SUMMARY OF FINDINGS

Initial planning of this EPA/FDA joint inspection was for coverage of three long-term studies on test substances of concern to [illegible]. Additional studies of Bureau of Foods interest were added to the initial work load.

Inspectional and investigational discoveries required us to expand our coverage to other studies. These new discoveries required alterations of the priorities initially established. Studies demonstrating the most serious problems were:

1. 621-[illegible], [illegible] Soap Co., Ltd., Two-Year Chronic Oral Toxicity Study with Mighty in Albino Rats

which involved unrecorded, unreported substitution of untreated test animals well after the initiation of the study:

2. 621-02311, Monsanto Company 18-Month Carcinogenic Study with CP [illegible] Technical (Machete) in Albino Mice, STL-[illegible]-127 ✓ Machete

which involved the usage of extra animals, with only a portion of the extra animals being reported. Other significant problems were involved, including evidence of client's knowledge of situation prior to submitting their report to the U. S. Government;

3. 621-03204 (and forerunner study 621-00755), Monsanto Company Two-Year Carcinogenic Study with Monosodium Cyanurate in Albino Rats, STL No. [illegible] ✓ Two-Year

which disclosed poor animal care and observation practices, poor controls over test animals and tissues derived from them. Numerous discrepancies between the various records covering test animals. Missing raw data replaced by after-the-fact generated records. Disregard for a known compound-related problem. Issuance of a final report which claimed practices and animal observations that were not done as represented. Strong evidence of client's being knowledgeable of inaccuracies in the final report. ACL

4. 621-03205 (forerunner study 621-00755), Monsanto Company 18-Month Carcinogenic Study with Monosodium Cyanurate in Albino Mice, STL No. [illegible]-17 ✓ 18-Mo.

Widespread problems similar to those associated with 621-03204. Deliberate concealment of circumstances relating to animal mortalities. Issuance of final report claiming procedures and observations that weren't performed. Strong indication of client's knowledge of the deficiencies before they issued their report to the U. S. Government. ACL

MONS 016950

3. 621-05533, Mobil Chemical Company Two-Year Chronic Oral Toxicity Study with Difenox in Albino Rats

Use of extra animals which were started on the diets approximately 12 months after the original study was started. General lack of antemortem observations. Tissue masses reported on observation records that were not observed at time of necropsy. Unrecorded administration of antibiotics to experimental animals.

4. 621-05603, FDA/Bureau of Foods Study

Significant discrepancies in diet preparation and instances where protocol specified tissues were not observed. (This study was of lesser concern than those previously described.)

Due to our involvement with the aforementioned studies, little time was spent on an acute vapor inhalation toxicity study of concern to Bureau of Foods.

The inspection disclosed widespread departure from the Good Laboratory Practices concepts contained in the proposed GLP's. During the interval when the EPA studies were conducted, written SOP's were nonexistent. The firm's claim that it has unwritten established procedures which ensured proper conduct of studies to essentially the same degree as written SOP's was found to be incorrect.

What was initially represented as raw data has in part been found to be extracts from other records. Portions of the source records used in the compilation of the "raw data" were missing. In many instances, only photocopies of the "source records" were available.

Three of the final reports issued to Monsento Company contained claims for making animal observations at prescribed intervals even though those observations were not made at the prescribed intervals. There were indications that the client was aware that these observations would not be made, even before the studies were initiated. There were additional indications that anticipated toxicity problems known to both the client and test facility were deliberately overlooked. Machete PCL

Animal substitutions and the usage of unreported extra animals were suspected in some of the EPA studies evaluated. These situations were confirmed as having occurred.

The mouse study conducted for Monsanto Company utilized more animals than the protocol specified. Over 40% of the test animals involved in this test study were lost due to record-indicated autolysis. There was

no indication that any statistical validation of this study had been made prior to its submission to the client (Monsanto).

Although final reports claimed that animals were observed daily for abnormal behavior, this admittedly did not occur. Weekly observations for tumor formation in test animals were not done for studies 3205 and 2311.

Chlortetracycline and tetracycline were widely administered to test animals during an era of health problems. The usage of these antibiotics was authorized by the veterinary pathologist, David Sullivan. No records of their administration were maintained.

With respect to studies 3204 and 3205 conducted for Monsanto, there was an extremely poor accountability for the receipt and usage of the test substance, Monosodium Cyanurate.] ACL

PARTICIPANTS IN THE INSPECTION

The individuals who participated in this inspection were:
FDA
Kenneth O. Burgklin, Investigator, Edwardsville Resident Post, CHI-WI.
Wayne F. Grundstrom, Investigator, Champaign Resident Post, CHI-WI.
Walter H. Hansen, Bureau of Drugs, Pharmacologist.
Dowell Davis, Bureau of Drugs, Pharmacologist.

EPA
Dr. Arthur J. Pallotta, Consultant to EPA.
Dr. Larry D. Anderson, Pharmacologist.

MONSANTO
Dr. Gene McConnel, Veterinary Pathologist.
Dr. David Hool, Bio-Statistician.

The FDA and EPA participants' involvement with individual aspects of the inspection varied. Their signatures on the general report and sub reports covering this inspection are not intended to imply complete individual knowledge and responsibility for the entire text.

Drs. McConnel and Hool visited the establishment at the request of Dr. Pallotta through Dr. David P. Rall, chairman of the Toxicology Committee of NIEH. IBT-Decatur management agreed to allow both visitors access to records being reviewed. Their visit was limited to a single day (3/1/79). The primary study reviewed by them was 621-02311.

