

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

MARCH 24 and 25, 1986

SUMMARY MINUTES

National Toxicology Program
Board of Scientific Counselors Meeting
March 24-25, 1986

Summary Minutes

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NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING

March 24 and 25, 1986

SUMMARY MINUTES

The National Toxicology Program (NTP) Board of Scientific Counselors met on March 24 and 25, 1986, in the Conference Center, Building 101, South Campus, 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 and Expert Consultants). Members of the Board are Drs. James Swenberg (Chairperson), Norman Breslow, Michael Gallo, Jerry Hook, Jeanne Manson, Mortimer Mendelsohn, Frederica Perera, and Henry Pitot. Dr. Breslow and Dr. Mendelsohn were unable to attend the meeting.

Review of NTP Reproductive and Developmental Toxicology Programs

I. Overview: Dr. Ernest McConnell, Director, Toxicology Research and Testing Program, NIEHS, introduced the review by stating that these programs best exemplify an NTP effort that successfully integrates the resources and scientific activities of the NTP participating agencies (NIEHS, the National Center for Toxicological Research (NCTR), and the National Institute for Occupational Safety and Health (NIOSH)). Dr. Bernard Schwetz, Chief, Systemic Toxicology Branch, NIEHS, and Coordinator of the NTP Reproductive and Developmental Toxicology Program, then described the major areas of reproduction and fertility, developmental toxicology and short-term tests. He noted that since the last Board review three years ago a Board subcommittee had been formed to provide continuing guidance and consultation to the reproductive and developmental toxicology programs. Dr. Schwetz reviewed program funding and how dollars and staffing were allocated. Staff from the three agencies meet every three or four months to select chemicals for testing, to review contracts, and, in general, set program priorities. He concluded by outlining how the programs fit into the overall NTP efforts.

The review format used combined platform presentations with poster sessions for most of the projects described in these minutes. This was the first time posters had been used to complement oral presentations at a peer review of an NTP program by the Board.

II. Reproduction:

A. Testing and Methods Development in Reproductive Toxicology - Dr. James Lamb, now at EPA, described the major projects in methods development and validation: (1) Sperm morphology and vaginal cytology evaluation (SMVCE). This protocol involves addition of several endpoints to be performed at the termination of 90-day subchronic studies in rodents. SMVCE data, collected from 54 studies, provide an early warning of reproductive toxicity and aid in setting priorities for further studies; (2) Mating trial studies in rodents which involve exposure of male animals for 60 days and female animals for 30 days prior to a seven day mating period. Dosing continues through pregnancy and lactation with evaluation of offspring at fixed intervals; and (3) Fertility

assessment by continuous breeding (FACB). This protocol evaluates the effects of long-term chemical exposure on fertility and reproductive function in mating pairs of mice housed together continuously for 14 weeks, and is considered an alternative to standard multigeneration studies. The FACB assay seems to be a more sensitive indicator of effects of chemicals on fertility while evaluating a number of other endpoints and is less expensive and time consuming than multigeneration studies. The FACB assay seems to be a more sensitive indicator of effects of chemicals on fertility while evaluating a number of other endpoints and is less expensive and time consuming than multigeneration studies.

B. In Vivo/In Vitro Studies of Male Reproductive Toxicology - Dr.

Robert Chapin, NIEHS, described a primarily inhouse effort in applied research with four major program areas: (1) Target cell definition, i.e., where a chemical exerts its toxic action in the testes. He discussed studies with two testicular toxicants, dimethyl methylphosphonate and ethylene glycol monomethyl ether; (2) Development and evaluation of improved methods for structural preservation of testes from NTP chronic and prechronic studies to enable earlier and better detection of organ changes; (3) Investigation of early biochemical changes with emphasis on studying correlations between chemically induced histopathologic changes in the testes and increases in sorbitol dehydrogenase; and (4) Development of primary cultures of testicular cells, especially enriched with Sertoli cells which have been shown to be target cells for most testicular toxins. Future efforts will focus on optimizing culture conditions and characterizing endpoints.

C. Human Semen Analysis - Dr. Steven Schrader, NIOSH, said the primary goals are to develop reliable methods of assessing male reproductive potential and to detect deficiencies in reproductive potential due to occupational hazards. Until the last few years, sperm count (often quite variable) and sperm morphology were the only commonly used measures. Thus, a major activity has been development of a semen profile which is being evaluated in NIOSH field studies of workers exposed to ethylene dibromide or glycol ethers. Parameters in the current profile include: sperm count, viability, motility, velocity, morphology and morphometry, as well as semen volume and pH. Additionally, semen viscosity, osmolarity and biochemical markers are being considered for inclusion. A major effort underway is a longitudinal study over time in a cohort of men known to have neither fertility problems nor occupational chemical exposure to develop a baseline profile of "normal" values.

General Discussion: Discussion by the Board and ad hoc reviewers was concerned with coordination among the agencies especially in view of recent personnel losses, and plans to replace staff and maintain continuity in program areas affected by the losses.

III. Short-Term Tests:

A. Evaluation of Two In Vitro Teratology Test Systems - Dr. Richard Morrissey, NIEHS, reported on progress and current status of the assessment of (1) the mouse ovarian tumor cell attachment inhibition assay (MOT), and (2) the human embryonic palatal mesenchyme cell growth inhibition assay (HEPM) as in vitro teratogenesis testing systems. The objectives of these studies are to: (1) test and evaluate protocols suitable for inter-laboratory utilization; (2)

compare intra- and inter-laboratory variability; (3) propagate and cryo-store large lots of mycoplasma-free ascites MOT cells and HEPM cells; and (4) develop standard assays that can incorporate exogenous metabolizing systems, using model teratogens. These objectives contribute to long-range NTP goals of improving criteria for selecting chemicals for whole animal testing, and of helping to assign priorities for testing chemicals. Evaluation and comparison of the two assays is being based on tests of 45 chemicals in each system at two different laboratories. Dr. Morrissey said analyses of the data from the first 13 chemicals indicate good qualitative and quantitative agreement between the two contract laboratories and that HEPM cell growth appears to be more sensitive to chemical toxicity than MOT cell attachment.

