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REPORT ON CARCINOGENESIS TESTING, EVALUATION SUBMITTED TO NTP; CALLS FOR CONTINUED RESEARCH

The Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation, established last year by the National Toxicology Program Board of Scientific Counselors to examine the current state of science and develop recommendations for methods that NTP should use in the detection and evaluation of carcinogens, submitted its final report to the Board last month. The report offers a series of recommendations for each of three general subject areas—short term tests, subchronic

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In Brief

NOMINATIONS OPEN FOR BRISTOL-MYERS AWARD; NEW SURGICAL ONCOLOGY CHAIR AT SOUTH FLORIDA

NOMINATIONS ARE being accepted for the eighth annual Bristol-Myers Award for Distinguished Achievement in Cancer Research. Albert Owens, director of the Johns Hopkins Oncology Center, is chairman of the selection committee. The committee is made up of representatives of 15 research institutions which participate in the $7.3 million program of unrestricted grants for cancer research funded by Bristol-Myers. The prize is $50,000. Nominations will be accepted from medical schools, free standing hospitals and cancer research centers until Dec. 1. For forms and further information, contact Secretary, Awards Committee, Bristol-Myers Co., 345 Park Ave., Rm 43-38, New York 10154.... **UNIV. OF SOUTH** Florida has established a $1 million endowed chair for research in surgical oncology with funds from anonymous donors. The university's Cancer Research Center will include a 162 bed, $45 million hospital, now about one third complete, with a scheduled finish date of August, 1985. Twenty beds will be dedicated to clinical research, and 20,000 square feet devoted to basic research, with space for 14 senior investigators, their assistants, fellows, and technicians. There also will be 28 intensive care beds, 12 pediatric beds, and two laminar flow rooms.... **GEORGE KHOURY**, chief of NCI's Laboratory of Molecular Virology, will deliver the 1984 G. Burroughs Mider lecture on "Enhancers—Regulatory Elements in Eukaryotic Gene Expression." The lecture will be given Sept. 12, 8:15 p.m., in the NIH Clinical Center Jack Masur Auditorium.... **WESTERN EUROPEAN** lung cancer study, analyzed for elevated risks associated with cigar and pipe smoking, found significantly increased risks for both relative to nonsmokers, although below those of cigarette only and mixed cigarette and cigar smokers. The differences were strongly related to inhalation practices. The study, by Jay Lubin and William Blot of NCI's Environmental Epidemiology Branch, and Bonnie Richter of Johns Hopkins, was reported in the August issue of "Journal of NCI."

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NTP PANEL COMPLETES REPORT ON STATE OF THE ART IN TESTING, EVALUATION

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studies and related issues, and chronic studies and regulatory aspects.

The Panel met with NTP staff, reviewed the literature, and received oral and written presentations from the scientific community and other interested sources. A draft report was widely circulated, and more than 50 formal responses and numerous informal contacts were considered in preparing the final report. Responses were received from trade organizations, scientific bodies, governmental groups including NTP staff, and concerned individuals in the U.S. and abroad.

Several comments concerned topics which were relevant but not specifically included in the topics covered in the report. "Since many comments were extensive and well documented and often included innovative and thoughtful suggestions, we have arranged to make all of the comments available through the National Technical Information Service repository service, PB-84-225945," the report introduction states. "We recognize that there are additional topics and issues that need to be considered by the scientific community and that several of the topics considered in this report have not been fully resolved. In these areas we consider our efforts to be a reasonable first step and recommend that the NTP Board of Scientific Counselors conduct workshops and other activities designed to maintain and promote the productive and cooperative interaction which has characterized the activities of this Panel."

