studies but this did not appear to be the case with regard to other endpoints. Dr. Lucier agreed that the procedures for selecting agents for cancer bioassays were more formalized and prescriptive but noted that there are procedures and peer review involved in selecting chemicals for other endpoints and this is where the interdisciplinary faculties are helpful, e.g., in selecting chemicals for endocrine disruptor studies. Dr. Stegeman added his concern that too many resources may be going to cancer studies, and thought there could be more efficient use of resources if other endpoints could be integrated into bioassays. Dr. Bucher commented that since bioactive compounds often have more than one target, screens are built into each step of the testing process for immuno-, neuro-, and reproductive and developmental toxicity, so that chemicals exhibiting activity can be subjects of more specialized studies. Dr. Henry said it was helpful to hear different agency priorities but what was not clear was a strategy linking nomination/selection with epidemiology and human effects. Dr. Longfellow argued that lacking human effects information, mechanism-based studies might serve to shed light on commonalities between animals and humans. Dr. Lucier commented that wherever a commonality could be found within a class of chemicals, that commonality should be pursued so carcinogenicity can be predicted, e.g., the benzidine dye initiative, and currently, the toxic equivalency factor (TEF) issue in terms of Ah receptor binding in toxicokinetics and gene expression for the hundreds of chemicals in the environment with dioxin-like activity. Dr. Matthews said that we always have problems of competing priorities for limited resources and this was why the benzidine dye initiative was a good example in that there are literally hundreds of benzidine and congener dyes for which metabolism studies on a few carefully selected members could predict carcinogenicity for many of the class. Dr. Stegeman noted that asphalt fumes were chosen on the basis of human exposure and not chemistry, and urethane-ethanol was selected because of its presence in alcoholic beverages; however, in some cases there are other alcohols present in significant amounts so wondered how which alcohol is a toxic component was reconciled. Dr. Schwetz commented that some mixtures are so important that we have to evaluate their toxicity even though we may not be able to extrapolate from one mixture to another. So there needs to be agreement on generic questions that could be answered about mixtures, e.g., can toxic effects seen with a mixture in the laboratory be extrapolated to a much lower level of human exposure to the same mixture. Dr. Miller said that in her practice, health effects of mixtures to which people are exposed are real world concerns, and made a plea for development of better biomarkers. Dr. Friedman-Jimenez noted that only a small fraction of chemicals nominated are studied and wondered how others that may be of public health importance can be assessed. Dr. Lucier replied that although less than 500 chemicals have been looked at in bioassays, many more than that are evaluated for genetic toxicity, and in the case of mixtures, receptor interactions have been measured. Dr. Matthews said that metabolism

studies are done on many chemicals that don't proceed to a bioassay, and in some cases the findings from a metabolism study will suggest a lack of toxicity or carcinogenicity were the chemical to be further studied. Dr. Mirer stated that human exposure and potential public health problems should be the primary factor in selecting a chemical for study. Dr. Henry opined that NTP needs to define a strategy for test development if human health is a driving force. Dr. Lucier agreed and said that at a future meeting besides looking at nomination and selection we need to gain input on strategies for developing the tests we use. He noted that recently an RFA for developmental gene expression was awarded with NTP funds to help support establishing a sounder basis for developmental toxicology research. Dr. Lucier explained a strategy for how NTP uses advice from outside experts and will use results from new RO3 grants as part of enhancing the experimental design of a two-year study to provide more and indepth information about the toxicity of a chemical. Dr. Henry said there needs to be such a strategy for help in selection of chemicals. Dr. Mirer reiterated that he still found it hard to understand why some high exposure chemicals were not selected for study.

