National Toxicology Program
Board of Scientific Counselors Meeting
January 14 - 15, 1980
An Overview

Action Abstract: Following the two-day orientation meeting, Dr. Norton Nelson, Chairperson, NTP Board of Scientific Counselors, established three ad hoc subcommittees to review three existing subject-specific areas within the NTP and to determine if the NTP's needs are being optimally satisfied:

- NTP Chemical Nomination and Selection Subcommittee
  - Dr. M. Hitchcock
  - Dr. C. Harper
  - Dr. M. Horning (Chairperson)
  - Dr. T. Shepard
- NTP Report Review Subcommittee
  - Dr. M. Horning
  - Dr. M. Mendelsohn
  - Dr. N. Nelson (Chairperson)
- NTP Automated Data Processing Subcommittee
  - Dr. J. Dunbar
  - Dr. M. Hitchcock
  - Dr. M. Mendelsohn (Chairperson)
  - Dr. A. Whittemore

Meeting Overview

The recently appointed NTP Board of Scientific Counselors met for two days at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina; this initial gathering of the NTP Board members signals a strengthening and further solidification of the NTP [attachment 1: Federal Register Meeting Announcement].

To start the meeting, Dr. David P. Rall, Director of both the NTP and the NIEHS, introduced the eight members [attachment 2] (appointed by the Secretary, DHEW) to the 60 attendees -- the NTP staff, the NIEHS staff, scientists from other governmental and industrial organizations, the public, and the press. Dr. Rall stressed the

immediate purposes of the meeting: to present a synopsis of the NTP programs, goals, and plans; to describe the relevant programs of the four NTP components [National Cancer Institute, National Institute of Environmental Health Sciences, National Center for Toxicological Research, National Institute for Occupational Safety and Health]; and, most importantly, to orient the NTP Board of Scientific Counselors to better define their role [attachment 3: Meeting Agenda].

As stated at the opening by Dr. Rall, the NTP Board of Scientific Counselors will provide scientific oversight of the NTP. The NTP Board will advise the NTP Director and the NTP Executive Committee on scientific content, philosophy, and policy of the NTP and will evaluate the merit and overall quality of the science conducted in the NTP components. Defined to the Board as our standard, the National Toxicology Program (established in November 1978) develops scientific information about potentially toxic and hazardous chemicals which can be used for protecting the health of the American people and for the primary prevention of chemically-induced disease.

The National Toxicology Program centralizes and strengthens the DHEW's activities in toxicology research, testing, and test development/validation efforts and provides toxicological information needed by research and regulatory agencies [reference: Federal Register 43(221), 53060-53061 (November 15, 1978)].

An overview of the NTP was given by Dr. Rall [references: NTP Annual Plan for Fiscal Year 1980, NTP Review of Current DHEW Research Related to Toxicology, Federal Register 45(28), 8888-8918 (February 8, 1980)]. Key orientation statements included: the NTP Board reports to Dr. J. Richmond (Assistant Secretary for Health); the prominent goals of the NTP divide into three interlocking entities:

- to expand the toxicological profiles of the chemicals nominated, selected, and being tested;
- to increase the number and rate of chemicals under test;
- to develop, coordinate, and begin to validate a series of tests/protocols more appropriate for regulatory needs. .

The NTP Executive Committee [attachment 4], which meets at approximately monthly intervals, receives the Board's directives, selects chemicals for testing, and approves the Annual Plans; the Annual Report on Carcinogens will contain known chemical carcinogens, numbers of people exposed, regulatory actions, efficiency of regulations, action proposals, and chemicals needing further or expanded testing; toxic waste dumps, agent orange, and asbestos continue as current and urgent problems; and the NIH/NTP components (NCI and NIEHS) have formed a steering committee which meets twice per month [members:

Dr. D. P. Rall, NTP; Dr. J. A. Moore and Dr. J. Goldstein, NIEHS; Dr. R. A. Griesemer and Dr. C. Grieshaber, NCI; and Ms. S. Lange and Mr. P. Waugaman, Secretariat].

Dr. N. Nelson (chairperson) congratulated Dr. Rall and the NTP for showing considerable progress during the 15 months since the formation of the NTP, indicated that NTP has been responsive to congressional goals, and urged relative governmental agencies (DOE, EPA, USDA, and others) doing toxicology research and testing to become more intimately involved with the NTP.