Recommendations in the 280 page report are summarized:

Short Term Tests

Evaluation of specific tests

*Detection of mutagens in body fluids or excreta—Measurement of urinary mutagens is not currently part of the NTP testing protocol. Because it is currently being applied in some human studies, it is recommended that studies on levels of mutagenic material in blood and urine be carried out in bioassay test species as a part of the prechronic testing of at least a few selected chemicals in order to provide a background of information on the quantitative relationships between carcinogen intake and mutagenicity of blood and urine. These chemicals should be chosen on the basis of their mutagenicity as established by the short term test battery, and if possible, should include chemicals encountered in the workplace so that parallel human studies could be possible.

*Detection of covalent adducts—It is clear that the complexities of this field necessitate extensive further research in method development and careful validation in animal models before interpretable data can be obtained from studies in human populations. However, the potential usefulness of the information to be gained justifies the additional research effort.

We therefore recommend that NTP introduce into its program studies on covalent adduct formation in animals treated with chemicals under the carefully controlled conditions of the bioassay protocol. Similarly, clinical monitoring of adduct formation should also be approached on a sound scientific basis. At this stage, requisite methology is available for only a limited number of model compounds, but studies on them would provide extremely valuable data for validation of these methodologic approaches and interpretation of data obtained by parallel studies being conducted in human populations. In this context, the NTP program represents an extremely valuable, perhaps unique, source of such quantitative data in animals.

*DNA damage and repair—The rat hepatocyte UDS test using metabolically competent cells should remain on NTP's standard battery of short term tests. Chemicals of specific classes known to require metabolism by the intestinal microflora should be tested in the in vivo/in vitro test. In addition, when a chemical induces hepatocellular tumors in the bioassay, but is negative in the in vitro hepatocyte UDS test, it should be tested in the in vivo/in vitro test. This will assist in understanding the mechanisms of liver carcinogenesis in cases involving microbial metabolism. Interspecies comparisons between human and rodent hepatocytes using chemicals known to be carcinogenic to humans and animals will further validate this system. Unless unique advantages of other tissues become apparent, minimal effort should be exerted in this direction. One such area, however, may be the use of urothelial cells.

The lack of quantitation between carcinogenic potency and UDS response makes UDS a less appropriate choice for studies on internal dosimetry than studies on specific adducts. However, the correlation between specific adducts and carcinogenic potency may not be perfect. Nonetheless, if compound related UDS is present, it represents a qualitative indication of potential genotoxicity.

*Micronucleus test—Presently, this is not employed in the NTP genetic toxicology screen. New test protocols and staining procedures should increase its usefulness. In light of this, it is recommended that NTP evaluate the micronucleus test as a secondary or tertiary screen and if useful consider using automated methods. When compounds produce inconsistent results in a battery of short

term tests, blood samples could be collected during prechronic testing for analysis of micronuclei. It also would be useful to evaluate with this technique any chemical that has induced leukemia.

*Sister chromatid exchange—(1) Continue to employ the SCE in vitro assay using Chinese hamster ovary cells in the NTP standard battery of short term tests; and (2) include an assay for SCEs in the proposed in vivo test scheme. Information sought on SCE frequencies would include intra-individual variation over time; interindividual variation within a dose group; differences in mean values between dose groups, and the dose response relationship; and levels in tumor bearing animals compared to levels in tumor free animals within a dose group.

*Chromosomal aberrations—Assays for chromosomal aberrations are available which have been fairly extensively applied both to in vitro systems and in animal and human tissues in vivo. There is quite wide agreement about the practical utility of using aberrations as indicators of carcinogenic potential in screening of chemicals, and about their potential usefulness as biologic dosimeters in animals and humans, and for detecting genetic response in human populations.

The use of lymphocytes is recommended for parallel testing in in vitro systems, laboratory animals, and humans since they are a readily available tissue. Furthermore, a significant proportion of lymphocytes is long lived; therefore the cytogenetic effects of a dose accumulated from chronic exposures is likely to be measurable. In particular, NTP should retain the CHO in vitro assay in its genetic toxicity prechronic battery and should include chromosomal aberrations among the short term tests applied in the proposed in vivo animal study of model compounds.