VI. Concept Reviews:

Support Contract for the Interagency Center for the Evaluation of Alternative Toxicological Methods -- (Attachment 3) Dr. William Stokes, NIEHS, presented the concept, and Dr. John Stegeman, Board member, served as principal reviewer. Dr. Stokes said that one of the objectives of the NTP has always been to develop better test methodologies but Public Law 103-43, the 1993 NIH Revitalization Act, had mandated specifically that NIEHS "develop and validate alternative methods for acute and chronic safety testing, develop criteria for their validation and regulatory acceptance, and recommend a process for their regulatory acceptance." In response, the NIEHS established the *ad hoc* Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Comprised of 15 Federal agencies, ICCVAM was charged with assessing existing Federal criteria and processes and developing a report establishing criteria and processes for the validation and regulatory acceptance of alternative testing methods. Public comments were received and an NTP workshop was held in December 1995 to review the draft report and provide recommendations for implementation. The final report was projected for release in February 1997. One of the major recommendations was to establish a permanent ICCVAM to coordinate test method development, validation, and review activities within the Federal government and to communicate with stakeholders throughout the process of test method development and validation. To support the activities of ICCVAM, an Interagency Center for the Evaluation of Alternative Toxicological Methods is proposed. The Center will be located at NIEHS and consist of 3 to 5 government staff augmented with a Center support contract. The contract will provide technical and administrative support necessary to carry out ICCVAM and related activities as spelled out in the concept statement.

Dr. Stegeman said that if alternatives to traditional methods are to be adopted in a wise and efficient way, there must be some sort of central office to bring together the many different groups involved. The center should be able to bring good science to bear on the evaluation of alternatives. He said the resources appear to be available but expressed concern that this effort not divert resources from other programs and thought that selection of the right people as staff would be crucial for success. Dr. Stegeman said that given that alternative tests may be implemented in many industrial laboratories, there should be genuine practical uses for the results. Because the center will not be developing methods but serving to facilitate communication and review, he raised several questions as to the focus, functions and operation of the center that needed to be addressed, including

how priorities will be set among methods awaiting evaluation, the degree of scientific consensus regarding acceptability of a method, and who will determine makeup of review panels. Dr. Stegeman supported approval of the concept proposal.

Dr. Miller asked for an example of a test that might be evaluated. Dr. Stokes replied that the *ad hoc* ICCVAM had been requested to evaluate an *in vitro* method for assessing dermal corrosivity. A review is ongoing and an expert peer review panel will meet in Spring 1997. Dr. Henry said there didn't seem to be much emphasis on the '3Rs', i.e., refinement, reduction, and replacement of animal use which she thought to be a major objective of the legislative mandate. Dr. Lucier said the '3Rs' were important and expected a reduction in animal use to occur. Dr. Bingham expressed concerns that this effort might draw resources away from other NTP programs and thought the scope needed to be narrowed and sharpened. Dr. Lucier assured the Board that no other activities will be curtailed because of this initiative. Dr. Stegeman moved that the concept be approved. Dr. Mirer seconded the motion, which was approved unanimously by the Board.

Support for the Preparation of the *Biennial Report on Carcinogens* --

(Attachment 3) Dr. Bill Jameson, NIEHS, presented the concept, and Dr. Carol Henry, Board member, served as principal reviewer. Dr. Jameson said that the *Biennial Report on Carcinogens* (BRC) is prepared in response to section 301 (b) (4) of the Public Health Service Act. He reported that over the past two years there had been at the initiation of the Director, NTP, a review of the BRC to broaden input into its preparation, broaden the scope of scientific review associated with the Report, and provide review of the criteria used for inclusion of substances in the BRC. Dr. Jameson noted that the Board had played a primary role in this review process and as part of the effort to broaden scientific review, a new subcommittee of the Board had been established. He said that among the recommendations made by the Board was one that when available, mechanistic information should be used in evaluating whether a substance should be listed in or delisted from the BRC, and another was that the Board acknowledged incorporation of mechanistic information will require an expansion of resources. Dr. Jameson said the current support contract was established to assist in preparing the BRC for printing, and the current scope requires support for about 20 new chemicals per year for: (1) identifying, gathering, collating and summarizing use, exposure and regulatory data; and (2) a small effort for retrieval of carcinogenicity data to augment data provided by the NTP. Proposed changes are to expand the scope of work to include gathering and summarizing data for up to 25 chemicals on carcinogenesis, epidemiology studies, genotoxicity, ADME (absorption, distribution, excretion and metabolism), mechanisms of action, and all other relevant data. Thus, the objectives are to provide required support for: (1) literature searches; (2) data summaries; (3) document preparations; and (4) data gathering for production, use and regulatory information, as well as final preparation of the BRC.

