BY THE U.S. GENERAL ACCOUNTING OFFICE

Report To The Chairman, Subcommittee On Oversight And Investigations Committee On Energy And Commerce House Of Representatives

National Toxicology Program: Efforts To Improve Oversight Of Contractors Testing Chemicals

The National Toxicology Program is a cooperative effort among Department of Health and Human Services agencies to conduct tests on chemicals to determine whether they have a toxic or cancer-causing effect. The program is the responsibility of the Department's National Institute of Environmental Health Sciences.

GAO's review showed that to address concerns discussed during November 1983 congressional hearings about oversight of program testing conducted largely by private research contractors, the program has (1) assumed responsibility for day-to-day contract management from a management contractor, (2) reorganized its project management team, and (3) established detailed quality assurance reviews during and after testing. GAO also found that program officials were monitoring private contract laboratories closely and acting to correct identified problems.

This report also summarizes information GAO obtained and analyzed covering several concerns expressed to the Subcommittee Chairman by a former program testing contractor, the Gulf South Research Institute, concerning program officials' handling of its contract.

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UNITED STATES GENERAL ACCOUNTING OFFICE
WASHINGTON, D.C. 20548

HUMAN RESOURCES
DIVISION

B-211085

The Honorable John D. Dingell
Chairman, Subcommittee on Oversight
and Investigations
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

At your request, we have reviewed the National Toxicology Program's efforts to improve its oversight of its chemical testing contract laboratories since hearings were held on these activities before your Subcommittee in late 1983. The program is the responsibility of the National Institute of Environmental Health Sciences. We also reviewed several concerns raised by one of the program's contractors--Gulf South Research Institute--as a result of the National Institute's termination of the firm's contract.

This report describes program actions taken or underway which should help insure the reliability of the contracted tests and also discusses the concerns raised by Gulf South. The National Institute provided oral comments on matters discussed in this report. We have incorporated those comments where appropriate.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its cover date. At that time we will send copies to the Secretary of Health and Human Services, the Gulf South Research Institute, other congressional committees and interested parties and make copies available to others upon request.

Sincerely yours,

Richard L. Fogel

Richard L. Fogel
Director

GENERAL ACCOUNTING OFFICE
REPORT TO THE SUBCOMMITTEE
ON OVERSIGHT AND INVESTIGATIONS
HOUSE COMMITTEE ON ENERGY
AND COMMERCE

NATIONAL TOXICOLOGY PROGRAM: EFFORTS TO IMPROVE OVERSIGHT OF CONTRACTORS TESTING CHEMICALS

D I G E S T

The National Toxicology Program (NTP) was established in 1978 as a cooperative effort among Department of Health and Human Services agencies to conduct scientific testing on the effects of chemicals that may be toxic or carcinogenic. There are over 50,000 chemicals with which the American public may come in contact through the use of pesticides, cosmetics, food additives, etc. The effects of chemicals NTP selects for testing are generally unknown or in question. The testing of chemicals takes 5 to 6 years to complete.

The program is the responsibility of the National Institute of Environmental Health Sciences. Since its inception, the program's chemical testing process and the primary quality assurance activities related to the testing of chemicals have been done largely by private contractors. The testing results are used, for example, by the Food and Drug Administration and the Environmental Protection Agency to help decide how the tested chemicals or products containing these chemicals should be regulated.

As of March 1985, 248 chemicals had been tested and reported on by NTP, and another 195 were in various stages of testing. During GAO's review, these tests were being conducted by 16 private contractor laboratories and a U.S. Department of Energy facility. The laboratories are monitored by an NTP project management team and quality assurance contractors, who independently analyze the testing contractors' performance.

In January 1984, GAO was requested by the Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, to assess the adequacy of NTP's oversight of its contract research activities and to respond to concerns expressed to the Chairman by an NTP contractor, Gulf South Research Institute. The issues discussed in this report were initially

identified during November 1983 Subcommittee hearings. (See p. 1.)

NTP EFFORTS TO IMPROVE MONITORING OF CONTRACT LABORATORIES

Until May 1982, the monitoring of contractor testing laboratories was performed primarily by Tracor Jitco, Inc.--a private contractor. Beginning in May 1982, NTP officials began carrying out the management oversight responsibilities for laboratory contractors previously carried out by Tracor Jitco. Currently, NTP's project management team performs oversight functions through annual program reviews, quarterly site visits, reviews of monthly contractor progress reports, and day-to-day telephone discussions with contractor staffs performing the research tests.

Since NTP assumed these added responsibilities, it has implemented changes to improve internal program coordination and communication. Since March 1984, all NTP personnel, previously in two locations, have been consolidated and relocated to Research Triangle Park, North Carolina.

Meetings among NTP management team personnel have been held regularly since February 1983 to improve coordination of their oversight responsibilities and discuss testing results. In 1984, NTP began to develop a project officer handbook, which will (1) better define the officers' roles and responsibilities for monitoring contractors and (2) establish uniform guidance for overseeing contract laboratory performance.

To better monitor and analyze testing results, the management team uses an automated data management system, which collects, stores, and reports specific information generated by the contract laboratories. As of June 1985, all live animal test data were being tracked through the system. (See pp. 11 to 14.)

NTP has also increased its activities to help assure the quality, integrity, and reliability of ongoing and completed tests. Pathology reviews and quality assurance audits of testing laboratories are performed by four contractors under NTP supervision. NTP has used

Experimental Pathology Laboratories, Inc. to review pathology test results. In addition, in late 1983, contracts were awarded to three quality assurance audit firms--Argus Research Laboratories, Inc., Dynamac Corporation, and ImmuQuest Laboratories, Inc.--to (1) perform detailed audits of chemical tests conducted both during and after the live animal testing phase and (2) assure better adherence to good laboratory practice standards. These standards were established by the Food and Drug Administration in 1979 and voluntarily adopted by NTP in 1981 for its testing contractors to follow.

NTP APPEARS TO BE MONITORING CONTRACTORS CLOSELY

To assess the adequacy of the day-to-day project management activities after the phase-out of the Tracor Jitco management contract, GAO reviewed NTP project files for 16 contractor laboratories (NTP's oversight of Gulf South Research Institute was reviewed separately) from July 1982 through June 1984. GAO also talked to program project officers about these laboratories. GAO found that NTP was (1) conducting annual program reviews and site visits and (2) assuring that corrective management actions were taken to resolve NTP concerns identified at laboratories.

GAO judgmentally selected five laboratories that appeared to have evidence in the project files of testing problems. These problems occurred in areas of chemical testing where NTP officials agreed that significant problems might compromise or jeopardize a test's results.

GAO's detailed review of documentation for the five testing contractors noted "action items" requiring correction ranging from minor concerns, such as the need to update a training file, to major items, such as disposing of organs that could likely be affected by the test chemical rather than retaining them so that possible future questions about test interpretation could be answered. The range of action items identified at the five laboratories ranged from 0 to 34 for program management site visits and from 10 to 53 for annual program review visits. Corrective actions were underway or had been completed on the items GAO reviewed.

For the nine annual reviews performed at the five laboratories during the 2-year period, at least five of the eight key members (six discipline leaders, the project officer, and chemical manager) participated in each review. Of the 72 opportunities to participate, key members participated 59 times.

NTP had taken action to disqualify five laboratories (two examined by GAO, along with three others not examined by GAO) from conducting new chemical tests in 1984. According to NTP officials, while the test results of the two laboratories in GAO's sample had not been compromised, NTP was sufficiently concerned about the overall performance to deny them future tests. (See pp. 14 to 18.)

INCREASED EMPHASIS ON QUALITY ASSURANCE ACTIVITIES TO ENSURE TEST RELIABILITY

Two types of quality assurance reviews--a more detailed review of the live animal testing phase and post-life audits of all test results before publication of a technical report--were begun by NTP in 1983 to improve test reliability.

Primarily because of questions initially raised concerning the reliability of test data submitted by the Gulf South Research Institute, NTP gave priority to the post-life audits of test results over the detailed reviews of the live animal test phases. As a result, NTP delayed the live animal reviews (which included examinations of laboratories' compliance with good laboratory practices) until April 1984 and had not scheduled all the reviews to begin until September 1984.

GAO reviewed live animal reviews conducted by NTP quality assurance contractors at five laboratories as of September 1984. The reports for four of these laboratories indicated no significant problems relative to test performances. The other report disclosed problems with one laboratory's performance. NTP has acted to terminate three ongoing tests at this laboratory.

GAO reviewed post-life audit reports for 38 laboratory tests that had been conducted as of August 1984. Seven of these audits were

conducted by NTP. Audits of 30 tests showed that test results had not been compromised. Two tests at Gulf South Research Institute were shown to be compromised, and NTP had not reached a final conclusion on six other Gulf South tests.