Specific recommendations are: conduct in vitro experiments prior to in vivo testing to determine S-stage specificity of the test substance in order to avoid the possibility of false negative results; analyze cells in their first post treatment mitotic division over a complete cell cycle to mitigate cell cycle dependency; select an adequate sample size, and randomize both control and study cultures and conduct a blind analysis of slides; for human studies, carefully select control and exposed groups and account for confounding variables such as drugs, radiation exposure, cigarette smoking, etc.; and conduct experiments over a range of dose concentrations to obtain dose response data.

Human somatic cell mutation assays—Because these methods can, in theory, assay for mutations in vivo in rodents or humans using accessible tissues (erythrocytes or lymphocytes), they are very attractive and their development should be encouraged. However, such tests are insufficiently developed at present to be included into either the NTP standard battery of short term tests or into the in vivo testing scheme proposed here. They are in need of further validation and should be considered as promising candidates for inclusion into either test battery in the future.

*Sperm abnormalities—The mouse sperm morphology test has a low sensitivity to detect carcinogens. In addition, positive responses may arise from spermatotoxic as well as from mutagenic agents. The recommendations for the sperm morphology assay are difficult to make because of the mixture of advantages and disadvantages of the test. However, sperm is one of the few candidate tissues which is readily available from humans and rodents and is suitable for in vivo monitoring of genetic damage, and use of this tissue should be encouraged. The mouse sperm morphology test has a reasonably well developed historical data base of responses to carcinogens and noncarcinogens, and the assay is sensitive to a subset of mutagens that are active in the male germ cells, perhaps more so than existing germ cell mutational assays.

The mouse sperm morphology assay, at present, is in need of further evaluation as a predictor of carcinogenicity. We recommend that, if used, it be employed in a highly selective manner in the NTP prechronic testing, specifically for those chemicals whose chemical structures indicate that they may be potent carcinogens or be active on male germ cells. We recommend that the assay be considered for inclusion into the in vivo test scheme that is proposed in this report.

*Short term tests for transformation and promotion—It is evident from NTP validation studies (and other studies in the literature) that an inability to metabolize procarcinogens is a serious and limiting deficiency of the Balb/c 3T3 system (and probably cell transformation using C3H/10T1/2 cells as well). Use of the system has identified a few carcinogens which go undetected by other more rapid and inexpensive assays for genotoxicity. Routine screening or further extensive validation with this system, except as noted below, would not appear to be a wise allocation of resources until such time as an exogenous system for metabolic activation is available for routine use. Funding of research by NTP to develop such an activation system should be given a high priority. Validation studies have demonstrated the Balb/c system to be an accurate predictor of carcinogenicity for direct acting carcinogens, polycyclic aromatic hydrocarbons, metals and some aromatic amines. Use of the 3T3 system for screening chemicals which belong to these classes may be indicated.

The Balb/c 3T3 system is, of course, potentially

sensitive to carcinogens which have weak or negligible activity in other assays for genetic damage. Several such problem carcinogens have been identified by other systems (ie., 5-azacytidine, diethylstilbesterol, asbestos, arsenic and benzene). If such chemicals are not included in ongoing validation studies, they should be. Comparison of the ability of the different cell transformation systems to respond to such chemicals is in order and may succeed in identifying systems with the greatest sensitivity to such substances.

Future validation studies in all cell transformation systems should include more negatives and also suspected human carcinogens.

Further validation of the SHE/SA7 system is in order, with emphasis on the following considerations:

1. How do results from this system compare with results obtained from assays for DNA damage?
2. How responsive is the system to nonmutagenic carcinogens?
3. What is the specificity of the assay?

The C3H/10t 1/2 system appears to have limitations similar to Balb/c with respect to metabolism. Unless these can be overcome, use of this system should probably be limited except as noted in points 2 and 3.