B. Evaluation of Drosophila As a Teratology Screen - Mr. Ronald Schuler, NIOSH, said the objective was to investigate the potential of a test system using Drosophila melanogaster to screen for teratogens. The system had been developed and refined inhouse. Testing of 17 known teratogens produced positive findings in varying degrees. The NTP Board reviewed the project and recommended a data base be developed using a select list of 47 known teratogens and non-teratogens. Currently, this evaluation is being conducted under contract. Areas of concern include: how well Drosophila data correlate with teratogenesis data in mammals; important endpoints; number of endpoints required; and economic advantages of the test system. Mr. Schuler commented on a planned research project wherein activity of the enzyme ornithine decarboxylase (ODC) will be measured in Drosophila larvae in testing the hypothesis that certain teratogens indirectly interfere with polyamine synthesis through inhibition of ODC activity.

C. Short-Term In Vivo Reproductive Toxicity Assay (Chernoff/Kavlock Test) - Dr. Bryan Hardin, NIOSH, noted that the assay had been proposed for use in reducing the backlog of chemicals recommended for reproductive toxicity testing by the NTP, in structure-activity (class) studies, and to develop preliminary data for establishing priorities for conventional testing. He described the current protocol and said tests have been completed on 60 chemicals including two class studies (glycol ethers and phthalic acid esters). Results were consistent with conventional test data, particularly for glycol ethers. Dr. Hardin suggested the assay be made available to Chemical Managers for use in contract laboratories conducting prechronic and chronic studies as it does not involve any techniques that are beyond the capabilities of these laboratories.

General Discussion: Initial discussion focused on whether the in vivo test provided enough information, should be more than one dose level, etc. There seemed to be some agreement that the assay's value was in helping to set priorities and for class studies.

IV. Developmental Toxicology:

A. Neurobehavioral Teratology Testing and Methods Development - Dr. Carole Kimmel, EPA, and former coordinator of the NTP Program, summarized the design and conduct of the six-laboratory collaborative behavioral teratology study and discussed the results which had been presented at a symposium and workshop in

September 1985. She reported that the results indicated that behavioral teratology data are reproducible if adequate attention to study design and testing procedures are maintained. The sensitivity for most of the test procedures was excellent, requiring no more than a 5-20% change from control values to detect a statistically significant effect. Dr. Kimmel commented that uses of the tests in risk assessment included: (1) elucidation of the long-term consequences of perinatal findings; (2) establishing the relationship of behaviorally effective doses to overtly toxic doses; and (3) helping focus on the types of effects which may be important to monitor in an exposed human population. Currently, six of the tests are being used by NIOSH to evaluate behavioral teratologic effects after inhalation exposure of animals to selected alcohols.

B. Postnatal Toxicity Studies - Dr. Lori Dostal, NIEHS, said objectives were to: (1) characterize the toxicity of chemicals to neonatal animals relative to that in adults, and (2) study the transport of drugs and chemicals through the milk and evaluate the effects of chemicals on the quality of the milk. She described completed studies characterizing the transfer of diethyl-hexylphthalate and DDE through the milk of rats and effects on the quality of lactation, and a planned study with cimetidine. A long-term goal is to characterize the transfer of several compounds with different physical/chemical properties through the milk of rats, and to compare the results, when possible, to those in humans.

C. Cardiovascular Functional Teratology - Dr. Mark Toraason, NIOSH, said this was a NIOSH focus because cardiovascular disease is the number one cause of death in the U.S., a high incidence of congenital malformations are associated with the heart, and, finally, the heart appears to be a target organ for glycol ether toxicity. The objective is to develop and use new and improved methods for assessing functional impairment in fetal and neonatal animals following in utero exposure to developmental toxins. Dr. Toraason described studies characterizing physiologic (electrocardiographic) and biochemical (inhibition of ornithine decarboxylase activity) alterations in neonatal and fetal rats exposed prenatally to the teratogen ethylene glycol monomethyl ether.

D. Inhalation Reproductive and Developmental Toxicity Studies - Dr. Bryan Hardin, NIOSH, noted that a concept for this effort had been presented and approved by the Board in March, 1984. He described the five tasks to be completed under an ongoing interagency agreement as being: (1) review of available information on a chemical and test recommendation; (2) development of specific protocols; (3) engineering and analytical studies; (4) range-finding studies to select exposure concentrations; (5) conduct of definitive studies, and (6) preparation of a final report. The definitive studies selected were (1) conventional teratology, (2) behavioral teratology, (3) female fertility assessment, (4) dominant lethal assay, and (5) sperm head morphology. He said seven chemicals had been selected for study. For one, 1,3-butadiene, all in-life studies were completed. The others selected were n-hexane, tetrahydrofuran, acetone, isoprene, chloroprene, and methylethyl ketone.

E. Developmental Toxicity Testing, and Special Studies in Developmental Toxicology - Dr. Richard Morrissey, NIEHS, listed the findings for chemicals evaluated in conventional teratology assays during FY 1983 to FY 1986. He

discussed a study in progress with 1,1,1-trichloroethane (methyl chloroform) in drinking water. Dr. Morrissey said special studies were conducted inhouse to provide timely data in response to special public health needs. Among these were inhalation studies with methyl isocyanate in response to the Bhopal disaster, dermal studies with 5(4-nitrophenyl)2,4-pentadiene-1-ol(NPPD) ("spy dust"), gallium arsenide and arsine gas, chemicals to which workers in the microelectronic industry are exposed, and 2-methoxyethanol, a widely used industrial solvent. Finally, he discussed chemical interaction studies of TCDD with other polychlorinated compounds or thyroid hormones in the induction of cleft palate.

V. Summary and Future Directions: Dr. Schwetz discussed how the effort and corresponding resources in research and development or support contracts are allocated among the major program areas. Since there is increasing demand for teratologic and reproductive toxicity testing, no decrease in testing is foreseen. About 20% of the contract resources are allocated to applied research/methods development. He described new and future projects in the areas of reproduction and fertility, conceptus dosimetry (including placental transfer and pharmacokinetics), neonatal toxicity, developmental toxicity, human studies and studies done as needed in response to environmental events.