Dr. Rall responded that in the spring 1980, the Secretary, DHEW, will review, evaluate, and decide the future of the NTP.

Dr. N. Nelson accepted the proposed two-day agenda.

Dr. J. A. Moore, Deputy Director, NTP, detailed for the Board and the attendees the current research, testing, and validation efforts being done by the member agencies under the aegis of the NTP.

The program segments of the NTP are grouped into two categories -- toxicological research and testing, and coordinative management activities [attachments 5 and 6]. The strategy for test development and validation reviews existing and emerging methodologies to identify those which may be adequately sensitive and reproducible. Those offering improvements over older methods will be selected for validation. When basic research findings suggest new areas of toxicology testing, NTP will undertake the appropriate methods development and validation. Existing methodologies that are being examined for modification include techniques used to detect impaired liver or kidney function and neurobehavioral toxicity; new areas for methods development and validation include behavioral teratology, immunotoxicology, and short-term tests for presumptive carcinogenic potential. Fertility, reproductive, and cardiovascular toxicology continue to be inadequately addressed within the NTP; new test systems need to be developed and are being pursued.

Test methods validation signals a two-stage process:

- does the procedure(s) yield test results that are reproducible within and between laboratories?
- does the test(s) predict for toxic potential in humans?

The latter demands that the NTP continue to keep abreast of and to examine closely any results from human epidemiologic studies that correlate or contrast with experimental test data. The NTP approach to testing directs toward developing new and better test methods. This overture does not imply flaws in traditional toxicology and regulatory test requirements but reflects rapid

advancements in testing methodology and expanding boundaries of scientific knowledge. Thus, NTP plans to validate possible alternatives that may be more reliably performed, yield new toxicologic data, give results relevant to human disease, and develop a testing approach that produces equivalent results in a faster, more economical manner. Often testing results impact on regulatory or public health issues and the NTP will meld these innovative techniques with "standard" methods to ensure results that are germane and of utility to regulatory and public health needs. When standard methods are used, the NTP will attempt to incorporate those standards presently espoused by regulatory agencies, such as the life-time rodent bioassay.

The research activities described in the 1980 Annual Plan were reviewed and updated project by project -- see page 7 [references: NTP Annual Plan for Fiscal Year 1980; NTP Technical Bulletin 1(1), November 1980]. Also emphasized were the financial and people resources dedicated to the NTP as well as the overall DHEW effort in toxicology research [reference: NTP Review of Current DHEW Research Related to Toxicology, NTP-79-8]. Activities ongoing in other governmental agencies received mention and discussion.

Highlights: Fiscal Year 1980 budgetary estimates for the Public Health Service ($6.75 billion), for health research by all Federal agencies ($3.4 billion), for environmental health research by all Federal agencies ($670 million), for PHS toxicology-related research ($260 million), for NTP toxicology-related research ($69 million). The latter amount comes from the four charter member agencies: NCI - $46 million, NIEHS - $11 million, NCTR/FDA - $7 million, NIOSH/CDC - $5 million [attachment 7]. Illustratively, expanding the FY 1979 figures (total = $41 million) to the four major NTP program areas (attachment 8) shows general toxicology ($12 million), carcinogenesis ($12 million), coordinative management ($11 million), genetic toxicology ($5 million).

Nineteen PHS agencies support toxicology-related research: of the $262 million identified above, 84 percent ($219 million) resides with the four NTP components (44 percent for basic research, 47 percent for testing and validation, and 9 percent for methods development).

For toxicology, PHS agencies anticipate 588 in-house person-years in FY 1980; 93 percent (544) of which originates from the NTP members. These agencies contribute 176 person-years to the NTP.

Dr. Rall defined three areas upon which the NTP Board should concentrate: quality of the science and scientists within the NTP; quality of the program design (areas over- or under-emphasized); chemical nomination and selection process (need to minimize significant omissions for nominating chemicals), examine current experimental designs and protocols, information generation and dissemination.

Dr. R. Griesemer, Associate Director, NCI/NTP, communicated the workings of the NCI/NTP carcinogenesis program. Members of his staff dealt with particular areas of expertise (Dr. J. Douglas, Dr. C. Grieshaber, Dr. T. Hamm). The professional staff associated with the three branches of the carcinogenesis testing program were identified (attachment 9).