Dr. Henry said her remarks would draw on her experience as a member of the new BRC Subcommittee which met on November 18-19 to review chemicals for listing in the 8th BRC. As preface, she noted the legislative mandate, the wide and accepted use of the document, and its use as a critical tool in public health protection. Dr. Henry said the resource materials provided for the first reviews were somewhat inadequate and needed to be enhanced particularly where a delisting action is being considered. She said there was a need to augment Federal staff support including provision of a nomination manager for each chemical. She said one data gathering need for the contract was the acquisition of epidemiology and human exposure information. Dr. Henry said there needs to be a strategy for information retrieval and management of this support. She recommended

approval of the concept with the understanding that there be a sufficient level of Federal staff involvement, to develop a strategy for information retrieval and management, and to develop some measure of improvement to the process. Dr. Friedman-Jimenez urged that within the review group for the BRC there be more expertise in epidemiology, including not only cancer epidemiology, but also expertise in occupational, nutritional, molecular, and genetic epidemiology, as well as professionals with expertise in exposure assessment. Dr. Henry moved that the concept be approved with her augmenting recommendations. Dr. Karol seconded the motion, which was approved unanimously by the Board.

Dr. Wilson thanked the Board for their involvement in the review process. Dr. Lucier announced that the presentations planned on Federal agency activities on endocrine disruptors would be deferred until the next meeting, probably April or May 1997. He said another major agenda topic for that meeting would be a discussion of the nomination and selection process for reproductive and developmental toxicology studies.

These Summary Minutes have been read and approved by the Chair of the National Toxicology Program Board of Scientific Counselors as certified below.

Date: _____

Kenneth R. Reuhl, Ph. D.
Chair
NTP Board of Scientific Counselors

[Billing Code 4140-01-P]

Department of health and Human Services

Public Health Service

National Institute of Environmental Health Sciences

National Toxicology Program

National Toxicology Program (NTP) Board of Scientific Counselors' Meeting

Pursuant to Public Law 92-463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors, 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 December 13, 1996.

The meeting will be open to the public from 8:45 a.m. to adjournment with attendance limited only by space available. Preliminary agenda topics include: comprehensive presentations and discussion with the Board about the NTP nomination and selection process, and presentations of ongoing and planned research on endocrine disruptors by several Federal health research and regulatory agencies. There will be reports of recent activities by the Board's Biennial Report on Carcinogens Subcommittee and Technical Reports Review Subcommittee. The Board will review concept proposals for a contract to establish an Interagency Center for the Evaluation of Alternative Toxicological Methods, and for expanding the scope of support services for preparation of the *Biennial Report of Carcinogens*.

The Executive Secretary, Dr. Larry G. Hart, National Toxicology Program, P.O. Box 12233, NIEHS, Research Triangle Park, North Carolina 27709, telephone (919) 541-3971, FAX (919) 541-0295, will have available a firm agenda with times and a roster of Board members prior to the meeting and summary minutes subsequent to the meeting.

Dated:

Kenneth Olden, Ph.D.

Director
National Toxicology Program

Environmental Toxicology Program
Division of Intramural Research
National Institute of Environmental Health Sciences

CONCEPT REVIEWS

Prepared for:

National Toxicology Program
Board of Scientific Counselors

December 13, 1996

CONCEPT REVIEWS

National Toxicology Program
Board of Scientific Counselors

December 13, 1996

Table of Contents

| | |
|---|---|
| Background on Concept Reviews | 1 |
| Title: Support Contract for the Interagency Center for the Evaluation of Alternative Toxicological Methods | |
| Presenter: W.S. Stokes | |
| Primary Reviewer: J. Stegeman | 3 |
| Title: Support for the Preparation of the <i>Biennial Report</i> <i>on Carcinogens</i> | |
| Presenter: C.W. Jameson | |
| Primary Reviewer: C. Henry | 5 |

BACKGROUND ON CONCEPT REVIEWS

NTP contracts, interagency agreements, and grants support a variety of activities — toxicologic characterization, testing, methods development, and program resources (i.e., chemistry, occupational health and safety, animal production, pathology, quality assurance, archives, etc.).

Prior to issuance of a Request for Proposal (RFP) or a Request for Application (RFA), a project concept review is required. These project concepts in many instances may consist of more than one contract, interagency agreement, or grant. Concept reviews are needed for new projects, recompetitions with changes in statements of work, and projects ongoing for five years or more since the last concept review.

