DR. KENDALL: Good Morning everyone.

DR. UTELL: ... Interest beyond the general scope of the deliberations on this matter and I am not aware of any financial interest that I would have in this particular matter. Dr. Kendall.

DR. KENDALL: Thank you Dr. Utell. My name is Ron Kendall, I direct the Institute of Environmental and Human Health at Texas Tech University and Texas Tech University Health Sciences Center. And also I am a professor in the program. We have a relatively broad base of funding that includes many federal agencies and industrial grants as well as state grants. At the present time the work that we do embraces the effects of chemicals on the environment and human health and we do get into some human surveillance studies which proceed through institutional review board upon review. And this has particularly been related to initiatives with the Department of Defense. Other than that, the University of which I'm employed, embraces standard procedures regarding evaluation of human exposure through their institutional review boards. At this time, I submit all financial information and confidential information as consistent with my chairmanship of the SAP. I, at this time, have no knowledge of any financial interest that may be improved as a result of the outcome of this meeting. Other than that, we look forward to moving forward to have a successful day. Dr. Portier would you like to continue?

DR. PORTIER: Yes, hello. I'm Chris Portier from the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina. I'm Chief of the laboratory of Computational Biology and Risk Analysis and Associate Director of the Environmental Toxicology Program.

I've done no research on any of the matters before the board. Certainly, my institute does do clinical research and I have been involved in clinical research and designing studies and making sure they're executed properly. I've made no previous public announcements on this issue nor any testimony, etc. Certainly my employer is interested in the matter as member of the National Institute of Health. But other than that, I don't have a specific role as an individual in that interest. And to my knowledge I have no financial interest that would be increased or decreased following this discussion. And no research grants associated with this matter. Thanks.

DR. WEISS: I'm Bernie Weiss. I'm a professor of Environmental Medicine and Pediatrics at the University of Rochester School of Medicine and Dentistry. My research is in the general area of neuro-behavioral toxicology. Right now, I have two NIH grants on neuro-toxicology one of TCDD dioxin and one on mercury vapor, both of which explore the developmental neurotoxicity of those kinds of exposures. I'm also involved at the human level with a project we've maintained in the Safe Shell Islands on the developmental neurotoxicity of metal mercury. I've written some on pesticides pointing out the questions rising from neurotoxicology, but I'm not now involved on any research on pesticides and I have no fiduciary interests of pesticides at this time.

DR. MCCONNELL: Hi, I'm Gene McConnell, I'm president of ToxsPath, Incorporated, Raleigh, North Carolina. I'm trained as a veterinarian and did a residency in comparative pathology. I also have boards in toxicology. My background with regard to human testing is that I was a subject of human testing when in college for a

rabies vaccine and subsequently, in half of my career in the military, I was subject to several human tests of various sorts. Some of which I don't know if they are still classified or not, but none of them in the area of pesticides that I am aware of. Subsequently, in my role with the National Institute of Health, we worked on various chemicals, as anybody knows about the National Toxicology Program. The only one I can think of that I worked on of a pesticide nature was melathighon and melaoxon in which I reviewed the slides on that study as part of my work and subsequently published a paper in environmental research on the results of that. I have no financial considerations with any company that makes, distributes, or uses pesticides that I am aware of. I've done no work either for pay or expenses for pesticide companies, nor have I done any work for public interest groups that have, in the same way, that have interest in pesticides, nor have I done any work for any advocacy group that has a stated position on this subject. I have no stocks in any of these companies. The only thing I would add to this, that I can think of is that I have been asked to participate in an issue session at the Society of Toxicology this coming March, that's going to address this same issue. Other than that, I have nothing else.

DR. MESLIN: Good morning, I'm Eric Meslin. I am the Executive Director of the National Bioethics Advisory Commission. At the previous meeting of this group, I advised the group that I am here in my capacity as a Bioethicsist, not in my role as the Executive Director of NBAC. However, I think it's worth noting for the record, that the National Bioethics Advisory Commission not only is interested in, but has had a long

standing interest in the Federal System for protecting human subjects. It was part of NBAC's original charge signed by President Clinton in 1995, but the commission evaluated the adequacy of federal human subjects protections, and most recently the commission was asked by the President's science advisor to return to this charge and to develop a comprehensive report on this subject. Very recently, Chairman Schapiro, the chair of NBAC wrote to all of the senior executives, department secretaries, and agency heads, including the head of the EPA, requesting information in regards to this particular report that NBAC is working on. So I wanted the group to be aware that although I'm not here representing the Commission, but rather in my private capacity as a Bioethicsist, I did not want there to be any perception of conflict in that regard. I have no financial conflicts that I am aware of. I am a philosopher by training. I have no research grants in this area nor have I had research grants in the area of pesticide use. My own academic training, however, in bioethics has involved extensive research on the ethics of human subjects experimentation.

DR. DEGEORGE: Joseph DeGeorge from the Center for Drug Evaluation and Research,Food and Drug Administration. The Associate Director for Pharmacology and Toxicology in the Office of Review Management, which is responsible for overseeing clinical trials and safety of those clinical trials. I've been with the FDA for about 10 years and within the FDA served as a reviewer for pharmacology/toxicology data and as a team leader and in establishing policy that is involved in the setting of safety of standards for clinical trials. I have no particular interest, financial otherwise in pesticides or other environmental

chemicals, other than the fact that I'm a consumer and a gardener and basically a normal person who is expose to pesticides and those? chemicals. Thank you. Dr. Ellis.

DR ELLIS: My name is Gary Ellis. I am the Director of the Office for Protection from Research Risk at the National Institutes of Health. I am also the chairman of the Human Subjects Research Subcommittee of the Committee on Science of the National Science and Technology Council out of the White House office of Science and Technology Policy. In that role, I chair a group of federal representatives which includes the Environmental Protection Agency. Having said that, I have no authority over the Environmental Protection Agency other than convening authority. I have no assets or financial interest related in any way to the subject matter. I am on record several times as stating that I believe, with regard to protecting human subjects and research, that any time one interacts with or intervenes with a person or uses that person's private identifiable information that, that person is owed two things; first informed consent and second prior ethical review of the activity by a local institutional review board.

DR. KENDALL: Dr. Kahn.

DR. KAHN: I'm Jeff Kahn. I am the Director of the Center for Bioethics, at the University of Minnesota. I'm also a Professor in the Department of Medicine and in the School of Public Health and Division of Health Services, Research, and Policy. All of my research funding is Federal Government, nothing from the EPA, however. Nor do any of the faculty in my center have any EPA funding. I have no financial interest in anything that would bear on the considerations here

today. I noticed, however, that there was a statement signed by the American Public Health Association-some of the materials that were submitted in advance of this meeting. I should say, I am on the governing council of the APHA, although I was not consulted related to the signature on that particular letter. I think that's about all that relates to the proceedings here.

DR. FIEDLER: I'm Nancy Fiedler. I am an Associated Professor in the Department of Environmental and Community Medicine at Robert Wood Johnson Medical School, which is a part of the University Medicine and Dentistry of New Jersey. And I am also a member of the Environmental Occupational Health Science Institute in New Jersey. My career over the past 15 years has been involved in occupational health and in doing surveillance studies which have included a study, which I published on the chronic exposure to pesticides and pesticide use. I have current funding from the National Institute of Occupational Safety and Health. I've been funded by both the Federal Government and by private industry. As I mentioned, I've done exposure studies, threta-epidemiologic studies, I've also been involved in control exposure studies with other collaborators at our institute. I do not personally have any funding from the Environmental Protection Agency, however, other members of our institute do have funding. I do not have any, that I can think of, financial interest in any company or research grant, currently that pertain to the topic at hand today. I do have financial interest in mutual funds, but I have no idea what companies they invest in. So, at any rate, I don't believe I have any financial conflicts of interest.

DR. KENDALL: Sam.

DR. GOROVITZ: I'm Sam Gorovitz, a professional philosophy with pubic administration at Syracuse University an old bioethical war-horse. It occurs to me that 15 years ago, I spent a summer as a full-time consultant to OPRR, but apart from that I've had no specific involvement in these issues and there is no conflict of interest, real, apparent or potential that I am aware of.

DR. NEEDLEMAN: I'm Herbert Needleman. I'm Professor of Psychiatry and Pediatrics at the University of Pittsburgh. My work is engaged in the studies of led at low dose on cognition and behavior of children and now of adults. I'm on the advisory board for the children's health environmental network. I'm on the board of directors for the Western Pennsylvania Conservancy. And I'm co-chairman of the University Tenure and Academic Freedom committee none of which pay me a sue.

DR. KENDALL: Routt Reigart just walked in and welcome, sir.

DR. REIGART: My name is Routt Reigart and I'm professor of pediatrics at the Medical University of South Carolina. I guess the only thing of relevance is I'm chairman of the board of advisors of the children's environmental health network.

DR. UTELL: Thank you for your thoughtful comments. I think that this part of the process is an important step in terms of providing background on all of the panelist. At this point, we need to work our way through any administrative procedures and perhaps we'll start by asking Larry Dorsey to work us through that process.

DR. DORSEY: Before we do that, Dr. Utell, we were talking earlier, the staff's done a lot

of work, a lot of work, getting us here and coordinating everything. Dr. Utell, I think that every member of this panel thanks the staff, and both the Science Advisory Staff and the Science Advisory Board, and we're sorry that Dr. Rondberg can't be with us, the designated federal official from the Science Advisory Board, but we welcome Ms. Conway. And Mr. Dorsey, and Dr. Irene thank you for all your effort, and Ms. Shirley Percival. But, before you take all that to heart, there's a lot more work to go. So that was just my way of introduction.

DR. IRENE: Good morning everybody, I'd like to welcome you to the Joint Science Advisory Board and Scientific Advisory Panel meeting on Data for Testing on Human Subjects. This is the second meeting on this topic. We have reconvened here with this panel from the December 1998 meeting and unfortunately, Dr. Kaplan and the original panel could not be here today. He had a conflict in schedule. And Dr. Payton unfortunately had an emergency had to leave. Other than that, we have the original panel members here. I am a co-designated federal official, and I'm looking forward to today's meeting. I'm sure there will be very lively discussions. As a designated federal official, my role is to serve as a liaison between the panel and the agency. To be responsible for ensuring provisions of the Federal Advisory Committee Act and to ensure that those provision are met. To conduct an open meeting under FACTA, which means that all materials are available to the public, all discussions are open, and everyone is allowed to participate. And finally, to ensure that participants on the panel are aware of the Federal conflict of interest laws, and each participant has filed a standard government ethics form, and

that form has been reviewed and is on file to ensure compliance with the ethics regulation.
All materials are in the public docket, any questions posed by the panel and by the Agency and other documents related to this meeting, are available in the docket. Overheads will be available in a few days, and background documents are also available on the EPA website. Now the docket phone number is area code 703-305-5805. The address is 1921 Jefferson Davis Highway, Crystal Station 2, Room 119, Alexandria, VA. The websites are on the agenda, and I will actually read them in a moment. All materials for this meeting, are currently in the docket, and most are on the website as well as the material from the first SAP/SAB meeting on this topic. The two websites are on the top of the agenda, that you should all have. And finally, when the report is finalized it will also be available and posted on the website. Thank you.

DR. UTELL: Larry or Cathleen, any additional comments?

DR. CONWAY: I don't have any, Larry?

DR. DORSEY: Just one point of fact. We will have a transcription of the meeting. Since I don't know when it will be available, I won't venture a guess, but there will be in fact a transcript of the proceedings of today's panel discussion.
I think at this point, we probably should move ahead with the background materials, presentations to be made, by the Agency. Dr. Steve Galson who is the director of the Office of Science Coordination and Policy is here to provide us with some introductory and background materials. I might emphasize that Dr. Galson has really played a very important role

in trying to help us move the process forward. Both Dr. Kendall and I, truly appreciate his involvement to this point.

DR. GALSON: Excuse, Dr. McConnell a point of clarification.

DR. MCCONNELL: Yes, a point of clarification. Back to this other thing, I'm sorry, Steve. I have a question regarding procedures. This is a joint meeting between the SAB and SAP who have different procedures in the sense that with the SAP, everything has to be said at the table or it cannot get in the report. SAB is not that way. SAB, you can do things for background and so forth to get into the report. Two questions: One, which are we operating under today? And number 2, all those comments and so forth that were made at the previous meeting, we don't have to go back over those again do we?

DR. UTELL: Dr. McConnell, I think raises a very important issue and actually I plan to touch on it a bit later, but we do have a joint meeting of the SAB and the SAP, and there are some differences in procedures, and in fact, some of those cultural differences, I think, lead to why we needed to get together for a second time. In general, we're going to try to meld the activities of the two committees. I believe we've made an agreement, as I said this meeting will have a transcript so that will be the procedural operation.

The process of putting the materials as we're going through the development of the document up on a website so everyone can share in everyone else's comments, we've made a commitment to do that as well. Which is a little different than the SAB standard operating procedure, but much more in keeping with SAP. We would like the document to reflect the deliberations of the committee comments

at the meeting. We should not have much in that document that was not discussed at the open meeting. To say if there was a brilliant insight that came along later and was added as a footnote, it's possible, but our goal, Gene, is really to try and capture in the report, the discussion and the opinions of committee members, as sighted today in the discussion. Now, obviously, some of the write-ups take place following the meeting, and we need to count on committee members to try and incorporate what was said here, and that often can be sensitive in terms of what was said and what gets written, but we need to try and keep to the material that was discussed and presented today. Sorry to be so long-winded, but it's not always straight forward, because some of these things do get written up after the panel meets.

DR. MCCONNELL: I know what I was worried about is, for instance, the Common Rule, the Helsinki, of course, which we went through some detail at last meet, we don't have to go through those again

DR. UTELL: No. No. The materials that have been presented at the previous meeting are clearly part of the record and Dr. Ellis walked us through that. We've not asked him to repeat that he's here for informational purposes, but clearly not for presentation.

DR. MCCONNELL: Thank you very much.

DR. KENDALL: I like to turn it over to Mr. Dorsey to add any comments to your questions, Dr. McConnell. We were going to address these questions subsequent to the EPA presentation. Just for the audience and for the committee's update, as we have discussed in previous phone conferences and other communications, we would ask EPA to revisit and refocus and

completely crystallize the charge today, so that we can refresh ourselves. Secondly, we would then review, which Dr. Utell has already done a good job of, the essence of our operating parameters and then we will move forward. So, Mr. Dorsey any comments to add to this or Dr. McConnell's questions.

DR. DORSEY: Thank you. And I think Gene has a really important point. I think what we have done in one of the operating memos we put together, probably better define the process of working together with the SAB. One point I think is very important, if there are significant comments concerning the issues to be discussed today, and you feel very important that these comments should be included in the report, at least raise the issues to the other panel members. We can, you know, attach an appendix to the report, we can add a statement after the fact. But really, if you have an important comment, we asked that that surface at this meeting, and allow other panel members to discuss it. I think we've all agreed, and Sam and I, really encourage you all to do that, because I think it will give us a better report. And we'd like to move this report along. Our purpose today is to refine some of the comments and allow you the chance to discuss some issues that we could not resolve in drafting the report. But really, our goal today is to try to resolve some of those issues, agree where we can agree, and agree to disagree, and to get the report drafted and close out the operation of this committee. But Gene, thank you for that comment.

DR. UTELL: I think we're going to give Dr. Galson one more chance. And we'll proceed.

DR. GALSON: Thanks a lot. On behalf of the management of the Environmental Protection Agency, I want to thank all of you for being here, this is really a fabulous panel and we're very appreciative of your time, of your commitment to public service, and your expertise. A number of people have asked me where this is an unprecedented occasion to reconvene a panel after they were unable to agree on a report. And I want to assure you that the Agency has convened many federal advisory committees over the years, on tough contentious issues, and it frequently takes many meetings for these groups to come to decisions or conclusions. Perhaps, the only thing that might be unusual about this group is that we didn't anticipate before hand, the difficulty that the panel would have. In any case, we thank you for your commitment again and particularly to this issue that crosses the usual disciplinary boundaries of the Scientific Advisory Panel and the SAB. The advice that you give us will be very important to the future of human testing of pesticides, and influential in the evolution of EPA's human testing policies in general. It will have enormous impact on the pesticides that are regulated and approved for use by the EPA.

I want to take just a minutes to acknowledge the really hard work of the EPA staff, in particular, Mr. Carley, Dr. Irene, Mr. Dorsey, Ms. Percival, Mr. McHugh, and Dr. Lewis, sitting at the back table. This has been a particularly tough group to get together to reschedule and it's really important that everybody recognize the hard work that has gone into it. I also want to especially acknowledge, Dr. Utell and Dr. Kendall, for your commitment to bringing this group

together. If it wasn't for that, we wouldn't be able to do this, we would have been stuck in limbo there. So, with that, I want to turn things over to Marsha Mulkey, the Director of the Pesticide Programs Office, who will focus a little bit on some of the substantive background that's bringing us here today. Thanks.

DR. MULKEY: Well thank you and let me add my greetings to all. And my thanks to the panel for your service. We remain very pleased and very grateful that you have taken on the effort of helping us with this thorny and challenging issue, which his vitally important to us as an Agency and of particularly vital importance to the Office of Pesticide Program. And it is because of that sense of urgency that we have worked so hard to try to make it possible for you work fully and freely, and in a way that can be helpful to us. This second meeting does not have a new purpose. In fact, our whole point in convening you is to allow you the opportunity to complete your discussions of the issues which arose as a result of the original charge which we made to you last December. We expect and understand that you will pay particular attention to issues which may have appeared to divide you or at least on which you have had some difficulty coming to a common way of thinking about and speaking about them. But we trust that you will keep your focus on the original set of questions we posed, and on the practical implications of those questions, for the particular issues of the pesticide program, as we go forward, with our own thorny and challenging path of implementing the Food Quality Protection Act of 1996.

By way of background, we think it useful to tell you that in many ways relatively little has changed. Since we convened

you and told you about the context in which we were asking you to look at these questions. We continue to receive, in the Office of the Pesticide Program, a number of unsolicited reports of human test subject research submitted in the context of our Pesticide Regulatory and Licensing Program. These studies in particular, having to do with systemic toxicity studies for the purpose of helping to establish a NOAEL and therefore, on our part, a reference dose as a departure point for regulation. We also have continued since at least July, 1998 to adhere to the posture that we will not take any final regulatory action based upon our reliance on this kind of human test subject study, unless and until we have in place a policy which allows us to assure ourselves that these studies meet appropriate high ethical, and scientific standards. It is also a part of the context in which we all operate and important for us to all remember, that EPA, like many other government agencies, does conduct itself, some research involving human test subjects; subject to the Common Rule and in compliance with it. And also that there are many tests on pesticides as on other substances involved in Federal Regulation which do involve human subjects other than this context of systemic toxicity for NOAEL studies. So that we receive and even require, studies involving human test subjects on such things as skin sensitization or pharmakinetics and other kinds of studies. And that, whatever policy we develop needs to be comprehensive enough to allow us to have a consistent responsible ethics and science based approach to this whole range of human testing beyond this narrow and particularly challenging universe on which you are focusing.

There have been some developments--we've been busy. We have not been brought to a halt by this or any other issue. We have continued to make a large number of all sorts of regulatory decisions in the pesticides program including the licensing of new compounds and the reassessment of existing tolerances and the re-registration decision making regarding older chemicals. For at least some of these chemicals, we do-have had in our files other kinds of human testing materials relating to NOEL type testing and during that period none of our final regulatory actions have relied on any of those studies. However, it has been a pretty rare situation where we had such studies in our files and we have been active in making final regulatory decisions. But there have been a few such instances. At the time that we introduced our problems in this area to you we gave you a little context relating to the Food Quality Protection Act. I think it's important for us to clarify that there is no provision of the Food Quality Protection Act, itself, that speaks directly to the question of how pesticides are to be tested for their toxicity or how the Agency or any registrant or licensee should handle the testing of pesticides in human test subjects. It is not directly addressed by the Food Quality Protection Act. What the Food Quality Protection Act did do, was change some of the regulatory landscape relating to pesticides as it related to the relative safety standard, reasonable certainty of no harm; that is to say, without necessarily reference to, for example, a balancing benefits, it was a health-based standard, as well as certain specific provisions relating to, among other things, additional safety margins to protect against the possible extra sensitivity or unusual exposure of children. And so that, in addition to whatever safety margins the

regulatory agencies might or narrowly include, we were asked to include a ten-fold safety margin to protect infants and children unless we could, based on reliable data, determine that it was not necessary. So that, in at least some instances, the retention of the full additional 10-fold safety met margin to protect children is necessary under the new statute or at least some additional safety margin beyond the standard safety margin. This of course, the combination of the new health-based standard, and the additional safety margin for children, could and does create a dynamic in which some compounds must be regulated more rigorously than they might have been done prior to the Food Quality Protection Act. And there is some evidence that that context has created an environment in which pesticide companies and others may seek out ways to reduce the uncertainty and/or therefore the safety margins through other means, such as the testing of pesticides in human subjects. So that's the relationship. It's an indirect definitely unintentional, and I suppose debatable connection between the Food Quality Protection Act and the testing of pesticides in human subjects. But it is the case that if we have available to us scientifically sound and sufficiently rigorous data in human test subjects that we can accept, on ethical grounds as well, there is the potential for reducing the otherwise applicable safety margin that is the safety margin, that we would otherwise apply to assure that the extrapolation from animal data to human effects, is sufficiently protective. And that, therefore, can lead to a dynamic in which as a result of the availability of test data on humans, it is possible from a regulatory framework to allow what may be as much as 10 times as much exposure under the same safety standards. I say may be as

much as 10 times because the lowest dose rate in the animal study is not always the same as that in the human studies. That is, the lowest safe dose rate. So, it's not an automatic 10-fold, it depends of course on the results in the two types of studies.

In the context of this we have some special concerns and special needs. We need good science, we need a way of determining what is sound science in this arena. We need good ethics and we need consistent ethics. We need the ethics that we can apply to ourselves and to the relevant remainder of the folks with whom we interact. So we need measures like that in the common role which we are consistently applying to ourselves; available to apply in these larger contexts. We need to be open, transparent, through a participatory process, have a policy that everybody understands, can predict, and can order their behavior around. So we need a process for policy development which is informed by, among other things, the kind of issues that you are helping us, and we look forward to your advice regarding. We also need an approach which has enough dynamism to reflect the realities that have to do with the changes in both science and ethical standards over time. We expect to work very hard in sound policy development. We are hopeful to have the benefit of your advice, and we look forward to it at the earliest possible time, but we have a very clear need to proceed with policy development. We expect your advice to be a matter of public record. We expect our policy development to be an open and participatory process which includes all the other federal agencies with special reference and deference to the Department of Health and Human Services, which has the leadership within the Federal government for this subject matter, as well as all the

relevant players within our own agency and we expect an open and public participatory process before we reach the end of the day on policy development.

Now we have submitted to you a summary of these kinds of systemic toxicity studies that we have received since the passage of the Food Quality Protection Act and you will note that we have received six of these studies in the period between your meeting in December and the present. And we expect to continue to receive something like that kind of pace of these unsolicited, but submitted studies, and the last six on your list are the six that we received in that period.

I would like to conclude with just pointing out a little bit about the scope of what we are seeing just in this relatively short period, less than one full year, not much less, but a little less than one full year. Not all these studies are oral administration, there are dermal and interrelation studies included. So, the universe is sort of broader than a single root of exposure testing. Not all of this group of six involve cholinesterase inhibitors so obviously we're not limiting ourselves to a single kind of measure although the majority, the overwhelming majority of these kinds of tests that we have received are cholinesterase inhibitors. Not all of these studies are neurotoxicants, although I think all but one are. So that's not necessarily a limitation that allows us to know what we're going to be dealing with. And they're also not all insecticides, although again I think all but one are. So the universe on which we may continue to receive these kinds of studies in this current environment is pretty broad, and we hope that your advice can help us deal with that reality, along

with the others we've tried to help you understand.
I don't plan any further remarks, but I want to add my thanks to John Carley who has done really yeoman's work within the Office of Pesticides Program to assure that we are able to provide for you, all the information we have that may be helpful to your deliberations to offer on behalf of our office and for that matter, the rest of the Agency, to try to find you information that may be worthwhile or useful to you in your deliberations. It was our effort to provide that through this submission and these remarks, and unless you have questions, I am eagerly awaiting an opportunity to hear what you folks have on your mind.

DR. KENDALL: Any questions from the panel for the comments from Ms. Mulkey or any further clarification comments regarding the EPA charge?

DR. NEEDLEMAN: Yes, I do.

DR. KENDALL: Dr. Needleman.

DR. NEEDLEMAN: Ms. Mulkey, when the EPA receives one of these newer human studies, do you have formal criteria to evaluate their scientific status?

DR. MULKEY: We have not never published any guidelines about how to conduct these studies. We do not have systematic published or open criteria. We have in the past, evaluated these studies on an individual case-by-case basis. Looking at all the information provided in connection with the study, together with all the remaining information we may have about the compound, including all the other studies. So part of the difficulty and challenge for us in this area, is that, unlike most of the other information we receive, not everything,

but most of the other information we receive, we have not set forth the guidelines, the rules of the game, if you will, regarding this kind of study.

DR. KENDALL: Dr. McConnell.

DR. MCCONNELL: Yes, Ms. Mulkey, regarding field studies, where you take worker exposures, can you tell this panel, I think it would useful for many of the people on this panel, what's involved in those kinds of studies, and what kind of information you get out of them, and what you do with that information?

DR. MULKEY: Let me see if we have somebody here who can do a more thorough job then I might.

MR. LEIGHTON: My name is Tim Leighton, and I work for OPP's Health Effects Division. I review exposure studies and generally when we see biomonitoring studies, we will see passive dysemmtry also and we will use both of the data sets. But basically to do these studies, the registrant will go out, do a study based on the label criteria, and from there we'll collect basically urine samples and we'll get an absorbed dose and that data is compared against, basically, what we do is animal studies or in the past using the human tox studies and we'll use that for a comparison to get a ratio and do our margin of exposure calculations.

DR. MCCONNELL: So they're for exposure primarily, they're not toxicology studies?

MR. LEIGHTON: Definitely.

DR. KENDALL: Thank you. Chris

DR. PORTIER: If I could have a quick follow-up question. If I understand this correctly, the exposure studies you've just described would only differ from a clinical study in the sense that you

would know the exposure exactly, the external exposure in the clinical study as compared to the observational study where you would have to infer what that exact exposure was?

MR. LEIGHTON: For the exposures that are done on these guideline studies that we have they are based on what is allowable with the label and they're usually done certainly, not done more than the maximum rates so we know what the individuals are exposed to. I don't know if that answers your question or not.

DR. MCCONNELL: But you're not looking for metabolites or phthalates or absorption percentages, distribution.

MR. LEIGHTON: No, what we're actually looking for is the absorbed dose of the parent chemicals, is what we're trying to get back to.

DR. MCCONNELL: But, you don't know what percent each of that would be, because you don't know what the dose was, is that correct or not? I mean, you don't know what exactly how much the person was exposed to, but you know how much was absorbed in the body?

MR. LEIGHTON: The way we have the potential exposure, the actual residues . . . (end of side A)

DR. KENDALL: Did you have any follow-up questions?

DR. GOROVITZ: Yes, a follow-up question for Ms. Mulkey. The review of the reports submitted since the last meeting gives us some information about the studies, their intended purpose and their subject matter, but no information about sample size. Can you tell us anything about that?

DR. MULKEY: John can provide some of that.

DR. GOROVITZ: I'd like to have some idea of the range.

DR. CARLEY: These studies, concentrating on the six that have come in since last year, which were not included in the information we gave you last year about size. And those are the six beginning with methomyl at the bottom of the first page of the table. These are, with the exception of the last one, the dermal study, these studies all follow a pretty consistent protocol. There are going to be five or six dose levels designed in front and at each dose level there are going to be from say 6 to 10 subjects, some given the compound, some given placebo, and it's a rising dose protocol designed to be terminated when they produce a statistically significant decrease in cholinesterase.

DR. GOROVITZ; Thank you.

DR. KENDALL: Dr. Kahn.

DR. KAHN: In relation to the same. . .

DR. KENDALL: I just wanted to inform the committee, we are moving, I want you to go on and take that question, but we are moving to a presentation by doctors Fiedler and Gorovitz that will more deeply resolve, I think, the questions related to EPA charge, ok. But go ahead, Dr. Kahn.

DR. KAHN: A quick question of fact. Of the chart that we are referring to, where were these studies performed? Do you know that?

DR. CARLEY: The corpyrapotts? study was performed in Nebraska by MDS Harris, the second one on the back page. All of the remaining studies were performed in the U.K. In all five cases the clinical stage was at Inverest Clinical Research in Ettenboro.

The last one, the analytical phase was done at ICI Central Labs also in the U.K.

DR. KENDALL: O.k., thank you for the questions. Let's move forward with the agenda, I will note for everyone, that as we stated at the top of the agenda, time allocations may be revised. In other words, as we move through this process, Dr. Utell and I will be managing the agenda that will help us achieve our goal of bringing this to a conclusion today. In the meantime, in the process of our subcommittee and committee operations, we've had several conference calls among other communications and we've identified a subcommittee made up of Doctors Fiedler and Gorovitz to discuss or evaluate the EPA needs and the context of our subcommittee's report. We've allocated time on the agenda to update the committee as to their progress. Dr. Fielder and Dr. Gorovitz the floor is yours.

DR. FIELDER: Thank you As Dr. Kendall mentioned, we had a couple of conference calls and I know that everyone here on the committee was invited to attend those calls and not everyone was able to, but out of those calls arose some of the issues that I'm going to highlight now from the background paper that was kindly provided by EPA. Just to say, by way of my own background that one of the concerns that came up in the conference calls, was that our committee did not have enough background information from EPA regarding the context for this committee, and short of just the Food Quality Protection Act that came up but also other issues that EPA was concerned with. So we requested a more thorough and complete background paper which has been provided to all of you. I'm not going to go through the specific history that is in this paper because I think it

was certainly very helpful to me and probably all the committee members, other to say and to reiterate that the paper indicates that EPA has never defined guidelines or protesting pesticide effects or establishing an NOAEL in human subjects, and that is part of our charge to begin to develop both scientific and ethical guidelines. What I want to highlight, and I must admit that I think that some of what I am going to highlight is my own personal take on this, not my opinion. But more my concerns as the report has developed and as I read this background paper of what I think we need to focus on, and certainly what in our conference call we felt that still needed to be dealt with today.

