MS. HALLORAN: This is following-up on Brandon's comments and the earlier comments. You are obviously working towards a risk assessment. What is happening, though, is you have got one endpoint message which is "Follow the dietary guidelines," and then this huge mass and growing mass of information which is coming out in literature, on the FDA website and so forth, without any interpretation by FDA, really, for the public because you are limiting yourself to this one endpoint of one sentence or two sentences of message to consumer.

So I was wondering if you had given any consideration to say a three-page status report which could be updated on a regular basis which would give the public the essentials of what you are looking into and the status of that work, you are looking into the levels in food, whether it causes problems in animals, whether you can extrapolate from animals to humans, what the human data is, sort of what we have gotten here today.

"Here is what we know. Here is what we

don't know. Because we don't know about how you extrapolate to humans, and we have got conflicting data on what happens in humans, we can't make a definitive discussion, but here is where we stand."

I think you could do that in a quick--I mean, it might be sort of difficult to arrive at consensus of all parties as to the exact wording of such a statement, but I was wondering if you had considered that possibility?

DR. ACHESON: That is a useful suggestion. Thank you. We will look into that.

DR. SCHERER: In fact, I guess building on what Jean is saying, it seems to me that that is exactly the issue because you are talking about an environment of transparency, of putting information out there and making it available and, at the same time, not wanting to overinterpret the data.

But the problem that I see is that the consumers are liable to overinterpret the data. I would rather you interpret the data than have a lot of the media and consumers interpret the data and not really understand what it is saying. I think

that is the real issue.

DR. DWYER: I was just concerned--this is already public domain, isn't it?

DR. ACHESON: What are you referring to?

DR. DWYER: This sheet that says, Exploratory Data on Acrylamide in Foods.

DR. ACHESON: Yes; I believe it is.

DR. DWYER: I am concerned that it doesn't have standard errors or anything on it. I guess they are fairly small, are they? Or are they? It gives a precision that, perhaps, is not warranted.

DR. ACHESON: You are talking about the analyses, themselves?

DR. DWYER: Correct. Again, they are small numbers, like 10 or 2 or 6. What is it?

DR. ACHESON: Dr. Troxell can address that, if that is okay with the Chair.

DR. TROXELL: The problem with the survey, the exploratory survey, is the within-lot or between-lot variability and the sampling kinds of problems. The analytical error is very small. Generally, those levels are at least two analyses

that are clustered very close together. So the analytical precision is quite good.

DR. DWYER: So, on this thing that says, Home Pride Butter Top Wheat Bread, that is a sample of two pieces of bread from two different supermarkets?

DR. TROXELL: No; it is a sample of one product and I think they probably use, like, 100 grams. I think they were using portion size for preparing the sample. So, yes; there can even be some within-sample variability. But, as far as the analysis goes of the analytical result, it is an accurate analytical result. There can be sample-preparation errors and there can be errors, of course, between one loaf of bread versus another which would be variations between loaves or lots and so on.

DR. MILLER: I don't think that they looked at a hundred different loaves, different brands of loaves of bread, to get the variation.

DR. DWYER: What I am after is whether Mayer's Butter Top Wheat Bread and the Home Pride

Butter Top Wheat Bread are really different. One is 52 and one is 96.

DR. TROXELL: We agree that there can be variations in one run versus another of a product as well as one day's production versus this next, maybe the beginning of the day's production versus the end and, clearly, between lots. We just simply don't have thousands of datapoints to explore those variations.

We have done some of that exploring of variation to show that there is a lot of variation by doing that small chip study we did on Lay's Potato Chips. We saw--I will go into this now. I was going to mention this later--that we saw some clustering when we looked at a particular bag lot from a particular production.

But even from one day-code to the next, we could see some very distinct shifts in the levels. Those potato chips were produced on the same line in the same plant from potatoes harvested from the same farm, from the same cultivar but the potatoes may have been stored an extra week or whatever.

So, again, that gets to this issue that Dr. Zyzak was talking about, the variation in the glucose levels could vary depending on storage conditions and so on.

So these levels were extremely sensitive to conditions. And, yes, we have tried to reflect in our disclaimer in the beginning of the exploratory survey, how these levels can vary between lots and so on. We certainly haven't explored the full distribution on these products.

DR. TORRES: I think my question has been answered. Basically, you have convinced me that you have very good analytical methods but, also, you have convinced me that we have a lot of variability between batches and samples. So, when I look at these tables now, they don't tell me anything. I get more lost than helped by having more products listed.

Unless I really know what is the variability for a given product, I really can't make any sense out of it.

DR. LEE: Somewhat of a follow up for

Terry or anyone. Is FDA getting any feedback from industry on the analyses that are being published on the web? Are the numbers being generated by the private sector consistent, too high, too low, relative to the FDA or is it too early to tell that.

DR. ACHESON: I don't know whether Dr. Troxell wants to address that, but my understanding is that essentially the numbers we are generating are pretty much matching up with what others have found. We are not finding anything exceptional. I think that is probably an international story, too.

DR. MILLER: It just seems to me that we ought not to make too much of the specificity of these numbers. They give you an order of magnitude. That is, I think, just what you need. You know that there are certain products that have higher concentrations of acrylamide than other kinds of products and that there can be variation within that but it is certainly going to produce greater exposure than some other products that are much lower. So that ought to be looked at.

