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P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

RESPONSES SO FAR SUPPORT OUTSTANDING INVESTIGATOR GRANT; NCAB MEMBERS OBJECT TO SALARY COMMITMENT

NCI has received about 50 responses so far from members of the scientific community, 8,000 of whom were asked to submit critiques of the draft of parameters for the proposed Outstanding Investigator

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In Brief

REAUTHORIZATION BILL COULD GO TO HOUSE FLOOR NEXT WEEK; PACKWOOD BLOCKS ACTION IN SENATE

BIOMEDICAL REAUTHORIZATION bill (HR 2350), which includes renewal of the National Cancer Act, may go to the floor of the House next week. The bill has cleared the Rules Committee and could be brought up any time after Congress returns from recess July 11. In the Senate, the reauthorization bill (S 773) has been reported out by the Labor & Human Resources Committee but is being blocked by Sen. Robert Packwood (R.-Oregon). Packwood put a hold on it when he learned an amendment would be offered forbidding fetal research. When that impasse will be resolved is anyone's guess. Work on the appropriations bills, as usual, is dragging. The House Labor-HHS-Education Appropriations Subcommittee has not scheduled the markup of its bill; the Senate counterpart will not schedule its markup until the House subcommittee finishes its job. With the month long recess in August and the usual hassles which afflict health and welfare money bills, don't look for Congress to get an appropriation measure to the White House before the Oct. 1 start of the 1984 fiscal year. It appears that NCI and NIH will have to limp along again with the uncertainties of operating under a continuing resolution for months. Until at least one house or the other passes an appropriations bill which restores the money cut from the Cancer Centers Program, the 20 centers whose core grants are up for renewal in 1984 will be left twisting in the wind. . . . **RIVERSIDE HOSPITAL** in Newport News, Va., had the distinction of becoming the 1,000th approved hospital cancer program in the program administered by the American College of Surgeons Commission on Cancer. The approvals program now includes 1,013 hospitals. . . . **ASCO ELECTION** of officers and directors in San Diego, in which Philip Schein was named president and Sydney Salmon president elect, included reelection of David Ahmann as secretary-treasurer; Charles Coltman and Steven Rosenberg as new directors; and Virgil Loeb to fill Salmon's unexpired term on the board. Continuing directors are Lawrence Einhorn, Eli Glatstein, and Sharon Murphy. Saul Rosenberg is immediate past president. . . . **MEAD JOHNSON** has committed $16,000 annually to ASCO for an award to a young investigator, "someone just beyond a fellowship to help in his/her investigation," Ahmann reported.

AMOS COMMITTEE DRAFT OF OIG RULES OPEN TO CRITICISM; THERE IS SOME

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Grant Program. Most of the responses are generally supportive of the program, although nearly all offer suggestions for changes in the parameters. A few oppose it because they fear it would siphon money from existing funding mechanisms.

The draft was brought in May to the National Cancer Advisory Board by Harold Amos, who chairs a committee appointed by the President's Cancer Panel to draw up recommendations for the program. The Panel, in its meetings around the country during the past year, heard repeatedly from scientists that a new funding mechanism is needed to support outstanding scientists which gives them more freedom and flexibility with longer award periods. Stability in funding and less paperwork were the goals.

Amos was a member of the Panel at that time, and Chairman Armand Hammer appointed him to head the committee. Amos agreed to continue with the committee when his term on the Panel expired earlier this year.

The draft turned out to be more controversial than Amos had expected, at least as far as members of the NCAB were concerned.

Aims and objectives of the Outstanding Investigator Grant, the draft said, are:

"To provide eligible investigators with stable financial support and research flexibility over a finite period of time, and to encourage investigators to embark on long term projects of unusual potential in cancer research. This award recognizes an investigator because of his or her established preeminence and productivity. Emphasis will be placed on evidence of recent substantive contributions, i.e. seminal ideas and innovative approaches to resistant problems."

There was no argument by NCAB members over that. But Board members Maureen Henderson, Robert Hickey and Irving Selikoff objected to the requirement that evidence of institutional commitment to the applicant should include salary support "at least to the current level, but may not be less than 50 percent."

"That requirement from institutions would eliminate a large number of them," Henderson said.

"Yes, that was discussed," Amos said. "But there was a strong feeling that universities should make a long term commitment."