The SHE cell transformation system has amassed an impressive literature performance. NTP should determine whether or not the extreme technical difficulties associated with this system can be overcome and the system employed in a reproducible fashion by multiple laboratories.

The modified RLV/RE cell transformation system currently being evaluated by NTP shows promise and deserves additional validation and/or development. However, the biological significance of the modified assay's endpoint for the carcinogenic process is unclear. Efforts should be made to determine the relationship of this assay to the process of oncogenic transformation and the role of the retrovirus in generating chemically induced responses. These latter efforts should be assigned higher priority than routine screening or extensive validation.

*Long term recommendations—Tests should be conducted under optimal conditions. Failure to do so limits their utility, may lead to marginal low level responses of uncertain significance, and may limit reproducibility between laboratories.

Resources devoted to the use of cell transformation systems as screening tools have far exceeded those allocated to understanding the cellular mechanisms of transformation. As a result the mechanism of transformation is unknown and may vary from system to system. It is thus impossible to state which system provides the most relevant indicator of carcinogenic potential. Clearly, much work is needed to more carefully standardize and optimize the conditions under which the assay is conducted. Many of the questions which need to be addressed can only be answered through basic research on mechanisms.

Cell transformation systems can be used to study and evaluate the ability of chemicals to influence multiple aspects of the complex process of carcinogenesis (i.e., cocarcinogenesis, promotion, progression). The principal strength of these systems may be in this potential, which unfortunately, has not been exploited. Better use of cell transformation systems to explore these aspects of carcinogenesis should be encouraged.

Finally, NTP should recognize that the more commonly used cell transformation systems do not utilize cells with tissue or species origins of greatest concern to chemical carcinogenesis (i.e., cells of epithelial and/or human origin). It is possible that transformation systems using human epithelial cells will be available in 10 years.

*Promotion—The recognized multistage theory of cancer includes promotion, yet little is known about the actual mechanisms involved. A factor greatly complicating the task of identifying critical mechanisms and then developing definitive tests to detect and measure promoters is their observed wide range of effects... Another complication is the possibility that the same chemical may act primarily as a promoter in one tissue and as an initiating agent in another... The result is that short term tests for promotion are now insufficiently developed for inclusion in a short term test battery. More studies are needed on the mechanisms of tumor promotion so that reliable short term tests can be developed.

This is a major gap in short term testing because of the estimated wide extent of human exposure to promoters or late stage carcinogens (e.g. cigarette smoke, asbestos) and the observations that certain promoters (TCDD, TPA) have induced tumors by themselves at low doses. There is a lack of evidence that epigenetic agents such as promoters necessarily pose a lesser cancer risk to humans than do genotoxic agents.

Development and validation of tests for promotion should therefore be a priority with NTP. Potential candidates include (in vitro) cell transformation models (e.g., C3H, 10T1/2, T3, hamster embryo cells, mouse epidermal cells, human foreskin cells), cell adhesion, metabolic cooperation; (in vivo), 2-stage animal models (e.g., mouse skin, mouse lung, Fischer F 344 rat liver).

Subchronic studies and related issues

The chemical selection process—The development by NTP of a set of definitive criteria for each of the selection elements would provide a more uniform

and justifiable process for chemical selection. NTP should consider a methodology to make appropriate use of the exposure factor in the chemical selection process given its important role in assessment of risk. The NTP Board of Scientific Counselors should ensure that the opportunity is maintained and enhanced for participation of interested parties in the review of decisions made between the subchronic test and the chronic bioassay.

Suitability of continued use of Fischer 344 rat and B6C3F1 mouse—For the present, it is recommended that NTP maintain the two species presently used for carcinogenesis bioassays. Based on data available both within the program and without, the NTP Board of Scientific Counselors should explore whether continued use of both a rat and mouse strain is needed for detection of carcinogens given the range of assay tools available to the oncology research community.