General Discussion: Concern was expressed by the reviewers as to whether there are many chemicals, especially environmental agents as opposed to drugs, that are not getting adequate assessment for reproductive effects. In response, it was noted that at least one program staff person is on the Chemical Evaluation Committee. Also about 90% of the chemicals currently undergoing prechronic evaluation are having sperm morphology/vaginal cytology assays performed at the end of 90-day studies.

VI: Report of the Director, NTP: Dr. David Rall reported that (1) this was the last meeting for three members of the Board, Dr. Hook, Dr. Manson and Dr. Swenberg, and thanked them for their valuable service to the NTP; (2) the NIEHS budget in FY 1987 would be the same as in FY 1986 although cuts under the Deficit Reduction Act could have very serious cumulative effects on various programs. One project which will have to be deferred is the NTP/EPA interagency agreement on validation of health hazard predictions made by EPA for chemicals under the premanufacture notification requirement; (3) Dr. James Wyngaarden, Director of NIH, was reelected for a second year as Chairman of the NTP Executive Committee; and (4) a symposium, "The NTP Today-Selected Issues", was held at the recent Society of Toxicity annual meeting in New Orleans. Despite being held on the last morning, the symposium was attended by about 200 persons. Dr. Ernest McConnell handed out copies of a recent Federal Register notice announcing completion of seven prechronic studies and requesting information as part of an effort to inform the public and allow input prior to the design and initiation of long-term studies (Attachment 3). Dr. McConnell said the proposed study to evaluate mouse strain differences via chemically-induced hepato-carcinogenesis, which had been concept reviewed by the Board in October 1985 and deferred, was still being rethought.

VII. Review of Chemicals Nominated for NTP Testing: There were 13 chemical nominations to be considered by the Board. All had been reviewed previously by

the NTP Chemical Evaluation Committee (CEC). Dr. Swenberg chaired the review and Dr. Dorothy Canter, NIEHS, member of the CEC, and Dr. Victor Fung, NIEHS, NTP Chemical Selection Coordinator, served as resource persons. Each Board member present had been asked to serve as principal reviewer for two or three chemicals. Following oral presentation of each chemical review and discussion, a motion was made and voted on by the Board members.

Dr. Canter noted that two chemicals reviewed by the CEC in October, 1985 were not included because they had already been designated as priority chemicals by Executive Committee agencies -- styrene by NIOSH and t-butylhydroquinone by the FDA.

The Board's recommendations, priority for testing, and additional remarks and/or caveats for the 13 chemicals reviewed are summarized in Attachment 4.

VIII. Discussion of Levels of Evidence of Carcinogenicity: Dr. McConnell presented a background and overview noting that the five categories of evidence of carcinogenicity had been first used by the NTP Technical Reports Review Subcommittee and ad hoc Panel of Experts (Panel) at their meeting in June 1983. The Panel used the levels in evaluating 49 studies (172 experiments) during the eight meetings from June 1983 to December 1985, and concurred with staff on 165/172 experiments. On October 30, 1985, the Board reviewed an NTP proposal suggesting moderate changes to the Note to the Reader, the section in the Technical Report containing the Levels. The major addition proposed centered on a more explanatory narrative or listing of factors that would aid in evaluations that might be on the borderline between adjacent levels. Following review and discussion of a revised proposal by the Panel on December 9, 1985, a revised Note to the Reader section along with explanatory and background information was placed in the Federal Register (51FR 2579-2582, January 17, 1986) and comments requested within 45 days; 35 written responses had been received prior to this meeting. From these responses, two issues were most frequently mentioned -- those having to do with benign neoplasia and those with terminology. There were nine responses stating that there should be no changes.

In addition to the list of qualifying factors to consider in the evaluations, Dr. McConnell discussed tentative changes proposed by NTP staff in the categories of Clear Evidence of Carcinogenicity and Some Evidence of Carcinogenicity. Dr. Swenberg stated that the Panel had found the levels to be very useful in evaluating the conclusions in the Technical Reports, and saw a need only for "fine tuning" the wording. He thought the explanatory narrative or list of key factors would allow more flexibility and objectivity in the evaluations.

The other Board members present as well as some current and recently retired members of the Panel each gave their comments. There seemed to be a consensus among the discussants that the list of key factors would be helpful. Considerable discussion centered around the conclusion of Clear Evidence of Carcinogenicity when based on a finding of increased incidence of benign tumors as to whether there should be a caveat of "if there is evidence of progression to malignancy".

Among other suggestions made was one that there be an annotated summary in the abstract of the report including information on experimental design, results by sex/species/dose and conclusions. Another discussant proposed that the word "carcinogenicity" in each of the five levels be changed to "carcinogenic activity". During time allowed for public comment, presentations were made by representatives from the American Industrial Health Council, the Pharmaceutical Manufacturers Association, and the National Institute for Occupational Safety and Health.

Dr. Swenberg summarized the major issues or modifications arising from the discussion which he felt needed action by the Board. These modifications and the final actions taken by the Board were as follows:

(1) Addition of a statement on statistics to the list of key factors. Dr. Pitot moved and Dr. Hook seconded the statement, "The statistical significance of the observed tumor increase", be included in an appropriate place. The motion was approved by 4 Yes (Y) votes with 1 Abstention (A) (Dr. Manson).

(2) When an interpretation of "clear evidence of carcinogenicity" is based on an increased incidence of benign tumors, this should be so noted in the concluding paragraph of the Abstract of the Technical Report. Dr. Pitot moved, Dr. Hook seconded and the motion was passed unanimously.

(3) A statement concerning regression/progression of benign neoplasmas should be added to the list of key factors. Dr. Gallo moved and Dr. Hook seconded acceptance of the statement, "Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present it is impossible to identify the difference. Therefore, where progression is found to be a possibility the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant". The motion was passed unanimously.

(4) A statement should be included in the Note to the Reader to emphasize that NTP strengths of evidence are based on NTP data as contrasted with conclusions drawn by other organizations based on all available evidence. Dr. Gallo moved and Dr. Hook seconded acceptance of the statement: "The NTP program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence". The motion was passed unanimously.