First of all, I think that EPA is asking for guidance from us in a more operational sense and more specific terms than probably what we will come to or what we came to in our last report. And, as I read the background paper there are two areas: One area of research that has gone on and continues to be published are the incidence follow-up and epidemiologic studies, and both scientific and ethical guidance for those kinds of studies and what are considered acceptable or not acceptable. The second, and probably much more contentious are those that are considered controlled human exposure studies that go from oral to dermal dosing studies and pharmacodynamicable metabolism studies. That is the area that is probably going to take most of our time, I would think. But that we need to consider, first of all, the scientific guidelines and what we think are areas that where we may be able to outline what is completely unacceptable and then what are acceptable kinds of procedures in these studies, if at all. And, that we need to make the distinction between what would be

acceptable for an epidemiological study or an incident follow-up and what would acceptable for a controlled human exposure study. I will just go through some of the things that I think EPA is asking and they need to develop a policy on from, first of all the purpose, and these were outlined in our phone conversations. What is the purpose or intent of the study? That was something that was discussed at length because it was the committee's concern last time that if the purpose was entirely for financial reasons, then that may not be acceptable, but I think then that the committee needs to address what would be acceptable as a purpose for a controlled human exposure study, as compared to an epidemiologic study. The second area then, would be to operationalize the dose not that we can give a specific dose, but how does one arrive at the procedure for deciding whether a dose administered is acceptable and ethical, and what are the scientific standards for that. Is it the lowest possible dose, is it the dose that's based on animal studies, and how many animal studies, and what kind of animal studies need to precede the human exposure study. How many subjects is something that we did address, but maybe not quite specifically enough with regard to, is there adequate power in the study? One of the concerns that has brought up in the past, is that many of the studies that we see, involve less than 10 subjects. All healthy male volunteers. The committee expressed a lot of concern about using sensitive populations or subgroups and that that would be problem, and yet, we also have to balance that against the generalized ability of studies. If they are only done with healthy male volunteers, then that may not be of any use scientifically and therefore not be an ethical study. And to the extent

possible, I think it's important for us to look at the science and then also look at the ethics, they are intertwined, but we need to address both issues. And then, also to outline the range of effects and how those effects are measured to consider, is simply blood cholinesterase an adequate measure of an adverse effect or do we want to consider, it has been suggested and discussed many times before by EPA and some of the background documents we received, or do we need to consider more specific measures of neuro-behavioral, neurological effects, are symptoms adequate, what are the most sensitive, measures from least to most sensitive and what would be adequate from a scientific standpoint and then from an ethical standpoint? And so these, I think, are the more specific issues that need to be addressed. Do we have an adequate understanding of the risks in any protocol and what might be acceptable risk and what is unacceptable risk? And to begin to address these issues in this committee and come up with, if not an answer, which I'm sure we can't, but a range from totally unacceptable to more acceptable, and probably or possibly, using some of the things that have been suggested by Dr. Weiss, for example, in terms of case representation may help us come to some of these decisions. But my reading of the background paper suggest that these are the things we need to operationalize more specifically and to put into the current draft of the report that exist now. And I want to turn it over to Dr. Gorovitz.

DR. GOROVITZ: This committee has been described, I think, falsely as hopelessly deadlocked. That seems to me not at all the case. This committee hasn't quite reached closure, and what I want to do is take a moment and emphasize what I think are

the substantial areas of agreement, because they inform the approach that we take to the issues that are as yet unresolved.

The last draft of our report, which is, when I say last, I mean most recent, not final, is still a work in progress, made it clear, I think, that the committee is of or very nearly of, a single mind with respect to a broader array of important issues. I just want to mention what I take some of those to be, and others may in the course of our discussion, offer some corrections if necessary. But I think we're all agreed that:

We want to advocate the highest standards of respect for human subjects in any research with human subjects.

And we have a pretty clear idea of what those high standards require.

We believe that to justify the intentional exposure of human subjects to substances via any means, that potentially could harm them at all, requires a high threshold of justification. That bad science is unethical. There's no question about whether scientific protocol could be ethical if it is scientifically unworthy.

Further, I think we're agreed that bad science occurs, not necessarily mal-intended but certainly science such that nothing useful could be justifiably concluded from the research and therefore the doing of the research was unethical. Unethical in part because it exposes subjects to risks in part, because it constitutes the waste of resources.

We're agreed also that the justification of human subjects research cannot be to facilitate the purposes of industry or agriculture to say that is not to say that those purposes are not legitimate purposes. Not purposes which themselves are worthy of some regard and some respect, but that is not the concern of

this Agency, that is not the concern of this committee. From our point of view, human subject research in the domain of toxic substances can be justified only in pursuit of the public health. And that for us is a kind of touch-stone of acceptability.

We all have a special concern with vulnerable populations, that is, with children, with the elderly, with those in fragile health, and we understand that protocols which tell us about the reactions of a small number of healthy adult males, are not justifiable as a bases for extrapolation, but the susceptibility of people in these vulnerable constituencies. Now, they may yield some other information that could potentially be of use indirectly, but that special concern for the highly vulnerable is a very high priority for us.

We're all agreed, I think, that the evidential potential of unintended exposures is inadequately explored. That incidence follow-up is an opportunity that should be seized when it occurs, and the maximum amount of information extracted from those circumstances provides a way of advancing the public health without intentional exposure to anybody.

And I believe we're also concerned about a particular risk benefit issue and that is, that it's not enough to know that there are low risk and high potential benefits. It matters also who bears the risk and who potentially will yield the benefits. There has to be not just the appropriate numerical relationship or quantitative relationship between risks and benefits, but a just and fair and appropriate distributional relationship.

Now, that said, I believe we agree that where human subject research can advance the interest of public health, and can satisfy high standards of ethical propriety, it should be allowed. Where

we are unresolved at this point, has to do with the operational clarity with which that threshold has been described. And so, our focus has to be on the question, can there be human subject research that can advance the public health and stay within the constraints of the highest ethical standards, and if so, what's the threshold that the argumented favor of such research must reach in order to be justifiable. That is, as I see it, our challenge and it's one that I think we can meet.

DR. KENDALL: Excellent. Just excellent. Any questions from the Committee on that, Dr. Fiedler and Dr. Gorovitz were just really a pleasure to work with in the context of our communication, at least via conference call, which I thought was very effective. But we put them on a mission, and I think they did a lot to crystallize. We agreed on considerable amount actually, and the committee is not deadlocked a bit. We just need a little more time to, work together, I think to bring to closure some of these issues. And I think you hit the nail on the head. Committee, further clarification? Because the issues a process, some of the questions that have evolved, the issues of process, we have to enlarge, to be dealt with. We're going to have a transcript of the meeting. We are sharing the information openly as needed. We are going to be following up with additional discussion, if necessary via, particularly draft iterations of the report. Larry

DR. DORSEY: The Issues of Process as we've melded the SAP/SAB issues, Dr. Utell and that was mainly communication just working together having a little time to do that. But these points, that Dr. Fiedler and Dr. Gorovitz have made, are really what set the stage, the important stage for this meeting today. I want us

to either agree or disagree on that so we can move on. Any disagreement? Dr. Meslin.

DR. MESLIN: When you started your choice of agreement or disagreement, I didn't get my hand up quick enough. It was for agreement, not disagreement.

DR. DORSEY: I'm trying to make sure we've got this clear.

DR. MESLIN: I regret I wasn't on the call, and I applaud and congratulate my colleagues for putting together such a helpful summary. I wondered whether in your discussions you added to your list of concerns about risk benefit, questions about the persistence of the benefit over-time or in contrast. The reversibility of the potential harm. As you quite rightly pointed out Sam, it's not simply a low risk versus high benefit, but what's the likelihood that the risks get manifest as a harm, would last for a period time and could be reversed relatively quickly? Did that come up in your conversation? I suspect that there might be another area of agreement, that the irreversible risks and the persistent benefits are the kinds of things that we should focus on as well?

DR. KENDALL: Dr. Gorovitz.

DR. GOROVITZ: Sure, that is, one doesn't understand what the risks are unless one understands both their severity and their temporal characteristics and their reversibility. We've also been concerned about latent risks. That is, harms that may emerge quite sometime in the future, and that, therefore by hypothesis, will be invisible in the short-term.

DR. WEISS: And that's part of the agenda for the next part.

DR. KENDALL: Any further? Dr. Ellis, I was hoping you would step in at this point and tell us if we're ethically sound here.

DR. ELLIS: That's too profound a judgement. First, let me add my thanks to Dr. Fiedler and Dr. Gorovitz for distilling their thoughts. And I have a question for Dr. Gorovitz. I heard Dr. Fiedler distinguish between two classes of studies involving humans. On the one hand, data may be derived from incidence, follow-up epidemiologic studies, on the other hand, there's a class of studies--controlled human exposure, controlled dosing. Does that dichotomy play into your scheme Sam? The way I heard your scheme, it transcends that those two classes.

DR. GOROVITZ: Well, I think the answer is yes and no. That is, I think that's a distinction that has some significance. The general values, which I described as affirming apply to both categories but in non-identical ways. That is, if one undertakes to cause exposure deliberately, then that must itself be justified and that piece of the story is missing in the follow-up to an unintended exposure. So, sure, I see these as distinguishable and substantively different categories, but even when one is following up an unintended exposure, that can be done in ways that are ethical or unethical. And even there then, we need to maintain high ethical standards in the way in which the subjects are treated by the effort.

DR. KENDALL: Any further points of clarification? If not we'll move to the public. Dr. Kahn.

DR. KAHN: If I may. I'm in the same position as the last time.

DR. KENDALL: I want to affirm that you're welcome to make a good comment here.

DR. KAHN: Even if you said no, I don't think it would matter. Let me just ask how an issue fits into what we just heard from doctors Fiedler and Gorovitz. And that is a question, I think that came up from our EPA staff about the FQPA sort of being used as sword upon itself. And that is, potentially creating an incentive for testing to subvert the 10-fold safety factor. And whether that's an issue that's on the table, one, an issue for us to consider. Is that a policy judgement that we're here to try to address? And secondly, if so, where does it fit within the scheme of it you've just played out for us? That's two-part question 1. And the second question is sort of an attention to the risks that, I didn't hear anybody talk about, and that is whether there is a risk to the environment that we have to also be attentive to? By allowing higher levels of pesticide into the environment, whether that's a risk that ought to be put into our risk benefit calculations, as well. Is that clear?

DR. KENDALL: Yes, Dr. Gorovitz/Dr. Fiedler would you like to respond? Then the committee. If there's a time that we spend a few minutes conversing as the committee, it's right now. So, I think we really need to get, if necessary, we're going to public comment, but if we can get the groundwork laid right now, following up, the very thoughtful presentation of Dr. Gorovitz and Dr. Fiedler, I think we will accelerate our ability to have a very positive outcome today. So, I'd like to ask if Dr. Gorovitz and Dr. Fiedler would like to try to address Dr. Kahn's very thoughtful comment.

DR. FIEDLER: Ok. Someone may disagree with me, but in terms of the FQPA unintentionally subverting the 10-fold protection factor, it's not my understanding that we are in the position to question that or to address that other than through the science and ethics. Because it's possible that in doing a study, you may actually increase the protection factor. So, and I don't want to pick on you, but I don't think the word subvert, is exactly.... I understand why you said....

DR. KENDALL: To provoke the discussion.

DR. FIEDLER: Right. So, I don't think that's our charge as much as it is to address the specifics of the studies that will then determine what the protection factor should be based on data. With regard to your second part and the environmental issues, I think that's a very intriguing question. It's not my understanding that this committee is convened to deal with that but rather to deal with risks to human subjects from the two different types of studies. Cause I think that's a whole other dimension to this that could then reverse what we're discussing if you're concerned about the environment and what might come out of this.

DR. KENDALL: I think that's a good point, Dr. Fiedler and I really think Dr. Kahn, in terms of the environmental question, although there are many of us here at the table that are deeply concerned, I think our charge is really to look at the human testing issue and the science and the ethics surrounding that issue. I think very well put by Dr. Gorovitz to advance the public health and stay within the boundaries of ethics, and based on good science to get the appropriate information.

DR. KAHN: It's a question of how broadly to construe public health in this context. You asked sort of for a discussion about the parameters, I think, of what we're here to do, and so I think it's helpful for us to have that discussion now and whether we want to go that far or where to draw the line, I guess is the question. And where risks and benefits ought to be understood as sort of stop being part of our concern.

DR. KENDALL: That's a good point. I think Dr. Meslin had his hand up first.

DR. MESLIN: Just very quickly to follow-up Jeff's point. In distinguishing between the intended exposure to individuals which would apparently fall within our charge, I haven't yet heard how one distinguishes between the individuals located geographically near a release of a pesticide in the environment and those several states away, who many months or years later, as was described in terms of latent harm, would also be the unintended or incidentally exposed subjects. I realize that there's a distinction here between what constitutes a human subject and what constitutes an individual who as a part of the public, will be the unintended recipient of that experiment. And maybe it's worth drawing the line and agreeing that it's something we can't cross over for the point, but I haven't yet heard a response to Jeff's question about where the human subject definition begins and ends, particularly with respect to the unintended exposure issue.

DR. KENDALL: Dr. Reigart were you going to address this point or should we follow it up with Dr. Gorovitz? Pardon?

DR. REIGART: Go to him.

DR. KENDALL: Dr. Gorovitz are you ready to help us better define that line?

DR. GOROVITZ: I'm not sure we need to define the line, characterized that way. That is, Eric Meslin has distinguished between subjects, that is, those who are enrolled in a protocol and, the victims of an unintended exposure. And I see no reason why a follow-up study has to be geographically proximate to the release. That is there could be an incident in California, and it could make perfectly good sense to see if there is any evidence of an impact in Kansas. This is the kind of thing that has happened following large scale events, like Chernobyl and Bhopal and it's a little harder to get a grip on large scale temporal distances, but, in my conceptualization of following up on unintended incidence, no part of that was immediate proximity. Now, there's always the question, who will undertake such a study, with what motivation, and what funding, and what intellectual resources. But, from our point of view, I don't think that there is a line to be drawn that says, we stop at the border of a county, or a state, or a particular farmer's field.

DR. KENDALL: The point is, through with terms of the charge of the committee, and considering these issues, is the direct administration knowingly? I think that's where some of the concerns have arisen and I think there is somewhat of a line, between the direct administration to a subject versus the exposure and the normal working conditions of the use of the product.

DR. GOROVITZ: Point of clarification. There's clearly a line between the subject of an intentional exposure and the victim of an unintended exposure.

DR. KENDALL: Exactly, exactly. Well put.

DR. GOROVITZ: Where there is not a bright line is between the geographically proximate victim and a more remote victim, either geographically or temporally.

DR. KENDALL: Can the committee live with that? OK. Dr. Reigart, thanks for your patience.

DR. REIGART: I actually would like to ask of Ms. Mulkey and Mr. Carley a factual questions, based on the submissions and the context of what Dr. Gorovitz stated which is, he made a distinction between protection of human health by experimentation versus other goals. And the question I have is Ms. Mulkey said, that if some of these NOAEL studies in humans were accepted as evidence of the human NOAEL, you could get rid of an interspecies uncertainty factor of 10. Is that what you said?

DR. MULKEY: That makes it possible.

DR. REIGART: The question I have is, of the studies that have been submitted, were the humans approximately the same NOAEL as your animal NOAELs?

DR. MULKEY: I think the right answer to that is there is a fair amount of variability. But they're rarely, the humans are rarely ten times more sensitive than the animals. The direction tends to be, that if you use human NOAEL and remove, and do not have an additional safety factor that you have, you're going into the direction of having a higher reference dose.

DR. REIGART: OK. So the tendency of the studies you've received, would be to raise the reference dose, which would presumably lower the degree of human protection. Is that...?

DR. KENDALL: Dr. McConnell.

DR. MULKEY: ....That's misleading. The reason people are saying no, is that they're reacting to the tail end of what you said. The tendency is to raise the reference dose. Whether that lowers the degree of human protection is what people are reacting to. If you have a standard of reasonable certainty of no harm, and you have met that standard, people would say that the degrees of human protection greater than the standard are not appropriately to be described as reduced degrees. I think that's why people in the audience are saying no.

DR. REIGART: OK. I'll insert a "might" down in there. It might under some circumstances.

DR. MULKEY: It generally would lead to a regulatory choice to tolerate more exposure.

DR. KENDALL: Ok. Dr. McConnell. Thank you Ms. Mulkey.

DR. MCCONNELL: Yes, I was just going to add to that that way back when, when 10X was chosen instead of 100X or 1,000X or 1X, the reason was, that there was quite a bit of information already known at that time, that for most pesticides or any other chemical, in fact, that the difference between animals and humans was within a range of about 10X, would cover 95 percent of the chemicals. There are examples, as you know, where humans are 3,000 times more sensitive than an animal, and conversely there's some where the animal is much more sensitive then the humans. So that's the background of the 10X. It just a working thing, but it's based on some science.

DR. KENDALL: Dr. Portier.

DR. PORTIER: Yes, I want to get back to Dr. Kahn's original point, in terms of trying to delineate the discussions of this group. I think the discussion we just had, has pointed clearly that the impact of the human studies will not be on the FQPA safety factor but the inter-species safety factor. And I think part of our discussion has to resolve around the issue of, since this is in fact a stated goal of these studies, is this stated goal an ethical goal? and is this stated goal a scientifically defendable goal? cause, I think that is clearly very important here, and I don't think we discussed that at the last meeting and I want to make sure we get that issued discussed here.

DR. KENDALL: Yes, that's a good point. I think we attempted to address it, but we going more delineate at this time.

DR. KAHN: Chris, I appreciate your saying that; because that really does encapsulate what I intended to ask, so thank you. Maybe, let me ask Sam. One of your points was that human subject research could not be justified by the financial interest of industry. I think that was close to a quote. Did you mean by that, the kind of thing that Chris just articulated? That is, an effort to increase the Reference Dose as being in interest of industry or what did you mean? maybe I should ask it more objectively, what did you mean by the statement that human subject research could not be justified by the financial interest of industry?

DR. GOROVITZ: I take it that the Agency's mandate has to do with protection. And it's protection of a specific kind. It's protection of the environment. Protection of the health of people in the environment. And so, if a piece of research which is potentially risky for

subjects is to be justified, there has to be a legitimate purpose being pursued by that research, and that purpose has to be gaining information that can be put to use to enhance or secure the health of the public. Now, that can be compatible with the interest of industry or it can be at variance with the interest of industry and that distinction, it seems to me, should be none of our concern. Our concern should be, is this piece of research capable of yielding information the proper use of which can enhance the protection of the public health without regard to whether that thwarts or facilitates the purposes of industry.

DR. KAHN: And that goes to the intent of the study or not?

DR. GOROVITZ: Well, I think it goes to the way in which the study is likely to be used and not just the intent. Now we haven't talked about this yet, but intent is very difficult to discern because intent, is nearly always packaged in highly palatable language. I mean the purposes that are affirmed in the undertaking of a study, are nearly always noble. It's a separate question what the purpose actually is. And so, I have a tendency to think very hard about what the likely consequences will be of the study, without investing much credence in the nominal intent.

DR. KAHN: I totally agree, which is why I asked you that question so I think it's important for us to focus on that. We're not going to be able to understand the intent. We can't read people's minds. And so, I think consequence, and that goes to risk, is a much more useful construct, both. I think we're going to get there after the public comment.

DR. GOROVITZ: We're agreed on that.

DR. KENDALL: Dr. Weiss.

DR. WEISS: I'd like to ensure the committee that I do have a day job. But, I'm also serving on another EPA SAB committee which we started out calling the Integrated Chris Project. And it's there that concerns like yours about ecological effects and economic issues like cost benefit ratios and all of these other issues, have been taken up in an attempt to provide for EPA the kind of a structure that allows it to deal with many different facets at once. I don't think it's the purview of this committee, to expand so far beyond it's original intent as to take up those issues. I think we'd be better off sticking to the problem of volunteer studies and their ethical implications, otherwise, instead of one day, we'll be here for several months.

DR. KENDALL: That's well put. Can the committee agree to that?

Light Voice: Yes, I think the point was really to express sort a of how far do we go and I think we've got there.

DR. KENDALL: OK. Dr. McConnell.

DR. MCCONNELL: Yes, I thought Dr. Gorovitz's presentation and Nancy's was just elegant. Absolutely, cut to the quick, as we say. I think in doing that Sam, in particular, you cut to the number one concern of the agency. At least if the bullets are in order of importance, which may or may not be, but I think they are, but the very first bullet, concern of the agency is we want to rely on data meeting the highest scientific and ethical standards. The most appropriate and the most reliable available and in very importantly to me, able to support the most accurate assessments of potential risk. And I

think, you know, that's exactly where you were heading with that. That, you know, it's got to be scientifically credible, ethically credible, and that it allows the agency to give the public the best estimate of the potential risks out there and that's what this should be about. And I concur that it's probably cleaner to stick with human volunteer stuff than to get into many of these other issues which will just complicate the day.

DR. KENDALL: Good point. Dr. Portier.

DR. PORTIER: I need a clarification from Ms. Mulkey bBefore I state my question. If a pesticide company for a pesticide that already is approved decides to do a human testing study, are they mandated under law or under your rules to divulge that information to you regardless of the outcome of the study?

DR. MULKEY: Yes. In brief yes. There's a provision that requires the reporting of all adverse effects and we have interpreted that as requiring reporting of all these kinds of studies. Regardless of outcome.

DR. PORTIER: Regardless of adversity?

DR. MULKEY: Yes.

DR. PORTIER: I have no comment cause that dealt with again, the parameters of where we would discuss this.

DR. KENDALL: Ok. Further comments? If not, we'll move forward. OK. Dr. Utell and I have been talking up here and relating to the agenda and proceeding forward. First of all, we want to inquire with the committee, their willingness to remain at the table through lunch to have a working lunch, the lunch served at the table. Will you do that for us? OK. I

will submit a document, the choices will be limited, but the times vital. But we will have literally a working lunch beginning at 12:00 noon. Mr. Dorsey.

DR. DORSEY: We will of course need to allow time for people who need to check out of the hotel, so we'll incorporate that into your thirty minutes.

DR. KENDALL: OK. So, we will have a break, but a short one. So we will have served a lunch at 12:00 noon. We will continue through the process of working through the lunch. We will give you time to check out as appropriate.
Another modification is, I think the committee came here to do business today. I'm proud of this committee, and Dr. Utell and I have been talking just about the hard work that's gone on just before the meeting. And before we get to the public comment, we thought it would be most appropriate to invite our guest from the FDA, Dr. Joseph DeGeorge, to provide us some briefing on the policies and acquisition in use of human testing data at FDA. So we are going to invite him to come forward to make his presentation and then we will take a very short break and then proceed into the public comment, have our working lunch and continue forward to closure.

DR. DEGEORGE: Thank you for the opportunity to come here today and speak a little bit about an area where we have experience where normal volunteers are exposed to chemicals, although clearly they are intended for pharmaceutical use.
Now, I'm going to focus on primarily early pharmaceutical development because that's probably more relevant to this process and the entirety of pharmaceutical development. In my presentation, I'm going to go through early drug development process itself, who's responsible for what, what

guidances are available to various participants, what kind of data is actually necessary to allow the conduct of these studies, what the purposes of these studies are; both the animal studies and the human studies, and actually how we do those selections. The Drug Development Process is really divided up into three components; The discovery phase which is entirely in the hands of industry is then deciding what is a chemical that they would like to pursue as a therapeutic. There is the development phase which is really called development which is talking about immediately before and including human testing as part of up to the marketing phase, and then there is the post-marketing phase. And within the early non-clinical development really the pharmaceutical companies have to rely on available guidance in terms of what studies are available. They don't often come speak to the Agency at that point. During clinical development the first phase of that, being the first in human studies, that's actually where they're planning to do those studies. After they do those first studies, there are additional animal studies that we get, so we get a recurring event. That is, we get animal data based on guidance, if it's available, allowing clinical trials, assuming it's adequate, more animal data guiding the second phase of clinical trials, more animal data, guiding the latter phases of clinical trials, and then there's a total package with lots of human exposure plus all that animal data and that's part of the marketing process. And that's the evaluation of market. So, I just want to point out that the data we get early (new tape) ...is, we have limited regulatory studies which are said, these are what you need to do before you can talk to us about doing human studies. And I'll talk about those in a moment.

So again, in the discovery process is a, who's responsible in discovery is sponsor an investment risk. If they want to spend their money testing the pharmaceutical in animals and evaluating it, that's their aspect. We don't really get involved in that. They are also responsible for the non-clinical early development and this is immediately before coming to the Agency with a package, let say that would support the clinical trial. They are responsible for having basically identified the toxicities and import based on regulatory guidance which we provide, and also they have a stewardship responsibility for the product. They are going to be responsible for the safety of those subjects.

In first the human studies, at that time, it is really FDA that evaluates that data-set before they go into humans and states, and we have to sign a form, each of the various disciplines evaluating the processes; we think it is reasonably safe to proceed with the proposed clinical trial, we've evaluated the clinical trial plan, we've evaluated the toxicology data. We've evaluated the underlining chemistry information, and each discipline has to sign that form for it to go forward into humans.

We actually are responsible for making sure that the communication of the sponsor of the Study is communicating to the investigator, is accurate. In the investigator's brochure, we look at the animal data, we make sure that all the risk are identified in those animal studies are, in fact, communicated to the investigator, so they can be aware of them. Additionally, we try to be sure that that information is communicated to the research subjects. Although, we are not automatically charged with evaluating informed consent. That is really the function of

the IRB. So the IRB even evaluates the informed consent, although we can, if we identify information that we think was not in the investigator brochure, that we think is important to human risk, we can insist or demand that that information be placed in the informed consent. Although we didn't have any evaluate that consent formally. What we ask, we can ask for it and receive it, but that really is the responsibility of the IRB, as is the ethical conduct of that study, and we've heard a lot of discussion about that today. Now here are the various guidances that are available to support or to provide information to both industry and the Agency and investigators, about what studies, what information needs to be provided. There's the code of Federal Regulations, (CFR 21, Part 312) speaks mainly to new investigational products, what you need to conduct, it does it very generally. There are various guidances which then elaborate on this. The guidance for industry on the content and format, investigation, new drug application, INDs for Phase 1, studies for drugs including well care drugs, biologics basically. This is an elaboration of the safety kinds of information that needs to be available to the Agency before human studies are conducted. It really elaborates only a part of the information carried out/described in the CFR.

There is an international document. This is actually what's called M3 Non-Clinical Safety Studies for the Conduct of Human Clinical Trials From Pharmaceuticals. This is a document that was agreed to by the European community, by the Japanese authorities, and by the FDA as a standard for the type of information that should be available before administering any chemical to humans either for Phase 1, Phase 2, Phase 3, and what kinds of

information should be available for marketing. I think that's in your information package. There is also another document on Single Acute Dose Toxicity Testing which clarifies some issues in relation to first time single dose studies in humans. I'm going to talk about that because I think that also would be informative to this group. The CFR basically states that they have to have a clinical plan. That there has to be adequate information on the pharmacology provided to the Aency, that was the basis for the decision to test the product in humans to begin with. They have to have a toxicology summary that relates, that is, in the toxicology packages related to the duration of human testing is being proposed and the type of human testing, and who the subjects are. They are to describe the pharmacology and disposition; this way it was put into the Federal Registry which I think is pretty much admin basically, if known. It doesn't have to be available. They have to describe any human experience. They have to discuss the IRV involvement and it also describes what are the specific aspects of Clinical Holds, which is the Agency's action to say, you cannot test this in human subjects under this condition. And it proscribes for us what those decisions must be based on. And in Phase 1, it is solely based on safety. It is whether or not the product is safe. In later phases, it can also be based on whether or not the study objectives will be useful and will meet the Agency's regulatory needs for improving a product.