The following summarizes these presentations and their discussion:

During FY 1979, the NTP was testing 201 chemicals for carcinogenic potential in lifetime rodent bioassays; of these, 79 chemicals were started on bioassay in FY 1979. During the year, tests were completed and reports issued on 95 chemicals. Under the conditions of the tests, 47 (49.5%) were considered negative, 39 (41%) positive, and 9 (9.5%) equivocal carcinogens. Reports of 44 more of these chemicals are scheduled for issuance in FY 1980. Dependent upon actual resource availability and allocation, testing on 75 to 100 chemicals will be initiated in FY 1980.

The NTP objective: to assure that the most important chemicals from a public health point of view are tested and that the end results are relevant to the research and regulatory agencies. Further, to provide better information for assessing human risks associated with those chemicals found to be carcinogenic in experimental animals.

A lifetime bioassay in rodents is the current procedure utilized to determine carcinogenic potential of a chemical. The NTP does not propose alternative methods but acknowledges a need to develop and validate less expensive and more rapid methods that may allow chemical testing priorities to be established or in some instances to supplant the need for lifetime bioassays.

For instance, in vitro mammalian cell transformations are potential short-term assays for indicating carcinogenic potential of a chemical. Transformation assays being evaluated include BALB/c 3T3, Fischer Rat Embryo (RLV infected), hamster embryo, and C3H 10T½. In FY 1979, tests on 31 chemicals were initiated in hamster embryo clonal assays and the BALB/c 3T3 focus assay. These chemicals were selected on the basis of adequate lifetime carcinogenesis bioassay results and on the mutagenicity data derived from standardized Salmonella assays. This validation initiative will be completed in FY 1980.

An in-progress testing program will better permit comparison of standardized Salmonella assay results with lifetime rodent bioassays.

The mouse lung adenoma model is proposed as an in vivo system for determining carcinogenic potential of a chemical in a relatively short period of time. Lung adenomas are indigenous in aging strain A mice. Treating this strain with drugs and selected environmental contaminants

known to be carcinogenic has shortened the period of tumor occurrence and increased the number of adenomas in a dose related fashion. Conclusions similar to those obtained from the lifetime bioassay were obtained with this model for over 70 percent of a limited number of chemicals. In FY 1979 a project plan was completed that will evaluate and validate lung adenoma occurrence in the strain A mouse as a model to rapidly screen and set priorities for candidate test chemicals. Sixty chemicals previously tested in lifetime bioassays will be tested in the strain A mouse during FY 1980 and an additional 30 chemicals in FY 1981.

During FY 1980, the appearance of precursor (preneoplastic) liver lesions in hepatectomized rats treated with carcinogens will be evaluated as a potential in vivo model for predicting carcinogenesis at an earlier stage.

Carcinogenicity testing traditionally begins with young adult animals (typically six-week old rodents). However, human chemical exposures often occur during in utero development and infancy, as well as throughout life: exposure of pregnant workers; use of drugs; accumulation, persistence, and excretion via mother's milk; neighborhood contamination; and others. The adequacy of lifetime bioassay methods compared to methods that also include prenatal and neonatal exposures is being evaluated using four chemicals: a commercial polybrominated biphenyl, phenytoin (diphenylhydantoin), ethylene thiourea, and chlordecone (a chemical with estrogenic properties).

Inhalation bioassays for carcinogenicity usually involve an arbitrarily determined duration of exposure. The required specialized facilities are expensive and commit scarce technical staff for extended periods. Ongoing studies with mice, rats, and hamsters use a design which varies the age of animals and the duration of exposure to a known carcinogen, vinyl chloride. The testing hypothesis seeks to compare tumor response among species and to analyze exposure regimens that provide a predicted carcinogenic response. These studies, projected for completion in FY 1980, may provide meaningful bioassay results using a shorter duration of exposure.

The length of time necessary to complete a bioassay (from chemical selection to report issuance) continues to be misunderstood or misinterpreted. The long used phrase "two-year bioassay " ordinarily refers only to the time the experimental animals are under test; this may be a source of confusion. Routinely, a longterm carcinogenesis bioassay consumes 64 months or 5.3 years [attachment 10] when such elements as chemical nomination and selection, data analysis, report preparation, and so forth are included (see attachments 30, 31, and 32). The time period lengthens when short term prescreen testing must be done prior to selection. Add to this the identification and investigation of potential contractors for bioassay (attachment 11), the calendar stretches even further.

