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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE

ACRYLAMIDE

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Jean Halloran
Ken Lee, Ph.D.
Harihara Mehendale, Ph.D.
Robert Russell, M.D.
Clifford W. Scherer, Ph.D.
J. Antonio Torres, Ph.D.

GUEST SPEAKERS:

Robert Brown, Ph.D.
Tim Fennell, Ph.D.
Stephen S. Olin, Ph.D.
Sorell Schwartz, Ph.D.
David Zyzak, Ph.D.

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C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. MILLER: Good morning. I am Sandy Miller and I am Chairman of the Food Advisory Committee. I want to take this opportunity to welcome the members of the committee and the subcommittee that are with us today, and our guests and staff members, to deal with the issues that are concerned with acrylamide and food safety.

Before we go any further, let me take this opportunity and ask each of the members of the committee to introduce themselves briefly and then we can go on to the next agenda item.

DR. MEHENDALE: I am Dr. Mehendale from the University of Louisiana and the Monroe School of Pharmacy.

DR. RUSSELL: Rob Russell. I am Director of the USDA Human Nutrition Center in Boston at Tufts.

DR. TORRES: Antonio Torres, Oregon State University Food Science.

DR. BUSTA: I am Frank Busta, Professor

Emeritus at the University of Minnesota.

MS. DEROEVER: Catherine DeRoever, the executive secretary for the Food Advisory Committee, FDA.

DR. MILLER: I am Sandy Miller, as you all know.

DR. DWYER: I am Johanna Dwyer at Tufts New England Medical Center in Boston.

DR. DICKINSON: Annette Dickinson, Council For Responsible Nutrition.

DR. LEE: Ken Lee, Ohio State University Food Science and Technology.

MR. SCHOLZ: I am Brandon Scholz, Wisconsin Grocers Association.

DR. SCHERER: Cliff Scherer, Cornell University, with an interest in risk communication.

DR. MILLER: Thank you. The committee has been organized for the purposes of reviewing an Action Plan prepared by the staff in order to deal with the issues of acrylamide in food.

I am not going to provide the background to this because this will be done by some of our

speakers in time, but I want to remind the committee that, as you will see, what the committee is being asked to do is to review the Action Plan, not to make a decision concerning the safety of acrylamide in food. As we continue our activities I want to focus on that issue rather than the ancillary issue, although there are questions concerning safety that are going to have to be resolved.

Let me also remind all of the speakers that we have a number of people to speak and to make sure that everybody gets their proper time, we are going to have to stick very close to the time schedule. What I will do, I will interrupt you when your time begins to run out and then as you continue to talk, continue to interrupt you and, if necessary, I will adjourn the committee until you sit down. But it is really important. Quite seriously, it is very important that people stick to their time.

I will also at periodic times ask the committee if they have questions and, hopefully,

these will be questions for clarification rather than comment. We will come to comments and opinions at the end of the meeting.

Before we move on to our opening comments, Kathy DeRoever has some comments she needs to make concerning conflict of interest.

Conflict of Interest Statement

MS. DEROEVER: Good morning. As you have heard, I am Catherine DeRoever, executive secretary for the Food and Drug Advisory Committee. First, I would like to welcome all of you to the meeting, particularly the members of the committee, Dr. Miller, Dr. Busta, Dr. Dickinson, Dr. Dwyer and Mr. Scholz; the members who serve on our subcommittees who graciously agreed to be here today, Dr. Lee, Dr. Mehendale, Dr. Torres; and also our temporary voting members--Jean Halloran, as you can see, has not arrived yet but Ms. Halloran, Dr. Russell and Dr. Scherer have been appointed as temporary voting members for the purpose of this meeting by the authority granted to the Center Director, Mr. Josepph Levitt, in the Food Advisory Committee

Charter.

Second, the following announcement addresses the issue of conflict of interest with respect to this meeting, and is made part of the record to preclude even the appearance of a conflict of interest. The issues to be discussed at this meeting are issues of broad applicability. Unlike issues in which a particular sponsor's product is discussed, the matters at issue do not have a unique impact on any particular product or manufacturer but, rather, may have widespread implications with respect to foods and their manufacturers.

To determine if any conflict of interest exists, the committee has been screened for interests in the food industry. As a result of this review, in accordance with 18 USC, Section 208(b)(3), Dr. Busta, Dr. Dwyer and Dr. Miller have been granted a particular matter of general applicability waiver that permits them to participate fully in the matters at issue. Copies of the waiver statements may be obtained by

submitting a written Freedom of Information Act request.

Our invited guest speakers have also been screened for conflicts of interest. Dr. Saunders, who I understand is being replaced by Dr. Brown, and Dr. Zyzak are employed by the regulated industry. No other conflicts have been reported.

I now turn the meeting back to Dr. Miller.

DR. MILLER: Thank you, Cathy. For opening comments, Mr. Joseph Levitt, Director of the Center for Food Safety and Applied Nutrition, will make some remarks.

Opening Comments

MR. LEVITT: Good morning. Let me again welcome you to our wonderful Washington, DC area in the middle of winter. I last saw this committee in the heat of summer. So, I guess, we have a way of playing these things around the weather. At least the subcommittee that Dr. Busta so ably chaired in December was in the middle of a snow storm so here we at least waited till some of the dig-out occurred.

Today's subject is acrylamide. We are at what I think of as phase two of this process. Phase one I would describe as discovery, where we all heard less than a year ago, last spring, of new findings reported from Sweden on acrylamide levels in food. That created a lot of activity that many of you know about and you will hear about in more detail. Phase two is what I call formulating a course of action. That is what we have been doing for the last six months or so. We presented a Draft Action Plan at a public meeting at the end of September, presented that to the Subcommittee of Contaminants and Natural Toxicants in December and are trying to finalize that today. Phase three, therefore, would be the implementation and finding solutions.

This has been such an important issue that actually phase three started before phase two was over. We are happy also to be sharing continued results of research that has been ongoing.

So, what you will hear today in summary is as follows: Number one, you will be hearing a

summary of our plan, including the subcommittee's review and suggested improvements to that that have been incorporated. You will be hearing continued findings of research that FDA has conducted and, for the first time, our overall exposure assessments on acrylamide. You will be hearing a presentation from industry research later this afternoon, preliminary research on how to reduce the levels. That is really a major goal here. The results, though preliminary, look very encouraging from what we have heard, and we are pleased to be able to present that to you today.

So, in less than a year I think you will find, as all of us involved, that an awful lot has been done in less than a year though, clearly, a lot more needs to be done to see this important issue through to its conclusion.

As always, what we want from you is your best advice. How can we best crystallize, direct and target this plan to accomplishing what we need to do in the shortest time possible, recognizing that research does take time, that it does take

work by a lot of people in order to try and solve a problem of this degree of complexity?

With that, it is my pleasure to make way for the FDA Deputy Commissioner, Dr. Lester Crawford. Thank you very much.