PERSONS INTERVIEWED

Notices of Inspection and FDA credentials were presented to Mrs. Barrie M. Phillips (1/16 and 2/1/78 - Exhibits V1/2) and John H. Mennear (2/[illegible] and 27/78 - Exhibits V3/4). Both parties were present when the purpose of the inspection was initially discussed. Both were present when our summarizing discussion was held. Drs. Phillips and Mennear were periodically advised of inspectional findings.

Fred D. Current, Corporate Counsel, was present throughout most of the inspection. He was informed of inspectional findings throughout the course of the inspection. Most of our request for records and client files were directed to Mr. Current. Mr. Current assumed the responsibility for the security of IBT-Decatur archives during the current inspection.

Dr. John W. Goode, provided some information concerning the firm's conformity to proposed GLP regulations during the interval from 1972 to 1976. He gave limited information regarding the source of directives issued from IBT-Northbrook.

Dr. David J. Sullivan provided information concerning the animal health problem which necessitated widespread administration of antibiotics to test animals. He also discussed the operations of IBT-Decatur's pathology department.

Kenneth F. McCollum provided considerable information concerning deliberate acts committed in studies conducted at IBT-Decatur. He specifically identified studies 621-06363, and 621-02311 as studies containing serious problems. He identified individuals who were responsible for committing some of the deliberate acts. He advised us of the individuals who gave the orders which resulted in the commission of these acts. Mr. McCollum was the initial party to advise us of what animal observations were being made and which ones weren't being made. He signed an affidavit covering his personal knowledge of test animal substitutions that took place in study 621-06363. Machete

Leslie D. Morrow provided some initial leads concerning the usage of extra animals. He identified some of the parties who had completed records on some of the studies. He admitted his personal involvement in study 621-02311, where unreported extra animals were used. He signed an affidavit pertaining to this study.

Hope E. Ryder (formerly Davis) Mrs. Ryder was a former laboratory technician at IBT-Decatur and a principal lab technician on studies 621-03205 and 621-02311. She described some of the animal problems she'd experienced on these studies and how they were concealed by the records she maintained.

She signed an affidavit concerning her knowledge of problems associated with these studies.

Stephen R. Small Mr. Small was a former laboratory technician at IBT-Decatur. He also worked on studies 621-03205 and 621-02311. He was familiar with the occurrence of the problems disclosed by Mrs. Ryder. He also was familiar with the generation of after-the-fact records. Mr. Small also signed an affidavit covering his knowledge of problems and record keeping practices at IBT-Decatur.

Peter D. Brown Jr. Mr. Brown was a current employee of IBT-Decatur. He was the laboratory technician who made the animal substitutions in study 621-06363. He signed an affidavit concerning his involvement in the substitutions.

Stephen R. Bertsch provided information as to his experience and responsibilities as a laboratory technician. Provided information concerning diet preparation. Discussed record keeping practices associated with study 621-03204, at the time he served as a laboratory technician on this study.

William J. Kavanaugh described his record keeping procedures on study 621-03204. Also described his experience and responsibilities as a laboratory technician.

Dirk Shelton accompanied us on an inspectional review of an ongoing rat study known as "Study X".

Mrs. Isabelle H. TeVault described the record keeping procedures used by the autopsy and histology department of IBT-Decatur before it became the pathology department. Mrs. TeVault signed an affidavit concerning her knowledge of these operations.

Kay Doman provided photocopies of the labor detail reports pertaining to studies 621-03204, 621-03205, and 621-02311.

Linda Beal Ms. Beal discussed the sign-off procedures by IBT-Decatur management. She stated that the scotch-taping of signatures to final reports occurred at Northbrook. She identified Ms. Bunny Pae as the Northbrook typing supervisor most familiar with the practice of scotch-taping signatures to final reports.

Additional information provided by the aforementioned individuals has been included in narrative sections of our reports. Information provided by additional parties has been included in the body of these reports, when relevant. A list of additional persons interviewed follows:

Mary Jane Chladny, Pathology - Group Leader, Histology
Dave Billerman, Pathology - Group Leader, Necropsy
Dennis Lindberg, former Assistant Manager, now Assistant Director, Inhalation Toxicology
Yvonne J. Tenchcom, Quality Assurance Supervisor
J. Drew Watson, Customer Services Specialist
James Kush, Animal Care Supervisor
Blair Wingard, former Diet Prep Supervisor, Assistant Toxicology Group Leader
Ed Haynes, Diet Prep Assistant
Ronald Householter, Receiving Clerk
Pete Enlen, Lab Tech

Curriculum Vitae for most of the above IBT employees are submitted as Exhibit A.

Non-IBT Personnel:

Monsanto people -
Dr. James Lavenia, Senior Toxicologist, Monsanto Company
Dr. Frederick L. Johannson, Senior Toxicologist, Monsanto Company
Dr. Robert L. Gates, FMC Corporation, Project Manager, Agricultural Chemical Division

INDIVIDUAL RESPONSIBILITY

Industrial Bio-Test Laboratories, Inc., Decatur, Illinois, has become the headquarters for all IBT operations. All operations conducted at the Northbrook, Illinois, facilities are to be transferred to Decatur.