DR. LEE: Actually, where I was going with that question is is there any reaction to these numbers? Are they being used for any purpose other than saying, "Oh; this is interesting. We need to study this further." Is there anyone actually proposing to do something on the basis of high content or low content?

DR. ACHESON: I can't speak specifically to what is industry's reaction to those numbers. I am not privy to those internal discussions. But, clearly, industry are taking this serious, hence the presentations that we had yesterday where they are looking at the science behind formation and potential mitigation strategies.

So, yes; I think people are reacting to numbers, both ones that we have generated, ones that they have generated and other countries have generated.

DR. LEE: What about states like California? Are they going to label products on the basis of these numbers?

DR. ACHESON: I have no idea.

DR. MILLER: But, Ken, California, the presence of a genetic carcinogen alone in any concentration is sufficient to have a label.

DR. LEE: That's right. What numbers are they going to use?

DR. MILLER: They don't have to have any numbers. It is a genetic carcinogen. Therefore, at any level, it is unsafe.

DR. LEE: So what you are saying is the difference between 0 and 1.

DR. MILLER: The difference between 0 and 1; yes.

DR. LEE: Whose 1 and whose 0 are we using?

DR. MILLER: That is up to the--I don't know what they are going to use.

Terry, do you want to comment?

DR. TROXELL: I believe what you are referring to, Dr. Lee, is California's Prop 65 where they have a specific law relating to carcinogens known to the Governor, reproductive toxicants known to the Governor. It is my

understanding that the trigger level there would be 0.2 micrograms exposure.

If they move forward with that level, then there would be, as far as that probably comes out in a consumer portion from a package. I think, from the portion sizes that we have given you yesterday, you can see that there would be a large number of foods which would require some kind of labeling. But that is a law specific to California, specific to Prop 65. The FDA and the federal government do not have any relationship to that.

DR. MILLER: Where did they get the 0.2 micrograms? Is that the limits of detection?

DR. TROXELL: No; that is based on a risk assessment, I believe, that they use. I think they use $10^{-6}$ risk. No? $10^{-5}$ risk. I am being corrected. They use $10^{-5}$ risk and they derive 0.2 micrograms from a portion of food from a particular product. Therefore, with respect to your point, though, if a particular lot would rise to that level, I suppose they would have to label that lot.

MR. SCHOLZ: I just have one quick question back to the exploratory data and the discussion of how many samples. Have you considered, or would you consider, reporting on here the number of samples that you used to make the test?

DR. ACHESON: Yes; we could certainly look into that. I think it is important to emphasize that this is ongoing. This gets added to every week. It is current data. It is up to date, but--

MR. SCHOLZ: I understand that.

DR. ACHESON: You are asking what is the n value on any particular--

MR. SCHOLZ: Yes.

DR. MILLER: Unless there are any other burning issues, we have gotten into part of our discussion already. We will come back to this.

Thank you.

Finally, Terry Troxell is going to summarize the charge and the questions.

**Summary, Charge and Questions**

DR. TROXELL: I am not going to go into

detail because that would be reinventing everything we have just done. What we tried to do was cover the events that led to the development of our action plan and the events in the intervening five minutes that we have used in revising the action plan including the subcommittee meeting and the recommendations therefrom.

Then I summarized the action plan and you have detailed copies there.

Then we provided a series of presentations to provide the current status of the work to assist the committee in commenting on the action plan. Those, of course, included the mechanism of formation, reduction strategies, our exposure assessment, adduct levels, the animal to human extrapolation, tox studies and the implications.

What we didn't do at this meeting, and, actually, we covered this in more depth at the subcommittee meetings, we did not go in depth into the analytical method. We have a solid method at this point and we are encouraging development of other methods and also proficiency examples need to

be used among everybody so the results are accurate.

The other thing we didn't do is we didn't go over the data and talk about this within-lot variability and show some of the relationships and so on. I just mentioned a point I was going to bring up, how some subtle differences c can lead to distinct within-lot variations.

But the other thing, of course, was that the data was limited. In some categories, that seemed to contribute to the exposures, like we have only seven datapoints on cookies at this point and we had very few datapoints on toast. Of course, how was that toasted? How does that represent consumers' practices.

So there are those limitations. But, nevertheless, our exposure assessment did come in within the range. But the total population exposure assessment probably won't change all that much even though we get much richer data. It is going to be those individual components that contribute to the exposure. They are going to move

around some.

So, anyway, we have provided you a pretty good snapshot, we hope, on which to base your discussions of the action plan and give us the input.

So, then, I want to turn to the charge, again, and that is we are asking the committee to evaluate the revised action plan as tool for providing the scientific basis from which to assess the significance of acrylamide in foods and the potential public-health consequences.

The first question is; does the revised action plan meet its intended goal of serving as a tool for this purpose. The next question is; the new data on acrylamide levels, exposure and potential interventions have become available in recent months. Does the action plan accommodate these new data? Please comment on the new data including exposure assessment of potential interventions.

The last question; does FDA's consumer message stresses the importance of eating a

balanced diet. Given the uncertainties associated with the current state of scientific knowledge, FDA has concluded that there is not sufficient data to revise this message. Please comment.

So I think, hopefully, we are at the point where you can move into your discussion.

Thank you.

DR. MILLER: Terry, before you go, could you clarify in the second question, the last sentence, "Please comment on the new data including exposure assessment of potential interventions." What, exactly, do you want this committee to do in that regard?

