UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

14 SEP 1978

OFFICE OF TOXIC SUBSTANCES

Dear Registrant,

Since our request that registrants perform an audit of studies performed at Industrial Biotest Laboratories Inc., many registrants have contacted both EPA and Canada's Health Protection Branch (HPB) with questions regarding the actual performance of such an audit. In addition, several audit reports have been submitted which are unacceptable.

In order to assist registrants in the validation process, EPA and HPB have scheduled a meeting which will give you an opportunity to ask questions as well as discuss common or unique problems. The meeting will be held on Tuesday, October 3, 1978 at Howard Johnson's Airport Hotel, 2650 Jefferson Davis Highway, Arlington, Virginia 22202 from 9:30 a.m. to 5:00 p.m. It is requested that each registrant send no more than two representatives to the meeting.

EPA and HPB have developed a manual in response to inquiries received from a number of registrants concerning the approach to be taken in auditing and validating IBT studies. This manual will be sent to you under separate cover prior to the meeting.

If you have any further questions regarding the meeting, please contact Fred Arnold or Ann Dizard at 202-755-8026. We appreciate your continuing cooperation in this matter.

Sincerely yours,

Robert V Brown for

William A. Wells
Acting Director
Special Pesticide Reviews Division

U. S. ENVIRONMENTAL PROTECTION AGENCY

Arlington, Virginia
Tuesday, October 3, 1978

INDUSTRIAL BIO-TEST LABORATORIES, INC.
AUDIT MEETING

The proceedings in the above-entitled matter was held at the Howard Johnson Motor Inn, Banquet Room, 2650 Jefferson-Davis Highway, Arlington, Virginia, commencing at 9:45 o'clock, a.m.

PANEL MEMBERS:

FRED T. ARNOLD
Acting Branch ~~Chief~~ Chief
Regulatory Analysis & Lab Audits
Special Pesticide Review Division
U. S. Environmental Protection Agency

DAVID CLEGG
Head, Pesticide Section
Foods Directorate
Health Protection Branch
Health and Welfare, Canada

DR. ARTHUR PALLOTTA
Consultant
Special Pesticide Review Division
Office of Pesticide Programs
U. S. Environmental Protection Agency

DR. LAMAR B. DALE
Acting Chief
Toxicology Branch
Hazard Evaluation Division
Office of Pesticide Programs
U. S. Environmental Protection Agency

FRANK SANDERS
Product Manager
Registration Division
Office of Pesticide Programs
U. S. Environmental Protection Agency

JOHN ULFELDER, ESQ.
Attorney
Office of Enforcement
U. S. Environmental Protection Agency

MITCHELL BERNSTEIN, ESQ.
Attorney
Office of General Counsel
U. S. Environmental Protection Agency

P R O C E E D I N G S

MR. ARNOLD: Good morning. I guess we might as well get started. We are still missing one of our panel members and I expect that people will come wandering in here for the next few minutes, but we've got some introductory comments to make and some discussions that are sort of general to cut across all the issues that are related to the IBT validation effort.

My name is Fred Arnold. I'm the Acting Branch Chief for the Regulatory Analysis and Lab Audits in the Office of Pesticide Programs and I got involved in the Lab Audit Programs several years ago.

We intend to deal with questions relating to Industrial Bio-Test as a separate issue from the rest of the joint audit programs which are being carried on cooperatively with the Food and Drug Administration.

Ed Johnson, the Deputy Assistant Administrator of Pesticides and Steve (Jolnick), Assistant Administrator, both asked me to extend their welcome to all individuals who are attending this conference. They have taken a very active role in our Lab Audit Program and, particularly, in questions dealing with Industrial Bio-Test.

As you are no doubt aware, the questions which were

raised by findings of the Food and Drug Administration, when they performed the first audit at Industrial Bio-Test, raised extremely serious questions for the pesticide regulation process because we do have a rather large number of Industrial Bio-Test studies in our data base.

This is particularly important now since the Agency is finally beginning to move forward on the re-registration effort and, since there are 4,500 tests in our files from IBT, all of which are subject to some scrutiny and question right now, it's an extremely critical piece of information in that process.

For that reason, we have devoted a substantial amount of resources to, first, try and determine in our own minds the kinds of problems that may have been encountered in testing performance at IBT and whether those problems create any kind of a significant question for us in a regulatory vein.

We have determined that they are serious based upon approximately 12 detailed study audits which we completed at Industrial Bio-Test and from the continuing findings that we get as registrants submit validations to us. It's, I am sure, a very serious question and issue from the point of view of sponsors of other studies and registrants who have submitted

IBT data to EPA or its predecessor agency.

At one time, we discussed what the options of the Agency were. The most extreme would have been to purge our files of all IBT data and either impose a data requirement on the registrants or initiate a more extreme action in the case when the entire toxicological data base was essentially destroyed by that action.

We determined that that was neither in EPA's interest or the public interest or the registrants' interest because a large number of studies, which were performed at IBT, were performed satisfactorily. Our experience has indicated that. I think the experience of most of the registrants to date has indicated that.

There is another subset of tests which, although may not have been completed in the manner in which the report was written and the manner in which the sponsors anticipated the tests were carried out, nevertheless, do provide useful, significant toxicological information upon which we can make findings of safety and upon which registrants can audit their compounds.

There is another subpopulation of the test which we have found are entirely invalid for any purposes, either for

regulatory purposes or for trying to determine the toxicological significance of the compound.

Without a detailed audit to determine where the tests lie, there is no reasonable way that the Agency can proceed, either in re-registration efforts or in making regulatory decisions on the safety of the compound.

So I would like to stress the importance of the effort, although it may appear to be another data requirement which EPA, as ~~some~~ part of ~~a~~ the Federal regulatory body, has imposed upon this private sector.

We don't see any way to conceivably proceed, in a timely fashion, without doing this because, if the registrants chose not to audit the studies, we would either purchase, buy or we would have to devote resources to ourself and that would tie us up for years and also tie up the re-registration process.

To underscore the seriousness of it, we have had a number of discussions with representatives of other Governments. They say they have attempted to understand the significance of IBT and to evaluate whether or not EPA is proceeding in a fashion that will provide sound information for their regulatory decisions.

In two instances, the representatives of other

governments came to Washington with the expectation that they would go home and recommend to their administers that they cancel tolerances and cancel registrations in their countries which relied, in a significant way, on IBT data.

After reviewing our procedures and after understanding a bit more the concept problems and the ability to determine the problems, they both chose to await the results of the validation effort and make their judgments based upon the best available information on each study.

In another instance, we have formed an agreement with the Government of Canada to jointly review all IBT data which either Canada or the U.S. feels are significant, and that is certainly a very small number of the total tests done by IBT.

We are splitting the workload around Canada to review a portion of the tests, the U. S. to review a portion of tests and we will adopt each others conclusions. That doesn't mean that we will adopt each others regulatory recommendations, but we will adopt some of the conclusions and we don't intend to redo each other's work.

The reason that we initiated this conference was to provide some uniformity to the validation effort. We think that we have a perspective on the types of testing procedures

and other problems that you will come across as you review your individual test data and, rather than attempt to answer individual questions as they come up, which would slow you down and it would certainly slow down the process of determining the acceptable and the unacceptable tests, we prepared a manual. It's kind of a guide to, first, how do you perform an audit, and, secondly, what exactly would the records look like and how the records are reviewed in an orderly fashion. It's not mandatory. It's meant just as a working guide to assist registrants or consultants as they review their individual data.

We have also prepared -- and I think it was distributed this morning -- an outline for submitting a validation report. Again, that's certainly not mandatory. It's a format which we have found extremely useful in preparing our own reports as well as useful in reviewing the work of others. It's one that has been used by a number of sponsors and they have found it an acceptable method to report their findings.

We met last evening with representatives from Industrial Bio-Test to discuss the current status of their Validation Assessment Team, the current status of their microfiche efforts, and they asked me to pass on several general comments that are going to be of interest to everyone, and requested

that any questions that you may wish to pose to them, that you do it individually, either during a break or after the meeting. They will be available this evening after the conference.

They have requested that to avoid any possibility of making a general comment or a specific comment to one question and having it interpreted as a general policy.

The first point that I would like to bring up regards the status of the microfiche effort at IBT. They have completed the microfiche of all product studies which were completed and mailed out to sponsors as of January, 1978. Chronic studies include all studies 90 days and longer. The only exception to that are about ten studies which are currently being completed in a file which they have characterized as a bits-and-pieces file.

That file will contain individual pages or a very small number of pages that had no major data base within their files. The bits and pieces were correlated with the idea that, after all the studies were copied and sent to registrants, the bits and pieces could be merged into those studies or, to the extent that nothing was related, nothing was available except the bits and pieces file, they would be sent on to the registrants.

The bits-and-pieces file, by itself, is not sufficient to carry out an audit. It is not a major data base. Therefore, if you haven't received microfiche copies of the studies, to date, in all likelihood you will not receive a large body of data upon which to prepare a validation report.

If there are studies you are interested in and they fall within the chronic classification, and you haven't received them, I suggest that you take action on your part to contact Industrial Bio-Test, because addresses have changed over the years, mail delivery is variable, there is a possibility that the studies have been microfiched and you have just not received them but, if you determine that they have not been sent to you and all that remains is bits and pieces, I suggest that you don't exert any resources towards attempting to validate that study because there won't be any data base upon which to do that.

They have commented upon time records which are available at Industrial Bio-Test. These records, we have found, are useful in terms of determining starting and ending dates on some studies for which the records are incomplete; for determining the individuals who are responsible for carrying out the studies.

Prior to 1972, there is difficulty in going back to the time records because they are on individual time and

accounting sheets. Post-'72, they have been computerized. So to recall them will be much easier.

Again, this is an issue that, as you visit IBT, if you determine that it is important to substantiate the beginning or the ending or determine who is involved in a study, you can deal individually with them. Prior to 1972, there will be some difficulty.

We have suggested a review of animal ordering receipt records. IBT informs me that, in many cases, animals were received or ordered, not for an individual study, but for en masse to service a number of studies which were going on at the same time. So that, by itself, may not determine your population size if the records are incomplete in that area. It's a possibility, but it's not something that is always going to provide the information that you may want.

The records on the receipt of test material are available at IBT. In most cases, a substantially larger amount of material was sent by sponsors than was actually necessary to complete the studies at Bio-Test.

Certainly, if you determine that less material was actually sent to IBT than was necessary to complete the protocol, that ought to be a flag of a problem, but the fact that more

was sent is of no particular concern to us, nor should it be of any particular concern to you.

For those of you who haven't dealt personally with Industrial Bio-Test in the validation effort, we have received copies of their Validation Assessment Team procedures and guidelines. We have, I believe, made some copies of those and they are available this morning, and they will define the relationship between sponsors and IBT as they, again, attempt to work together to resolve questions which cannot be resolved through review of the microfiche alone.

I would like to point out that Industrial Bio-Test has been willing and continued to operate in this effort. However, they are not providing the resources to perform the audit for sponsors. Their resources are there to resolve unanswered questions, to provide guidance to individuals, and may be contacted to shed some light on a particular phase of a study, and to provide assistance in reviewing the records at IBT, but they will not initiate validation efforts on their own, nor do they expect to take a substantial part in defining areas for validation which the sponsors have not initiated on their own.

IBT does have the pathology material under the same storage system which they have utilized in the past. It's a

private subcontractor who maintains all the slides, tissue box -- that material. In the instances when we have attempted to look at pathology material, it has been available. We are satisfied that the current method of handling and storing that material is satisfactory.

I am aware that some questions have arisen regarding the ultimate ownership of pathology material -- whether it belongs to the sponsors or whether it belongs to IBT. Bio-Test has taken the position that they will remain in the custodial role and that they will make that material available to registrants and sponsors on an as-needed basis. Their facilities will be available; their lab facilities. However, they will not provide the technician's support nor the pathology support. You either reread or prepare new pathology material.

In several instances, registrants have employed consultants to carry out this validation effort. Bio-Test has requested that we point out that the consultants must have a written authorization from the sponsor before they can release the records and material to the consultants. Upon receipt of that authorization, they will cooperate with the consultants in the same way that they have attempted to cooperate with us and the sponsors.

That also goes to the situation where the original sponsor of a study has subsequently either sold the registration rights or the data to a second registrant. In that instance, they would need authorization from the original sponsor to provide access to the subsequent owner.

Any questions dealing with any study which has been closed out at IBT, where the final report has been prepared and mailed, should be referred to Fred Current or a member of the Validation Assessment Team, and that goes whether it deals with a validation effort or any other inquiry on an IBT study.

They are continuing negotiations with several individuals on the sale of the assets of IBT. That does not include any of the past records or their validation effort. IBT will, regardless of the subsequent sale of the assets, remain a corporation for the purpose of assisting in the validation effort and for retaining and managing the records of all prior studies.

We have had the opportunity to review a number of validation reports and, when I say "we," that goes for Canada and the U.S.

Dave Clegg has completed 45 audits of all types of studies carried on at different times. This certainly is not

an exhaustive nor a statistical sample, but his results, to date, are that 16 of the studies are completely invalid for any purpose for which they were originally intended. Five or six of the studies, although they are deficient in significant areas, do provide a substantial body of information upon which we, as regulatory bodies, feel we can make decisions. The remainder of the studies appear to be completely valid for all the purposes for which they were originally submitted and will continue to be valid for registration in pesticide matters.

The major problem areas have been in the chronic studies. That's been Mr. Clegg's experience and that has certainly been our experience. I would say that our experience has been similar to this and, in addition, the early vailidation reports which we have received, our policy has been to review the entire microfiche data base, to gather an understanding of how the registrants are proceeding with the validation and to assure ourselves that we are making consistent decisions with our colleagues in Canada.

We haven't found a single study, to date, where the microfiche is fully consistent with the validation report. The kinds of problems that we are seeing are, I think, random errors in reviewing records, transcribing tables and reperforming

certain kinds of numerical, statistical analyses. I would suggest that it's going to be much more efficient if the original effort on the validation is a rather intensive effort, rather than having to bounce back and forth a number of times.