Opening Comments

DR. CRAWFORD: Thank you, Joe and thank you Dr. Miller. I would like to share a few thoughts with you with respect to the agency's current position on acrylamide, but before doing that I want to recall a couple of points of nostalgia to be sure that I run over my time, Dr. Miller.

[Laughter]

One is that I used to be on the Food Advisory Committee back in the golden days when we successfully solved the problem of food biotechnology--

[Laughter]

--and also somatotropin and then finally Ephedra. But we didn't have a chairman like Dr. Miller. That is for sure. Even earlier, about

half a mile from here, my first stint at FDA was out in Beltsville, vaccinating pigs. So, I am happy to be here.

[Laughter]

Somebody is out there vaccinating pigs right now.

First of all, let me just say that we are fully committed to developing better knowledge of acrylamide in foods and passing this information along to the public as quickly as possible. We have had a number of issuances on acrylamide, and we are about to have another as a result of this meeting.

At this point we simply don't know what the actual human health risk of acrylamide might be at the low levels found in food. We know it causes cancer and reproductive problems in animals in high doses and is a neurotoxin in humans at high doses. That is why the FDA created an Action Plan that Jim just talked about and that Terry Troxell will talk about a bit later to understand the risk that might be associated with acrylamide in foods, and to

reduce levels of acrylamide in foods, including active involvement of this committee.

As a result, we are learning more about acrylamide levels in a broader range of foods than has been previously analyzed. We are also learning more about acrylamide forms in foods and steps that may help reduce acrylamide formation.

Based on our current understanding of the science, FDA continues to advise consumers to eat a balanced diet, choosing a variety of foods that are low in trans and saturated fat and rich in high fiber grains, fruits and vegetables.

The purpose of the meeting, as Joe has said, is to seek input from the committee to assist FDA in analyzing and finalizing the revised Draft Action Plan. The revised Action Plan includes greater detail and reflects new research activities and comments from the subcommittee which we received on December 4 and 5 of last year.

We are releasing 110 additional test results in the spirit of openness and transparency. The findings released today are generally similar

to the preliminary results FDA released previously.

FDA exploratory survey findings on levels in foods have shown substantial variability among a wide variety of foods, as well as substantial variability within foods. The initial exposure assessment has found results similar to those conducted by organizations worldwide, such as the World Health Organization and the Food and Agriculture Organization.

The exposure assessment has found that many foods contribute to acrylamide exposure. No single food accounts for the majority of acrylamide exposure for the U.S. population. Some foods that have lower levels of acrylamide contribute appreciably to the overall exposure because they are commonly consumed. Researchers are seeking ways to get acrylamide levels down. Preliminary data are encouraging and we are convinced that there will be some techniques and some technologies developed that might help and we are eager to learn more about that from presentations that will be made at this meeting.

With that, I will conclude and will officially declare, from my position as Deputy Commissioner, that I was on time, Dr. Miller. Thank you.

DR. MILLER: Thank you. I am always happy to be present at rare events.

[Laughter]

I wanted to remind Dr. Crawford that the function of this committee is to provide advice, not to make decisions on implementation, and if a problem still exists that is not because the committee didn't give good advice.

[Laughter]

That brings me to the next issue. As I said before, the function of the committee is to review the Action Plan and to review the conclusions made by the Subcommittee on Contaminants and Natural Toxicants and to add or make recommendations concerning any changes in this plan.

There are three basic issues we have to think about as far as the Action Plan is concerned.

One, as mentioned, is the toxicology. How strong is the data? What does the data tell us in terms of calculating risk? And, what else needs to be done in order to provide a stronger base for an agency Action Plan?

Secondly, exposure and, as Dr. Crawford mentioned, some additional data is being released today. Is that right? It is going to be released today, some additional exposure data?

DR. CRAWFORD: Yes, 110 additional analyses.

DR. MILLER: All right, I wanted to be sure I heard that right. Thirdly, as was pointed out, there are available technologies for reducing exposure to acrylamide and to determine whether or not these are important in order to reduce the potential risk from exposure from this material.

In order to accomplish these tasks we have a number of speakers who will talk about the different subjects, but I think the committee ought to focus on these issues, and we will come back to them at the end of the meeting when we have our

general discussion concerning recommendations that we need to make to the agency.

The first speaker this morning to talk about the Action Plan is Dr. Terry Troxell, who is director of the Office of Plant and Dairy Foods and Beverages, CFSAN. Terry?

Development of the Acrylamide Action Plan

DR. TROXELL: Good morning. We bring you another simple problem to solve, like biotech and Ephedra.

What I would like to do first thing is to go over the charge. You all have the charge and questions in your packets. I think we should focus on that for a minute so we orient the meeting. The charge is to evaluate the revised Action Plan as a tool for providing the scientific basis from which to assess the significance of acrylamide in foods and potential public health consequences.

The first question of the committee is does the revised Action Plan meet its intended goal of serving as a tool for providing a scientific basis to assess the significance of acrylamide in

foods and its potential public health consequences?

The second question is 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 the exposure assessment of potential interventions.

The final question is FDA's consumer message stresses the importance of eating a balanced diet. Given the uncertainties associated with the current state of the scientific knowledge, FDA has concluded that there is insufficient data to revise this message. Please comment.

[Slide]

For this talk I want to go over the development of the plan and the content, FDA's overall goal and ongoing work on the Action Plan.

[Slide]

This all began back on April 24 of 2002 when the Swedish national food agency surprised the world with a report that acrylamide was in numerous foods, surprised the world partly because cooking

process had been thoroughly studied and the mutagenicity, and so on, had been worked on for many years and this one was missed apparently because it wasn't positive in the Ames test.

Basically, what happened then was that many, many countries began developing methodology. The methodology was not initially available. We knew we had an LC/MS/MS method but we basically had to go from scratch, pretty near scratch, to develop a method. Then, as I said, we started thinking through the problem to try to clear up what in the world could be underlying the formation.

We posted our first version of our LC/MS/MS method on June 10th and we have updated it two times. It is either being updated on the web or was just recently updated, in the last couple of days. It is an excellent method of linear quantitation for 10 ppb.

Due to the intense interest worldwide in the subject, the WHO and FAO put on a consultation only two months after the announcement by the Swedish authorities. FDA sent three scientists to

this meeting and the consultation concluded that acrylamide was a major concern.

We posted our original Action Plan on September 20th so it didn't have the benefit of the next meeting, which was our interagency round table for which FDA brought together various components of CDC, NIOSH, National Institute of Occupational Safety and Health, and the National Center for Environmental Health. Of course, our National Center for Tox. Research was there and NIEHS of NIH was also at the meeting to exchange information on what was going on with acrylamide research and pathways and work of interest to various groups. So, we began our process of trying to organize the work to deal with the problem. Finally, we had our public meeting on September 30th and that was the first time we presented the plan.