DR. TROXELL: You have heard new information that hasn't been presented before the exposure assessment, some of the intervention work. Certainly, there is this Mucci study on epidemiology. We are looking for any comments the committee may have relating to that and then, of course, how that might relate to further work on the action plan. So we are giving the committee a chance to comment on this new information.

DR. MILLER: I am not sure the committee can comment on that. We have already had some extensive discussion already concerning the exposure, the question of numbers and variation and so on.

Are there any questions for Dr. Troxell before we begin our discussions?

Thank you.

**Public Comment**

DR. MILLER: Since no one has registered for public comment, we are going to move right on, then, to the discussion of the questions.

**Discussion and Committee Recommendations**

DR. MILLER: I would propose, if you would all agree, that, in order to get the discussion going on the first question, that we ought to begin by--I think we ought to compliment the agency and the subcommittee that worked with the agency on the action plan for what I think is a very comprehensive document.

If anyone disagrees with that, let's comment on that now. Then we can go on to any

recommendations we want to make concerning further modification of the thing.

Are there any objections to making that part of the record? Okay.

DR. BUSTA: May I add to that? I think that, being the chair of the subcommittee, I was impressed at the responsiveness to the recommendations of the subcommittee and the integration of those recommendations into the revised plan. I think the parallel nature of the plan, multiple research activities going on simultaneously, is a very positive approach to an unknown situation so that you are not required to wait for one system to complete before you move on to the next one.

DR. MILLER: Any further comments? There were several issues that came up during our discussion, meaning from generic, general types of things to specific recommendations that we really ought to determine whether we want to include as part of our recommendations to the agency.

It seems to me one of the most important

procedural issues in this whole process is the need for coordination and integration of the data. There are increasing numbers of laboratories that are getting involved in this activity. Clearly, what is needed is integration of a lot of data. Dr. Schwartz, this morning, indicated the complexity of the physiologically based pharmacodynamic model.

That data comes from a lot of different points and a lot of places. I think that that portion of the action plan that talks about how this is going to be coordinated, should be more specific and recommendations should be made about who is going to be responsible for coordinating the activities and so on.

It is really a vital issue because this is an extremely complex subject. I think that this is one of the more difficult ones that FDA has dealt with. It is not a simple matter and there is obviously difference in metabolism among species and the kinetics are different among species.

There ought to be some attempt made to

have some uniformity in doses and so on and there needs to be these coordinating mechanisms which are not really spelled out very well or in much detail, I should say, in the action plan.

Does anybody want to comment on that?

DR. RUSSELL: I would just say another area where that coordination needs to be spelled out is in the food-matrix issue because if everybody starts using different food matrices, we are going to come up with very different results, both kinetic and dynamic and end results, biomarkers or tumors, for example.

DR. MILLER: I think that is a good example of what needs to be done.

Let me remind the members of committee, under the rules of the Chairman, unless you specifically say so, you will be recorded as agreeing. I discovered that is a much better way of doing it than trying to get everybody to say yes or no. It saves time.

DR. DICKINSON: I would like to add just one more example of another area that needs to be

coordinated that Johanna mentioned several yesterday, several other agencies that are looking at food composition; for example, the USDA, obviously, has a very large food-composition database group that I don't think specifically got mentioned yesterday and should have some information to contribute.

DR. MILLER: Do we know if USDA is doing acrylamide and glycidamide? Terry do you know that analysis?

DR. TROXELL: They certainly are fully aware of the problem and, as far as I know, they are not looking at it. There is some data on the products they regulate and pretty much they are either nondetects or extremely low levels.

DR. MILLER: It would seem to me that, given the nature of the potential public-health hazard associated with this material, or these materials is a better way to say it, that it seems to me that everybody who has capability ought to be involved to one extent or another.

So that is a recommendation.

DR. DWYER: Sandy, just going a little further, I think what you expressed was the need for coordination and integration of the data especially for developing models but also for other purposes. It seems to me that the action plan needs to designated who--that is, which agency within the government will take the lead or will be given the lead to coordinate.

These steps need to be spelled out, it seems to me, not only with respect to the plan but the time frame and not only for reporting and keeping everyone within government marching to the same drummer but also Ms. Halloran pointed out some kind of updating on a periodic basis of the consumer's needs to be thought of.

This, it seems to me, requires action at the highest levels of the agency; that is, at the Commissioner level or perhaps, even, the Secretary level within the department because it is going to involve collaboration between different cabinet-level agencies.

DR. MILLER: Right. We will come back to

that last point about the consumer issue. There is another issue concerning funding which I want to raise to the committee's consideration after we get through some of this.

DR. MEHENDALE: I think we discussed yesterday that one area that was not addressed sufficiently is the coverage of stressed populations.

DR. MILLER: That is what I was going to bring up next.

DR. MEHENDALE: Okay. If I may just go on, one other point is we also had some discussion on perhaps trying to set a workable timetable to identify the low dose versus the high dose, in fact, so that what we learn from those things may have global impact on many other studies. So that might be quite desirable to do that.

DR. MILLER: This stress issue is important, and there are multiple stresses that could be look at, but it seems to me that is one of the things that ought to be coordinated, again, is which stress population you may look at. As a

model, if you are looking for a model, you may want to use nutritional stress. If you look at the human population, you may want to use any stress that could conceivably cause entry inoculative enzyme.