"The majority of us deal with professors whose total salary come from outside sources," Henderson said. "Our university has no money to commit to salaries."

"The intent is to nudge universities in that direction," Amos said.

"The desire to respond is there, but the ability is not," Henderson said.

"University administrators have not assumed responsibility for supporting investigators whose research funds go a long way to carry those institutions," Amos said.

"Could institutions which pay 100 percent of salaries reduce their commitments and rebudget that money for something else?" Hickey asked.

"As things stand now, no," Amos said. "The salary would be negotiated on the current basis."

"Isn't that a bit unfair?" Hickey asked.

Elliott Stonehill, who is executive secretary of the Panel as well as of the Amos committee, said that the requirement is that the current institutional commitment be maintained, except that those institutions which pay less than 50 percent of the applicants' salaries would have to increase it to that level.

NCI Director Vincent DeVita, who has been supportive of the OIG concept, pointed out that another provision in the draft provides for carryover of funds from one fiscal year to the next. "With no pressure to spend it all in the fiscal year, 100 percent might cost less than it does now," DeVita said.

Selikoff commented that if the number of investigators eligible for the award is sharply restricted, that would defeat the purpose of the program. "Someone whose salary is supported by an endowed chair would have no reason to apply," Selikoff said.

DeVita disagreed. "Seven years of guaranteed support, with the roll over money, is pretty attractive."

Amos said that the 50 percent requirement "is a serious point for us to consider. There is a lack of flexibility here," and he agreed that modifications to provisions in the draft should be considered.

DeVita sent copies of the draft to about 8,000 scientists, along with a letter asking for criticisms and suggestions. Their recommendations will be presented to the NCAB at its October meeting, and to the next meeting of the Panel, which has not yet been scheduled.

The draft document sent out by NCI included notations of the provisions considered controversial by the NCAB and by the NCI Executive Committee. They were:

- Eligibility would be limited to those who have received through competitive review a minimum of 10 years of consecutive support (past plus committed) immediately preceding the grant application. The objection was to 10 years.
- The letter of intent should be sent to the director of the Div. of Extramural Activities, and if the applicant is considered ineligible, the DEA director would so inform the applicant. Some felt that decision and action should be made and taken elsewhere at NCI.
- Review would be by an ad hoc initial review group, with subsequent review and approval by the NCAB. That was not a point in controversy, but a suggestion that review be by mail ballot to 10 re-

viewers selected from a larger panel of about 200 scientists was. ("The Executive Committee was split down the middle on this," DeVita said. "I liked it, but the rest of them didn't.")

- A review criterion was the question, "Is the applicant's stature in the field based primarily on his/her individual accomplishments or on collaborative efforts?" Some felt this either was not relevant or would be very difficult to establish.
- Individual grants will not exceed $250,000 in direct costs per annum in the initial year. Disagreement over that amount.
- Normal OIG support will not be in excess of the investigator's current total grant support. Why not, if it can be justified?
- For the duration of this award, OIG recipients will not be eligible to receive additional NIH research grant or research contract support. Some feel that flexibility on this point would make it easier, and offer a more fair approach, to obtain investigator salary support if they could retain access to other NIH grants.
- It is expected that approximately 20 OIGs will be awarded the first year, and the tentative goal of 50 active OIG awardees be reached in approximately five years. Some do not like the idea of having a goal of 50, feeling that the program should achieve the limit on its merits. Others feel that 50 is too many.

Twenty to 50 OIGs would cost, at the maximum individual limit of $250,000, from $5 million to 12.5 million a year in direct costs.

That would be a healthy drain from the NCI budget, if in fact it did represent a demand for additional money. However, DeVita and Stonehill pointed out that it really is only a reallocation of an investigator's own NIH support. It would in essence convert his existing three or five year grants into a seven year grant, and free him from the necessity of reapplying two or three times during that period. It would give him more flexibility in pursuing his research. It would not be a lifetime award.

The complete draft document, minus those items reported above, follows:

ELIGIBILITY

There are no age restrictions for eligible investigators. Consideration will be given to exceptional young investigators who may not meet all of the eligibility criteria. Applications will be considered only from domestic U.S. institutions.

Letters of intent are strongly recommended, and must contain a curriculum vitae, including complete bibliography of the investigator, and a summary of the intended applicant's major scientific contributions; and a record of all federal and nonfederal support awarded for the 10 years prior to the date of the letter.