From 1972 through 1976, the Decatur facility was subordinate to Northbrook. Directives came directly from Northbrook. The former manager of the Decatur facility (John M. Goode) claimed that the directives often bypassed him entirely. Northbrook personnel most responsible for issuing policy and procedural directives were identified by Dr. Goode as:

1. S. Kennedy
2. M. L. Mallagar
3. James Plank
4. Florence K. Kinoshita

Dr. Goode stated that these individuals usually contacted Kenneth E. McCollum directly. Kenneth E. McCollum would then discuss the contact with Dr. Goode if it involved a serious problem.

Kenneth E. McCollum, Section Head, Toxicology and formerly the Senior Group Leader of Toxicology, was identified as the primary intermediate concerning the receipt of orders from Northbrook and seeing that they were executed at Decatur. Mr. McCollum said that, "Everybody and their brother at Northbrook called me." Kenneth E. McCollum received the orders on the number of animals to be included in the final report on study 2311, from James Plank.

Kenneth E. McCollum routinely included the claims for daily observations for abnormal behavioral reactions and weekly observations for signs of tumor formation in his rough draft final reports. Mr. McCollum claimed the example specimen of a final report which he used as a format for his rough drafts contained these same statements and he just included them in his rough drafts.

Mr. McCollum specifically brought the problem of substitution in the Mao Soap Company Study, #621-06363, to our attention. He signed an affidavit covering his knowledge of the substitutions and from whom he received his orders to make them.

Upon advice from his attorney, Mr. McCollum has refused to sign any more affidavits concerning his knowledge of poor practices and deliberate acts resulting in the issuance of falsified reports to clients.

Leslie D. Morrow, Toxicology Group Leader, had considerable knowledge of questionable practices and record keeping procedures associated with studies of current inspectional concern. Mr. Morrow was involved in the order-giving process associated with Monsanto's Machete Study #621-02311. He claimed to have done much of the rough draft final report write-up on this study. He explained how the animals in 2311 were selected as extras after the study was completed. He gave some generalized explanations on the usage of extra animals in studies. He assisted in identifying the individuals who made entries into the records on studies which we received.

Mr. Morrow signed an affidavit regarding some of the record keeping practices on study 2311.

OBJECTIONABLE PRACTICES AND CONDITIONS

The objectionable conditions and practices discussed were generally those associated with studies conducted between 1972 and 1976. There were instances where an objectionable practice or condition was detected in current operations. These will be so indicated as a current objectionable condition or practice. The objectionable conditions and practices will be discussed under subheadings considered appropriate for the situation.

Personnel

Animal laboratory technicians that were interviewed during the course of our inspection and collateral investigations admitted that they lacked any prior experience in the area of the work they were responsible for at IBT-Decatur. Among the employees who admitted their lack of experience were:

1. Mrs. Hope E. Ryder (formerly Davis)
2. Stephen R. Small
3. Steve Bertsch
4. Peter B. Brown, Jr.

Mrs. Ryder admitted that she assumed the full duties of a laboratory technician after a couple of days of on-the-job training. Kenneth F. McCollum stated that Northbrook personnel had initially trained laboratory technicians at the Decatur facility. These Northbrook trainers had taught the laboratory technicians to give attention to individual animal mortalities and disregard other observations. There were no written job descriptions setting forth the duties and responsibilities of a laboratory technician during the era of primary concern.

Interviews with past and present laboratory technicians revealed that between 1972 and 1976, each individual technician was responsible for 5 to 6 long-term toxicology studies in test animals. The laboratory technicians estimated that they were each responsible for approximately 2000 animals at any given time during this interval. Labor detail reports covering some of the studies audited (3204, 3205, and 2311) disclosed that technicians were spending less than one hour per day on any one of these studies. Final reports for studies 3204 and 3205 claimed that abnormal reactions were recorded daily. Final reports for 2311 and 3205 claimed that weekly observations for signs of tumor formation were made. mochete

Dr. John Goode stated that he had signed off on an average of 600 to 650 studies per year. He claimed that this volume of reports did not allow him very much time to verify their accuracy before he signed them.

Study Director

From 1972 through 1975, IBT-Decatur lacked a study director who:

1. Had ultimate responsibility for implementation of the protocol and conduct of the study;

2. Assured that the approved protocol was followed;

3. Assured that the tests (and when necessary, the control substance) or mixtures therefrom had been appropriately tested for identity, strength, quality, purity, stability, and uniformity;

4. That the test systems were appropriate;

5. That personnel clearly understood the functions they were to perform;

6. That all data was accurately recorded and verified;

7. That unforeseen circumstances that may have affected the quality and integrity of the non-clinical laboratory studies were noted and documented;

8. That the responses of the test system, whether anticipated or not, were documented.

Quality Assurance Unit

From 1972 through 1975, the firm lacked any type of unit which performed quality assurance functions set forth by the proposed GLP's for a quality assurance unit.

Animal Supply Facilities

Inspection of the room where laboratory animal rations were held disclosed it to be rodent-infested. Nine to ten wild mice reportedly had been trapped in this room over a recent two to three week period. Mouse excreta pellets were observed throughout this room and upon stored bags of laboratory feed held therein. Some of the bags of laboratory animal feed had been rodent-gnawed through all layers to the contents. Bags of feed throughout this room bore stain patterns typical of rodent urine defilement. These stains were apparent under normal light.