As of May 1985, a total of 63 audits had been conducted, and according to an NTP official, no additional tests were found to have significant problems. GAO's review showed that the quality assurance contractors were generally following NTP-established standard operating procedures. (See pp. 19 to 24.)

CONCERNS EXPRESSED BY GULF SOUTH RESEARCH INSTITUTE

After the November 1983 congressional hearings, the Gulf South Research Institute expressed concerns to the Subcommittee Chairman that (1) NTP terminated Gulf South's contract because of its performance problems but had not terminated other firms' contracts for similar reasons, (2) NTP had assigned pathology work removed from Gulf South to the Experimental Pathology Laboratories after Experimental Pathology had performed quality assurance reviews of the work and reported it unacceptable, and (3) NTP had judged Gulf South's completed tests against good laboratory practices standards that were not yet in effect.

The Chairman asked GAO to examine these concerns and also to determine whether payments made to Gulf South or Tracor Jitco could be recovered in instances where NTP identified poor performance.

GAO found that:

--NTP was acting to identify and resolve performance problems at several contract laboratories and, in 1983 disqualified five firms from competing for 1984 contracts because of past poor performance.

--None of the Gulf South pathology work that NTP assigned to Experimental Pathology had been previously reviewed by that firm. In addition, most of the Gulf South work originally assigned to Experimental Pathology was turned back to NTP because of other work NTP assigned to Experimental Pathology. NTP has since

taken actions to prevent its quality assurance contractors from also doing pathology support work.

--Continuing pathology problems and serious questions about the overall quality of Gulf South's tests, rather than Gulf South's failure to adhere to good laboratory practice standards, were the primary cause of the NTP termination action. (See pp. 25 to 30.)

GAO believes it is unlikely that funds expended on the terminated contracts can be recovered because the cost-plus-fixed-fee level of effort contracts did not expressly provide that reimbursement of allowable costs would be contingent on test results of a certain quality or require contractors to bear the costs of correcting defective performance. The National Institute of Environmental Health Sciences has acted to incorporate such a provision into future testing contracts. (See pp. 30 to 32.)

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GAO held discussions with NTP officials and the President of Gulf South to help assure the accuracy of the information in this report. However, GAO did not discuss its observations or conclusions or request official agency or contractor comments on a draft of the report.

Contents

ABBREVIATIONS

EPA	Environmental Protection Agency
EPL	Experimental Pathology Laboratories
FDA	Food and Drug Administration
GAO	General Accounting Office
GSRI	Gulf South Research Institute
HHS	Department of Health and Human Services
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NTP	National Toxicology Program

GLOSSARY

Carcinogenicity	Having the effect of producing or causing cancer.
Chronic test	The long-term testing method used by the National Toxicology Program (NTP) to determine the toxic effects of the chemical during rodents' life expectancies. This method enables NTP to predict the chemicals' hazardous effect on humans.
Gavage	Administration of nourishment of chemical dose directly to the gastrointestinal tract through a tube.
Histopathology	A branch of pathology concerned with tissue changes that accompany a disease. At NTP this includes dissecting and examining test animals, preparing slides from animal tissues, and interpreting the slides.
Identification of animals	Animals are tagged in the ear or around the leg with identification numbers for tracking. These tags are occasionally lost and can result in misidentification.
Pathology	The study of the nature of diseases and the structural and functional changes produced by them.
Prechronic test	The short-term testing method used by NTP to determine the gross toxic effect of a chemical on rodents. NTP uses this method to determine which organs are affected the most by the chemical and define the specific testing requirements for the long-term test.

Project management team	NTP staff members who maintain oversight over chemical tests--the team includes the project officer, the chemical manager, and various scientific experts in such fields as pathology and toxicology.
Protocol	The specific requirements for testing a chemical--NTP's standard protocol typically uses two rodent species (rats and mice) with multiple doses administered to groups of 50 animals, beginning at weaning and ending after 2 years.
Target organs	The specific body organs that are known or suspected of being affected by a chemical--NTP identifies these organs for closer examination when determining a chemical's hazards.
Toxicity	Of or relating to exposure to poisonous substances.

CHAPTER 1

INTRODUCTION

On January 5, 1984, the Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, requested us to examine certain aspects of the National Toxicology Program's (NTP's) contracting activities. The Chairman was concerned about the adequacy of NTP's practices and procedures to oversee laboratories that conduct scientific testing on the toxic and carcinogenic effect of chemicals for the National Institute of Environmental Health Sciences (NIEHS). NIEHS is a Department of Health and Human Services (HHS) agency under the National Institutes of Health (NIH). Federal agencies, such as the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA), use NTP-reported test results to help decide how tested chemicals or products containing these chemicals should be regulated.

The Chairman's concerns arose after NTP's 1983 withdrawal from publication of a draft report on the effects of methylene chloride. NTP withdrew the report because of discrepancies in test data, including misidentification of animals and inaccurate records which compromised the test's results. The problems had also been noted by an industry group--the Halogenated Solvents Industry Alliance.[1] Because of these problems, the Chairman was concerned about (1) whether there were problems regarding other chemicals NTP was testing, (2) how NTP monitors and oversees tests performed by its contract research laboratories, and (3) whether corrective actions were being taken to prevent identified problems from occurring in the future.

The Chairman highlighted these concerns in November 1983 Subcommittee hearings on EPA's hazardous air pollution control program, at which time NTP's management of the testing being performed on chemicals was also discussed. The Chairman also asked us to examine the propriety of allegations made by the former NTP contractor who had performed the methylene chloride test--Gulf South Research Institute (GSRI)--that it was unfairly treated by NTP.

In a 1979 report,[2] we identified problems in the management of the National Cancer Institute testing program which was

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[1]An industry group representing solvent manufacturers and users.

[2]Operations of the National Cancer Institute's Carcinogenesis Program (HRD-79-51, Mar. 30, 1979).

the predecessor to NTP. Our report highlighted problems with the program's management contractor, Tracor Jitco, Inc. In our report, we pointed out that Tracor Jitco was not informing federal officials of all deficiencies found during inspections of testing laboratories' activities or requiring laboratories to correct the deficiencies. The National Cancer Institute had not been aware of the situation because it had not monitored Tracor Jitco's efforts in reviewing the laboratories' activities, nor had it performed its own verification of the adequacy of Tracor Jitco reports.

BACKGROUND

NTP was established in November 1978 as an HHS effort to coordinate research and testing activities of several of its component agencies and provide information about potentially adverse health effects of chemicals to regulatory agencies and others, such as the medical and scientific communities. There are over 50,000 known chemicals with which the American public may come in contact through their use of various products, such as pesticides, cosmetics, and food additives. Testing of chemicals accounted for about 70 percent of the fiscal year 1985 NTP budget of $77.4 million. The balance of the program resources are being directed toward developing improved testing methods. As of March 1985, NTP had concluded testing and reported on 248 chemicals, and another 195 were in various stages of testing. At the time of our review, NIEHS was using 16 contractor laboratories (including GSRI) and 1 Department of Energy laboratory to test NTP chemicals. (See app. I.)

The three HHS agencies that provide the funding for the NTP program are NIEHS; the National Center for Toxicological Research under FDA, and the National Institute for Occupational Safety and Health under the Centers for Disease Control. The latter two agencies do not provide funds directly to NIEHS but independently fund projects and tests that meet NTP goals and objectives. NTP's Director (also the Director of NIEHS) and the central administrative and management control of the NTP program are located at NIEHS headquarters in Research Triangle Park, North Carolina. NTP's funding sources for the last 3 years are presented below.

Funding for NTP

Agency	Funding FY83	FY84	FY85
	-----(millions)-----		
National Institute of Environmental Health Sciences	$63.8	$69.9	$69.9
National Center for Toxicological Research	6.9	5.2	5.3
National Institute for Occupational Safety and Health	2.1	2.2	2.2
Total	$72.8	$77.3	$77.4

Oversight of NTP's activities is the responsibility of an Executive Committee (see app. II)--comprised of heads of federal research and regulatory agencies--which advises NTP on (1) testing needs and (2) selecting and setting priorities for specific chemicals to be tested. Scientific oversight of the NTP program is provided by a Board of Scientific Counselors, composed of nongovernmental scientists.

NTP'S PROJECT MONITORING

Chemicals being tested are monitored primarily through NTP's project management and quality assurance systems. The project management system, which focuses on all aspects of laboratories' operations, is carried out by NTP staff composed of program managers, project officers, chemical managers, discipline leaders (described below), and contract officers. The quality assurance system is largely conducted by several contractors that perform quality assurance reviews during and after the tests are conducted. NTP's quality assurance staff manages the program's quality assurance contracts and assures the contractors' reviews adequately cover testing laboratories' compliance with good laboratory practice standards and other testing requirements. NTP manages both of these systems through its program managers (the Acting Chief of the Carcinogensis Toxicology and Evaluation Branch; the Acting Director, Toxicology Research and Testing Program; and the NTP Director), who play major roles in coordinating all the activities of the project management team and quality assurance staff. They coordinate the interaction of the project management staff and quality assurance staff and provide feedback to other NTP staff.