[Slide]

The next event was the JIFSAN/NCFST workshop on October 28th to 30th. JIFSAN is our Joint Institute for Food Safety and Applied Nutrition. It is a consortium with the University

of Maryland. Our National Center for Food Safety and Technology is our consortium with the Illinois Institute of Technology. This workshop brought together researchers from many countries, four months after the original consultation, to thoroughly review the status of methods, mechanisms and formation for reduction of exposure, toxicology and risk communication. The workshop led to a list of priority research for each category. In addition to this, JIFSAN is operating the WHO/FAO acrylamide in food information network on the web to try to bring together research from around the world.

The next event was our subcommittee meeting in the snow storm of December 4th and 5th. At that time, of course, we presented the original Action Plan and got very valuable comments from the group.

[Slide]

The Action Plan outlines FDA's goals and planned activities on acrylamide in food over the next several years. The plan discusses intentions

to work with other federal agencies and participate in international efforts. We saw from the very beginning that there was a large amount of work to do, and work that would cost a lot.

It was our belief that we could get the answers that we needed as quickly as possible by leveraging our efforts and as important was a means to coordinate work with researchers and communicate throughout the process in order to accelerate the solutions. For example, several labs discovered concurrently that asparagine and glucose through their reaction were the primary cause of acrylamide formation.

It would be useful if there was a way of limiting redundancy in order to optimize our efforts. However, the desire of academics and other researchers to publish gets in the way of that because they want to hold their work until the publication occurs. In any event, the Action Plan and coordination we are trying to foster, we believe, will move this effort in the right direction.

[Slide]

The original Action Plan included sections on testing foods, toxicology formation, methodologies, meetings and collaborative projects, consumer messages and regulatory options. The revised plan, summarized in the next talk, covers the same areas pretty much in more depth, with the addition of a couple of new sections.

[Slide]

The scientific review at FDA and WHO indicated cause for concern, as I indicated. Actually, although we note neurotoxicity here, the consultation did not expect neurotoxic effects from acrylamide levels present in foods. But discussions since then, for example at JIFSAN meetings, suggested that more work was needed to be done to characterize potential neural development of effects in chronic exposure.

Another factor that was involved in developing the Action Plan was that the consumption was in the tens of micrograms range. In contrast to that, food additives and water purification

effects of exposures were 100 to 1000 times lower. Also, the scientific review, as I have said, indicated that there were quite a few gaps and a lot of work needed to be done.

[Slide]

The results were intense worldwide interest, as indicated by the desire to have the consultation very shortly. Our optimal desire, of course, would be to harness that intense interest and at least try to influence it toward a better coordination and less redundancy. Research indicates acrylamide is formed through traditional cooking practices. As I said, it appears to be the product of one of the standard cooking reactions that is essential to cooking foods at processors and in the home. The reaction produces desirable flavors and browning. Thus, acrylamide is formed in a wide number of foods and is going to be a challenging problem for chemists.

[Slide]

We developed an overall goal for this project, and that is, through scientific

investigation and risk management decision-making, to prevent and/or reduce the risk of acrylamide in foods to the greatest extent feasible.

[Slide]

As far as ongoing work, we revised the plan based on the subcommittee's input as well as other developments along the way. We will present that plan today and will look forward to your assistance in finalizing the plan.

[Slide]

What is going on in the future here? Of course, our work on the projects is outlined in the plan. Then, there is the CCFAC meeting coming up shortly, March 17th. Of course, as we have discussed, there is intense national interest and we expect that the CCFAC will undertake new work at this meeting on acrylamide. As part of our effort to coordinate and share information on acrylamide, we are proposing a formal workshop on acrylamide in conjunction with the CCFAC meeting. The WHO and FAO have adopted that proposal and we will be conducting a workshop at the meeting. Finally, the

WHO and FAO JECFA, the Joint Expert Committee on Food Additives, which also evaluates contaminants, will be looking at acrylamide sometime in 2004. Whether it is February or June is not clear but they will be evaluating, and that is the group that does the risk assessment that flows into the CCFAC committee which is the risk management group.

There are tens of meetings on acrylamide going on all over the world, as well as in the U.S., and we have just highlighted a few of those but there is just very intense interest and it is hard to know which ones to highlight and which ones not to highlight.

[Slide]

Anyway, in the next talks we will be betting a report from Dr. Kim on that subject and then I will come back and summarize the revised Action Plan. Thank you for your attention. Any questions?

DR. MILLER: We have some time if there are any questions of clarification. Johanna?

DR. DWYER: Thank you for an interesting

introduction. I have one question on one of your early slides where you mentioned that the Swedish report came out in April, and then you developed a method which you released on June 20th. Why was the Swedish method not available?

DR. TROXELL: Again, they released a method but they were waiting to publish the work.

DR. DWYER: And they would not release it to the authorities?

DR. TROXELL: Right, they released a sketch of the methodology which helped accelerate our development of the method pretty quickly and observe it in an appropriate LC Mass Spec. method.

DR. MILLER: Any other questions? If not, thank you. As you know, the organization of the Food Advisory Committee consists of the committee itself and several subcommittees. This issue was referred to the Contaminants and Natural Toxicants Subcommittee, which you have heard about already Dr. Henry Kim is the executive secretary and he will present the report of the committee. Henry?

Report of the Contaminants and Natural Toxicants

Subcommittee (CNTS) Findings

DR. KIM: Thank you, Dr. Miller. As the executive secretary for the Contaminants and Natural Toxicants Subcommittee, I was asked by Dr. Busta, who is the chairman of that subcommittee, to present a report of the subcommittee meeting's findings and it is my pleasure to do so this morning.

[Slide]

For my presentation what I would like to talk about is briefly on the purpose of the subcommittee meeting, as well as the presentation that was made at this meeting, and then talk a little more in detail about the subcommittee's discussions and recommendations that were made.

[Slide]

The purpose of this subcommittee meeting, which was held on December 4th and 5th of 2002 was to present the major components of the FDA's Draft Action Plan and then to seek advice and recommendations from the subcommittee.

[Slide]

In presenting the FDA's Draft Action Plan, the subcommittee was asked to evaluate whether the research steps outlined in FDA's Action Plan are scientifically adequate to describe and address the public health significance of acrylamide in food.

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In addition, the subcommittee was posed with three questions. That is, given what we know of acrylamide, that is, the toxicology, the occurrence, formation, exposure and risk, one, are the research steps appropriate to describe and address the public health significance of acrylamide in food? Two, are there gaps in the research plan or areas where emphasis should be increased? Three, are there priority research needs that should be addressed first?

In order to facilitate our responses from the subcommittee on the Action Plan, FDA representatives presented five major components of the Draft Action Plan, that is, the toxicology, the occurrence, formation, exposure and risk.