(5) The NTP should attempt to use an annotated format to present data by sex/species/dose in the Abstract of the Technical Report. Dr. Gallo moved and Dr. Hook seconded that such a format be attempted. The motion was passed by 4Y to 1 No (N) (Dr. Perera).

(6) All Five Levels - Dr. Gallo moved and Dr. Hook seconded that "Carcinogenicity" be replaced by "Carcinogenic Activity". The motion was passed by 3Y to 2N (Dr. Manson, Dr. Perera).

(7) Clear Evidence - A revised definition proposed by NTP staff was further modified to indicate that evidence for progression of benign could come from the NTP study or other studies. Dr. Perera moved that the following definition be used: "Clear Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy". The motion was passed unanimously.

(8) Some Evidence - Dr. Hook moved and Dr. Gallo seconded that a revised definition proposed by NTP staff be accepted, as follows: "Some Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence". The motion was passed by 3Y to 1N (Dr. Perera) with 1A (Dr. Manson).

(9) Equivocal Evidence, No Evidence and Inadequate Study - Motions were made and passed affirming the change from "Carcinogenicity" to "Carcinogenic Activity".

ED. NOTE - Changes recommended by the Board were incorporated in draft Technical Reports reviewed by the Peer Review Panel on August 19, 1986. The revised Note to the Reader (titled Explanation of Levels of Evidence) and Levels of Evidence were announced in the Federal Register 51 No. 66, Monday, April 7, 1986, pp. 11843-11844 (Attachment 5).

AGENDA
 BOARD OF SCIENTIFIC COUNSELORS
 NATIONAL TOXICOLOGY PROGRAM
 MARCH 24 AND 25, 1986

CONFERENCE CENTER, BUILDING 101, SOUTH CAMPUS
 NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
 RESEARCH TRIANGLE PARK, NORTH CAROLINA

Monday, March 24, 1986

Open

Review of NTP Reproductive and Developmental

Toxicology Programs

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|-------------------------|---|---|
| 8:30 a.m. - 9:00 a.m. | I. Overview | Dr. B. A. Schwetz and
Dr. E. E. McConnell, NIEHS |
| 9:00 a.m. - 11:00 a.m. | II. Reproduction | |
| | a. Testing and Methods
Development In
Reproductive Toxicology | Dr. J. Lamb, EPA |
| | b. In Vivo/In Vitro Studies
of Male Reproductive
Toxicology | Dr. R. E. Chapin, NIEHS |
| | c. Human Semen Analysis | Dr. S. M. Schrader, NIOSH |
| | d. Discussion | |
| | e. <u>Posters</u> - Reproduction
and Short-Term Tests
(Executive Dining Room,
Cafeteria) | |
| 11:00 a.m. - 12:10 p.m. | III. Short-Term Tests | |
| | a. Evaluation of Two <u>In
Vitro</u> Teratology
Test Systems | Dr. R. E. Morrissey, NIEHS |
| | b. Evaluation of <u>Drosophila</u>
As a Teratology Screen | Mr. R. L. Schuler, NIOSH |
| | c. The Chernoff/Kavlock
Test As a Reproductive
Toxicity Screen | Dr. B. D. Hardin, NIOSH |

- 1:00 p.m. - 4:00 p.m. IV. Developmental Toxicology
- a. Neurobehavioral Teratology Testing and Methods Development Dr. C. A. Kimmel, EPA
 - b. Postnatal Toxicity Studies Dr. L. A. Dostal, NIEHS
 - c. Cardiovascular Functional Teratology Dr. M. Toraason, NIOSH
 - d. Posters, Developmental Toxicology (Executive Dining Room, Cafeteria)
 - e. Inhalation Reproductive and Developmental Toxicity Studies Dr. B. D. Hardin, NIOSH
 - f. Developmental Toxicity Testing, and Special Studies in Developmental Toxicology Dr. R. E. Morrissey, NIEHS
 - g. Discussion

4:00 p.m. - 4:30 p.m. V. Summary and Future Directions Dr. B. A. Schwetz, NIEHS

Tuesday, March 25, 1986

Open

8:30 a.m. - 8:45 a.m. Report of the Director, NTP Dr. D. P. Rall, NIEHS

8:45 a.m. - 10:45 a.m. Review of Chemicals Nominated for NTP Testing Board
Dr. D. Canter, NIEHS

Closed

11:00 a.m. - 1:00 p.m. Evaluation of Programs and Personnel in Reproductive and Developmental Toxicology Board and Consultants

Open

1:00 p.m. - Adjournment Discussion of Levels of Evidence of Carcinogenicity Board and Staff

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

MARCH 24 and 25, 1986

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DEVELOPMENTAL TOXICOLOGY PROGRAM REVIEW ON
MARCH 24 and 25, 1986