If a determination is made to maintain a two species bioassay protocol, give serious consideration to replacement of the B6C3F1 mouse with a strain having an established lower and less variable spontaneous incidence of important tumors that are induced by chemicals. In addition, continued investigation of the use of other species as adjuncts or replacements for the ones now in use should be undertaken.

Toxicological and chemical disposition for selection of doses for chronic studies—The use of the MTD as described in this report should be continued. The rationale for selection of the doses for a chronic study and the procedures relating to utilization of the data from subchronic studies and other sources in this process should be included in all NTP bioassay reports.

NTP should continue to develop criteria and methodologies to evaluate and employ toxicological and pharmacological data as well as human exposure estimates where appropriate to select doses for the chronic study.

Pharmacokinetic studies should continue to be conducted before or during the prechronic phase of a bioassay so that a data set as complete as possible will be available to aid in the design of the chronic protocol and the interpretation of the results of the chronic study.

Factors affecting dose route and vehicle—Exposure to compounds in the carcinogenesis bioassay should reflect the predominant human exposure route where possible taking into account the need to achieve adequate dose levels for an appropriate study.

Should special circumstances indicate that an alternative exposure route may be necessary, an appropriate supporting rationale should be provided including the development of pharmacokinetic and toxicologic data associated with the surrogate exposure route.

Since inhalation exposure represents a significant route of human exposure to environmental chemicals, NTP should develop a data base for a selected group of substances tested by several routes to aid in determining whether a single exposure route is adequate to assess carcinogenicity.

Design of chronic studies

Design considerations—For routine bioassays use a design employing three test doses plus control; distribute the animnals equally among groups and continue to use 50 animals of each sex and species in each dosage group, including controls. For special studies or special needs the numbers of groups and number and distribution of animnals within groups may be altered.

Selection of species and dose—The MTD as currently defined in this report should be employed in whole animal bioassay for carcinogenic agents as the highest level administered.

NTP should continue to use metabolic and pharmacokinetic studies in selecting doses below the MTD.

A continued search for species other than the rat, mouse, and hamster which satisfy reasonable criteria for chronic bioassay studies should be encouraged.

Although strongly recommended, chronic bioassay procedures by NTP need not be restricted to inbred or hybrid lines of rats and mice.

In order to understand a possible factor in the background incidence of neoplasia, serious consideration should be given to a study by NTP of the effect of restricted dietary feeding on the spontaneous tumor incidence.

Selection of route—Bioassays, in general, should employ a route or routes relevant to anticipated human exposure unless not possible for technical reasons.

Bioassays which, for technical considerations, use gavage or other atypical routes should be backed up by pharmacokinetic studies which measure peak blood level, "area under the curve," or other relevant measures for the typical and other routes.

Selection of vehicle—A number of nominally acceptable but unvalidated alternatives to vegetable oil gavage exist. These include the use of aqueous suspending agents, microencapsulation, and highly polar nonvegetable oils. Those should be considered, but since they have not been extensively used and validated, further study is needed.

The nature and extent of potential confounding effects from vegetable oil gavage, including altered susceptibility to the test agent, should be evaluated.

Duration of study—In view of the rate of appearance of spontaneous tumors as the test animals age, NTP should carry out studies using both ongoing assays and the recently completed assays to determine the optimum termination point for the bioassay.

Use of an in utero exposure system—The in utero design should be considered where the test agent has reproductive or teratogenic activity. It should be considered when the pattern of use, nature and degree of exposure, pharmacokinetics or metabolism or other data suggest that this is a more appropriate means of testing.

Husbandry requirements and quality control—A proper laboratory animal environment is a combination of facilities, personnel and management. Performance standards bring all of these into operation. Management must assure compliance.

A clear statement of goals and objectives in a study will help to define the performance standards appropriate to that study in the specific facility. These performance standards relate to disease control, sanitation, husbandry, cage placement and rotation and environmental control. Each bioassay should include contemporary quality assurance, good laboratory practice and related activities.