As I said, in the guidance on the content format, guidances are something that the industry can look at, but they can chose alternatives. The regulations are not an alternative, but the guidances, they can have alternative approaches. Basically, this describes

that in the clinical protocol for Phase 1 studies it really can be an outline, but they have to provide the detail about the safety aspects. It says; "You have to have limited chemistry information." That the pharmacology and distribution kinds of data can be provided in the summary format, that is the animal data that supports that, and generally, lacking this information is not a reason for a Clinical Hold, although, sometimes that information can bear in the safety and in that setting it could be a reason for a Clinical Hold, not having it. They have to provided an integrated toxicology summary and provide full tabulation of all the animal data, so that we can evaluate it and reach our own independent conclusions about what that data says. And it also says that we will evaluate NON-QA reports before they are fully finalized but they have to provide that within 120 days. The ICH Guidance is basically, and this sort of gives the outline of what the minimal data set is for first and human studies. And, although it allows for patients, we are talking primarily about healthy volunteers, there is a difference of what those Phase 1 studies may be, say in Japan, or who may be involved in those studies, and in Europe and in the United States. And in the United States, it can include women with the minimal data set where as, that is less likely to occur because of the data necessary in Japan or the data necessary in Europe. Consider it necessary. But this an international standard in general, it says we should have safety pharmacology studies--those which assess critical organ function. Those are separate from toxicology kinds of studies that look at respiratory functions, neuro-function, and cardiovascular function. That they should have some exposure information

from animals that's kinetics metabolism but it is not critical, and is not expected to be comprehensive at this very early phase of development. They should conduct local powering studies to the relevant target sight of administration. That there should be an assessment of Genotoxicity based primarily on in vitro data at this point in time. Looking at mutagenicity and clastogenicity and that they should have repeat dose toxicology studies between 2 and 4 weeks of duration in a rodent and a non-rodent species. And that's pretty much the data set prior to going into human. Now the FDA has published a guidance which I mentioned, which is the Single Dose Acute Toxicity Testing for Pharmaceuticals. It's a specific guidance about what to do for acute toxicity testing. And it says prior to Phase 1, you should have a single dose study and it should be by the route of administration intended, as well as, by the intravenous route to get a full elaboration of the toxicologic potential, considering you may not actually get absorption by the intended route in the animal species. So that's the reason for the two routes. But it says that you might be able to address this with other data from other studies such as repeat dose studies have you in fact collected data that can address that point. I think one of the important points about this document is that is says that when Single Dose (SD) studies are used as the primary basis to support Single-Dose studies in humans for Phase 1, these studies should be, what we call extended acute. And that means you may dose once in a 24-hour interval, but you're going to follow through toxicity and then through reversibility to try and look at the full spectrum. But, the point is, that a Single-Dose study in animals and two species can support single dose studies

in humans without that repeat dose toxicity testing. Now, what level of doses and what would be considered the safety margin from this study versus a repeat dose study might differ.
Now we'll go to the study objectives. First, non-clinical objectives are ready to find the toxicity profile for both species and just try and get an understanding of what the toxicological possibilities are. We do want to establish in those studies, No Observed Adverse Effect Level and for pharmaceuticals what that is defined as, that effects related to the primary pharmacodynamics function of the drug occurring at levels which are not considered adverse are acceptable as a identification of a NOEL. I'll give an example because it will make it a little easier. If you had a drug which is an anti-coagulant, and you had a slight change in the prothumin? time, that would be an NOAEL. It would not be NOEL. That could be considered an adverse effect in general but because we know that that is the intended pharmacology, we know that that is in fact a level effect which is below that causing significant biologic prohibition it's considered an acceptable level of event and that is what we use to define an NOAEL.
We are trying to determine in these Studies what types of toxicities should we be especially alerted to. For clinical trials, for example, if we see QT prolongation, changes in the cardiovascular function, we might say that all subjects in the study need to halt their monitoring while hospitalized. We are trying to identify if there is an identifiable relationship, a clear relationship between the exposure to parent compound or to a metabolite or to something else and how that relates to the toxicity and how that crosses of species in terms of

that relationship. In other words, is trying to get, "Are species comparably responding and what are they comparably responding to; Dose, exposure, metabolites, and then trying to use that to structure our clinical trial. We sometimes establish an upper limit of dosing for humans. We are always trying to establish the upper limit for the first dose level, but we are sometime saying with these data," "you can go no higher than this level because of the nature of the toxicity that's being observed." One might not be very readily monitored, would be an example, such as some neuro change in say, his pathology and the brain. Very difficult to monitor in a clinical trial. And of course, we trying to determine whether or not the toxicity is irreversible, all those factors go into our consideration of the first dose for humans.

In the clinical trials, Phase 1, and I'll talk mainly about the Normal Volunteer Study or the Healthy Volunteer Study. The purpose of those studies is to define what's called tolerance. That's the word, tolerability. That includes defining the safety or toxicity in human to some extent. It is trying to define some level of toxicity. It is also determined by availability in the pharmacokinetic parameters, and we what to know about that. Its to identify doses which will be used in Phase 2 studies which are generally in patients to try and establish dose ranges. And then occasionally, this is used to identify biomarkers of effect, but that's rare, because generally you don't have a good surrogate biomarker for effect, but sometimes you do. Now one of the things it also tries to do is these data contribute to our information about what are the appropriate animal models to do further testing in. How good are the animal models strains and species that have been tested to support

the initial study in directing us to potential human toxicities. If we see toxicities that are not observed at all in the animal models that we have tested to date in these clinical trials, we want to go back and reevaluate what the animal models are, to get a better handle on what the potential adverse effects are.

Now in Phase 1 studies, they are usually and this is defined in the CFR as 2280 Healthy Subjects. The study designs usually are Single Dose levels where a subject receives a single dose level, 30 milligrams, something like that. There are 3 to 6 subjects at each dose level and if the first 3 to 6 subjects pass through without adverse events being reported, then the next group gets another higher dose level. And there's this escalation. There's also a design where individual subjects may actually get dose escalation. They may get 3 to 6 dose levels, generally three. But there will be overlapping. The first 2 or 3 subjects will get, say 20, 30, and 50, and they'll go through that find, and then another group of subjects will start out at 30, 50, 60, or something like that. So there are different designs that can be used. The end points of this studies are, toxicity is clinically observable kinds of toxicities, vital function effects, heart rate, respiration, blood pressure, those kinds of things, headaches, things that you can't identify actually in animal models very readily. The limit dose that's usually clinical to monitor so we might stop the study at the limit dose, say, "you have gone up as far as the animal data support that clinical safety, you can go no higher because we have no way of monitoring for safety above this level." And again, biomarkers or PK can also be end-points. And these studies are generally as I said, they may include males and

females, usually they're males. But they tend to be in-patient studies. That is, they are in hospitalized settings or on wards so that they can monitor the subjects for the full course, not only just through the first 24-hours, but to however long it takes to address any longer term effects that might occur.

Now the Standard Design Studies for Phase 1, the Toxicology Studies, in the Rodent Repeat Dose Studies, and I'll talk about the more usual approach which is the repeat dose approach, is generally there are 10-20 per sec, per dose level. They are usually in the rodent and in a non-rodent it's usually 4-6 animals per dose levels. So it's not a lot of animals for the Non-Rodent study. There's usually a control free dose level for each of the species and a needed dose to toxicity or to maximum feasible dose and they should include a NOEL in that study because otherwise they're going to have to do it over again to help us pick a starting dose. A recovery group is often included, it's not always included, but if it is it's usually for the high dose effect, and there may be separate animals which are assessed, particularly with rodents for kinetics, because it is difficult to collect sufficient blood samples from those animals and have it not effect the toxicology. And again, the end point is toxicity. We include clinical observations. There's clinical chemistries, hematology, gross pathology and histopathology, and the last two are things that are not part of the clinical trial, obviously.

Now in practice in terms of selecting the dose, it varies, in fact, with the study objective and the subjects that are allowed in that study, if it is a study to look at PK, then you don't have to have the same dose selection to a particular level. One might be able to

get the PK at a very low dose level in those human studies to look at metabolism, clearance, absorption. For pharmacodynamics, again, if you know that the dose in humans that is expected to have the pharmacologic effect is much much lower then the dose which is potentially a toxic level, you don't have to go as high in that setting either, so the dose can be much lower. But, for normal, healthy volunteers, and tolerance studies, the usual approach is to define the toxicity profile and the NOEL in the both test species, that we then determine what an appropriate dose metric is for comparison across species. It maybe milligram per kilogram. It may be milligram per meter squared. It may be based on a pharmacodynamically measured physiologic PK model, a lined distribution basis. There are lots of different metrics which one can scale across species to find out the most accurate and use that. Once we have determined what the most appropriate, and if we don't have a reason for a particular species being more appropriate than the other, and it's the most sensitive, if for example, we know that for a class of compounds, dogs always exhibits emesis but that is not a finding in humans ever for that class of compounds. It would discount that effect at the emesis level. We then take this most appropriate species or most sensitive and determine a human equivalent dose using that metric to scale across species which ever we determined is appropriate. We then look at trying to add safety factors and the usual is 10 and it can go up or down from that, based on what you have in terms of additional information. If you know that the animals often are not adequately sensitive, then we're going to add a lot of safety factors. If the toxicity of concern is not reversible there's going to be a larger safety

margin and, if it is clearly reversible, if it's a steep dose response curve, it's going to change that safety factor. So a lot of considerations would go into what the size of that safety factor is. But, if everything is on average it usually turns out to be about 10 I guess, because that's the way we count. This is then applied to the human equivalent dose and that predicts the upper limit of the safety-starting dose. Now then we will still go back and look at the pharmacodynamic effect levels and how those interplay with this upper dose. If the dose can lowered to achieve the same goal of the study, it gets lowered. And of course, we also will determine an upper limit dose if that's appropriate given the toxicities that are observed.

Here's some comments that I have about Phase 1 Clinical Trials and I think some information that might be useful. First of all, it's always healthy volunteers and they have very little personal benefit other than altruism in terms of scientific at helping the science of the world. And I say this because for 9 out of 10 chemicals that go into development, two of them die before they get into humans because the animal toxicity in those regulatory stages was too significant and they said we're not going to do this. So we never see those. But the next 7 or so out of 10 die in various phases of clinical trials. Phase 2, at the end often or Phase 3, Phase 2 and 3, but by the end of Phase 1, three out of those have already dropped out as having no potential therapeutic benefit. And the reasons for failure, are that these are observed toxicity clinically that they thought was inappropriate for the kind of indication that was going to be used or, that the potential for toxicity was inappropriate because they dosed to a level that they thought was where they

would expect pharmacodynamic action and they know that if they go higher or they anticipate that they go higher, there will be toxicity and so they don't feel they can continue dose escalation to effect so that's a potential toxicity. That it's poor PK. The drug is not absorbed in humans, it was absorbed in rats and dogs but not in humans and therefore, it's not going to be very useful. Or the PK is very variable which is another cause for concern at least in pharmaceuticals. And absence of evidence of efficacy is something that they only get generally at the time of marking after those Phase 3 studies, and things that go that far, about 1 out of 2, make it as a therapeutic. But there's a lot of drop out early and a lot of chemicals put into humans that never become drugs as part of drug development.

Now, by design, toxicology studies almost always identify significant toxicity. Almost always can cause some irreversible harm in that animal model. That's the intention, these products are all biologically active and so they almost all have some significant toxicity. The non-clinical data, however, can be used adequately to support safe initiation of clinical trials. Our experience is we're rarely significant adverse events, they are not within the range of acceptable based on the ethic committee standards, based on the FDA standards, based on the sponsor standards. But, you have to keep in mind that even though we test, probably by the time that the development is completed, a thousand or so animals, or a few thousand animals, and several thousands of human subjects, we often don't identify all the toxicities until you get into the market setting because you're not going to see, for example, in a clinical development plan, if the incidence of an adverse event is 1 in

10,000, you have no hope of seeing it in the clinical trial database, and if you do see it, it will be probably dismissed as a spurious finding, because it's one out of 5,000 subjects. So, I think that even when you complete the development plan, there are still toxicities that are potentially adversed to human subjects that maybe unacceptable in terms of broad use, and we detect this hopefully through adverse of that reporting. Thank you.

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DR. KENDALL: Thank you Dr. DeGeorge. Any points of clarification? Dr. McConnell.

DR. MCCONNELL: Yeah, Dr. DeGeorge, I want to compliment you on that presentation. I think it's extremely important for the panel to have that background, number one. Number two, it's unfortunate we didn't have that at our first meeting, because I think it puts a lot of this into context. I have a couple specific questions. In my having reviewed data for the FDA, and reviewed data for pharmaceutical companies, animal data, to present to the FDA, and similarly having reviewed data submitted to the EPA for pesticide registrations, I think it's important for the committee to know that there's probably a factor of at least two maybe three times as much animal data for registration of a pesticide then there is before that particular pharmaceutical goes into Phase 1, Clinical Trial. After the whole thing is finished, it may be comparable, but at least into Phase 1. Second, I guess this is a question. Is food additives, are they treated differently then pharmaceuticals?

DR. DEGEORGE: I can't speak for that for the Center for Foods, but actually they are. They follow more, I would say the EPA paradigm for types of data and evaluation of that data.

DR. MCCONNELL: That was my assumption. But anyhow, and final question is, do you treat data differently that's generated in Europe or Japan from that generated in the United States?

DR. DEGEORGE: No. In fact, that's part of the whole reason for the ICH Conference on Armatization?. That was to make sure that the data, the types of study designs, and the supporting data generated in any region would be

acceptable for use in the other regions, including human data.

DR. CONWAY: Just a follow-up on that question. Is that a change in policy or HAS FDA, for many years, accepted data generated on an international basis?

DR. DEGEORGE: We have accepted it generally. Many pharmaceutical companies are global companies and in fact, have done often both their pre-clinical and early clinical trials in Europeans in fact, or in Japan, and we sometime don't get any U.S. base data sets to evaluate.

DR. KENDALL: Dr. Portier.

DR. PORTIER: Yes, I'll echo Dr. McConnell's comments about the clarity of your talk. Thank you very much. A couple of questions though. I'll buy your ethical argument for the volunteers about altruism, but I want to ask a couple of questions about the altruism argument. First of all, would it be a general rule that in most cases, the individuals who are being tested in the Phase 1 Trial, are of the same group that is likely to be tested for whatever disease endpoint this drug is intended to study?

DR. DEGEORGE: I guess I don't know exactly how to answer that. I will say that in fact, screening out of subjects, in terms of limiting certain people who can participate as Phase 1 subjects, often means screening out those who have that disease. For example, we would not allow in a Phase 1 study, in normal volunteers, somebody could be considered normal would have asthma but for certainly the participation of Phase 1 study to treat asthma, those subjects are generally ruled out from the patient population, from that study population.

DR. PORTIER: Let me reclarify then. Does the study population have the potential to get the disease, as a general rule?

DR. DEGEORGE: We have to acknowledge that we all have the possibility of getting various diseases. So yes.

DR. PORTIER: So the altruism argument in this case, could also be to some degree, personal?

DR. DEGEORGE: I suppose that it could be personal in a sense that if you are worried about the potential for disease and you think that this is a potential therapeutic that in fact, you might say, well I do that. But recognize that only 1 out of 10 actually becomes a therapeutic.

DR. PORTIER: The second has to do with the justification for the sample sizes in the Phase 1 trial. Are there guidelines which clearly define how you justify the sample sizes?

DR. DEGEORGE: Non-clinical or clinical?

DR. PORTIER: Clinical.

DR. DEGEORGE: The clinical ones, are actually I sighted from the Code of Federal Regulations; that's the defined Phase 1 design. And they can deviate from that, but clearly there's an intent to try to get early information such that you can get to the more definitive kinds of studies about efficacy or effectiveness to try to move from those studies where subjects have very little personal benefit, to those where the subjects may actually gain some benefits.

DR. PORTIER: But are there no clear discussions of power, sample size, efficiency and estimation issues associated with what you would clearly do in a clinical Phase 2 or Phase 3 study?

DR. DEGEORGE: I can't speak to that but as I said, those came from our Code of Federal Regulations. I assumed that those are based on when they wrote those it must have been based on some particular desire to have a certain size effect being identified.

DR. KENDALL: Dr. Fiedler.

DR. FIEDLER: I just want to follow-up with what Chris was asking about. Just a point of clarification. It sounds to me like, other than people being healthy for the Phase 1 Clinical Trials, you don't exert any guidelines or recommendations for the kind of subjects, in terms of generalizability. We do allow women and men, but beyond that in terms of representation of various ethic groups or a concern for generalizability or a sensitivity, for example, different demographics including weight, for example, which may effect metabolism of drugs. That you don't make those recommendations or exert those kinds of guidelines.

DR. DEGEORGE: I think those come out based on an individual protocol analyses in relation to what the potential disease population would be. I should point out that we actually received some pharmaceuticals for investigation where they don't even come in with a therapeutic intent. They come in with a pharmacologic class. So we may not know that, but if we knew there was some impact, we'd like to see some other broader subjects in there, but with 20-80 subjects, that's not the intent of these studies to define. Even if you had all the ethic classes and all the mix in there, the ability to detect a signal as specific for those would be very limited.

DR. KENDALL: Dr. Kahn.

DR. KAHN: Just a follow-up on the altruism or the motivation question. Most of the subjects in a Phase 1 trial are paid. Compensated for their participation. Is that a fair statement?

DR. DEGEORGE: I believe that's true.

DR. KAHN: And let me ask you, you said most Phase 1 trial participants are healthy subjects, healthy volunteers?

DR. DEGEORGE: Thanks correct.

DR. KAHN: But not all, obviously by that statement. So, are there certain classes of compounds in which healthy volunteers are not allowed to participate? Or, could you say something about the classes of compounds where there are not healthy subjects and why that's the case?

DR. DEGEORGE: I can say that healthy patients of pharmaceutical companies are allowed to include patients in Phase 1 Studies. It depends on,again, the endpoints on what they're trying to achieve, so they are allowed, number 1. It's rare, because it's a belief that the disease complicates the decision to detect the toxicity in small sample sizes. So, that's one reason why they're generally not included. There are some areas where the therapeutic intent, the first study in humans actually, to some degree a therapeutic intent trail, and this might be in cancer subjects getting sitatoxic therapy. We don't use the same starting criteria, for example, on those subjects, instead of using some factor of a NOEL, we might actually for a sitatoxic agent, we would dose the first human subjects at something on the order of one-tenth of a lethal dose in the animals. So, clearly, if you're going to be using that high a dose level, you want to be sure that person

has a potential for getting benefit. So for oncology drugs, when your talking about sitatoxics, you're often involving in-stage cancer patients who exhausted their therapeutic option. And so they're going into this with something that's both altruism and hope for the future.

DR. KAHN: And healthy subjects would be excluded because the risk is deemed too great?

DR. DEGEORGE: In that sense, we know from the class of compounds that the severity of the toxicity is going to be achieved at those levels or the potential for long-term toxicity, such as carcinogenesis is to great a risk to actually subject to normal volunteers.

DR. KENDALL: Further points of clarification? Dr. DeGeorge, thank you very much and for just a well thought-out presentation to the panel. It's a couple minutes before 11:00 a.m. Dr. Utell, we've talked about a break. I think there's an agreement that we need a break. We will proposed a 10-minute break and we will start precisely at 10 minutes after 11:00. And I think Dr. Utell want's to discuss quickly the parameters for the public presentation period, which I think will be important as we will start our working lunch at 12 noon sharp. Dr. Utell.

DR. UTELL: Yes. Just in terms of procedures, we'd like to limit the oral presentation to 5 minutes if they go over 7, we won't have time for any questions, but we're going to try and stick to the time-table we have available. Presumably everyone has written comments that will available for the panel as well. So we'll come back at 11:10 and move forward with the public comments.

DR. UTELL: Re-assemble and proceed. Can I ask the committee members to please take their chairs. We're still missing a few committee people. Ok, we'll go ahead and I'm going to ask Dr. Wilinga to initiate the public comment. Again, we're going to ask you to stick with 5 minutes and if 7, we will bring it to closure. Is there anyone else on behalf of NRDC? Ok, well, that was within the time limits. Mr. Kenneth Cook, on behalf of the Environmental Working Group. And if you have written comments, please provide them to staff and for circulation.

Mr. COOK: Thank you for this opportunity to present public comments. I'll be brief and focus on a few key issues. A year ago, July, the Environmental Working Group published a report that attempted to rise questions about the use of human subject data in the context of pesticide policy making. At that point, we concluded that the Food Quality Protection Act, had inadvertently created a pretty strong incentive for pesticide companies to increase their efforts to conduct human studies and submit the data for purposes of pesticide regulation. Pretty much as laid out in the EPA Staff Paper, that was presented for this second meeting of the panel. We also commented at the time, in some detail, that we felt there was very little guidance, if any, that EPA was following through which they could think critically about the quality both scientifically and ethically of these studies and were in fact, accepting a number of them or seemed to have, in our mind, accepted a number of them over the years fairly uncritically with respect to this science and ethics. Today I want to focus on just a few main issues that I think bear some elaboration based on the EPA Staff Paper and what you've been talking about so

far this morning. First, with respect to the Food Quality Protection Act, one might get the impression, I think this was inadvertent, but you might get the impression from the EPA Staff Paper and from the discussion that there has been, as a result of FQPA, there have been a number of instances or it's likely that there will be instances, where an additional 10-fold safety factor will be applied to the traditional 10-fold, and 10-fold safety factors that have been in place before the law. But in fact, it has been very rare that EPA has applied this additional 10-fold safety factor in the deliberations it's taken so far in individual chemicals. And what that means is, if there is a policy that moves forward that would result in effect, in eliminating or significantly reducing the intra-species safety factor, you might actually have in the implementation of the Food Quality Protection Act, as the agency has implemented it, you might actually have a lower safety margin than you had before the law was enacted. So it's not just a simple trade-off of the FQPA, children's uncertainty factor, versus the intra-species. We've actually seen in most cases the agency not imposing a 10-fold safety factor. Often having no safety factor or a 3-fold safety factor. A second issue related to this point is that, there have been very few final decision on an pesticides in this class and certainly in the categories for which studies have been submitted that are listed at the back of this staff report. So there has been, in only a very narrow sense, a moratorium of any kind. In fact, the Agency is continuing to accept, read, and review these studies in the course of their examination of the full set of data. So that is taking place and has been taking place. I want to focus a minute or so on the question of benefits. Because I

think this is a matter that's crucial and distinguishes pesticides from pharmaceuticals. At the obvious level, the people who are in the trials, as Dr. Portier said, was able to determine from the back and forth, are people who might, like any person, come down with some of these diseases. And so, one would think that it would be an important distinction to make, that with respect to pesticides, the point at which someone has administered the dose is almost always involuntary. Fewer taking a drug that has gone through clinical trials and has been approved by the Food and Drug Administration, and where the risks are accepted at the ethical level during the course of review, the patient gets a chance to make the same decision when they're deciding whether or not to take a drug that's recommended by their physician. They volunteer to take that drug. That's not the case almost ever with pesticide exposure for food or occupationally.

DR. UTELL: You have one minute.

Mr. COOK: The chemicals we're talking about, by and large, are older chemicals. The question of benefits is therefore pretty complicated. Because there are a number of instances where, if by accepting human studies, a pesticide is allowed to be continued to be used or in fact used at greater levels in food, you might actually by approving a pesticide on the basis of a human study, block the introduction of an even safer compound down the road. This is the crucial fact of pesticide regulation. And finally, the question of benefits. It seems to me, in the absence of them from pesticides, very much compounds the question of what motivates people to participate in these studies. The study that was submitted for chlorpyrifos?,

for example, is a good example. This is the web page from the lab that presented the study for chlorpyrifos. I've submitted this to the committee and want to ask you to take a look at it. No benefits, and the MDS Harris lab advertises by saying earn extra money and you call the phone number 474-PAYS. I would suggest that there's an industry here, in the waiting, that is prepared to take advantage of and perhaps create a whole set of risks that are inappropriate for pesticides that might be accepted for pharmaceuticals.

DR. UTELL: Thank you. We're going to need to move on. Mr. Edward Gray, Vice President of Jellinek, Schwartz and Connolly.

Mr. Gray: Good morning everyone and thank you for the opportunity to be here. I have distributed through the secretary, a copy of my talking points which you should all have I think by now or I guess maybe you're just getting them. I would warn you that there's seems to be some extra pages that crept onto the back side of it through the hijix of our xerox machine. We've apparently copied some of the things twice. You can tear the back part away. Our company represents pesticide manufacturers, and I've done a fair a lot of work over the last several years, working on cholinesterase regulation issues with some of our clients. One of whom ChemiNOVA has sponsored one of these studies, it hasn't been submitted yet, it will be soon. We have submitted the protocol to this Committee in the ACPA submission. Attached to my comments is a letter from Inverss which is, as we noted early, a company that did most of these recent studies. Which lays out in a descriptive brief way, why these things are alike and some reasons why they are different from the Phase 1 studies for investigational new drugs that were just talked about by the FDA representative. Basically, these studies are a kinder, gentler, Phase 1 study. They are designed not to explore the high levels that might show frank adverse effects, but rather to find a level where biomarkers are first noticed. I wanted in my paper to make three or four points that would give some more context, mainly historical, to this panel's debate. EPA's presentation basically starts out in the middle of 1998, when they suddenly realized they had an issue with pesticide ethics. But they really haven't explored the background which goes all the way back at least to 1972 when Congress enacted a provision in FIFRA that expressly says that it's unlawful to conduct human

testing unless there's informed consent. And if you look at the Committee debate, you will see that they clearly recognize the benefits of pesticide testing in humans as well as the downsize in the END OF SIDE 1.
(TAPE 2)....Adapted the Common Rule regarding human testing. At that time, they decided not to apply it to testing done by people that are seeking Agency approval for things like pesticides. This contrast with the way FDA approached life where they apply the same Common Rule to all things for instances, food additive application, color additives, and like, even though they're not drugs and even though FDA doesn't go through a review process prior to the testing. I personally think that the Agency should adopt rules, much like the FDA's. It wouldn't be bothering me personally at all, if they adopted some sort of pre-screening approach and had guidelines. I think if they had done that 10 years ago or 8 years ago, we'd all be in much better shape right now. I also think we should remember that there has been a long history of EPA favoring human testing and particularly with neurotoxicants and particularly with cholinesterase inhibitors. My paper shows that the guidelines for neurotoxicity risk assessment that were finalized in 1998 and published for a noticing comment in 1995, expressly recognized the value and ethical ability to gain human testing data from neurotoxicants that have short-term reversible effects. And another document that's important to look at is the OPP Guidance, it's now a science policy document, regarding cholinesterase inhibition, which makes it clear that when available human data are equivalent to the available animal data, the human data should take precedence. These are all things that I don't think have been discussed, but I

think are extremely relevant to your debate.

To me it's a little bit ironic that we're here talking for the first time about the need for a policy and about you know, how on earth could we ever use human testing in connection with pesticide regulations. The previous speaker made it clear, he published a report in 1998. EPA instantly recognized that this was a big political issue and instantly was shocked to find out this was going on and this panel was appointed and here we are. We know why some people oppose the registration of these kinds of pesticides. But we also know, that is an issue that should not bear at all on your consideration on what is good science and what is good ethics.

And finally I'd like to talk a little bit about numbers and test power. I'm no statistician and I'm not here to talk about formulas. I'm here to talk about what do we use if there aren't human data? and how many animals are in those animal studies that we would use? I went and read the guidelines that were published in 1998 by OPPTS. I found that there were 30 studies that use animals, toxicity studies, and I laid out here a table of the numbers. Thirteen of those study types required five or fewer animals per test group. Another nine of those study types require 6-10 animals. Six more require up to 20. Then there are two that require 30 or 50 respectively. I think from what little I know about power analyses, I think the same kinds of formulas would apply whether you're talking about testing people or rats or rabbits. And it seems to me that we should recognize that under EPA's Weight of Evidence Approaches, it's not any single study that determines safety. It's the combined weight of all the

studies, and when we look at pesticides with all these 30 different kinds of studies, we have an awful lot of information that can be looked at. Thank you very much.

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DR. UTELL: Thank you. Our next speaker Dr. Angelena Duggan, Director of Science Policy for the American Crop Protection Association, will be substituting for Mr. Agroom?.

DR. DUGGAN: Good morning, thank you. I'd like to thank EPA and the panel for the opportunity of representing the ACPA member companies at these deliberations. This is a very serious issue that we've undertaken and member companies have been concerned about some of the information that was forthcoming in the wake of all of these discussions and we hope that at least some of the comments that I will make today and, Dr. Brent, following, will clear up some of the misconceptions. First of all, I'd like to make the point that these issues that we're discussing are not unique to pesticides. Wanting to bring us back to some of the excellent comments made by Dr. DeGeorge. In particular, he had said a lot of chemicals are put into human test that never become a drug. And what we're talking about here are chemical substances, not the intended use of the product, and the testing that we are considering today must be made the considerations on the basis of the validity, the ethics, and the safety assessment that the value of those data will provide to us. Pesticides do benefit society and I'll have more to say about that and these benefits are comparable to pharmaceutical drugs. Volunteer testing, I don't want to belabor that. I think we all know the type of information that we can gain from this type of evaluations, but other then to say, that this information cannot be replaced or conjectured in many cases from animal data. Volunteer studies are conducted according to ethical and scientific standards. Ed Gray had made a point that FIFRA, we would not be in compliance of FIFRA, if

we did not conduct our studies according to the volunteer and informed consent mandates. These studies are done at laboratories that have a long history, a lot of respectability in this area. The fact that they are off shore is irrelevant to the situation. These laboratories can ensure that these ethics and scientific standards are maintained. And I'll have something to say in a little bit more detail about FQPA standards. The same products that are used in crop protection to provide the bountiful food supply that we've, in many cases come to take for granted or right as Americans, certainly, these are the same products that benefit us in public health. They are just as useful in controlling diseases and preventing it and certainly insect vectors. Bubonic Plague would still be with us if we couldn't squash it down very quickly and it does show up. We've only to read the newspapers, the recent occurrences in New York, the scares over Encephalitis sweeping through the population and the product that was used is one of the products, an older product that is particularly under fire. So these compounds do have their uses and benefits and we cannot over look that. The EPA and international authorities like the JMPR have longed recognized the value of providing information that clears up defaults and uncertainty factors and replacing these with more relevant data. Addressing inter-species valuability does not nullify intra-species protection. The 10X intra-species uncertainty factor is retained in establishing the reference dose. It has been retained pre- and post-FQPA. The human volunteer data, when submitted, is not the trump card. It does not automatically nullify inter-species valuability. The studies still needs to be reviewed by EPA, and the EPA has always has and still has, the

opportunity to apply the extra 10X safety factor if it is warranted. I'd also like to say that in speaking for our industry, we are a heavily regulated industry. We operate as all industries do, to maintain the public trust. This involves not only obligations to our customers, consumers, and farmers, it also involves obligations to our shareholders, stock holders. And in providing the trust that our products can be used safely. They need to be reviewed extensively by the regulatory authorities. And in this regard, we seek to provide EPA with the best data. FQPA has afforded the opportunity to look at the information that we had about our particular chemicals to understand where we had gaps, to understand where we should do things better. The fact that there have been, as some would describe, a plethora of human studies, although that is not entirely true, I think it's in a category of less than 10 as a result of this legislation, has not meant that registrants are seeking to get around something. They are seeking to provide information for EPA to make a better decision, a more informed decision about their products. In some cases, they have replaced old studies because these studies certainly did not measure up to current scientific standards and in some cases, these did involve new information. If the registrant has undertaken the judicious testing of these volunteers, then we believe it is appropriate and it does benefit the regulatory process. And if the registrant does submit these datas to EPA, EPA should consider these studies in the weight of evidence for risk assessment to improve the regulatory process. Thank you.