Other items of interest included small rodent bioassay guidelines (attachment 12), concepts of a bioassay program (attachment 13), spontaneous tumor incidence in untreated mice and rats (attachment 14), experimental design and protocols, bioassay reports scheduled for review (attachment 15), chemical classes under review (attachment 16), and a structure class study report on aromatic nitro compounds (attachment 17).

Areas in need of continuous monitoring and strenghtening concomitant with science advancements: chemical selection; literature gathering; safety and handling; chemical procurement, analysis and storage; species and strain selection and use; animal breeding and shipping; experimental oversight; investigative data and histopathologic slide utilization and storage; technical report preparation and dissemination; and chemical combination testing.

Dr. Moore stated that the toxicology research and testing within NTP divides into three major disciplines: genetic toxicology, general toxicology, and carcinogenesis (see previous section). Other program areas have been arbitrarily assigned to one of these three, even though much interaction occurs; for example, interprogram utility of *Salmonella* mutation assays within the genetic toxicology and the carcinogenesis programs.

The screening program consists of four phases or tiers that progress in complexity from simple systems composed of microbial or mammalian cells in culture, to *Drosophila* systems, to specific whole animal mammalian systems, to data evaluation and report generation [attachments 18 and 19].

These four ongoing and interacting testing/research phases are summarized below.

Genetic Toxicology - Mutagenicity assays identify structural and functional DNA perturbations in germinal and somatic cells. Effects in germ cells are important for predicting potential undesirable effects on fertility, on the developing conceptus, and on subsequent generations. Somatic mutation may predict for physiological alterations in the exposed person and may forecast for potential induction of cancer.

In FY 1980 the NTP will increase the rate of *in vitro* microbial mutagenesis testing to 300 chemicals, will commence parallel testing in cultured mammalian cells at a rate of 70 chemicals, and will begin Phase II testing utilizing *Drosophila* systems at a rate of 30 chemicals per year. All chemicals selected for general toxicology and for lifetime carcinogenesis bioassay will be first tested using the *Salmonella* mutagenesis screen.

General Toxicology - Prior to conducting and interpreting any specialized experiments in carcinogenesis, reproductive toxicology,

teratology, or neurobehavioral toxicology, the effect of the chemical on the general health of the test animal must be known. During FY 1980, studies will continue to develop a composite toxicologic screen that will identify vital organ damage (hepatic, renal) which results in a generalized toxicity and one that gives presumptive evidence of specific toxicities relating to fertility and reproduction, neurobehavioral toxicology, and immunology. The screen will also establish the range of doses over which toxicities occur, the variability of toxicity between male and female rats and mice, and, in certain instances, will establish the basic disposition pattern of a chemical as a function of dose and time. Then, presumptive evidence of specific organ system toxicity will be further studied by the appropriate test procedures.

The NTP continues to identify and develop more sensitive methods for detection of injury to hepatic and renal function. Renal toxicity methods being reviewed and validated include kidney functions (concentrating ability and excretion rate of major nephron segments) as well as early indicators for cellular damage (presence of selected intracellular enzymes in urine).

Briefly outlined below are the major areas within the realm of general toxicology: chemical disposition, immunologic toxicology, neurobehavioral toxicology, pulmonary toxicology, and reproductive and developmental toxicology.

Chemical Disposition - Developing knowledge about the absorption, distribution, metabolism, and excretion of chemicals selected for testing remains a major objective of the NTP. Information necessary for the proper design and interpretation of toxicology and carcinogenicity studies includes knowing if a chemical accumulates in the body, causes toxic effects directly or through formation of a metabolite, and whether these events occur only at certain dose levels or if there is a species difference in pathways or rate of chemical disposition.

Resources available to NTP in FY 1979 were principally through two university contracts, to be strengthened in FY 1980 by recruiting two scientists to the NTP intramural component and expansion of contract capability from two to four laboratories. This will permit 12 to 15 chemicals to be studied in FY 1980 with a planned increase to 24 by the end of the year.