Letters of intent will be reviewed by an ad hoc NCI review committee convened by the director, Div. of Extramural Activities, with advice from the NCI executive committee.

A prospective applicant investigator who is approved for consideration will be so advised and invited to submit an application for Public Health Service Grant (PHS 398).

The PHS 398 application will be completed in accordance with instructions in the RFA to be published for the OIG. The prose portion of the application must not exceed five typewritten pages (single spaced).

A letter indicating clear and continuing institutional commitment to the applicant must be submitted. This commitment should include salary support at least to the current level, but may not be less than 50 percent. Adequate physical facilities, staff and administrative resources appropriate to the role of the OIG principal investigator must be provided.

REVIEW OF APPLICATIONS

Significance of the applicant's work:

What has been the impact of the applicant's work on the field of cancer research?

Is his/her research cited often and as incentives for others' research efforts?

Has the applicant developed new experimental approaches crucial to the progress of his/her area of research?

Has he/she contributed to the collection of important reliable data?

In what way is the applicant's work seminal in nature?

Has the applicant productively exploited his/her own breakthroughs and/or those of others?

What will be the significance of the investigator's continued work in the field described above?

Does the proposed work break new ground or continue previous work?

Are the questions posed of significant interest and importance to cancer research?

Will this work provide impetus for others working in related areas?

Capabilities of the applicant:

Has the applicant made significant contributions in the areas of teaching and research training and/or clinical research? Comment on the applicant's communicative, pedagogic, and organizational skills.

Are the institutional and administrative relationships favorable?

Does the applicant have adequate administrative support?

Have the applicant investigator and his/her institution presented a workable plan for phaseout of the applicant's current research support and conversion of staff and facilities to support by the OIG? Are there any problems anticipated? Will there be any particular benefits or disadvantages for the institution?

AWARD SIZE AND CONDITIONS

Grants normally will be awarded for seven years; the OIG is renewable, but it is not a lifetime award. Application for competitive renewal should be submitted at the end of the fifth year. The procedure, requirements, and mechanism for renewal applications will follow the guidelines for initial applications. Renewal will be based on accomplishments during the period of the award and on the projected direction for the subsequent grant period.

The actual dollar award will reflect specifically the investigator's current and projected research needs evaluated by the Initial Review Group, and reviewed by the NCI Executive Committee.

Salary support will be included for technical staff, research staff and graduate students, but not for other academic faculty or institute equivalents. No other principal investigator may be included.

Other expenses, as would be included in R01 grants, are legitimate costs. Capital equipment costs are not included in the $250,000 ceiling.

Unexpended balances may be carried over from one grant year to the next. This and other fiscal considerations, such as annual inflationary factors and rebudgeting flexibility, will be in accord with NIH and OMB policies and regulations, and within the limits stated above.

Obligations of the awardee:

Application may still be made for training grants, construction grants and capital equipment grants, which are excluded from the restrictions of the OIG.

The OIG principal investigator is required to commit at least 75 percent of his/her time and effort to the research project proposed.

Those who may not have received DeVita's invitation to criticize or comment on the draft may do so by writing to Dr. Elliott Stonehill, NCI, Bethesda, Md. 20205.

Members of Amos' committee are Renato Baserga, Walter Bodner, Paul Boyer, Renato Dulbecco, Elvin Kabat, John Mendelsohn, Elizabeth Miller, Arthur Pardee, Sheldon Penman, Robert Pollack, and Keith Porter. Victor Braren is the NCAB representative on the committee.

WASHINGTON, FOX CHASE, ICC AWARDED FIRST OF NEW NCI CCRU, CCSP GRANTS

The Univ. of Washington, Fox Chase Cancer Center and Illinois Cancer Council were the first to receive grants in NCI's new approach to cancer control research. They were the only three approved applications out of 28 submitted.

The Washington grant, with Maureen Henderson as principal investigator, will support a Cancer Control Research Unit, for studies in defined populations. Eight CCRU applications were submitted, and Henderson's was the only one approved.

Reviewers approved five projects which the Washington CCRU will undertake—cancer prevention with retinol in persons with asbestosis; chemoprevention of lung cancer with retinol; prevention of cervical cancer with folic acid; efficacy of breast cancer self examination; and work site smoking cessation and relapse prevention.