Project management activities

A management team oversees contractor performance through annual NTP project program reviews, quarterly site visits, review of monthly contractor progress reports, and day-to-day discussions through telephone contacts between NTP and contractor staffs who are performing the research tests.

The management team and their responsibilities are:

--Project officers are responsible for monitoring and evaluating the contract laboratories' technical performance.

--Chemical managers plan and provide scientific oversight in the conduct of laboratory tests through each of the various testing phases and evaluate and oversee publication of test results.

--Discipline leaders are experts in one of six scientific areas: toxicology, pathology, chemistry, health and safety, animal care, and quality assurance. They assist the project officers in monitoring research involving their respective scientific areas of expertise.

--Contract officers provide the administrative and oversight of NTP's contract laboratories to help ensure their compliance with all technical and administrative contract requirements. They also administer the contracting process for determining whether private laboratories are qualified to perform future chemical tests.

The management team also uses an automated data management system, which collects, stores, and reports information produced primarily from the live animal and histopathology (see pp. 5 and 6) portions of prechronic and chronic test data.

Quality assurance activities

NTP's quality assurance activities address the integrity and reliability of ongoing and completed tests. These activities are carried out by four NTP quality assurance contractors (three are audit contractors and one concentrates on reviewing pathology). The contractors are responsible for (1) assuring that each chemical being tested by the contract laboratories adheres to the study protocol, (2) reviewing test data for accuracy and consistency, and (3) identifying and reporting to NTP management situations that may affect the integrity of the test results.

NTP uses Experimental Pathology Laboratories, Inc. (EPL), to review the pathology results of each test. It also uses a panel of pathologist consultants to resolve differences between the pathology quality assurance contractor and the testing laboratories' interpretation of test results.

In late 1983, NTP awarded contracts to three audit firms--Argus Research Laboratories, Inc.; Dynamac Corporation; and ImmuQuest Laboratories, Inc.--to (1) perform more detailed audits of chemical tests both during and after the live animal phase and (2) assure better adherence to good laboratory practice standards. These contracts are monitored by NTP through regular progress reports, site visits, and reviews of the detailed audits by NTP staff.

As of June 1985, NTP was planning to establish a new Office of Quality Assurance, which would consolidate the NTP quality assurance functions under one person who will report to the Acting Director of the Toxicology Research and Testing Program. The office is to have experts in pathology, toxicology and chemistry in addition to the current quality assurance coordinator. Some of the quality assurance duties have been temporarily assigned to other staff until the new office is established.

TESTING PHASES

The testing process for chemicals is complex and made up of sequential phases that require as many as 5 to 6 years to complete for each chemical. The phases are (1) chemical nomination and selection; (2) live animal testing; (3) histopathology (preparing, examining, and interpreting test results); and (4) reporting. NTP research contractors perform the live animal testing and histopathology phases.

Chemical nomination and selection phase

A chemical can be nominated for toxicological testing by federal and state agencies and industry. The nominated chemical is reviewed and evaluated by NTP representatives and selected scientific experts. NTP's Executive Committee makes a final decision concerning whether to test the chemical. If the decision is made to test the chemical, it is assigned to an NTP chemical manager. The chemical manager develops a test protocol, and the chemical is scheduled for contract testing with a private laboratory.

Live animal testing phase

In testing a chemical's toxicity and/or carcinogenicity, NTP uses a 14-day and 90- to 120-day prechronic and 2-year

chronic exposure tests with live animals to predict whether the chemical's use in the marketplace presents a significant health risk. The prechronic test allows NTP to determine whether to enter the chronic phase and also to set the various dose levels and identify target organs to be observed during the chronic test phase. Because the life expectancy of rodents is 2 years, these tests are designed to measure the effect of a chemical on the animals during their lifetimes. Upon completion of chronic tests, the animals are sacrificed, and the histopathology phase begins.

Histopathology (post-life) phase

The histopathology phase, which begins with the sacrifice of the animals at the laboratory, includes three steps:

--The first step involves dissecting and examining animals. Designated organs and body parts are removed by technicians, who visually check for abnormalities or tumors in the animals. Portions of all or affected organs and the identified tumors are removed and encased in wax blocks. The remaining portions of organs and body parts are placed in plastic bags to be retained in NTP's repository, which holds the results of the programs' tests.

--The second step entails preparing slides of tissue sections. Sections are taken from each of the wax blocks. At this point, the slides are ready for a pathologist to read.

--During the third step the pathologist reads and interprets each slide (about 25,000 per test) to identify and diagnose abnormal tissues. Once all slides are read by the pathologist, NTP analyzes the results of the pathology data and determines the effect, if any, the chemical had on the animals.

Reporting phase

In the final phase of the testing process, NTP prepares a draft technical report, which reflects NTP's interpretation of the data and conclusion concerning the chemical's toxicity and/or carcinogenicity. The draft report goes through various program reviews, and the raw data that support the test are audited by NTP quality assurance audit contractors to verify data adequacy and accuracy. Before NTP publishes a technical report, it is also submitted to a peer review committee made up of nongovernmental scientists to evaluate the report for technical and scientific merit. The committee meeting is open to the

public, which also gives interested parties the opportunity to comment before the report is published. Once a technical report is published, it becomes a public document. Thus, any of the federal regulatory agencies may use it when making a decision about controlling the chemical if it is determined to be toxic and/or carcinogenic.

OBJECTIVES, SCOPE, AND METHODOLOGY

We conducted our review at NIEHS offices in Research Triangle Park, North Carolina, and Bethesda, Maryland, and at FDA in Rockville, Maryland. Additionally, we visited a testing laboratory to observe an on-site annual NTP program review. We also visited the four NTP quality assurance contractors to discuss their responsibilities and to review their audit files and reports. Most of our fieldwork was performed between January and December 1984. Since December 1984 we have held discussions with NIEHS staff to obtain additional information on NTP's most recent efforts to improve its contract oversight.

To review the practices and procedures for overseeing contractors, we reviewed the two principal components of NTP's monitoring system: project management and quality assurance. In addition, NTP gave us information on the feasibility of its assumption of full responsibility for quality assurance audits. We also reviewed (1) applicable NTP policies and procedures, annual plans, contract files, and documentation relating to NTP's project management and various quality assurance reports and (2) NTP's actions regarding its termination of GSRI.

We held discussions with NTP officials and the President of GSRI to help assure the accuracy and completeness of the information contained in our report. However, in accordance with the requester's wishes, we did not discuss our observations or conclusions or request official agency or contractor comments on a draft of this report. Our work was otherwise performed in accordance with generally accepted government auditing standards.

Project management activities

We discussed with NIEHS program and management officials NTP's overall chemical testing program. This included NTP's oversight of chemical tests that are performed by contractor laboratories and various quality assurance measures applied to these tests. Additionally, to determine how corrective actions are taken, we discussed the extent that information related to these laboratories is communicated among these officials.

To determine NIEHS' contracting procedures, we discussed with NTP officials how they monitor the laboratories and quality

assurance contractors. Further, we discussed the process used by NTP to determine whether potential contractors are qualified to perform chemical tests. Also, we discussed NTP restrictions placed on the quality assurance contractors to prohibit contractor personnel from auditing tests they might have worked on.

To assess the adequacy of the day-to-day project management activities after the phaseout of the Tracor Jitco management contract began in May 1982, we reviewed the NTP project files for 2 years--July 1982 through June 1984--for 16 testing laboratories that were under contract with NTP during this period. This did not include GSRI, which we reviewed separately.

Through our examination of NTP monitoring documentation and discussions with NTP staffs, we identified, and NTP officials agreed on, 13 areas of chemical testing where problems could occur that might compromise or jeopardize a test's results. These were identification of animals, labeling of slides, dosages of chemicals given to animals, histotechnique (slide preparation), animal care facilities (temperature, humidity, ventilation), quality of staff, outdated laboratory procedures, too many tests given the laboratories' staff and facilities, necropsy (all tumors identified), compliance with protocols, compliance/noncompliance with good laboratory practice standards and/or standard operating procedures, lack of chemical analyses, and research laboratory quality assurance. Whether a test's results are compromised or jeopardized depends on the significance of the problem. For example, small deviations in applying assigned chemical dosages to animals would not be considered as significant as consistently applying incorrect dosages, which would more likely affect tumor growth or toxic reaction.