The project concept reviews are conducted by the NTP Board of Scientific Counselors and are open to the public so long as discussions are limited to review of the general project purposes, scopes, goals, and various optional approaches to pursue the overall program objectives. The meeting will be closed to the public, however, if the concept discussions turn to the development or selection of details of the projects or RFPs/RFAs, such as specific technical approaches, protocols, statements of work, data formats, or product specifications. Closing the session is intended to protect the free exchange of the advisory group members' opinions and to avoid premature release of details of proposed contract projects or RFPs/RFAs.

The Board members are asked to review the project concepts for overall value and scientific relevance as well as for fulfilling the program goal of protecting public health. Specific areas should include:

- a. scientific, technical or program significance of the proposed activity;
- b. availability of the technology and other resources necessary to achieve required goals;
- c. extent to which there are identified, practical scientific or clinical uses for the anticipated results; and
- d. where pertinent, adequacy of the methodology to be used in performing the activity.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONCEPT TITLE: Support Contract for the Interagency Center for the Evaluation of Alternative Toxicological Methods

PRESENTER: William S. Stokes, Toxicology Operations Branch, ETP

OBJECTIVES: An Interagency Center for the Evaluation of Alternative Toxicological Methods is proposed to support the activities of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).^{1 2} ICCVAM is being established to coordinate test method development, validation, and review activities within the Federal government and to communicate with stakeholders throughout the process of test method development and validation. ICCVAM will be composed of representatives from NTP Executive Committee agencies and other relevant Federal regulatory and research agencies. The Center and ICCVAM implement Public Law 103-43 that directs NIEHS to develop criteria for the validation and regulatory acceptance of alternative methods, and to develop a process to achieve regulatory acceptance of scientifically valid test methods.

BACKGROUND AND APPROACH: The goal of ICCVAM and the supporting Center is to promote the scientific validation and regulatory acceptance of new test methods that are more predictive of human and ecological effects than currently available methods. To achieve this goal, the Center will provide support to the ICCVAM to facilitate scientific peer review and interagency consideration of new test methods of multi-agency interest. Emphasis will be on methods with an appropriate biological basis for the species of concern that provide for improved toxicity characterization, savings in time and costs, and, where possible, the refinement, reduction, and replacement of animal use. The Center proposal also includes the opportunity for interagency and public-private partnerships to enhance the level and scope of activities of the ICCVAM.

Peer Review Panels will be asked to develop scientific consensus on the usefulness of test methods to generate information for specific human health and/or ecological risk assessment purposes. Expert review panels will be convened to evaluate the adequacy of current methods for assessing specific toxicities, to identify areas in need of improved or new methods, and to evaluate proposed validation studies. Agencies would use this information to establish priorities for appropriate research, development, and validation efforts in collaboration with interested parties. Products of the review process will be published reports that present a comprehensive peer review of the data substantiating the validity of a new method. The ICCVAM will forward recommendations regarding the scientific validity and potential acceptability of test methods to agencies for consideration. Each Federal agency will then, according to its regulatory mandates, determine the regulatory acceptability of a method.

A Scientific Advisory Committee composed of knowledgeable representatives from academia, industry, Federal and state government agencies, public interest organizations, and the international community will review and provide advice on the activities of the Center.

¹ "Final Report: National Toxicology Program Workshop on Validation and Regulatory Acceptance of Alternative Toxicological Test Methods," March, 1996. National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.

² "Validation and Regulatory Acceptance of Toxicological Test Methods," ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Final Draft Report; October 15, 1996. National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.

The Center will be located at NIEHS and consist of 3-5 government staff augmented with a Center support contract. The support contract will provide technical and administrative support necessary to carry out ICCVAM-directed activities, which will include:

- Assessing the completeness of submissions and determining if there are sufficient data for test methods to undergo independent public scientific peer review;
- Arranging for scientific peer reviews;
- Organizing expert panels and/or workshops to assess the validation status of a method or group of methods;
- Providing recommendations and results to research and regulatory agencies;
- Communicating with interested stakeholders, and facilitating communication during the development and validation process with appropriate agencies; and
- Preparing, publishing, and distributing reports and information about new test methods, including the maintenance and updating of Internet accessible information.