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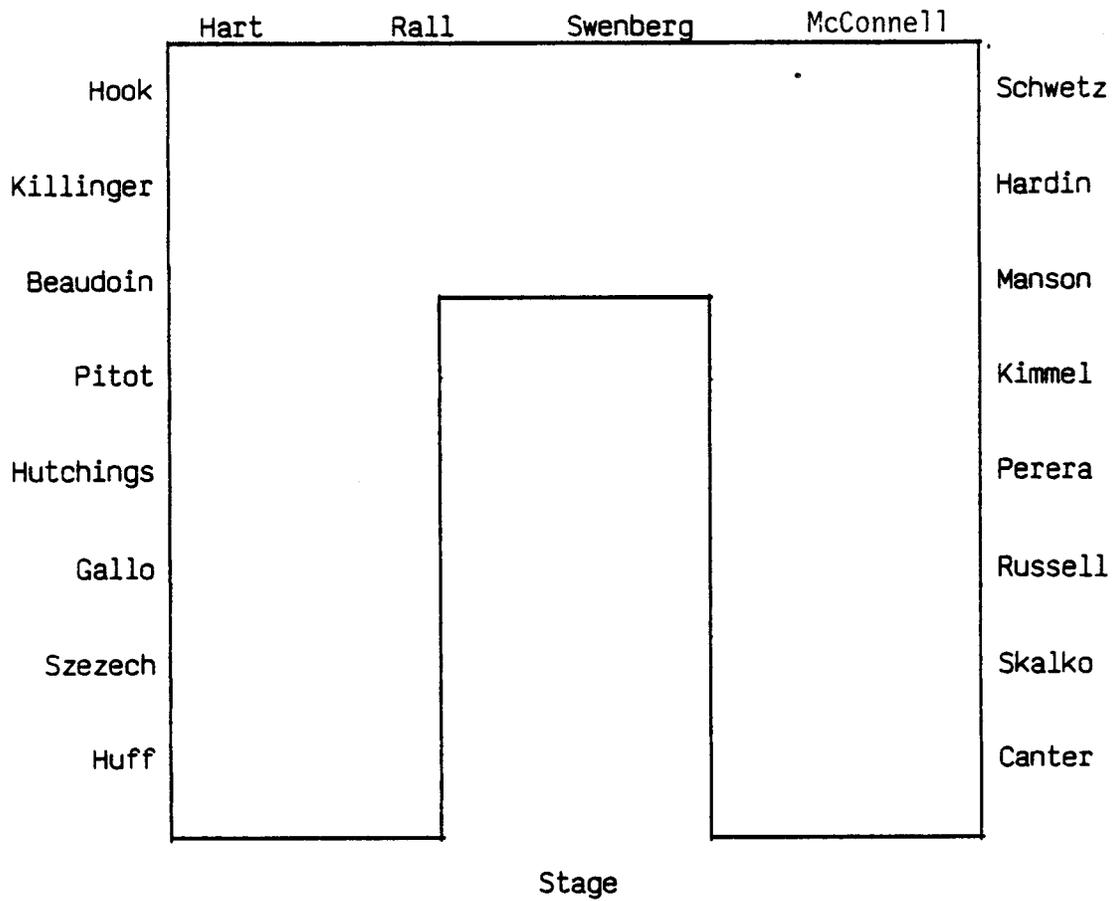
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NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

Conference Center, Building 101
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

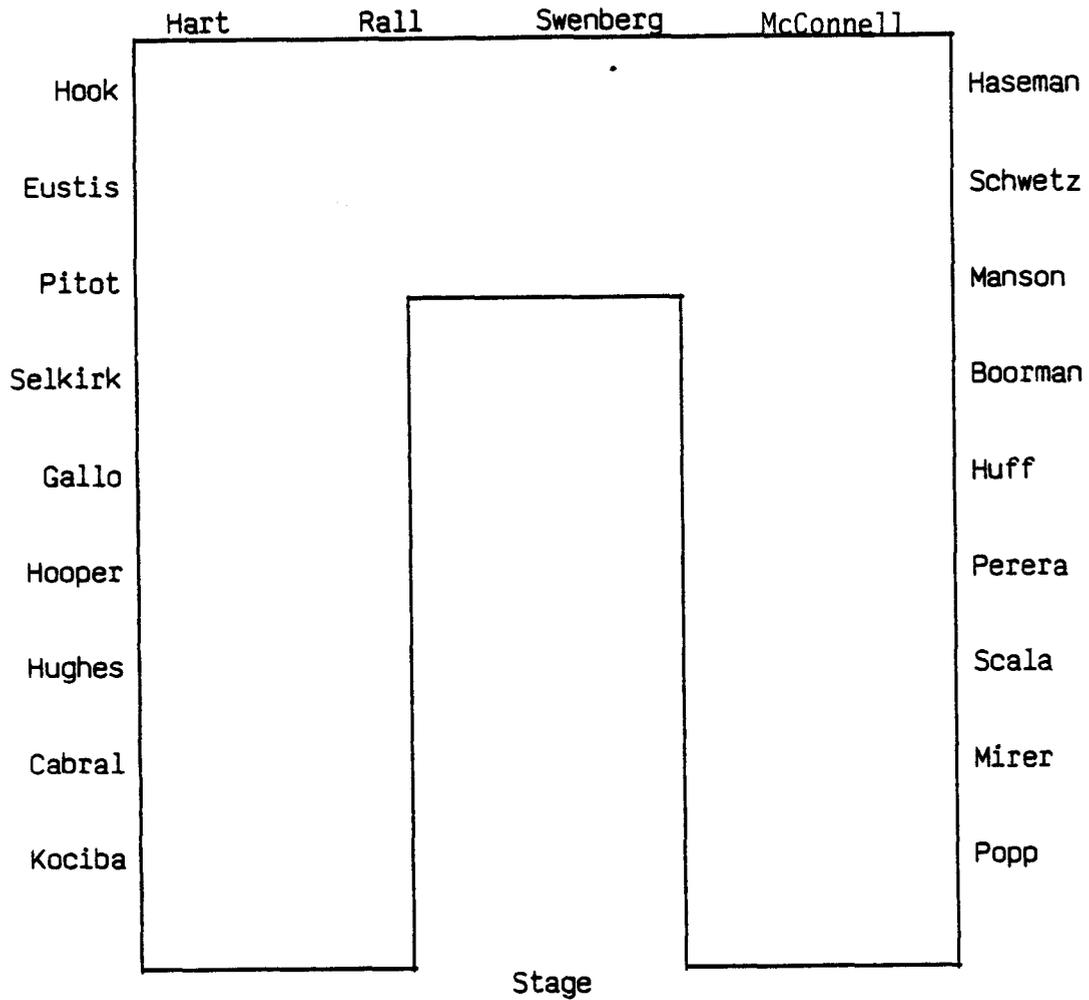
March 24, 1986
March 25 (a.m.), 1986



NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

Conference Center, Building 101
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

March 25 (p.m.), 1986



Public Health Service
National Toxicology Program
Board of Scientific Counselors Meeting

Pursuant to Pub. L. 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, Research Triangle Park, North Carolina, on March 24 and 25, 1986.

The meeting will be open to the public from 8:30 a.m. until adjournment on March 24. The preliminary agenda with approximate time are as follows:

Review of NTP Reproductive and Development Toxicology Programs:

8:30 a.m. - 12:10 p.m. - Overview and platform and poster presentations on intramural and extramural projects in reproductive toxicology and evaluation of short-term assays for teratologic and reproductive toxicologic effects.