We reviewed NTP's oversight documentation for its 16 testing contractors to identify possible problems that would affect test results if not corrected and NTP's actions in these areas. At the time of our review, 10 of the 16 contractors had tests in the live animal stages; 6 had tests that were in the histopathology or reporting stages but had no tests in the live animal stage. Based on our initial reviews, we found that 8 of the 16 contractors appeared to have problems in at least 1 or more of the 13 areas and/or numerous NTP-identified "action items" (deficiencies). Four of these eight had tests in the live animal stage. We selected five of the eight for detailed review.

To address current NTP day-to-day management, we included the four contractors that were conducting live animal tests. We also selected one contractor from the other four that had no

tests in the live animal phase. Two of these laboratories had been disqualified from participating in the competition for new contracts.

For our more detailed review of the five contractors, we selected action items from NTP program reviews and NTP site visits contained in each of the six NTP scientific discipline areas (toxicology, pathology, chemistry, health and safety, animal care, and quality assurance) with particular emphasis on action items that, in our judgment, might affect test results if not corrected. We discussed with NTP project officers and chemical managers the severity of the action items to determine whether the items were significant enough to affect the test results. We also obtained documentation to show when and how the items were resolved by NTP and the laboratories.

Quality assurance activities

To determine whether NTP implemented its various quality assurance reviews, we reviewed documentation to assure that quality assurance reviews were being performed. We also obtained copies of the quality assurance review reports to determine the overall results of the reviews. Because of the scientific nature of these reports, we did not determine their adequacy or the significance of the findings. Rather, we interviewed NTP officials to identify the major report findings that indicated that the tests' validity could be compromised. Additionally, we visited the four quality assurance contractors to discuss and document how they carry out their responsibilities.

At the three NTP contractors' locations performing quality assurance audits, we reviewed the NTP standard operating procedures used in performing the live animal reviews and the post-life audits. We reviewed the standard operating procedures for their coverage of the discipline areas NTP focuses on in its chemical test management. We analyzed the five live animal audits that had been conducted as of September 30, 1984, to determine that standard operating procedures were generally followed and reviewed the auditors' documentation of their performance of the audit procedures. We also reviewed back-up documentation for nine post-life audits--three at each contractor--out of a total of 34 such audits performed by these contractors to assure that the standard operating procedures were generally followed and applied. We selected these audits from those the contractors had conducted as of September 1984. The number of post-life audits conducted by any firm ranged from 9 to 14. We also reviewed 38 completed post-life audit reports, including 7 prepared by NTP as of August 31, 1984, and interviewed NTP staff to determine whether the reports contained deficiencies that would question the validity of a study and the

actions NTP had taken as a result. We also interviewed NTP staff to determine that deficiencies were being communicated to NTP program managers and project officers.

To determine how NTP implemented and monitored good laboratory practice requirements, we reviewed audits of these practices between February 1982 and July 1983 and interviewed NTP staff and management regarding the implementation and review of the practices. FDA, as part of its regulatory process, inspects some of the same NTP contract laboratories for adherence to good laboratory practices.

For the pathology reviews, we examined the documentation prepared by the pathology quality assurance contractor to assure that test results were being evaluated. We also interviewed NTP's staff to determine the reporting of the results of these reviews and the communication of problems to project management. Because of the scientific nature, we did not determine the adequacy of the reviews.

Gulf South Research Institute

We interviewed the President of GSRI to obtain and clarify concerns raised by GSRI. We discussed those concerns with appropriate FDA, NTP, and affected private groups or contractors to determine their validity. We also reviewed site visit reports, annual program reviews, monthly progress reports, internal memos, contract files and correspondence, FDA inspections of GSRI, NTP personnel files, and applicable HHS regulations.

CHAPTER 2

CHANGES IN NTP'S PROJECT MANAGEMENT PROVIDES MORE INTENSIVE OVERSIGHT OF CHEMICAL TESTING

In view of performance difficulties experienced with its management contractor, Tracor Jitco, and to overcome other project management shortcomings, NTP began in 1982 to make changes to improve its project management activities to help insure the integrity of chemical tests. NTP assumed full responsibility from Tracor Jitco for monitoring laboratories by phasing in oversight of laboratories between May 1982 and May 1983. It also consolidated and reorganized its project management team, revised its policies and procedures for carrying out the oversight activities, and established regular meetings to discuss and deal with project management concerns about laboratory operations and chemical tests being performed. Additionally, NTP began using an automated data management system to provide up-to-date information on the chemicals being tested.

Since assuming direct responsibility for managing the chemical test contracts, NTP has closely monitored and evaluated laboratories' performance by maintaining frequent contact with laboratory representatives, reviewing documentation on the status of each test, and conducting site visits and audits of the contractor's laboratory facilities. Additionally, NTP is taking steps to resolve identified problems, including terminating tests and disqualifying laboratories for new tests.

NTP HAS CONSOLIDATED AND REORGANIZED ITS STAFF

NTP has implemented changes to improve program coordination and communication among the project management. NTP chemical managers and project officers worked in different offices and in different geographical locations before March 1984. Some of these officials were located in Research Triangle Park, North Carolina, while others were in Bethesda, Maryland. Because of the need for better communication and coordination among the NTP staff, all of the project officers and chemical managers were consolidated into one office--the Carcinogenesis and Toxicology Evaluation Branch--and relocated from Bethesda to Research Triangle Park in March 1984. Previously, the project officers and chemical managers communicated on a day-to-day basis primarily through telephone or memoranda. With the relocation, they more easily discuss the quality of work being performed by the various laboratories and act more quickly on identified problems.

In February 1983, NTP also began having regular meetings to discuss and review testing status and provide better coordination among the project management team--project officers, chemical managers, discipline leaders, and contract officers. Quarterly meetings are held by chemical managers and discipline leaders, and monthly meetings are held to address project officers' concerns. The meetings give the project management team an opportunity to discuss and develop initiatives to resolve common problems regarding program operations, particularly monitoring and evaluating laboratories. Contract officers also periodically attend the monthly project officer meetings to discuss and clarify the project officers' roles and responsibilities pertaining to the contracting process.

In 1984, NTP undertook the development of a project officer handbook, which will better define officers' roles and responsibilities. A previous handbook was written in 1981, before NTP assumed full responsibility from Tracor Jitco for overseeing the contract laboratories. The new handbook, which was nearing completion in late June 1985, will include updated guidelines for conducting site visits, a format for NTP site visit reports, and follow-up procedures for the project officers to ensure all action items (deficiencies) are resolved.

Project officers, who are assigned responsibility for monitoring one to three laboratories, use various methods to help assure that the laboratories' tests are scientifically sound, cost efficient, and conducted in a timely manner. These methods include interacting with laboratory personnel, making site visits, reviewing progress reports, insuring compliance with quality assurance requirements (such as good laboratory practices), and informing the NTP contracts' office of performance deficiencies identified. Additionally, NTP is implementing an automated toxicology data management system for the project managers to use for monitoring test data.

The project officers coordinate and conduct quarterly site visits to contract laboratories, including annual reviews to help assure that they are properly performing NTP tests. During these annual program reviews, conducted during one of the quarterly site visits, the project officers--in conjunction with all or most of the discipline leaders (see p. 4) and other project management team members--perform a comprehensive review of the testing program at each laboratory. During these 2- to 3-day reviews, the officials inspect the laboratory facilities, recordkeeping techniques, and training programs, along with safety and compliance with quality assurance procedures.

Additionally, they discuss and review with the key laboratory technical personnel the specific chemical protocols and standard operating procedures used for the NTP tests. Quarterly site visits are less detailed than the program reviews and are conducted by the project officer assisted by project management team members when expertise is needed to deal with special problems.

Upon completing site visits or program reviews, the project officers--in collaboration with all other participants--prepare written reports summarizing the results of the visits and submit them to their superiors, including the Acting Director of the Toxicology and Research Testing Program. These reports address specific action items that require the laboratory's attention. The project officers are responsible for seeing that all action items are resolved and keeping NTP management apprised of the progress in correcting them.

Project officers frequently interact with laboratory personnel to discuss resolution of action items identified during site visits as well as to stay abreast of the progress of all tests.

NTP requires each private testing laboratory to designate a principal investigator to monitor tests and coordinate with the NTP project officer. Project officers told us that they communicate almost daily with the laboratories' principal investigators either by telephone or through memoranda concerning various chemical test issues or concerns. Typical items discussed include

--the overall status (progress or difficulties) of various chemical tests,

--the reason for contract modifications and the associated cost,

--the reasons for changes in report submission dates,

--the interpretation of and changes to the test protocol, and

--the discussion or resolution of deficiencies identified during site visits.