Pathology requirements—Every animal must be subjected to a thorough post mortem examination conducted by, or under the direct supervision of, a pathologist as there is only a single opportunity to examine a given animal.

The existing heavy burden of microscopic pathology can be reduced through use of either the inverse pyramid or selective inverse pyramid method of identifying target tissues in some or all test groups. Statistical inferences from the use of inverse pyramid methods should be examined by NTP staff.

Statistical issues in the interpretation of data from NTP whole animal carcinogenesis bioassays—Results of a complete statistical analysis should be made available to the Technical Report Review Committee. Among the various statistical tests available, the test for a linear trend in tumor rates with increasing dose generally provides the single most sensitive and appropriate statistical indication of the presence or absence of a carcinogenic effect. The assumptions that underlie its use should be checked by further analysis of the dose response curve including pairwise comparisons of the control with each dose group. These tests should be age adjusted by a method appropriate to the presumed relationship between tumor and death, and additional information should be sought from serial sacrifice experiments regarding this relationship.

NTP is encouraged to utilize historical control data, especially recent data from the laboratory that conducted the bioassay, in the interpretation of results of chronic studies. Further analyses should be conducted of the accumulating database to determine the key sources of extraneous variation in tumor rates. Primary reliance should be placed on the comparison of treated animals with concurrent, randomized controls for evaluation of commonly occurring tumors. High priority should be given to ascertaining the extent of extraneous within assay variation through use of replicate control groups and the analysis of data from recent FDA studies that utilized such a design.

Analysis of the NTP database should continue regarding possible negative associations between tumor types and other factors that may contribute to the observation of negative trends.

Errors and error rates—Continue monitoring of the quality of bioassays in contractor laboratories by NTP. Systematically analyze the kinds and rates of errors in the conduct of bioassays and develop interventions to reduce or eliminate such errors. Further develop the criteria for carcinogenicity in experimental animals and establish a list of noncarcinogenic substances for reference use by the scientific community.

Combining benign and malignant neoplasms in evaluating carcinogenicity—Where substantial evidence exists within the specific study that progression occurs from benign to malignant neoplasms in the same organ, then the incidence data may be combined to aid in the evaluation. Neoplasms of the same histomorphogenic type may be combined even if they occur in different anatomic sites. Neoplasms of different morphologic classification may be combined when their histomorphogenesis is comparable.

Categories of evidence of carcinogenicity—NTP should continue to develop a system for interpreting the findings of each bioassay (sex and species) with regard to the strength of the experimental evidence supporting the conclusion. These interpretations at present do not take into account potency or mechanism of action.

The proposed categories of evidence of carcinogenicity are as follows: clear evidence of carcinogenicity, some evidence of carcinogenicity, equivocal evidence of carcinogenicity, no evidence of carcinogenicity, and inadequate study of carcinogenicity.

John Doull, professor of pharmacology at the Univ. of Kansas Medical Center, was chairman of the Panel. Other members were Richard Adamson, director of NCI's Div. of Cancer Etiology; Perry Gehring, Dow Chemical Co.; Richard Griesemer, Oak Ridge National Laboratory; Kim Hooper, California Dept. of Health; Sanford Miller, FDA; Ruggero Montesano, Internation-

al Agency for Research on Cancer; Ian Munro, Canadian Center for Toxicology; Frederica Perera, Columbia Univ.; Robert Scala, Exxon Corp.; Andrew Sivak, Arthur D. Little Inc.; Bernard Weinstein, Columbia Univ.; and Gerald Wogan, Massachusetts Institute of Technology. Representing the NTP Board of Scientific Counselors were Norman Breslow, Henry Pitot, and James Swenberg.

Copies of the report may be obtained at no charge from Steven D'Arazien, NIEHS, Box 12233, Research Triangle Park, N.C. 27709.