1:00 p.m. - 4:30 p.m. - Platform and poster presentations on intramural and extramural projects in developmental toxicology. Concluding remarks and discussions.

The meeting on March 25 will be open to the public from 8:30 a.m. to 10:45 a.m. and from 1:00 p.m. until adjournment. The preliminary agenda with approximate times are as follows:

8:30 a.m. - 8:45 a.m. - Report of the Director, NTP.

8:45 a.m. - 10:45 a.m. - Review of Chemicals Nominated for NTP Testing. (Thirteen chemicals will be reviewed. Of these, five were reviewed by the NTP Chemical Evaluation Committee (CEC) on October 23, 1985, and listed in the Federal Register, Volume 51, No. 6, pp. 3262-3263, January 24, 1986: (1) n-Butyl acrylate; (2) 12-O-Hexadecanoyl-16-hydroxyphorbol-13-acetate;

(3) Methyl ethyl ketoxime; (4) alpha-Methylstyrene; and (5) Tung oil. The remaining eight chemicals were reviewed by the CEC on January 8, 1986:

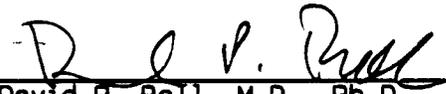
(1) n-Butane; (2) Catechol; (3) 2-Chloronitrobenzene; (4) 4-Chloronitrobenzene; (5) Furan; (6) Furfuryl alcohol; (7) Isopentane; and (8) Pentamidine isethionate.)

1:00 p.m. - Adjournment - Discussion of Levels of Evidence of Carcinogenicity.

In accordance with the provisions set forth in section 552b(c)(6) Title 5 U.S. Code and section 10(d) of Pub. L. 92-463, the meeting will be closed to the public on March 25 from approximately 11:00 a.m. to 1:00 p.m. for further evaluation of NTP programs in reproductive and developmental toxicology, including the consideration of personnel qualifications and performance, the competence of individual investigators, and similar items, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

The Executive Secretary, Dr. Larry G. Hart, Office of the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, telephone (919) 541-3971, FTS 629-3971, will have available a roster of Board members and expert consultants and other program information prior to the meeting, and summary minutes subsequent to the meeting.

Date



David P. Rall, M.D., Ph.D.
Director,
National Toxicology Program

advisory committee of experts. A petition is to be in the form of a petition for reconsideration under § 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the *Federal Register*. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before March 3, 1986, file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), 90 Stat. 554-555, 571 (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: January 23, 1986.

John C. Villforth,

Director, Center for Devices and Radiological Health.

[FR Doc. 86-2111 Filed 1-30-86; 8:45 am]

BILLING CODE 4160-01-M

Public Health Service

National Toxicology Program; Announcement of Completed Short-term Toxicology Studies on Seven Chemicals; Request for Comments

As part of an effort to inform the public and allow interested parties to comment and provide information on chemicals prior to designing of studies for long-term toxicology and carcinogenesis studies, the National Toxicology Program (NTP) will routinely announced in the *Federal Register* the list of chemicals for which short-term toxicology studies have been completed.

Short-term toxicology studies on the chemicals listed in this announcement

have been completed and the National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) is in the process of evaluating the results. A decision on whether additional studies including long-term toxicology and carcinogenicity studies are needed will soon be made by the NTP. If you have relevant information (such as current production, use pattern, exposure levels, toxicological data) to share with the NTP on any of these chemicals, please contact the responsible NTP Scientist within 30 days of the appearance of this announcement by telephone or by mail to: NIEHS/NTP, P.O. Box 12233, Research Triangle Park, North Carolina 27709. The information provided will be considered by the NTP while determining which chemicals require additional studies and in designing these studies.

1. *9-Aminoacridine Hydrochloride* (134-50-9): 14-day dermal, 14-day feed, and 90-day feed studies in Fischer 344 rats and B6C3F₁ mice. Contact Person: Dr. W. Eastin, Telephone # 919-541-7941.

2. *Benzethonium Chloride* (121-54-0): 14-day and 90-day dermal in Fischer 344 rats and B6C3F₁ mice. Contact Person: Dr. W. Eastin, Telephone 919-541-7941.

3. *Bromobenzene* (108-86-1): 4-day dermal, 4-day inhalation, 90-day dermal and 90-day gavage in Fischer 344 rats and B6C3F₁ mice. Contact Person: Dr. J. Roycroft, Telephone # 919-541-3627.

4. *Butyl Benzyl Phthalate* (85-88-7): 180D-day feed study in male Fischer 344 rats. Contact Person: Dr. E. Rauckman, Telephone #919-541-7981.

5. *Codeine* (76-57-3): 14-day and 90-day feed studies in Fischer 344 rats and B6C3F₁ mice. Contact Person: Dr. J. Dunnick, Telephone # 919-541-4811.

6. *D-Alpha-Tocopheryl Acetate* (58-95-7): 90-day gavage in Sprague-Dawley and Fischer 344 rats. Contact Person: Dr. K. Abdo, Telephone #919-541-7819.

7. *Tricresyl Phosphate* (1330-78-5): 14-day gavage, 14-day feed, 90-day gavage, and 90-day feed in Fischer 344 rats and B6C3F₁ mice. Contact Person: Dr. R. Irwin, Telephone #919-541-3340.

Please submit all comments and suggestions on chemical(s) by telephone or by mail to the responsible scientist (listed above) within 30 days of publication of this notice. Any submissions received after the above data will be accepted and utilized if possible.

Dated: January 23, 1986.

David P. Rall, M.D., Ph.D.

Director, National Toxicology Program.

[FR Doc. 86-2126 Filed 1-30-86; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

Closure of Public Lands in Ada County, ID

Correction

In FR Doc. 86-421 beginning on page 1044 in the issue of Thursday, January 9, 1986, make the following corrections:

On page 1044, third column, twelfth line from the bottom, remove the dagger "†".

On the same page, third column, eighth and ninth lines from the bottom should be corrected to read "Section 8, W½W½, SW¼SE¼NW¼, W½E½ SW¼, SE¼SW¼."