NTP also requires all laboratories to submit monthly progress reports, which provide testing status information to the project management team. The reports provide a status summary of all ongoing chemical tests at the laboratory, including recent animal observations, animal mortality rates, status of

slide preparation, and key personnel changes. The discipline leaders also review their respective sections of the monthly progress report and provide feedback to the project officers. Project officers prepare written summaries on the laboratories' progress and/or deficiencies based on their own and the discipline leaders' feedback. These summaries are provided to the Acting Chief of the Carcinogensis Toxicology and Evaluation Branch and the Acting Director of the Toxicology and Research Testing Program for review of the adequacy of laboratories' corrective actions taken or underway.

Since November 1981, NTP has been implementing its automated toxicology data management system to collect, store, and report specific information produced primarily from the live animal and histopathology portions of tests. The system provides on-line access to data collected on tests for NTP managers' use in monitoring various testing phases. The system also provides mechanisms to prevent recording inconsistent or inadequate data resulting from human error. For example, if an animal is recorded as having died, no new data regarding feedings, etc., can be entered on the system for the animal. As of June 1985, all ongoing tests in the live animal stage were included in the system.

THE PROJECT MANAGEMENT TEAM APPEARS TO BE MONITORING LABORATORIES CLOSELY

We found NTP has generally documented its management actions regarding site visits, annual program reviews, and contractors' follow-up actions. In addition, NTP is identifying concerns at the laboratories and requiring corrective actions to resolve them, and most of the members of the project management team are regularly participating in the annual reviews. We also noted that through its contracts award process for conducting tests in 1984, NTP disqualified several firms as candidates for future testing because of problems with their past performance.

NTP is identifying and resolving problems at laboratories

Our analysis of NTP program review, site visit, and other documentation indicated that NTP documented items needing corrective action as well as their resolution. The laboratories are correcting identified action items. According to project officers responsible for the respective laboratories, the action items we selected for detailed review, for the most part, had not been found as compromising test results. Generally, most members of NTP's project management team participated in the annual program review visits.

Our detailed review of NTP documentation for 5 of the 16 testing laboratories other than GSRI that were performing or completing research for NTP noted action items ranging from minor concerns, such as updating a training file or sending NTP a copy of an organization chart to major items that may have affected test results such as disposal rather than retention of organs that could likely be affected by the test chemical for possible future test interpretation. The number of action items for site visits ranged from 0 to 34 and from 10 to 53 for annual program review visits for the five laboratories.

For all five laboratories, we noted instances where corrective actions had been initiated. For example:

--An NTP program review at one laboratory found several slides containing multiple sections of the same tissue that had been excluded from the laboratory's interpretation of its test results. The NTP pathology discipline leader attributed the problem to inadequate quality assurance in the slide preparation procedures. The laboratory initiated a quality assurance step to insure proper tissue accountability and slide quality and later included the step as a requirement in its standard operating procedures.

--An NTP site visit to another laboratory found poor internal communication. Examples included (1) inconsistent and unsatisfactory scheduling and reporting to the laboratory management and to NTP of completed analyses in the chemistry area and (2) lack of involvement of senior scientific staff in animal care and toxicology. Based on the findings from this visit, the laboratory implemented monthly meetings with all the key discipline staff members, which NTP believed should improve communications.

--Based on an NTP site visit to a laboratory, NTP requested that the laboratory remove the principal investigator who was the laboratory's central contact with NTP and overseer of site work. NTP pointed out that recent incidents involving the principal investigator had jeopardized several tests. Problems included the principal investigator's lack of active participation in the daily performance of tests and poor supervision. Also, NTP guidelines and standard operating procedures had not been followed. The laboratory later notified NTP that it had removed the principal investigator. The NTP project officer has since determined that the tests were not compromised and the results will be valid.

--During a program review and two live animal quality assurance reviews, NTP determined that a laboratory failed to follow prescribed procedures by disposing of animal livers after preparing the necessary slides rather than retaining them for submission to the NTP archives. According to the Acting Chief of the Carcinogenesis Toxicology and Evaluation Branch, this will not compromise the test if the results are conclusive relative to the chemical's carcinogenicity. However, if the test results are marginal, the tissues that have been thrown away become more important as NTP experts would want to reexamine those tissues to assure themselves that their final decision about the test's carcinogenicity is reliable. The branch chief said that it would be some time before NTP knows the full impact of the laboratory's actions. In the interim, NTP has taken several actions against this laboratory, including terminating several ongoing tests in the live animal phase and removing the pathology segments of other tests from the laboratory. (See p. 20.)

Our analysis of documentation for the 2-year period--July 1982 through June 1984--showed that most key members of NTP's project management team routinely participated in annual program reviews of contract laboratories. For the 9 annual reviews performed at the 5 laboratories during this period, at least 5 of the 8 key members (6 discipline leaders, the project officer, and the chemical manager) participated in each review, and of 72 opportunities to participate, key members participated 59 times. (Members may not attend because of conflicts in scheduling, etc.) Additionally, one or more project management team members accompanied the project officers on the regular site visits during the 2-year period for the five laboratories.

Also, to determine whether compliance with technical contract requirements (such as adherence to test requirements, modifications to contract, and approval of changes in cost estimates) is being maintained, the project officers keep the contract officers informed about the laboratories' performance on NTP's testing. This information is considered in awarding future contracts.

During the contract award process conducted in late 1983 to decide which laboratories would be eligible to conduct new tests in 1984, 5 of the 16 laboratories, not including GSRI, (1 with in-life testing in process and 4 with no ongoing in-life tests) were disqualified as candidates for future testing contracts because of poor past performance.

--Laboratory A had repeated substandard slide preparation quality, poor laboratory animal disease surveillance, and poor management practices, even after the NTP officials pointed out these problems.

--Laboratory B's animal care practices and procedures were not satisfactory as noted in NTP site visit reports, which suggested inadequate professional involvement and supervision. Additionally, the laboratory's slide preparation quality had been judged by NTP as unacceptable and its pathology as poor. NTP decided, however, that the deficiencies had not interfered with NTP's ability to make a final decision on test outcome. Problems included mislabeled slides, missed organs in two studies, and a high rate of animal deaths.

--Laboratory C's pathology problems led to the deletion of pathology work from the NTP tests. Pathology problems included differences between the laboratory's and NTP's diagnoses, poor slide preparation, and cases of inadequate tissue trimming and handling.

--Laboratory D's health and safety plan was outdated and did not include current NTP requirements. Possible cross-contamination of NTP studies by other test chemicals, particularly around shower areas, caused the results of one test to be questioned.

--Laboratory E's poor animal care performance resulted in excessive deaths, making the outcome of the test less reliable, and prompted a recommendation for the cancellation of further testing of one chemical.

Of those disqualified, two were included in our detailed review--one with in-life tests ongoing and one with no ongoing in-life testing. The disqualification of these two laboratories was based on concerns other than the interpretation of final test results. We noted, however, a live animal quality assurance review in August 1984 at the laboratory with the ongoing testing found problems to still exist (see p. 20). As a result, NTP has terminated several ongoing studies at this contractor.

OBSERVATIONS

NTP discontinued its management contract with Tracor Jitco because of problems with Tracor's monitoring of NTP research contracts. NTP assumed full responsibility for project monitoring, reorganized and consolidated its staff, initiated regular

internal meetings to discuss and resolve common project management concerns, and began to establish new operating procedures for research oversight. All these changes help to insure that problems occurring at contract laboratories are identified and resolved. Moreover, our review of NTP monitoring documentation in the 2-year period following NTP assumption of management responsibility for the oversight of testing contractors showed that NTP is following its established oversight policies and procedures in monitoring testing laboratories and is taking action to correct noted problems.

CHAPTER 3

INCREASED EMPHASIS ON QUALITY ASSURANCE ACTIVITIES TO IMPROVE TEST RELIABILITY

The Subcommittee's November 1983 hearings highlighted concerns about the adequacy of oversight by NTP of its contract research. This concern included NTP's quality assurance oversight of chemical tests. At the time of the hearings NTP had recently initiated several efforts to address these concerns by contracting with three organizations to perform quality assurance audits of chemical tests during the live animal and post-life phases of a test. Currently, the process of fully implementing new quality assurance reviews to address the concerns continues.

IMPLEMENTATION OF A MORE DETAILED QUALITY REVIEW FOR THE LIVE ANIMAL PHASE

In early 1983, NIEHS sent out requests for proposals for contract quality assurance audits of NTP chemical tests and awarded contracts to perform more detailed reviews of laboratories during the live animal test phases and to improve NTP's good laboratory practice enforcement. However, because of the questions that arose about the reliability of test data for GSRI's methylene chloride test, NTP redirected the three contracts (which in February 1984 amounted to about $739,000 each) to audits of completed test data of all NTP studies about to be published. As a result the live animal reviews were delayed until April 1984 and NTP had not scheduled all the reviews to begin until September 1984.