[Slide]

First, Dr. Canady talked about information that we already know in addition to data that we need, and what we are planning to do to obtain those additional data with regard to the five toxicology elements that are shown on this slide. That is toxicokinetics, animal carcinogens and human neurotoxicants, reproductive/development effects and safety and risk assessment.

[Slide]

For the occurrence component of the Draft Action Plan, Dr. Musser discussed the development and performance of the LC/MS/MS method for the quantitation of acrylamide in a wide variety of foods, and also presented results of the exploratory survey data that was collected through November 15th, 2002.

[Slide]

Then Dr. Jackson provided an extensive summary on the current state of knowledge about mechanisms, the precursors and factors affecting acrylamide formation, and identified additional research needs in this area, and then discussed two

major elements regarding acrylamide formation in the Draft Action Plan, that is, understanding the conditions leading for acrylamide formation and developing methods to prevent or reduce acrylamide formation.

[Slide]

For the exposure component of the plan, Dr. DiNovi talked about the FDA approach for conducting exposure assessment using the occurrence and consumption data to estimate exposure, and then talked about the two exposure studies that were conducted by Sweden and FAO/WHO and indicated that the FDA was currently conducting an initial exposure assessment which is to be completed shortly.

[Slide]

Finally, Dr. Acheson talked about achieving a balance with respect to the importance of balanced diet, risk from exposure to acrylamide in food and potential dangers of inadequate cooking for addressing the complex issue of reducing risk to consumers from the presence of acrylamide in

food.

[Slide]

Some of the other presentations that were made just briefly, Mr. Levitt provided an opening remark sort of to kick off the meeting, if you will. Dr. Schwetz talked about scientific overview of acrylamide in food, focusing mainly on the work that was done at the FAO/WHO consultation in June. Then, Dr. Lineback, the Director of Joint Institute of Food Safety and Applied Nutrition, provided an overview of the JIFSAN workshop on acrylamide that was conducted last October. Finally, public comments were made by a representatives from National Food Processors Association, SNF and the American Council on Science and Health.

That is what happened on the first day of the meeting so now I would like to move on to the second day of the meeting, which was devoted mainly to discussions by the subcommittee members about the various components of the Draft Action Plan, as well as responding to the three questions that were posed to them. So, I would like to first talk

about the responses that were made by the subcommittee members with respect to the three questions and then highlight some of the major recommendations that were made on five components of the Draft Action Plan.

[Slide]

In response to question one, are the research steps appropriate to describe and address the public significance of acrylamide in food, the subcommittee generally supported the overall Draft Action Plan as well as the research plan that was outlined in the plan.

[Slide]

In response to question two, are there gaps in the research plan or areas where emphasis should be increased, the subcommittee felt that more detailed information was needed in the plan in discussing the risk assessment, human toxicology and epidemiology studies, as well as animal tox. studies and sampling and analytical variability and food consumption data by various population groups.

[Slide]

In response to question three, are there priority research needs that should be addressed first, the subcommittee generally felt that the priority as outlined in the draft plan, that is, the methodology, occurrence, formation, exposure and then risk--they felt that this outline was appropriate but there were suggestions made that perhaps an explicit statement about the priority in the plan may also be appropriate.

The subcommittee also recommended that the toxicology and risk assessment studies should move forward quickly because these types of studies take a long time to conduct, as well as focusing on developing a rapid and inexpensive method to analyze a wide variety of foods and to provide science-based risk communication messages.

Now I would like to move on to highlighting some of the major recommendations that were made by the subcommittee on various components of the plan.

[Slide]

In the area of toxicology the subcommittee

recommended that more human studies should be conducted, such as physiological studies looking at absorption, metabolism, distribution and excretion, as well as toxicokentic studies of ingested acrylamide in humans. They also recommended that more detailed discussion about studies with respect to animal neurotoxicity and genotoxicity should be made; as well as animal bioassay studies, particularly the short-term studies; as well as looking at the dose-response relationships at lower levels, that is, between the no observed hazardous effect level and the levels at which there is tumor formation; and also looking at the mechanism of action in these bioassay studies.

Finally, they also suggested that the Action Plan should look at discussing biomarker-exposure relationship in smokers. They felt that data from those type of studies may be useful in conducting biomarker studies for acrylamide exposure from foods.

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In the area of epidemiology the

subcommittee recommended that a separate section on epidemiology should be included in the Draft Action Plan, talking more about the human epidemiology studies such as identifying the study populations with higher or lower exposures to acrylamide from various diets, as well as investigating epidemiology studies of workers exposed to acrylamide to determine whether those types of studies may be applicable to food exposure.

[Slide]

With regard to the exposure assessment component of the plan, the subcommittee recommended that the Action Plan should highlight the exposure assessment element of the plan more prominently by providing information about data bases that would be used to conduct the exposure assessment; as well as looking at improving the ability to blind the data that will be released to the public, such that that will facilitate more data sharing; as well as obtaining quality data, and to statistically determine when enough samples have been collected, such that the exposure assessment can be conducted;

as well as obtaining inputs from the exposure assessors in the type of foods that should be sampled; and, finally, to use food consumption data by various population groups.

[Slide]

With respect to risk assessment, the subcommittee recommended that more information should be incorporated into the Draft Action Plan, particularly in discussing the importance of conducting a risk assessment, as well as the methods for conducting that risk assessment and on how to incorporate new data as they become available.

[Slide]

Finally, this is the last recommendation section within the area of risk communication. The subcommittee recommended that more emphasis should be made on the risk communication activities by FDA and to provide, as I mentioned previously, science-based information for dietary choices, as well as involving dietetic and nutrition associations in communication efforts, such as the

American Dietetic Association and the American College of Nutrition and, finally, to disseminate consumer and cooking messages through extension services.

[Slide]

In summary, the subcommittee spoke positively about the FDA's Draft Action Plan and generally agreed with the approach and the planned research activities that were outlined in the plan, and then provided some very valuable recommendations with respect to toxicology, epidemiology, exposure and risk assessments and risk communication.

With that, I turn the meeting back to Dr. Miller.

DR. MILLER: Thank you, Henry. Are there any questions or comments?

Questions of Clarification

DR. BUSTA: I just want to compliment Henry on doing a very succinct presentation of our two-day meeting. There are other members who were at the subcommittee meeting if there are additions,

but I think you summarized in a very succinct manner a lot of comments.

DR. KIM: Thank you.

DR. MILLER: Dr. Torres?

DR. TORRES: We heard a lot about variability within food, within food batches and then I see that the plan does include studies on the formation of acrylamide in foods. But when I look at the subcommittee recommendations there seems to be nothing in that area of formation and I am a little bit surprised about that. I don't see any specific recommendations about the formation kinetics of acrylamide. We see so much variability within food, between foods, between batches of food, however, I don't see any recommendations for further studies on formation.