BILLING CODE 1506-01-M

Conservation and Recreation Areas; Intent for 1986 Amendment Review of the California Desert Plan

AGENCY: Bureau of Land Management, Interior.

SUMMARY: Notice is hereby given that the Bureau of Land Management is initiating the 1986 Review of the California Desert Conservation Area Plan in accordance with the amendment procedures outlined in Chapter 7 of the Plan. The purpose of this review is to consider the need for possible amendments to the Plan based on requests from individuals, public and private organizations, and the Bureau's own observations.

DATE: Proposed amendments are being accepted from the Public until March 17, 1986.

FOR FURTHER INFORMATION CONTACT: Gerald E. Hillier, District Manager, California Desert District, 1695 Spruce Street, Riverside, California 92507.

SUPPLEMENTARY INFORMATION: Requests for amendments or changes in the California Desert Plan are now being accepted from public agencies, interested individuals, and organizations. Supporting rationale should be provided for each proposed change. Requests will be considered in light of the following criteria:

(1) Is the proposed amendment based on new data not considered when the Plan was developed?

(2) Does the information represent a change in legal or regulatory mandate?

(3) Is the supporting detail sufficient and the problem clearly stated so that the request can be considered?

(4) Does the information represent a formal change in State or local government or agency plans?

Testing Recommendations for Chemicals Reviewed by Board of Scientific Counselors
on March 25, 1986

Chemical* (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
A. Chemicals Reviewed by the Chemical Evaluation Committee on October 23, 1985			
1. n-Butyl acrylate (141-32-2)	EPA	-Chemical disposition studies by inhalation and dermal routes (Moderate) -Carcinogenicity in mice by inhalation route -Reproductive studies (Low)	-High production -Potential for worker exposure -EPA regulatory interest
2. Methyl ethyl ketoxime (96-29-7)	EPA	-In-depth toxicological evaluation to include behavioral studies by inhalation route -In vitro cytogenetics (Low)	-Potential for worker exposure
3. α -Methylstyrene (98-83-9)	EPA	-In-depth toxicological evaluation -Short term <u>in vivo</u> reproductive toxicity assay -In vitro cytogenetics (Low)	-High production -Lack of toxicity data
4. Tung oil (8001-20-5)	Dr. C. Lawyer	No testing	-Nomination is based on concern that 12-O-hexadecanoyl-16-hydroxyphorbol-13-acetate (HHPA) is a tumor promoter and a constituent of tung oil. However, no evidence that HHPA is a constituent of commercially available tung oil.

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
5. 12-O-Hexadecanoyl- 16-hydroxyphorbol- 13-acetate (53202-98-5)	Dr. C. Lawyer	No testing	-Lack of evidence for exposure
B. Chemicals Reviewed by the Chemical Evaluation Committee on January 8, 1986			
6. n-Butane (106-97-8)	EPA	-Defer	-Reconsider after evaluation of data from industry subchronic studies in rats, and completion of NTP mutagenicity studies
7. Isopentane (78-78-4)	EPA	-Defer	-Reconsider after evaluation of data from industry subchronic studies in rats
8. 2-Chloronitrobenzene (88-73-3)	EPA	{ <ul style="list-style-type: none"> -Prechronic studies - subchronic to include testing for hematopoietic and cardiac effects -Reproductive studies (High) }	{ <ul style="list-style-type: none"> -Potential for exposure -Known toxicity -Positive mutagenicity data -Suspicion of carcinogenicity in limited animal studies -Concern about lack of reproductive toxicity data -Review results of subchronic studies regarding advisability of carcinogenicity studies for one or both isomers. -Structural activity relationship between isomers - review 3-chloronitrobenzene as a potential nomination to complete class study of chloronitrobenzenes. }
9. 4-Chloronitrobenzene (100-00-5)	EPA		

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
10. Furan (110-00-9)	NIEHS	-Chemical disposition and metabolism studies, including assessment of covalent binding -In vivo bone marrow cytogenetics -Unscheduled DNA synthesis (High)	-Significant commercial compound -Chemical carcinogenic in NTP studies -Look at potential for <u>in vivo</u> genotoxicity
11. Furfuryl alcohol (98-00-0)	NIEHS	-Carcinogenicity study in rats by oral route -Chemical disposition and metabolism studies -Genotoxicity studies (Moderate)	-Potential for exposure -Structural interest -Differential toxicities of furan, furfural and furfuryl alcohol in NTP prechronic studies -Chemical disposition and metabolism, and genotoxicity studies should precede carcinogenicity study
12. Catechol (120-80-9)	NIEHS	No testing	-Nominated to complete class study of hydroxybenzenes. However, sufficient data to characterize the toxicity of this class should be obtained from the current NTP testing of other hydroxybenzenes. -Information on catechol is expected from the metabolism study on benzene
13. Pentamidine isethionate (140-64-7)	Dr. Edgar Martin	Defer	-Deferred in order to contact Orphan Drug Review Board to ascertain if NTP toxicological testing would be appropriate

*Listed in order of review by the Board of Scientific Counselors.

Dated: April 1, 1986.

Jackie E. Baum,
Advisory Committee Management Officer,
HRSA

[FR Doc. 86-7560 Filed 4-4-86; 8:45 am]

BILLING CODE 4160-15-M

Office of Human Development Services

Federal Council on the Aging; Meeting

Agency holding the meeting: Federal Council on the Aging.

Time and Date: Meeting begins at 9:00 AM and ends at 5:00 PM on Wednesday, May 28, 1986 and begins at 9:00 AM and ends at 3:00 PM on Thursday, May 29, 1986.

Place: Department of Health and Human Services, HHS North Building, 330 Independence Avenue, SW., Washington, DC 20201, OIG Conference Room, 5542 (Fifth Floor).

Status: Meeting is open to the public.

Contact persons: Pete Conroy, Room 4243, HHS North Building, 245-2451.

The Federal Council on the Aging was established by the 1973 Amendments to the Older Americans Act of 1965 (PL 93029, 42 U.S.C. 3015) for the purpose of advising the President, the Secretary of Health and Human Services, the Commissioner on Aging and the Congress on matters relating to the special needs of older Americans.