Portions of the rodent-defiled laboratory feed were sampled under 78-[illegible]. A copy of the Collection Report and accompanying continuation sheets and photographs are submitted as Exhibit VB. Management destroyed 8/50 lb. "chewed" bags after the sample was collected.

A Receipt for Samples and List of Observations (FD-483) listing the insanitary conditions encountered was issued to Dr. Barrie M. Phillips, President, on 1/27/78 (Exhibit V5/6).

Facilities for Handling Test and Control Substances

Since September 1977, a room in the basement of the facility has been used for the storage of newly received test substances. Receiving records show that 74 test substances have been received since then and several currently in use or to be used are now stored in this room. In addition, hundreds of to-be-disposed-of test substances from completed inhalation studies were stored haphazardly throughout the room.

The room was extremely filthy. Rodent pellets were found on the floors and benches and actually on containers of test materials. Storage shelves on which test materials were placed showed areas of spillage and in at least two instances, containers of in-use test substances were found to be open and exposed directly to the environment. Containers of test substances were stored on top of one another and were inadequately segregated to preclude the possibility of cross-contamination due to leakage or possible mis-identification. Some products were stored directly on dirty concrete floors.

Odors in this room were so intense as to pose a potential health hazard to anyone breathing them. Entry into this room necessitated the wearing of a gas mask. There are no temperature or humidity controls or special venting and the room appeared to be under negative pressure to the corridor. Dr. T. Kent TeVault, Safety Director, is currently in charge of the conditions in this room and Ron Householter is in charge of receiving test materials into this area and subsequent distribution. Dr. Barrie Phillips, President, toured this area on 2/8/78.

Also, there were six fiber drums stored in the corridor outside the room, which contained "to be disposed of" test substances. The drums were not identified adequately and certainly were not stored in a controlled area. In addition to the main test material storage area in the basement, there was also a smaller secondary test material storage room located just down the hall from the diet prep area. This room is locked at night but there is open access during the day. Test substances are stored in closed glass and/or metal cabinets. Neither of these cabinets nor the rooms have a special venting system other than the normal air circulation in the room.

Photographs depicting conditions encountered in this room and in the hall are submitted as Exhibit VC.

Specimen and Data Storage Facilities

Up until the current inspection was underway, the firm lacked a limited access facility for the storage and retrieval of all raw data and specimens.

Maintenance and Calibration of Equipment

The firm had failed to establish that its diet preparation equipment was functioning as intended.

Standard Operating Procedures

There was a general lack of written standard operating procedures for operations performed by this facility from 1972 through 1977. Some may have existed for clinical pathology.

Management claimed that established procedures had existed for the conduct of studies and that these were well understood by the individuals performing the work. They felt that these unwritten established procedures had, to some extent, satisfied the intent of written SOP's since everyone understood what the established procedures were for their particular jobs. Observations of current employee practices combined with interviews of present and past employees disclosed that employee understandings were not as claimed by management.

On 1/10/78, the room housing a rat study known as 9535 was inspected. The technician in charge of the study (Pete Inloe) accompanied the investigators. This technician called Investigator Buercklin's attention to a female rat designated as animal #258. He advised Investigator Buercklin that this animal was sick and had been placed on a water bottle. This lab tech was not in a position where he could observe the animal when he called its health condition to Investigator Buercklin's attention. A subsequent check of this lab technician's animal observation book on study 9535 disclosed that he had already recorded a health observation entry for that day and had found all animals to be normal.

On 1/25/78, we observed another ongoing rat study known only to us as study "X". Laboratory technician Dirk Shelton was handling this study. We were informed that it was established procedure for the technicians to determine the size of tissue masses by using calipers. Mr. Shelton admitted that he had been estimating the sizes of the tissue masses he observed without making any actual measurements. We learned that a written SOP had been issued to all laboratory technicians directing them to record their animal observations into their animal observation logs at the time they made their observations. In spite of this directive, Mr. Shelton had maintained his 1/19/78 written observations on this study on paper towels. We observed that animal #119 was in poor condition and had a granulomatous-like lesion on its left hind foot. Animal #42 had a bloody nose and sore left and right front feet. Both were omitted

from Mr. Shelton's 1/10/78 observations records. Dr. Pallotta detected rats with respiratory difficulties indicating the animals were in extremis and should be considered for sacrifice. This condition had not been recognized by technician Shelton.

Management claimed that it was established procedure to record data at the time an event occurred or within a few days of its occurrence. Records were encountered which indicated that the data had been recorded a year or more after the event had occurred.

Interviews with former laboratory technicians disclosed an established practice which was being followed. This practice was to make a "TDP/TNT" (Too Badly Decomposed/No Tissues Taken) entry into mortality log sheets to account for animals which were lost or had been destroyed by the laboratory technician.

Animal Care

During the inspection, we learned of a health problem associated with oncology studies during 1975/77. Dr. Soave initially informed us that the health problems had occurred in the latter part of 1975 and the early part of 1976. He claimed the problem had been caused by pneumonia and had necessitated the administration of tetracycline to all animals on some of the studies underway at this time.

A later interview with Dr. Sullivan disclosed that chlortetracycline and tetracycline had been administered to all test animals in several studies. Dr. Sullivan described the problem as strep-induced pneumonia. Records disclosed that chlortetracycline had been purchased for this condition as early as May of 1975 (Exhibit VDa). Dr. Sullivan admitted that he had prescribed both the chlortetracycline and tetracycline for the studies jeopardized by the murine pneumonia. He admitted that he had no idea as to whether or not the administration of these drugs would interfere with or impact upon the studies being conducted. No records of this health problem or the widespread administration of antibiotics were maintained. None of the clients whose studies were involved were notified of the administrations of the drugs.