We will continue to review all the microfiche data until we feel we have learned enough to establish a reasonable kind of sampling process. So that we can sample for key assumptions and conclusions and satisfy ourselves that the validation report is truly reflective of the raw data and should stand by itself in our registration files.

We have attempted to consider large aggregates of the raw data, which are available at IBT, to determine the bare minimum data requirements beyond which we don't feel the validation is going to be fruitful.

If you will refer to the proposed outline, which you were provided with this morning, if there is no material, no data, that relates to test material in dosage levels, that's been a key problem that we have observed in IBT studies. Lack of control on the way diets were prepared, the way test material was administered. If there is no material on that, our suggestion would be do not proceed with your validation effort. It's a fundamental piece of information. If it's not available, all

the remaining conclusions are very hard to construct.

The same goes for information on body weights. If all you have got relating to body weight is whatever is in the report which you received and subsequently transmitted to EPA or the Food and Drug Administration, we suggest you not proceed with the validation of that study.

In the case of a pathology study, if you have no information on the mating procedures which were utilized, again, that study probably is not going to be one which can be validated or one which we would accept as a sound basis for making our determination on that test.

Gross autopsy sheets or records must be available on all animals for which histopathological material was taken. If that information is not available, we suggest that you not attempt to proceed with the validation of that study.

Also, as kind of a guideline, about 75 percent of the gross autopsy sheets are to be available on all animals in the test, regardless of whether there has been pathology or not. That's kind of a guideline, but we found a number of instances where observations were made at the time of gross autopsy and were never followed through in histopath. So tissue mass was never commented on later. It has been a significant enough

problem that we have identified this as being a fundamental piece of information which we will require.

Certainly, all the records relating to histopathology must be available.

In the area of animal accountability, the guideline which we have used and will continue to use is that any animals which are unaccounted for -- the raw data -- should not be used to form conclusions or findings which are submitted in the validation report.

If the protocol calls for 25 animals, per sex, per group, and only 15 animals can be accounted for from the time they went on test material until the time they went into pathology, then that's the population you ought to deal with in the validation report and ignore any conclusions on the other ten animals which may have been introduced midstream in the study or for which various cryptic notations will be found in the raw data.

That pretty much covers the introductory comments that I want to make. I will say that the stenographer is here at the request of Industrial Bio-Test to maintain a record of this meeting for purposes of assisting in later validation assessments. They have informed that, if anyone wants a copy

of the transcript, they ought to contact the stenographic service directly. The firm is here in Washington. It's Stewart, Poe & Oglesby, 711 - 14th Street, Northwest, Washington, D. C. 20005, and you can contact Ann Tipton, who is the stenographer today.

I would like to introduce the members of the panel here, and take this opportunity to thank them for their cooperation that they have provided to myself and others who have had to attempt to steer the course and where we are going with IBT.

This is a corps of people upon which all major decisions are discussed and they represent various views, both of EPA as well as Canada.

On my extreme left is Mich Bernstein who is with the Office of General Counsel. He has advised us on data requirements under (PIFRA) as well as certain regulatory positions that we have discussed in the past.

On his right is John Ulfelder with our Office of Enforcement. The Enforcement individuals get involved in Lab Audits when questions of the nature raised by IBT become apparent because they have legal as well as scientific issues related to them.

On my extreme right is Frank Sanders who has been

attempting to coordinate the efforts of the Registration Division in their ongoing registration process with the procedures and guidelines which we have been developing to review the IBT data.

I know a number of you, your first contact with us may have been not because of a prior test which was performed but because of an ongoing registration action where IBT data was cited as the basis for an amended use or as a tolerance.

Frank will be available to discuss the current operating procedures and guidelines within the Registration Division. I will request that we take any issues dealing with the registration status first and then deal with the more general questions of validation after Frank has had a chance to respond and, that way, we won't tie up his valuable time all day long.

Lamar Dale is the Chief of the Toxicology Branch of the Hazard Evaluation Division. He represents a major scientific resource which I have at my disposal to review the IBT data as well as to determine the significance of the anomalies which are uncovered.

Actually, there are very few tests ever performed -- long term tests -- that are done exactly as the protocol might have originally stated. The variability in animals is enough

to account for that and we've relied upon L.D. and his staff to guide us in the significant questions of validity and attempt to ignore those which are just due to random fluctuations that might be expected at any time in any facility.

Art Pallotta many of you may know. He is a consultant who works full time with me on IBT. He offers perspective not only of toxicology but also of administering Bionetics prior to Litton's purchase of Bionetics. So he is familiar with the kinds of problems that are encountered in testing as well as the test procedures which were the state of the art at various times in the past because, in the validation effort, we judge the quality of the study against the standards of the time. Not against the standards which are proposed today or may be proposed two years from now.

Dave Clegg is with the Health Protection Board in Canada. He has the same function that we do to determine which tests are valid, for pursuing scientific questions and regulatory decisions.

The procedures which they have suggested to us for cooperation have proved extremely satisfactory to date and we certainly anticipate that it is going to save resources for our individual governments as well as reduce the amount of time

which will be required to review all of the IBT data which we have identified as being critical to our decision-making.

John Ulfelder has several comments that he would like to make to provide a bit of a background for the Enforcement Division's perspective at this time.

MR. ULFELDER: I am going to be brief and to the point. I am here in a sense, I guess, to represent the heavy hand of enforcement, but, basically, this is a scientific workshop to outline the procedures that you all will have to follow in auditing and validating IBT studies.

It's not a fishing expedition by the Agency. As you know, the Government has two major responsibilities here. One is we have to make a series of regulatory decisions about products that are on the market and questions that may have been raised about their safety or the hazards they pose.

Validation procedure that IBT is assisting us with and that you all will be principally responsible for is designed to try to raise some of the questions on these individual studies relating to specific products and chemicals and to give the Government some base for making further decisions about what may or may not have to be done on a product-by-product basis.

The second area that we are concerned with is in areas

where problems have been pinpointed. What kind of responsibility is there? Where do the problems come from? How do they arise?

I would just like to urge that, in the course of conducting your own audits and validations, if you come across information which you have reason to believe is important information that the Government or EPA should know about how a particular study was conducted, we would expect you to focus in on that information and inform us what you may have found. This is aside from -- obviously, the basic job here is to determine whether a particular study is valid or invalid.

We are also concerned about possible reasons for the invalidity of particular studies.

I would just like to point out, also, in conducting your own validations, on page 77 of the Manual, there is a form -- Certification Form -- which is expected to be filed with your validation report and that Certification Form makes it absolutely clear that the Government expects the validation to be completely accurate -- as accurate as possible -- and certainly not falsified in any respect.

These forms will be signed by responsible representatives of the individual firms undertaking the validation.

This meeting, as I say, is principally to answer your questions about how you can go forward and conduct an audit and validate a study, and how you can, from the scientific point of view, come up with the answers to the question of whether the study is valid or invalid, and that should be the focus of this meeting.

I am just here to be responsive to any questions that may arise that relate to aspects of this process that relate to EPA's enforcement responsibilities, but we have a group of people here, who have been working hard on the problems and questions that are involved here, and are prepared to try to give you the best guidance they can, so that the documents you prepare are the best we can possible do under the circumstances.

MR. ARNOLD: Thank you, John. I'm going to ask Art Pallotta to quickly review the concepts and the experiences which he utilized in his preparation of the guide for validations. Art was the principal architect of this.

Certainly a number of people reviewed it and contributed towards it but, basically, Art felt that it was an important piece of information which should be shared with registrants and which would substantially reduce the effort and resources that would be involved in this.

I would like to make on additional point. In instances when you come across a study which either because of the data which indicates it is invalid or lack of data upon which to perform a validation, you, in your own interest, probably should begin either submitting an additional study, which you may know of or which you may have in your files which was not referenced in the original submission, or originate new testing in that area. New tests certainly ought to be carried out in conformity with the guidelines today, whether it is attempting to redo a test as it was done eight or ten or five years ago, rather than wait for the Agency to notify you of a data gap, which could come up either in the reregistration process or, in the event that it is a more significant concern of the Agency, we may contact you upon our determination that the study is invalid, to attempt to spread out the testing requirements which, certainly, are becoming large to the Office of Pesticides Programs in toxics and a number of other external factors.

In the case of an invalid study, if it is a requirement of registration, you won't be wasting your time to initiate a study at this point.

DR. PALLOTTA: I think, first of all, we should probably say why we drew up the guide and also why the meeting.

A number of validations were coming into the Agency which were simplified statements, such as the raw underlying data that, for this study, was reviewed and supports the report submitted to the EPA.

In our experience, in the auditing of these 12 or more reports at EPA, plus the validations that have been coming in that were more complete, it certainly indicated that there were few studies that did not have discrepancies, errors and omissions.

This is a guide that is not mandatory, as Fred Arnold indicated. It is a technique that our team used when we went out to the Decatur facilities and we found it very useful. I hope all of you received the guide before the meeting and had an opportunity to review it.

Basically, in going through it, we found the first and most important thing to do was to review the correspondence files. This gave a very good understanding as to what the intent of the sponsor was and what IBT personnel's response to their inquiries were.

The major point was reviewing all of the data and trailing every single animal in the raw data and eliminating those animals which could not be trailed from their receipt

to the laboratory to their death.

Now, in the case of the types of report, we would like to see you take the reports, that you submitted to the Agency itself, and highlight those discrepancies where, say, for example, body weights were different for a particular animal, and a single line drawn through the erroneous data and corrected data replacing it.

When all the trail is done -- that is, to the end of the study -- if a significant number of animals are missing, and I think, in the vast majority of cases, you are going to find this, then statistical analyses are going to have to be re-done to come to some conclusions.

In your validation reports, also, we would like, as indicated in the guide, in coming to the conclusions of valid or invalid, steps that could be taken to salvage a borderline report.

I think that there is a large number of you in the audience who are certainly familiar, or who have become familiar at least, with the IBT situation, that are experts in the auditing of data. I would like to have some idea of those who would want to go into actual details of the guide versus -- I mean, do you want to go page by page?

The intent was only to give examples of both forms and some of the discrepancies. We have additional discrepancies. This by no means represents all the kinds of discrepancies that were counted. It is only to just give you some ideas of the things that you should be expecting to do in the validations.

Would you rather do it page by page or just open it up to questions and answers? All those in favor of just going right into questions and answers just throw up your hands.

Why don't we go into some of the additional problems? It looks about fifty-fifty.

I think the problems in the manual itself are self evident. We are trying to use IBT forms. We changed, obviously, the project numbers. All compounds are blacked out and so are sponsors.

Some of the additional types of problems that were encountered -- a very common problem was this problem of the extra animals.

There seemed to be at least three and maybe four different types of extra animals that were used. The first group of extra animals were those which were a common practice in the years past, and that is, when the study was initiated, a few extra animals per group were ordered to replace those animals

which would not adapt to the caging or the watering systems that were being used. Then after several weeks -- maybe three to six weeks -- they would be discarded.

The second group of animals were these animals that went on a diet at the beginning of the study and they were gang-caged within a room and not identified except as to the level of test material being given to them. As an animal died, the individually caged animals, they were replaced by one of the animals that was receiving the test material.

A third group of extra animals were those animals which were actually control animals. That is, not receiving any test material, and were used to replace animals that died during the study.

Now, in the audit trail, it was very difficult to find all of these and, certainly, the latter was probably the most difficult because of the lack of recordkeeping on any of the extra animals.

These extra animals in the second category, for example, although they were receiving test material, were not animals that had any body weights taken or were, for example, used for hematology or certain chemistries.

We gave some examples on how we audit trail and

found these extra animals. Sometimes, it was very overt -- that is, the 50-plus-extra group was crossed out and 80 animals were indicated in the protocol.

In other cases, the receipt of animals indicated a very large number of animals were being ordered by a study number but, as Fred indicated, we have subsequently found out that the receipt of animals was not always indicated by project number and, therefore, an audit trail by that technique may be not so helpful.

The final area, where we were able to definitely get extra animals identified, was in the histopathology laboratories because autopsy sheets were either marked GC, EX, Extra -- that type of notation. I'm sure for many of you who have reviewed some of the audit studies, you have encountered many of these types of things that were in the upper righthand corner of the gross autopsy area.

The actual starting dates and termination dates. We have encountered many studies that, although they may have been started as two-year rat studies, for example, actual termination occurred after 18 months. Even in that type of study, we have actually encountered animals that have continued on past the 24 month period, and that's why it is absolutely important

that every individual animal be accounted for. The statistics we performed gave us a great deal of difficulty because of the lack of standard deviations.

That means that, unless you get into the raw data, you could not see the actual standard deviations. So, therefore, in a very large percentage of the test studies, it is going to be necessary that you reanalyze the data by your own statistical methods.

One of the biggest problems we did encounter were the reports were there was no adverse effect. Body weight gain certainly becomes very important at that point because, as you all know, so many times only body weight is effected in histopatholoy and that does not account for the lack or gaining of any body weight.

Certain additional data, as you are trailing animals, would probably lead to the fact that an animal was substituted in the study itself. For example, if you are following an animal by body weight that would suddenly go from 350, in one month or one week, say, down to 250, it would certainly raise your eyebrows, when the animal is in good health with no other clinical signs of illness, that it was most likely a substitution. You should pay close attention to that type of thing,

because we really want to end up only with those animals that we feel secure or have received the animals during the entire test period.

I think Dave had a few examples that he would like to bring up.

MR. CLEGG: Art is being a little unfair on this. He has written down most of my examples and he has used them.

There are one or two which, perhaps, I should mention. One of them relates to the timing of studies in terms of how long was the study performed, as Art pointed out, and, also, the availability of the test material when the study started.

Now, we have come across the 90-day study where the study started on, let's say, the 1st of June. The invoice for shipment of the test material from the firm was the 9th of June, and the diet preparation sheets are for the 12th of June.