Notice is hereby given pursuant to the Federal Advisory Committee Act (PL 92-453, 5 U.S.C. App. 1, Sec. 10, 1976) that the Council will hold a meeting on May 28 and 29, 1986 from 9:00 AM-5:00 PM and from 9:00 AM-3:00 PM respectively in Room 5542 in the Health & Human Services North Building, 330 Independence Avenue, SW., Washington, DC 20201.

The agenda will include: Swearing in three new congressionally appointed members of the Council—Mary J. Majors, Iowa; Tessa Macauley, Florida; and Jon B. Hunter, West Virginia. An update on Long-Term Care Insurance by representatives of companies and organizations involved in this field; a presentation on the financing of elderly housing by the representatives of nonprofit Retirement Elderly Housing Trust; a presentation on new technologies and environmental housing design for senior Americans by the National Association & Home Builders Foundation representative; and update on the National Institute on Aging by Dr. T. Franklin Williams, Director; a discussion of the Joint Training and Partnership Act by representatives from the National Governors Association and Department of Labor; in addition, a

substantial amount of time will be devoted to FCoA committee meetings prioritizing subject areas of interest for 1986.

Dated: April 2, 1986.

Ingrid Azvedo,
Chairperson, Federal Council on the Aging.
[FR Doc. 86-7672 Filed 4-4-86; 8:45 am]

BILLING CODE 4130-01-M

Public Health Service

National Toxicology Program (NTP); Notice of Modifications in the Levels of Evidence of Carcinogenicity Used To Describe Evaluative Conclusions for NTP Long-Term Toxicology and Carcinogenesis Studies

In June 1983, the National Toxicology Program (NTP) began using five categories of interpretative conclusions in their Toxicology and Carcinogenesis Studies Technical Report Series. The use of these categories or levels was implemented in order to differentiate better and evaluate the "strength of evidence" of the experimental findings in its studies and to replace the restrictive classifications in common use that a chemical "was" or "was not" carcinogenic under the conditions of the particular study.

The levels of evidence were formulated with the underlying need to allow scientific flexibility and to promote better understanding among the Program Staff and the NTP Board of Scientific Counselors Technical Reports Review Subcommittee (Peer Review Subcommittee) and those who subsequently must rely on these findings.

The levels of evidence have been included in the Note to the Reader section located on page 2 of each Technical Report. Since their adoption (from June 1983 through March 1986), they have been used to evaluate 53 toxicology and carcinogenesis studies representing 202 separate experiments. There was a consensus among the Subcommittee members that the levels of evidence of carcinogenicity as used for the Technical Reports were an advancement.

The Subcommittee, members of the Board of Scientific Counselors, and members of the Board's *Ad Hoc* Panel on Chemical Carcinogenesis Testing and Evaluation have consistently urged continued use of these categories, with minor adjustments made where necessary to reflect their concerns as well as advances in knowledge. On October 30, 1985, the Board in public session reviewed a proposal suggesting incorporation of certain changes. The

major addition proposed for the levels of evidence centered on a more explanatory narrative in the Note to the Reader that would assist Subcommittee members who review the Technical Reports as well as promote further understanding for those who use these Reports. Following review and discussion of a revised proposal by the Subcommittee on December 9, 1985, a revised Note to the Reader section along with explanatory and background information was placed in the *Federal Register* (51 FR 2579-2582, January 17, 1986) and comments requested within 45 days.

In response to the *Federal Register* announcement, 39 written comments were received and reviewed by Program Staff and members of the Board and Peer Review Subcommittee. Proposed modifications were discussed at length by the Board in public session on March 25, 1986, with adequate time allowed for public comment. As a result, several changes were recommended by the Board and accepted by the Program. The following revised Note to the Reader, not titled Explanation of Levels of Evidence, reflects these changes and will appear in all future Toxicology and Carcinogenesis Studies Technical Reports evaluated by the Peer Review Subcommittee. The section will appear immediately after the Abstract section of the Report. The last three paragraphs of the previous Note to the Reader will continue to appear on page two under that title.

Explanation of Levels of Evidence

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

Negative results, in which the laboratory animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans.

The NTP Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP; epidemiological studies; and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment:

- Two categories for positive results ("Clear Evidence" and "Some Evidence").
- One category for uncertain findings ("Equivocal Evidence").
- One category for no observable effects ("No Evidence").
- And one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study").

These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity, as well as to emphasize consistency. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that

are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because a major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

While selecting a conclusion statement for a particular experiment, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present it is impossible to identify the difference. Therefore, where progression is known to be a possibility the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;

- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;

- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);

- The presence or absence of dose-response relationships;
- The statistical significance of the observed tumor increase;

- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;

- Survival-adjusted analyses and false positive or false negative concerns;
- Structural activity correlations; and
- In some cases genetic toxicology.

These factors together with the definitions as written should be used as composite guidelines for selecting one of the five categories.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

The term chemical carcinogenesis generally means the induction by chemicals of neoplasms not usually observed, the induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly found. Different mechanisms may be involved in these situations. Etymologically, the term carcinogenesis means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words tumor and neoplasms are used interchangeably.

Comments on the revised levels of evidence and Explanation of Levels of Evidence section will be welcomed at any time. Please communicate your comments to Dr. Larry G. Hart, Office of the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709. We would anticipate reviewing the usefulness of the revised levels of evidence in two to three years.

Dated: April 3, 1986.

David P. Reif,

Director, National Toxicology Program.

[FR Doc. 86-7811 Filed 4-4-86; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of the Assistant Secretary for Housing—Federal Housing Commissioner

[Docket No. D-86-816; FR-2225]

Orders of Succession for General Deputy Assistant Secretary for Housing—Deputy Federal Housing Commissioner and Subordinate Officials in the Office of Housing

AGENCY: Department of Housing and Urban Development (HUD); Office of the Assistant Secretary for Housing—Federal Housing Commissioner.

ACTION: Order of Succession.

SUMMARY: This Order of Succession revises the designation of officials authorized to serve as Acting General