For the most efficient use of limited resources, preference in selection of work strives toward developing a core of knowledge based on chemical class characteristics that can be used to predict disposition patterns of new chemicals within that class or in chemically related classes. Studies on three major chemical classes continue: halogenated polyaromatics, benzidine-based dyes, and haloalkyl phosphates.

Chemicals belonging to the halogenated polyaromatics include several polychlorinated biphenyls (PCBs) and a chlorinated-dibenzodioxin,

-dibenzofuran, and -azobenzene. Disposition of selected PCBs has been studied comparatively in the rat, dog, and monkey; the biologic half-life of a PCB in a species depends upon the capacity of that species to metabolize the PCB to an excretable polar compound. Species vary widely in ability to metabolize PCBs: dog > rat >> monkey. Excretion of unchanged PCBs prior to metabolism is negligible in all species studied. Current work concerns identifying metabolites and establishing the disposition pattern of 3, 4, 3', 4'-tetrachlorobipehnyl, one of the more toxic PCBs, in the rhesus monkey. These studies, to be completed in FY 1980, may advance our ability to better interpret the public health significance of PCB experimental toxicology data.

Information about the chemical disposition of chlorodibenzodioxins resides primarily on 2,3,7,8-tetrachlorodibenzo-p-dioxin. This knowledge base will be expanded in FY 1980 through study of octachlorodibenzodioxin, the chemically related 2,3,7,8-tetrachlorodibenzofuran, and the stereo-chemically related 3,4,3',4'-tetrachloroazobenzene. Comparative species assessment will be done using the rat, guinea pig, and monkey.

The benzidine-based dye studies are designed to determine whether the biological conversion of benzidine-based dyes (as well as o-tolidine- and dianisidine-based dyes) to the free precursors (benzidine, o-tolidine, and dianisidine, which are carcinogens) is a general phenomenon. Thirteen dyes are being studied in the dog and will be completed in early FY 1980 [Attachment 20]. Interim results indicate that benzidine-based dyes revert to benzidine and excretion of benzidine in urine occurs after administration or exposure to benzidine-based dyes.

The haloalkyl phosphates include fire retardants and insecticides. Two of these compounds [tris (1,3-dichloroisopropyl) phosphate ("Fyrol FR-2") and tris (2,3-dibromopropyl) phosphate ("Tris")] are being studied to determine if these structurally related haloalkyl phosphates follow similar patterns of tissue distribution, metabolism, excretion, and covalent binding.

A continuing priority of chemical disposition studies under NTP is the extrapolation of laboratory data to humans. One way to facilitate more accurate extrapolation of chemical metabolism information from animals to humans involves developing *in vitro* animal and human cell cultures that proportionally reflect *in vivo* metabolism. The initial *in vitro* systems to be studied use tissues from rats, dogs, and monkeys.

Immunologic Toxicology - NTP is committed to studies that establish the role of immune assessment in toxicologic characterization of chemicals. Six immunologic functions were selected in FY 1979 as part of a test battery: 1) *in vitro* lymphocyte response to mitogens; 2) *in vitro* macrophage function; 3) antibody response to a T&B cell-dependent antigen; 4) delayed hypersensitivity; 5) host resistance; and 6) sensitivity to endotoxin. In some instances the preferred method to assess a specific immunologic function can only be determined through a comparison of methods. Research on methods selection will continue

in NTP laboratories with validation and interlaboratory comparison through contracts awarded in FY 1980. An interim immunology test battery is being selectively used in the NTP toxicology screen. Methods for indepth characterization of immunosuppression are also being developed in NTP laboratories, and a framework for collaborative studies has begun with selected chemicals among NTP laboratories.

Neurobehavioral Toxicology - Laboratories within the NTP are actively engaged in the development and validation of methods for testing neurologic and behavioral effects of chemicals.

A standardized test battery, previously developed, is being validated by evaluating the effects of nine neurotoxic chemicals: 1) acrylamide, 2) d-amphetamine, 3) arsenic trioxide, 4) chlordecone, 5) lead acetate, 6) methyl mercury, 7) polychlorinated biphenyl, 8) sodium salicylate, and 9) triethyl tin. Two objectives stand paramount: 1) to determine the ability of neurobehavioral procedures to detect an unexpected neurotoxic effect and to ascertain the capability of each test to provide an expected negative result; and 2) to generate a profile of effects for each substance so that tests assumed to measure the same or similar functions can be compared for relative sensitivity. The test battery includes methods that assess sensory function, motor strength and coordination, associative and cognitive factors, and emotionality.