The other two grants were to support Cancer Control Science Programs—essentially the same as CCRUs but without the defined population requirement.

Paul Engstrom is the PI for the Fox Chase grant, which includes three projects—cancer control in an urban neighborhood; cancer education programs for older citizens; and cancer education and management for patients.

Dick Warneke and Shirley Lansky are the PIs for the Illinois Cancer Council grant, which will support three projects—secondary prevention: comparing traditional and self directed continuing medical education; compliance with referrals for evaluation of possible malignancies; and swallowing rehabilitation in cancer patients.

Staff members of NCI's Div. of Resources, Centers & Community Activities were deeply disappointed that more grants were not approved in the initial round (***The Cancer Letter,*** May 13). However, four more—three CCSPs and one CCRU—are under review. Three were submitted following the first round, and one was deferred. Recommendations from that review will go to the National Cancer Advisory Board in October.

The payline on those four will be flexible, as it was for the first round (Henderson's was the only application scoring better than the 175 payline which governed most NCI grants). Enough money has been set aside to fund all four if they score well enough.

Meanwhile, new RFAs for another round of CCRU and CCSP awards are being processed, with major changes included. They may be ready for release in August. DRCCA hopes to fund five grants in each program.

SAMUELS' NCAB COMMITTEE SUBMITS DRAFT OF QRA STATEMENT TO BOARD

The National Cancer Advisory Board's Committee on Environmental Carcinogenesis has nearly completed its task of developing a "Policy of Risk Assessment of the Health Effects of Hazardous Exposures to Populations." Put more simply, the job entailed the writing of an NCAB position on the controversial subject of quantitative risk assessment.

Committee Chairman Sheldon Samuels presented a draft of the paper to the NCAB in May, and said that a final draft would be sent to members by mail. A poll will be taken by mail or phone on its acceptance prior to the Board's October meeting.

The committee met four times and attempted to answer five questions posed by Samuels:

—Definition of quantitative risk assessment (QRA) as distinct from qualitative risk assessment.

—Which models or paradigms of QRA have been, are, or are likely to be heuristic in terms of data fit, testability and predictive experience?

—Is QRA practical in terms of data adequacy of both dose and effects?

—Are the regulatory issues which involve QRA separable from the scientific problems of QRA?

—Who should do QRA?

Samuels and his committee were aware that an official policy developed and approved by the NCAB probably will have a profound impact on both research and regulation of environmental chemicals. The draft statement does not duck the tough issues but does attempt to carefully explain its answers to the five questions.

DEFINITION

QRA "is defined as the assessment of both hazard and exposure information for purposes of estimating the likelihood that hazards associated with the substance will be realized in exposed individuals or populations," the statement says, and then continues:

This assessment involves two steps. The first is hazard identification/characterization (qualitative risk assessment), in which toxicity to humans as determined from observations on human populations and/or from experimental systems is characterized. The second step, termed quantitative risk estimation, is the process by which the risk of disease or death in a population exposed to a toxic agent is related quantitatively to the pattern of exposure, including factors such as the intensity and duration of exposure. In quantitative risk assessment it is essential that both hazard and exposure information be considered. The quantitative process also includes an estimation of uncertainties.

In evaluating the risk of exposure to a particular agent, the first step is to consider the qualitative evidence that the agent is likely to be a carcinogen in humans. This evaluation relies on information from a variety of areas, including epidemiology. Epidemiologic studies provide important information about carcinogenic effects in humans because they associate human cancer incidence with exposure to particular chemicals, industrial processes or lifestyle factors. Clinical case reports and descriptive studies are of interest, but case control and cohort studies are of greater value.

Another source of information on the carcinogenicity of chemicals is long term animal toxicology studies, in particular the rodent bioassay. Identification of a substance as a carcinogen depends on showing that the test substance causes an increase in the incidence of tumors or a decrease in the latency period.

Additional confirmation of carcinogenicity is provided by positive results observed in more than one animal species, in more than one bioassay or in different laboratories, and the demonstration that the occurrence of tumors follows a dose dependent relationship. In animal bioassay studies, factors considered include the increase in tumor incidence in the treated group compared to controls, the number of tumors diagnosed per animal, and the percentage of tumors at a given site which are malignant. Both historical and contemporary control tumor rates are compared with those in the chemically treated group.