Another issue which is implied, I think, in the action plan but isn't discussed and I think is extremely important, given the potential difference in metabolism at different dose levels, is dose selection. I would really suggest that the action plan have an explicit process for selecting the doses and that this also be coordinated.

If there are no comments about that, another issue was neurotoxicology. I think we have opportunity to read with some great concentration the action plan in the sense that I don't think that that was emphasized to any great extent in the action plan, unless I missed something.

It seems to me it is one of the issues that keeps coming up. The reason I think it is important to be mentioned is, again, this issue of coordination and integration and the utilization of

resources. This is an expensive activity. If neurotoxicology is not going to be considered, and there is a potential toxicological endpoint, then that ought to be specified and explained. But it certainly ought to be discussed in the action plan, which has come up several times in our discussion.

DR. TORRES: I was a little bit convinced that the neurotoxicity for food exposure was not such a hot issue. Given the always financial constraints, I feel comfortable with having it not so much emphasized in the action plan.

DR. MILLER: I agree. I am not arguing that point. What I am saying, though, is that, given the fact that it has come up several times means it is being considered. I think that if the FDA is not going to look at it as an important component of the acrylamide story, they ought to specify in the action plan why they didn't.

DR. MILLER: When we are talking about stressed populations, I also wanted, again, to emphasize age as a variable in this thing, is there a difference between infants and children and the

elderly population. The older I get, I become much more interested in this. So I think age needs to be emphasized as one of the variables in the studies.

DR. TORRES: Along the same lines, I don't know if we have information about the consumption patterns of different ethnic groups, if that will affect, in terms of the estimation of how much they are consuming of acrylamide.

DR. MILLER: That is actually an interesting question because it is not only ethnic groups but also geographic location, cultural patterns. I don't think that is something that could be done right away, but something for long-term consideration.

Also, again, we talk about stress, we can talk about nutritional stress, caloric limitations and so on. That may be an important consideration.

DR. BUSTA: Is Dr. Robie here? How easily can you adjust your system to take into consideration different populations and different groups in different areas and different regions?

It seemed like, listening to you, that wouldn't be very difficult.

DR. ROBIE: To do that, the data are available. The CSFII survey data indicate ethnic group, socioeconomic group, things like that. The way that we have the data right now is in the database that allows us very easily to do the age. So when we do the two years and older population, two to five, we could do teen-age boys or lactating mothers, women of child-bearing age, things like that.

It is not trivial to do ethnic group or geographical location, but it can be done. It wouldn't be as easy as just changing the age group, is what I am trying to say, with the database as we have it. We would have to go to the raw data, and do it. But it could be done.

DR. MILLER: My own feeling is that is something that needs to be done but not, certainly, one of the highest priorities. It seems to me that you first need to have a better idea of what the risks are and then, from that, you can determine

whether what you are looking at is of significance or not.

Terry, can I ask you a question? Has any thought been given to how these models are going to be developed when all the data is collected? Is this going to be left to chance that somebody is going to sit down and write a paper by collecting all the models so that you have a PBPK that comes out of it? Has thought been given to that?

DR. TROXELL: I think Dr. Canady has to comment on the PBPK. Certainly, we have Dr. Bolger's group and Dr. Carrington, are kind of leaders in quantitative risk-assessment approaches so they can build the quantitative risk assessment model. But I don't know about the actual plans for the PBPK.

By the way, while I am here, it did slip my mind that--you asked a question earlier about USDA and I mentioned FSIS. But we have involvement from other components of USDA, ARS, Dr. Lahote has been in methods. We have been getting ARS involved and actually Rick also reminded me that FSIS was at

our interagency meeting and participated.

So we really have tried to go out to a wide range of groups to bring to bear as great a power of energy as we could.

DR. CANADY: Our thinking with regard to using toxicokinetic information was to use the available information including physiologically based pharmacokinetic modeling to inform dose selection, species-to-species extrapolation within the NTP-NCTR studies. The thought to use a specific human PBPK model is something that we need to consider in more detail based, in part, on the recommendations we have heard so far and that is something we need to take forward.

But, again, the thought was to use the PBPK models that were in existence to help inform dose selection. The ones that are in existence are animal-based models, rat models, essentially.

Does that answer your question?

DR. MILLER: Yes. You propose to do this all in-house?

DR. CANADY: The idea to develop a human

PBPK model is something that we are just hearing from the committee as a recommendation. It is not something we had decided to undertake prior to this meeting. We were considering using animal PBPK models to help inform dose selection and low-dose extrapolation and species-to-species extrapolation, to use the full dataset.

DR. MILLER: You would have to do a human PBPK to do that. You would have to do a human model to do that, to look at species difference including, I assume, humans.

DR. CANADY: Right. You can use the animal-based models to include more previous studies in your evaluation of the overall dose response. But then you are right. Extrapolating to humans, obviously, you do need to do some sort of modeling, whether it is PBPK or allometric, as Dr. Schwartz was talking about earlier, is a decision that needs to be made.

What I am hearing is that the recommendation to use a full model, a human model, is--

DR. MILLER: Right. You already know that you have a material that has species differences in so many different areas, it would seem to me worthwhile.

Let me make just one more comment about funding. This is clearly an expensive activity. It isn't clear to me where all the funding is going to be taking place. The industry is doing a substantial amount of work and some of the other federal agencies are proposing, or are considering--I think the report says, the action plan says, they are considering.