DR. KIM: Yes, I did mention in the formation slides that Dr. Jackson presented formation information and did go into some of the additional research needed, such as looking at factors like pH, temperature, moisture content and those types of research activities. But I did not

kind of highlight that in this presentation because of lack of time to present everything that was discussed at the meeting. There was a whole lot of discussion on all the major topics and I just wanted to focus on the major components of the plan.

DR. MILLER: I think the point is that this issue which is, of course, vitally important wasn't highlighted as one recommendation for the Action Plan in your presentation.

DR. KIM: Well, I can add that to the recommendation list.

DR. MILLER: That is the point that Dr. Torres was trying to make. It is a vital issue and is certainly deserving of the same emphasis, at least in my view, as other aspects such as toxicology.

DR. KIM: Yes, I would agree with that.

DR. MILLER: Do you want to say something, Terry? You look anxious.

DR. TROXELL: I always look that way. Our original Action Plan did highlight research on

mechanism and formation. So, I think the subcommittee recognized that and I know that no recommendations came out on that, to change that. They just agreed that we should keep pushing on those aspects because they are vitally important.

DR. MILLER: I think the report ought to reflect that. It is an area that obviously got missed because in reading the report, it doesn't come across. Johanna?

DR. DWYER: Thanks for a good report. One thing that troubles me about this whole area is the database that one is using to get at the foods. Just a cursory reading of the report we were given this morning doesn't seem to highlight that for further attention. My concern is this, I know that on page two or three of the Action Plan you talk about FDA doing some analyses and then we were told that today more values will be released, but the question is how to capture all the values that are there, not just these but others. We went through this with methyl mercury where we found out that there is a lot more data out there than we had in

the database. I wondered what efforts would be focused on all the different government agencies that may have data on this.

DR. KIM: I was told that this will be addressed in the revised Action Plan. There were discussions about data collection. I think with respect to FDA--we obtained data from surveys--I don't know, maybe Dr. Busta or Dr. Lee may have some additional thoughts.

DR. DWYER: I am talking about the presence of this compound or compounds in food, not the further step of taking those data and trying to get exposure estimates for food. I am talking about the database that is used to say the French fries have this much, the broccoli has that much.

DR. BUSTA: I thought Henry covered that under the exposure assessment in improving the ability to blind the data and facilitate the data sharing, and maybe that should be more explicit but when I see that I think that there a lot of data in the food industry that, if they were made blinded, would be made available but might not be offered

freely if it said somebody's brand.

DR. LEE: Just to amplify on the subcommittee's recommendation, a lot of time was spent on the JIFSAN website and ways to share acrylamide data, and there was also a lot of discussion about the need to at least single-blind acrylamide levels in food so an industry that has a lot of data on acrylamide content of its products would not be in danger of being fingered as a source in the diet. So, I think that thought is there and, in all fairness, Henry gave a great summary but couldn't get into that level of detail in his presentation.

DR. MILLER: Other comments? This is not a clarification, Henry or Terry, but how much emphasis--excuse me, let me go back, I think it was you, Terry, who said something about acrylamide not being positive in the Ames test? Did I hear that correctly?

DR. TROXELL: That is my understanding, and when they did research on cooking carcinogens that form in foods, and so on, apparently that is

probably the reason acrylamide was missed among the other chemicals that are formed.

DR. MILLER: But it is genotoxic?

DR. TROXELL: Yes.

DR. MILLER: That is what I thought. That is why I didn't understand why it didn't show any results the Ames test.

DR. TROXELL: If you want further clarification, Dr. Canady probably can provide some.

DR. MILLER: It is a matter of curiosity, but thank you. Any other comments? If not, we are actually ahead of time. I think what we are going to do is--Terry, why don't we move on?

MS. DEROEVER: We have a technical difficulty.

DR. MILLER: We have a technical difficulty? All right, we will take a break and return in about 30 minutes.

[Brief recess]

DR. MILLER: Our next speaker is Dr. Terry Troxell, who will describe the revised Action Plan.

Terry? I assume these are revisions that were made in response to the recommendations of the subcommittee.

Revised Action Plan

DR. TROXELL: Right. Thank you. You should have the revised Action Plan before you and also those 110 new data points should be in your packet. They are kind of at the bottom of the packet, under "exploratory survey."

[Slide]

I am going to go very briefly over the revised Action Plan that we updated based on the input from the subcommittee, as well as the public, and also all the things that have happened in the meantime. Like I said, we put out the first Action Plan before the interagency meeting that we had, also before the JIFSAN meeting, and so on. Again, what we are looking for today is we are seeking your input to assist us in finalizing this.

[Slide]

What I am going to do is summarize key changes; review the major goals of the plan; walk

through the action sections; and then highlight the changes section by section.

[Slide]

The major change, of course, is that we reorganized the plan. It now has a more logical flow, at least from my viewpoint. We have added new sections on exposure assessment, epidemiology and risk assessment and this is in response to subcommittee recommendations. We added more details and updated the information. The plan is about double the size of the previous plan and this also was in response to the subcommittee.

[Slide]

There are seven sub-goals to our work. I already mentioned our overall goal before. The first sub-goal is to develop rapid and inexpensive screening methods and validate confirmatory methods of analysis. The second is to identify mechanisms responsible for the formation of acrylamide in foods and identify means to reduce acrylamide exposure. Again, we know at this point that asparagine and glucose with high heat are

responsible for most of the formation of acrylamide. What we don't know at this point is how to quench that reaction.

[Slide]

The next goal is to assess the dietary exposure of U.S. consumers to acrylamide by measuring the levels in various foods and estimating the dietary exposure.

[Slide]

The next goal is a rather long one and I am not going to read this but basically what it says is that we are going to explore the toxicology and epidemiology, and we are going to use quantitative risk assessment to determine the risk and the uncertainty associated with those risk calculations.

[Slide]

The next goal is to develop and foster public/private partnerships to gather scientific and technological information and data for assessing the human risk. We believe this is really essential and at the core of getting this

work done and also it will harness that interest around the world by all parties, academia, industry and the governments.

[Slide]

The next goal is to inform and educate consumers and processors about the potential risk associated with acrylamide throughout the assessment process and as knowledge is gained.

[Slide]

The next goal is to provide all the essential elements for risk analysis, that is, risk assessment, risk communication and risk management. That is kind of a sum-up goal because that kind of covers the waterfront of what we need to do on this process and pretty near in any project we have on food safety.

[Slide]

There are nine sections detailing the actions toward accomplishing these goals. They cover the methodologies, research on formation, measuring exposure, toxicology and health effects, epidemiology, risk assessment, meetings, inform and

educate the public, and then further actions. I will now look at each of those sections.

[Slide]

As I said, our LC/MS/MS method was posted on the web back in June. We have recently updated it. Dr. Musser of CFSAN and his group have done an enormous job of developing the method and analyzing around 400 samples to date. This is in addition to the numerous analyses they have done in determining the characteristics of the method.