Other relevant studies include elucidation of structure activity relationships, studies on metabolites of the carcinogen, and characterization of chemical and physical properties of the compound. Additional information about carcinogenicity of a compound is also obtained through numerous other studies, including cell transformation, studies on binding to DNA, various genotoxicity assays, and metabolism studies, including those in which metabolism in species in which the long term animal tests were conducted are compared with metabolism in humans who have been exposed. Most recently, human epithelial cells and tissue explants have been used to provide information on potentially carcinogenic chemicals.

The second step in quantitative risk assessment is exposure assessment, a procedure as important as hazard assessment. Significant progress has been made in mathematical modeling, data monitoring, and laboratory approaches for determining the behavior of chemicals in the environment. Exposure assessment is a highly complex activity because any analysis must take into account various routes of exposure, different concentrations, human activities, biological conversions, chemical reactions, environmental transport mechanisms, and analytical limitations in the ability to quantify chemicals at trace levels.

When hazard exposure and assessment are completed, the final step, quantitative risk assessment, can be performed. This process applies data from epidemiologic studies, from long term bioassay studies, and from other sources to describe the relationship between dose of the substance and the probability of toxic response.

The dosage in animal bioassay studies is exaggerated to compensate for the necessarily small study size of animal test systems. In order to anticipate effects at low levels, based on what experiments revealed at higher dose levels, the dose response relationship must be extrapolated into the low dose region. This region may be orders of magnitude below the dose level used in laboratory studies. Extrapolation from these studies involves the use of various methamatical models. No single model can be universally accepted at the present time. The development and selection of models should be increasingly influenced by an expansion of our knowledge of underlying biological mechanisms, such as the interaction of carcinogen metabolites and DNA.

The end point in quantitative risk assessment of chemicals for carcinogenicity is a final review and evaluation of hazard and exposure information, taking into account the uncertainties known to exist. The amount and reliability of information available on the numerous parts of an assessment will vary from chemical to chemical. It is important to make decisions about a chemical without overemphasizing any single aspect of the assessment. In addition, it is frequently necessary to make decisions about a chemical when the information available about it is imperfect and/or incomplete.

These uncertainties (and the other uncertainties apparent at each stage of the risk assessment process) should be clearly and explicitly stated to assist the management of the risks under study.

Moreover, while we are confident that research will reduce the arbitrariness of the selection of assessment methods, it is not probable that the need to make value judgments will be eliminated. The nature of these judgments should also be clearly and explicitly stated.

MODELS

The quantitative assessment of human carcinogenic risk from exposure to environmental agents often consists of extrapolating evidence from effects observed under one set of conditions in one population group or biological system to estimate the magnitude of effects expected under a different set of conditions in the human population of interest. This extrapolation involves, in part, mathematical models of the carcinogenic process which are necessarily simplistic representations of a complex biological stochastic process.

One class of these models, dose response models, is used to

describe the presumed mathematical relationship between the level of carcinogen exposure (the dose) and the magnitude of its carcinogenic effect (the response). These dose response models fall into two general categories: (1) tolerance distribution models and (2) models based on quantitative theories of carcinogenesis or other toxic responses.

The biologic basis for the class of tolerance distribution models assumes that the toxic reaction to a particular stimulus is a deterministic process which depends upon an individual's "tolerance level;" a level of the stimulus above this tolerance will produce a specific, singular toxic response with certainty, whereas a stimulus level below this tolerance will produce no response with certainty. Because of variability (both biological and environmental) among members of the exposed population, their tolerance levels will vary, sometimes within quite wide limits, to produce a "smooth" dose response relationship for the population as a whole. This simple deterministic concept of an individual's tolerance for a particular toxic agent is not likely to provide a reasonable representation of the mechanism of carcinogens which act directly on DNA at the cellular level. However, indirect carcinogenic action (e.g., stimulation of enzymatic action or cell proliferation) may be describable by such models for individuals.

Another class of dose response models is based on the concept of "hit theory" applied to initiation of the carcinogenic process at the cellular level. Once the cell has been "hit," the process of carcinogenesis is assumed to continue independently of the carcinogenic exposure. These models are axiomatically developed from a theory of the interaction between particles and targets necessary to produce a biologic response. These models were originally derived to explain radiation carcinogenesis, but have also been used for chemical carcinogens.