It seems to me the agency has to look for a designated source of funds in order to pay for much of this research. Also, it is noticeable that there is not a lot of academic activity going on in this area. If we look at the people who are doing the work, at least here in the United States, it's either industry or federal agencies and so on.

I would suggest that it might be worthwhile for the Commissioner and the NIH Director to get together and develop an extramural

program that could be funded. NIH ought to get involved. This is a public-health matter of some importance and it seems to me that this committee ought to recommend that kind of interaction to look for funds that could underwrite these very expensive and very important modeling studies that we have been talking about.

Let's move on. If some thought comes to your mind, we will have an opportunity, when we finish, to go around and if anybody has anything additional to add.

DR. LEE: Just to clarify your last comment, Sandy, about academic activity. Are you thinking primarily on the toxicological and pharmacokinetic side? What about the formation prevention? Is that something you were thinking about?

DR. MILLER: That is not usually something that is in the NIH mandate. It seems to me that is something that USDA--there is an area that I think either USDA or RAS could play an important role in which they do fund studies of this kind.

DR. DWYER: What kinds of studies?

DR. MILLER: Formation and intervention studies. Basically, we are talking about processing modifications.

DR. LEE: Right; and, for that matter, recurrence.

DR. MILLER: The dietary composition studies that USDA does, acrylamide and developing methods for acrylamide, would be appropriate.

DR. LEE: But I think you are quite correct in that a coordinated approach towards funding the essential elements of this plan is--

DR. MILLER: Right.

DR. DWYER: That would probably also include CSRAS, not just ARS which is mostly intramural.

DR. MILLER: Okay, good. Let's move on to the second question about whether or not the action plan accommodates the new data on exposure and possible interventions and so on. Does anybody have any comment to make about that as far as the action plan? We are focusing on the action plan.

DR. BUSTA: This is Frank Busta. I thought that, in a number of places in the action plan, there were statements about building on the data, working with the data. I took it for granted when I said that the parallel approaches were appropriate, but, to me, that would be very important is to build in data from one area while you are investigating another area simultaneously, whether it is formation or methodology or toxicology. That interchange really needs to be constantly exchanged. That was also covered in your coordination.

DR. MILLER: I think another way of putting the question, and I think what you are are saying it does, is that the program is sufficiently flexible to make changes as the data change. As I read it, it seems to me that it is. Would you all agree?

[Agreement.]

DR. DWYER: I wondered--it seems to me, and maybe I am reading the wrong part of the action plan--I think it is Page 2 and onward--if it could

specify a little more precisely. What I am concerned about is is there a "there" there? In other words, are these effects--can we somehow specify, or encourage by whatever means, whether it is extramural activities of other agencies or whatever, that a number of different epidemiology studies be done to base, or to put all the eggs in the basket of one study that was done in Europe, so far, seems unwise, and to base everything on just one cohort study when there are many, many around, would seem to be unwise, too.

So it seems to me we need a lot of different studies of that and that we should specify them.

DR. MILLER: I am not sure exactly what you are--because, I thought that they did mention--they have a whole section on epidemiology and they talk about--

DR. DWYER: Maybe I have got the wrong page. The pages are not numbered. What page would you say?

DR. MILLER: I would strongly advise that,

in the future--I am talking to the staff, now--that, in the future, when documents are given to the committees, the pages ought to be numbered.

DR. BUSTA: It is the fifth action item.

DR. MILLER: There is a whole section on epidemiology. Do you see it?

DR. DWYER: Yes. I am not sure it is as detailed as it needs to be.

DR. MILLER: Down in the second bullet, it talks about monitor large numbers of individuals, et cetera. They are asking that.

Dr. Torres?

DR. TORRES: One area that I find that is too little in the report is research on formation. Since we see so much variability in the products that we are measuring, I think we are relying a lot on the industry research and not enough on public research, and even the size.

DR. MILLER: That is what we were talking about before with USDA. That is the kind of research they fund. And they do. I think that our recommendation is that they be brought in this

consortium, if you will, with the specific mandate of operating, trying to look for methods of mitigation and also exposure, and calculating the concentration.

DR. TORRES: Before, we were talking about the integration question but here I am talking about what should be targeted, that there should be more emphasis on formation than what we see.

DR. MILLER: Right; that is what we were talking about before. We have got to make sure we make a note of that.

What did you specifically want, Johanna? What did you specifically want in terms of the epidemiology? What ares you suggesting?

DR. DWYER: Specifically, the Framingham studies, the Women's Health Initiative, any other large-scale studies that are funded by the federal government, not just one or two but they should all be looked at. I realize this is a huge task, but there are a lot of big studies that the NIH and other groups in the federal government have large investments in already. There us one in Hawaii,

too. I don't know if that is useful, if you are talking about stress groups, Dr. Kolonel's study.

DR. LEE: I hate to jump around like this, but going back to what Dr. Torres' comments were about the database and developing information on formation and occurrence, there are really four sources of that information. There is what we are talking about with USDA or otherwise federally funded HIH, NSF, wherever you can get that done. There is the academic world which, of course, could be funded by that way.

We are talking about the international community which is feeding into the JIFSAN and the WHO websites. We are also talking about the private industry that has, of course, a vested interest in monitoring these levels.