In other words, by the time the diet was prepared, according to the raw data, the study has been underway for 12 days for a 90-day study.

This does not necessarily invalidate the study, of course. You can still get some information from it, but the whole base line, which you are working from, has to be altered to deal with an 88-day study or whatever length it is and

conclusions have to be drawn on this sort of basis.

Another area where we have run into trouble is where the raw data base is such that there are very marked changes between the final report which was submitted and the raw data. The type of thing I've got in mind here is perhaps relating to (Coenstray's) determination where, on a number of occasions, we found that the so-called no effect level from the raw data base is lower than the no effect level that was calculated from the final report. In other words, there is a change in the basis for calculating your acceptable data for your test material.

This, of course, is going to have some reflection, or bears the potential of having some reflection, on the regulatory stages of a compound. This is something we will probably get into later on.

Art is happily pointing to one of his, now, giving me something back. Since he is using the example, let him talk about it. [illegible]

DR. PALLOTTA: There are so many. I am sure we will never be able to cover all of the problems, actually. I don't mean that to be accusatory, but really the large number of studies that had to be reviewed -- and I'm sure you will start finding many, many things that we didn't find, but we did

encounter, for example, clinical chemistry or hematology results, in one study, where, actually, the raw data indicated it was entirely different dogs from another study. That type of thing happened also.

MR. CLEGG: Fred, if I can just take the floor for a moment, again. I'm not relating specifically to examples, but one or two things that have been said previously.

For instance, John mentioned the certification form which has to be forwarded. The example in the notebook, in fact, is the one that is applicable to the United States. There is also -- and I think anybody who is involved in IBT who had contacted us has copies of this -- a form which is somewhat different which was sent out by the Canadian Government.

This is also required to be signed. We are finding, in Canada, that, in some cases, what we are getting is the American form which is completely useless from our point of view.

Certainly, we don't have the various rules and regulations that are laid down in there. So it has no meaning at all.

We would appreciate it very much if you would make sure that you send the correct form when you are submitting data to Canada, rather than just copying exactly what is sent to EPA. It saves us a lot of effort in having to go back to firms and

asking them to fill out the right form and then return them to us.

Another point I would like to make as well, which relates to some other comments that Fred Arnold made. He indicated that a study could be considered to be invalid if certain data was missing. However, I think it should be pointed out that it is necessary, from the point of view of both our governments, that some form of validation should be done on these. They can't just be dropped because data is missing. We must have some sort of report indicating why there is no validation and I think this is fairly important.

Similarly on those, if any adverse effects, which would otherwise be missed, are picked up in the raw data which have not been in the final report, then these should be indicated to the government involved because, since the main function of both agencies dealing with this is the protection of public health, if there is some adverse effect we are not aware of, then we're not doing our job efficiently. So it is essentially to have some sort of validation on all studies which have been requested for validation even if it's only a few lines indicating why a validation can't be done in any depth or why a validation shows that the material is going to be

invalid or the study is going to be invalid.

I'm pointing out that, if there are any adverse effects which may appear from that raw data, even though they can't necessarily be validated, they indicate this compound may have (cross generic or inter generic) types of potentials, I think this is essential to both our governments.

DR. PALLOTTA: I would like to reemphasize something that Fred said, also, and that is that both we -- Canada and the U.S. -- have decided we are going to review, not report by report but by compound.

In other words, we would like to have all of the data submitted on a compound before we initiate our actions.

I would also like to emphasize one last point, Fred, and that is, in those studies which you have difficulty with validating and feel they fall into the salvage possibility, that you indicate in the report those steps that you feel would be necessary to salvage.

A VOICE: A point of clarification, Mr. Arnold. You said, for example, if you don't have diet preparation sheets, not attempt to proceed with the audit and I heard Mr. Clegg state that you should continue with the audit with all possible information. Could you clarify this point?

MR. ARNOLD: When I discussed the bare minimum, our conclusions would, in all likelihood, be -- and I'll state parenthetically, certainly feel free to contact us if you feel differently -- that there are fundamental pieces of information that are listed that are critical for us to make a determination that a study is valid; that it can stand alone; that it can remain as a basis for making regulatory decisions.

There is a great deal of other information that may be in the reports which shed some light on the toxicity of the compound or the various characteristics associated with the compound. That's what Dave is talking about.

Review it and find out if there is, in fact, something in that study which suggests a finding other than that originally tendered to either EPA or Canada, but in terms of anticipating that you can prepare a validation report which is going to suffice to meet our requirements, lacking that data, I think it is highly unlikely.

A VOICE: Are you finding cases where diet preparation sheets and dosage feeding level forms are not available for these studies?

MR. ARNOLD: I'll let Art and Dave answer that.

MR. CLEGG: Yes, we are finding quite a lot where the

diet preparation sheets are either incomplete or, in fact, are missing almost totally. However, the majority of cases we do find the calculations which were the bases for determining what amounts of the test compound should be added to the diet for diet preparation. I don't say it is always there, but it is frequently there.

We have also found, in at least one case, that these calculations were inaccurate.

DR. PALLOTTA: Also, the timing for mixing has been a problem in many of the cases that have been reviewed. Where a large batch of mix had to be prepared, mixing only occurred for, say, five minutes and it is indicated in the raw data.

One additional point which we overlooked, and I know it is very important to a great number of you, and that is control animals. We are aware of the fact that common controls were used in a very large number of these tests performed at IBT. We have agreed on the policy of accepting common controls in spite of the fact that these common controls may have been in another room.

I would like to put some caveat on that because we are not fully aware of all of the problems that were associated with common controls but I think, if you received raw data on

your test animals, and no control data, there is a very good possibility that IBT, through the VAT program, may be able to uncover this data, because the animals were in another room.

Now, obviously, timeframe is going to be extremely important. We have encountered where these common control animals were started at the same starting date as the test animals; we've seen them starting just a few weeks prior to; and, sometimes, towards the end; and, sometimes, not anywhere during the study.

So, I think we are going to have to take each of these cases case by case, but, when you have these interviews with VAT, they will do everything they can to dig out the common controls that were used on your study, both negative and positive.

A VOICE: (Inaudible.)

MR. ARNOLD: Let me repeat that question. Can you use contemporary but historical control data to validate one study when the control data relates perhaps to another study?

MR. CLEGG: This is what I was just about to add to what Art said. As far as weight concern, we are trying to get some sort of basis for a common control which would be applicable to IBT studies on a year-by-year basis. As yet, we

haven't been able to do this, because we haven't got enough data.

I can't say that I am very happy about this on scientific grounds, but we are trying to run this as a salvage operation and, if we can come up with something which gives us a reasonable base line for controls which may be applicable to a number of studies, then, when controls are not available, we'll compare them against those controls.

DR. PALLOTTA: I would like to emphasize, though, if there are common controls, they should be used over the historical data.

A VOICE: Have validations for tests, such as bird and fish tests, been offered? If they have, what has been the experience as to whether most of these have been validated or not validated?

MR. ARNOLD: Let me respond, first, and then I will ask someone else to.

We have not requested that kind of data in our review of the files. There have been cases when a pending action had some acute data from Bio-Test which the Product Managers and Registration Division have requested. I haven't seen a whole list of such studies but perhaps Mr. Sanders would give an idea

of what the experience has been to date.

MR. SANDERS: In the Registration Division, we have not received that many new acute studies. From an administrative standpoint, if we do receive acute studies, opinion applications, that study should be validated.

As to the disposition of that, perhaps we can deal with that some other time.

MR. ARNOLD: We haven't, within the group that I work with, looked at any acute data. I think Dave Clegg has had the opportunity to review a small number but I don't believe it is representative. I don't know if he can base a conclusion on it or not.

MR. CLEGG: Well, as far as we are concerned, we've looked at one or two acute studies but only in relation to dermal toxicity and interrelation of toxicity. We have not looked at any wild life studies. The number we have looked at, I'm sorry, I can't give you any indication. I think we've only looked at about three in each category and it's insufficient to make any statement.

A VOICE: I don't know that we will ever ask for validation of those.

MR. ARNOLD: Our first priority is to review the tests

in support of tolerances.

A VOICE: There are so few instances in which they have made that point.

MR. ARNOLD: It may have come up in the registration process but it's not going to be a common question.

A VOICE: Our company has already been asked for a validation revision of wildlife. We have been asked to submit this.

MR. ARNOLD: Well, I did say, if you have a pending registration action and if that is relying partially on IBT data, they will ask for a validation but whether we will ever get back into the files to review the 3,800 additional tests, which we really haven't done anything about, is highly questionable, at this time.

A VOICE: But what happens to all the applications for registration in the meantime? We have been asked to supply this data.

MR. ARNOLD: The review of those test results will not proceed until the valication is received. When the validation is in, the validation plus the original submission goes for review and they process it just like they would any other registration action, but they won't proceed with any valuation of

that data absent validation.

We are trying to avoid creating additional issues and problems for the future.

We've got one kind of a situation where, in the past, we have accepted a large number of tests which now are questionable. Knowing that there is a potential for problems, we would like to avoid that for the future, and there are a small number of tests involved because, basically, they are ones that have been completed in the very recent period for which auditable information ought to be available, but we won't proceed without that.

A VOICE: I would like to ask Dr. Pallotta a question concerning putting all your data on one (inaudible). It's an impossibility in most cases. We have not received the microfiche on several tests. The Registration Product Specialist is asking us for some study, for instance, and we have that. So we have submitted that.

I feel that it would be an ideal situation if you could put all the tests in only one product, but it's not a practice way of action.

DR. PALLOTTA: I think Fred addressed that problem earlier and IBT has indicated that, at the end of the year --

MR. ARNOLD: At this point, they have provided all the data to sponsors on chronic studies which were completed, mailed out as of January 1st, '78.

Now, if you haven't received a test that falls in that category from any of the three IBT facilities, one of two things has happened. Either, there is no raw data for you to audit, or it's been sent to a wrong address or there has been a mail mix-up. So I suggest that you contact IBT.

We've now been waiting about a year to proceed with this validation effort and I recognize that the problem of cataloguing and microfiching five million -- or some number like that -- pages of records, correlating it and providing it to sponsors for review takes a lot of time. A great deal more time than anyone originally anticipated.

For that reason, we haven't taken any actions, but I think the point to keep in mind is that we are not going to begin with the review of a compound -- a historical compound. One for which we noted a concern in our letter of correspondence last July. We are not going to proceed with a review of one study when another one is being audited. We'll wait until we get the entire auditable data base and we'll review it at one time to determine, first, are the studies valid and, to the

extent they are not, what do we know of the toxicity of the compound in question.

Otherwise, it requires us to go back several time to salvage bits and pieces of information from this study and that study and it would slow you down and it would slow us down.

If you don't have the data base, obviously we can't ask you to audit it, but we are pointing out that it is our understanding that, if you don't have the data base now, in all likelihood you are not going to get it.

DR. PALLOTTA: Just adding to that, if you have received some of your validations, after you have met with some of the IBT VAT effort, you still do not have any studies, then you can assume that those studies are invalid because of lack of raw data.

A VOICE: Well, it's more complicated than that because, before we got the microfiche, we went to make copies of the raw data. So we know the raw data is there. But, everytime we call IBT, it's another two months before that can be sent. So we've waited, now, for about a year and it's just one of those things.

MR. ARNOLD: I don't believe we have been exerting an undue pressure on anyone to perform something that physically

can't be done.

A VOICE: More than pressure is on us because, as a registrant, we would like to continue registrations and yet you can't do that without --

MR. ARNOLD: Because you are tied up by IBT data. I suggest that you raise the question with Mr. Current, perhaps during a break, but his information to us is that it has all been sent out, absent a very small number of tests in the bits and pieces file.

A VOICE: (Inaudible.)

MR. ARNOLD: We discussed that last night and I suspect that the majority of the metabolism studies would not fall within that 90-day and longer classification.

It doesn't mean that some of them might not have been microfiched and sent but, at this time, they can't make a broad general statement about these studies less than 90 days, and that's where the majority of the metabolism studies would fall.

A VOICE: Again, with that letter I'm referring to, we received a letter from EPA saying these studies had to be validated in one year. Now, again, you are telling me that these studies will not be looked at until you have the entire package is in. We sent the validation in six months ago and it

apparently is sitting on somebody's desk. So this metabolism work isn't done. We don't have this information. We may not get it for quite a while and, when we do get it, it's going to take time to validated it. So things will be held up.

MR. ARNOLD: We have proceeded on a piecemeal basis to date, and we've decided that it's just not sufficient because of the number of issues that are raised in the validation reports. We have to go back over the same information more than once.

So we are going to not proceed with the entire review of the chemical in question until we've got all of the IBT validation effort in hand.

That's strictly from the point of view of efficiency because we can't make a decision, in many cases, on pesticides until we've had a chance to review all the data because of fundamental errors in key studies and there is just no way around it.

I know it creates a problem for you. I'm hoping IBT is almost to the point now of being able to make a blanket statement, "You've got it all. If you don't have it, there is no more information," and everybody can kind of bite the bullet and decide what they are going to do.

It is extremely frustrating for me and everyone else involved here, too. We're not attempting to sandbag you. It's just that there are too many uncertainties for us to proceed when you've got a significant problem with key studies.

A VOICE: (Inaudible.)

MR. ANROLD: No. Both Dave Clegg and I have attempted to go from the total of all the IBT data down to ones where we really have a concern and, basically, they are the ones upon which we have based the public health hazard. Now, the fish and wildlife, the acute studies and the precautionary statements are another matter, but we're not going to hold up our review on those. We've not even asked that they be audited. We're dealing, now, just with the ones in support of tolerances.

MR. CLEGG: If I may, I would just like to cut in. I'm not quite sure that this has come over very clearly from the Canadian standpoint, anyway.

We are,in fact, looking at studies as they come in, in terms of checking the audits and validations, and we are goind through the raw data on these.

What we are not doing -- I think this is what Fred is talking about -- is going back to the companies until we have the whole data base on that compound.