A generalization of the single event hit theory which explains cancer initiation is the multistage, or multievent, theory which assumes that the carcinogenic process consists of a series of cellular changes. These cellular changes are assumed to be heritable, are characterized as being of slow and improbable occurrence, and may or may not be affected by the particular carcinogen in question. Once a cell has progressed through all the stages, i.e., it has attained its full malignant potential, it then proliferates to a clinically detectable tumor. Other exposure related risk factors (e.g., proliferation of partially transformed cells) can also be included in the theory. Other theories, based on multiple cells, have also been proposed.

These quantitative theories of carcinogenesis have produced a variety of dose response models which have different risk assessment characteristics. Each dose response model is based on a number of critical assumptions concerning the carcinogenic process. A major limitation of these dose response models is that their currently untestable assumptions have a significant impact on carcinogenic risk assessments, and without additional basic knowledge concerning the mechanism of action, pharmacokinetics, DNA-adduct formation, etc., any choice from among these models cannot be made with confidence.

PRACTICALITY OF QRA

Scientific opportunities generally arise when two or more research areas converge and/or advances in methodology occur. Research in the laboratory has recently provided us with both critical information on mechanism(s) of carcinogenesis and new technological advancements including those in molecular biology. Epidemiology has clearly demonstrated the importance of environmental exposure to carcinogens. It is now practical to integrate laboratory determinations into more classical epidemiological approaches to chronic disease. The potential of biochemical and molecular epidemiology to predict cancer risk on an individual and population subset basis, instead of a total population level, and prior to the onset of clinically evident cancer may represent a significant contribution to risk assessment.

NCI is performing intramural research in this area and is supporting extramural programs through the traditional R01 grant mechanism and through issuance of requests for applications. . . .

The uncertainties inherent in quantitative risk assessment are many and varied. High dose to low dose extrapolation is the single most imprtant source of this uncertainty. Assumptions concerning the relationship between exposure level and carcinogenic response are necessary for this extrapolation since the response rates at low dose levels are often too small to be accurately measured with limited experimental or epidemiologic sample sizes. A quantitative estimate of the risk at a particular low dose level is highly dependent upon the mathematical form of the presumed dose response relationship; differences among models of 3-4 orders of magnitude are not uncommon. More accurate high to low dose extrapolations are not possible without knowledge of the mechanism of action, studies on DNA adduct formation and information on metabolic disposition of the particular carcinogen in question, since the dose response relationship is likely to depend upon these factors.

Part of the mechanistic knowledge concerns pharmacokentic information on the fate of the toxic agent once it enters the body. Nonlinear kinetics may be an important determinant of the nonlinear dose response often observed in experimental animal studies conducted at high dose levels. A critical problem in the application of pharmacokinetic principles to low dose quantitative risk assessment is the potential change in the pharmacokynamics as the level of the toxic agent decreases. The presence of saturation kinetics at high doses may pose problems in quantitative risk assessment based on high dose experimental results. As an example, the metabolism of inhaled vinyl chloride has been shown to be a saturable process which provides a possible explanation of the nonlinear dose response observed in animal studies. The lack of relevant dose related pharmacokinetic information adds another measure of uncertainty in quantitative risk assessment within a single species.

Quantitative risk assessment across species, commonly referred to as the mouse to man problem, involves potentially more uncertainties than risk assessment within a species. Methodologies for making this animal to man extrapolation rest, in part, on pharmacokinetic considerations of species similarities in absorption, distribution, metabolism and elimination of the chemical carcinogen as well as DNA adduct information and DNA repair processes. Although no single experimental animal species mimics man in all respects relevant to the pharmacokinetics of a particular chemical, animal to man extrapolation is often made with the critical assumption that all the relevant biological parameters are the same in humans and animals. Unfortunately, often very little is known concerning interspecies variations among these biological parameters and these potential species differences make interpretation of animal to man extrapolations both uncertain and arbitrary.