DR. UTELL: Thank you very much. Our next speaker is Dr. Stanley Berent, Director of the

Neuro Psychology Division at the University of Michigan, Medical School.

DR. BERENT: Thank you. Together with my colleague Dr. Jim Albers, who's name is also on that slide, we co-direct a neurobehavioral toxicology program at the University of Michigan and so my comments will also be speaking for him as well. I was asked to come here today by the American Crop Protection Association to speak, and I'm pleased to do that and appreciative to the committee or the panel for allowing me to address them. My own background includes a history of studies of chemicals that are intended for a variety of uses, medicinal as well as other uses. I've been funded for research by industry as well as government agencies and I teach relevant methodologies and content courses in addition to history of serving as consultant to various groups, including industry and government. Publishing in relevant areas, and perhaps most importantly to my comments today, I've been involved extensively in review processes including independent review boards and consensus panels, again for institutions, agencies, government, and private industry. Because of time, I'm going restrict my comments to relate to basically what is a simple underlying idea. What we're talking about, I think, or what the panel is considering are biomedical evaluations and I consider them to be biomedical evaluations regardless of the intended use. And I think the idea of considering the use or the ultimate purpose for research should be approached cautiously, in terms of evaluating the worth of a project, because it can lead to a disruption of our usual standards for evaluating such research. Testing of any chemical substance must comply with rigorous and

ethical and scientific standards. And so doing, I would like to encourage the building on the history of review in biomedical research to ensure that human studies receive peer, specialty, legal, and community oversight. A keystone in that process has been the Independent Review Board which allows for peer review, it allows for representativeness of science, specialty, philosophy, ethics, legal considerations, and perhaps importantly, the community. That review concerns appropriate scientific design where it potentially impinges upon subject safety. It looks at all of the kinds of issues that have been talked about by the Committee the informed consent of volunteers, including the idea of the level of possible coercion that's involved. The idea of how much is paid to a subject to participate, whether that is coercive or it is not coercive, and even the kind of advertising content that goes to the public to seek volunteers. And importantly, it includes other aspects of ethical soundness. Criticisms have been leveled at the IRB process, but these criticisms should be looked at as a process to motivate actions to improve the process, not as an invitation to disrupt or disband the process. It's still a good process and I think it should apply to all human research designs. An alternative to rely solely on regulation as an alternative to an IRB or peer review process, seems to me to be a slippery slope. One that invites a few to decide what might be best for the most and takes it out of the hands of science and puts into the hands of regulatory bodies in a way that destroys the balance, that I think has existed and evolved over time. There are perhaps more commonalties between evaluations of chemical substances intended for medicinal use and those intended for other uses then there are

differences. And differences in the study purpose did not imply differences in underlying methodology. Regulatory requirements often drives some of these differences and may influence the purpose of the research, but the underlying methodology should be based in science, and the kinds of reviews applied to that science should be the same in both instances. The idea that money drives a study and therefore it is bad, seems to me, to be somewhat an unrealistic consideration considering that we live in a capitalistic society, we live in one where money drives many things, and in fact, as regulators we often use that incentive to encourage research to be done in one area or another. And whether or not one believes philosophically that that's a good or a bad motive, should not enter into the review of whether a study is a sound one, an ethical one from a scientific perspective. The idea of different ethics for different purposes of studies is unfounded, and I believe unwise and can lead to bias rather than to objectivity in evaluating research. If one purpose is good and another is bad, it loses site of the methodology implored and whether it is good or less than good methodology. The overall objective, regardless of whether or not of the purpose of the study, is to be able to establish the safety of a chemical substances. Perhaps the most important item here is that results create knowledge to benefit society, not the individual volunteers who are taking part in the study. The individual volunteers may be driven by a variety of motives including that they are going to be paid or that they are going to have a sense of having been altruistic by participating. But the makers and users of all chemical substances that employ human use, should have an obligation to scientifically demonstrate that the

substance does what it is intended to do. That they establish the limits on safe use for such a substance. And the research that is done provides a scientific basis for doing later cost benefit analyses. I believe that the best way to accomplish this is via science and via the standards proven methods for evaluating the safety and ethical considerations of that science. Thank you.

DR. UTELL: Thank you very much for your comments. Our next speaker is Dr. Daniel Byrd on behalf of CTRAPS, is that correct?

DR. BYRD: Dr. Kendall and Dr. Utell and members of the Committee, thank you for the opportunity to make public comments. I spoke to you at the previous meeting. What I'm going to say today is a brief extension of that and I've prepared written comments for you which you may read at your leisure or not as you wish. I like the framework the Committee is coming up with, it doesn't differ from the framework that I am use to employing or that I've seen for example employed in clinical trials of anticancer drugs in an earlier incarnation of my life. I don't quite understand what else you can do. What concerns me. The puzzle for me, is the specifics of the examples that I hear discussed. The risks of testing an organophosphate insecticide in a human safety study are risks of interviews which nobody has dealt with so far. Risks of taking urine samples, risk of blood samples, unanticipated effects, and most prominently, misapplication of dose, either a dose miscalculation or misadministration in some way. These are real risks. No one is trying to say that the subject population has no risk. When you balance that, the Committee has discussed the in-admissibility of financial gain for agriculture or for the pesticide manufacturers. I agree with the Committee about that. Rather than calling it risk benefit balancing, in fact, I refer to it as a risk, risk balancing. The risk is the risk to the population of people consuming foods. And so you have to look at, I think in some detail, the risk to the study subjects, balanced with the risk of unavailability or diminished use of the pesticide for people consuming foods, and the food supply is a public health consideration. We look at some data which is available through USDA and the Food Stamp program. You can show in the Food Stamp Program that restrictions in

the availability of food stamps directly lead to increased admissions to emergency rooms of people in diabetic crisis. Those people are almost entirely former food stamp recipients. So there are risks of diminished food supply. There is such a thing as the safety of the food supply. There is such a thing is the availability of the food supply, and that broad social benefit or absence of risk, it seems to me, is the appropriate balance point. I have yet to hear it brought up in the Committee's discussions. It remains a puzzle and because it's not getting down to specifics there's a puzzle behind that, that's the one that troubles me the most. It seems to me when Congress sets up a pesticide registration process, or Congress sets up a food additive process through FDA, it implicitly recognizes that there's a benefit to society of these products. Otherwise, why have them? Why not say, no pesticides? The republic will survive the absence of pesticides, believe me, so there is a recognition of a general benefit, and I think part of the difficulty here is that no one pesticide with maybe one or two exceptions, can bear a very detailed analysis of the benefits of an improved food supply. Now, until you take all the organophosphates off the table, and then look at the social consequences of that maneuver, you have trouble justifying a human trial for any one pesticide. Furthermore, your task is even more complex than that, it's a differential task. What's it like with the availability of human data versus animal data only? Sometimes there's a decrease, sometimes there's an increase. In our experience, which is over a limited number of pesticides what you allow into the food supply when you do human testing is an increase of about 2 to 3-fold. Not an increase of 10-fold. But that's based on a very limited

number of samples, it almost an antidotal observation. Surely it's not 10-fold. So you know, the task for you all if you want apply the logic is, how much increased public health benefit do we have for the broad population of 260 million food consumers because of this difference in allowable tolerance that relates to the difference between human and animal testing. I think most of the minor organophosphates, you must simply could not generate the data for that. So the fact that there's not a discussion on the table--I mean maybe I'm wrong, maybe you'll disagree with me about sort of, what the appropriate balance point is. But if you agree that's the appropriate balance point, how do you move beyond that to the problem availability of data? Thank you.

DR. UTELL: Thank you very much. Our final speaker, public comment to this morning is Dr. James Wilson on behalf of Resources for the Future.

DR. WILSON: Thank you. I am Jim Wilson. I am senior fellow at Resources for the Future. I do not represent Resources for the Future, we're a bunch of cantankerous scholars and we speak only for ourselves. I am here. My travel this week was underwritten by NOVARTIS so I could come to this and a couple of other meetings, but I don't represent NOVARTIS either. I don't think they would like what I'm about to say. I've only recently begun to look at the methods used to--I'm sorry prefatory remark. I want to raise a thought with you about the difference between the past and future. What it sounds like, from listening this morning, is that you are mostly concerned with developing guidance for how studies are to be conducted. From henceforth, even if henceforth is defined as perhaps the

middle of 1998, after all, if archeologist can decide that 1950 is the present, EPA can go back some point in time. It seems to me, the Agency might appreciate some of your thinking on the subject of, what do we do about studies that were conducted many years ago before 1970, perhaps even back to the beginning of the century because certainly, some of those are still useful today. I only recently became interested in the problem of analyzing risk, of things like these organophosphates pesticides and looked at some of the documents that the Agency has produced. And frankly, I am appalled because the analyses don't provide the information certainly that I'm interested in. I think the public as a whole, is interested in, and I would hope that the policy makers within the Agency would like to know as well. We're faced with things that disappear from the body relatively quickly that are probably eaten mostly every day or certainly frequently there are other exposures as well and the exposures are not relatively constant in day-to-day terms. Sometimes we get a little and sometimes we get a lot. And the problem to analyze, the problem that the Agency has to face in deciding what's safe, is what's the probability that say, eating one potato from a lot, that itself on average meets the tolerance, what's the probability that a single hot potato exists and you'll eat it and be poisoned thereby? And the way the data are analyzed now don't do anything to give us that information. The methods that are used rely on a deep assumption and they come from data that are built on the assumption that the day-to-day change in intake is small. And it's very difficult to take these NOEL based Reference Dose Numbers and say anything about the probability that somebody will be harmed given an overall distribution

of stuff in the food supply that may contain spikes, may contain advert value. Now in fact, at least in some instances, we can make reasonable estimates of that probability. The Center for Disease Control has undertaken studies of elimination of a number of the common organophosphate pesticide and we can show the distribution of what is a reasonable representation of the intake of the pesticide and it's metabolic products day-by-day and get a distribution of what is the apparent intake of these things in the population. And we can compare that with a distribution that can be constructed in principle that relates the percentage of the human population that exhibits some physiologic change that we want to use as a marker, say at 20 percent reduction in blood cholinesterase. We can do that based mainly on the studies in animals that allow one to be able to allow a relation to that physiologic change to some harm. But we require the human studies to calibrate the animals. We require the human studies to go from one to other. And since many of these studies data are from the past, for the Agency and for the industry to be able to address this central problem of toxicity of organophosphate insecticide, we need to able to use the existing data whether new data developed or not. So I hope that you'll take that into account and provide some thought to the Agency on how to deal with this problem. Thanks.

DR. UTELL: Thank you very much for your comments. This brings to conclusion the request for an opportunity to address the committee. I want to thank all of the speakers for their thoughtful comments as well as for keeping to the time-table. Dr. Kendall is now going to lead the charge, serve lunch, and continue

the committee deliberations and will watch.

DR. KENDALL: I'm still impressed with the committee and it's willingness to persevere this morning. We've made excellent progress in my opinion, and I think the public comment period was quite good, as was the previous discussion by the panel follow-up by, I think real clarification related to some of the FDA processes. We have assigned another subcommittee that's been working to look at a restructured version of one of the drafts of the last meeting and the continuing process of development of our subcommittee's report. So, our lunch is arriving momentarily according to Mr. Dorsey and it will be served hopefully relatively quietly, and each individual member of the panel will be responsible for paying Ms. Percival. And the numbers are provided in a rounded number which should facilitate us.
I would like to push forward if doctors Reigart and Weiss have the where with all currently to move on and to discuss our restructure version of Draft 4. Gentlemen, are you prepared to do that? Can you do that? I think the committee is ready to hear from you. Yes, Dr. Gorovitz.

DR. GOROVITZ: We do need at some point to have the once promised and now forgotten checkout opportunity.

Dr. KENDALL: Yes, I didn't forget that because to me, we could take a break immediately after lunch. I think Ms. Percival has somewhat cleared things if we need to checkout say 1:00 or so, we're going to be fine. I have not forgotten that Dr. Gorovitz, and thank you for reminding me though. But I don't want to lose the lunch period. And I think we've got the information on the table. I really want to hear, I think the committee does from

Doctors Reigart and Weiss. Lunch will then move in immediately followed by an opportunity to checkout. OK. So I'd like to ask Doctors Reigart and Weiss to update us related to their work. And the committee has received their drafts and materials. OK.

DR. REIGART: Let me say that I've accepted this subcommittee task on a conference call and it was the worst error in judgement in my life. Because I was given about 3 days to produce a draft and was supposed to get feedback before it was distributed to anybody and Thanksgiving came along and it got distributed in the crudest possible fashion, so. And I received one comment from Dr. Weiss's who said, where did you want this to go in the new report? And I said I don't want it to go anywhere because this was entirely a rough draft that wasn't intentioned to be put in as is anywhere in any single place. I should further say that the materials I've prepared are about 90 percent words from Draft 4 of the committee, and about 10 percent my own words, which were just sort of placed around the words from the draft. I did read Dr. Fielder's comments this morning for the first time and I fully agree with her comments.

DR. KENDALL: Good, Good. We know your charge was difficult and for the audience's sake, it was Section 3.2 in the previous report, which moves towards further defining the criteria around which we would recommend and/or support or not support human testing.

DR. REIGART: Yes. Having said that, I'll just very quickly go through the way I reorganized it. First, in the conference call, there really was, despite some comments heard this morning, a strong desire on the part of the subcommittee members to look at the intent of the studies. And

I think Dr. Gorovitz touched on that this morning. Again, that the intent should be to improve human health protection and that other studies, he considered not acceptable and there was some wording in the paragraph regarding use of studies, just to establish an NOAEL which, by and large, said that we did not consider that to be an appropriate intent, although there were some qualifications. Clearly that needs further discussion. Is it or is it not appropriate to use these studies to establish an NOEL. The second section were materials that had to do with basic study design, sample size, how you ascertain appropriate subjects, whether susceptible populations, subpopulations, such as children or women, perhaps particularly pregnant women is appropriate. Second issues related to the ascertainment of subjects as to their generalizability which includes not just women and children extrapolations, but populations that might be more or less sensitive to the subjects at question. What I was looking at with sort of the risks continuum and some of the words that I found in there that spoke to it and a lot of these have already been touched on this morning. The idea, as Dr. Gorovitz said a lot better than these words do, that looking at unintentioned incidence or studies of field workers or other sort of either observation or epidemiologic studies may be far less challenging than experimentation with intentional administration to human volunteers. Second issue is Rid of Exposure and I think Ms. Mulkey spoke about putting pesticides on skin to look for sensitization or irritation as being a somewhat different route of exposure than systemic. I should say that the draft material actually equated all roots of exposure and said there's no difference. But I've heard different

views about that and I thought it worth further exposure. The key issue of Dose. We've already heard this morning, some discussions of low dose studies for PK and PD studies versus dosing to certain toxicities and I think that at some point, we have to grapple with what level of dosing is appropriate for human experimentations and particularly, the discussion that is danced all around in the drafts of whether or not it's appropriate to induce neurologic symptommentology? and if so, under what conditions. It's stated in the draft that some members of the Committee said neurotoxicants should not be used to toxicity under any conditions, and others felt there are parameters under which it was acceptable. I think if we don't reach, if not closure on that, get close enough on that issue, we're not going to be giving very good guidance to the Agency. And the next issue, which is closely related is target organ. I did personally have a great deal of discomfort with attempts to draw parallels between ozone inhalation studies and direct administration of neurotoxicants. I think target organ is an issue and the draft danced around that as well. It said there is no difference, in one place, and in another place it said there was a difference. So I think that is something we ought to resolve as a committee. And we're sort of at the end. I think all of you have read this document, as I said. It's 90 percent what was in the old one, shortened. I took out as much of the extraneous words as I could. I put in a slightly different frame work and reorganized it, which it was what I was asked to do, but I have no intention whatever that this be incorporated as is, in the draft. I meant it entirely as a way of discussing and highlighting some of the areas where we seem to have some differences.

DR. KENDALL: I think that was well done and I don't think anyone contended that the draft you presented would just go into the document. It presented for us a working document that followed up. I thought it was a really excellent teleconference that we had several weeks ago, so Dr. Reigart thank you for making that decision to help us. You did respond to the challenge and I think you've put a number of issues on the table.

DR. UTELL: I would add to that because I think it really crystallizes where the agreement on some these issues begins to maybe get a little muddied. And what we need to work through later today are frankly some of the issues that you've illustrated for us and we're going to try and spend some time tackling them. But, I wish we could just lift it and include it in the report but clearly that's not the intention.

DR. KENDALL: And I think too, some of the process to move forward, I think we need to have some discussion on the points you just put on the table. In addition, there will be some needs for follow-up writing and maybe a little bit of re-crafting of the document. I haven't looked at you yet on that, but I'm observing. For everyone's comfort level, I think that we will need some follow-up. We won't get it all done as far as crafting it and putting it into the document today, we'll need just to get the issues out and go forward.

DR. REIGART: I wonder if Dr. Fiedler would. I don't know if anyone read her comments. I finally got to see them this morning.

DR. KENDALL: Let me ask the committee this. First of all, I just wanted to give you the respect of having the opportunity to present your information. Dr. Weiss anything to add to Dr. Reigart's

material. Both of you did work together.

DR. REIGART: He has some of his own to present, I'm sure.

DR.KENDALL: And then I'd like Dr. Fiedler to respond with some of the follow-up. OK.

DR. WEISS: Well, during the conference call, Ronald suggested that we take one example of a pesticide and discuss how we would view human experiments with it. When I tried to do that, I decided it wasn't worthwhile. And instead, I sympathized five different scenarios which I thought, ranged from relatively innocuous to possibly hazardous for human volunteers so that they're all fixed and hold. I took the next step, which I'd like to show you on a transparency. What tried to do here, and perhaps I can get the committee to cooperate with me in making these ratings, is to look at two dimensions for each scenario. One that I've labeled as health risks ranging from say no adverse effects to prolonged neurotoxicity and then another dimension that I provisionally labeled ethics risk. And I think for each of these scenarios or other scenarios that you can develop, we can look at these two dimensions and for any group of experts, like this committee, or a group of bioethesis or a group of risk assessors, we can survey where these things might fit. For example, if you find a particular scenario or protocol submitted to EPA to produce a widely divergent estimate of either one dimension or the other you would like to review what is in it. If you find it neatly clustered at the upper corner, you would totally reject it. EPA might decide that any clustering of evaluations in the lower left would be a protocol that's acceptable to them. And

I think for getting, not a committee consensus, but committee evaluation, maybe this is the kind of thing we might try with those five scenarios.

DR. KENDALL: Dr. Needleman.

DR. NEEDLEMAN: That's an interesting exercise, but I think it assumes that you can accurately place each individual case according to those two vectors. For instance, health risk rate effects I think it's very difficult to say with confidence, what is of no effect and what is mild acute discomfort. But we've learned, if anything, that some outcomes which appear to be invisible or of minimal consequence, end up as a long term effect. So there's a great deal of error around each one of those five categories.

DR. WEISS: Yes, you're absolutely right. These are all sort of subjective on the part of the rater and what this exercise does is tell you something about the rater's viewpoint of where these lie. No, these are not absolutes.

DR. NEEDLEMAN: But it's an exercise in the sociology of science, I would prefer that we try and focus down and get more precision about whether given investigation is scientifically rigorous and then the more difficult question about whether it's ethically appropriate. And I think this could be fun, and it could give us an idea about how we all feel about this, where we lay out on this, but I don't think it's going to produce more precision and confidence for EPA in deciding whether to accept a given study or not.

DR. WEISS: I'm not sure that we are in any position to formulate those kinds of tight rules or, that's the problem.

DR.REIGART: I took Dr. Weiss's test and sat down and tried to do his health risk ratings and his ethics risk ratings. I found it somewhat interesting and useful in terms of clarifying my own thoughts on it, but there needs to be a broader range. Insufficient evidence is clearly an obvious choice here and that should immediately throw the whole document back at whoever sent it out. Insufficient information to make a judgement.

DR. WEISS: There are other dimensions you could put up here, for example, you could devise an axis called scientific validity which I didn't put in there. But, if you'll noticed in what I proposed, I have a space there for critique, where we would use for comments on things like the statistical power of such an experiment. Remembering one of those, I had a very small end. And you might decide that an end that size for a question that large was an ethical risk, if you only wanted to have two dimensions which you can project on an overhead. It's true, it's an exercise Herb said, but I thought it made more sense to construct different scenarios rather than take one product as Routt suggested and see how we would evaluate different kinds of approaches to it.

DR. KENDALL: Dr. Fiedler, I'd like you to follow-up on some of the comments made by both, doctors Reigart and Weiss and where do we go from here.

DR. FIEDLER: Ok, first of all I'll make my disclaimer. I really appreciate the work you did and I think you got put on the spot and responded beautifully. I didn't make my comments to be personal, but rather to probably reflect my own frustration with sort of our process.

DR. REIGART: I clearly would not take it personally, I hope you didn't think that I was saying that. But they were well deserved.

DR. FIEDLER: And I suppose that my comments to the draft were really my attempt to try to clarify my own thinking and probably to push the committee to get down to what I call "brass tacks" and stop being quite so polite. Because I think we've been tremendously polite in many respects and that we now need to move to more specific, maybe decision points. And I thought that what Bernie just presented is an attempt to do that. No so much, I also tried to do your test. I couldn't rate any of them because as an IRB member, I would have given them all back to the investigator and said I need this information/that information. OK, I suppose you knew that knowing what you usually like. But, I think that they do provide a discussion point for all the committee to go through almost each of those protocols and then to maybe begin to establish some of the guidelines that we would want for each of the areas or questions that we need to address. And I thought that what Routt provided at the back of his document, about the questions that remained to be addressed, would be useful for us to go through and have those kinds of discussions. Because many of the questions here are questions that I raised in my critique of this document and I think have been raised by many, many other people. So, in terms of structure, I think it would useful for us to possibly do these questions or address these questions maybe using Bernie's example as one method for us to begin to grapple with, starting with purpose and going on with the subjects, or starting with purpose and intent and is there sufficient animal data to justify this experiment that is proposed, and going on from there. I think also what we receive from the FDA in terms on how they proceed and their process for deciding whether or not they are ready for human studes is a very reasonable guideline for us to use in now, our deliberations. But of course, all of this presumes that we, as the committee, feel that we can provide guidance for a controlled or intentional human exposure study and there may be even right there disagreement as to whether we would even support that. So we may need to acknowledge that there are people who on this committee feel we shouldn't do this at all. And you know, that may be the first place to start.

DR. KENDALL: Ok, I think that's a good point and I think we had a good opening this morning by areas of agreement. There were many operationally. You articulated, I thought, very important points that we can literally walk through and discuss as a committee. What Art Kaplan had to say at the last meeting, the terms of the foundation upon which you would recommend and/or accept human testing data were only through processes that would be the most compelling. If you remember that, the most compelling. And that's somewhat of an elusive term and a concept, but it sets the stage and perhaps we should ask the question, if the committee is still, and I think there was general agreement that, "only under the most compelling circumstances, should actual dosing occur with humans with experimental pesticides that could have health consequences, particularly neurotoxicologically." And that's kind of the general closure at the last meeting we had, from my perspective. Any disagreement on that?

DR. MCCONNELL: Yes, I don't know if it's a disagreement Ron, but it certainly may be a difference of opinion. But as you identified, I don't know what the term compelling means.

DR. KENDALL: Well that's what Art Kaplan said and that's what we generally had. It was in our record and it has appeared several times in draft. So, OK.

DR. MCCONNELL: I realize that, but what I'm saying is that to compelling can be for different reasons. I think that if it helps in the risk assessment, to make it more accurate so that you and I, if we are exposed to vegetables with pesticides on them have a better appreciation for what that true risk is, I think that's very compelling. You may not think that's

compelling. That's kind of where I'm heading.

DR. KENDALL: Well, I think that's fine. That's what Dr. Fiedler was trying to get at, that point. In other words, what's our general base of starting here, in terms of a general agreement or disagreement. Would anyone disagree with what Dr. McConnell just had to say? Dr. Gorovitz.

DR. GOROVITZ: Well, just as he began by saying, he wasn't sure that what he was about to say was disagreement, I'm not sure that this is disagreement. But I have some sympathy for the (Kaplan-ist Gustoff?). What I mean is this, there are basically two different ways in which one could think about this, among others, but these are quite removed from each other. One of them is, it's research like any other. Anybody who want to do research, testing these substances on human subjects should feel free to do it provided that there is an appropriate regard for safety and informed consent and no fundamentally unjust practices in the recruitment of the pool of subjects and so on. There's a different way that one can come at it and that is from the point of view of the Agency and what the agency encourages, sanctions, wishes to promote, wishes to think of as part of its way of doing business. And that might go something like this: Before we were received, I'm not talking now about messy points of transition, but a future steady-state. Before we were received as relevant data to our decisional purposes, the results of studies with human subjects, we must be assured of certain things. First, that the protocol came to us for pre-screening and approval. Second, that extensive and in our judgement, adequate animal toxicity studies were done first. Third, that the study has the

statistical power to generate information that is genuinely useful from our point of view that is useful for our public health protection purposes. Which is to say, that there's a threshold that's fairly high that has to be met before the EPA will say, "yes we're willing to receive this and count it as part our evidential base." And it might be that for different purposes, for a different Agency, for a different context, a study that doesn't meet all of those criteria would be allowable. And I think perhaps, Art couldn't be here today, I was hoping because I did speak to him about this and there was some chance he might do at least a cameo appearance, but he's hard to miss and I don't see him, so I don't think he's here. And I don't want to pretend and speak for him, but I think part of what he had in mind was sort of, in this latter category, that is saying, that there ought to be a threshold that's not trivially achieved before the agency will accept as clean information, the results of a study with human subjects tested with intentional dosing of pesticides. And I think that's right.

DR. KENDALL: Exactly. And I think the committee, according to Dr. Fiedler and others is concerned to make sure that threshold's appropriate and has appropriate parameters around it, that can be governed and evaluated, and revisited in the future in a way in which we as a group, would be comfortable with making the kind of recommendations we're going to make.

DR. GOROVITZ: If I could just add a footnote to that. We've had representations that the studies are done in professional laboratories by well intentional people who are very concerned to do things in appropriate ways scientifically and ethically. And it may well be that that is the norm. But of course, protections are not designed exclusively for the norm, but to try to pull

in the deviant ends of distribution, and we know, and have had vivid descriptions of research that does not bear scrutiny and what we want is to construct a filter that's fine enough to screen out the kind of research, not that we can imagine being done, but that we know full well has been and is being done.

DR. KENDALL: I think as we approach, I think some of the problems that came forward the last discussion was a real uncomfort level as to what those criteria would be, how the process would be evaluated and regulated, to the point where, when one is presented with those kinds of circumstances, the initial response is a very negative one, until as a responsible scientist, when I think we've identified there some scientific problems here, power analyses. etc., as we establish our criteria to determine what that threshold should be. Ok. As I listened to your points this morning, Dr. Fiedler, and they get into the science underpinning the ethical approach to the study; the number of subjects, their being informed, the power analyses to determine how many subjects there should be, not just for financial reasons only, but to advance public health benefit. Ok. Our lunch is right over there and there's several of you I want to hear from. We can continue right on. Dr. Needleman, are you so compelled to say what you want to say? Do you need to say it right now, or can you wait until we serve our lunch?

DR. NEEDLEMAN: I rather say it without the crunching of lettuce leaves.

DR. KENDALL: Ok. You go ahead. Proceed.

DR. NEEDLEMAN: If you read the transcript, Art Kaplan asked me under what circumstances I would allow the administration of newer toxicants to humans. And I said, "only the most compelling." Then the

conversation went on from there. So I know what I meant. What I meant was I needed to have the information in order to make an informed decision. And I do not think that need is present. And later, I will expand on that, to say that the kind of information that is obtained from these human studies, is non-informative. Therefore, unethical. Now we can eat.

DR. KENDALL: Ok, well put. I look forward to that presentation, because I thought that you provided a very nice document to the committee, very thoughtful. I have no problem having a--this is the kind of discussion we need right now to move this thing forward. I have no problem having that discussion with our lunch, with us. If those of you, Dr. Needleman, do not want to listen to any crunching then let's just break for 15 minutes and eat our lunch. I want us to be to the point as Dr. Fiedler said, we're going to get down to brass tacks. Ok, let's go ahead and get our lunch and take 15 minutes to eat our lunch.

DR. GOROVITZ: Is this when we should check out too?

DR. KENDALL: Yes. Let's say 15 minutes, get your lunch, we will continue on in about 15 minutes.

LUNCH BREAK

DR. NEEDLEMAN: .... subject to large Type 2 errors. In 1976, Jim Birchfield and Frank Duffy, Jim Birchfield is the co-director of the Epileptsy Center in Rochester, and Frank Duffy followed up a group of people who had had one exposure to organophoshpates. And a year later, using quantitative electroencephalogram fast boyd? transfer, a form of analyses, found that there was a significant change in their brain waves. That you couldn't see on clinical examination of

the EEG but using a more quantitative technique you could. So that, that raises a question of when you give a brain poison, particularly in the venue of this discussion, is organophosphates, and you say that you haven't produced an adverse effect, you better be very sure that you haven't. And if that effect is very small, it requires large numbers of subjects and I reviewed, because Mr. Carley was gracious enough to send me a large number of this human studies, I looked at those, and the subject numbers are extremely small and nobody ever attempted a power analysis. Now they have very good statisticians in VEREST etc.?, they've produce elegant outputs, but they neglect that. And there's a reason that they neglect that is because the power is woefully small. And I'll talk about that a little later.

DR. DEGEORGE: But the point is that's still going to the definitive endpoint being defined by that human data set and trying to set that as the only use of the data. And I was trying to point out that you might have discovered, absent detecting that in humans, that the animal models that you were using were less sensitive in terms of, or potential less sensitive because exposures were lower in those animals, given the same dose or however you're scaling across species. Or that the biomarker in the animal was observed at a much higher level than the biomarker was first observed in humans. And that could tell you in fact, you're assumed safety margins are much overestimated. So you can use the information, it's still useable.