It doesn't mean to say that the data, which you have submitted, is not looked at. It is being looked at. At least, as far as we're concerned in Canada, but we can't go out on individual studies and respond to them for the simple reason we don't have the manpower to write all the letters which would be required of us. It would be a horrendous task, from that point of view.

What we are doing is auditing, validating and filing our opinions on each study and, once we have done that, when we have the complete data base, it will be re-reviewed and comments will be sent out that these studies were considered valid and these were considered invalid.

If there is any argument about that between your consultants or yourselves or ourselves, then, we're not infaliable, we are quite prepared to sit down and talk about it and discuss it and find out whether there is any difference that can be reconciled, if necessary.

Then, finally, when we have dealt with this, we will come up with a registration situation by looking at the total data base, but we can't do anything about registrations or the tolerances, per se, until we've looked at that total data base, because we don't know what is going to be available.

MR. ARNOLD: That is certainly an accurate reflection of what we are doing and the reason I say we are not proceeding on chemicals is because, oftentimes, any communication that we get with regard to the registration status of the chemical, it is that status that we are not proceeding with until we have had a chance to examine all the studies.

A VOICE: What is the Agency's action going to be? We write a letter saying we are unable to validate a two-year chronic dietary study, but we have initiated another two-year study under today's protocols which we feel is substantial.

MR. ARNOLD: In that instance, and I think we will start with the assumption that that is a critical piece of information, we would request that you provide us with interim sacrifice records on the new test as it is carried out.

We would, in all probability, if it is a compound that has a large number of tolerances and one where there is a fair potential for exposure in food chains, reevaluate our prior tolerance decision based perhaps on a 90-day test with -- I'm not even clear on that. Dr. Dale will comment on how the 90-day tests are used to make interim tolerance decisions in the old context.

We would not proceed with registrations of significant

new use patterns for the compound, nor would we proceed with the tolerance actions until we had what we thought was an acceptable data base.

As far as the "me too" kinds of registration decisions on that compound, we would proceed regardless of whether it was IBT data or not with the assumption that there is a certain market for a pesticide and whether its put between ten or two people doesn't really matter much and, if we essentially had made the decision to have the chemical on the market, we don't really care how many people are using it in a particular product.

A VOICE: (Inaudible.).

MR. ARNOLD: There is another point. If, in the validation of a compound, we determine that, in fact, not only did the study perhaps fail to adequately identify no effect levels, we might demonstrate adverse effect and then the Agency feels compelled to take an action on it but, as you are all aware, the cancellation and suspension actions talk about unreasonable adverse effects, and lack of a data base is unreasonable but it's not an adverse effect by itself.

So, in the extreme case, when the data base that the registrant thought they submitted turns out to be shot full of holes and unusable, then we might have some additional information

that causes you concern, we could proceed under a tolerance provision or voluntarily work with the registrant, modifying some use patterns against some additional data.

We are going to be very flexible. We've got to. It's that kind of a situation.

A VOICE: I would like to ask Mr. Sanders a question. In the event that we do have a registration being held up in the absence of validation for fish and wildlife, since additional registration seems to be an actuality, is it possible that registrations will be granted on a conditional basis that validation occur or new studies be instituted if not validated?

MR. SANDERS: I assume you are talking about a new use?

A VOICE: Not necessarily, no.

MR. SANDERS: In connection with conditional registration, suspect data has no bearing, generally speaking. We are talking about similar or identical products.

In other words, if you make an application that is similar or identical to a registrants product and we don't know, based upon our data base, whether or not you have relied upon suspect data or not, we would issue you a registration anyway and this is, at this point, something that may be new to many of

you because we have not fully developed implementation of conditional registration, as you know, but, tentatively, that is the direction we'll go.

A VOICE: What you are saying is that, in this instance, you may grant registration and make collection of this other data a condition, is that correct?

MR. SANDERS: That's correct. This is not a new use. We're talking about carrying a registered product. With respect to new uses, it may be a little difficult because we may require new data.

A VOICE: How could that be followed up, now, in an instance where registration actually exists?

MR. SANDERS: In re-registration, suspect data, as I understand it -- and Fred can talk more about that -- at that point the references that were used to support that registration have to become apparent and, at that time, we would determine whether or not suspect data was or was not used.

A VOICE: Okay. Thank you.

MR. ARNOLD: In the process of re-registering a compound, basically, the Agency takes everything it's got in its files and dumps it on the table and tries to construct standards from that. What do we know of the toxicity of the compound?

I don't really think that this is going to be a problem that is going to come up in the re-registration process. Hopefully, most of the compounds, we will already have the critical tests either validated at that time or we're going to know that there is nothing to validate. Somebody is probably initiating another test because there is a data gap and they've got a certain amount of time to complete that data gap, in which time we have additional registration.

This fish and wildlife question which, I think, is perhaps something that may have been raised in the current registration matter, it's kind of a problem that is going to peak and go away because there are very few tests coming out of IBT, right now, that have been referenced by registrants for new actions and those that are coming out, they have records and they've gone through an IBT assurance program with IBT, which was initiated prior to this whole validation concept.

So, records are available and our experience has been that the studies can be reviewed very quickly.

A VOICE: (Inaudible.) The problem is, if we assume, now, this microfiche data that we have is all we're going to get and then there are instances where you have 100 (inaudible) saying, "You don't have the microfiche," it really makes for a

tough decision.

MR. ARNOLD: I realize that. I understand that that is the reason why individuals have been reluctant to proceed with the validation on part of the data base which, subsequently, may become modified and augmented with additional data.

Right now, it is my understanding that, on the chronic studies, if you don't have any data on it, you're not going to get any data except for unrelated pieces of several pages in this bits-and-pieces file.

I think you might begin working under that assumption that, if it's not lost in the mail, you're not going to get it.

In cases where you've got a data base on a study and it falls in this chronic classification, in all likelihood, that's all you are going to get. You may get some pieces of communication when they go to microfiche the bits-and-pieces file, but that's not significant information and it's usually not related to a study for which they have built a large data base.

So, I think, at this point, for the majority of studies, you've pretty much got what you are going to get and you can proceed and, in the case where you may have gone into Bio-Test -- I've known several instances where sponsors went

into Bio-Test, prior to Bio-Test attempting to build their own library and classification system, and copied data which has subsequently not been microfiched and sent out.

I just don't have any wisdom to offer on that problem other than talking with Bio-Test, because I find it a rather peculiar situation myself.

DR. PALLOTTA: Let me try and see if I can give you an example of this type of problem.

Let say there is a two-year rat study and all of the hematology data is missing but you do have all of the rest of the information and you can validate without this hematology. It appears to us that, by relatively simple target organ type studies, you can indicate bone marrow effects on a relatively short-term basis which would be helpful to support that particular study.

That's an example of the type of salvage material we will accept.

A VOICE: I'm not so concerned about the bits-and-pieces file. I'm concerned where we actually have knowledge or hard copy data and didn't receive any on the microfiche.

MR. ARNOLD: In that instance, I would certainly expect that you would proceed with the validation on all the data that

you have. If you've got hard copy that wasn't microfiched, then, obviously, between the time you retrieved your own data and the time subsequent microfiche were made, it got lost -- unaccounted for -- but certainly no longer available in microfiche form. You should proceed with that.

I don't intend to limit our review of data to just the records provided by IBT. I think that, oftentimes, sponsors may have records or correspondence. Perhaps they have hard copy or hematological reports which were submitted during the course of the study.

Any information that relates to it ought to be used to review and build a proper perspective on the study.

A VOICE: Shouldn't it be possible, at some stage, to get a statement from IBT, rather than make an assumption that they have supplied all the data?

MR. ARNOLD: Well, I certainly hope so. I've been attempting to kind of get it nailed down, now, for a long time, simply because I feel it reasonable to insist that registrants pursue in the effort and it is one that has been very frustrating when there is a possibility that there is additional data out there.

I'll see if we can, perhaps, get some guidance from

the managers of the Validation Team, and I pass on to you what they have passed on to me and I interpret that as it is time for everybody to kind of face reality and there is not going to be a large body of data that's going to come to the surface in the next month.

There is a possibility -- a very strong possibility -- of problems in being able to contact their prior clients because of people moving, people selling rights to data, changing company names. For a number of reasons, they have difficulty trying to provide the records that they have to the sponsor who is likely to be the one who wants it.

MR. ULFELDER: One point about the question of hard copy. I think, in submitting a validation report, it is essential that you indicate whether you are using a copy you obtained previously, or either contemporaneous to the delivery of the study report, or whatever, or however you obtained it, as opposed to microfiche data which you have been given by IBT as part of the microfiche process that took place over the last year.

For our purposes, in reviewing the validation reports, we would like it noted as to what the source of the data was, whether it was microfiche or some other source.

MR. ARNOLD: I wonder if we could take about a ten minute break, right now.

(Whereupon, a short recess was taken.)

MR. ARNOLD: Perhaps we can reconvene for about 45 minutes and then we will take a luncheon recess.

Let me just provide some additional comments upon availability of microfiche.

Again, the representatives of Bio-Test urge each sponsor to contact them individually about the status of what's been sent, what records are available, what records might be available in the future and they will provide an oral assessment to you of what's been sent and what's the likelihood of anything else being made available.

They will follow that up with a written confirmation that you can proceed on, but they suggest that the oral assessment would be enough for you to proceed, and I would certainly expect then, given an oral report for them of what is available, that you could proceed on this validation for which there is data and begin to make any assessment of those studies for which there is no data to determine whether or not you might be able to reference and support additional studies to the Agency in the case of data gaps we're beginning to test.

We'll continue to be flexible. I think we have in the past and, if we haven't been, I would appreciate it if you would bring that to my attention, if we have constructed a system of constraints where there is no feasible solution to the problem.

Several points were brought up to me during the intermission that I told you I was not making clear. Conclusions reached on your part or on our part that a critical study is in doubt, our process will be to examine the entire data base which we have, whether it includes tests other than IBT tests. Perhaps tests which were not referenced to any particular tolerance petition but that do bear on questions of human safety. We'll look at all available information to construct as much of a data base as possible concerning the toxicology of the chemical.

In the instances where you are aware of other tests which you feel are relevant in the light of certain missing data which, at one time, you assumed was satisfactory, please point that out to us. The last letter from Ed Johnson made that request in addition to a number of others.

Basically, what we were requesting was that, in the event you determine that your toxicological data base is not

as was originally presented, what do you suggest we do about it? Do you have additional data that suggests the chemical is safe and, therefore, there is nothing to be worried and tests are underway, or are there tests which have been completed in the public domain by NCI or by whoever that bear on your compound and that you think support the continued registration and continued use patterns? Certainly, provide us with any information that you know of in those circumstances where, by your own assessment, the data base just doesn't support the prior conclusions.

There is one additional point. Apparently, addendums were often prepared for IBT reports -- addendums dealing with one phase of the work -- and the individuals involved in the validation assessment work have found, at times, in going through file cabinets, items which may have been prepared after the original report was completed, but they do supply more insight.

They are stand-alone kinds of documents. They have been sent on to the recipients of the original data and, again, a communication directly to Bio-Test can provide you any information that they might have on these addendums -- these stand-alone pieces -- that are cropping up, inadvertently, but they are cropping up.

I guess the best thing to do is to continue with trying to answer your questions. It seems like the questions are certainly good.

DR. PALLOTTA: One other comment was made during the intermission and that is, especially among the larger companies, you might find an awful lot of the missing data in your own files.

If you are anything like EPA, the data tends to get lost in the archives that you may have in your own companies.

I think we also want to make some comments about on-going studies. As all of you are aware, a good number of the scientific staff at IBT have left and many of you have studies that are ongoing. We would strongly urge that you provide some supervision in work until its completion.

MR. ARNOLD: I guess one additional point to be brought up there. If you are not aware -- you soon will be, if you have an ongoing test -- it is now a Bio-Test policy not to sign the reports and the reason for not doing this -- and I'll give you the reason they gave me and you can pursue it individually with them if you would like to -- is that the current management was not in charge of a number of these tests at the time they were started or at times during the

conduct of the test.

A number of scientists, who may have been involved in the early states of a test, are no longer there and nobody can state, categorically, that everything reflected in the report, in fact, is borne out by the raw data. In the sense we are requiring all tests be validated, the validation will be the proof of the pudding. Either the data supports the conclusions or it doesn't.

We have Reto Engler, who is Dr. Dale's Branch Chief, who has developed a policy and transmitted it to more and more registrants that unsigned reports would not be acceptable. That is not the policy of the Agency. We discussed it last night with Ed Johnson and we reviewed the prior registration revision practices and, at times, tests have come in that were not signed.

We have not, in the past, insisted upon that, although it is certainly expected, and we are not going to create a double standard now.

I might point out that, in reviewing the results of an IBT test, when current management is unable to sign the report and reflect that this report is fully accurate, it certainly raises questions in my mind and I think it ought to raise

questions in anybody's mind, given the circumstances that there is no affirmation that, in fact, everything happened as stated, but our policy will be that the validators are going to speak for themselves and, if IBT feels compelled, because of a corporate point of view -- I don't believe it is because of a basic scientific inadequacy. My understanding is that they don't necessarily question it but they have no way to prove to themselves that everything is entirely supportable.

Given that -- their requirement -- we will accept unsigned reports along with the validations and we will review those just the same as we do any other test.

A VOICE: You stated that acute studies are not being requested by your group. However, they are being requested by other groups in EPA. Now, acute studies have some problems because all the guidance that I've received to date refers to long-term and they point out the importance of protocol and the importance of receipt of animals. (Inaudible.)

Now, I'm getting consultants coming back and saying, "I can't validate your study because, one, there is no protocol, and, two, there is no receipt of six animals or 50 animals ever being used." Would you elaborate on the importance of those two items for an acute study?

MR. ARNOLD: I will attempt, and then I will pass this burning issue on to Dave Clegg.

Actually, in discussing it, we don't know how to audit an acute oral study and we really haven't asked for very many of them. The only ones we've had are the ones that have come up in a registration procedure.