The primary purpose of NTP quality assurance reviews during the live animal phase is to identify potential problems and initiate corrective actions early in a test to better assure the reliability and validity of the final test results. The live animal phase reviews cover three discipline areas that are central to test outcomes--toxicology, chemistry, and pathology. Each contractor's review team consists of a toxicologist, chemist, pathologist, and histotechnician. Their respective duties are:

--The toxicologist examines body weights, survival rates, environmental conditions, dose administration, data tracking, and instrumentation records within the toxicology discipline area.

--The chemist examines chemical storage, stability, inventory, and analysis; dose preparation; and instrumentation records.

--The pathologist and histotechnician examine pathology records and relate them to live animal records, carcass identification, missed lesions at time of dissection, slide/block matches, and tissue accountability.

In addition to verifying these data, the three audit contractors' review teams also (1) identify problem areas and (2) point out corrective actions needed by the laboratory to avoid discrepancies in the conduct of the tests. According to the NTP quality assurance coordinator, the results of thorough reviews of all segments of one chemical test are representative of how a laboratory would conduct any of NTP's tests since the protocols are similar and the laboratory generally uses the same staff and facilities to conduct all NTP tests. The results of the quality assurance reviews are shared with NTP's project management team, which later uses the results for its annual program reviews at the laboratory. With this information the management team can identify the extent of the problems in a laboratory's other chemical tests and document actions needed to resolve them.

We examined the five live animal reviews conducted at contractor laboratories as of September 30, 1984. Reports for four of these reviews indicated no significant problems relative to the laboratories' test performances. The other report indicated several problems with one laboratory's performance. An NTP annual review 5 weeks later at this laboratory also identified significant problems. Because of the problems identified with the laboratory, NTP has:

--Terminated three ongoing tests because it questioned the laboratory's ability to conduct the tests correctly.

--Removed the pathology portion of six other tests because (1) the laboratory had lost several key personnel and (2) had experienced delays in meeting schedules for the pathology work.

According to the NTP quality assurance coordinator, the standard operating procedures for the quality assurance contractors in conducting live animal phase reviews have not been finalized. During our visits to the three quality assurance contractors, we reviewed the documentation for the five live animal reviews completed and noted the contractors were generally following NTP's draft standard operating procedures for the reviews. According to the quality assurance coordinator, NTP

expects to finalize these procedures by November 1985. Also, according to the quality assurance coordinator, NTP's future plans for live animal phase reviews include at least one audit per year per laboratory. At least one chemical per route of administration[1] for each laboratory will be reviewed, unless problems identified indicate other tests should be reviewed.

NTP'S PATHOLOGY REVIEWS

NTP has a comprehensive program to determine that the contract laboratories' pathology data support their interpretation of test results.

An NTP quality assurance contract pathologist verifies a laboratory's pathology work. Later a group of pathologists made up of representatives of government and private industry review the laboratory's pathology work and independently analyze any discrepancies identified between the laboratory's pathologist and the NTP quality assurance contract pathologist's diagnoses.

NTP initiated pathology quality assurance reviews in 1978 to evaluate all contract laboratories' pathology work submitted on a chemical test. These reviews have been performed by Experimental Pathology Laboratories, Inc. (EPL)--a quality assurance contractor. In conducting these pathology quality assurance reviews, EPL checks the slides and animal tissues to determine the quality of the slides and whether all slides and tissues are present. Also, a pathologist reads slides for a sample of the animals to verify the accuracy of the laboratory pathologist's diagnosis.

Since 1981, all differences in pathology diagnoses are submitted to a Pathology Work Group, consisting of four to six pathologists from academia, the private sector, and NTP. These pathologists reach a consensus on their diagnosis for each difference. When the Pathology Work Group's opinion agrees with the laboratory no other action is taken. However, when the Group's opinion agrees with that of the quality assurance pathologist, the slides and other supporting data are returned to the laboratory pathologist for reconsideration and resolution of the differences. According to documentation provided by EPL, more than 200 completed tests had been evaluated by EPL as of October 1984 and more than 100 had been reviewed by the Pathology Working Group.

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[1]NTP's routes of administration are the way in which the chemicals are administered to the animals. The most frequently used routes are inhalation (in the air), dermal (painted on the skin), oral (mixed into the water and food), and gavage (direct ingestion into the stomach with a tube).

DATA AUDITS OF POST LIFE TEST RESULTS SHOW THAT GENERALLY TESTS HAVE NOT BEEN COMPROMISED

With the completion of chemical tests and before issuing technical reports, NTP subjects the data developed as a result of the tests to a complete data audit. The additional pathology review in the audit focuses on original documentation, whereas the EPL review focuses more on test interpretations.

The audits are currently performed by the three quality assurance contractors who also perform the live animal phase reviews. The data audits are designed to verify the completeness and accuracy of the data generated during chemical tests. These verifications include checking individual animal data records, opening a sample of the tissue storage bags to determine whether animal tissues are present, counting and verifying slides, and reviewing all chemistry and toxicology data. A sample of tissues, such as target organs, are examined to verify that all tumors were identified, removed, and made into slides. The results of these data audits provide NTP additional assurance of the quality of the chemical test when interpreting the data and publishing technical reports.

In conjunction with our visit to the three quality assurance contractors that performed these data audits, we reviewed 9 of the 34 contracted audits completed as of September 1984, 3 for each of the three contractors. Based on our review of the audit documentation as compared to requirements of the NTP standard operating procedures, the quality assurance audit contractors generally appeared to be following procedures. Before the award of audit contracts, NTP had performed seven audits. These were conducted to get an initial assessment of whether laboratories other than GSRI had problems and were used in developing procedures for the data audits by the quality assurance contractors.

At NTP we also reviewed the executive summaries of all audit reports completed as of August 31, 1984. At that time, NTP and its quality assurance contractors had performed 38 data audits at nine laboratories. In reviewing the reports on these reviews, we noted that they are lengthy and technical; however, each report has a brief executive summary, which is less technical. To determine whether tests had been compromised, we obtained copies of the 38 summaries, reviewed them, and interviewed NTP staff to determine whether they contained deficiencies that would bring into question the validity of the study audited. We also identified the actions NTP has taken as a result of these audits.

NTP has determined that (1) 2 GSRI studies had been compromised (for the 6 other GSRI studies audited, NTP is withholding final conclusions until all 24 unpublished GSRI studies have been audited) and (2) none of the 30 studies conducted by the other eight contractors had been compromised. Based on the conclusions in these summaries and comments from chemical managers and the Acting Director of the Toxicology Research and Testing Program, we did not identify any discrepancies that would influence the final interpretation of the tests.

We found that the audit summaries indicated instances where information was lacking or standard procedures were not fully followed. According to the Acting Chief of the Carcinogensis Toxicology and Evaluation Branch, it is possible that the reliability of the test results could be challenged even though NTP judges them scientifically sound and uncompromised.

NTP's current emphasis is to complete data audits on all chemical tests for which technical reports have not been published as well as continue auditing tests as they enter the draft report stage. As of May 1985, there were 19 unpublished tests ready for audit. Also, as of May 1985, 63 audits had been reported on, and according to the Assistant to the Director of the Toxicology Research and Testing Program, there have been no other studies found to be compromised. Additionally, NTP plans to perform similar data audits of selected chemical tests that have already been published. These will be identified by an NTP Subcommittee of Audits composed of representatives of the various regulatory agencies that are on the NTP Executive Board.

NTP'S VIEWS ON MOVING QUALITY ASSURANCE EFFORTS IN-HOUSE

In conjunction with its expanded contract quality assurance measures, NTP is increasing its in-house quality assurance staff to improve its management of its quality assurance contractors and its oversight of the quality assurance function. As of June 1985, NTP was planning to establish a new Office of Quality Assurance, which consolidates the NTP quality assurance functions under one person, who will report to the Acting Director of the Toxicology and Research Testing Program. The office will also have experts in pathology, toxicology, and chemistry besides the current quality assurance coordinator. The staff will monitor contractor quality assurance efforts and oversee NTP's quality assurance system.

The Acting Director of the Toxicology Research and Testing Program believes that having all quality assurance activities in-house would provide NTP direct control over these efforts and, therefore, help assure stricter management of the performance of these quality assurance reviews. There would be little

need for additional facilities because many of the quality assurance reviews are performed at laboratory facilities or in NTP space already allocated to quality assurance efforts. According to the Acting Director, the cost for in-house quality assurance would be about the same as the cost currently incurred for NTP staff and quality assurance contracts. Specific cost data were not available.