DR. NEEDLMAN: If it were collected in these studies, it was not.

DR.KENDALL: Ok. Now this gets right to the essence of what you mentioned this morning. The effects identified as part of the experimental design and subject

analysis, and the power of the experimental design from a statistical level. And I think both Dr. Portier and Dr. Needleman are prepared to talk about that subject and the committee will deliberate on it. Dr. McConnell did you want to address at this point.

DR. MCCONNELL: Yes, well, I wanted to address Herb's point and Dr. DeGeorge's point and subsequent to our last meeting, I did a survey of trying to find pertinent human studies that might be of value to talk about here today. Because I think one of the things that was missing, in addition to the FDA side, was that we really did not address the types of studies that we're talking about and the value that these studies might have. I must admit we're all influenced by our background, where we grew up, what churches we went to, and our training and our experience, and, in fact are often said that we're prisoners to that and I have to admit that myself. So the examples I'm going to give you, of course are based only with that background. Having grown up around a farm, on a farm, and spent half my career in the military and the other half at NIH, I was asked to chair a committee when I was on the committee on toxicology with the National Academy of Sciences, and that was to address a pyrethrum?, which is a well known insecticide/pesticide with neurotoxcie potential. The Army, whether you all know it or not, in Dessert Storm impregnated the uniforms of the people in that battle with pyrethrum?. The reason being that, if any of you are students of military history or not, but even as recently as Vietnam, there were twice as many lost battle days to disease as there were from enemy contact. And it's always been that way and it was much more so in the second world war. And many of these diseases are insect-born. So the Army, knowing

that this is a problem, impregnated the battle fatigues, battle dress uniforms (BDUs) with this material in the hopes of keeping the insects away, and those that got on them would be involved. Well, in Dessert Storm, as some of you know, you know it's a terrible area for schmenisis? parts of it have a lot of malaria and so forth. And the consequence of using this was that we had far further infectious disease situations in that war then we have ever had before. Now, if one had used the animal data to make a decision in that regard, you would not have impregnated those uniforms with pyrethrum?. Because in studies in animals, about 40 percent of a dose applied to a mouse, is absorbed through the skin which would make this incredibly high for a human, and you'd never allow it particularly in a chronic exposure situation as they had. In monkeys, it's 23 percent absorbed, but in human volunteers it's one percent absorbed which made a great deal a difference. So without that human volunteer information we probably would not have had that in our battle fatigues. I just point that out as an example. But, however, you cannot go across from one insecticide to another because studies that were done at, well, I have the article here, with Periforce? or Durabain?, just the opposite occurs. A high amount of that material is absorbed through the skin when it's applied to the skin. So you can't take animal data and necessarily predict what's going to happen in humans. In fact, there are many examples where you cannot. Again, both of these are neurotoxic. One's an OP, the other's a pyrethoid, and then the other example, based on my experience was that when I was at NIEHS, probably the most potent carcinogen I ever studied was 1,3-buytadyene. Now it caused levels of tumors and Chris can point this out that

we had never experienced with any other chemical in mice particularly, less so in rats. We did a follow-up study and found that as low as 6 parts per million, they also saw a carcinogenic effect in mice but not so in rats. Now there's a discussion, which are we more alike a rat or a mouse? Because if we're more like a rat, the exposure to 1,3-buytadyne probably is not significant. If we're more like a mouse, it probably is, in particularly at environmental levels. So there are invitro studies that suggest that the rat is more like a human than the mouse, but obviously, the definitive proof would be a study in human. And it was interesting, and subsequent to our meeting in the June issue of Toxicological Sciences, there is this paper where they're using human volunteers for this specific purpose to understand whether the pharmacodynamics and kinetics and metabolism and so forth are more like a rat, than a mouse. Now this study is interesting, however, in that it's funded by EPA, co-funded by EPA and NIH, with some help from an outfit called NIEHS. But the thing I find interesting is that the OSHA Standard is 2 parts per million, the lowest level in mice that caused a neoplastic response is 6.25 parts per million. And this study is being done at 5 parts per million. Now, I'm not critical of this study, I think there's absolutely good case to make where there's no reasonably certainty of no harm to these individuals, but I can assure you, no matter which way this comes out, it's going to have an important impact on how this chemical is treated by the regulatory community and whether it presents a human health risk or not. So I think, as they say in toxicology, human data always trumps animal data, it always has and it always will. And if conducted properly, I

think that's what we should be getting to here, it's of utmost importance and whether it's a neurotoxin or not a neurotoxin, as long as you give levels that don't produce any kind of clinical effect, for instances, those that would be used in ADME studies, I think that it's absolutely important in fact, to do these studies, and possibly ethically it would be wrong not to do these studies, if you and I and our children are going to be exposed to these materials in our food supply. Isn't this the chemical that you'd want to know most about? I was going to save that for later, but it's off my chest and now I'll feel much better for the rest of the afternoon.

DR. KENDALL: Well, I'm glad you will and I think those were good points and they still get to the point of the compelling issues and what is our threshold to recommend and/or encourage acceptance of these kinds of data. Dr. Needleman do you want to respond. I'd actually like for you to proceed with your presentation. And Dr. Portier, it seems appropriate for Dr. Needleman to respond.

DR. NEEDLEMAN: Before we get to sample size discussions, there's an issue floating around

DR. KENDALL: Does he need to be here to here you?

DR. PORTIER: Oh, I don't know, Dr. DeGeorge raised it and Dr. McConnell also.

DR. NEEDLEMAN: You're confusing two different types of objectives in the studies in trying to justify all the studies for the two different objectives. So, let me get to the two objectives. Dr. DeGeorge was pointing out to us that oh yes, there's information to be gained in terms of metabolism from during these studies in humans and the comparative and

metabolism between humans and animals. Nobody's going to doubt that statement. That is a fair and clear and safe and easy statement to make, provided you've got a clear definition of what you're trying to make a comparison of and that you've considered enough variation in the population to be certain that you are able to tell if there is or is not a difference at the acceptable level. So, whether it's power or whether is biological believability, I don't doubt that. Whether you do it or not, I'm not going to get into the ethics of it, but at least in that case, we have a scientifically defendable hypothesis that can be well laid out and clearly understood and clearly studied. It's an estimation problem and potentially a testing problem. On the other hand, when we look at an issue in risk assessment where we're attempting to do something as vague and unclear as the estimation of a NOEL in a population, which is only dependant upon the sample size and entirely dependant upon the doses chosen, I have a clear difficulty from a scientific perspective of justifying such a study. I don't see that it adds to the scientific literature, and the only thing it does is add to the regulatory process. And I'm not sure that's justifiable in this situation. And that's what I think is the substantial difference. So when we talk about justifying studies, I think we need to be very clear about what the objective is, in terms of the human clinical study .we're looking at.

DR. KENDALL: I think that's well put. I think the committee is supportive of those delineations. Dr. DeGeorge, do you understand?

DR. DEGEORGE: I actually agree. And I also would point out that there's also the notion of the biologic marker, not just

exposure, as to whether or not the models you've been using to make all your conclusions are appropriate. So it's a further point.

DR. KENDALL: Dr. Portier.

DR. PORTIER: I'm going to pick on the–I believe this is from the American Crop Protection Association. One of their examples, to illustrate some of the problems that I see for the scientifically defendable study. They gave two examples, one which was melathion which the stated goal of the study was to establish a NOEL in the population based upon three people in each exposure group, up to maybe 10 people in each exposure group. That's a difficult study to believe the scientific believability of. But the Thyrocarbonate? Study, ok. There, they were doing exactly what we are talking about. The stated goal was to look at the adequacy of metabolite as a biomarker to quantify absorption. Ok? The used six individuals in doing the study in the humans and concluded that there was a substantial difference between the six individuals and the rodent population in terms of the percentage of each metabolite in the urine of each type. No statistical test was done. No concept of the variance associated with the two different studies. I don't know that I can believe that answer or not believe that answer because from my point of view, they didn't give me an answer. All they gave me was a description of the two percentages that were different. And so even then, you have to be very careful in looking at it. And if I can finish with my one last comment from Dr. Gorovitz, while he's here, I liked his definition of compelling. I think you did an excellent job of compelling me that your definition is in fact compelling. The only difference I see

here is something that's not necessarily considered by an IRB for a pharmaceutical and isn't in the list of things you gave up, and that is, the description of the value of alternative less ethically challenging studies. As scientist, we always think, well if this is scientifically credible and has a good hypothesis, and it's a pharmaceutical, yeah, we should study it. It's a good idea to take it a step further. But here, we have to consider the fact that there are exposed people in the population, especially for an existing pesticide, and we have to make sure we add that in the list to the IRB because they wouldn't normally look at that.

DR. KENDALL: Make sure your mike's on.

DR. FIEDLER: I'd like to respond to what you just said, cause I think it leads us almost to what we need to first consider in those examples. Because, on the one hand, what you're really saying is that the data does not address the stated purpose that they're collecting. In other words, with three subjects trying to talk about the NOEL for the population, that's a guideline right there for most compelling. That the purpose is not in line with the study design. So that's one guideline that we could offer. I mean it sounds very simple, but that's one.

DR. KENDALL: Then let's offer it and committee, we agree with that.

DR. FIEDLER: Then the second related to what Dr. Gorovitz was talking about with regard to the ethics of the exposure and whether or not there's an adequate literature review present that documents that this would be the next plausible step in the scientific process and that all other avenues to address this

question have been exhausted. Such as case control studies of exposures that are ongoing already, animal literature that leads up to this point. So, to me, that's the beginning of beginning to develop guidelines of whether or not a study is sufficiently compelling. Does that...?

DR. KENDALL: Exactly. Dr. Gorovitz's is that compelling? To me that's compelling.

DR. GOROVITZ: That's persuasive.

DR. KENDALL: Now you're on persuasive. Those are two very important points. And the third one gets to the concept of power related to the experimental design and the hypothesis posed. And I know, that Dr. Needleman has been waiting in the wings to talk about this power analysis process and Dr. Portier has several things to add to the record as well. And I think Dr. Fiedler, we're making progress here to articulate the points in which we left the last meeting without closure. Dr. Gorovitz do you want to explain difference between compelling and persuasive?

DR. GOROVITZ: No, I want to ask a question, because I am not sophisticated about research design or statistical power. And I think I understand the information that's been presented to us about sample size, but there seems mean asymmetry which nobody has mentioned unless it was when I was out of the room, checking out. And that's this: If we administer a low dose of a substances to a small sample, half a dozen adult males, and they all seem to be symptom free, and free of any kind of distressing markers, I'm persuaded we've learned essentially nothing from that. On the other hand, if all six of them fall over in a fit of wrenching and riving, it seems to me we've learned something quite powerful

from that. And it's this asymmetry that confuses me in respect to sample size, because it does seem to me we can learn that something's a bad thing from a very small sample. What seems to take the very large sample is a confident judgement that it's not a bad thing. Would somebody who knows what're they're talking about speak to this?

DR. KENDALL: Dr. McConnell, you want to speak to it?

DR. MCCONNELL: Yes, I'll speak exactly to that. But Sam, what if I told you that same six people at this very very low exposure showed you an absorption, a metabolic distribution excretion pattern very similar to a rat or to dozens of rats. Would that be useful information?

DR. GOROVITZ: I understand that point. That could alter your degree of confidence in the results of the animal studies.

DR. MCCONNELL: Exactly.

DR. GOROVITZ: Well, that's what...

DR. MCCONNELL: I see the main value of these studies as Bernie pointed out, I think in his very initial discussion and, as Dr. DeGeorge pointed out, that the main value of these human studies is not to establish a NOEL or an NOAEL, but rather to better understand what we learn from the animal data.

DR. GOROVITZ: Yes, I got that, but the studies submitted, don't seem to have that character.

DR. MCCONNELL: Well, that's to me a different issue, and I think that's one maybe we should focus on . You know, what's the ideal and then I don't know we can help the Agency in terms of what's already been submitted, but I think we can help the agency in what needs to be submitted,

number one. Number two, I think one of the things we forget here, is that there will be new pesticides coming out. The myriad of pesticides that are on the market today probably will be quite different ten years from now. And what concerns me, and I've heard very little discussion on this, is that, do we want to wait until these pesticides are introduced, based on animal data, then put in the field, monitor field workers, and see what happens. Or, would it be a better use and more prudent from a public health standpoint to have a small number of human volunteers as we've been talking about prior to this material being introduced into the public. To me, ethically, it's the latter.

DR. GOROVITZ: My question was very specific. It had to do...

DR. KENDALL: ...I'm going to try and answer your question.

DR. GOROVITZ: No, I think I got an answer. It was about this asymmetry and I understand that point. But, I gather there's agreement that a small sample that shows no adverse effects has very little relevant evidential force.

DR. UTELL: If you're looking at presumably just symptoms as your outcome, then you're probably right. Six people with exposure and no clinical symptom, one would be very hard pressed to make a judgement that it's safe or not safe. It would add very little.

And I think what we're hearing is sort of the almost a diagram that's having several branches. There are certain pieces of information in terms of pharmacokinetics that might well be established with small numbers and frankly, may be very important. The clinical testing, in terms of symptoms or even biomarkers–it be wonderful if we had biomarkers, but they're few and far between--one would have to do a lot

of studies and even then proving the negative is extraordinarily complex.

DR. KENDALL: I think what the committee is worried about Dr. Gorovitz is general speaking, preceding any potential human test, we would have a substantial amount of animal toxicology data. And I think we would not, based on that information, suspect the extremely consistent effects at a very high level of response. We would more suspect, if any negative effect occurred, generally speaking, it would be latent. It would perhaps be in a small percentage of the subjects. Therefore, this is what worries Dr. Portier and others. Do we have enough subjects in the experimental design to detect that effect if it's of small percentage of the subjects. And we've heard Dr. Needleman argue that the effects, although in a small percentage of the population, could have significant consequence latently, down the road, in the case of individuals/humans under test. I think it's not these extreme polls you're talking about, it's more, in other words, six out of six respond versus zero out of six respond, it's more the 1 out of 100 and did we have the experimental design in place to get that.

DR. MCCONNELL: Is there any example of a chemical, that you know of, that you give at levels that cause no harm as we would identify it clinically? You know one or two exposures of that chemical and then find even a single example where 2 years from now or 20 years from now you had a problem? Can you think of any chemical like that? First, you had just one or two exposures at a level that produced no clinical effects in that person.

DR. NEEDLEMAN: I just cited a paper to you that was the only...

DR. MCCONNELL: I know, but they had clinical effects. Those people got exposed to a point the first time, and correct me if I'm wrong.

DR. NEEDLEMAN: No, you're wrong.

DR. MCCONNELL: You didn't see anything the first time but you saw something.

DR. NEEDLEMAN: That's correct.

DR. MCCONNELL: I have to see that paper.

DR. WEISS: Gene, that's certainly true (bad sound) neurotoxicity literature.

DR. MCCONNELL: That's different, but we're talking about healthy adults. That's a separate issue and I accept that, absolutely.

DR. KENDALL: Ok. So the issue of experimental design and statistical power is highly relevant and it's one that I think substantiates a strong endorsement by the committee. And I think also, Dr. McConnell, the issue of the variance in various populations does have a high degree of relevance as to our threshold because a healthy adult male, we've agreed upon, is different than a child.

DR. MCCONNELL: And that's why you have the intra-species safety factor and the second safety factor to protect for children. You're exactly right.

DR. KENDALL: Dr. Weiss?

DR. WEISS: APTP. APTP was a contaminant in designer drugs on the West Coast.

DR. MCCONNELL: I know what the drug is, a Parkinson-like disease.

DR. WEISS: Right. One exposure was enough to destroy enough cells in sub-(unclear) to produce later on Parkinson Disease.

DR. MCCONNELL: I understand. But, but if you had had that first exposure that produced nothing, would you expect Parkinson later?

DR. WEISS: No, that's the surprise.

DR. MCCONNELL: No, I mean that had no initial disease within a...

DR. KENDALL: Where this is headed, Dr. Kahn, I'm going to acknowledge you in just a second. Dr. Fiedler I'm making an extraordinary attempt here to go through the issues you raised this morning. I'm looking at these constantly and I will be revisiting with you the issue of the rewrite of Section 3.2. Because as we articulate the responses to the very important points you made, this really gets at the issue of many of our past differences which are moving towards; there's a lot of agreement here. There's a lot of agreement. There's a lot more agreement than I thought we would have at this time of the day. That's why I'm glad I gave you lunch now. But seriously, I am tracking your points. And I will be asking you, and Dr. Utell, at this point I've got the microphone so, but we're working together. He told me if I got knocked out of the chair, he would take over until I got back up. But anyway, seriously, and Dr. Reigart we will be revisiting back with you because I think what you put on the table already is a very, very, worthy and worthwhile first draft to go after this point. And as we integrate Dr. Fiedler's comments and I think with some very good input from Dr. Gorovitz, we're starting to move towards a Section 3.2 that we can live with. Dr. Kahn, thanks for your patience.

DR. KAHN: Maybe this is born out of (?), but it sounds to me like we're not asking for any stronger power analysis for human

testing than we would in animals. Is that a fair statement?

DR. KENDALL: Dr. Portier.

DR. KAHN: Oh, so maybe it's not a fair statement.

DR. KENDALL: You want to go ahead and just make your statement now? Dr. Needleman, thanks for your patience, I'm going to come back to you. I want you to make your presentation. Make your statement for the record.

DR. PORTIER: Ok, so I have a handout that I sent out to you. It's my comments on testing pesticides in humans. It was my attempt to look at statistical power. Dr. Needleman did an excellent job with binary outcomes of yes and no. But I thought we needed to look at the biomarkers issues. This explains to you how a statistician would approach the question of, can I address this issue. I did a little bit of background on Type 1/Type 2 area. A little bit about NOELs. Then I went to a paper by (unclear) measured the (unclear) cholinesterase in that is red blood cells, not plasma--that's a mistake on my part--so I could get an idea of the variability. Then I broke that variability into two different components: the inter-individual variability and the individual variability, that is, within the individual variability, and that is completely out of the sky on my part. There's absolutely no justification of what I did, because I don't have data that suggest either way what it is. Fifty percent of the variance was given for cross individuals, fifty percent of the variance was given for within individuals. That's how I broke it up here. Then I asked the question: If I do a study of a particular size, what is the probability that I would see an

effect of the magnitude at the top of this Table 1? So, for example, if I did a sample of size 10 people, and I took blood before I did the sample, and compared that against the blood measurement later on, and that blood measurement was predicted to be a 50 percent drop in the acetycholinesterase level, I'd stand 100 percent chance of detecting that in those 10 individuals. The power is one. There's absolutely no chance I wouldn't miss it. But if I was looking for a 10 percent change, then the chance that I'd see it, is only 56 percent, so there's a 44 percent chance that I won't see it. So, in terms of NOAELs and NOELs, if they were solely based upon statistical arguments, which I know they are not, then you'd stand a 44 percent chance of calling that 10 percent drop a NOEL, when it's really there. And such is through the entire table. You can see that as you look for smaller and smaller changes, you get larger and larger sample size required to achieve what is normally referred to as a nominal statistical power of about 80 percent. That's what we generally target. Now, the proper way in which human studies are generally designed, are to, you decide on the effect you'd like to see. If you're really trying to predict something, like a metabolism rate, then you get an estimate of what you'd think the metabolism rate would be and some concept of what you think the variance would be, and there are ways of doing that from animal data, certainly. [end of tap]

Of the mean, then you'd take that variance and the other estimate and you can calculate those sorts of things in the same way I've done it here. So you can again design a study so that you can account for the variance and know how accurate you are in the estimation of a parameter. In terms of the question: Is

it ethical to, why would we do larger studies in humans than we would do in animals? That's the question at hand here. Part of it is that in animals, when we do these types of studies, we look at a lot more end-points. So, that's hard to reflect in these tables because the analyses is done on a single end-point at a time. But generally, in the animals, themselves, we not only look for biomarkers of affect but we're actually looking in the tissues and we're seeing the effects. And that increases our ability to believe that we have or have not seen an effect. So that's part of the issue. The second part of the issue is, since you can't really define a No Observed Adverse Effect in any study–EPA knows my feelings on NOELs and low Ls, and their use in risk assessment, it's especially important in a human study to define what you're trying to find. And so, If I were designing a study to improve the risk assessment, and say really, there's no effect here, I'd first go to my medical consultants and say, what change in the acetycholinesterase is not of any clinical importance? And if they told me 10 percent, then I'd look at this paper right here, and I'd say ok, then we need to do roughly 50 people. If we do 50 people, we're guaranteed sufficient statistical power that if this exposure exceeds 10 percent, we will see it. And that's how you would define it, to avoid this question of NOELs and low Ls. You've defined the scientific endpoint as a clear target, then you try and avoid that target to be able to make some clear statement about not seeing it.

DR. KENDALL: That's well put. Dr. Fiedler does that satisfy your proposal this morning of the issue of the science, the underlining science? Ok. Does this add

to this particular point? Dr. McConnell.

DR. MCCONNELL: Yes, I would just say that maybe to short-circuit this thing a little bit for our report, is that, we've identified that the science has to be satisfied before the ethics are satisfied. And that, rather then getting into specifics of how to address that science, it would be better left to the Agency and whoever's looking at this data. Hopefully before it's ever done. Before it's ever submitted, and I'll get to that later, then the specifics here. I think the concept is well taken that the data has to be scientifically sound or it's not ethically and justifiable. We've said that already. And I think that's what Chris is speaking to and the numbers are going to depend on the endpoint that you're after, the variability of that endpoint, etc., and I'm not sure that helps us to be worrying about what that specific endpoint is at this point, although I appreciate the example which points out the problem that the Agency will have.

DR. KENDALL: I think the point is: is that we must define appropriate scientific endpoint that we can justify with appropriate statistical and experimental design underpinning, so we can defend it ultimately. But Dr. Meslin, did you agree that the science needs to precede the ethics?

DR. MESLIN: You've may have detected my head shaking side to side versus the up and down.

DR. KENDALL: I detected something. I want the issues on the table. Right now, this is our hour.

DR. MESLIN: I would only ask the committee to consider one of the implications of that. Which is if you assume that

science stands alone and can answer only to itself as to what is or is not appropriate, and then afterwards one then ask whether what we've already decided is scientifically acceptable now passes ethics muster you're setting up a kind of--you're setting up a situation in which the ethics always seemed to be secondary and an additional hurdle to traverse. I don't object to the principle that's been stated, but I think what we've heard already supports a view more like, science and ethics are jointly necessary.

DR. KENDALL: Absolutely.

DR. MESLIN: And the selection of both the methodology, sample size, outcome measures, all have ethical parallels. They have reasons in ethics as well as in science. So I support what the committee has been saying regarding Chris' suggestion. But I'm only slightly concerned that the tone of that recommendation or that language, would lead your audience to the mistaken impression that science is always far more important, because we're addressing it first and spending our time, and then we'll get to the ethics when we can which tends to be titrated down to things like consent forms, and IRB review, which we seen in other areas of human subjects experimentation become rather procedural in nature.

DR. UTELL: You know, I think going back to Sam's introductory remarks this morning. He said it a little differently then Gene did. But I think we're on the same wave length, when, if I'm quoting you correctly, I think you said bad science is unethical.

DR. GOROVITZ: I think I said bad science is always unethical.

DR. UTELL: And that. I think we want to avoid sort of the diagram that puts science here and ethics here. But that comment really supercedes all of this. Bad science, you just can't make a case for it and again, a little differently stated than Gene.

DR. MCCONNELL: But that's also true for animal studies as well as human studies.

DR. UTELL: Oh, absolutely.

DR. KENDALL: Dr. Fiedler mentioned this morning that science and ethics are intertwined. In that realm, I think that's an issue that we need to affirm or not by this committee because it was really, to a large degree, the breakdown of the ethics issue that probably brought us to this next meeting then, was the basic issues of power analysis among others. So to me, this is an extremely important point and I wanted to be sure that Dr. Meslin and Dr. Fiedler could come to some agreement on that.

DR. FIEDLER: I think we are. I think the only thing I was thinking when you were talking. I don't know what this characterizes is that: This science is, a good science is necessary but sufficient. And so then, you go.

DR. KENDALL: Dr. Portier, you had your hand up. It's ok. Alright, Dr. Needleman, you're going to get a gold star for your patience and I'm going to need to ask you to be a little bit more patient. What would you do in my case? Marsha Mulkey, the Director of the Office of Pesticide Programs has asked to address the committee. And I'd like to acknowledge--I mean to have her here and setting through this entire panel discussion.

DR. MULKEY: All I really need to do is correct something I said this morning.

DR. KENDALL: Why don't you do that.

DR. MULKEY: Ok. I'll try and make it very brief. I really regret interrupting the flow because obviously the flow of your discussion is what we came for. But I gave at least a too fast one, or perhaps an incorrect answer to Dr. Portier's question this morning about Adverse Effects Reporting. The obligation that pesticide companies have to report Adverse Effects is very complex. It's set forth in a whole set of regulations at 40 CFR 159. And, with respect to the duty to report a toxicology study. If the toxicology study shows any effect at all, and it's the first one, you have a duty to report it, first occurrence of that effect, first study. Subsequence studies that are in effect enveloped by the first reported study wouldn't have to be reported. However, if the subsequent study were in a different species and there was an effect, whether or not enveloped by the first study, it would have to be reported. A study which had no observed effect would not have to be reported probably. Now the rules are susceptible to a fair amount of heavy reading and enforcement cases sometimes could be debated. So they're not real sort of absolutely, ipsi-dix?, all you'd have to do is look. But I think I left the impression that any toxicity study would have to be reported regardless of results. I think that was inaccurate.

DR. KENDALL: Dr. Portier.

DR. PORTIER: The ethical question I was getting at, at the time, we were discussing rules concerning what should be reported to EPA in advance of doing the study or not in advance of doing the study. And my

concern is, in terms of, if we find any studies that are ethical or potentially ethical and give guidelines for it, that if those studies are not reported in advance to EPA that they will be done. That EPA may not get studies, that in fact potentially have some positive effects and hence, you'd be seeing a bias set, and by accepting the bias set, you may in fact spawn further studies of bias sets. And that's my concern about whether or not those will be reported to you or not. It all are reported, it's not an issue. If the reporting is a subset, it could be an issue because you could in fact spawn more studies and that would definitely be a non-ethical point of view by the Agency.

DR. MULKEY: It's a complicated arena. But I believe that the impression I left was that all studies had to be submitted regardless. A more accurate impression was that our interpretation of the duty is, any study that showed an effect in a new species or in an existing species that had not already been reported at that level or higher, would have to be reported.

DR. KENDALL: Very good. Dr. McConnell.

DR. MCCONNELL: Just a quick one. But, in terms of your core studies that you require for registration, be they negative or positive, that data has to be submitted, correct?

DR. MULKEY: It has to be submitted, but in theory, multiple versions could be conducted. And that's what Dr. Portier was concerned about. And what I'm saying is, if multiple versions were conducted, any that showed an effect greater than the one submitted would also have to be submitted under those rules.

DR. KENDALL: Very good.

DR. MULKEY: OK, thank you.

DR. KENDALL: Any further points of clarification for or questions

DR. MULKEY: Thank you. Alan, thanks a lot for allowing me to interrupt.

DR. KENDALL: Absolutely. Absolutely. Dr. Needleman, thank you. The floor is yours.

DR. NEEDLEMAN: Sure. I'm just going to take a couple of minutes to go over some of this stuff. I'm not a statistician, but power analysis is part of my bread and butter. I do it all the time in grant applications and writing papers, etc. It's a very important consideration. It's relatively new. Twenty-five years ago if the psychologist wanted to study subjects, he'd grab a handful and bring them into the lab and run his test. Same thing with the number of animals. It wasn't until the 70s maybe that the issue of Type 2 errors began to be raised. Type 1 errors is false positives. Accepting things as real that are not real, much more neglect was paid to false negatives, missing effects that are there. And in the 70s, Jacob Cohen and others began to write about this and people begin to look at power analyses. And now, you cannot get a grant accepted by a reviewing body without doing a fairly sophisticated power analysis and many papers will not be accepted without one. The power analysis is fixed by three things: The size of the effect, the alpha level, (that is the false positive rate that you set in the beginning), and the number of subjects. If you have any two, the other one is determined. Now, the effect size is the critical thing I want to focus on. How big is the unknown effect of a toxicant? If, as Sam Gorovitz said, it's a strong effect,

you don't even have to do statistics. If it kills half the people in the room you don't have to do a Ky-square? or a T-Test. If it's a 10 percent effect, you probably don't have to do anything. It's visible to the human eye. But there are very small effects that have enormous health significance. Bernie Weiss and I have both written on this. If the IQ shifts due to low level lead exposure is 4 points at the median or at the mean, that's impossible to see in the distribution of people. You have to do large scale epidemiologic studies. But that shift of 4 points increases the rate of severe deficit from 4 percent to 16 percent. There's a 400 percent increase at the tale of the distribution. So a small effect distributed across the population is enormously important. It also, by the way, reduces the number of people at the top end of the distribution so that the number of people with superior function, IQs above 140 are reduced by 5 percent. One of the effects of low level lead exposure maybe that it truncates, deprives the society of 800,000 brilliant children each year. Ok? That was the approach I used in looking at the power analyses in this endeavor. I have no idea of the effect size of this exposure to cyrene-? or azinphos methyl, but I do know that if it were a 1 percent increase in the rate of deficit, I'm talking about neuro-developmental deficit. If it increased it by 1 percent it would be virtually invisible unless you looked very carefully with large numbers. Then I know that there are 16,358,000 children under 5 in this country. If there was a 1 percent increase, in the rate of deficit, that would be 160,000 children who would be experiencing the effects of that, I was very liberal in calculating the power analysis for this purpose. I said, I would accept a 1 percent increase in the

rate as a detection level. And I had made the assumption that in the population, the percentage of deficit is about 1 percent. So then I could ask, how many subjects do you need to find a 1 percent increase, from 1 percent to 2 percent in the human samples? And the tables are in the thing that I showed you. There is a mistake in the table. I used three authorities, Jacob Cohen, Jim Schleshoman, and a statistical package I have called Stat Power. In the Schleshoman, it says, "define an increase in the rate of deficit from .01 to .02 with an alpha of .1," that's a fairly generous alpha and the beta .1 requires 7,118 subjects in each group. That's wrong. It's 2,518. You do not need 14,036 subjects to define it. You need 5,036 subjects. Just 2,518. And you see that's in very nice agreement with my package. Then taking the number of subjects in most of the studies that Mr. Carley sent to me 10, 50, I calculated the power to find an increase in 1 percent. And you see for 10 subjects, the power to find an increase in 1 percent rate of deficit is .15. For 50 subjects, it's .22. Now that's as if you had a bowl of marbles, and you had 100 marbles, and 80 of them were white and 20 were black and you reached in what is the odds of finding the effect? It would be 2 in 10. Twenty-two in 10. Is that acceptable? Not on your life. And so, I concluded from this, as I was a co-chairman of an IRB at the Children's Hospital in Pittsburgh for a couple of years, and we said that if a study was not effective it was unethical. That a study which has a power of .15 or .22 to find an effect, is by definition inadequate and unethical.