Expected benefits of this initiative include:

- increased efficiency and effectiveness of test method review;
- elimination of duplicative efforts across regulatory agencies;
- utilization of shared expertise across the Federal system;
- optimal utilization of scientific expertise outside the Federal government;
- decreased total transaction costs and time to evaluate new and revised test methods;
- elimination of redundant testing;
- increased likelihood that new test methods will meet the needs of agencies; and
- increased harmonization of testing requirements across the Federal government and internationally.
- adoption of improved testing methods that may also be cheaper, faster, and provide for the refinement, reduction, and replacement of animal use.

¹ “Final Report: National Toxicology Program Workshop on Validation and Regulatory Acceptance of Alternative Toxicological Test Methods, “ March, 1996. National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.

² “Validation and Regulatory Acceptance of Toxicological Test Methods,” *ad hoc* Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Final Draft Report; October 15, 1996. National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONCEPT TITLE: Support for the Preparation of the *Biennial Report on Carcinogens*

PRESENTER: C. W. Jameson
Toxicology Operations Branch, ETP

OBJECTIVES: The scope of work for this contract includes support for literature searches, data summaries, document preparations and the gathering of production, use and regulatory data in support of the preparation of the *Biennial Report on Carcinogens* (BRC). This contract will provide the above listed support for the NIEHS BRC Review Committee, the NTP Executive Committee BRC Working Group, and the NTP Board Subcommittee for the BRC. In addition, this contract will also prepare the camera ready draft of the BRC for submission to the Secretary, DHHS for final approval.

BACKGROUND: The *Biennial Report on Carcinogens* (BRC) is prepared in response to section 301 (b) (4) of the Public Health Service Act which stipulates that the Secretary of the Department of Health and Human Services (DHHS) shall publish a report which contains a list of all 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. This responsibility has been delegated by the Secretary to the Director, National Toxicology Program (NTP). The Director, NTP, initiated a review of the BRC in 1995 to broaden input into its preparation, broaden the scope of scientific review associated with the Report, and provide review of the criteria used for inclusion of substances in the BRC. This review was completed with the approval of the revised BRC criteria by the Secretary, DHHS in September, 1996. The major change in the BRC which will take place as a result of the approved revised criteria for listing substances is to include consideration of all relevant information, including mechanistic data. This also allows for removal of substances from the BRC when new information becomes available. In the application of these proposed revised criteria, 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 sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. Another major change that has resulted from this review activity was the establishment of an expanded, formal review procedure for the inclusion or removal of substances in the BRC. This expanded review procedure provides outside peer review with the establishment of a new, standing subcommittee of the NTP Board of Scientific Counselors which adds another comprehensive peer review step to this process. Anyone may nominate a substance to be considered for listing in or delisting from the *Biennial Report on Carcinogens*. Each petition received will be evaluated by formal procedures which includes initial review by a NIEHS/NTP Review Group, made up of senior scientists of the NIEHS/NTP staff, which will be followed by consideration by the NTP Executive Committee's Working Group for the Biennial Report on Carcinogens and also in open, public meetings by a standing NTP Board of Scientific Counselors Subcommittee for the BRC.

The current contract was established to assist in preparing the *Biennial Report on Carcinogens* for printing. The current scope of work for the existing contract was written to require support for the identification, gathering, collating, and summarizing existing data on use and exposure as well as the regulatory information for each chemical to be included in the Report. The current scope also contains a very small amount of effort for the retrieval of carcinogenicity data to augment the data provided by NTP for substances under consideration for listing in the BRC. The contractor provides support for inclusion of approximately 20 new chemicals per year in the Report as well as updating the regulatory information contained in the immediately preceding report.

PROPOSED CHANGES IN THE CURRENT STATEMENT OF WORK:

The current contract expires in October, 1997. The present scope of work is not adequate for literature searches, data summaries, document preparations and other support activities required for the three different review groups to apply the revised BRC criteria in their considerations of petitions for listing or delisting substances. The scope of work for the recompetition will be expanded to include gathering and summarizing data and information on ADME (absorption, distribution, metabolism, and excretion); genotoxicity, carcinogenesis and epidemiology studies; mechanism of action and other relevant data as it relates to applying the criteria in consideration of listing or delisting of up to 25 new chemicals per year, as well as the updating process needed for final publication of the *Biennial Report on Carcinogens*.