In addition, other sources of uncertainty in quantitative risk assessment include: (1) environmental and genetic heterogeneity and interaction; there are many environmental factors that one may be exposed to through occupation (e.g., asbestos), lifestyle (e.g., cigarettes), or of intrinsic origin (e.g., hormonal imbalances) which may affect one's susceptibility and response to a particular carcinogenic exposure; (2) differential effects for exposure rate and duration; the presumed relationship of risk to the rate and duration of exposure can have substantial consequences when quantitatively estimating risk from one exposure situation to another; experimental studies of

dose fractionation have shown that no general relationship exists; (3) reliable epidemiological data only exists for a few agents to which humans are exposed and generally there is an absence of dose measurement. Also little information is available on intrauterine exposure; (4) the identification of agents and effects is obscured by latency factors; (5) the spectrum of tumors is sometimes overlooked because of a focus on unique associations (e.g., vinyl chloride and angiosarcoma); (6) diagnostic uncertainties may lead to underdiagnosis; (7) quantitative risk assessment is expressed in static terms even though a dynamic situation is addressed and finally (8) qualitative factors such as data quality, multiple studies from different sources (e.g., chemical structure/activity and various "mutagenesis" tests), multiple tumors within a single experimental animal species, multiple experimental species/strains giving different qualitative and/or quantitative results, the combination of negative and positive studies, and competing risk all have a potentially important effect on quantitative risk assessment.

The current methodologies for the quantitative assessment of human carcinogenic risk rely on necessarily simplistic and currently untestable assumptions. However, as further knowledge of chronic diseases and toxicity mechanisms is acquired, this information should help provide a basis for more valid quantitative estimates of the risk to humans of environmental carcinogens.

REGULATORY VS. SCIENTIFIC ISSUES

NCI contributes to the development of information on quantitative risk assessment through its activities in the area of information dissemination, by providing advice and expertise to regulatory agencies, and through its efforts in the field of chemical and physical carcinogenesis research, epidemiology, and most recently in the new area of biochemical and molecular epidemiology.

NCI provides assistance in an informal way to regulatory agencies responsible for performing risk assessments by keeping their staffs abreast of new developments in the area of carcinogenesis research and risk assessment methodologies. This informal interchange involves providing the agencies with accepted journal articles, reports and summaries of research findings pertinent to risk assessment; it also includes conferences focusing on issues of importance to risk assessment which are attended by representatives from NCI, the Food & Drug Administration, NIOSH and other agencies.

The committee felt that NCI activities in environmental carcinogenesis were appropriate and that they should be continued.

In the 1970s, NCI pioneered a carcinogenesis testing program through which scientists established a standardized way to evaluate the carcinogenic activity of chemicals in mice and rats, which seem to be good predictors of chemicals carcinogenic in humans. Of the 30 agents for which there is human evidence that these agents are associated with cancer in humans, all (with the possible exception of arsenic) are risk factors for cancer in laboratory animals.

In 1981, the carcinogenesis testing program was transferred to the National Institute of Environmental Health Sciences from NCI, an action which provides for direct management by the National Toxicity Program of the NIH components of the program. Nevertheless, NCI maintains a significant level of involvement in the carcinogenesis testing program by nominating chemicals for testing in the bioassay program and by membership on the NTP Executive Committee, which selects the chemicals to be tested.

NCI also provides advice and the expertise of its staff to other government agencies, including those with regulatory functions. It provides assistance in an informal way to agencies by keeping their staffs apprised of new information and developments in the area of carcinogenic research.

WHO SHOULD DO IT?

There was general agreement among members of the committee, invited guests, and representatives from the regulatory agencies that scientists who perform quantitative risk assessment should be chosen on the basis of their qualifications and should possess expertise in the areas under consideration. In addition, it was felt that while scientists who perform quantitative risk assessment should continue to work both in research and regulatory agencies, an atmosphere which promotes objectivity and sound scientific independence should be created, i.e., one separated from the regulatory process itself.

The committee concurred with the National Academy of Sciences, which in its report on risk assessment recommended that the process of risk assessment and risk management should be separated. It was also the consensus that the research agencies should continue to try to improve the data base, improve techniques that quantify exposure levels and continue to develop mathematical procedures applicable to risk assessment. In addition, risk assessments, regardless of where in the government and by whom they are performed, should be peer reviewed, made available to the scientific community and subject to comment by the surgeon general (or the assistant secretary for health).

Circumstances might arise in which a particular institution within the HHS would have information pertaining to a risk assessment (e.g., bioassay data from NTP, epidemiology data from NCI, exposure data from NIOSH), not available to other institutions or agencies. In such a situation, the surgeon general (or the assistant secretary for health) should be responsible for marshalling whatever resources are available to perform a risk assessment.