Drew Watson was responsible for setting up and initially monitoring the medication system (Exhibit VDb). No analysis was made on the dosage administered (estimated at 30 gms/7 gallons water) and if the solution was a pale yellow color it was assumed the concentration was satisfactory. By interviewing current employees who had been associated with the antibiotic treatment of various studies, Mr. Watson determined that 25

different studies had been dosed with either chlortetracycline or tetracycline. A listing of the studies believed to have received these antibiotics follows: 5507, 5746, 6001, 6138, *5555, 6365, *6363, 6138, 4[illegible], 6350, 8022, 7074, 7875, 7876, 6352, 6954, 6644, 6[illegible], 6[illegible], 7037, 5[illegible], 5517, 6002, 6233, and 9563. (* indicates studies given inspectional coverage.)

Additional corrective measures taken to combat the mortality problems during 1975/77 were as follows:

1. Installation of chlorinators in the main water line, in mid-February, 1977 (local contractor C. W. Burns). Clorox bleach (no testing by IBT prior to use) is added, resulting in a chlorine level of 3-7 ppm at watering stations per Edstrom Chlorine Test Kit.

2. Increased housekeeping including cleaning and sanitizing of rooms, carts, and cages. Cleaners and sanitizers used then and now are Pepco D-C Germicidal Cleaner (synthetic detergent), Foam Now (degreaser), and Mikroklene (an iodophor sanitizer).

3. "Bad" studies were moved to various rooms in order to isolate them and prevent transfer of problems to other studies (see Exhibit VE).

4. Personnel access to animal rooms was limited.

None of the studies performed at IBT-Decatur and reviewed by the inspectional participants had utilized a unique animal identification system. Several of the studies involved the gang-caging of test animals. Studies 3205 and 2311 involve the gang-caging of mice (10 per cage). Study #3204 involved the gang-caging of rats (3 per cage). The lack of a unique identification system would have prevented a lab technician from associating an observation with a given animal in the mouse studies and made its reliability questionable on the rat study. Currently, an ear-punch animal identification system is used (Exhibit VE).

From 5 to 6 different mouse studies, including 2311 and 3205, were housed in the same room during overlapping periods. Laboratory technicians admitted that escapes were quite common. The incidence of mis-sexed animals detected at late dates in the studies gives reason to suspect mix-ups. Laboratory technicians admitted that they attempted to return escaped animals to their appropriate cages whenever possible. Their means of accomplishing this without a mix-up hazard could not be determined.

Extra Animals

At least four different categories of extra animal usages were practiced at IRT-Decatur. These categories were:

1. Usage of 10 animals (5 of each sex) for control and each test level for the first four to six weeks of a study. These animals received the same diets as study animals and were used as replacements for animals which wouldn't drink, were mis-sexed, or otherwise couldn't adjust to the environment of the study. These animals assumed the identity of the animals replaced.

2. Extra animals maintained the entire duration of the study receiving the same range of diets as test animals. Final report failed to reflect the actual number of animals tested (Study 2511).

3. Untreated animals which corresponded in sex and weight to animals which died during the study, used as replacements for these dead animals. No records were kept on the replacements. These substitute animals assumed the identities of the animals they replaced. The substitutions took place several months after the study was initiated. (1973).

4. Untreated animals were started on the same diets as test animals well after the study was underway. During the investigation, the term 'mini study' was used to describe this category of extras. At least 3 mini-studies were set up during 1976/77, for longer term studies that were experiencing high mortality. This reportedly was done under direction from Northbrook management. The mini-studies consisted of from five to twenty animals per sex per group of young/specially ordered animals. Animals within these mini-studies were housed primarily in room 206. These animals were fed the same diets as the corresponding test animals. They were checked for abnormal behavior and mortality but not for food consumption or weights. Management explained they primarily needed these animals for histology and that they planned to carry them through for the full two-year testing period. Tissues were collected and saved on post-mortem animals and pathology records identify these tissues as 'extras'. Animals from these 3 mini-studies have been disposed of. There are few records relating to the conduct of the mini-studies.

Early in the investigation, Dr. Goode said they had experienced high mortalities in 75/76, probably due to pseudomonas, and this resulted in "extras" being used. On 1/19/78, Les Morrow first alluded to this category of extras. On 1/20/78, Ken McCollum indicated that Ortho study 5535 would be included in this category. Later in the investigation, 2/24/78, it was learned from Peter Brown that during '76 and '77 there were several 'bad' studies which were involved here. Dr. Brown said that he recalled a meeting in Ken McCollum's office in December of 1975 where Dr. McCollum

assigned these "bad" studies to himself and Drew Watson. Mr. Watson did not recall the specific meeting, but did confirm the assignment of the "bad" studies and the associated followup, including mini-studies. The above four individuals identified the following as "bad" studies: 6365, 5533, 5287, 5129, 5510, 5346, 5347, and 5000.

Mr. Brown said that study 6363 later became a "bad" study but that a mini-study was not set up for it. Records indicate that the other studies did have parallel mini-studies. Mr. Morrow said that mini-studies for studies 5346 and 5347 had been requested by the client.