In the case of a protocol, I agree there is going to be a unique protocol, especially if the study was reported to be a certain type and there is some information to suggest it was carried out that way, or there is going to be a small body of information.

In the case of animal receipt, I think it is fairly clear that animals for acute studies were not ordered individually. It's really not irrelevant. I mean, if you have information on it, that's fine, but it certainly would not be a fundamental kind of information on an acute study.

The reason we have not issued any guidelines on how to audit an oral acute is that we really don't know. For that reason, we didn't ask for the vast majority of those studies to be audited. We really have no basis for deciding whether there is a problem in that area or not.

If there are individual instances when the registration

process has requested information of that nature, the basic intent that we have in performing an audit is to provide substantiation that the test is actually carried out in the manner reflected in the final report, and I think that goes across the board, no matter what kind of a test you happen to be looking at.

We are not so much concerned with whether the final report was the best kind of a test to do or whether it meets today's standards. It is, does the raw data support the conclusions in that final report that, at some time in the past, we made decisions on and, if it does, and we made a bad decision, then we just didn't do a good job of protecting the public health but, if we made a wrong decision because the report was incorrect, those are the ones we want to find out and we want to try and fix.

A VOICE: Essentially, you are saying, in acute, it is more important to have an audit than a scientific validation?

MR. ARNOLD: Yes, I think that's what I'm saying.

MR. CLEGG: I'm not quite sure why it was passed to me, but I do have a comment in relation to this.

As far as we're concerned, with acute oral studies, we have not requested any validations, nor do we intend to.

There are a number of reasons behind this which are, perhaps, worth considering lightly.

First of all, the relative cost of obtaining the information for an acute study, going through an audit and validation procedure, this is probably just as great as repeating the study, particularly with acute oral studies.

My own reaction to this would be that, if there is a necessity for an acute study to be verified, then the easiest way to do it is to repeat it and not bother with audits and validations. That's for acute orals.

Now, whether the same is true when you are dealing with acute inhalation or acute dermal, I'm not quite so sure. I think, in all probability, since you are assessing certain specific time intervals, the irritation scores or this type of thing in both those types of studies, then it may be worthwhile getting the data and going through it and doing a validation on it but, as far as acute orals are concerned, I think the probability of a request for these is going to be low.

There may be an odd one which will crop up where a compound is close to the cut-off point in terms of labeling or various LD-50's that are used there and where we have some doubts, if one is very close to that cut-off point, then we may

ask for a repeat, but I don't really believe we are going to ask for validations on any acute orals.

MR. ARNOLD: I would also add that it is not now our intention to ask that registrants go back and audit all those kinds of studies that historically exist in our files.

As a general guideline, from the discussion that we had with Mr. Johnson last night, in the case of acute studies or subacute fish and wildlife, as a general rule, when it appears to be reasonable, if we have asked for a validation, that it should be validated unless, one, there is comparable data elsewhere -- which means a similar study has been done in a different facility. There is no sense in going back and auditing a study which already exists and, by its mere presence, it is sufficient.

Or, if the study can be reperformed quicker and less costly in the case of, perhaps, an oral acute study, we suggest that that might be the better way to proceed than attempt to spend the resources in validating an acute study.

A VOICE: There is a big distinction. When you are talking about studies that are being requested which, as I can see, wouldn't be requested unless we submit something. (Inaudible.) Now, is Canada still taking that position that, if

it's an IBT study that is submitted for new use, that it will not have to be validated?

MR. CLEGG: At the present point in time -- in fact, just before I came away -- a memorandum went up to our senior executives to determine whether this stand should continue.

The feed-back I have got on it is not complete by any stretch, at this point in time, but the general consensus of opinion, as far as it has gone, is that this stand will no longer be taken.

MR. ARNOLD: Since it is an issue that has surfaced a number of times, I'll make the commitment to discuss, specifically, the question of those tests which we don't ourselves have any idea how they could be really audited or validated, such as an oral acute study, and give you a guideline, because I don't know how many times that has been caught in the registration, like the experimental use permit, new application kinds of decisions. I'll try, the remainder of this week, to get an idea of how many times it's happened.

My feeling is it is very infrequent. It sounds like you may have been the major recipient of the problem. I will see if we can get some guidance to ease some of your problems. It sounds like this problem has created an unreasonable kind of

a situation and one which probably should never have happened.

I'm going to talk to Mr. Johnson about it and I would suggest for those of you who are in that kind of a problem, why don't you give me a call about next Tuesday. My number is Area Code 202-755-8026.

MR. CLEGG: I have one additional comment I would like to make in this area. I don't know whether this is the case that is being discussed. It may be.

On area where we have run into trouble with acute studies are those which are being done as range-finding tests for neurotoxicity studies and, under these sort of circumstances where the dose which is given does not tally with the acute LD-50 in the hand then, obviously, there is need for some sort of validation or at least some comments back as to why they, instead of using the LD-50 or half the LD-50, why they have used the best level for a neurotoxicity test which is much lower.

As far as I know, in the acute studies encountered, that is the only situation where we have, in fact, raised any queries. I may be incorrect.

If the gentleman who is asking the questions would like to talk to me afterwards, I will try and sought this out

for him.

A VOICE: One other question. Earlier, you indicated that you were going to divide these up between the U.S. and Canada. How do you intend to divide these?

MR. ARNOLD: I asked Dave to do them all. That was the first provision.

MR. CLEGG: I refused.

MR. ARNOLD: Actually, to date, the division has pretty much been one of very frequent communications between us and chemicals that they had a greater interest in, perhaps, because they had a pending decision and one in which they were already into the data base, they've gone ahead and proceeded with it, and we've done kind of a similar thing.

We're proceeding with several that were of interest to us for other reasons and we were able to kind of move ahead.

We've also taken, from the schedules that we have received from registrants which, although they are no longer relevant in an absolute sense, since basically everything has gone well beyond the original kind of concept of how long it would take to get the data together, we do think it still reflects the relative way in which the registrants will submit data, and we'll get all the studies on Compound X before we go

on to Compound Y, and we've taken a cut at that so that we don't get redundancy. We are attempting to kind of stay several steps ahead of the receipt of the data.

We do both need copies of the microfiche simply because we have got to maintain the integrity of our files. I am not sure that it would be of particular importance -- or maybe it would be. Maybe you would prefer that one or the other review your data.

I suppose we could share with the people at least our tentative conclusions as far as who is going to do what. I think the validation findings are going to be the same. We, so far, have attempted to do several independent ones and we have reached, basically, the same conclusions.

MR. CLEGG: It's just sort of up in the air.

MR. ARNOLD: If you have a question as to "Who is looking at my data?" by all means ask us and we'll tell you.

MR. CLEGG: This, basically, is part of a discussion, I think, between Mr. Arnold and myself. I have the feeling that it would be far wiser, once a compound has been allocated to one of the particular agencies, we notify the firm in question that their compound is being looked at either by EPA or by HPB.

Then, if there are any further questions which arise,

then at least they know who they are dealing with. If they have come up with something which suddenly alters one of their validations -- for instance, somebody in the coffee break was telling me that they had an ongoing procedure and they had gone back to the raw data and they had modified, as a result, some of their original validations they had sent in.

If this type of thing happens it is, obviously, to the advantage of the firm to get that to whichever country is dealing with that particular compound as soon as possible. So, for Canada, if it is agreeable with EPA, I will be quite prepared to indicate which compounds we are actively dealing with and, as they are allocated -- and I should say, now, that so far only 22 out of the 50 or 60 compounds involved have been allocated -- we will notify the firm whose compound it is. Does that sound reasonable?

MR. ARNOLD: Certainly. It sounds like a very reasonable way to proceed.

MR. CLEGG: This, incidentally, does not mean that correspondence should only be directed to the one country. Anything relating to either compound, for the sake of completeness of the files, should be directed to both countries, but, if it's an urgent situation and you want to contact us by

telephone, then at least you know where to go to straight away.

A VOICE: Not sending microfiche of raw data, a lot of the raw data could be in your own files. Now, that could certainly cause a problem. Now, is it allowable to send copies of our own data to you instead of microfiche ones? The letter I received said raw data should be microfiched.

MR. ARNOD: I would certainly prefer that we get the microfiche. You just have no idea what we would have if every registrant dumped all the raw data on the steps of the east tower of EPA.

The microfiche we can slip into a study which has been submitted and it becomes something that's fairly easy to keep intact for the future.

All the raw data, on the other hand, would be very difficult to deal with. If that's all you've got and you don't want to microfiche it, by all means provide us with that data, but I would certainly prefer that we deal with the microfiche because of the large volume.

If that's not something that you find acceptable, give us the raw data and I suppose that we will, at some time in the future, microfiche it. It just increases the potential for creating, perhaps, a very unmanagerable situation where we can't

even tie the raw data back into the studies because the problems that Bio-Test has had in trying to build this library are probably typical of the problems we might encounter if we started the five million pages of records relating to our 123-some compounds.

MR. CLEGG: If I may, Fred, one thing from the point of view of contact between us. Fred gave you his telephone number. It might be a good idea for those who have compounds in Canada to give them mine. It's Area Code 613-996-3833.

A VOICE: Fred, you mentioned, more than once this morning, declaring a study valid. We have religiously avoided reaching positive conclusions of the study because of the wide variety of definitions a valid study can have. (Inaudible.) Would we basically try to point out what data appears to be real in a study and which statements we cannot verify from the raw data, rather than attempting to say the entire study is valid or not valid. Would you comment on that concept?

MR. ARNOLD: Yes. The cut that we are making between -- the black and white cut between valid and invalid is, first, if a study is valid, then it needn't be repeated. It stands alone. It answers all the questions that it was originally intended to answer and the raw data supports the conclusions

in the report.

Now, there are certainly, perhaps, a large number of studies that are going to fall in the middle where perhaps a two-year chronic feeding study offers a great deal of information about the toxicology of the chemical but is not appropriate for an assessment of cancer. In that case, the study might have to be repeated, but many of the conclusions that can be drawn in it are valid conclusions.

The reason that we have asked the sponsors to comment upon the validity of a study is because it is a very difficult conclusion to reach. There are no guidelines.. No one every had to go through this kind of a process in the past and we have limited resources.

Any additional scientific input that we can receive from the registrants we would appreciate, and their comments upon the validity or invalidity, with regards to whether the study can stand alone for its original purposes, we are still waiting to see.

It's a conclusion that we are going to have to discuss in many cases because it basically tries the decision of whether or not a study needs to be repeated. That's a financial and a time burden that will be imposed by the decision and it's

not going to be made lightly.

So, whether you reach that conclusion in your original submission to us, or whether we discuss it after we evaluate the study, is going to have to be discussed.

In those cases where we determine that a study is invalid and must be repeated, I think, oftentimes, the validation reports sort of speak to that issue because they note deficiencies in major areas, but then go on to what can be determined from the study.

I think that the next step is to say, "We have initiated new studies because of the deficiencies. However, we feel that the following scientific information can be used in the regulatory decision process." That's what we're looking for.

A VOICE: (Inaudible.)

MR. ARNOLD: The question is whether we can predict a range of time between the receipt of the validation and the regulatory decision.

No, I can't, because, in many cases, the validations will be reviewed and, in the situations where the tests are valid or perhaps where the test needs to be repeated but it's not a burning kind of a question and we have additional

information that kind of adds insight, the first formal response from the Agency would come during the re-registration process when the generic standard is constructed. That could be several years.

The data will be reviewed because we will have to separate those compounds from which we really don't feel any desire to speed up the new testing if it's called for from those compounds where we do have a major concern on data gaps.

I believe that Dave's goal, right now, is to complete his review of the IBT data sometime in 1981. Is that correct?

MR. CLEGG: Well, at the present moment, the resources which have been allocated for this by Canada should be available until the 1st of April, '81. On this basis, we're hoping we will have everything sorted out by that time, but this is so dependent on, (a), when we get data and, (b), the volume of data that we have to deal with.

At the moment, the rate of data flow for the last three months has been extremely low and, as a result, we've had some people who were diverted on to other work because there hasn't been enough on the IBT coming through for us to be able to keep a steady flow on it.

It is very difficult, therefore, to assess how long

things are going to take, because it is really dependent on you people how fast you get it to us. Equally, it is going to work the other way around because, if we get a sudden dollop of it -- a tremendous amount of material -- then, obviously, it's going to take us longer to deal with the individual studies in that large a quantity coming in than if we are dealing with them as a steady flow.

I know that this is something which is always a problem in any submission to the government and I don't know how you deal with it. Again, we would hope to have decisions made by April, '81, and, hopefully, if the data is in our hands, we should have decisions prior to that date. I think that's all one can say at this point in time.

MR. ARNOLD: As we review a compound, when we know it is of significant concern, we certainly won't wait until the re-registration process to bring it up.

On the average, an average compound that we have raised questions on, has about five tests associated with it and that's simply taking the number of pesticide active ingredients and dividing it into the tests that we've requested.

Our outside estimate on the review process, if we have to get back into the entire data base because of significant

anomalies and a determination that the major body of data is not reliable, it takes several months to get in and look at all the underlying data.

Now, I'm not sure that there is such a thing as an average test. We have a number of compounds that have 20 or more tests that we've questioned and then some that have only one or two. So I'm not sure that the average makes sense, but, for our budgetary purposes, we've looked at about two man months to get back in and assess it and, if we reach conclusions that have an impact upon your registration process, for those who have registered compounds, we'll share those with you immediately.

Looking at the schedule that we have for the receipt of data, I hope that we're going to have all the data in hand during the next year and we're reviewing it as it comes in.

We've got three compounds that are under review right now because we have all the data for them. In addition, we have a number that come in where it is just a study or two, and we've looked at that.

I believe, in all instances, we have communicated back with the registrants because it has been a learning process to try and understand what the validation process was that they carried out and shared, with them, our conclusions, and I

think we will try to continue to do that.

Certainly, if it is something that is going to impede registrability or new decisions on a compound, we're going to notify the registrant of that as soon as we make that determination.