I am going to diverge a second to make a point. Acrylamide has been a real team effort here, at FDA. It is not only my office, Office of Plant and Dietary Foods and Beverages, that is involved, but the Office of Food Safety is doing the exposure assessment, the Office of Systems and Support, the office in which Dr. Musser has done the analyses, and there are others in CFSAN like the food safety staff and the Office of Science. In the FDA in a broader sense, our National Center for Tox. Research is doing an enormous amount of work on toxicology and our Office of Regulatory

Affairs will be running total diet study samples. This gives a sense of the energy going into developing the science around this issue, and is being repeated in many countries by many different kinds of parties.

With respect to validation, while there are certain excellent methods for determining acrylamide, Dr. Musser's method is an excellent definitive method that we believe should go through the full AOAC validation process.

Then, there are screening alternatives. We want to explore, and are encouraging others to explore the screening methods. Dr. Diachenko's lab in CFSAN is presently looking at use of LC/UV as a screening method. We believe the equipment, the LC/UV detectors are available in many labs around the world and this could provide a simple means for people in many countries to get a handle on the screening levels.

[Slide]

So, what is new in methodologies? Our second update is being posted for our LC/MS/MS

method. We are explicitly talking about AOAC validation rather than just validation and we are currently exploring LC/UV alternatives.

[Slide]

Research on formation, CFSAN's Division of Food Processing and Packaging is located in Chicago at the National Center for Food Safety and Technology. NCFST has the capability of doing pilot process research so we can take the bench-top research on reduction, whether done in academia or done in industry labs, and test it under pilot processing conditions. Currently, NCFST is planning research on the formation of acrylamide during home cooking of toast, French fries and other foods. This seems to be a gap that we don't believe others are pursuing. The laboratory out there has the capability of measuring surface temperatures of food and also looking at the degree of browning so we can actually bring some science to bear on what would be happening in the home with toasting and frying of foods.

Also, the interaction of academia and

industry, again, we expect that reduction strategies will vary with many types of food in which acrylamide is formed. Therefore, it will take the efforts of the food science departments like Mike Pariza's Food Research Institute at the University of Wisconsin and the food industry to do the heavy lifting on research in this area. You will hear from Frito Lay and Procter and Gamble this afternoon on their progress on reduction strategies. Procter and Gamble will talk about the mechanism, Frito Lay will talk about reduction strategies.

[Slide]

So, what is new in the research on formation? NCFST is going to investigate scientifically home cooking.

[Slide]

Now to get at some of the questions we had this morning of measuring exposure, as I think I said earlier, Dr. Musser's group has done about 400 locally collected food samples thus far with this additional 110. These are the analyses we have

used in our initial exposure assessment that you will be hearing about later, and we have handed out that data. I hope you each have a copy of that.

We are contracting through JIFSAN, our consortium with the University of Maryland, for 400 to 500 more foods to be analyzed, and these will be collected across the country, so we will get a national scope now, by our field forces.

In addition, we have begun testing total diet study foods. The total diet study look at foods as eaten and serves as a good indicator of exposure to contaminants--I mean, that study looks at contaminants and pesticides, and looks at nutritional minerals, and so on. So, it will be a means for us to understand what the kind of gross exposure is and then what our progress is on reduction.

As far as other testing goes, we plan to continue testing in subsequent years in part to fill in the distributions. You will see in our exposure assessment presentation that there are too few samples in many categories so we need to fill

those in. As was discussed earlier, JIFSAN is compiling data from industry and academia which will fill gaps in distribution and help solve this data problem.

We also understand that Europe has compiled a large amount of data. The U.K. apparently has a database that may run up to 4000 samples but their processing conditions may be somewhat different than processing conditions in the U.S., therefore, they may not always be directly applicable to the U.S. situation. But we think it is really important for us to tap into the data that is out there from all parties to basically fill out the distributions for each of the food categories and understand the variability on exposure.

[Slide]

Then there is exposure assessment and I am going to pretty much skip over this part because Dr. Robie will be thoroughly discussing our methodology but, again, we will be periodically updating that exposure assessment as more data is

compiled and, hopefully, we will be bringing to bear this blinded data that industry can make available to us.

[Slide]

So, what is new in exposure? Well, it is a new section and we put in a lot more details in the revised Action Plan on what we are going to do, and those details include information on how we are going to model the database we are going to use.

[Slide]

Now we move on to toxicology and health effects. Toxicology will provide information for risk assessment and consist of two general areas, animal toxicology and human toxicology.

[Slide]

Now I am going to pretty much summarize the next three or four slides with the following: There are basically four things we want out of this work. One, we need a better understanding of the carcinogenicity, neurotoxicity and germ cell toxicology in rodents.

Two, we really need to understand the

bioavailability of acrylamide from food versus water in which most of the studies have been done.

Three, we need to understand the difference between high and low dose metabolism at high doses and, again some others may need to correct me because, as they always say, I am not a toxicologist, I am only a "Troxell-cologist." So, at high doses the p450 pathway produces glycidamide which is thought to be the penultimate carcinogen, but at low doses a smaller fraction of acrylamide may go through the p450 pathway. So, it is really important for us to understand the high versus the low dose differences.

Fourth, we need to understand the differences in metabolism and processing of acrylamide between animals and humans.

For carcinogenicity we need to understand the levels of adducts that form on ingestion of acrylamide. There is a very convenient biomarker adduct that is formed with hemoglobin. Once the relationship is established between acrylamide intake and adduct formation we will be able to use

the adduct levels in red blood cells as a convenient means of understanding population exposure to acrylamide. Of course, that will integrate everything. That will integrate the acrylamide from smoking and occupational and all possible sources.

We don't really believe that this adduct with hemoglobin leads to adverse effects. In fact, it probably prevents acrylamide from ultimately reacting with the DNA. It is the DNA adducts after enough insults to the DNA that are thought to lead to the tumor production. So, we need to also understand the correlation between acrylamide intakes, the hemoglobin adducts to the DNA adducts, and we need these studies for rodents where we can study cancer production at the highest doses and we need these studies on humans who are exposed to very low levels from foods. Such studies should significantly reduce the uncertainty about the risk to humans but, so everybody is clear, we never are going to be totally precise in this. There are still going to be fair uncertainty bars but we can

reduce those uncertainty bars by quite a bit.

The challenge is going to be to measure adducts in situations where there are low levels of exposure because, obviously, at low level exposure you are forming very few adducts and, therefore, you are having difficulty pulling those out in your analysis. Many of the studies that we list on the next several slides can contribute to these key needs in a relatively short time for toxicology. To me, a relatively short time for toxicology is one to two years. So, with that having been said, I think I have summarized the short-term studies at the National Center for Tox. Research on bioavailability and adducts.

[Slide]

Then, they are going to be doing a gold standard, you know, NTP bioassay. The subchronic and mechanistic components of that will be done fairly fast and will contribute to our understanding of the toxicokinetics and can be pumped into physiological-based pharmacokinetic modeling. But obviously definitive results on

number of tumors that are produced in the rodents won't be available for many years because that takes a lifetime of study in the rodent.