So, just for the sake of completeness, we need to recognize that industry is going to develop a fair-sized database on acrylamide formation, content and prevention. To the extent possible, FDA needs to make it possible for that industry to share those data without jeopardizing their own

brand. Maybe a third-party intervention can occur so that, if a manufacturer discovers a very high level of acrylamide, that does get published to the website with the brand name on it and they can enhance the scientific advance by having that cooperative arrangement.

DR. MILLER: Perhaps we ought to say that we need to develop a method that encourages the sharing of data from both the public and the private sector.

DR. LEE: Yes; that would help.

DR. MILLER: Because it is not only the concentration and exposure but it is also methods of communication. What I was thinking was that we need to mobilize the academic community and that depends on grants and so on in order to expand the population of researchers that can come up with new ideas about how to deal with this issue, because the companies, correctly so, concentrate on their own products. We need to have it somewhere else where maybe broader approaches to the problem can be reached.

DR. TORRES: I think, also, we should come up with some recommendation also on the structure of the data. Having just a number, without having the number of samples, what temperature was the process, a little more specificity. Otherwise, it is really difficult to make any conclusion about what does the number tell me.

DR. MILLER: You anticipate, again. In the second question, there is a comment about the new data, including exposure assessment and potential interventions. I think the committee would generally agree that we need to continue collecting more information on exposure, increasing sample sizes and the distribution samples and so on and so forth. That is a vital part of the ultimate risk assessment that is going to determine that.

So that needs to continue. There needs to be some agreement on how this data is reported and what part of the data is concerned. It is very important, as we pointed out, that we know what the source of variation is in this data. Is it lot-to-lot? Is it day-to-day in the processing?

Is it the age of the oil in the frying? Whatever it is.

The data that were collected now in the rush for everybody simply to collect more data to determine what the actual exposure is, there has been a tendency to do a lot of samples of small lot size rather than concentrating on doing a more detailed analysis in a particular lot to get some idea what the variation is in things like lots, and so on.

DR. DWYER: What I am terribly concerned about is that we don't get off on something like--remember, back in the '80's the business of coffee? Do you remember that, Dr. Miller? Caffeine and the business of the rats that had the intraperitoneal infusions and how everybody was talking about not drinking more than a couple of cups of coffee a day.

DR. MILLER: We were talking about it before, with caffeine and spinal birth defects. They weren't infused. They were actually fed it. But the issue there is the same issue that we are

dealing with here is that caffeine is metabolized differently in people than it is rats and in dogs and so on.

The result was that the results that were observed in rats simply didn't apply to people because the active component was not produced in humans. It was only produced in rats. I think that was the point why the toxicology and the multispecies analysis of the data, or the ultimate component of the design of the experiments is so important because we already know that there are species differences in metabolism and kinetics in this material.

I think that is what we have talked about when we talked about Question 1. I think the action plan needs to reflect the importance of doing the multispecies thing. It talks about it, but it doesn't emphasize the importance of it.

DR. BUSTA: Could I ask a question. Is it implicit when we are looking at new data that, somewhere along the line, if we decide--is there a way of deciding that it is not a problem and that

we stop or, because we have got an action plan, do we keep looking and looking and looking because we have got all this stuff to do?

DR. MILLER: I think there is another way of putting that. That is a policy decision and it is an issue that I think that is not part of the mandate of the committee to discuss. But, nevertheless, I think there is another way of putting it, that the action plan needs to have built into it periodic reviews. It has got to be reviewed periodically.

I would suggest that it needs to be reviewed at least by the subcommittee of this Food Advisory Committee on a regular basis.

DR. BUSTA: Trying to prove something is not is very difficult.

DR. MILLER: That is in the negative, and that is not possible. But I would strongly advise that the action plan, itself, have built into it these periodic reassessments by an outside group and I think that the subcommittee of the Food Advisory Committee could serve that role. That is

a good point.

Are there any comments concerning the potential interventions? I am not sure exactly whether we are competent to determine whether or not the work that is going on looking at dimensions is sufficient, but I think that, until the committee comes up with something, it is never sufficient. It looks like what is available now is not reasonable or feasible to be implemented.

Are there any other comments on Question 2? We can come back to this later. Let me propose that we break for lunch and be back in an hour, and then we will try to finish up. That means you should be back at 1 o'clock.

[Whereupon, at 12:00 p.m., the proceedings were recessed to be resumed at 1:00 p.m.]

A F T E R N O O N  P R O C E E D I N G S

[1:00 p.m.]

**Committee Recommendations**

DR. MILLER: Let's reconvene and move on to the last question concerning the consumer message. The question has been asked for comment is, given the uncertainty of the scientific database, FDA is not, for the moment, going to change its recommendation to people to continue eating a balanced diet.

I think there, in listening to discussions, we had a good part of this discussion already. It isn't clear what a balanced diet really is, although, in the draft action plan, it defines a balanced diet as a variety of foods that are low in transfat and saturated fat and rich in high fiber, grains, fruits and vegetables, which is better than just saying a balanced diet.

But the question is what else can FDA do that we could recommend as part of the action plan that would develop into a more useful consumer message. Jean Halloran recommended that the agency

publish a two- or three-page interpretive paper for consumers that explains the difficulties of looking into this explaining what the problems are, the lack of scientific data and what needs to be done.

Jean pointed out that FDA has published in the FDA consumer magazine an article on acrylamide which we have distributed to everybody. The question is is this the kind of thing we are talking about or are there further things that could be done that would be useful for this.