DR. KENDALL: Ok. Dr. Ellis.

DR. ELLIS: Thanks to Dr. Needleman for that analysis and my response from a regulatory perspective is first to salute him as a IRB chair because he was exactly right. The regulations used these words: That in order for an IRB to approved such a study, risk to subjects must be minimized by using procedures which are consistent with sound research design.

DR. NEEDLEMAN: Yes.

DR. ELLIS: It's very simple.

DR. NEEDLEMAN: Let me read one thing that I meant to before and that is, from one of the studies that the registrant submitted. It's azinphos-methyl INVERESK. And under statistical methods it says, and they have good statisticians at INVERESK. A sample of 50 subjects, 10 in each dose group was considered appropriate for the study of this type. No formal sample size was done. It's inexplicable why a group with this amount of talent and resources didn't do a sample size.

DR. KENDALL: Point well taken. I think that's one of the areas that Dr. Fiedler mentioned this morning, in terms of the power of the experimental design. May I be so bold to step back a little bit, but not a tiny bit. To think about what are some of the things we are encouraging to EPA, as we are an advisory panel and have the opportunity to provide advice, so on. And perhaps just to offer this based on Dr. Gorovitz's very elegant presentation this morning to enhance the operational clarity related to the proposed receipt of data involving human testing of pesticides. Our committee encourages the advancement of public health and encourages strongly to stay within the boundaries of ethics on the experimental test proposed based on good

science. To me that gets after the issues. And we've defined, in many ways already today, the ethical boundaries, and a lot of it surrounds itself in appropriate experimental design, such that one could achieve a result based on a hypothesis within reason with the resources applied to it, and at the same time utilizing a subject and the process of that experiment. In other words, we didn't waste our time. And waste or potentially harm people without the potential to get a positive result. Ok. So this statement Dr. Gorovitz, was paraphrased from you almost verbatim, I tried to capture it. But fundamentally, we want to encourage the advancement of public health. But, at the same time, we are strongly encouraging, Dr. Needleman, that we stay within the boundaries of ethics on the experimental test proposed based on good science. And so, to me that just wraps it together. We still have some issues to talk about, because I haven't heard anybody say today that they are opposed under all circumstances, any level of human dosing of any level or any time, under any situation. Nobody stated that so far today. What we've stated consistently is, that there must be boundaries and justification, and it must be based on good science and it must have appropriate parameters which are ethical and regulatable and validate. And so that's why I go back to the statement I just made in the context of Dr. Gorovitz, the presentation this morning. One of the things that is an issue is the intentional dosing of neurotoxic agents, that Dr. Needleman has raised early, among others, and I think we need to talk about that. But I haven't heard today, said, that under no circumstances should one never consider any level of human testing in the context of an

experimental process with pesticides. Ok, Dr. Gorovitz.

DR. GOROVITZ: You just restated a point of view, essentially in the spirit of what I said early. I simply want to be explicit about the fact that I'm not content with that level of generality. Especially when we talked about good science. I am not content.

DR. KENDALL: We understand that. We understand.

DR. GOROVITZ: To the agencies or to the scientists, were we in a situation where we had lots of leisure time to explore the issues, I would want to argue not just that scientific judgement and ethical judgement must be contemporaneous and parallel, but that one can't really thoroughly disentangle them. And, that even the evaluation that a piece of science is good science is in some ways ethically laden judgement. That said, I want to make sure that our report is explicit in saying something substantive about what appropriate sample size means. Not an algorithm that will allow the cranking out of a number, but some illustrative examples of what we consider not satisfactory, what we consider exemplary. If we just say good science requires interrolia? appropriate sample size for the purpose, then we're not providing a level of specificity in guidance, that I feel an obligation to provide. I think we need to say more about what that means to us specifically.

DR. KENDALL: Well, I think we have.

Dr. GOROVITZ: We have here.

DR. KENDALL: Exactly. And I accept you comments. I'm looking for the building blocks of consensus. And there's a lot more consensus here than I thought there was.

I believe there was a lot. But it's substantial.

DR. GOROVITZ: The necessary things that were said, I want them to show up on the page.

DR. KENDALL: Ok. Now in the meantime, around these words, we've been hanging definition. We've been talking about good science, about power analyses, about appropriate hypotheses that are tied back to the data collection process. All these issues should surface and will surface in the Section 3.2, Dr. Fiedler. We've talked about the issues of age differences. We've talked about many of these issues and the importance of the intertwining of science and ethics, Dr. Meslin. So, I really feel that we, as a committee, are hanging the criteria and the boundaries on these words and will attempt to do so in more clarity and more transparency when we draft this next iteration. Dr. Kahn, you had, Dr. McConnell.

DR. KAHN: Gene's being waiting longer.

DR. KENDALL: That's fine. Dr. McConnell.

DR. MCCONNELL: I would just like to ask us to try to answer the question about whether what we're talking about here is any different than any other kind of research. Because everything you've just said, and really what Sam said, applies to biomedical research generally. And if that's where we going, then let's just say that. There's lots of discussion and lots of regulation, lots of information out there about how to do good research on people.

DR. KENDALL: Well, we've identified already that there apparently are an appropriate and unsubstantiated research projects coming forward, to ask a question with a we don't know what the right answer and/or

question was, Dr. Needleman. That's the point.

DR. KAHN: Let me just push the point a little bit and say is this like everything else or is it different? And if it's different, how is it different? Let's try to answer that as a group.

DR. KENDALL: Well, we've identified it's different because ....

DR. KAHN: Let's be precise and on the record if we can, and maybe you're going to do that.

DR. NEEDLEMAN: I'm going to try. It's different. We've heard something about all chemicals are the same, this is not true. This is a molecule designed to kill nervous cells. It has a special status for that reason. These are of a family, some of the derivatives were considered as nerve gases and they have been employed as nerve gases. So that I think this exerts a cautionary principal that you cannot ignore except at ethical peril. You must be very careful about this.

DR, KENDALL: That's well put. Dr. Reigart, I'm going to ask your comment on that in a minute. Dr. McConnell.

DR. MCCONNELL: Yes. I think that there's something that needs to be put on the table here. I think, with all due respect, Herb, that you're focusing on OPs.

DR. NEEDLEMAN: When people say with all do respect, I get my gun out.

DR. MCCONNELL: Yes, I do too. But anyhow, focusing on OPs while understandable, is not what this meeting should be about.

DR. NEEDLEMAN: When I was invited on the committee, I was given a piece of paper and it said

you start with the hard ones first. The organophosphates. Is that not right?

DR. MCCONNELL: No. I mean, I'm talking conceptually using human studies for the Agency.

DR. NEEDLEMAN: I'm trying to answer Jeffrey Kahn's question about are these different than other chemicals. And I said yes. Organophosphates are a different kind of chemical.

DR. MCCONNELL: Well, I think they are a different kind of chemical but not specifically in regard to risk. Obviously you and I look at that differently, particularly at lower levels. But let me suggest something here. With regard to what Dr. Gorovitz's was presenting and Dr. Portier on the right numbers of people, and how powerful this needs to be, I think all of that is very pertinent and important, but I think it may not be important for this meeting other than to say, those things need to be considered.

DR. NEEDLEMAN: Great.

DR. MCCONNELL: And if I were the Agency, I would have a separate meeting where I address those particular kinds of issues to give the power to these different endpoints that you're interested in. Second, I think that if you're looking for recommendations to the EPA as you suggested, part of this would answer Dr. Gorovitz's concern, is that: Possibly the agency should develop a paradigm similar to what's used in FDA. And that is, before any of this data is generated, that the protocol and what have you, would be submitted to the Agency to look at both for scientific reasons and ethical reasons and is the data even needed. I think if that had been done, prior to some of these submissions that have been submitted, we

probably wouldn't be here today. It wouldn't be a problem. So I'd like to see that in the report, Mr. Chairman, that we give some positive input back to the Agency, other than just, we don't know what to do here exactly. But we're getting there as you say.

DR. KENDALL: No, we haven't said, we don't know what to do, I think this goes back to Dr. Kahn's comment and Dr. Gorovitz, I don't want to leave this comment because Dr. Needleman and respond, Respond please.

DR. GOROVITZ: Jeff Kahn asked are they different? Dr. Needleman said yes, and gave one reason why. I say yes, and I want to give a completely distinct reason why, and that is this: Pharmaceutical products, when they've been tested and are put to use, are put to use in very targeted ways, in general, they are administered individuals. Pesticides are administered to populations, not to individuals. Now that seems to me a very important distinction between the two and it has consequences for the level of concern that we bring to bear in the assessment of risk. Because what we can do with pharmaceuticals is ask of each distinct individual patient, is there anything known or discoverable about this person that suggests the standard therapeutic intervention is perhaps not prudent in this case. But with respect to those things that are released into the environment which is what happens with pesticides, which is why it's an EPA issue not an FDA issue, we cannot separate out the highly susceptible and the vary vulnerable. They are in the population to which the substances are administered and that's a fundamentally important difference.

DR. KENDALL: Excellent point. What other differences from the panel that would answer Dr. Kahn's question. I think we as a panel,

the majority at least, believe there is a difference.

DR. MCCONNELL: Define. You mean toxicologically at very very very low levels where.

DR. KENDALL: The point is..

DR, MCCONNELL: I'm not sure you have a consensus.

Dr. KENDALL: Well, that's ok, that's ok. We don't have to be in total consensus of this. Because in our early discussion, considering, setting aside just the basic principles of toxicology, just setting that aside, just for a second, we have defined that this issue, because of the criteria already mentioned, is one that probably resulted in multiple meetings of this panel. Because we are talking about products with qualities that expose populations, a spectrum of which maybe very vulnerable. And I think there's a lot of concern for that. And then how do we create the data to do the appropriate risk assessment? I think there's been some concern for that considering the products were being developed for marketable consequences for profit making. Although there are high levels of benefits too, we've identified that. Dr. Kahn, does that start to get after these points?

DR. KAHN: Those are two different things. I think the last point you just made about the consequences or the motivation for the research is somewhat different than do we treat the subject in this research differently or have different standards for what counts as degrees of risks that we take to be acceptable.

DR. KENDALL: Ok.

DR. KAHN: But I think that that's an important point that you made to, which I'd like

to talk about in some more detail if we have time.

DR. KENDALL: We're going to go after it right now, because this is starting to get me. I think, listening to the committee on this because I think in drafts that Dr. Reigart brought forward and many others, is that, this does engage a somewhat different set of circumstances that are maybe not exactly the same as a pharmaceutical process development. Dr. DeGeorge.

DR. DEGEORGE: By comment clearly pesticides are different than pharmaceuticals. They have different uses, as regulators we do different risk assessments. We don't effect or allow them into the environment or into the exposed population at non-effective levels for pharmaceuticals. Who would want that? Yet, we certainly don't want the pesticides in the human population at effective levels in terms of toxicity. So yes, there are different regulatory standards in terms of how you regulate the product. I'm not so sure that correlates with a different toxicologic data set other than in pharmaceuticals, you have controlled clinical trials and healthy, and actually not healthy in the diseased targeted population, which you then accept the specific risks for that population. Now you don't get that in pesticides and hopefully you're not going to recommend that as a pesticide testing. But, the fact is, that they still are a chemicals, there are pharmaceuticals that never make it to become or there are chemicals that never make it to become a pharmaceutical. They are neurotoxic. They are chemicals that never become a pharmaceutical because they are cardiotoxic. All these things go through a test process. It's the safety of the assessment to collect that initial data. Can you do it

safely? Can you do it ethically? And what, how are you going to use that information and then judging your risk assessment. If you don't think the power size is big enough to make a particular determination, then clearly you shouldn't use that information and maybe the study shouldn't have been done. But the distinction, and this is something, I would say and maybe I side with Gene on this that the distinction is that chemicals are in fact, all have toxicology. All of them have it and how we use that information and how you collect the relevant information for human risk, maybe there are some different criteria in terms of, you know, the long term exposures, but for these early studies, I questioned the decision that you can't do a particular kind of test under any condition.

DR. KENDALL: I think fundamentally those of us that have studied toxicology, the dose does make the poison. However, what Dr. Kahn is getting at, is that we maybe creating risk for those that have no knowledge of that risk when we expose the population, particularly the vulnerable components. And we cannot target the pharmaceutical delivery. We may, in fact, may never have that opportunity in the context of large scale applications. So, these are some of the issues, that I think has elevated the concern of the committee, that it makes sure it's best science is done regulated by EPA, in order that we hopefully reduce that risk as much as possible. It's in the boundaries of ethics. Dr. Reigart's been patient. This is his area.

DR. REIGART: I didn't put my hand up before, but I am now. It seems to me, in thinking, one of the questions I asked when I wrote this little piece was, we didn't seem to agree on when you should administer neurotoxicants.

DR. KENDALL: We're not through with that one. We're not through with that.

DR. REIGART: But, I think in a way that's one of the essential differences. In pharmaceuticals, we have tried to design pharmaceuticals that are not neurotoxic and we're looking for lack of neurotoxicity before we give it to human volunteers. No pesticides are designed as neurotoxicants. That's how they do their jobs against the targeted pest. And so there isn't a central difference. We're saying, ok, this is something that's designed as a neurotoxicant, now what dose can you give to people without getting neurotoxicity, rather than saying, we think this is not a neurotoxicant, but we're going to administer it to humans to see whether, even though we think it's not a neurotoxicant, we see among other side effects, neurotoxic effects. So, I think this is an essential difference between yes, they're our chemicals, but in one case, we choosing them for absence of neurotoxicity and the other, we choosing them for neurotoxicity, but then trying to figure out how we get away from that in people. And that, to me's a real difference in what you're attempting with your toxicity studies.

DR. KENDALL: Point well taken.

DR. REIGART: By the way, one other SAP, this is not SAB, this is a SAP, discussed the issue of neurotoxic pesticides and developmental neurotoxicity testing and came up several times, the conclusion that all neurotoxic pesticides deserved a battery of tests which was new and different, which is the developmental neurotoxic testing.

DR. KENDALL: That's a good point. Dr. Fiedler, I'm hoping you're listening real carefully because, I'm really going to count on

you. Dr. Utell and me, we're going to look to you and Dr. Reigart to come back to this subject, along with Dr. Gorovitz and Dr. Weiss, in the written form. And I think too, just to make sure, for the record, we understand all pesticides are not necessarily neurotoxicans. We, as part of the charge, and Dr. Needleman, you are correct, and the context that the organophosphates and the carbonates being that their exertion of toxicity is through a mechanism of concern to us here or the lead ones related to some of the questions and issues being faced by EPA. But these are not the only ones. And in fact, they are not the only ones in the recent test. Ok, some of you remember. Some of the recent submitted test. But these seem to be the lead ones that have the relevance, that gets back to Dr. Kahn's question: Are these issues different? And they're different. I think we're hearing maybe not in total consensus, but we are hearing, it appears to me, that the majority of the committee does feel there's some at least elevated responsibility to address these particular materials, in a way that may be somewhat more intense than a standard pharmaceutical test. Being that they are potentially exposing to population, to agents that may have latent effects, as demonstrated in the literature by Dr. Needleman, that is of high degree of ethical concern to our committee.

DR. KAHN: No, I like that. And I also like Ralph's point about what the side effect in a pharmaceutical trial is the effect in a pesticide. A very important piece that we ought to be articulative about.

DR. WEISS: Wait, wait, wait, hold it, hold it folks.

DR. KENDALL: Dr. Weiss and then Dr. Portier, you've been very patient cause you got...

DR. WEISS: Let's talk to what was said. I think what Sam said earlier about the intent, although that's very hard to specify, is really the core of what we're discussing. As a matter of fact, a lot of drugs are designed to be neurotoxic. Look at all the anti-psychotic drugs. And in fact, organophosphate compounds are being used in the treatment of Alzheimer's Disease. So we have the same class of compounds, in one context being used therapeutically for a very serious disease, and in another context, like in human volunteers, the study that another way for another purpose, and I think that's part of a distinction we have to make. Nancy was right. I booby-trapped all of my examples. All of those scenarios with questions that I thought would provoke the committee. That I think would illustrate for EPA, the kinds of dilemmas that it would have to resolve when it judges the appropriateness of human testing.

DR. KENDALL: Dr. Portier.

DR. PORTIER: You asked if anyone on the committee felt that all human testing of pesticides was unethical. I'm not going to make that extreme of a statement, Ron, but...

DR. KENDALL: I said, I did not, I have not heard today, any statement along the lines that under all circumstances, there would be no human testing with pesticides. I have not heard that today.

DR. PORTIER: I'm a statistician. There's always a small probability. There may be such a case, I haven't seen it yet. So that's what I wanted to say. My problem is, we've spent a lot of time discussing the science and, sure, we want scientifically valid studies. We spent a lot of time talking about the risks,

that's great. Two equal compounds. One a pesticide, one a pharmaceutical, exactly the same potential risk to the study population and it boils down to the benefit. And we haven't discussed the benefit at all, in terms of the benefit to the individual in the study. And again, I'm a statistician, I see things sometimes a lot more black and white than I probably should, but as I read the Helsinki Agreement, I don't see it here. I'm very hard pressed. Very hard pressed, to get past that one requirement in that protocol that there has to be some benefit other than financial to the individual participating in the study. And that benefit can't be, as I read it, a benefit to the general population. That is one of the preclusions. And if I'm wrong, I'm wrong. I need some clarification on this. Because that's where I have a real problem with these.

DR. MCCONNELL: Can we go back to that. I thought in the Phase 1 trials this morning, as you were describing it, Dr. DeGeorge, that there was exactly the same issue, the individual volunteer--it's not a benefit to that individual. As you presented it, it was to presumably understand mankind or society as we go forward, but I don't think it's very different.

DR. PORTIER: That's why I asked my very specific question about.

DR. MCCONNELL: But I thought it was addressed a little bit this morning but...

DR. PORTIER: Whether or not the individual could potentially get the disease. What is the essential benefit to the individual in that situation, in the sense, that they could eventually choose to take that therapy to deal with the disease. They're making the individual choice on their own, that at some point, they

might see a benefit in this. Now find me, even that simple thread in this case, where I can understand where this might be of benefit to an individual and they would choose to participate in such a study, where they see some benefit that's not financial, and I'll be much more, much happier. But that's the ethical issue here.

DR. DEGEORGE: I have to reemphasize a point about that because clearly, most of the time subjects in Phase 1 studies have no disease, and are unlikely to receive any benefit from their exposure they get at that time. Beyond that, as I tried to point out at the end, 9 out of 10 chemicals put into humans, never become therapeutic so they could never get a benefit from that exposure, other than the fact, that, eventually some therapeutic may be discovered to treat that disease and therefore help mankind.

DR. KENDALL: Dr. McConnell, thank you Dr. DeGeorge.

DR. MCCONNELL: I think maybe I can give you a rope not just a thread. You realize that this pesticide might be put on a piece of lettuce, even if Herb eats it and he may not be aware of it. But there is a potential that if you're this volunteer for this particular pesticide, and if it's used on lettuce, there's a pretty high probability that you might be exposed to that pesticide, and I would expect it would be a benefit to you, for you to know what the potential toxicity in humans is of that particular pesticide. In fact, I think it cries for knowledge. If I or my kids or my grand kids, or...(end of tape)

I want to go back though to the benefits and as I've seen Phase 1 Clinical trials with human volunteers, I must say Chris I've never seen the volunteer that I can think of who's forward to participate

because he thinks the new drug for hypertension may be the one that ultimately he or she is going to benefit from. And I think on a sort of individual basis as much as I don't like the idea in certain sense of being exposed to a neurotoxicant. The possibility that would have some benefit to the individual I think it is probably greater than it would with a Phase 1 clinical problem most of which as you said don't go forward anyways.

DR. KENDALL: Dr. Gorovitz.

DR. GOROVITZ: I want to begin with a request that Gary, Eric, Jeff feel free and indeed even eager to correct or respond to our supplements of what I'm about to say. But it does seem to me quite broadly acceptable that people participate in research where there is no reasonable expectation that they will benefit substantively from the results of the research provided that there are benefits to the research and that the risks are acceptable and general quite low. But I also wanted to mention that the standards for the ethical assessment research, the Helsinki Code, the guidelines from CFIOMS (the Council for International Organizations of Medical Sciences), are at present very actively under reconsideration and review. The World Medical Association is in the process of reconsidering whether contemporary times require any changes in the Declaration of Helsinki. What's prompted this has been primarily the recognition of the kinds of therapy that are available for infectious diseases in the developed world, don't seem to match the needs in developing countries where there are epidemics and there doesn't exist an infrastructure or a budget that makes possible the kind of therapeutic responses that are common here. The National Institute of Health is

interested in this, the European community, there is countries in Europe, so the reason I'm mentioning this is just to say I think we overly constrain our own judgement if we look at the kind of black letter reading of a particular classical declaration and say we've got to be a literalist in interpreting this, and make sure that what we do squares with that. Even as those who have responsibility for those documents are recognizing that a literalist interpretation is not appropriate. I don't mean to be giving you a rope because when I think about pesticides, I think about the fact that pesticides can be organic, they can be biological, and there is, I think, inadequate attention to or investment in the development of nontoxic pesticides. If we are really concerned about the public health we want to do whatever we can to facilitate those kinds of developments. But I do think that it's a mistake to lock the door because of particular phrases in those documents.

DR. PORTIER: Let me follow up then because its still _____ to me. How do I draw the line? or how does EPA draw the line between what's beneficial to public health?, which is what Jean was talking about, which has nothing to do with benefit to the individual or if it does it creates some serious moral dilemmas for people in control of public health about deciding how far do I go and that's my question here.

How far do I go in allowing a risk to a population for which I see no direct obvious benefit to establish a benefit for the health of the public?

DR. GOROVITZ: In response to that specific point and I want to reiterate something that I said at our previous meeting and that is, we are dealing with issues which in the last analysis require the exercise of

informed judgment. We can't write algorisms for these decisions. We have to affirm an array of values, illustrate what we consider exemplary models or scenarios, and call for the bringing to bear of informed and sensitive judgment in a way which is itself is subject to retrospective scrutiny. My own position on that is you've got to be absolutely candid with subjects when you tell people they are going to ingest a crop protection agent when what you are actually asking them to do is eat something designed to be toxic, you are right at that early stage engaged in unethical behavior and so there's a lot that we can say that substantially solid but where you draw the line that is just how much risk in exchange for just what sorts of benefits, there isn't an algorism for that. It isn't quantifiable and that's why its hard to measure. But, I think we can say things that take us in that direction that are pretty solid like, its never acceptable to be duplicitous in dealing with subjects. Its never acceptable to be coercive in corralling subjects. We had last time, a stunning example in which a half of a dozen of employees of a company which had an interest in the outcome used some of its own employees misrepresenting to them the reality of what was going on and they weren't even embarrassed about it. We really need to put an end to the possibility of that sort of thing but in doing so we are not gonna be able to write regulations that will enable someone algorithmically to determine whether the risk is low enough.

DR. KAHN: What Sam just said. You said, Sam I don't mean to throw you a rope, but ropes can be used both to hang and to save, and I think if we need to be careful when the risk and the benefit are split apart in the way that Chris

was worrying about. And I think I made this point the last time we met.

DR. GOROVITZ: You did, yes.

DR. KAHN: That the acceptable risk is lower when the benefit doesn't accrue to that individual subject. I'm sort of doing the ethical calculation and so we can't allow risk to be brought off with the benefit to society. Lots of risks to a small population is outweighed by the benefit to all of us. That's a recipe for exploitation. As Sam rightly points out, there's no sort of mechanism by which you say this is too much and this is enough but I think that's the kind of juggling we really have to do. You put your finger on it and I think its sort of how much risk is acceptable when we are talking about research which offers no potential for direct medical benefit to the subjects themselves.

DR. FIEDLER: Can I.

DR. KENDALL: Yes you can speak to that Doctor Fiedler, and I think that will be very difficult for this panel to determine what level of risk would be acceptable outside of the fact that we are establishing some parameters we just mentioned.

DR. KAHN: ...We've just said

DR. KENDALL: Ok we just said it, yeah. Ok, Dr. Fiedler.

DR. FIEDLER: Well I don't know that I agree with much lately, because I think that in terms of whether a pesticide is different than other chemicals is a problem for me because I can think of for both examples that were given I can think of examples where there are other things that have been administered to humans or given to humans in research protocols or at a

community-wide level. In fact led is a perfect example of a community being exposed unbeknown to them at levels and we see toxic affects. So you can't distinguish it on that basis. You can't distinguish it on the basis of it being a neurotoxicant because we allow people to drink alcohol and in fact in research protocols alcohol is the positive control to look at the affects of our outcome measures. So that's certainly a neurotoxicant that's well known. And we also do a lot of experimental protocols where there is no benefit to the subject. I sit on a IRP, I look at them all the time and where we balance it is that we look at risks and we say is this minimal risks. And I think as a committee, we have an obligation to at least give some specific or guide, I'll stop using that word, I know I've used it 100 times today, but some guidance about what are minimal risks, what do we consider, what in this body can be give as examples if nothing else, of minimal risks. No, I agree, we can't come up with an algorism. That's impossible to do for every scenario. But I think we could give some examples of minimal risk. And finally, my concern that came up last time and it comes up this time is that you know we build a mouse trap somebody else is going to figure out a better mouse trap or how to get around it. I tried to trap mice with peanut butter, it didn't work worth a damn. The point is that there are regulations and there's the Common Rule and we have the IRBs and no matter what we lay out we can all haul out a bunch of examples of how people have violated those and are not approaching these things ethically. I don't think that doing more of that is going to move us ahead because no matter what we say there will be violations because that's the nature I think of human beings. So now we have to just move ahead assuming that or

hoping that if there are violations then Gary Felkus will find out about them and do something about them and we can simply operate, you know, as if people are going to abide by the rules that are laid out.

DR. KENDALL: You're feeling better now about... Minimal risks, does the committee choose to have a discussion on how to minimize risks? Dr. Meslin.

DR. MESLIN: I'm still struggling with Jeff's challenge to the group and that the risk of throwing an oar into this already somewhat turbulent water. I would suggest that it is about strategy to try and draw the line between these areas using a chemical criterion like pesticide versus a pharmaceutical for reasons that Nancy just gave. I think it would be a bad idea to distinguish it on any of the grounds that we've heard so far. Precisely because what we are experiencing as a group is exactly what IRB's around the country experience on a daily basis. Which is trying to make risk judgements on behalf of other people who are not in the room at the time. Now the challenge that Jeff gave us was whether or not one could distinguish between testing that goes on in the pesticide and environmental protection world at large versus the testing that goes on with human subjects in the medical or biomedical world. Sam and I had a little side bar at the break which I'm happy to share my portion of it and Sam can correct my representation of his, but I don't know that there are two easily separable worlds--the EPA world and the HHS world so to speak. Rather, I think that a more appropriate criterion to see whether there is any difference is that there is something more of a graduated or progressive line that is being drawn. Where on the extreme, everyone would agree that when

you intentionally administer something to some person, whether it be a pesticide or a Clorox bleach or tomoxifin or anything else that might harm them, and you are doing it for reasons other than the intended benefit of them, and you are following what we might regard as the kind of clinical trials paradigm, or you are intending using the Common Rules definition to produce generalizable knowledge. You're engaged in the human subjects activity that requires disclosure, consent, IRB review, and many of the other procedural and substantive research ethics criterion that how Helsinki and CIOM and the Common Rule and the ICH and any other instrument around the world adopts. Now just to repeat, the point I used was the direct administration, the intentional intervention into the life of another person. The further you move away from that paradigm, and this is, I'm gonna say with all due respect, but it's not to a person. It's with all due respect to the EPA. They are relatively new to this paradigm, but for what we heard from one of our public commenters before, this has been on the table since 1972. It's a relatively new phenomenon to be adopting the biomedical research ethics model for pesticide testing. We may be trying to shoe horn one into the other. So I would suggest that a heuristic exercise, if anything, the committee may wish to consider something more along the lines that the further you move away from a model of the direct administration of a substance, into an individual, which as Sam and I said at the break if you looked at two people one who you were giving a pesticide in a vile and ask them to drink it and the other you are asking them to drink some chemotherapy metaphorically, you wouldn't be able to tell the difference, as to whether you were testing them for EPA purposes or testing them for HHS

purposes. But the further you move away from that model to the indirect population based administration, the more you will have to make explicit in your risk judgements, in your risk assessments, those facts that are simply subjective and in a sense speculative on behalf of the group and those which have objective factual basis. I would submit that there is at least an emotive response that Sam has described when you start talking about the administration of a pesticide to an individual. It doesn't match up with the biomedical model that we have been occupying our self with the last 30 years. The only other point I would raise, which I thought Sam might have gotten to but didn't when he gave his description of the limitations of Helsinki, is that there is an often stated, poorly understood, but unfortunately relied upon phrase called the "therapeutic misconception" that seems to exist in research involving human subject for people who actually believe that they might be getting a benefit because a physician or someone wearing a white coat is administering it to them when in fact they may not be getting that benefit at all. I don't know whether the "therapeutic misconception" exist or even would be expected to exist in the administration of a pesticide. So those are some of the intuitive or emotive or nonobjective or non quantifiable criteria that I agree with Jeff, we are going to have to describe, for purposes of the report but may not be able to specify with an awful lot more detail. If we do not only will here I'll step out of my requsal? role for a moment, both the National Bioethics Advisory Commission would love to hear this group's definition of minimal risk. So would the ICH. So would the Council of Europe. So would the _____ Council of Bioethics. So would every organization

that's struggling including Gary's, to make clear what the definitions are so that researchers and IRB's can properly review and use them.