Apparently responsibility for setting up and closing out these mini-studies originated at Northbrook. Les Morrow said that he knew that Jim Plank and Keplinger had contacted Ken McCollum several times on the mortality problems they were having in 1975 and on. Mr. McCollum said, "Yes, I did talk to Plank and Kep, they saw status reports and were aware of the high mortality."

Mr. McCollum also said that much of the time, Plank and Keplinger also talked to John Goode about this. He said that he had discussed the mortality problems many times with Dr. Goode and that Dr. Goode had told him to order animals and set up the extras. Ken McCollum said that, although he could not readily locate them, he felt there were receiving records for the new/specially ordered animals used in the "mini"-studies. Mr. Morrow said that Dennis Lindberg and Dr. Goode were in the animal rooms during the mortality problems and knew what was going on.

Drew Watson said that in his opinion, the decision to set up the mini-studies was made at Northbrook, probably by Dr. Keplinger. He said that he felt this way since if Ken McCollum had a decision he couldn't resolve, he would call up Keplinger. He made the same general comments regarding the disposition of the animals. Mr. McCollum said that his discussions regarding disposition of these extra animals were with Dr. Goode. No records could be found regarding the final disposition of these extra mini-study animals. Mr. Brown said that these animals were disposed of by putting about 20 rats at a time in a plastic bag garbage can liner, taking these animals to autopsy, and gassing them with CO_2 there. He said that Ken McCollum told him to do this.

Information on post-mortem animals processed by pathology had previously been reviewed by Dave Billerman, IBT histopath technologist, at the request of Walter Hansen. Mr. Hansen related the following "extras" figures: 4921 (122), 5287 (12), 6365 (186), 5346 (192), and 5347 (153). Billerman said the figures he gave Mr. Hansen were obtained from path sheets. He said that when Mr. Hansen requested this information, that he recalled some of the studies that had "extras" and then he went to the archives to check

the corresponding files for "extras" path sheets. He said that path sheets were prepared only for RM's "extra" animals and these RM's were autopsied and tissues were saved. He said that he had no recollection of disposing of "extras" when the mini-studies were stopped and they had no records covering this. He said that he did not even exactly recall the time that toxicology disposed of these animals since many times toxicology would bring up animals in plastic bags and they would gas them in the laboratory and then pathology would dispose of them in the incinerator.

As is evident by the above discussion, records relating to "mini" study extras are scanty. A "Daily Mortalities Log" (Exhibit VI) which partly, according to Les Morrow, is source data, has some information. Les Morrow said that the reason for keeping these records was that it gave them a summary for ready reference purposes in evaluating the overall mortality problem. Mortalities for mini-study extras (Note that most are in room [illegible]) are sometimes identified as "Ex". In addition, these records have information on the number of studies being run in a single room, the general picture of mortalities and other information over a specific time period, movement of animals from room to room, information on bleeding deaths, and other entries.

Test and Control Substances

This section describes "generic" problems relating to the receipt, testing, and handling of the test substances in diet preparation in the rodent toxicity department. Included here are general observations on audited studies, (2311, 3204, 3205, and 5533) and Bureau of Foods study 5600 and information from employee interviews, other studies, and current operations.

Machete

Test and Control Substance Characterization

Upon receipt, test substances were not tested for identity, strength, or purity prior to use, and no sponsor certification of such was on file. The only information known about the test substance prior to use was that which was on the container label and/or receiving records. Currently, container labels generally bear the test substance name and/or study number, and possibly lot number, and date but not expiration dating or appropriate storage conditions.

There were no stability tests or reserve samples on the audited studies and currently this is not a practice unless requested by the client.

Test and Control Substance Handling

Most test substances have been received through the IBT-Northbrook, Illinois facility. Receipt is a responsibility of the Project Center, a section of the Quality Assurance Department.

Receiving records of test substances have been kept in one form or another since September of 1972. The 1972 and '73 receiving records were kept in a yellow loose-leaf 5 x 7 paper tablet. The remaining records from [illegible] to June 10, 1977, were kept in bound log books. Since June 1[illegible], 1977, receiving information has been recorded on a "Test Material Log" tablet. Information recorded in these logs contains basically only that information that would be on the shipping records and/or label of the product. In many cases, no lot number or purity was recorded. Examples of the types of receiving records being kept are submitted as Exhibit [illegible]. In-house distribution/control records for test substances were limited. Records found were running inventory type records (Exhibit [illegible]) and/or sparse general test substance withdrawal "Test Material Use" records (Exhibit [illegible]) available for only the period 1/3/74 through 10/28/74. These records were not always accurate.

Present storage conditions of test substances and base diets were deplorable, as discussed in the previous Facilities section of this report.

Mixtures of Substances with Carriers

Analytical testing of diets (mixtures) has been minimal (none of the audited studies and others only on client request). Although there have been recent improvements, results indicate test animals may not have consistently received the prescribed dosages. Prior to 1977, no diets were tested for stability and no reserve samples were obtained.

Due to the lack of analytical testing and associated records, an effort was made to interview involved personnel (past and present) in order to evaluate as well as possible the firm's capability in the diet preparation area.

1. Dr. John Goode said that he felt they were getting a homogenous mix in their diets. He based this on a NCI paper or report, which evaluated the design and adequacy of Hobart paddle/knife mixers similar to IBT's. His evaluation was not made on actual operations or sampling done at the Decatur facility. In addition, Dr. Goode mentioned that without methodology, there would be no way they could test the diets and/or test materials and thus he indicated that he felt it was a client responsibility to initiate such testing.