An interim neurobehavioral test battery will also be selectively utilized in the NTP toxicology screen. A test capability for more extensive characterization of six chemicals per year will be developed by contract in FY 1980. The neurobehavioral toxicity of chlordecone is being accomplished in NTP laboratories in response to public health concerns from the state of Virginia. These studies include the description and the persistence of effects in adult rats and in rats exposed during development.

Pulmonary Toxicology - Toxicity testing of inhaled materials rarely includes an assessment of pulmonary function. In recent years a number of techniques have been developed that measure indices of pulmonary function in rodents -- static lung volumes, static and dynamic lung properties, diffusion, and information about the distribution of ventilation. The applicability of these measurements in the assessment of pulmonary toxicity as well as their sensitivity compared to pathologic evaluation of lung damage remains to be demonstrated. Through contract agreements, NTP has initiated a series of studies centered around a comprehensive comparison of morphologic change versus functional change to validate the usefulness of respiratory physiology techniques. Six compounds will be evaluated using the rat and hamster at three dose levels during FY 1980 and FY 1981.

Reproductive and Developmental Toxicology - Fertility and reproduction are major areas that require toxicologic methods development and testing. Because these are areas in which personnel and resources available to NTP are in short supply, innovative methods development is not proposed,

and efforts will be confined to test procedures that settle within the capabilities of general toxicologists.

Teratology plans in FY 1980 represent a continuation of programs outlined in FY 1979: 1) evaluate definitive human and animal chemically-associated teratology data to insure that this information is being most effectively utilized; 2) examine laboratory data to determine the range of doses that indicate linearity of response and permit identification of biomathematical procedures for low dose risk estimation; and 3) examine fetuses histopathologically for comparison with traditional methods to determine the adequacy of current methodology.

Testing of chemicals for teratogenic effects will continue at a rate of 8 to 10 per year: chemicals in progress are ethylene chlorhydrin, ethylene oxide, formaldehyde, pentachloroanisole, toluene, and the xylenes (o-, m-, p-, and mixed). Results are scheduled to be reported in FY 1980 [Attachment 21]. Five additional chemicals have been scheduled for testing: caffeine, dimethylaniline, ethoxy ethanol, lead monoxide, and 2,3,7,8-tetrachlorodibenzofuran; whereas, an additional 34 chemicals have been selected for test [attachment 21a].

Incidence of behavioral disorders and learning deficits observed in children, together with the demonstration of behavioral dysfunctions in animals following prenatal exposure to a variety of chemicals, suggests the need for behavioral evaluation of neonates in the safety assessment of new drugs and chemicals. Incorporation of behavioral evaluation into testing guidelines should be determined after reviewing data that have been produced under standardized and validated test conditions. The effects on behavior resulting from prenatal exposure to chemicals initiative (behavioral teratology) is to identify and develop screening methods which: 1) yield valid and reproducible results within and among laboratories; 2) are sensitive to toxic alterations produced by a range of agents with varying toxic potential; 3) predict toxic effects in humans; and 4) are cost efficient.

In FY 1979 a test protocol was developed and studies initiated that will standardize these tests for the reliability and sensitivity of six behavioral methods using three chemicals known to cause behavioral teratogenic effects -- Vitamin A, methyl mercury, and d-amphetamine. The planned activities for FY 1980 are to conduct pilot studies, select six laboratories to conduct the studies, and begin the test validation experiments.

Dr. F. deSerres, Associate Director for Genetics, NIEHS, offered the initial conclusions from the international collaborative study to evaluate a range of short-term assay systems for their ability to predict chemical carcinogenicity. Testing (30 assay systems and 42 chemicals) was completed in FY 1979 with decoding and combined analyses being accomplished now. At an NTP public meeting in early December 1979, the coordinating committee delivered a preliminary assessment of results from the three-year study (attachment 22).

Dr. J. E. Huff, Senior Toxicologist, NTP, catalogued the information generation and dissemination activities of the NTP (attachment 23). Areas needing attention: coordinating the various literature gathering efforts within the NTP, defining and beginning an NTP publication and reports procedure, establishing an online management information system, and developing an action plan for an integrated technical information component.