The NCTR will be looking at neurodevelopmental effects and also there will be mechanistic research on germ cell toxicology and neurotoxicity by the National Institute for Environmental Health studies.

[Slide]

Then there will be the adduct studies that CDC is going to be party to, as I mentioned.

[Slide]

We are looking at using the NHANES study and measuring adducts to understand population exposure to acrylamide. As well, NIOSH is looking at this area and the acrylamide manufacturers are doing a variety of toxicokentic studies. So, we are trying to bring all parties to bear in the process.

[Slide]

Before I leave this area, again, there are many groups that are going to be expected to

contribute to this work, and this work costs millions. We are trying to facilitate the research that needs to be done in all areas, but outside the agency it will be up to the researchers, their priorities, and how much they can invest to see now far they go. This will be particularly true for doing epidemiology studies which I will discuss a little later.

[Slide]

So, what is new in the tox. area? We have listed a series of new toxicology studies, new areas, neurotox. and germ cell tox. and industry working on toxicokinetics. We have talked about doing PBPK modeling and so on. Since the early report, we now know that the NTP is going to be doing a chronic bioassay.

[Slide]

Let's move on to the epidemiology area. Some of the work on adducts is viewed as epidemiology so it is kind of cross-cutting. Of course, we are going to be exploring the feasibility of prospective studies and also we will

be using all the studies that are reported in the literature, whether they are going to be on worker exposure or food exposure.

Now I will go to a little description of my view of the epi. area here. There are basically two avenues of epi. studies in my view, the occupational and the food exposure. If I understand it right, occupational studies are most likely to be able to tell us that acrylamide at high levels can cause cancer in humans. I think occupational exposures may be the highest. Thus far they have not shown an effect. This may be due to the fact that not enough years of exposure have been studied.

The other avenue, of course, is intake from foods. Can epi. studies make a difference? Dr. Acheson will discuss the Mucci study, which was published several weeks ago, in his talk. I believe that is tomorrow

This was a case control food intake study and no effect was seen. The basic problem, as I see it, is that we should have an epi. study that

can detect a lifetime risk of 1/10,000 and we don't want to wait 50 years for the result. If the study can only detect 1/1000 risk then we are not any better off than what the rodent studies can give us. So, I have asked our experts if it would be possible to detect such low risk. I don't have the answer yet but the initial reaction is that it would be very hard, at best.

The kind of study we have been discussing at the FDA is to do a case controlled study within one of the ongoing prospective studies, like the Nurses Health Study. They have collected diets as well as blood samples for the study. Many pieces would need to come together in order to do such a study but, if they did come together, it could be done in one to two years.

But consider the complications. How accurate are the diets? Misclassification would reduce the power of the study. Further, because acrylamide is in so many foods, it will not be possible to find a population that is exposed versus not exposed. What we are talking about is

groups that may vary in levels of exposure by maybe 10-20 microgram differences. Then, there is the further complication with food in that an array of chemicals make up the composition of any foods. So, if one sees an effect or doesn't see an effect, is it because of acrylamide or is it because of other chemicals that are also present in the foods that are being looked at which have carcinogenic and also anti-carcinogenic effects?

So, there are a lot of difficulties in looking at these food studies because of the confounding factors and many other factors that are also involved concurrently in causing various effects. So, in sum, we are exploring epidemiology but we need to carefully consider any study to determine if it will likely provide added value once it is completed.

[Slide]

So, what is new in epidemiology? Well, it is a new section. It explains how the epi. data could benefit FDA work on acrylamide, and a number of studies and collaborations are under

consideration.

[Slide]

The next action section is risk assessment. Clearly, when we have adequate information we want to characterize potential risk, including the uncertainty analysis. We think that key data needs are bioavailability, biomarkers, metabolism and toxicokinetics.

[Slide]

We would revise the risks assessment when significant developments materially change the assessment.

[Slide]

So, what is new in risk assessment? We have given an explicit section to risk assessment and it outlines our goals, data needs and expected output of the risk assessment.

[Slide]

The next section is meetings which we will continue to participate in and convene meetings as appropriate. As I said earlier, we convened the interagency meeting and we participated in the

JIFSAN meeting, and so on. I am not repeating the meetings here because I went over the key things that have been going on in the first presentation.

[Slide]

The next action section is to inform and educate the public. We are, and have been, committed to communicating with the public throughout this process. This is the third public meeting. So, that is one form of our communication and transparency on the acrylamide issue. Also, our website has a lot of information on our Action Plan, on levels and so on. Also, there has been an FDA Consumer article published in the January/February issue.

[Slide]

We have a message and do not believe that we have enough science at this point to change it. That message is eat a balanced diet; choose a variety of foods that are low in trans fat and saturated fat and rich in high fiber grains, fruits and vegetables. We may recruit diet and nutrition organizations to help spread that message and

changes to the message.

[Slide]

What is new in this section? We have expanded it to indicate that we have a continued process of risk communication going on and participation of outside organizations.

[Slide]

The last section is further actions. One of our further actions, of course, is to develop and revise regulatory options as additional knowledge is gained on acrylamide in food. Another action is to encourage industry to adopt feasible, practical and safe processes that are successful at reducing acrylamide, as needed.

[Slide]

Another action is to develop and revise the consumer message about dietary choices and cooking, as additional knowledge is gained to assist consumers in making informed choices. Finally, any adjustments to messages would be made as dictated by the totality of the science

[Slide]

In conclusion, the Action Plan outlines goals and planned actions. It was revised to reflect comments of the subcommittee and new information from many sources. It was reorganized, with new sections added and more details. Finally we are here seeking your input to assist us to finalize the plan. Thank you for your attention.

Questions of Clarification

DR. MILLER: Thank you. Before we begin the questions, let me just introduce Jean Halloran. Comments or questions?

DR. RUSSELL: Yes, I was wondering if it is known which p450 enzymes are involved in creating the ultimate carcinogen. The reason I am asking that is that you might be able to target certain populations whose p450 enzymes, for example, are turned on or induced for a particular effect of this carcinogen because more carcinogen would have been formed. One example would be people who drink alcohol where certain p450 enzyme profiles are turned on, and if those enzymes are the same ones that are involved in forming the

carcinogen you may be able to target more supopulations that may be at particular risk. So, the question is do we know that or is that a part of the puzzle also?

DR. TROXELL: I don't know that. Dr. Canady may be able to comment on that.

DR. CANADY: Rick Canady, FDA. 2E1 is the enzyme and it is pretty clearly implicated in the conversion of glycidamide and it is one of the things that we are looking at in designing studies.