According to the Acting Director, another advantage to NTP would be further eliminating the possibility of situations and concern about contract audit staffs having worked previously on some part of the test being reviewed. He believes that having all of the quality assurance staff employed by NTP would preclude them from having worked on similar projects in the private sector. Therefore, NTP would have complete control over the personnel who would perform the reviews, and there would be less opportunity for private industry and special interest groups to question NTP tests. He cited as a potential problem for NTP recruitment the limited number of pathologists who would be available for recruitment for these quality assurance positions and the large salaries ($70,000 to $100,000) they would demand.

The Acting Director also stated that bringing these activities in-house would require NTP to increase its personnel ceilings or divert positions from other NTP efforts. Increasing NTP's authorized personnel would also require congressional approval. He believes that the current emphasis on contracting out for many government services would make it very difficult for NTP to convince HHS to bring these quality assurance functions in-house. Furthermore, the Acting Director stated that diverting other NTP positions to the quality assurance efforts might affect the efficiency of the other NTP efforts. NTP believes obtaining an in house quality assurance staff has merit but has not taken actions to pursue obtaining the staffing for these functions.

OBSERVATIONS

NTP recognized weaknesses in its quality assurance program and has initiated two additional quality assurance efforts. NTP's contracted live animal audits have provided additional assurance about the accuracy and reliability of tests while they are being conducted. It also has provided NTP with a more thorough means of identifying possible problems and, where such problems are identified, has enabled NTP to discontinue tests before additional work is performed. Similarly NTP's post-life data audits have resulted in NTP's identifying problems with completed tests and has provided a new means to anticipate and respond to possible concerns about tests' reliability and validity before issuing formal reports. This has included withholding certain reports from publication.

CHAPTER 4

CONCERNS INVOLVING

GULF SOUTH RESEARCH INSTITUTE

After the November 1983 congressional hearings, GSRI expressed concerns to the Subcommittee Chairman that (1) it had been treated differently than other contractors in that NTP terminated its contract but had not terminated contracts with other laboratories for poor performance, (2) findings based on a review conducted by the Halogenated Solvents Industry Alliance on GSRI's testing of methylene chloride were not verified by NTP, (3) its testing activities were characterized by NTP in the November hearings as only acceptable when GAO had reported in 1979 that its performance was "good" overall, (4) NTP had assigned pathology work removed from GSRI to the Experimental Pathology Laboratories after EPL had performed quality assurance reviews of the work and reported that it was not acceptable, and (5) NTP judged GSRI's completed tests against good laboratory practice standards that were not yet in effect. The Subcommittee Chairman asked us to examine these concerns and questioned whether the payments made to GSRI or Tracor Jitco could be recovered in those instances where NTP identified poor performance.

NTP's decision to terminate GSRI's contract was based on continuing problems with GSRI's pathology activities and concerns about the overall quality of GSRI tests. As discussed in chapter 2, NTP has also experienced problems with other laboratories' performance and has disqualified those laboratories from further testing contracts. It has also terminated some individual tests at these contractors.

Similar types of problems identified with methylene chloride by the Alliance were also highlighted in an NTP audit of the test's documentation. Also, GAO's 1979 report pointed out that GSRI's testing conditions were good overall but noted testing deficiencies that could affect the quality of its tests. None of the pathology work on studies removed from GSRI and assigned to EPL had been subjected to EPL's quality assurance pathology review. NTP's action to terminate the GSRI contract was based on factors related to GSRI's continuing pathology problems and questions about the overall quality of GSRI's tests rather than its failure to adhere to good laboratory practice standards.

Despite documented poor performance, we believe it is unlikely that costs can be recovered from GSRI or Tracor Jitco. The existing contracts--which were cost plus fixed fee levels of

effort--did not expressly provide that reimbursement of allowable costs would be contingent on test results of a certain quality or require contractors to bear the costs of correcting defective performance. HHS' General Counsel had also raised this concern earlier and has assisted NIEHS in correcting this problem for future contracts. NIEHS has acted to strengthen its contract provisions to hold contractors financially accountable for poor performance.

NTP'S TREATMENT OF LABORATORIES

Our analysis of NTP's oversight documentation on GSRI and the other 16 laboratories showed that between July 1982 and June 1984, NTP was making site visits, annual program reviews, and quality assurance and pathology reviews at all the laboratories and taking action to resolve performance problems.

Gulf South

GSRI's poor performance was documented based on NTP visits and reviews, and other documentation. In September 1982, NTP transferred the oversight of GSRI from a contract management firm, Tracor Jitco to an in-house function and established a new contract with GSRI to continue in-life testing on eight chemicals and complete post-life pathology work on eight other chemical tests. The new GSRI contract with NTP cost about $2.4 million. This contract was awarded with NTP's knowledge of prior performance problems with GSRI and NTP's belief that GSRI was acting to overcome the problems.

Between November 1981 and July 1983 NTP, Tracor Jitco, and EPL documented repeated instances of GSRI performance problems, including poor slide quality and histopathology, slide labeling discrepancies, missing wet tissue and/or blocks, unrecognized tumors, poor tissue accountability, and incorrect diagnoses. Pathology problems were also documented by a NTP's Pathology Work Group. This group, made up of consultants from government and private industry, reviews problems identified by EPL in its pathology quality assurance reviews.

NTP acted in March 1983 to reduce GSRI's pathology work under the September 1982 contract. NTP assumed pathology responsibility for five ongoing studies where pathology work was in the preliminary stages or had not yet begun. GSRI was to complete the work on the remaining 11 studies. As discussed on page 28, NTP assigned the pathology work to EPL for the five studies. Later one of these studies was assigned to another contractor. The work was assigned under existing NTP pathology support contracts. The support contract with EPL was in addition to an existing EPL pathology quality assurance contract.

EPL had not previously conducted quality assurance reviews on any of five studies.

In October 1983, NTP terminated its contract with GSRI because of continuing pathology problems and questions about the overall quality of GSRI testing. NTP allowed GSRI until May 1984 to phase out and complete certain of its testing activities.

Regarding GSRI concerns raised about the verification of the results of the June 1983 Halogenated Solvents Industry Alliance's review of GSRI's test on methylene chloride, NTP later, through an audit of the GSRI test data identified similar types of problems, particularly regarding the accuracy of test records.

Also, in the 1983 hearings, NTP characterized GSRI's work as only "adequate," while our 1979 report pointed out that GSRI's testing conditions were "good" overall. Our analysis supporting the overall rating was based on examining the conditions and procedures employed by GSRI at that time under contract with Tracor Jitco through the National Cancer Institute's testing program. Despite the "good" rating, we noted deficiencies that could affect the quality of the tests GSRI was conducting at that time. These were:

--Pathologists not having all necessary data on the animal conditions while reviewing slides.

--Animals killed by improper chemical dosing techniques being designated as "natural" death.

--Temperature or humidity alarms not functioning properly.

GSRI advised us at that time they were taking action to correct these deficiencies.

Other laboratories

NTP was also acting to identify and resolve performance problems on other contract testing laboratories. As discussed in chapter 2, our analysis of contractor oversight by NTP between July 1982 and June 1984 of the contracts that NTP had with the other 16 laboratories to conduct chemical tests showed that because of poor performance, NTP took action against five firms in addition to GSRI. During the contract award process in December 1983, NTP disqualified these five firms for new contracts because of past poor performance. This decision was based on problems that it had found to be occurring before December

1983. Areas where problems occurred included pathology, management, animal care, and health and safety. At the end of 1984 NTP also took action to terminate several tests at one of the five laboratories because of problems NTP identified including the laboratories' failure to follow prescribed procedures.

EPL'S ROLE IN REVIEWING GSRI WORK

Another GSRI concern was that NTP had assigned EPL to review GSRI pathology work and when EPL found the work unacceptable, NTP assigned it to EPL.

In its role as NIEHS' pathology quality assurance contractor, EPL had performed reviews on several chemicals GSRI studied. However, under an existing EPL pathology support contract, NTP assigned to EPL five other GSRI chemicals that EPL had not reviewed. Because GSRI had raised concerns about the assignment of their work to a quality assurance contractor, NTP acted to prevent pathology quality assurance contractors, such as EPL, from receiving any pathology work on studies being performed by the NTP laboratories.

The Acting Director of the Toxicology and Research Testing Program stated that NTP had two contracts for pathology support--one with EPL and the other with Clements Associates. At the time pathology work was taken from GSRI, Clements was unable to do all the work. EPL was initially assigned work on all five studies. One of the five studies was later transferred to Clements. The Acting Director and a Vice President of EPL told us that the NTP-EPL support contract ended before EPL could perform most of the work. Accordingly, EPL performed initial pathology work on the four studies but turned most of the work back to NTP at the end of its contract because of other tasks NTP had assigned it.

After our discussions with NTP officials about EPL's role and the concerns raised by GSRI, NTP took a number of actions to prevent its pathology support and quality assurance contractors from involvement in similar situations. These were:

--Including a provision in its 1984 request for proposal and in its pathology quality assurance review contract which restricts the successful bidder from competing for the pathology support contract. According to the chief contract officer, this restriction was added to prevent the reoccurrence of situations that occurred with the GSRI pathology work.