Information Generation and Dissemination -- The National Toxicology Program must ascertain the toxicology of selected chemicals and assure that results will have regulatory significance. The end product is information -- scientific information necessary in deciding societal issues relative to our health and environment. To provide that information, the NTP identified two important aspects: first, information must be disseminated to other scientists so that peer review and feedback assure scientific quality; second, since the scientific product helps society evaluate identified toxicological risks, information must be disseminated to not only the regulators responsible for protecting against potentially hazardous risks, but also to those exposed to the risks. Thus, the NTP will establish and use a coordinated communications network to disseminate toxicological information.

The value of information arising from NTP will depend in part on the quality and timeliness of information received into the program. The NTP will therefore actively seek information from all sources: Federal, state and local governments; trade associations, industry, labor; academia; professional societies and public interest groups; the press; individuals; other countries; and all other interested parties. Information received could include nominations of chemicals to be tested; critique and questions about scientific procedures, policies, priorities, and resource allocations; and any other suggestions for program improvement. To encourage multiple communication, NTP program materials must be disseminated widely and rapidly, and questions answered in a timely manner.

Communication is critical to a successful NTP. While the final NTP product will be information useful to individuals, the first priority for FY 1980 must necessarily be in areas of management and quality monitoring of the testing program, and in developing and validating the necessary battery of tests so that useful information may be produced. Consequently, some of the planned activities [discussed in the Annual Plan] may not be fully accomplished in 1980.

The NTP program for information generation and dissemination includes:

Scientific Coordination and Peer Review
Technical Report Preparation and Dissemination
Interagency Coordination
International Coordination
Public Awareness and Inquiry Response

NTP Publications - The 1980 NTP Annual Plan contains information on the NTP's research, testing, and validation efforts for the coming fiscal year as well as for the previous fiscal year. This 117-page report divides into ten sections: Introduction and Executive Summary, Background, Participating Agencies, Oversight and Review, Planning Assumptions and Program Balance, Organization, Toxicology Research and Testing Overview, Coordinative Management Activities, Information Generation and Dissemination, and Annual Report on Carcinogens.

A companion to the NTP Annual Plan is the 334-page NTP Review of Current DHEW Research Related to Toxciology. This compilation emphasizes three major areas: DHEW Agencies' Role in the Support of Toxicology Research, Testing, and Method Development; Chemical Compounds Currently being Tested by DHEW Agencies for Toxicological Properties; and Toxicology Methods Currently being Developed by DHEW Agencies.

The NTP TECHNICAL BULLETIN series will serve as the NTP communication medium to keep all those interested in the NTP informed about the NTP's most current and proposed activities. The first issue was distributed in November 1979; the second issue will be mailed during January/February.

Dr. T. Cairns, Acting Director, National Center for Toxicological Research spoke about the NCTR and the program portions responsible and responsive to the NTP [attachment 24]. [The newley appointed Director of the NCTR, Dr. R. Hart, also attended the meeting]. The NCTR organizational chart (attachment 25) shows the NTP activities depicted as dashed containers and the toxicology decision tree [attachment 26] reflects the potential flow pattern of a chemical.

NCTR was established in 1971 to undertake a research program in toxicology; the current emphasis continues on toxicology; 300 staff and 500 contract people work in 400,000 square feet of renovated space (1×10^6 square feet available).

A memorandum of understanding between the FDA and NTP shows an annual staff dedication of 42.8 persons and a contribution of $7 million. Office of Scientific Intelligence (7 person years) receives chemical nominations and prepares NTP Executive Summaries for the NTP Executive Committee (attachment 27; discussed below by Dr. Fishbein); the Toxicology Data Management System (TDMS; 3 PY; attachment 28); Teratology (11.1 PY; discussed above by Dr. Moore); Mutagenesis, heritable translocation (5 PY; section by Dr. Moore); Compound Evaluation (16.7 PY; attachment 29; see section by Dr. Griesemer).

This continuing yearly commitment to the NTP absorbs 33 percent of the NCTR's human and financial resources and capabilities.

Dr. L. Fishbein, Director, Office of Scientific Intelligence, NCTR, annotated the NTP Chemical Nomination and Selection Procedure.