2. Ken McCollum said that in general, samples have been and are being analyzed only on client request. Records in the test material inventory log (Exhibit VII) show that between September '75 and March '77, about 45 samples were sent out for analysis. There were no corresponding records prior to this time period. Ken McCollum could not recall any specific instances where they got analyses back, and could not readily locate any sample results. He said that in most cases, they were not getting feedback from their clients, and if they did get feedback it would only be because there were problems with the analysis. He said that some of their clients did collect diet samples when they came to the plant for tours, but they had never responded back so he assumed the results were satisfactory. In general, regarding analysis of diets, Mr. McCollum said that IBT management did not tell them to check closely on this and he felt that it should have been their responsibility to do so.

3. Blair Wingard, diet prep supervisor from May '75 through October 7, said that he did recall sending some samples to Northbrook in care of Ronald Wingeder. The studies he could recall on which samples were submitted to Northbrook were 4149, 5746, and 5608 (Bureau of Foods study). The Bureau of Foods study is discussed under a separate heading of this [illegible]. No records were readily available for study 5746, but study 41[illegible] was in Messrs. Morrow and Wingard's office (apparently in the report preparation stage) and Mr. Wingard offered to go through records and determine what was there on diet prep.

The final report for IBT 621-[illegible] dated March 26, 1976, shows that this study was done for Nihon, Nohykau Co. Ltd., and was a chronic oral toxicity study on 450 albino rats. Mr. Wingard's review of the file revealed only scanty and inconclusive diet and test material analytical results. Documents that he could find in the file relating to this are submitted as Exhibit VIa. In addition to the information obtained by Mr. Wingard, additional information relating to diet prep and sampling was obtained from other logs and is submitted as Exhibit VIb.

Mr. Wingard said that there were no records kept of samples collected and submitted when he worked in diet prep. Regarding feedback from clients and/or results from Northbrook, he said they did get some information back (always came first to Ken McCollum) but not much. He made the general comment that they were not right on the nose, were sometimes off, and sometimes they were close, but generally variable. He said that the problems they might have had in preparing the diets was the storage of premix for long periods of time (i.e., 2310/11 up to 10 to 15 weeks) before the last of the particular premix batch would have been used up. He did say that "extra" premix was stored in labeled plastic bags in the freezer.

4. James Kush assisted Mr. Wingard in diet prep during 1975 and was supervisor from October 75/77. He said initially there were hardly any samples sent out but that this increased in 1977. When samples were collected, they were at the client's request and were sent to Northrup. His recollection of studies sampled were the Bureau of Foods study, which he recalled had variable results, and a Standard study [illegible], in which they were checking calcium levels and in which analytical levels were apparently lower than expected. His evaluation of the adequacy of the job he was doing in diet prep was as follows: "No way to be sure, just added test substance and mixed".

5. Ed Haynes, diet prep assistant for the last two years, has been responsible for the day to day production of diets during that time period. He said that he has no knowledge of any records of analytical results and he just assured they were doing a good job.

6. Steve Dertsch has been the diet prep supervisor since October, 1977. He said that he was trained on the job and that Ed Haynes showed him how things were running, Les Morrow helped him with the calculations, and Jim Kush also assisted him.

Samples which had been collected since about June 1, 1977, are recorded in the Diet and TV Sample Shipment log. Evidently, there has been a tremendous increase in client interest in this area over the last several months. Mr. Dertsch said that they currently have seven clients which have requested analysis of feeds and/or test materials. These clients, types of samples requested, and reports of analysis Mr. Dertsch could locate are summarized in Exhibit VJ. Results appear to be well within acceptable limits. Mr. Dertsch said that he didn't know what they could attribute the improvement in this area to, but mentioned the immediate use of premixes and possible stability differences in test substances.

Although the current results showed a marked improvement, it should be noted that the analytical results shown in Exhibit VJ do not represent all or even a significant percentage of the samples that were or should have been collected, but only selected ones. Because of this, previously mentioned findings, and current diet prep deficiencies listed below, it is difficult to determine if in fact the diet prep area has the capability of producing a diet with the expected levels of test materials.

Current Diet Prep

Actual feed preparation and record keeping procedure at the present time are discussed in a three page "Diet Room" SOP. This record and associated documents are submitted as Exhibit VK. The SOP was prepared by Steve

Bertsch and reviewed by Ken McCollum. Mr. McCollum said that procedures in this SOP reflect generally what they have been doing since they began in 1972. In addition, reportedly equipment, including mixers and scales, has remained the same over the years of operation at IBT-Decatur.

A brief review of actual procedures used in the production of diets for IBT study #10363 on 2/8/78 revealed the following objectionable conditions which were pointed out to Mr. Bertsch at the time they were observed:

1. Test material premix was stored in an unidentified [illegible] gallon plastic drum during the mixing of the feed. Mr. Bertsch said that only he or Ed Haynes make the feed and since they only make one diet at a time, there is not much chance for mixup.

2. A Hobart scale, model 7212, with 50 gram gradations was used to weigh out exactly 2000 grams of test material premix. They do have an electronic Torbal balance that has a 2 kilogram capacity with 1/10th gram gradations, but apparently this scale is used only to weigh the smaller quantities of test materials and/or premix.