ACS EXPANDS PROGRAM OF SHORT TERM GRANTS TO PHYSICIAN INVESTIGATORS

"The accelerated pace of cancer research and the need for constant peer surveillance for expeditious translation into strategies for diagnosis and treatment suggests that support of the scientifically prepared physician will be critical for ultimate cancer control," the American Cancer Society said in announcing expansion of its research development program.

To strengthen programs in clinical investigation at both the basic and technical transfer or cancer control levels, ACS is offering short term grants to physicians. They will be peer reviewed on the basis of merit, relevance, and urgency, with direct budgets of $50,000 or less for 12-18 months.

Application can be made to the ACS Research Dept., in care of Saul Gusberg or Frank Rauscher, 777 Third Ave., New York 10017.

SYMPOSIUM REPORTS PROVIDE EVIDENCE THAT SILICA INCREASES CANCER RISK

A new controversy reportedly has developed in occupational cancer epidemiology: Does silica exposure increase the risk of lung and gastrointestinal cancers?

That issue was examined at an international symposium held earlier this year in Chapel Hill, sponsored by the Univ. of North Carolina and the Society for Occupational & Environmental Health. Carl Shy of UNC and Kenneth Bridbord of the NIH Fogarty International Center cochaired the meeting, which provided a cross disciplinary evaluation of the evidence.

David Goldsmith, assistant professor in the Div. of Epidemiology at the Univ. of California (San Diego), provided **The Cancer Letter** with this summary of the meeting:

Despite what is known about the dusty trades and silicosis, Carol Rice et al, UNC, have shown for the first time in a case control study that a dose response relationship exists between dust particle counts and the risk of silicosis. Using data from the North Carolina Dusty Trades File, she demonstrated that cigarette smoking did not affect the association. In a new study of South African gold miners, G.K. Sluis-Cremer and Patrick Hessel supported the lack of effect from smoking on either the risk of silicosis or on the progression of the disease.

The experimental research presented at the symposium provided the strongest evidence for silica's carcinogenicity. Intratracheal administration of Min-U-Sil (highly purified Si02 used for making glass) by Lloyd Stettler et al (NIOSH) and by Marty Holland et al (Los Alamos National Laboratory) produced adenocarcinomas and epidermoid lung tumors in lifetime rat studies. Holland and Dagle (Battelle Pacific Northwest) also produced pulmonary neoplasms in Fischer 344 rats using lifetime inhalation of Min-U-Sil at high doses. In all four animal studies, Min-U-Sil was being used as a positive control for fibrosis. Thomas Hesterberg et al (NIEHS) demonstrated that silica was weakly mutagenic in comparison with asbestos and fibrous glass in a newly developed transforming assay using Syrian hamster embryo cells in culture. In all cases, this is the first evidence of silica's mutagenicity/carcinogenicity without initiation by benzo(a)pyrene.

Goldsmith (citing a 1982 article in the "American Journal of Industrial Medicine) presented evidence that ceramics, sandblasting, metal molding, foundry work, firebrick manufacture and metal ore mining—industries with high silica exposures—had significant excesses of lung cancer as well as silicosis and other nonmalignant respiratory disease. Murray Finkelstein (Ontario Ministry of Labor) presented evidence that Ontario gold miners had excess mortality from silicosis, lung cancer and stomach cancer. In contrast, Sluis-Cremer and Brown found no exposure gradient for lung cancer among gold miners in South Africa or Colorado.

There was no disagreement that foundry workers had excess lung cancers as reported by US, UK, Danish and Canadian investigators. Anthony Fletcher (UK) demonstrated that British foundrymen have elevated stomach cancer mortality as well. However, Winifred Palmer (Control Data Healtcare Services) noted that foundry fumes and particulates contain exceedingly complex mixtures of polycyclic aromatics plus silica and ash, so attributing the excesses to one material was probably not justified.

Two reports, by William Graham (Univ. of Vermont) and Letitia Davis (Harvard) on the Vermont granite industry showed no association with lung cancer and a decline in the risk of silicosis. Terry Thomas (NCI) reported that several studies of lung cancer among dusty industries, including one on ceramic workers, are being pursued by NCI's Environmental Epidemiology Branch.