More chemicals are nominated for NTP consideration than can be selected for study. Early recognition of this pending asymmetry led the NTP Executive Committee to formulate perhaps the most important set of program guidelines within the entire NTP organization. These resultant eight chemical selection criteria [attachment 30 motivate an NTP matrix which operates throughout the NTP. All research, testing, and validation efforts start here [attachment 31].

Most chemicals are nominated and selected for testing because toxicologic information is lacking and because the potential exists for human exposure. Other important criteria include production levels, physical and chemical properties, agency interest, and significance to society. The NTP toxicology testing strategy: identify with assurance the major toxic effects for each chemical studied on chronic test. This includes (in addition to identifying chemical mutagens and carcinogens) damage to critical target organs such as the lungs, liver, and nervous system. Thus, Phase I tests result in a core of toxicology data essential to the proper design of more extensive studies. As an example, using the information from the Phase I rodent toxicologic screen, Phases II and III testing can be started with increased capabilities to confirm and better define toxicities identified in the screen.

Compound elements for the NTP Executive Summaries are:

A chemical agent
B surveillance index
C human exposure and health effects
D research hypothesis
E proposed categories of study
F assessment of recommended research
G rationale and nominator
H references

The NTP Chemical Evaluation Group consists of members from these agencies: CPSC, EPA, FDA, NCI, NIEHS, NIOSH, OSHA.

Dr. I. Baumel, Director, Division of Criteria Documentation and Standards Development, NIOSH, described in general the organizational [attachment 32] and functional aspects of the NIOSH, speaking in more detail about the toxicology oriented sections. Five specific disciplinary groups have been identified as NTP: behavioral neurotoxicology, reproductive hazards (teratology), mutagenesis and carcinogenesis test systems, respiratory disease research, and general toxicology.

Dual interests surround worker protection and risk assessment.

NIOSH contributes to the NTP $5 million (24 person years): 75 percent inhouse and 25 percent contract; 60 percent toxicology

evaluation, 30 percent basic toxicology, and 10 percent toxicology methods. All the NIOSH basic toxicology work resides in the NTP.

The Registry of Toxic Effects of Chemical Substances (RTECS) received descriptive attention.

Dr. Rall summarized the two-day meeting and listed five specific topics identified during the discussions as needing the Board's leadership:

1. Science Review
2. Chemical Nomination and Selection Process
3. Protocol and Experiment Design
4. Preparation, Review, and Dissemination of Information and Reports
5. Automated Data Processing

Dr. Nelson, following discussion of the above issues, appointed three subcommittees:

- NTP Chemical Nomination and Selection Subcommittee

  Dr. M. Hitchcock
  Dr. C. Harper
  Dr. M. Horning (chairperson)
  Dr. T. Shepard

- NTP Reports Review Subcommittee

  Dr. M. Horning
  Dr. M. Mendelsohn
  Dr. N. Nelson (chairperson)

- NTP Automated Data Processing Subcommittee

  Dr. J. Dunbar
  Dr. M. Hitchcock
  Dr. M. Mendelsohn (chairperson)
  Dr. A. Whittemore

Adjournment

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL TOXICOLOGY PROGRAM

TO : NTP Board of Scientific Counselors

DATE: March 19, 1980

FROM : Senior Toxicologist, NTP

SUBJECT: Initial Meeting of the NTP Board of Scientific Counselors (January 14-15, 1980) -- An Overview

The attached interpretation of the January Board meeting reflects the detail of the multiple presentations and the need to document this first gathering.

JEHuff

J. E. Huff, Ph.D.

Distribution:

Board Members

Dr. J. Dunbar
Dr. C. Harper
Dr. M. Hitchcock
Dr. M. Horning
Dr. M. Mendelsohn
Dr. N. Nelson
Dr. T. Shepard
Dr. A. Whittemore

Speakers

Dr. D. P. Rall
Dr. J. A. Moore
Dr. R. A. Griesemer
Dr. J. Douglas
Dr. C. Grieshaber
Dr. T. Hamm
Dr. F. deSerres
Dr. T. Cairns
Dr. R. Hart
Dr. L. Fishbein
Dr. I. Baumel

cc:

Dr. P. Craig
Mr. R. Cullen
Dr. J. Dean
Dr. R. Gryder
Dr. L. Hart
Dr. J. Haseman
Dr. C. Jameson
Dr. C. Kimmel
Dr. H. Kissman
Dr. A. Konvicka
Ms. S. Lange
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