A VOICE: Can you comment a little bit further about your timing for receipt of information, especially noting some of the larger companies (inaudible) and pinpoint dates and flexibility?

MR. ARNOLD: Well, originally, we had hoped that we would have all the validation reports within a year. We had asked for a schedule showing when they would be submitted and there were several exceptions to that schedule.

There were large companies that had been totally relying upon Bio-Test for their toxicology testing capability where there were several hundred tests involved. It was just unreasonable to expect them to come in at a rate of one a day.

In those cases, we said that we would be flexible but we did ask for a schedule of when we could expect to see those, so that we could kind of plan our resource commitments around that and try to be responsive. I think that is still a reasonable request, if you take into the light of the ability to get the

raw data from IBT.

If we could start, today, with the assumption that all the data is available that you are going to get, I don't see any reason at all that the majority of the registrants will not be able to provide those validations within a year and for us to be able to look at those and comment back.

It's really dependent upon when you can get the firm commitment from Bio-Test that you have got all the data that you are going to be able to work with and I, again, stress that you ought to contact them, take their assessment of the situation today, and proceed with that because I think, in most cases, the data which is available is out. It's just a little depressing when you come up and there is just nothing there, but I think that's a situation you have to face.

A VOICE: Is there a separate group set up to evaluate the validations or is this going to interfer with the evaluation of new submissions from a biological standpoint?

MR. ARNOLD: Yes. That's the juggling act that the Pesticide Program has been in for a number of years, now. I have resources in the budget to utilize consultants for IBT. There will be people to review the validations as they come in, spot check those against microfiche. Sort of the routine part

of it.

The issues that are raised will be referred to senior toxicologists, statisticians, that will be in a consulting capacity as well as Dr. Dale's staff. We don't intend to use the senior people to do the routine work of checking the raw data against the validation. We expect that to be raised up and, therefore, reduce the drain on the Toxicology Branch, which is currently in re-registration and RPAR -- you name it. So we are trying not to pull those back into the fray.

The unavoidable part becomes we won't, and we haven't in the past, asked consultants to make regulatory decisions for us. In the event that a determination is made, through the validation process, that a data base be significantly modified, we are going to have to have that reviewed by the Tox Branch people who normally pass on compounds, but, hopefully, that will be a very small number of compounds and the issues will be fairly well articulated when we get to them. That's what we've done in the past.

MR. CLEGG: May I answer that on the Canadian side. We have, in fact, set up a separate group to look at the IBT problems and we are doing, basically, what Fred has just said. his consultants will be doing and, then, after that, they will

go into normal patent submissions and be dealt with on this basis, going through various committees that usually decide what happens.

A VOICE: It takes a lot of time for industrial companies to funnel the data. (Inaudible.)

MR. ARNOLD: Somebody else brought that point up and I said, "What other sort of bombshells have you got hidden?"

Happily, we have almost completed the site business at all testing facilities. There are half a dozen or a dozen very small companies, on which we have toxicology data in our files, that we haven't been to, but they are very, very small.

We've been to 70 or 75 testing facilities and, if you haven't heard any comments about that testing facility, you can pretty much conclude that we didn't see anything that caused us to have a concern.

We have been, in general, satisfied in the way in which tests were performed. It's an understanding kind of a learning process. We learned that ten years ago people did things differently than they do today. For me, I'm not a toxicologist, so that's an enlightening thing for most people who are concerned.

The vast majority of the labs we've looked at, the

raw data records support the conclusions that were submitted and that's all we can ask for, and that's all we expect.

There are several labs where we had questions, one of which was IBT. So, obviously, we have dealt individually with registrants where we had questions on that, because, to our understanding, there is not another issue that cuts so broadly across the chemical industry as Industrial Bio-Test has.

A VOICE: One more related question is every company is developing data of their own. When are you going to start checking on those studies?

MR. ARNOLD: You are questioning, now, the data generated by the registrants. We have audited the registrants' facilities that are identified as toxicology testing facilities. There may well be resident labs -- fish and wildlife. We haven't got into that level of review but, when we began the toxicology data auditing program with the Food and Drug Administration, our intent was to review all the laboratories which had submitted data to either EPA or its predecessors to form an evaluation of how reliable the data base was for purposes of registration.

We didn't make a distinction between commercial labs, company-owned labs and university labs. We've attempted to go

to all of them, but we started off with a laundry list of about 340 testing facilities and that's really cut down to about 90 that are still in business today and ones which, in fact, did carry out testing or tests we were looking at.

We have been, as I said, very satisfied in the vast majority of cases with the ability to square away the test with the raw records. I suppose the reason that we haven't talked about that is it is sort of like "no news is good news" when it comes from us regarding lab audits. It's an internal kind of validation. Our own ability to make decisions which was suggested to us by the Congress. We've carried it out and we've identified one or two situations where we want to take a harder look. IBT is one. In the other cases, we don't intend to ask for validations.

I guess that's a question that came up this morning. When are we going to have to start validating our studies from this lab and that lab? That's not going to be a standard practice for EPA.

A VOICE: (Inaubible.)

MR. ARNOLD: Those labs that we were trying to look at with the Food and Drug Administration were good laboratory practice inspections.

A VOICE: Can I go back to the question on results of validation studies on new submissions on a compound. Perhaps there was a study that would not be valid but, in the overall assessment, changed the profile of the compound and the compound was up for new submission application. (Inaudible.)

MR. ARNOLD: The question, for those who didn't hear it, deals with a study which could not be validated for whatever reason -- either not enough date or the fact that it was determined that the study was really not appropriate for its purpose -- and it is supported by a new submission and I think you mean, there, perhaps a significant new use or a new tolerance. Something other than a B-2 or a rather routine kind of action. I'll let Dr. Dale speak to that.

DR. DALE: I'm not sure I got your question exactly. The question was, as you put it, you've gone back over and have found a study invalid but the total data didn't change your toxicological profile of the product and you are coming in for a new registration or a new use.

A VOICE: New use.

DR. DALE: Well, I would say, in my opinion, that it would go under the new guidelines in that case and, if the study was required, that you would do it again.

MR. ARNOLD: I think, with the final passage of the new law and the conditional registration and requirement the administrators make of finding safety under the concept of Commission (AUDI), that we really haven't sorted out how that is going to fit in there.

The way you describe the problem, it sounds like you could make a finding of safety because, basically, your entire toxicological profile would be supported by other pieces of information and you may, in fact, have a data gap, but the registration process could proceed.

I think it's going to take a little bit of time to sought out whether -- I don't think conditional registration process is anything that is necessarily going to trip when IBT comes up because the concept of conditional registration is that you don't look at all the data base when you make the decision on the conditionality.

There would be no way to identify the fact that there is an IBT study in there. I'm just not sure how we are going to try and fine tune that concept of conditionality with respect to IBT.

A VOICE: The reason I brought up the question is that, so far, (inaudible).

MR. ARNOLD: Well, I guess we cite a case in point that perhaps is analogous to your situation.

We have just reviewed the data base for a compound that has pending registrations. The entire data base was generated at IBT and the recommendations that have come from the Toxicology Branch are that the registration action should proceed in allowing the use of the compound, but that there are data gaps that must be solved.

Basically, several of the chronic studies, we feel, provided us with the majority of the information we needed concerning the chronic toxicity, but they didn't meet the requirements to assess carcinogenicity.

So I think our policy is going to become involved like that. If we're satisfied on the safety of the chemical, we'll proceed, regardless of where the data comes from, but, because it's an IBT test, it's going to be flagged and we're going to take a harder look at the data base, but we have not established the policy to hold it up merely because it's IBT.

In this re-registration process, we are going to come up with a lot of reasons for data gaps and uncertainties that are going to exist, and the concept was to try and proceed in an orderly fashion and fill data gaps and not interfer with

the ability to control pests and market pesticides.

A VOICE: I have a question that relates to the diet stability studies that we've been asked to do. One can calculate, with the protocol that has been suggested, that you could end up doing several hundred or even a thousand analyses.

We're wondering if it would be acceptable to do a "worst case" study first and then, if the chemical is stable under those circumstances, to delete some of the other time points and conditions of the protocol.

The worst case might be the maximum time -- I think three weeks was the maximum time in the protocol. Two temperatures -- pick the higher temperature, and go with that and then, if the chemical is stable, not bother with the lower temperature and the intervening time points that were recommended.

MR. ARNOLD: I would ask these gentlemen to comment on that.

DR. PALLOTTA: Yes, It goes like from A to Z. Even a chemist can tell you the compound's stability in many cases and the other techniques might not be necessary but, in general, if you have the raw data that indicates, for example, that the protocol calling for a weekly separation, and the raw data indicates as much as three or four weeks of supply before mixing,

I think we need some type of data to support that the compound was stable. I think it's a case-by-case condition we'll have to look at.

DR. DALE: Here, again, it would be the compound in question. If you questioned that the compound would, indeed, be stable. If your data shows it was, say, a month or so between mixing and the very nature of the compound in question -- the stability of it -- I would say do the minimum amount to show that, in that period of time, it was stable.

A VOICE: (Inaudible.) Would you accept a statement of the chemistry of the quality indicating it's stability or submission of a residue data that we have that we actually used?

DR. PALLOTTA: I think the food components would be absolutely necessary to do some analysis.

MR. ARNOLD: Stability in the diet that was fed. Oftentimes, we've found that the registrants had that information because, in fact, they did work that led up to the test protocol or that, as a result of doing similar kinds of tests a number of times, they developed that background information just to determine what the protocol ought to be.

If you have the information available that talks about the stability of a compound in the test material, don't redo

the test. If you have got it available already.

DR. DALE: Here, again, it would be case-by-case. If you have data which implies stability, we can talk it over.

DR. PALLOTTA: The real concern about this came about because of the large number of tests that did show that the diet perhaps was not made weekly when the protocol called for it.

A VOICE: Now, it's probably impossible to obtain the actual diets. There were lots of diets that were used in these studies. It seems to me that the difference between those lots might be as great as the difference between a rat and a dog kind of diet. So I'm just wondering if we can just go with one diet. That's what makes sense to me.

DR. PALLOTTA: It seems reasonable.

MR. ARNOLD: I would think if the diet that was used was not available or you can't reproduce that that, again, you probably ought to air on the side of "worst case," whichever is the diet which is least stable and utilize that because, if that one provides total assurance that the test material was stable in the compound, then I think everybody is satisfied.

MR. CLEGG: Can I pick up a comment on this, please. I think, in general, the proposal you are making is reasonable,

providing you know, in this particular instance, the fat content of the diet is similar in both cases. Otherwise I think, particularly in relation to that, you may have to do both diets or three diets or how ever many were used.

Again, of course, that's going to be on a case-by-case basis depending on the type of compound. There, I can see a complication.

MR. ARNOLD: It's getting about the lunch hour. How about if we break until 1:30.

(Whereupon, a luncheon recess was taken at 12:35 o'clock, p.m.)

AFTERNOON SESSION (2:00 p.m.)

MR. ARNOLD: I guess we might as well try and reconvene and push on with answering questions.

A couple of questions were asked during the lunch break, one of which dealt with the microfiche and how it should be submitted. I would prefer that we receive the microfiche as the validation study comes in, rather than just a large bundle of microfiche.

If you could submit the microfiche records attached to the validation report, it certainly is the easiest way and the least confusing. The least potential for getting pages and data mixed up.

There is another point. I understand that it's difficult to make copies of the microfiche from the microfiche records that were provided to you by IBT. IBT has retained the master copies from which copies can be made and they can do that with a very quick turn-around. So, if you need copies of it, you can contact, again, the Validation Assessment Group at IBT rather than attempting to try to make copies from the microfiche records you receive.

A VOICE: You mean copies of the microfiche or hard copies of the microfiche?

MR. ARNOLD: No. Copies of the microfiche.

A VOICE: Duplicates, in other words?

MR. ARNOLD: I'm not clear on the technology of how you duplicate those but, apparently, it's very easy to do it with the master copy retained by Bio-Test.

Are there additional questions or issues that may have come up during lunch or areas that you would like us to elaborate on from the manual?

A VOICE: Relating to your previous statement, in the case of submitted validation audit reports which did not have microfiche, can the microfiche come in as a bundle?

MR. ARNOLD: Yes. For any test that you have submitted, in those instances where we started going through the validation reports and we haven't seen the microfiche, what I've been doing is calling up the sponsors and finding out whether it's available in many cases or, in some cases, the registrants had the records prior to their production of the microfiche and that was the basis for the validation and that's why I think they came in absent the microfiche but, now, if the validation has been submitted and you have the microfiche, I would appreciate it if you could just send it in and we'll go ahead and line it up and attach it to the appropriate study.

Try and keep it in individual packages so that we don't have to burn our eyes out trying to make them match.

A VOICE: Would you, or somebody on this panel, be specific about the type of tests that you have validated now? (Inaudible.) Could you tell us just which ones are validated?

MR. ARNOLD: In our first communication with the registrants regarding IBT, we identified there were three general aggregates of tests that we were potentially concerned about.

The first were the tests in support of tolerance petitions. The second, I believe, were studies submitted in support of registrations for products with home uses; and the third was everything else.

We are interested, now, in the tests which support the tolerance petitions. The ones cited in the tolerance petition. I'm not sure this includes everyone, but it includes at least chronic feeding, reproduction, teratogenicity, oncogenicity and metabolism studies, as well as all neurotoxicity studies.

Those are the only ones, at this time, we have requested a validation on except for the questions that have come up in the registration process which is anything dealing with

IBT that is currently being put forward to the Agency.

At this time, we don't anticipate going into the second and third categories as an all out request for validations. We may, in the registration process, pose individual questions on data gap, but we're not asking for audit of all those studies at this time.

MR. CLEGG: May I just pick that one up a minute. We have a slightly different approach in this respect. Certainly the group of types of studies which Fred indicated are required by Canada and, in addition to that, we are also interested in those which relate to the environmental aspects of the use of pesticides and, therefore, we have requested or required validation of some of the dermal and inhalation studies specifically, so that we can get some feel for the potential problems with operator exposure, applicator exposure, formulator exposure, even manufacturing exposure.