3. Mixing kettles used with the Hobart mixers 1 and 2 are not adequately cleaned between batches. Reportedly, the kettles are washed two or three times per week and they are brushed out and wiped with a wet sponge between mixing of batches. Investigator Grundstrom observed Mr. Haynes brush out the kettle between different group level diets for 10363 and the residual material in the kettles was merely brushed out onto the floor in the diet prep room. Mr. Bertsch said that they had requested that they get vacuum cleaners.

4. "Clean" feeding jars and metal kick plates in the diet prep room had feed residue caked on them and did not appear to be clean. In addition, the "finish" on many of the jars was damaged, which may result in "lesions" and additional stress being put on the animals.

5. A used feed bag in the diet prep room area was being utilized as a container for scrap feed and test material premix wastes, and was not adequately identified.

6. Glass jars used for feed containers are not individually identified during feed consumption studies and this may lead to mixups. The method being used by the firm is that one jar on each tray of 30 is identified by a color coded paper tag

placed in the jar which also contains the test level and the study number. In addition, on the tray under this designated (corner) jar, they also place a piece of masking tape with the study number. Although no actual mixing were observed, the possibility for problems is there.

Closest thing to a direct accusation

Protocol

The protocols associated with the studies which we reviewed were unsigned, unsigned documents. Those used for studies 3204, 3205, and 2311 consisted of a total of 3 pages each. Beyond the cover page, all entries were triple spaces. Although studies 3205 and 2311 involved mice as the test animal, the second page of their protocols discussed rats as the test animal. None of the protocols mentioned the stability of the test substance. None of these protocols specified any method of animal identification nor were the types of housing to be employed mentioned. While the protocols for the studies 3205 and 2311 specified the usage of 400 mice each, at least 640 mice were used for each of these studies.

Monsanto ACL machine

Ramsey ACL

The protocol for study 3205 apparently was designed for Monsanto Company's Ramsey that was altered to read Monosodium Cyanurate. There were alterations of the protocols for 2311, 3204, and 3205, but the identity of the alterer(s) or the date(s) of the alterations were not indicated. Dr. Paul L. Wright, a former employee of IIT-Northbrook and currently a Monsanto Company employee, was identified as the individual responsible for the protocols used for studies 3204 and 3205. Dr. Wright was an employee of the Monsanto Company when the final report on study 2311 went to Monsanto Company. The correspondence encountered in the data pertaining to 3204 disclosed that Dr. Wright had reviewed the final report for this study when it was in rough draft form.

ACL

modifications to protocols by weapons

Machine

None of the protocols specified the types of records to be maintained.

Conduct of a Non-Clinical Laboratory Study

None of the studies which we reviewed had been conducted in accordance with their protocols. The protocols relating to studies 3205 and 2311 both specified daily observations for abnormal reactions and weekly observations for signs of tumor formation. It was known before either of these studies was initiated that these observations would not be made.

Knowledge of falsity

As previously mentioned, much of the data reviewed was not the result of a recording made concurrent with the observation. The data provided to us concerning study 3205 consisted of photocopies of records and not original

documents. Other data reviewed omitted the identity of the recorder and in many instances the date recorded on the document differed substantially from the date when the actual entry was made. The person who "witnessed" the entries in the mortality log book admitted that his signature was to indicate the data was in the log book on the data he witnessed it. He claimed his signature was not an attestment to the accuracy of the data therein.

Reporting of Non-Clinical Laboratory Study Results

ACL machete

Final reports issued to clients covering studies 621-[illegible], 621-[illegible] and 621-02311 contained statements which were contrary to fact. Another final report on 621-06363 concealed the fact that untreated substitutes had been used as replacements for test animals well after the study was underway. The client for this study had received the final report and reportedly had not been advised of the usage of replacement animals.

In some of the studies where final reports made claims for observations that weren't made, the clients were believed to have been well aware of the situation prior to their submitting the final reports to the U. S. Government. In at least one instance, the client is believed to have been knowledgeable about the usage of unreported extra animals (study 02311) prior to the submission of the final report to the Environmental Protection Agency.

machete

Monsanto Company and other co-sponsors (Olin and FMC Corporation) were aware of kidney problems associated with the treating of Monosodium Cyanurate prior to initiating studies 3204 and 3205 on this compound. There were indications that the kidney problems were deliberately overlooked in the conduct of study 3205 in spite of the client's awareness of the problems.

ACL

More detailed information concerning specific study deficiencies has been given in the specific study reports accompanying this inspectional report.

EXIT DISCUSSION

On 3/1/78, Investigators Grundstrom and Buercklin held an exit discussion with management. IBT personnel attending this discussion were:

Dr. Harrie M. Phillips, President
Dr. John Wennear, Vice President - Director of Research
Ray Roman, Vice President in Charge of Finances
Yvonne Bonahoom, Quality Assurance Director
Fred R. Current, Corporate Counsel

Exhibit VJ1 - Current diet analysis results.

Exhibit VK1/VK5 - "Diet Room" SOP and associated records.

Exhibit VL1/VL25 - Rough draft copy of transcript of the [illegible] exit discussion with management.

Kenneth O. Guercklin
FDA Investigator

Wayne [illegible] Grundstrom
FDA Investigator

Walter F. Hansen
FDA Pharmacologist

Arthur J. Pallotta
EPA Consultant

Larry D. Anderson
EPA Pharmacologist

Powell A. Davis
FDA Pharmacologist

kjs