In situations where originators of data are outside the research establishment, a special committee (similar to the Clearinghouse established by the NCAB in previous years) could be established by the surgeon general (or the assistant secretary for health) to evaluate the data. Deliberations of this kind should be conducted as peer reviews in meetings open to the public.

The peer review system in place within the department is adequate for the purpose of supervising the integrity of the risk assessment process. When an assessment is challenged, however, a mechanism should be available and used in a manner that will not delay, unreasonably, the use of the assessment.

The draft mentions the possible uses of QRA, the most obvious of which is by the regulatory agencies as one tool in the regulatory process. There are others, the report says—for management of populations at high risk of cancer because of environmental exposure to chemicals and physical agents; by industry for voluntary setting of priorities in the absence of regulations; and by government, labor and others to select populations for special programs of medical screening, education, and intervention.

"For any use, it must be understood that we are dealing with a primitive application of rough mathematical approximations using data usually generated for other purposes. Those who question the use of quantitative risk assessment for any purpose for most environmental agents make substantive arguments.

"The committee believes, however, that the development of this method ought to proceed on the basis of its potential good. Meanwhile, those who manage risk assessments should use the currently available methods with great caution," the draft says.

(Editor's note: The preceding report involved reorganizing the draft document submitted by Samuels in order to present together statements dealing with each of the five questions. The draft also included a review of NCI's intramural and extramural activities in environmental carcinogenesis and the Institute's contributions in that field. Those were omitted to conserve space.)

RFPs Available

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

RFP 200-83-0502

Title: *Carcinogenic risk assessment of the monohalomethanes*
Deadline: *Approximately Aug. 5*

Services for a quantitative assessment of the risk of developing cancer due to exposure to each of the following monohalomethanes: methyl chloride, methyl bromide, or methyl iodide.

It is anticipated that a firm fixed price type contract will result from this solicitation and that the contract will be for approximately 90 days. The contractor shall be required to review 15 articles for adequacy of data. These articles will be supplied by the government. The contractor shall develop a final report which shall include a presentation and evaluation of alternative mathematical models, an assessment of the health risks of working with the monohalomethanes, and the evaluation of the results and conclusions. The contractor is required to have experience in managing similar projects and must provide a support staff with experience in toxicology, epidemiology, and quantitative risk assessment, as well as other pertinent areas of occupational safety and health such as industrial hygienist.

RFP 200-83-2630

Title: *Carcinogenic risk assessment to cadmium*
Deadline: *Approximately Aug. 5*

Services for a quantitative assessment of the risk of developing cancer due to exposure to inorganic cadmium. It is anticipated that a firm fixed price type contract will result from this solicitation and that the contract will be for approximately 90 days.

The contractor shall be required to review 15 articles for adequacy of data. These articles will be supplied by the government. The contractor shall develop a final report which shall include a presentation and evaluation of alternative mathematical models, an assessment of the health risks of working with cadmium, and the evaluation of the results and conclusions. The contractor is required to have experience in managing similar projects and must provide a support staff with experience in toxicology, epidemiology and quantitative risk assessment, as well as other pertinent areas of occupational safety and health such as industrial hygienist.

Contracting Officer, PGO
Centers for Disease Control
255 East Paces Ferry Rd. NE
Atlanta GA 30305

NCI CONTRACT AWARDS

Title: Hyperthermia quality assurance program
Contractor: Allegheny-Singer Research Corp., $1,654,712; five years.

Title: Prime contractor for performance of protocol toxicology studies
Contractor: Battelle Memorial Institute, Columbus, Ohio, $348,309.

Title: Clinical trials monitoring services
Contractor: Theradex Systems Inc., Princeton, N.J., $5,356,702 (small business setaside).

Title: Programming and data entry services in support of the National Cancer Institute contracts management system
Contractor: General Software Corp., Landover, Md., $609,167.

Title: Cancer Control Program for Radiological Physics Center
Contractor: Memorial Hospital, New York, $611,499; 19 months.

Title: Technical writing, publication distribution and telephone answering services in response to cancer related inquiries
Contractor: Biospherics Inc., Rockville, Md., $360,250.

Title: Management Information System Support services (MIS)
Contractor: System Sciences Inc., $673,898.

The Cancer Letter _Editor Jerry D. Boyd
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