So we have got a request out that dermal and inhalation studies should be validated, whether they are IBT studies, where there are no replacements available.

MR. ARNOLD: We have not been able to make as thorough review of our records as Mr. Clegg has. He was able to go through and identify these studies from Industrial Bio-Test

which didn't have a correlated study from a different lab. So he was able to do a better job of targeting the ones that were of unique significance to him.

Our policy was to take a cut on the ones upon which we made findings for -- safety findings in the tolerance area and deal with any additional validations on an as needed basis in the re-registration process which they don't have ongoing.

A VOICE: I'm asking this question because we received all the reports which were to be validated. (Inaudible.)

MR. ARNOLD: This question came up a number of times and I think we dealt with -- probably every registrant received a letter because our records are not 100 percent accurate and, at times, we referenced tests which, in fact, perhaps, a registrant had not been the sponsor. So we did not refer to tests which were critical but which our records didn't make the link between sponsor, an active ingredient and the laboratory, and that's basically the mesh that we've got to do to identify in problem areas.

I think, at the outside, our records are about 80 percent accurate in terms of being able to do a quick recall of that -- a computer search -- without actually going through

all the data within rifle range, which we haven't done.

It will happen at some point in the future, but I don't intend to initiate anything like that right now.

A VOICE: Will it be necessary for the sponsor to account for each and every animal on study in the form of wet tissues and tissue blocks?

DR. PALLOTTA: Well, we understand that IBT does have, or has near completion, the inventory on all the wet tissues and slides and blocks.

A VOICE: Then EPA will accept that as the inventory that exists and that could become a part of the validation, then, for any particular study -- that inventory?

DR. PALLOTTA: Yes.

MR. ARNOLD: The only need to be able to identify the length of tissue and blocks back to the inidividual animals would be if the validation effort suggests the study by itself is incomplete without reperforming certain pathology or recutting new tissues which would provide more information, perhaps leading to a valid study.

In that case, you would have to be able to make the link but, unless you intend to pursue that additional work, we don't intend to get into pathology.

DR. PALLOTTA: The only concern we have, there, is that, in a vast majority of the pathology reports we have reviewed, the pathologist failed to indicate that the tissue was actually read as called for by the protocol and, in reviewing slides against blocks, we had some difficulty in missing tissues.

A VOICE: Unless you can validate that the animal received a given concentration of diet, you can't correlate it with the tissue.

MR. ARNOLD: That is precisely the reason that we didn't suggest that everyone go to the level of examining pathology material because, unless you first do the review of which animals you can describe the circumstances and tests on, there is no sense attempting to check pathology.

One of the problems that Art points out -- a problem that you may encounter if you go to pathology -- is that -- I'll state it as a layman and perhaps state it succinctly.

The the test protocol may have suggested that five organs were going to be examined but that, in preparing the blocks and slicing the tissues, some of the pieces of organs were imbedded further in the paraffin and you only get three organs on the slide. That's why it was impossible to ever examine the other two organs which the protocol might have

suggested and, in our review of the study five years ago, the lack of a organ would probably have been determined as "no significant finding" when, in fact, the truth of the matter is the organ was never examined.

That's a problem that I think you will encounter and that's the issue that we were raising on the concept of tissue accountability.

Slides may suggest to you that, in fact, tissues could not have possibly been examined because the blocks were incorrectly prepared and we certainly need to know that. I think that your review of the pathologist's notes, if you find that the protocol calls for an examination of a particular tissue and there are absolutely no notes relating to that tissue, it may well be the tissue was never examined rather than it was examined and nothing was noted.

DR. PALLOTTA: Again, I should reemphasize that should only be done on those animals that you can account for in the audit trail.

A VOICE: I suppose this brings up another question in my own mind on the audit trail and that is, if, in a study that was designed to determine the incidence of tumor from a particular substance, you have specifically identified animals

going into the study -- and let's just take the worst possible case -- there is not information inbetween but, at the end, these animals are, again, identified and there are tissues identified with those specific animals.

Let's just say, for hypothetical purposes, that the diet formulation was present in the raw data and that you could be confident, to some extent, that the diet was mixed and administered to the animals. So, in effect, what you have is animals going in and tumors coming out or the lack of tumors, whatever.

MR. ARNOLD: But no body weights, no observations inbetween?

A VOICE: No body weights. None of those kinds of observations.

DR. PALLOTTA: Obviously, these are the extra animals that we were referring to before.

MR. ARNOLD: The potential exists for the extra animals.

DR. PALLOTTA: If there is some evidence of these animals having been fed the experimental compound, even though they were gang caged and records were not kept as to say, for example, body weight, but were used to replace animals that

died during the study, and you are confident, by any type of record, that this animal can be tracked as having received the experimental diet, that animal we do want reported on.

MR. ARNOLD: Let me restate your situation. I think you said the situation might be that you have evidence that the study started with a certain amount of animals; you have evidence that that diet was prepared; and you seem to think that the diet was stable. Then the next thing you know about is some histopath report and you have nothing inbetween. You just know you started with some animals, you ended with some animals -- about the right number in there -- and you don't know if there was any switching around inbetween or what might have happened inbetween. Now what's the answer?

DR. PALLOTTA: Frankly, I think that has to be a case-by-case because, if you do have some records that indicate that these animals were, indeed, fed the experimental compound -- if you don't, there's no audit trail; if you do, then you have to state it as such.

The use of extra animals, per se, is not, in itself, an invalidation of the study, as long as those animals are reported out on. If you have data on them, report them out.

The problem is that in many of the IBT studies, they

started with 80 animals and the reports came out with 50 animals and the implication was that they started with 50 animals and ended with 50.

They used these extra animals and, if you could identify these animals and they were fed this material, then report them out the way it should have been in the first place.

MR. ARNOLD: I think, in the situation you described, you are basically saying you have no information on body weight, no observations made of the animals over the term of the test, no autopsy sheets, no information.

I think that, under the guidelines that we've kind of developed, that, basically, is a study that is not going to be -- you're not going to be able to validate that study and say it serves and suffices. It may well provide information which is useful in an interim kind of a thing but, fundamentally, the kinds of information that we're are missing would be the ones that are precisely associated with the problem we are most concerned about -- the conditions of the test during the study.

MR. CLEGG: I think one of your major problems with that is, if you started with 80 animals and the report indicates 50 all the way through. I'd love to see how you are going to go about sorting out your mortality rate. You're going to find

it exceedingly difficult. We are trying to do it and we can get some sort of estimate but really how valid that is, I wouldn't like to even guess at this point in time. So I think that's going to be your stumbling block. Straightforward mortality data as to what happened, how many died, where and when.

A VOICE: What would, in a situation like this, interview with technicians who are running these studies have as to whether or not 80 animals were started and 50 finished? Would this have any usefulness in an audit report?

MR. ARNOLD: I think, if you had nothing else other than some technicians report that that's what they did, that's not going to suffice by itself.

MR. CLEGG: I'm not quite so sure as Fred is on that one. I think, probably, if you got a notarized statement that was sworn to that 80 animals were started on that by the technician, then I think we could ignore it.

MR. ARNOLD: I didn't suggest ignoring it, but don't think, by itself, it is going to convert a study which is invalid in the sense of not being able to describe a number of key parameters to one which is fully acceptable and doesn't need to be repeated.

DR. PALLOTTA: If that could be used to support an

assumption you are making, I think that would be very valuable.

A VOICE: I have read reports that never mentioned extra animals being started. Toxicologists then admit that it's common practice. Now, when you audited these 90 labs or 300 labs or whatever you ran, did that mean that you found no cases where other labs used extra animals and didn't report it.

DR. REISA: (Inaudible.)

MR. ARNOLD: Let me summarize. It was a common practice to start extra animals because of the problem of acclimation to cage conditions. So that, several weeks into a study, if there was mortality, the animals could be replaced and the chronic study was not compromised but, as Diana pointed out, the distinction between what one lab did and another, in our concern about IBT, is the fact that the animals stayed around for a long time and were replacing dead animals, rather foreign to the study, and then, in the instance of the replacement, oftentimes, we didn't know whether the animal had been on the test compound or not.

So, all of a sudden, you no longer have a regime of animals which you know something about in terms of their exposure to the test compound. We certainly did encounter the practice of having extra animals to solve the problem because

of problems with their acclimation to their test conditions.

MR. CLEGG: Under these circumstances, you usually have a cut-off period in which those animals can be added into the study and in a number of recent protocols that I have come across, you find that this is usually around one month.

After one month, it is not normal practice to add animals into a study. Up to that point, provided he is duly recorded, then I think it is acceptable but, once you've gone beyond that, normally, no.

A VOICE: In cases where you identify introduction of extra animals, would these extra animals have the same number as the original animal?

MR. ARNOLD: That depends on the animal numbering techniques. I'll let Art answer that.

DR. PALLOTTA: We've seen all types. Where they just use the same number as the animal which died. I think you will come across all extremes, if you have enough tests to review.

MR. ARNOLD: One of the problems that you may run in to is the fact that, either during some period or some particular research, a practice was followed of numbering the animals after the test was completed. The animals were not identified during the test. They were identified at the termination of

the test in a first-in numbering kind of concept.

There is a cage identification and then a post-study identification. Therefore, the presence of an animal during the middle of a study doesn't necessarily jump out at you until you examine all the records.

Tbat's why I suggested it's a bit of a problem if you happen to have a test where the numbering system was the one that was created after the test rather than at the beginning of the test.

A VOICE: I was wondering if the EPA or the health protectors had found, in their audits, that the general health of the animals, not related to the chemical treatment, would invalidate any studies?

MR. CLEGG: I think the only answer you can give to that is the one that Art just muttered. It probably came over the microphone.

It depends on your survival rate at the end of the study and also depends on the purpose of the study. Obviously, if you only end up with five percent survivors, then it's very likely to invalidate the study.

A VOICE: Has that been a problem in the studies which you have received?

MR. CLEGG: We have come across it in some of them, yes. Particularly in the rat studies, as far as I'm concerned, and the mouse -- in both.

A VOICE: Now the auditors will have to make some judgment of their own, I presume, about the health of the animals as to the validity of the study, but is there any criteria which would -- do you care to comment on any criteria about the health of the animals in terms of longevity, in terms of how they survive the study, their general health?

MR. CLEGG: There are comments one could make on that but I think the only way you could handle this is on a case-by-case basis. I think to give a general comment would be asking for trouble. Quite rightly, too.

DR. PALLOTTA: I think I can give you an example of the difficulty you are going to have. In one two-year, 400 animal study we did audit, there were 14 entries about health on the 400 animals for two years -- 14 entries.

MR. CLEGG: If we're talking about the same study, about 65 percent mortality.

A VOICE: Pursuing that a little further, let's take an instance where survival is good but we have an incidence of CRD that's been 80 percent mortality -- an oncogenicity study

or a toxicity study -- in your opinion, is that a validated study, if you've got good survival, you've gone the duration, you've got all the parameters you are supposed to be looking it, and you've tested for oncogenicity?

MR. CLEGG: I'm not sure I quite follow what you are getting at.

A VOICE: The idea of an endemic disease in validating a study which is designed to test oncogenicity and climatisicity, we go a certain period, let's say, in a rat two years, or 18 months in a mouse, and the fact that you have endemic disease is indicated by pathology in the lines such as CRD, is that going to be an overwhelming factor?

MR. CLEGG: I can only answer that for Canada, in this point in time, because it is one of the things we haven't discussed jointly. My own reaction to that would be it would be highly improbable it would be a validated study.

I can think of certain circumstances where it might and that is where you chose lung. Usually, under those sort of circumstances, I would think it would not but, on occasion, you can get lesions in liver from endemic disease and in kidney, which would tend to mask any toxic effects of the compound you might be looking at.

Then, under those circumstances, you may possibly run into trouble in having this study invalidated but this would depend upon what was found in the target organ in the 90-day studies which, presumably, would also be available. Do you agree?

DR. PALLOTTA: Yes.

MR. ARNOLD: Are there additional questions or have we answered everything sufficiently?

A VOICE: If a study has not been submitted yet -- say a 90-day -- that would have to be validated in the normal course of the terms. I break validation into two sections. One would be an audit where you just turn raw data in before the validation or scientific validity of the study.

Now, if it's never been submitted, when it is submitted, it would have to be reviewed by EPA's toxicologists anyway. Is there any sense in the registrant paying someone to validate a study when it has to be validated again to be acceptable? That could be a large amount of money.

MR. ARNOLD: Well, I think this concept of separating an audit from a validation is kind of artificial because, basically, the validation relies upon the audit. You get the raw records. Now, we don't normally do that, as you are aware, on

studies routinely submitted to the Registration Division.

In the case of new IBT studies, we have requested that the registrants submit an audit report, which is the raw data supporting the conclusions that are in the report. As far as I know, IBT reports are still reaching scientific conclusions. They are just not attested to by signature, but they are still reaching conclusions.

We need to see the underlying data for that and we request that the registrant provide that data in a manner in which we can judge the validity of it.

So I'm not sure I can appreciate the distinction you are making between validation and audit.

A VOICE: The problem is this, some of the toxicologists would audit a study and do a damned good job of it. He could not, under what I've seen, validate that study because he doesn't have the qualification.

Now, somebody would have to audit that. Would audit a document and send it to EPA and they have to review it anyway to see that it is scientifically sound. Yet, if it is something that has already been submitted to EPA previously, it would also have to be validated before it was sent in.

MR. ARNOLD: I now understand your distinction. Dave

has pointed out that this concept of a doctorate and non-doctorate is not a key to whether somebody can validate, but I still think the point is somebody who is qualified, regardless of whether they are a doctor or through experience or whatever.

Diana has a comment to make and perhaps that would be the most enlightening.

DR. REISA: (Inaudible.)

MR. ARNOLD: Let me repeat it. I think I caught about 50 percent of it but it sounded like a reasonable way to proceed.