DR. KENDALL: Well put Dr. Meslin, well put. You will play an active role on this next draft. I do want to say this, my colleague here, Dr. Utell and I were talking and we as a group are going to develop this next draft. That must be affirmed. It won't be just individuals. Although individuals will be having some assignments and some subcommittee work etc. But we, as a group, will convey, I think, the essence of this communication I'm comfortable with. There is some difference of opinion related to the aspect of pesticides versus other materials and I think that's fine. I think Dr. Meslin put it well, as we move further away from the model of the direct control administration to an individual to a more generalized population exposure to a large degree may not be able to regulate their exposure. We've created a little bit different paradigm which I think there is some sensitivity to on this panel. I think that's fine. We really appreciate the perseverance of the committee so far today. It's been impressive. Dr. Ellis. We are going to take a break here in a couple of minutes. Dr. Ellis do you want to make a statement.

DR. ELLIS: Since you seem momentarily lost for words, I was going to suggest you laid out one extreme to see how far our consensus went. You said you haven't heard anybody say the objective or all circumstances and you had just about everybody then, Chris wasn't sure he could cling to it. Maybe you could keep going work backwards with some other gradations. For example, you might see how many people agree with this position that there shouldn't be human testing of

pesticides as a default situation but there are certain exceptions and then it's incumbent upon us to list the exceptions. Or it can back up further and say, pesticide testing on human beings is acceptable under certain restricted circumstances. And so, those are actually two different positions. It is a statement of policy by the EPA what the default settings. No use with certain exceptions or use under certain restricted circumstances. And, if you can get agreement on one of those positions then we have to write what the exceptions are or we have to write what the restrictions are.

DR. KENDALL: That's exactly where I was headed I just didn't know whether to do before the break or after the break. I would like to ask the committee, what is your prerogative?

Break.

DR. KENDALL: I think we need a break. Ok.

DR. MCCONNELL: I think you've got a consensus on that one.

DR. FIEDLER: Yeah, right.

DR. KENDALL: I have twenty minutes to three. At five of three let's be ready to go. That's fifteen minutes.

DR. KENDALL: Ok, this will reconvene our afternoon session.

DR. UTELL: I think I see a comment or a question from Eric.

DR. KENDALL: Ok there has been some discussion during the break. Dr. Meslin you had your hand up.

DR. MESLIN: It just occurred to me that as it was a very helpful discussion that we had just

prior to the break and that there seemed to be a lot of good momentum. Some of which I suspect will find its way into assignments for writing. And rather than sticking with the agenda, going straight to seven, I wonder if the committee would feel put upon if we broke earlier than the allotted time and then broke up into appropriate groups either for writing or planning for writing something on the order of breaking at 4:30 or so knowing that people have flight times. Not that everyone leaves the room at 4:30, but we might make more productive effort at that time.

DR. KENDALL: I think it would be valuable if the group could have a chance to have some writing time and to get together with some of the subcommittees which we will assign here in a few minutes. That will be very valuable time. I really think that over the next hour or so there is still a couple of critical questions we need to discuss. I personally believe that we will be able to discuss them and the Dr. Meslin proposal could go under a writing session seems warranted. Is there an agreement by the committee then?

MR. DORSEY: I think especially if we can, over the next hour, just make sure we work through the issues that Routt had raised, come to some general breaking point, and identify our groupS. We are certainly not going to write the report now, but if we can begin to have theSE bullet points where the working groups have agreed that they understand what they are going to compose, I think that would be a very valuable use of the remaining hour or so.

DR. KENDALL: There are a few things that we will follow up on. Dr. Portier had a point he wanted to make, and I would like to

start off here by asking Dr. Ellis to revisit the two points he made just prior to our break.

DR. ELLIS: Ok, let me get a little background in the regulations of the Department of Health and Human Services. There are different formulations for different populations and so beyond the Common Rule which is common to 17 departments and agencies. The Department of Health and Human Services has additional protections for children, for prisoners, for pregnant women, and so forth. And partly because they were written at different times, partly because the subject matter differs, there's different constructions. So for the involvement of prisoners in research under HHS rules, there's the flat out statement that prisoners shall not be included in research supported by this department with certain exceptions. For pregnant women for children, the formulation is a little bit different. There is the general sense that these individuals can be in research with certain restrictions. Those are two different stances. The default setting is important. It has symbolic but also real meaning and there's two formulations I proposed before the break. Just to restate it is, for EPA's purposes that the human pesticide testing not be done with certain exceptions. Or another formulation is the human pesticide testing is acceptable under certain circumstances. And either one of those requires us then to define either the exceptions or the certain circumstances.

DR. KENDALL: Would the committee choose to discuss those two proposals? Do you want discussion?

MR. DORSEY: Sure.

DR. KENDALL: Yes I do Because, I think the rubber has met the road, Dr. Needleman. And then I'm gonna go to Mr. Carley and Dr. DeGeorge about an issue related to how we are approaching pesticide versus nonpesticide issues. So what is your response, Dr. Needleman?

DR. NEEDLEMAN: Well if I wanted to follow Dr. Ellis' instruction I would say, that human testing for pesticideS cannot be done to establish an NOAEL. The reason is that you require 2,500 subjects in the group, minimally...

DR. KENDALL: I think we've generally agreed upon that in my recollection

DR. NEEDLMAN: Ok is that acceptable?

DR. KENDALL: Yes, I think we agreed on that already as a group.

DR. NEEDLEMAN: Fine, I'm very happy. There was so much philosophy floating around on that.

DR. GOROVITZ: But its not toxic.

DR. KENDALL: I think we agreed on that but according to Dr. Ellis's. More generally Dr. Needleman, do we, as a committee, support the proposal of there will be no pesticide testing except under certain exceptions or there will be pesticide testing that only follows certain guidelines?

DR. ELLIS: And I can accommodate Dr. Needleman's interest specific case under either formulation.

DR. KENDALL: Ok. I mean what's the mood of the committee? Right now we're setting the tone of the report and that was so important to us before. The tone of the report reflect the deliberation of the committee. So not being heard now

influences the tone of the report. Dr. McConnell.

DR. MCCONNELL: Yeah I prefer those second options.

DR. KENDALL: Which is what?

Both speaking: Which is permissive with certain restriction.

DR. MCCONNELL: Right. And as part of those restrictions I would say if there's adequate human data available, I see no reason why one should go ahead and do other human studies. Second, if human data can be obtained of equal quality through field studies I guess you call them, exposure studies, those probably you wouldn't want to do any human volunteer studies in such a case. However I would kindly encourage study in human volunteers of pesticides that are not on the market now but which are intended to be on the market, prior to marketing them, for the very reason that I don't want to expose people unless I know a lot about that chemical. Fourth, I would say that you would use human studies if there are significant data gaps which I think fulfills the question of compelling that would add to a risk assessment analysis.

DR. KENDALL: Those are some of the restrictions proposed. Other restrictions can the committee support this approach. In other words we are moving in a direction that the committee would encourage EPA to accept human testing of pesticides only with certain restrictions including ones that are already mentioned by Dr. McConnell and Dr. Needleman, and others. And we've talked about these and Doctors Fiedler and Gorovitz and Weiss and Reigart will begin to articulate this with all of us involved as to what those criteria are and we've talked about them today. I don't want to go over them again. Dr. Kahn.

DR. KAHN: I'd like to waive in favor of the other formulations.

DR. KENDALL: Redistribution?

DR. KAHN: Right. So I hope we can piece this out. I think that is more in line with the spirit of this kind of testing being different along the lines of the question that I asked. I think it sends a message the more restrictive formulation to the public about the EPA wanting to protect people. I think we don't want the impression to be that our government wants to test people like us with things that are poisons. That's not a good message to send. And a more restrictive formulation I think, puts that protection at a higher priority. So really more out the spirit than for any substantive reason. But I think that's an important reason enough.

DR. KENDALL: So Jeff maybe you can move it forward and say what would the circumstances be?

DR. KAHN: I'm not sure they need to be any different than what Gene laid out, but rather the beginning point, the default and the way we say it, I think is a matter of importance. I think Ron made that point when he introduced the question.

DR. WEISS: Yeah, but what you have to define for us is the difference. I mean you have to define for no observed adverse ethical level alright. One of these two contexts for they differ.

DR. KENDALL: Now we still go back to the original agreement that you did not disagree with me on, for the operational clarity of our committee, we have encouraged EPA to advance the public health in the context that human testing with pesticides, but stay strongly within the boundaries of ethics and the context of the

experimental process based on good science. Ok. That's what we said. We've said it and said it again. Now we come to the point of reflecting the mood of the committee and we have two proposals on the table. They are saying relatively the same thing but in a different context then they do reflect a different mood.

DR. KAHN: I think one says you may do testing on humans if you follow these rules or with these criteria versus we will only use humans under the following conditions, which to me sounds different and means something different. I don't know if that answers Bernie's question or not.

DR. KENDALL: Well it implies something different to me, Dr. Kahn and I would like. Further I see a lot of heads nodding to the positive and nobody said today never do it. A lot of people said today, only do it if we have the appropriate criteria in place to get a result that we can validate, that we can be responsible to.

DR. WEISS: Let me ask Jeff a question. Under your circumstances what would you consider an experiment with acceptable risks? And how will that differ from an experiment under the other guideline?

DR. KAHN: I don't think I know what the two choices are. I don't think the guidelines that I would accept would really be much different than what Gene has laid out. It's a matter of the starting point and the spirit of the mood of the group and how we explain this.

DR. KENDALL: Ok, I want to go the sexually in relation to_____. Yes, I knew it was. I want you to speak briefly to the point of pesticide, non pesticide and also this point the doctor uh...

DR. DEGEORGE: I just want to ask and this is a question specifically to Dr. Ellis. You are making a distinction and you actually pointed out two different subject populations that distinction applied to. Would you care to at least explain the basis for that distinction for those two subject populations? Because I think that's one case that only is an exception. The other case is permissive with some exceptions or some special considerations and it's the subject population to define that. I think it would be useful to understand why that distinction occurs...

DR. KENDALL: Dr. Ellis.

DR. ELLIS: I'm gonna invite my fellow scholars to help me out because we are now talking about the events of the 1970s and how they were translated into regulation. I think the overall answer is it's idiosyncratic, its not going to be a satisfying explanation. With regard to prisoners, prisoners were in wide use in the United States until the early 1970s and then because of misadventures in prisoner research, the pendulum swung strongly to the other end and we have language from 1978, that's when the prisoner regulations were finalized, that says, "in the Department of Health and Human Services no prisoner research unless with certain exceptions or restrictions."

DR. DEGEORGE: But does it have some bearing on the fact that coercion in prison may be a very strong motivator?

DR. ELLIS: Absolutely.

DR. DEGEORGE: And that's not considered one of the issues in coercion. It's not an issue for pregnant women of a child, or women in child bearing potential that may

actually bear on why that language came about?

DR. ELLIS: Well certainly I know the first part of the statement to be true about the issue with prisoners was the great influence they would be under by being captive. Any comments from my colleagues on where the pregnant women language came from?

DR. DEGEORGE: The exclusion is saying it's permissible with certain, you know, considerations -- special circumstances.

DR. ELLIS: Part of it has to do with the consent provisions for pregnant women where under the current regulations in some circumstances, the pregnant woman and her fetus - she's not viewed as an autonomous individual able to consent and the father's permission is necessary. I can't give a full _____ story.

DR. WEISS: Well isn't that historically linked to (solidamide-?)

DR. KAHN: Only in passing actually. It has to do with the study of fetal head perfusion in the Netherlands actually. That's the historical link. A Congressman's aide went and witnessed what he took to be quite gruesome sort of Frankenstein-like experiments in Europe and came back and reported this and then that language along with the (solidamide?) tragedy sort of led the protection of the unborn to be an important policy issue. I think that's the way the history has generally agreed took place.

DR. WEISS: Thank you Jeff.

DR. KENDALL: Ok, Dr. Portier, does your comment track this particular point? Because I'm going to let you make your other point in a minute...

DR. PORTIER: I'm on your question of which one do I prefer.

DR. KENDALL: Yes, yes which one do you prefer?

DR. PORTIER: _____ correlation. Having been unconvinced by the emphasis in fact basically shoved away from the concept of benefit to the individual, I'm at a loss to understand why I wouldn't do these studies. So I guess I'm in favor of the second version then because I find if the studies if they're done right scientifically correct which were already agreed to I see some value to them. So I'm not convinced on the ethical side that the benefits to the individual. So I would say then human pesticide testing with some restrictions.

DR. FIEDLER: Existing permissible with restrictions.

DR. PORTIER Permissible with restrictions. One comment on what Gene said, that was the second of the two that were mentioned. Gene said, that unless human data is obtained of equal quality from field study that's almost impossible. You would never get equal quality studies from the same size study and the field study as compared to clinical study. I think that wording has to be tossed around very carefully to link reach balance between those two.

DR. KENDALL: Ok, I think this is important to reflect the mood of this committee and I think we are justified perhaps have either opinion. But I'm moving towards the point of which I want to know exactly where this committee is, as we go to final closure. Ok. Dr. Ellis.

DR. ELLIS: It may be one or more restrictions to add on to this permissive formulation. In the current draft, I think there is

language that says no children are to be involved in human pesticide testing.

DR. KENDALL: Right, no children.

DR. ELLIS: There are other words used like elderly, that's not as well defined as children. I'm personally reluctant to use a word like that. A child I can use because it is defined by state law and in almost all states the age majority is age 18. There's a couple of exceptions. Beyond that, it becomes difficult to categorize different kinds of population.

DR. KENDALL: Pregnant women was a restriction.

DR. ELLIS: Well, actually I think it says females period.

DR. KENDALL: Females, pregnant women.

DR. ELLIS: You may want to deliberate, on whether that's a restriction committee wants.

DR. KENDALL: Moving back. We really got two proposals on the table. I think that ultimately may or may not bear on how the draft final is ultimately constructed. But I think its worthy of seeing where everybody is. Permissive with restrictions or restrictive unless exceptions are addressed.

DR. GOROVITZ: I want clarification.

DR. KENDALL: Yes, Dr. Gorovitz.

DR. GOROVITZ: I just want to make sure I understand what's the choices. As I understand this, the restrictions or the exceptions envisioned would be articulated in such, a way that the same set of protocols would be rejected by the two formulations. The same set of protocols would be accepted by the two formulations and the difference is in

packaging in how we represent the preferential tilt, the mind-set that...

DR. KAHN: Or the presumption. Is the presumption to test or not to test? May be that's a cleaner way to get at your question.

DR. GOROVITZ: I just wanted to make sure. I mean it's either true or its not true. That when we are asked to choose between A and B, their filtrational functions are the same and the difference lies elsewhere. Is that your intent?

DR. KAHN: Mine?

DR. GOROVITZ: Yes.

DR. KAHN: Yes.

DR. KENDALL: Ok. Dr. Meslin anything else to add to this? Because I want to go quantative on this and then move us forward because I've still got one other thing we've got to get through.

DR. MESLIN: Was your quantative in terms of voting or in terms of other data?

DR. KENDALL: Yes, I want it to reflect on the record as we go to final. I don't want it to be any vagueness in it. I want it to be absolutely the bottom line.

DR. MESLIN: I have a procedural question regarding the charge, and then I have a substantive suggestion.

DR. KENDALL: Proceed.

DR. MESLIN: The procedural question is, is there anything that prevents this group from sending up the chain where it is sending its report? It's considered judgment which may involve two very different although apparently similar, depending on the answer to the question that I propose next, recommendations regarding

the tone of the report. You are asking for advice from a group. If you are going to force consensus, then you may run certain risks. If you allow for the kind of full discussion that has some nuance that may benefit the EPA rather than harm it. That's my question, is that permissible?

DR. KENDALL: Yeah, I think right now. My colleague and I did not ask us to reach consensus today.

DR. MESLIN: Ok.

DR. KENDALL: We ask you to work together to reach closure. And closure doesn't necessarily mean consensus.

DR. MESLIN: Than that's helpful.

DR. UTELL: But I think you are raising a possibly very important resolution depending, I mean if there is a mix, it's not unreasonable to say here are different options. Is it packaged a little different but in fact they basically reflect the same types of recommendations and limitations. And we, as a committee, are sending them up as considerations without saying that either one is necessarily the way the majority of the committee would go. But nonetheless, they are very important messages, no matter which way the agency might choose to deal with them.

DR. MESLIN: So here is my suggestion. Jeff and Sam's exchange reminded me of an exchange that many other groups have had on this kind of at the margin discussion. Sam's description of Jeff's presentation was there wouldn't be any difference, and correct me if I'm misrepresenting you, in either the type or the number of studies that would be approved or rejected in either formulation but to take Jeff's point, it's the way that we

orient the report. It's the flavor of the report. That would be one defensive of Jeff's suggestion, and that could go forward as a policy approach. There's another approach that's complementary to that.

DR. KENDALL: We can handle that but one of the things that

DR. GOROVITZ: I want to hear the rest of...

DR. MESLIN: Yeah, this is actually the keystone to the point, which is, you don't have to get this group to agree on whether the same protocols either in number or type would be approved or rejected. But rather that is an issue of judgement following up on Sam's earlier remarks of this meeting and a previous meeting either at the IRB level or at the purity level, or indeed at the level of senior EPA administration. I can tell you that many other groups have had this same kind of struggle, and have hurt themselves trying to resolve, will it be 12 projects that are approved with Jeff's formulation, and 13 that are approved with Chris's formulation. Does this group want to approve more studies of pesticide irrespective of Gary's nuance distinction? Or do they not care about the number, only about the tone? If they care only about the tone, then Jeff's presentation is perfect. If they actually care about the number of studies and the types of studies even if its 13 or 12 or 14 or 16, then you might have to go to your quantification exercise. That's my.....

DR. KENDALL: Thank you for being here today. You've really contributed substantially. You kind of hold off, and all of a sudden boom hit us with these issues.

DR. MESLIN: It's not that my other day job, I don't spend my time thinking about the same problems.

DR. KENDALL: Dr. Gorovitz, what's your feeling on that?

DR. GOROVITZ: Gratitude?

DR. KENDALL: I knew that we could get an appropriate word from you. Gratitude. Dr. Fiedler, how should we proceed? Because the co-chairs do not want to take the leadership of the writing of our document. We want to be a part of the process. Therefore, the writing assignments and the construct of the document will reflect the flavor and the tone of the committee substantiated by the editorial input of the chairs and the co-chair.

DR.FIEDLER: Well I'm not sure but my belief is that these two options could be operationalized and maybe ought to be operationalized differently. And that if we were going to include both, because we can't decide on one or the other, then we would have to struggle with operationalizing each because to me, it does communicate a different tone. That means ultimately that it could be operationalized differently because if you say, a ban with exception, that suggest something quite different to me than permissible with restrictions. And the permissible with restrictions suggest that there would be the possibility of many more studies. With the restriction of you know no pregnant women, no children, those kinds of things. I also think, that this list that Gene gave, is up my alley in terms of the kind of things that I had hoped we would be able to get to but I would like to go even further. Maybe we can't do it today but adequate human data, I don't know what that means. So I would

like some examples of what you mean by adequate human data. Whether you put it under one option or the other in this tone thing, I don't care...

DR. KENDALL: I would suspect that this will be an evolving process for the agency to deal with. I think far beyond the role of this committee. Although with due respect, accepted and hopefully Dr. Needleman that will...

DR. NEEDLEMAN: I didn't hear what you said.

DR. KENDALL: In due respect sir.

DR. NEEDLEMAN: Is it an insult about the government or...

DR. KENDALL: No, I was talking to Dr. Fiedler. I figured you guys needed a little humor at this point of the day. Dr. Reigart.

DR. REIGART: This is sort of a generic comment, but the all four or five, I guess it ended up with five drafts we ended up with. Wasn't there a fifth?

DR. KENDALL: There was a fifth that never made it out...

DR. REIGART: Ok. I think I saw it.

DR. KENDALL: Yes sir. For iterations. We ran out of paper.

DR. REIGART: All of those, as much as all the junk in them, there is a lot of unnecessary words in them that bothered me, many of the specifics, but I think also in tone. I mean the last drafts were so permissive that you could have justified almost any kind of human research by certain readings of it so whatever we do I just can't buy a document anything close to as permissive as what we drafted before and whatever formulation we choose among these two and I would go

for a more restrictive one because I still think you are going to be able to drive a truck through whatever is written. I would tend to go for a more restrictive form or tone so that people would be less tempted to drive that truck through.

DR. KENDALL: And I appreciate that and I agree with you. Another thing for the committee to consider as this whole area is unfolding. Perhaps it should start more restrictive until we develop better parameters and monitoring capability in reviewing the process, as it moves forward. That's another plausible alternative. Not withstand the fact that we are not saying, not to do this ever, etc. We are saying that we are very cautious in light of the discussion we've had today. Dr. Gorovitz.

DR. GOROVITZ: I'm convinced that though we might intend the difference between the two formulations to be filtrationally indistinguishable. Probably they wouldn't be. That the difference in tone would, in the end, have some difference interpretation...

DR. KENDALL: Absolutely.

DR. GOROVITZ: At that point where judgement comes into play and therefore I think it matters substantively which tonality we prefer. And at this point see why it wouldn't be useful just to have a nonbinding straw pole to see what the distribution of preferences is. That is some of us may clearly prefer one tone. Some may clearly prefer the other. Some may have no such preference but it wouldn't take long to find out.

DR.KENDALL: Thank you, Dr. Gorovitz. That's my prerogative, but I want to move with the mood of the committee. Dr. McConnell has seconded to that. Dr. Portier.

DR. MCCONNELL: I second that.

DR. PORTIER: Well, my original interpretation was one thing, now you've confused me completely. Not knowing, seriously now that I'm looking at the wording that's there, I'm asking myself what does it mean to be permitted? I guess, I interpreted that to mean that this is no different than any other human clinical testing situation with the following exceptions. That was my interpretation of being permissive. Is that what we mean here? Because if that's not what we mean we have to be very clear before I can give you a firm statement about what this means because the opposite statement is clearly very different in my regard because it says this is very different than the usual clinical testing situation but we will allow it under the following conditions.

DR. KENDALL: Can you respond Dr. Gorovitz?

DR. GOROVITZ: Yeah, I think that your reading of the second branch is exactly right. On the first branch, I don't take it to mean this is no different than any other clinical stuff. I take it to mean the agency is willing to accept as part of the evidential base it will consider in making decisions, the results of this kind of research. Now that's neutral with respect to whether it's the same or different from other clinical stuff. That's a stronger claim than I think is entailed in the permissive formulation. I think the permissive formulation and the restrictive formulation are not about similarity or difference to other domains of research but are about what the agency will or will not receive and accept as part of its evidential base.

DR. KENDALL: Good point. Dr. Kahn.

DR. KAHN: I think we can argue that the criteria which we will write about what would be allowed. But to answer Chris's question, I intended, and I think I said this, if we can find a way to characterize this such that it sets it apart, it's different than other bio-medical research, that to me is an allotable goal. That's what I would like to see happen. So if that's the choice then, it just makes me more strongly in favor of the more restrictive formulation.

DR. KENDALL: Well, it seems to me if this was not different from the standard pharmaceutical process, then why are we here? I mean why are we here? I would just turn it over to Dr. DeGeorge and assume he would do a great job. I mean all of the criteria were laid out and so on. Why are we here? We are here because these are issues that are ones, that have required this level of debate.

The committee has ruled a motion. I've heard a second and I'm gonna call for the vote. Nonbinding straw pole. This is a reflection to the mood of this committee as we recommend to the agency the future of how these kind of results are going to be received and/or handled. That's what's been done here. Ok. I would like to have Dr. Ellis rephrase the two and state them as A or B and ask everybody to listen carefully so they make sure they vote for the right one.

DR. ELLIS: Thank you for that introduction. The two choices are first a restrictive formulation and second a permissive formulation. So the first, the restrictive formulation would be a statement along the lines that the agency should not accept data derived from pesticide testing on humans except in limited circumstance, and for purpose of the vote we are going to leave the

circumstances undefined. But the candidate circumstances would include for instance non-pregnant adults. Again no human pesticide testing except in non-pregnant adults. That's just a candidate. Maybe that's the wrong way to put it.

DR. KENDALL: Not in children

DR. ELLIS: Not in children. I would put it that away. Another candidate might be no human pesticide testing except where the activity is not greater than minimal risk. So, we hadn't discussed that previously. But those are the kind of statements that might be added to the restrictive statement of no pesticide testing except when. The second alternative or permissive statement we recommend that the data deprived from pesticide testing on humans are used and may be used except when derived from children, for example. And we had Dr. McConnell's other specifications. Again I'm gonna leave the specific statements unstated at this time. Now in either case, either the restrictive statement or the permissive statement, Dr. Needleman's restriction applies and that is that there will be no use of human data to determine NOAEL or neurotoxic agent. And so that will be explicitly stated in either formulation. So, the first was the restrictive. The second is the permissive.

DR. KENDALL: So fundamentally A is to reflect a mood of the committee of a restrictive process with exceptions, which we are going to articulate. We've done it today. We've done an excellent job and I'm confident it will be a very solid report. B is a more permissive strategy that does establish criteria, but it reflects that the panel encourages at least to the level that the criteria

will allow a more permissive structure to move forward.

DR. GOROVITZ: At most to the level where criteria will allow?

DR. KENDALL: At most. Thank you Dr. Gorovitz.

DR. GROVOTIZ: One, as I see it as restrictive with permissive exceptions. The second one is permissive with restrictive. Is that correct?

DR. KENDALL: That's fine. That's another way to put it. That's another way to put it but this became a point of important concern from this last report, Dr. Reigart, Dr. Kahn, I mean, Dr. Needleman. People have spoken to this today and I want this clearly reflected in our document and in our straw man vote and this does send a message. It sends a message no doubt as we conclude our efforts today in the collegiality that we reflected. And this has been an excellent, excellent day to discuss this with you. Dr. Meslin, you want to add something else?

DR. MESLIN: Just a really boring procedural matter I note again to the public who's here. The full roster contains 2 co-chairs, a number of members and consultants of which I note my colleague, Dr. Ellis, is listed as one and then three federal experts, myself, Dr. Portier and Dr. De George, are you expecting the federal experts to not participate in the straw vote and can we check whether Dr. Ellis is comfortable with being listed as a member of consulting rather than as federal expert?

DR. KENDALL: Dr. Meslin, I'm expecting you are a member of the panel. Dr. DeGeorge is not. He is a guest of the panel. Dr. DeGeorge will not vote. Dr. DeGeorge is not a member of the panel.

DR. MCCONNELL: He is listed in the same place as Dr. Meslin and Dr. Portier according to what I have here.

DR. KENDALL: That's just an error in the printing.

DR. MCCONNELL: That's an error.

DR. KENDALL: I really appreciate Dr. DeGeorge being here. You have added so much but being that you were not a part of the original committee and considering the process of the committee's deliberation, I hope that you understand where I'm coming from here. Ok. Dr. Portier.

DR. DEGEORGE: Dr. Kendall could I just ask a question here?

DR. KENDALL: I've got a motion on the table, its been seconded and...

DR. DEGEORGE: Well, the only reason I ask this is the issue that you said we would come back to before when you first started up and I think it is relevant back from the break, I think it is relevant to the vote that's being taken. Because people making this distinction may be making it thinking about this very part of the process and I think that Mr. Carley could speak to the issue and I will add pharmaceutical but I think it is important to make sure that it is understood what the distinction before we make the vote.

DR. FEIDER: Yes.

DR. KENDALL: Ok, very well. Mr. Carley.

MR. CARLEY: The distinction that we were talking about goes back to some of the discussion before the break reflect back to the part where Dr. Kahn asked the question are they different? There's some lack of specificity about what they were but basically pesticides versus

sort of everything else. And Dr. Gorovitz made the point that pesticides were when released into the environment expose to whole population rather than to targeted individuals. That's certainly true at the point of use. And that is why the EPA uses very different risk assessment methods from what FDA does when they are deciding. Dr. DeGeorge mentioned as an example in his presentation this morning, outside of toxic drugs that like 1/10 of the lethal dose for animals, I think. We are not talking about that sort of thing that is targeted to a specific individual and it may make good risk benefits sense in that case. But this question about how we do our overall risk assessment by releasing pesticides to the environment, is not the question that's on the table today, which has to do with the design and acceptability of specific studies. So, when you think about the differences and the analogy to the rest of biomedical science, you need to keep that in mind. It would be very helpful to us if you could address pretty sharply this question of where the analogy to the rest of biomedical science does and doesn't break down.

DR. DEGEORGE: And the reason I thought that, that was important because from the pharmaceutical perspective, at that first dose into human, and I'd assume it would be the same from the pesticide, they are both potential toxicants in humans with certain data sets available to evaluate that risk. After that point, they become something different.

DR. KENDALL: I appreciate that. Listening to this committee all day and thinking about the draft iterations we've had, I think that's what we are worried about is after that point. And it seems to reflect back into the charge. Help me committee, as we thought about it this

morning and went back through the charge again. It wasn't just receive a dose and let's not think about it again. We were asked to look at a process that involved the use of a product and how we were going to think about data acquired for that product and its reliability of that data into an ultimate risk assessment. And how then that data will be provided in an ethical means that we could live by as a civilized society that is concerned of its population and the vulnerability of certain populations. That to me, was a large part of that charge. Please correct me if it's not that. I mean that's the reason we are here today. To me, otherwise, I would have just turned it over to FDA. I would have given it to you. Most of us did not ask to be on this committee. In fact, this has been quite a challenge, Mr. Dorsey. I don't think Dr. Utell can share that concern. Yes, Dr. Gorovitz.