Followup of silicotics has shown a risk of between three and six for lung cancer. These find-

ings were reinforced by Peter Westerholm (Sweden), Georges Schuler (Switzerland), and Finkelstein. Goldsmith suggested that excess lung cancers could be produced by synergy between smoking and silica inhalation, similar to the enhanced lung cancer risk among smoking asbestos workers.

Although the animal evidence for silica's carcinogenicity appears to be strong, no consensus emerged on the human risk. Clearly, the risk of silicosis mortality from massive dust exposure is diminishing in most industries owing to greatly improved dust suppression and industrial hygiene monitoring. Even if the present silica standard confers a debatable cancer risk to workers, improved housekeeping and ventilation were advocated by Marvin Schneiderman (Environmental Law Institute), and Nicholas Ashford (MIT).

Proceedings of the symposium, "Silica, Silicosis and Cancer," will be published in December by Praeger.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda, MD. 20205. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring, Md., but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CN-55440-50
Title: Phase 3 trial of 4-hydroxyphenyl retinamide to prevent superficial bladder cancer
Deadline: Nov. 30 (anticipated)

The Div. of Cancer Prevention & Control of NCI is seeking proposals for provision of all necessary personnel, labor, facilities and equipment, not otherwise provided by the government, to provide necessary technical support to conduct phase 3 clinical trials in patients with an increased risk for development of bladder cancer. Increased risk in this instance means people who have had diagnosed and treated superficial bladder cancer. Subjects are to be randomized to receive active HPR or placebo. The period of performance will be five years.
Contract Specialist: David Monk
RCB Blair Bldg Rm 2A07
301-427-8745

RFP NCI-CB-51002-53
Title: Operation of a human serum bank
Deadline: Nov. 9 (anticipated)

The Diagnosis Branch of NCI's Div. of Cancer Biology & Diagnosis is seeking proposals for the collection, maintenance and distribution of sera obtained from preoperative or postoperative patients (if advanced) with various malignant diseases, from benign disease patients, and from age and sex matched healthy individuals. These sera are to be used for research in biological markers in cancer diagnosis. Extensive storage facilities and data management capabilities are required.
Contract Specialist: Eileen Webster
RCB Blair Bldg Rm 122
301-427-8888

RFP NCI-CM-57708-26
Title: Evaluation of dosimetry, calculating, and afterloading techniques for interstitial radiotherapy
Deadline: Approximately Dec. 7

The Radiation Research Program of NCI's Div. of Cancer Treatment is seeking contractors to be part of a collaborative effort to develop recommendations and guidelines for (1) the calibration of radioactive interstitial implant sources; (2) the caluclation of dose distributions in patients resulting from interstitial implants; (3) the verification of equipment and facilities not otherwise provided by the government.

It is anticipated that multiyear, incrementally funded, completion type contracts will be awarded for a period of three years. Each increment will be for a 12 month period.

A preproposal conference will be held approximately five weeks after the RFP issuance date on or about Sept. 28.
Contract Specialist: Carolyn Swift
RCB Blair Bldg Rm 228
301-427-8737

NCI CONTRACT AWARDS

TITLE: Efficacy studies of chemopreventive agents in animal models, including synthesis, bioavailability and encapsulation studies, master agreements only

CONTRACTORS: Biotek Inc., Woburn, Mass, Task II; Research Triangle Institute, Tasks I, II; Southern Research Institute, Tasks I, II; Southwest Research Institute, Task II; Battelle Columbus Laboratories, Tasks I, II; Dartmouth College, Task I; IIT Research Institute, Chicago, Task I; Arthur D. Little, Tasks I, II; SRI International, Task II; Litton Bionetics, Bethesda, Task I; Microbiological Associates, Bethesda, Task I.

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