The audit process basically defines how much raw data there is and, if that audit process comes through with all the data to support the conclusions that are in the report, that's all we need and we will review that report just like we would any other report, except we will not have the confidence that, in fact, it is reflective of what happened in the laboratory.

Now, if, in the audit, it turns out that the raw data doesn't support the conclusions -- there are either different conclusions, different mathematical determinations, of an effect level or an LD-50 or, if in fact, there are fewer animals to reach conclusions on than might have been represented in the report, -- at that stage, then, the registrant would have

to proceed with reaching some new conclusions, and those conclusions ought to be reached by somebody who is qualified to do it, just like you would with any other submission.

The submission should be based upon somebody's ability to reach a conclusion. So, if all the raw data is there, you send it into us and we can then proceed with our evaluation of the data.

A VOICE: I have one. I understand, at the present time, there are three levels of priority in relationship to validations of IBT.

Those materials where petitions have already been filed, materials of marketing products; those where the petition has been filed but is not a marketed product; and those where a petition has not been filed.

Now, in order for us to move along with some of these validations and audits and get assistance out of the Validation Assessment Team, I would like to have some direction from you to the people at IBT on how they move along with those materials that are in categories two and three, where the petition has been filed and it's not a marketed product, or the material has not yet been filed and we are awaiting the petition.

MR. ARNOLD: Yes, sir. I think you have probably hit

on an area where I think our basic interests are probably going to drive us to a different set of priorities.

From our point of view, our primary concern is the public health consequences of the decisions that we make. The fact that we have a petition pending creates a problem in that we are not going on with the registration of pesticides which the law requires that we do but, by the same token, we haven't created a public health question in the concept of exposure to the pesticide.

On the other hand, those that we have made decisions on and that are rather far-reaching decisions, our instinct is to concentrate on those because there is a potential for a problem and, if there is, we would just as soon identify it early and try to take some remedial action either by requesting new tests or, in the event of a determination of an adverse effect, some regulatory action.

I think probably, from the point of view of the registrants, the ones on the market are going to rise or fall in the long run on the basis of the data that comes out of the audit, but the new ones where you have exerted research and development efforts and money and aren't getting on the market, my impression is that that's where the registrants want to concentrate

the validation efforts, first, so that they can get on with the normal marketing of pesticides.

We haven't, as yet, given IBT a direction to concentrate on of one type or another simply because there was no way, in their creation of the microfiche library, that they could have proceeded other than just to do 100 percent of it. There was no way to do a little bit here and a little bit there, and that's why we have kind of all been standing around waiting while they could finish that first task.

Now, in the meeting with the Validation Team to answer the final questions, they have indicated that they will be responsive to the needs of EPA and Canada. Our first response is to deal with the chemicals where we have a major reliance on IBT data in the past.

However, we have already gone through a data base for a compound that has been sort of sitting and churning in the registration process for some time now. Lacking a rather strong and compelling argument from a registrant, we are continuing to try and concentrate on those pesticides that are on the market for which the major or the entirety of the data base has been generated from IBT and we have requested that the registrants use a similar kind -- I think, in the second letter that came

from Ed Johnson, we gave you, basically, a description of the kinds of factors we would use for creating a priority and suggested that you do the same.

There is no way that we can demand it but, certainly, our priorities are the high tolerance, high volume pesticides where the entire data base is with IBT.

A VOICE: It doesn't solve the problem.

MR. ARNOLD: No, it doesn't. I said that's why I think we have probably come to an impasse.

A VOICE: What I am suggesting is that perhaps, over the next six months, you have the immediate problem of working with the Validation Team on the marketed products -- public health products -- and then, those (inaudible.) But it seems to me, as time permits, they should then deal, particularly where some of the issues are rather minor as in the case of some of the newer products, that they try to get those out of the way.

Let's say, for the purpose of the discussion, you have a 90-day study and, for one reason or another, you don't even have the requirement for a two-year study on that particular material, the issues are much smaller than if you are looking for data on multigeneration or reproduction and the

investment in time of the IBT personnel will also, correspondingly, be rather small.

So, what I'm suggesting is that we do appreciate the immediacy to get on with those products that are on the market but you ought to, then, be in a position to have some direction from you to the people at IBT, as time permits, to work some of these others in.

MR. ARNOLD: Certainly. We've been assured, and I think we are all convinced, of the sincerity of the fact that IBT will continue to exist for as long as it is required to complete the validation effort, regardless of what happens to the sale of the assets.

If we weren't convinced of that, we would certainly be suggesting to the registrants that they push an ownership on that data and we might even be considering something to protect the integrity of our own decision-making process which, at this time, pretty much relies upon all the underlying data.

We've had very good cooperation, I think, to date with IBT and I think we recognize the problems they went into trying to pull together some sense out of 20 years worth of record-keeping, and I keep my fingers crossed.

I think we are very close, now, to the point of

saying, "This is as good a record system as you are going to get." We might not be satisfied with them, but there is no more, and we should get on with it and I'm convinced with their sincerity in trying to resolve any unanswered questions and, certainly, we will continue to try and provide some direction to the registrants and particularly to Industrial Bio-Test as they schedule visits.

Now, they are attempting to schedule visits on a chemical in line with our requirement or our needs to review a chemical rather than an individual test. So, when an audit is scheduled, they requested that we keep in mind the data base for a particular chemical and try to estimate the time required to get through that body of tests, and each chemical is going to be unique. So there might be several long-term tests that could require a fair amount of discussion. Others could have a number of less complicated tests and ones with, perhaps, a better data base that can be reviewed rather quickly.

They have indicated their willingness to be flexible and concentrate on this chemical rather than tests reviewed.

I think the registrants are in the same position as us in trying to construct a data base for a chemical rather than

for an individual test.

A VOICE: At the start of the meeting, you mentioned that there were some 45 studies that the people in Canada had audited. You gave kind of a percentage breakdown on how many were valid and what kind of questions came up and those not completely valid, and then you mentioned the concern of the EPA was based on 12 studies which had been audited jointly by the EPA and the FDA plus a build-up of information from registrants as they had asked for validation of studies from the EPA.

Could you give us an idea of the number of studies that would be and what the breakdown would be there in terms of the data that has been reviewed by the EPA?

MR. ARNOLD: Let me state that the 12 studies that were looked at were not a random cut of all the studies that were done. We concentrated on the chronic studies and that just happens to be the area that we think the greatest problem is probably associated with.

So, if we make a statement that we looked at 12 studies and we didn't find any that were entirely acceptable and we found X number that were invalid, that is certainly not representative of what might be out there.

I will let Art comment further, but keep that in mind

that ours was not a random cut.

DR. PALLOTTA: I hope you understand that our audits were audits that were performed at IBT that were intended only to give us an idea of how severe the problems were and approximately in what areas, and so forth.

They were not to validate studies. They were to get a better understanding of the problems and I think that ought to be very clear. They were selected studies in that sense.

MR. ARNOLD: As far as the conclusions which we have reached from reviewing registrants audits, I, unfortunately, am a little derelict. I didn't do that kind of a head count that Dave did before he came down and I just don't have the information. I am attempting to assemble it now.

Part of the problem is our two-phase approach to it. The one that we have asked specifically for audits and the other ones that have been caught up in the Registration Division and I'm having a hard time getting a count of exactly what is coming into the Registration Division.

They are going to start, hopefully, keeping me informed of what's going on. I don't want to get in the middle of it. All I want to know is who has asked for what and what they have received, so that we can make the most intelligent decisions on

this.

Dave just pointed out, I did mention that copies of the IBT formal conference procedures are available at the back desk. If you haven't received those, they outline the procedures which IBT will be working under in assisting you in resolving unanswered questions after you have reviewed your microfiche. So you might pick a copy of that up and begin to kind of work within those guidelines because I think, at this time, they don't have a lot of resources to expend and they are trying to figure a way that will most satisfy the registrants plus will allow them to do it in as timely a fashion as possible.

MR. CLEGG: I would just like to come back, if I may, to the question with regard to the number of studies which have been looked at.

I would emphasize, again, that the number we have looked at is very small and, therefore, to put any sort of statistical analysis or anything else on to the number we have looked at, with regard to the number which may or may not be found to be valid in the future, is not a very wise thing to do.

The idea, as far as we were conerned, was just to find out approximately what percentage may be invalid and, at the moment, we are running somewhere just over 80 percent, but

that does not mean that this is going to continue to be the case.

There was no particular selection of studies. We just took them as they came in and looked at them and they are not particularly going in any one particular direction. So, if you are looking at chronic, as Fred indicates, I suspect that you will find there is a higher incidence of invalid studies. However, if you are looking at, let's say, 90-day dog studies, then the probability is you are not going to find many of those which are invalid. In fact, I don't think we've found any so far, but then we've only gone through four or five.

A VOICE: On these validation packages, how many, percentagewise, have been found unacceptable when they are submitted to be validated?

MR. ARNOLD: I can't really answer that question. Let me explain what we have done to date.

Almost all of the validation packages that have come in, individuals have brought them into the office and we've sat down and we've started going through them and, in almost every instance, we've offered some suggestions, they've offered some comments and they've gone back.

So we have been receiving almost draft validation

reports and only in a very limited number of cases have we received final validation reports on those 640 tests that we asked about a year ago.

The ones that we have received -- in fact, if I'm not wrong, Arthur, I think we've been quite satisfied with the quality of the validation work. I mentioned earlier in the morning that we found no validations that were entirely consistent with the raw data and, also, that the errors are kind of random and I don't know whether they are significant or not.

I only raised it because, when that happens, if we're in a spot-checking kind of procedure, spot checking, calculation and looking at a diet prep, and we start to see errors in there, they are just going to slow it up, even small errors.

Large errors, if we are spot checking, the errors are going to cause eyebrows to raise and then we are going to have to get into it a little deeper.

So, to avoid that, I just said that the first effort ought to be as good an audit as you can make, recognizing these things can really burn your eyes out and it's awfully difficult to make these linkages, but to be as careful as possible.

We've been quite satisfied with the quality of the validation reports we've been receiving.

A VOICE: If the validation has not been reviewed by EPA for any reason, you could go for a year and get 20 validations and then you are doing something wrong that you had no idea you were doing wrong and you'd never be told. You would have done all this work and then you would have to redo it.

MR. ARNOLD: I think that's the reason why most of the registrants -- and I think we have met individually with at least six or seven different people in the room to date to review early on what they were doing, to see if they had answered the questions we want answered and, in all cases, when we suggested that we need more information and to put less reliance on something, the suggestions were taken.

I think we have now got down to a point where we can offer a format for a report that we think, one, is useful from the registrants point of view, and useful from our point of view. Six months ago we couldn't have done that.

We could have because I should say, often, EPA issues kind of interim guidelines and regulations. We didn't want to. We're still willing to work with registrants.

If you have questions on whether or not a procedure appears to be an appropriate procedure, by all means come in and ask us and we'll offer whatever guidance we can.

MR. CLEGG: Two things I would like to add to that before the next question comes up.

First, in terms of the validations we have looked at, as Fred said, we have found errors in them. I would like to indicate, straight away, that the errors do run both ways. They are not all errors in favor of the compound. Some were errors which were against the compound.

The way we have dealt with these is to go to to raw data and do our own validation and then compare them with the industry validation. That's the routine we have been using to date. Whether we will continue that way, I'm not sure.

Also, on some occasions, people who have done the industry validations have picked up some of the things we've missed. So I think it is a case of genuine errors and nothing other than that. I would like to make that point very clear.

The other thing, which relates to the receipt of validations and the possibility of having a 12-month time gap before a validation is looked at, I think this morning there was a little confusion over this and I'll try to clarify it by indicating that, in fact, when we have the raw data and the validation, these studies will be looked at.

It is the overall assessment of the compound which

will be delayed in time until we have the total data base.

So, if we find something which is completely unacceptable, with regard to the format or what-have-you of the validation coming in, I think the probability is that whoever submitted that particular validation is going to hear about it in fairly short order.

In fact, if I can exemplify this, we have one firm who came in, who sent in some validations and they sent in some microfiche within 48 hours. I phoned them and said, "Look, these microfiche are completely illegible. They were rather startled. They reply I got from them was, "God, we didn't expect you to ever look at that raw data."

DR. PALLOTTA: I would like to also comment once more that, on that sample report format that was handed out, that is one way in which you can speed up the process yourselves by following that format.

There will be inconsistencies and it will help in the task force, both in Canada and the U.S.A., to get the job done.

A VOICE: (Inaudible.)

MR. ARNOLD: Let me just repeat that. You are suggesting an old study was submitted and now you have a one-page correction to that old study. The question is, do you submit

just a page or two pages?

MR. CLEGG: That's quite acceptable. We've agreed because, in fact, some companies have submitted audits and validations and then have received additional information from IBT. So we will accept amendments and changes to audit validations and to the data base which is involved in this, if necessary.

MR. ARNOLD: This is a case where there is a page changed in the final report. Not additional data to support a conclusion, is that right?

A VOICE: Yes.

MR. ARNOLD: Well, it looks like we have either exhausted our ability to answer questions or your ability to ask them.

I will continue to try and work on a one-on-one kind of capacity with you and you have the assurance from IBT that they will be responsive to your requests for the status of the microfiche and if, again, it appears you are not getting an answer or you can't quite understand the status of your microfiche, I wish you would raise that with me, so I could perhaps go back to Bio-Test and find out specifically, because we do want to begin moving on with this and I think there is just a

natural inclination on everyone's part to avoid approaching those studies for which there is no data. So we should be in a position to find that fairly soon.

Thank you.

(Whereupon, the foregoing hearing was concluded at 2:45 o'clock, p.m.)

CERTIFICATE OF REPORTER

I, Elizabeth Ann Tipton, do hereby certify that the foregoing proceedings were taken stenographically by me and, thereafter, reduced to typewriting by me; that said transcript is a true and accurate record of the proceedings to the best of my ability.

Elizabeth Ann Tipton

Elizabeth Ann Tipton