MS. HALLORAN: I think the FDA consumer piece is very good and a very good start. But I would recommend creating something that is a little bit more formal in its format that explains what the agency is doing, that it has got an effort to put together a risk assessment in progress and that it is investigating the various things that you need to know in order to know whether there is a risk here, that might summarize the status of what it has found out and what is known that is relevant to that.

A lot of it would be the same as what is

in here. It would be just, I think, a slightly different approach. I think what is interesting about this is that it shows that, in a couple of pages, you can really present the gist of the issues and the material and the state of uncertainty and what you know and what you don't know in consumer-friendly language, pretty concisely.

So I think that is what is good about what is a model here. I would especially hope that FDA could create something that could be updated on, perhaps, a monthly or quarterly basis as new information emerges. I think that addresses the point you brought up of what happens when new studies are published, how are they put in the context of the whole and not just interpreted as one datapoint that could set people off in the wrong direction.

DR. MILLER: I think maybe we could put it this way; FDA should explore the possibility of developing a document for the website. Let me put it this way; if FDA is going to publish data that

it collects in terms of exposure and toxicology and so on, it ought to also publish some kind of interpretive document so people understand the strengths and weaknesses of the data.

That ought to go on the website the same way.

MS. HALLORAN: And put it in the context of current risk-assessment efforts and framework.

DR. MILLER: You are talking about something aimed specifically for consumers.

MS. HALLORAN: Yes.

DR. MILLER: So that they understand what they can use the data for and what they can't use it for.

MS. HALLORAN: Exactly.

DR. MILLER: Cliff?

MR. SCHERER: Just to add to that thought, it seems to me that it needs to be also targeted to organizations that are on the firing line of consumers answering these kinds of questions. They need to be notified and included in the process because there are sensitive health people out there

that react to any kind of information coming out.

I had a couple of other thoughts.

DR. MILLER: Please.

DR. SCHERER: As I look at the plan, it seems to me that there are a number of elements that I think are very positive. I really like the idea of transparency. I think the organization is to be congratulated on that. But, as we indicated earlier, that also brings up some problems that need to be addressed.

I think the plan, as it is there, is a sound start but it is simply incomplete, as Jean has pointed out. It is on target in the sense that I think the message can't be changed. It is right to say maintain good health, diet and so forth. But the part that is really missing is this idea of helping consumers interpret what is happening at the agency.

You don't want to cry wolf because credibility, in the long run, can be damaged seriously and then the effectiveness of being able to communicate with consumers is hurt. At the same

time, with all of the wolf-hunting activity going on, you have to explain what that is. I think that is the real essence of one of my concerns.

The idea that you just brought up, the idea that, in fact, studies are going to be coming out that some of them are likely to show that there may be a problem. There needs to be a mechanism in place in terms of thinking through a strategy, how are we going to begin addressing those. Do we have things in place that we know how to get out to other organizations to the extension service, to diet groups and so forth, that, if something happens and the media pick it up, you need things in place to be able to quickly get information out to those groups so they can address the concerns of the consumer.

It seems to me that the other issue that you need to think about in terms of the plan is that a lot of research activity is taking place. This is an incredibly complex message, even now, and it has the potential of getting more complex as more data comes in.

It seems to me that we know a lot about risk communication and how to tailor messages, how consumers react to messages, in a variety of contexts but it may very well be that some small amount of resources need to be devoted to trying to study this particular issue and help design a strategy based on the best research that we have. That may involve expanding some of the ideas of focus groups, for example, to find out how people are going to react to these kinds of messages, just to have the plan in place in the long run but to be sure that it is based on the best research that we have in terms of social science and risk communication because that is a critical part of what you are doing.

Then it seems to me that there is an area that needs to be incorporated in the plan and that is addressing, what shall I say, some of the off-the-wall concerns that may arise as a result of this. I am aware, for example, of a blizzard of e-mails attributing--you know, truth doesn't matter. It is perception that matters ...

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blizzard of e-mails coming from one segment of a discussion going on attributing to acrylamides in food to pesticide residues.

It seems to me that that is an example of a case that, whether it is true or not, there needs to be some way of trying to address that issue. Again, I would point out, the truth doesn't matter. We still have to try to address the concerns because it may very well be that, if that concern would continue to grow and the media pick it up, that could become the focus or the framing of the entire issue.

I don't think we want that to happen in the long run. You want it to stay on the science and what the science is saying, but you need to address that.

The other part, and I guess my last thought is that, in looking at past media coverage of the acrylamide issue, it is very apparent that, worldwide, there was a lot of media coverage in the international newspapers following the Swedish announcement and so forth.

U.S. coverage is just little blips. That is understandable because the media are focused on terrorism, the war. Eventually, that will go away and they will be looking for--they will get tired of it. Whether it goes away, they will get tired of it. So the pattern of the media will be that they will start looking for other kinds of things to cover.

If studies come out on this particular issue that shows there might be a risk, there could be, in fact, a blow-up of misinterpretation of the data. Again, I am simply emphasizing that there needs to be a strategy in place long-term that tries to address some of these things so that you have information essentially ready to go based on what happens in the media.

You simply don't want it to get out of control.

DR. MILLER: Let me see if I got your points. One is that part of the action plan should incorporate research in how to deliver a complex message on a complex subject.

DR. SCHERER: And consumer understanding; right.