DR. GOROVITZ: I dimly remember from some while ago there was some talk about just as quick and formal nonbinding straw pole.

DR. KENDALL: That was what we did. I yielded to the front table.

DR. GOROVITZ: But we haven't had that pole.

DR. KENDALL: Yes Dr. Gorovitz, thank you.

DR. GOROVITZ: I wondered if we might do it?

DR. KENDALL: Thank you. We have A) a more restrictive mood, B) a more permissive mood. Is that fair Dr. Ellis?

DR. ELLIS: Yes.

DR. KENDALL: Dr. Ellis, what is your position? I was going to move around the table and ask. Ok, then I ... Fine. Those that favor a more restrictive position, raise your

hand. Count them. Seven. Nancy's hand was up. Ok.

DR. MCCONNELL: I got 8, I got 8.

DR. KENDALL: Meslin's hand is up.

DR. KENDALL: It's 8. Those in favor of B, a more permissible position, raise your hand. Four. That's a straw man pole, nonbinding. We got it.

DR. PORTIER: I'm gonna give you my argument. I still don't understand the question we were addressing. Under either condition I gather we are still gonna have to stick to...

DR. KENDALL: Wait a second Dr. Portier. I think right now we are moving. What we did was reflected the mood of the committee in a nonbinding vote that allows the agency to better relate the posture of a group of people that were assembled to reflect on this topic. Nobody today has objected totally to human testing of pesticides. There is a majority of which, in a straw man pole non-binding, that offer a restrictive posture moving forward with appropriate exceptions, exceptions that will be identified by the committee. I am confident we can accommodate this committee, and we can identify the exceptions in a way in which...

DR. UTELL: Ron, before we drive it to hard, I think we want in the report to reflect the again the range of opinions whether it be some numbers or not I don't feel strongly about but I do think that we are driving a little hard in terms of which way we are trying to reflect the sentiment of the committee. I think that as we very much agree to do our goal is to reflect where there was indeed a range of opinion and to make that very clear to the agency rather

than to come down on necessarily one approach or the other.

DR. KENDALL: I think we've done that and that's in essence what we've voted for Dr. Portier. and if you'd like to then respond that's fine and we definitely, I think, have attempted all day to accommodate the range of opinion. I personally believe that there's enormous consensus on this committee. Enormous.

DR. UTELL: I haven't really figured out all the difference between A and B except 8 to 4.

DR. KENDALL: And that's not what's important. What's important is some perspective of mood. This was an issue before. It was a key issue on the previous report and I will not let that go unobserved out of respect for my colleagues at the table. Again, Dr. Portier any comment to add to this because what we try to do is move to our writing session. That's what we want to do.

DR. PORTIER: I guess, but I still have no idea what you just told me. If I were sitting there as the agency trying to decide on what's going on here, you have given me no information. Are you proposing to the agency that they write from scratch a full set of rules for clinical protocols and acceptance for studies for pesticides? Hence, your statement that you're started off with a statement that human pesticide--the agency should accept data derived from human clinical studies except in cases where. So are you suggesting they write the entire protocol or are you suggesting we are starting with FDA's protocol, but even then we will not accept anything unless you do this? In which case, I have some serious questions before the vote that you wouldn't let me ask such as the examples that Dr. Ellis gave are exact

flip side of each other. So I didn't see any difference between the two. On the other hand, if he had stated the question in part of the way that Dr. McConnell had put before, to fill significant data gaps, for example. So if you said these are not allowed unless they fill significant data gaps. That is a very different statement than the permissive statement. And that's why I had some confusion over which one I'm voting on and what that vote means. I still don't understand it.

DR. KENDALL: I think the take home message from this is not the vote. The take home message is that we are moving towards a posture of defining those criteria that will allow us to set these studies. When we choose to initiate that process in a restrictive fashion, and as we learned and provide the data that we can validate, I think, the mood of this committee was, we are willing to support this and encourage this literally. So to me, it's just a matter of I've got the notes from today and they were excellent. Dr. Gorovitz, Dr. Fiedler, Dr. Wise, Dr. Reigart, and the comments made. We have the substance to identify the criteria within the limits. I will not believe that we could identify all of the processes of minimizing risk in one afternoon writing.

DR. UTELL: But I think Ron before we go to much further, again I think you were close and we're getting a little caught up here both in sort of a A/B and the rhetoric. I think the committee has come to some very concrete consensus of how to go forward with some specific guidelines and criteria and I want to make sure that we don't get too caught up in agendas and that we try to come forward with utilizable recommendations. I think Dr. Ellis sort of set us on the right track but then we run the risk of

a sort of polarizing it at that point. As we go forward with the writing assignment, again, I think the message is very clear. No one is saying no pesticide testing under any circumstances. There are certain restrictions and we need to develop that kind of recommendation. I think what we need to do is begin to put some teams together who are going to prescribe this and that we make sure that our writing groups include folks who represent a mix of opinions so we don't get caught up in polarity... (tape stops) ... I really think we need to begin to make some of those assignments. We're not going to go any further. I'm worried that we will only have Dr. Portier asking us again A or B and I get confused myself. I'm not picking on you but I do think we need to now get beyond the rhetoric and say let's make some assignments and get this thing written up. Dr. Galson.

DR. GALSON: Just a real quick note. I know you all want to help us, so I want to just give you a couple comments that I think will help you help us. You seem to have agreed that doing studies that are designed to derive an NOAEL are not appropriate. This is giving us a lot of information and a lot of help. Most, if not all, of the studies that we've received are designed to do that. So if you've made a clear decision that that's not an appropriate use of human subjects, that's a very important piece of advice, and I would encourage you to make that as clear as possible whether there are any exceptions or anything else.

DR. KENDALL: That was by consensus.

DR. GALSON: That's the most important thing that I've heard that helps us so far. And just to perhaps help you avoid some issues, the use of children and

vulnerable populations in these studies have not been an issue. We haven't received studies like that.

DR. UTELL: But it certainly could be?

DR. GALSON: It could be but I don't think for the limited time you have you should worry to much about that. I'm not telling you not to give us that advice but I wouldn't worry about being to precise on that. It hasn't been an issue.

DR. KENDALL: Very well. Dr. McConnell.

DR. MCCONNELL: Yeah, I've got a couple of things here I think will be constructive for the EPA. But I'm not sure that there's a consensus on the panel. First, we talked around this a little bit but I didn't hear any clear understanding or what we would agree to, and that is do you think we should suggest to the Agency, let's put it differently. I think we should suggest to the agency that in future studies that involve human volunteers, that these protocols be brought to the agency prior to the conduct of that study for approval. I'm not talking about an IRB kind of exercise but from a scientific standpoint does this mean there are data sets, does it meet Portier's needs, etc.? Now I don't know if the rest of the panel agrees with that or not.

DR. KENDALL: Does anybody disagree?

DR. UTELL: Well, let me just say I don't disagree, but it puts the agency in a very unusual position where, in fact they, and you see this with a lot of bioassay-type testing where they've now brought in on that specific protocol and I wouldn't just take this out of hand. I think there is some advantage if the agency can develop a strategy for reviewing those kinds of potential protocols and

either pointing out strengths/weaknesses where they could not or might use them. But until that's done, I want to make sure that this isn't just aN instruction to review this and now once they've agreed, that they are somehow the sense that they brought in. It takes a lot of real hard work to think about how to get that as a interactive process. When it works its very effective, Gene, as you know but I think we need to be careful who.... And it might be something that we suggest they look at as they go forth.

DR. MCCONNELL: Well that's what I going to say. Suggested. If not, then can we suggest they start thinking about it?

DR. UTELL: Yes.

DR. MCCONNELL: Number two, can we suggest that they once while they are thinking about it that if they are going to accept human volunteer data that they think about what types of guidelines they might need just like they have guidelines for field exposures. They ought to be thinking about, in my opinion, developing guidelines for these kinds of studies.

DR. UTELL: That makes good sense.

DR. KENDALL: Excellent suggestion. I think if those guidelines had been clearer, we could have probably been a lot more aggressive than moving after these questions. And again, it's something that we are dealing with. We are moving towards as part of a process. Dr. Fiedler.

DR. FIEDLER: Yeah, I just want to know again for my own clarity, why we are saying that studies to establish a NOAEL are unacceptable?

DR. KENDALL: That goes back to...

DR. FIEDLER: I mean we have to put that in the report anyway. Exactly why are we saying that those are unacceptable?

DR. KENDALL: Because, Dr. Needlman.

DR. NEEDLMAN: The question was raised after more discussion, what were the specific steps that made us exclude studies with pesticides looking for an NOAEL?

DR. GOROVITZ: The summary of the reason why, were rejected.

DR. NEEDLMAN: Because they have the power of about .1 and the report no affect so

DR. FIEDLER: In that its just not feasible studies?

DR. UTELL: It's a good question though so if someone studied 1,000 volunteers. Obviously I'm carrying this to an extreme, you point is that you can't do this kind of a study with limited numbers of volunteers and come up with an answer.

DR. NEEDLMAN: It concluded it's no affect?

DR. UTELL: Right.

DR. NEEDLMAN: Creating false impressions.

DR. FIEDLER: If you define the affect as a symptom, right, or as a....

DR. WEISS: No it could be a biomark, Nancy.

DR. FIEDLER: Right, so are we saying that even something with a biomark is unacceptable?

DR. WEISS: Well remember, you probably don't, in the last draft when one of the contents which we saw human studies it was only part of a larger decision process so that if you would obtain human data it could necessarily have a better defined

scientific context than simply to shift the acceptable level. At that point you might want to go back or should go back and look at some of the more fundamental animal data. And see to what extent there are differences and then do more experiments to try to account for the differences. We saw this as a continuous process rather than one that ended with my experiment to establish or to start to establish the different affect levels.

DR. FIEDLER: OK.

DR. MCCONNELL: Now one more here. This may develop into a little bit of discussion, but you've all heard how I feel about pesticides that are not on the market yet. Should we as a group encourage the agency to ask for human volunteer data on pesticides that are not on the market now but for which they would probably register that pesticide based on animal data before that pesticide is used in the general public or to where significant numbers of humans are exposed.

DR. KENDALL: That would represent one of your exceptions with a major data gap?

DR. MCCONNELL: No, no this is almost on a positive side in the sense that the agency would be encouraging the development of such data. This is more than permissible. I would like to see it before I approve your pesticide to be used around my kids or my back yard or to kill my termites or whatever that you know under the same caveats that these other human studies are being done.

DR. KENDALL: And this is for the Pharmacokinetics information?

DR. MCCONNELL: Not for NOAEL's or anything like that but to understand to put the animal data

in perspective to be able to do a better risk assessment, to know how much material you will allow those field workers to be exposed to when they reenter a field, etc. Or before you put this material around your baseboards to try to keep the ants from coming in or before you apply it to your dog to try to keep the fleas off of him and on and on and on.

DR. NEEDLEMAN: I think you are asking for a blank check. I mean that's a question that is impossible to answer without specifics about what the test would be.

DR. KENDALL: I think it's a fair question and I think this committee has not rejected the concept of human testing with pesticides. It has not done that. It has reflected a mood and that's it and it has established criteria upon which it would encourage and/or support data being developed along those lines.

DR. GOROVITZ: It's a fair question, I'm prepared to answer. My answer is no.

DR. KENDALL: We have a no. Dr. Kahn.

DR. KAHN: I would say no because we sort of went through a process of talking about whether to encourage or discourage and if the presumption is not to do human testing then why would we require it as a matter of regulation? It doesn't make any sense to me.

DR. MCCONNELL: Because it's a new pesticide to which we have no... So you would rather wait until this material is sprayed on a field and people are going into that field for example or to get your human exposure information?

DR. KAHN: I would rather elaborate the criteria that we've been talking around and see whether your example meets those

criteria rather than say the EPA ought to require human data on

DR. MCCONNELL: I didn't say require, encourage or suggest which is a symantic.

DR. UTELL: I think your statement may still be to strong Gene, whether as we are writing this up this may be an area that they want to look at more intensely as they are exploring new pesticides. So I don't think we want to get in to require. It seems to meet a flow contrary to the sense of what this committee is all about. It might well be one of these areas where the agency has to look at. It might have value added but not as a requirement. I think that would be really overstepping. Routt.

DR. REIGART: I agree with that. I think as we define exceptions they would apply equally well to new as to old chemicals and there might well be on the part of the registrants a desire to do more of those studies. Like as you say don't have any idea how much is going to be absorbed in the field, they might really want to do a PK study that we would think would be ok, where they might not want to do it with an old chemical where they have already looked and absorbed some in the field so. I think it would meet the exceptions without any problem.

DR. UTELL: Ok. That's fair. Good point. Well taken.

DR. KENDALL: I'll accept that. Ok. Dr. Utell and I would like to go towards the writing assignments at this point to meet the spirit of Dr. Meslin's request to break into the subcommitee writing units approximately 4:30 or soon thereafter. Is everybody ok with that? And it really goes back I think to some of the issues that Routt put together in his almost final draft and I believe it

would be useful for individuals to volunteer for sections they would like to write rather than for Ron and I to sit here and make assignments.

DR. FIEDLER: What are the sections. I don't know what sections.

DR. UTELL: Will you sort of put it together with Draft 4? I think, when we were looking at Section 3.2, was the area that needed to be brought out and created a lot of the uncertainty as we went through it last time. I think that's ....

DR. KENDALL: Nancy and Sam, if you could revisit the background section and the charge since you reviewed that for us, we would appreciate that and the document section, the introductory section and the charge. Section 3.2 it was Routt who took the lead on this with Dr. Weiss. It has developed a straw man next iteration of that section. Today, a lot of those issues and that section is entitled Factors for Consideration in Identifying Ethically Appropriate Human Studies ok. I think that gets at the very essence of what Dr. Feedler and Dr. Gorovitz articulated this morning in addition to all of our other comments. Dr. Fiedler.

DR. FIEDLER: You asked us to review the background and charge of the original this Draft 4?

DR. KENDALL: Yes. Go back to that thinking about Dr. Mulkey's presentation this morning and then your presentation this morning as a part of the charge of our subcommittee conference call. And if you would look at that for us and at least in this next iteration with input from others. And again, this is the committee's report. This is not the chair's report. Yes Dr. McConnell.

DR. MCCONNELL: Mr. Chairman I think its 2 things, one its important that we know whether we are working here in writing this _____ work or are we working from one of the previous reports?

DR. KENDALL: We are working from draft 4 of the previous report.

DR. MCCONNELL: Ok, so we can use the same language, etc.

DR. KENDALL: Yes.

DR. MCCONNELL: Second.

DR. UTELL: But Gene, what we want to do is take the good parts of that draft and the pieces where there was discomfort. The part that Routt pulled out for Bernie to work on. Those need perhaps to be largely reconstructed, but the document... What we need to do is make sure it doesn't just read like a committee report which was all chopped up last time. Its going to take a lot of integration on our part but we would like to use that structure and build from the strength and identify the current pieces that are really worth disagreement.

DR. MCCONNELL: Fair enough. Second thing. Even though we didn't allow Dr. DeGeorge to vote. Can we have some of his information in this report?

Dr. UTELL: Sure you can have anything that you want. I think it would be very useful.

DR. KENDALL: And even for this vote, as far as I am concerned, that doesn't need to be articulated in the report. We don't need to say 8 votes versus 4.

DR. MCCONNELL: I wasn't talking about that. I was jerking your chain.

DR. KENDALL: Okay, well, you got my attention.

DR. MCCONNELL: What I would like to have is what he presented in the report.

DR. KENDALL: Exactly. Any material discussed at this meeting.

DR. MCCONNELL: Did I not say that?

DR. KENDALL: Yes.

DR. MCCONNELL: Ok.

DR. KENDALL: Yes. Fine.

DR. FIEDLER: So in other words, we can put in where we got that background document.

DR. KENDALL: You bet.

DR. FIEDLER: We can insert parts of that.

DR. UTELL: Right, it was part of the general discussion today so therefore it can well be incorporated. I think your comment earlier this morning Nancy was in fact that that background was much more valuable in some senses than the charge.

DR. FIEDLER: Oh, we can change the charge to?

DR. UTELL: Well, I didn't say that. We need to address the charge but to make it consistent.

DR. KENDALL: At this point Dr. Reigart.

DR. REIGART: I don't want to lead. I would prefer you choose another leader.

DR. KENDALL: Another leader. You've done a great job. I think the two cochairs would very much appreciate your taking a lead on this. Work with Bernie and perhaps select someone else to be part of your group.

DR. REIGART: _____ give it to Nancy.

DR. UTELL: Nancy has got an assignment. Let's make sure everybody has a role but Routt certainly I think you bring a lot of thought to this and I'd like to see it continue but you guys need to work as a team and identify a colleague to work with you.

DR. KENDALL: Routt, please do that for us.

DR. UTELL: Ok. Now, Dr. Meslin, we had identified an area that we wanted you to work on.

DR. MESLIN: Yeah, you told me it was on the ethics. Unless you want me to write about one and two tail sea _____.

DR. UTELL: No, no I think we'll pass on that. I think we need to work on the ethics and then something on study design that clearly...

DR. KENDALL: Can Herb and Chris walk through study design issues and offer some of those perspectives extracting from your prepared documents. Will you do that Chris?

DR. REIGART: Some of the piece that I was working actually touched on study design with the concept that if it's not a good design it's not ethical so maybe we could subdivide and let them do the study design and

DR. KENDALL: They've already gotten written materials on this.

DR. FIEDLER: What does the study design include though? Does that include...

DR. REIGART: It includes more than sample size.

DR. FIEDLER: Right. Does that include what you are measuring and how do you define...

DR. KENDALL: The experimental hypothesis, the data collection, the subject numbers, the

power analysis. Dr. Needleman has been part of an IRB doing these kinds of studies. Dr. Portier, I think they've got prepared materials

DR. REIGART: And they can speak to the issue of why it's not feasible to do appropriate and no...

DR. KENDALL: Dr. Kahn needs to go back to The Risk and Benefits to Subjects and Society. Dr. Kahn. Routt, I didn't hear you.

DR. REIGART: I was just hoping that in their study design, they, being Dr. Needleman and Dr. Portier, would address the issue of the inappropriateness of the available types of studies to determine an NOEL for humans because that' something that Herb...

DR. KENDALL: Herb are you prepared to address that?

DR. NEEDLEMAN: Certainly.

Dr. KENDALL: I mean we really hammered that point. The Judgement of Current and Past Studies, Dr. Ellis can you revisit that section?

DR. ELLIS: What section?

DR. KENDALL: Its section 3.4.1. It's the Judgement of Current and Past Studies. And I would like for you to reflect on that related to your role, as well as a member of the committee. We did a section on Oral Dosing. I didn't think we need that section any more. It just goes over the design. The oral dosing, it moves into the criteria section. Ok.

DR. REIGART: Say what now.

DR. KENDALL: Oral Dosing. We had it separated as section 3.4.2, that needs just to be moved back in to the criteria.

DR. KENDALL: And you've already done it. You did it already. And then Determining Compliance with Ethical Standards - That's not a long section but I would like Dr. Ellis read that for us and to make sure we capture the essence of that. Dr. Gorovitz, if we can ask you to just revisit the charge and just make sure that what you said this morning which was so articulate is constructive writing for the beginning of the report. OK.

DR. GOROVITZ: They don't belong in the charge.

DR. KENDALL: It belongs in how we frame the work of the committee to move into the deliberations or establishing the criteria. You may have to establish a transitional point.

DR. GOROVITZ: The charge is not a product of the committee.

DR. KENDALL: That is correct.

DR. GOROVITZ: Its an instruction to the committee.

DR. KENDALL: Exactly.

DR. GOROVITZ: It is what it is.

DR. KENDALL: It is what it is with our interpretation and you established that agreement and disagreement.

DR. GOROVITZ: Ok.

DR. UTELL: Alright. Now who haven't we given an assignment. McConnell are you doing something?

DR. MCCONNELL: I'm going to be writing on every part of this report.

DR. KENDALL: That's where I saw it.

DR. UTELL: I think in particular, the factors...

DR. MCCONNELL: I will expound upon those some of these examples...

DR. UTELL: I hate to put you on the statistical piece.

DR. MCCONNELL: Since our colleague from the FDA left I hope somebody is going to be contacting him about...

DR. UTELL: We will, we will make sure. He's actually outside the door.

DR. KENDALL: Dr. DeGeorge, are you outside of the door? Can somebody retrieve him. I think he's with Steve ...

end of tape 4)

DR. KENDALL: Request by panel members to have opportunities to consult with you. We'd like to know if that's appropriate and would you agree.

DR. DEGEORGE: If it'S acceptable for EPA for someone who's not on their board to participate in the draft of a board document, I'm willing to do. But I think that has to be a part of the process, if that's an acceptable part of the process.

DR. KENDALL: Well, I saw it more as a consultant to the committee. There were points of clarification, we may use some of your materials from today. I think we will, and so on. So, thank you for your willingness to do so. So Dr. McConnell your question's answered. He's here and so I look to you, Gene to look at the entire document. I know you've got a lot of interest in this. And I'd like for you to be our eyes to go back over it in a way in which captures so many things that we've discussed today as well as from the previous iteration. And if we all except the charge individually and execute, I think we're going to have an outstanding document to present to EPA. So, Dr. Meslin, we're

10 minutes early than your proposal of 4:30 to get together, and I think, this is a time to, if you need to chat with colleague or something just to get our writing started, this is a good time, And then the writing committee should be underway. Dr. McConnell.

DR. MCCONNELL: Yes, two things. One are we coming back?

DR. KENDALL: We do not need to reconvene.

DR. MCCONNELL: All right. Number two, then are you going to give us some time frames when you'd like to have some of this information back in?

DR. KENDALL: In terms of time frames, we would hope...

DR. UTELL: I think we need to have some materials within the next 3 weeks or so. And both SAB/SAP is looking for a sense of where this is going. Putting it together is going to be another project. But, we need to ask the working groups if we could have the working group reports in the next three weeks.

MR. DORSEY: I would agree with that. I would encourage you, if at all possible, if we can get the material by the middle of December, so we can get the first draft report. With the holidays upon us, people are going to be out the last two weeks of December. So from experience, If you can get it to us, say by 16th of December, so the people that are responsible for the major sections, then we'll compile into the report, get it out in your hands quickly, so you'll have a chance to look at it. But if you don't do it by the middle of December, I think we've lost December.

DR. UTELL: I think as Dr. Meslin mentioned...

DR. KENDALL: Well, let's agree to that.

DR. UTELL: If you do it today you have a much better chance of remembering what you'd said.

DR. KENDALL: We must do it. We must not delay past the middle of December, we will forget what we've agreed to. But, I think we need to. December the 15th? December 15th, let's have it in. As responsible members of the committee.

DR. UTELL: Should we deliver it to Larry

DR. KENDALL: Yes, to Larry.

DR. DORSEY: Stephanie Irene will be working with me. But you have our e-mail addresses and send it to Stephanie or myself. We'll work together.

DR. KENDALL: And then, as we get and compile this, this will all go back out to everyone. Everybody will see it and we will work together to come to closure and we will proceed as necessary to that.

DR. UTELL: I think that even more than you will see it, we will try to send everybody the write-ups that we get from each person. This is not going to be just the integrated report. You will get all of the comments, if you choose to go through them, they're yours. If you choose to discard them, that's your call. But either on the web or in terms of hard copy, we will get everything to everybody. That is the commitment.

Correct, Larry.

DR. DORSEY: Yes, we're going to work to that.

DR. KENDALL: Dr. Reigart.

DR.REIGART: I just want to clarify that, It seems to me that anything that goes out in hard ought to go out on the website.

DR. DORSEY: Ok, I, maybe Cathleen you can speak to the website. I can certainly be dealing with the hard copies and the materials, and I think the SAB will handle the website.

DR. CONWAY: I heard somewhat of a week read to lean on this issues. But I know that we have, our goal is to be able to do that routinely for SAB.

DR. UTELL: There is a real problem, though, with the website. And that is if you happen to be on another committee of the SAB, you have access to all of these websites. And there are some concerns that we don't want to open it up until we have the report. I just want to make sure, that in fact we haven't been restricted.

DR. DORSEY: Okay, I have a couple of suggestions for you. The website is innovative, it's a great idea. I think that it's still underdevelopment and there are some issues about security as far as comments with this committee. I suggest that we use our e-mail systems that we have used. You have everyone's e-mail addresses, the people working with you on your subcommittees. If you e-mail everyone all your comments, it really does facilitates exchange and information quickly. I also suggest that, please work within your groups to resolve any issues that you have generating the first draft. And along this line, it doesn't mean that you've reached consensus on every issue. I really encourage a lot of new information today, was discussed in view points a lot of different comments. My suggestion is that you capture where you can where there was consensus or

agreements on major issues. But also important comments, if we say, one panel member suggest that such-in-such, several panel member suggest that such-in-such. That's an excellent way of getting the information into the report. So think about, you know, putting those comments in there. Think about including everyone's comments when you're working together. And I really would like for the people to have responsibilities for the sections, to work among yourselves, to get the first draft to us and really work with everyone's comments. But, if we work with the e-mails, I think we will be just as productive as we would be with the website. I also can share, I'll get hard copies of anything that you need out to anybody. We can work with our Fed-X systems. Stephanie and I can work with e-mailing also. But, if we use that process, I think you'll find it will be productive.

DR. REIGART: This is a personal problem maybe. Our mail room doesn't work very well. And hard copies don't get to me and a lot of the stuff y'all Fed-Xed to me have gone and I never get them. So I need, I need an electronic version of everything.

DR. KENDALL: That's how we're operating.

DR. REIGART: And if it's going to be e-mail, that's fine. If it's going to be the website, that's fine. But I need an electronic version of everything.

DR. DORSEY: Along this line, you, everyone today, the SAB, I think Cathleen had sent the roster with the fax numbers and e-mail addresses, etc. Would you confirm that these are correct? A number of your e-mails have changed, we have had problems and if you're not receiving information, or there is a problem, I mean, we will try to do, where we can to get the

materials to you. But if you do have a correction, especially to your e-mail address, let Cathleen or myself know so we can get this corrected.

DR. KAHN: There's one other thing that I think we need to do this in an accurate way, which is a transcript. Last time, I think a big problem was the access to the transcript to so long. So, that's going to be, I think a big bottle-neck in the process unless we can do it quickly.

DR. DORSEY: Ok. We have the transcript with. We typically do not have transcripts of meetings. At the last meeting, after the fact, a transcript was generated, and we found out about it existed and we sent it to you. At this meeting we will have a transcript. As soon as it's ready, you will have it. And I hope that that will be available within a short period of time.

DR. KAHN: Three of four weeks?

Baskerville: 7 days.

DR. KENDALL: Seven days. Wonderful. Outstanding. You should proceed though from your notes and your recollection to write before the transcript.

DR. MCCONNELL: Don't read it too late at night, though.

DR. KENDALL: Dr. Gorovitz.

DR. GOROVITZ: There are two members of the committee that's not present. One expectedly, that's Art Kaplan, the other unexpectedly Marinelle Payton. What will their involvement be? Have they now fallen off the edge?

DR. UTELL: I talked with Dr. Payton this morning who was actually at the hotel and had to leave. And she clearly wants to be

involved in the process. It's hard to assign her to a working group. Dr. Kaplan more easily fits in to the ethics groups as it evolves. Frankly, he wasn't here to participate and I think what I would ask is that once the primary authors have developed their section, they ought to share it with them. In fact, they need to participate in the entire view because they're part of the committee.

MR. KENDALL: Mr. Dorsey wants to speak on this.

DR. DORSEY: And Mark, I agree with that. They are actually a part of this committee. Once we have a draft, all the materials will be sent to them for comment also.

DR. GOROVITZ: So the point is that the roster is incomplete in that Kaplan does not appear on this roster.

DR. DORSEY: He was a part of the original committee. He's still a part of this committee. He did not attend today's session, that's why he's not here. But he is part of the committee.

DR. GOROVITZ: But if somebody wishes to communicate by e-mail, you should bear in mind he needs to be added to this list.

DR. KENDALL: Can we get an electronic form including Kaplan and Payton out to everybody so they got a full address and full e-mail. Make sure Kaplan gets on there. Any further points from the committee. This has been an outstanding committee. Dr. Utell.

Dr. UTELL: No, Dr. Kendall I'm going to let you take the credit and the abuse. And it was a really a interesting day and we look forward to reconvening by e-mail and we'll share the work product. Actually, I hope that not everybody leaves. That was not the intent. But

to spend a few minutes outlining your writing responsibilities and dividing that up.

DR. KENDALL: And we have full confidence that by December 15th, we have the materials from you. We really need that to move forward. Other than that, any... Mr. Carley, you're the remnant of the EPA delegation. Any further comments you'd like to make, sir.

DR. CARLEY: I'm kind of exhausted too. And so I'll be extremely brief. Everyone else has already thanked you. I will thank you one more time. As happened last year, this has been a very stimulating, informative, and I think will prove a very helpful discussion. We look forward to your report and wish you the best of luck in reaching closure on same as early as possible.

DR. KENDALL: Thank you. Thank you, Mr. Carley. Members of the panel, it's been a pleasure to be with you again. Tremendous group of people. It's been our honor to work with you. And, Mr. Dorsey, Dr. Irene, Ms. Perceival, thank you. The SAP. We hope everybody feels at this point we can close. Do you have any further comments?

DR. DORSEY: Except to thank the panel and especially the chairs. Thank you very much.

DR. KENDALL: Well, this will close. Dr. Utell.

DR. UTELL: We're done.

Dr. KENDALL: It's been an honor to work with you, sir. And this will close the joint SAP/SAB meeting in the human testing of pesticides. Thank you very much.

End of transmission.....

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Transcipt of Joint Science Advisory Board (SAB) and Scientific Advisory Panel (SAP)

Open Meeting

Data From Testing on Human Subjects Subcommittee

November 30, 1999

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