--Modifying three quality assurance audit contracts awarded in September 1983 to require the contractor to notify NTP any time that assigned quality assurance tasks would present an actual or apparent conflict of interest between the contractor and the chemical manufacturer and/or user or when the use of specific contractor staffs would present a conflict of interest.

According to NIEHS chief contracting officer, NIEHS is also considering including a restrictive clause in pathology support and pathology quality assurance contracts. This clause would require the contractors to avoid any conflict of interest (such as having performed work on the tests being reviewed) when accepting work for NTP or when assigning staff to such work.

GOOD LABORATORY PRACTICE STANDARDS

Another GSRI concern was that tests it had completed before 1981 were being judged by NTP principally against good laboratory practice standards which were not then in effect. The standards were established by FDA in 1979 and voluntarily adopted by NTP in 1981.

Beginning in October 1980 NTP and Tracor Jitco began assisting testing laboratories in developing quality assurance measures that would meet the FDA's good laboratory practice standards.[1] This included requiring laboratories to conform, to the extent possible, ongoing studies to the standards and to begin all new tests under the standards. In October 1981 NTP required all its laboratories to be in compliance with good laboratory practices.

In 1982, NTP and Tracor Jitco began conducting good laboratory practice compliance reviews at the contract testing laboratories. These reviews focused on laboratories' overall operations. Ongoing studies begun before October 1981 would have been subject to review to determine the extent of the laboratory's compliance with the standards.

We found that NTP's most significant problems with GSRI's testing resulted from pathology problems and questions about the

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[1]Compliance with these standards is intended to ensure quality and integrity of testing data. These cover organization and personnel requirements, the proper construction and location of facilities, equipment design functioning and maintenance, requirements for standard operating procedures for testing facilities, written protocols for each study, and preparation of records and reports.

overall quality of its tests identified principally through NTP's contract oversight activities. As of July 1983, good laboratory practice reviews had been completed at 11 laboratories. Between April and September 1984, NTP's quality assurance contractors conducted reviews of five studies in the live animal phase. These reviews included examination of testing laboratories' compliance with good laboratory practices. In September 1984, the quality assurance contractors began to conduct regularly scheduled reviews of laboratories' studies in the live animal phase.

NTP is performing post-life audits of all completed tests before publication at its 16 laboratories and GSRI to assure test reliability. NTP has established post-life audit procedures for the quality assurance contractors to follow which include many of the features required by good laboratory practices. Particular emphasis in these audits is focused on whether the documentation supports the test results. The audits are not intended to evaluate a laboratory's compliance with good laboratory practices. However, problems noted during good laboratory practice compliance reviews before the study was completed would be taken into account.

As part of its process for regulating such products as food additives, drugs and biologics, FDA inspects laboratories for their adherence to good laboratory practices. Some of these inspections are at laboratories that do work for NTP as well as private industry. As a result of concerns raised by NTP about GSRI testing, FDA, between August and October 1983, inspected GSRI to determine its compliance with good laboratory practices. It reviewed five studies in depth and selected aspects of others. These studies were selected by FDA because they involved products subject to FDA approval.

In a June 1984 report FDA concluded that GSRI studies did not meet the standards. While FDA recognized that three of the five studies it reviewed were begun before NTP required GSRI to meet good laboratory practices, FDA told GSRI that it was requiring that any GSRI study submitted to FDA in support of any agency action--drug approvals, marketing applications, etc.--be validated using FDA-approved procedures.

RECOVERY OF COSTS UNLIKELY

The recovery of costs from GSRI or Tracor Jitco is unlikely in view of the type of contracts NTP had with these two contractors. NIEHS estimates it may cost $2 million to $11 million to reperform GSRI studies depending on their accuracy and completeness, which will be determined on the basis of audits by NTP and its quality assurance contractors.

The contracts in question were basically cost-plus-fixed-fee, level of effort contracts obligating the contractor to furnish a specified approximate number of staff-hours over the term of the contract in performing the contract tasks. The Tracor Jitco contract further required that it use its "best efforts" to accomplish the covered work and provided that Tracor Jitco's obligation would be deemed complete if it performed in accordance with "high standards of scientific and professional skill."

In return for Tracor Jitco's performance, NIEHS agreed to reimburse "all allowable costs incurred" not to exceed a specified amount, a base fixed fee for "satisfactory" performance and, if deemed "earned," an award fee based on periodic reviews. As consideration for GSRI's performance, the agency agreed to reimburse costs determined by the contracting officer to be allowable, plus a fixed fee. The contracts do not expressly provide that reimbursement of allowable costs would be contingent on the furnishing of test results of a certain quality or require the contractor to bear the costs of correcting defective performance in the event of invalid final test results.

The "best efforts" and "high standards" language in the Tracor Jitco contract could conceivably be construed as making recovery of allowable costs contingent on satisfactory results. However, given what we consider to be the essential nature of the cost contracts--payment in return for a level of effort--and the absence of any contract provision imposing the full risk of invalid test results on the contractors, we believe it is unlikely that NIEHS would be entitled to withhold or recover from the contractors amounts covering otherwise allowable costs and fees. We found that the HHS General Counsel's office also noted that the previous contracts did not provide any remedies in the event of the contractor's noncompliance.

Because of this problem, and pursuant to discussions with the HHS General Counsel's office, NIEHS is adding wording to its new contracts to hold contractors more accountable for the results of their testing. It is also considering adding a similar provision to its existing contracts. The contract provision incorporates by reference Federal Acquisition Regulation §52.246-8 (Inspection of Research and Development - Cost Reimbursement), which calls for periodic inspection by NIEHS, a final data audit before "acceptance," and reperformance or reimbursement to the government for the cost of work not meeting contract requirements. The provision provides that:

"If the Contractor fails to proceed with reasonable promptness to perform required replacement or correction, the Government may (1) by contract or otherwise, perform the replacement or correction and charge to the Contractor any increased cost or make an equitable reduction in any fixed fee paid or payable under the contract; (2) require delivery of any undelivered articles and shall have the right to make an equitable reduction in any fixed fee paid or payable under the contract; or (3) terminate the contract for default. Failure to agree on the amount of increased cost to be charged the Contractor or to the reduction in fixed fee shall be in dispute."

This provision also provides that:

". . . the government may at any time require the contractor to remedy by correction or replacement, without cost to the Government, any failure by the Contractor to comply with the requirements of this contract, if the failure is due to (1) fraud, lack of good faith, or willful misconduct on the part of the Contractor's managerial personnel or (2) the conduct of one or more of the Contractor's employees selected or retained by the Contractor after any of the Contractor's managerial personnel has reasonable grounds to believe that the employee is habitually careless or unqualified."

CONCLUSIONS

We believe GSRI's poor performance has been documented by NTP to justify the actions it took against the firm. We found no basis for GSRI concerns that NTP treated it differently from other testing laboratories in its oversight action. While EPL was knowledgeable about the overall adequacy of GSRI's pathology work, none of the GSRI studies NTP assigned EPL for pathology work had been previously reviewed by EPL. NTP has taken action to preclude pathology quality assurance contractors from also performing pathology work that they previously reviewed.

Despite documented poor performance, we believe it is unlikely that NIEHS will be able to recover contract costs from either GSRI or Tracor Jitco. NIEHS is incorporating a provision in its new contracts establishing a means of holding contractors more accountable for acceptable performance. We believe the provision represents a reasonable means to accomplish this purpose.

NTP TESTING LABORATORIES

Battelle Columbus Laboratories
Battelle Northwest Laboratory
Bioassay Systems Corporation
EG&G Mason Research Institute
Gulf South Research Institute
Hazelton Laboratories American, Inc.
Hazelton-Raltech, Inc.
International Research and Development Corp.
Litton Bionetics, Inc.
Lovelace Inhalation Toxicology Research Institute[1]
Midwest Research Institute
Microbiological Associates
Papanicolaou Cancer Research Institute
Physiological Research Laboratories
Southern Research Institute
Springborn Institute for Bioresearch, Inc.
Stanford Research Institute International

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[1]This is a Department of Energy laboratory facility.

APPENDIX II

MEMBERS OF NTP'S

EXECUTIVE COMMITTEE

Assistant Secretary of Labor for Occupational Safety and Health Administration, Department of Labor

Assistant Secretary for Health, Department of Health and Human Services (non-voting)

Director, National Cancer Institute

Commissioner, Food and Drug Administration

Director, National Institute for Occupational Safety and Health

Administrator, Environmental Protection Agency

Chairman, Consumer Product Safety Commission

Director, National Institutes of Health

Director, National Institute of Environmental Health Sciences

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