DR. MILLER: Consumer understanding. That is what we are talking about. Secondly, the action plan should also cover the possibility of developing a strategy of how to deal with consumer concerns, true or not, and, similarly, use that kind of information to develop a strategy of providing appropriate fact-based responses to the press and to the media as their concerns arise, or different strategies to then use for the consumer.

Did I miss something? I think there was anotner one.

DR. SCHERER: Preparation of release of studies as research becomes available, preparing for how to address that in the media.

DR. MILLER: That is an issue that is important that the agency continually update these materials. It has got to be uniform. You can't wait too long because, as the data becomes available, the modification of whatever material the agency is providing has to be simultaneous.

DR. SCHERER: I think it was brought up from a research point of view, it is almost a question of what is the trigger point, what will we need to know before you start really expressing concern that this is a human health risk. What if one study comes in next week that addresses certain issues? Does that raise the concern level of the research and scientific community and what is, then, the message that needs to go out to the media?

I don't see it as an and/or. It is stages. How do we begin addressing that without crying wolf prematurely, because we can only cry wolf so many times. Already, I think you reported that the media, this morning, were interviewing people and they were saying, "Ah; I don't pay any attention to that anyway."

DR. MILLER: That's right. Any comments? Any more comments on this issue of consumer messages and so on?

DR. DWYER: Just to reiterate. I think what Cliff and Jean have already said so very well,

the point that I think you both raised a little on the various professional consumer-related organizations. I don't think I have heard too much on this in the professional meetings I go to. This is a chance, I think, for the fine scientists within the agency to show their stuff.

There us nobody better than some of the scientists we have heard today talking about the models and about the human assessments that they are doing in terms of possible exposures keeping it rather simple, I would hope. But I think that is an important part of the plan, too. This is an issue where the agency has excellent people. You need to be sent around, more than five of them at the same time, to meetings. Perhaps this needs to be incorporated directly into the action plan. Keeping the FDA people here in Washington is not helping the agency's face out in the field.

DR. SCHERER: Just as follow on, I don't want to get into picky language, but the plan says, "will consider recruiting." I would hope that that would be changed to, "will

and seek the aid of home-economics organizations, diet and nutrition and extension services," because I think those are very important organizations to multiply the message that FDA has.

DR. BUSTA: I think we earlier mentioned the expansion of that group beyond what was listed.

DR. MILLER: Consumer organizations, without mentioning anybody by name.

DR. BUSTA: But the Institute of Food Technologists.

DR. MILLER: Just to reiterate, I think one of the important issues of the action plan is that there is substantial research also required in this area. This is not just applying some kind of formula approach to the problem and delivering a consumer message but just as research in toxicology or in chemistry or whatever is necessary, research on how to deliver this complex message is equally important and should be provided for. Whether it is being done in the agency or being done outside the agency, you need to know how to deal with this.

DR. DWYER: Just one additional suggestion

that might be considered in the action plan. I think it says it but it doesn't really say it explicitly that the Cooperative Extension Program is quite good at doing this. It is a nice example of two cabinet-level departments working together. Maybe there are some opportunities for that that should be specifically explored.

DR. MILLER: Let me just ask one more time if anybody has any comments they want to make, recommendations concerning modification of the action plan in any area.

MS. HALLORAN: I am not sure exactly where this falls, but I want to come back to the point that Annette made earlier that it does seem like not all foods are equally risky in this area. While FDA is not ready to give specific advice, still, if people are thinking about reducing their risk in advance of FDA's having a decision, there are some things that are more worrisome than others.

I don't know whether that can be incorporated in the consumer message, but I think

that would be useful if it were.

DR. MILLER: Comments?

DR. DICKINSON: I noted, when we came back from lunch, we had this FDA consumer piece. It does highlight certain foods that are high in carbohydrates and mentions that cooking at high temperatures is related, so at least that is a step in that direction.

DR. MILLER: Any other comments? The process from here on out remains as it has in the past. The staff will produce a summary of the meeting and outline the recommendations that have been made by this group, recommendations to the agency.

We will distribute this to the members of the committee. It will also be published on the website. You are apt to get it quicker from the website. Nothing personal. As I said, unless you have some really specific problems with the document, we will take it that you have endorsed the report with having actually do it. We just did it and will make it part of the record, unless you

have a specific comment that you need to have.

DR. DWYER: Dr. Miller, I don't check that website often, if ever. Therefore, I don't know if things are up there. I wondered if there is a blanket e-mail that you could send out when you post it to the website. You have my e-mail address.

DR. MILLER: One thing Cathy has is more information on us than we would like for her to have. She will track us down no matter where.

If that is all, unless someone has something to add, we have completed our work. Let me thank you all for your attention and your hard work on this. It is an important area and certainly one of the more complex public-health questions that I think the agency has faced. I hope and I believe we have made some important contributions to this.

I also want to thank the FDA staff people and others who have contributed to this meeting. This is the most important part of these meetings, briefing the committee.

Terry, do you want to make a comment?

DR. TROXELL: Yes. I just want to express our sincere thanks for your listening to our couple of days of presentations and for your deliberations, coming from such warm places as Boston and so on to sunny Washington. Thank you so much and have a good journey back.

DR. MILLER: We are adjourned.

[Whereupon, at 1:30 p.m., the meeting was adjourned.]

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# *CERTIFICATE*

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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