DR. RUSSELL: Another comment is that you mentioned in the epidemiology, perhaps just as an example, that the Nurses Health Study might be a population to look at. My only caution there would be that they are not a particularly representative group because they have other health habits. They may be more health conscious, for example, than the normal population that you are dealing with. So, it may be that a longitudinal population that has been followed that is more representative, perhaps a Framingham study for example, might be a better population group to look at.

DR. TROXELL: Thank you.

DR. SCHERER: I am just wondering whether any consideration has been given, or discussion, in terms of expanding a bit the risk communication section. For example, it seems to me that the idea of communicating all of this to the public is certainly a sound one but it seems to me that maybe a part that is missing is more of the preparation for how to do that. This particular risk, it seems to me, is in some ways potentially, if the science bears it out, what might be described as the perfect risk, risk challenge. It has all of the elements of being one of the more difficult ones to communicate. So, the idea would be that to some extent there needs to be some work done on understanding how to change human behavior in this case because that seems to me to be the real challenge.

DR. TROXELL: I think we would agree with you that it is always a challenge to provide messages and education that consumers will respond to. That is the challenge of any message and in

this case probably more so because consumers hear many negative messages and they are puzzled many times about which ones are really important to listen to. So, yes, a study of what would work and what won't work is important. You know, if we are going to go out with a targeted message, for example relating to cooking, we certainly want to make sure that what we do has scientific underpinnings like the toasting issue. We clearly don't want consumers to hear cook food less generally because then we would end up having more problems from pathogens. So, we would be reducing a risk from this a little bit but we could be creating an actual health hazard from people not cooking their hamburgers well enough.

DR. TORRES: When I look at where most of the studies will be done on formation, it seems that the focus is on the National Center of Food Safety. So, I have two questions. One is that most of the research at that center is fee-based access. So, if you pay a fee you have access to the research. So, the question is how accessible

would that research be to any industry?

Second, you mentioned that the focus should be on home use study so where would the non-home use study be done?

DR. TROXELL: Actually, most of the FDA research will be at the National Center for Toxicology Research. They are undertaking the NTP bioassay and all the mechanistic work. As to the studies relating to reduction, the National Center will do some of that work, and has the capability to do some additional work on pilot process testing, and that work will be fully available to everybody as early as possible and generally is presented as early as possible.

Yes, I think the Center does some private work but our Division is not involved in that kind of work out there. That is work that is between the researchers at IIT and particular industry members. We will only do a portion of the formation research. We don't have the capacity to do a large portion. We really need to depend on other organizations, other governments, industry

and so on to push the research on reduction forward. We also expect that is necessary because food is so complex we will probably need different strategies for different foods. While we can hope for a magic bullet to quench the reaction, that is something that I am not aware of anybody having a handle on at this point.

DR. TORRES: My question specifically is will we hear more details about the research done at the National Center for Food Safety. I agree with you that they do have the capability to do pilot studies and they have the equipment to simulate industrial processes, but I don't see that anywhere in this report.

DR. TROXELL: Well, part of our effort is to make information available as early as possible to help fuel the process of discovery. Obviously, the FDA is committed to that so we will make any discoveries available as soon as possible. Dr. Jackson, at the subcommittee meeting, presented on the mechanism and also showed some initial results on potato chip work. So, we are making our

research available as soon as possible.

DR. MILLER: Johanna?

DR. DWYER: Thanks for a good presentation. Just a couple of points, the first is I was delighted to see that you are using HANES, or are hoping to use HANES, but the number of subjects above the 95th percentile will be very small, as you well know, because the sample size is only 5000. But the notion of using blood and connecting it with diet and other exposures is very appealing.

I was taken by Dr. Russell's comment about longitudinal studies and Framingham is one example of a place where other agencies in the public health service have invested considerable money in maintaining sample sizes. The other one is the Women's Health Initiative which, not surprisingly, eliminates men but is very large, about 35,000 people I think in the randomized study and I think the observational study is even larger. That, again, is heavily supported by the NIH. It is one of the largest studies in the country. It would

seem like you would also want to explore that particular study when you look at feasibility of prospective studies. The advantage of that particular study is that the data and the assumptions that are used in the food frequencies are totally transparent because it is all federally funded, and basically the forms they use are things that were developed I think at NCI.

The second point is simply this issue again of getting all the data that are available on acrylamide levels in food into your database. It sounds to me like you are spending at least a million dollars, if not more, to try to do these assays of food within the agency. I haven't looked at the FDA budget lately but it strikes me that it is a lot of money, and if there are others who also have data on this we have to find ways--and food composition in general--to get this data into national databases for risk assessment.

DR. TROXELL: Thank you for those comments. Getting the data together on levels was a major discussion point at the JIFSAN meeting. It

looks to me like they are going to be able to compile, hopefully, an enormous amount of data that is going to fill in the gaps for us substantially.

Clearly, we are going to have to look at individual foods to see what kind of data we have for those distributions and where we need to fill them out. We will be consulting with our statisticians to make sure that we have adequate information. But, as you know, you can do an exposure assessment with one data point and it is just how good is that exposure assessment. So, we ultimately want to understand the distributions from the major foods.

DR. MILLER: More comments? I have just a couple of points. Clearly, some of this work is already in progress. Can you give us some idea of what the timeline is for your priorities about what is going to be done first?

DR. TROXELL: I am sorry, I don't have a timeline on each of these studies. Much of the tox. work is either in the planning stage or has already begun. There is short-term work from which

within a year or two we should be reaping benefits. Of course, the bioassay is going to be very long. We have just put in a proposal for the home cooking work for the National Center. It is going to take some time, I am sure, for JIFSAN to compile the database and so on but that work was begun a while ago to try to get the different players to submit some of their analyses.

We are--what?--ten months into this project. We started without a method and, obviously, the first thing we need is to be able to detect and to find out what we are dealing with so we are pushing forward as readily as we can. I don't know if that is enough. Dr. Canady may have some additional information on timelines.

DR. MILLER: Well, it just occurred to me that we are looking at an action plan that may already be in progress. Unless there is something seriously wrong, other than beating a dead horse, there isn't much you can do about changing it. The committee made a decision that they would like to see you modify some of the activities but if a

study is already under way it would be difficult to change.

DR. TROXELL: Well, I think any recommendations coming out of the committee would be carefully examined to see if something should be modified in approach to a short-term study or other studies. Things are not that far down the road, I believe, that they cannot be altered and, I mean, we are here to receive this input. It is important to us, very important to us that we get it as right as possible at this point so we have what we think is a good framework, a good template for proceeding, not that we won't need to evolve that template in another year.

DR. MILLER: The other question I had concerned funding. How are you, or are you, attempting to get other groups, particularly university research groups, involved in some of this research in order to expand the research base?

DR. TROXELL: We have tried to do some extramural proposals. I don't know that we have been successful in getting those through. It is

not clear to me how much we are going to be able to accomplish as, you know, the budgets are not growing at this point; they are decreasing. So we are hoping to tap into I guess other people's budgets.

DR. MILLER: That is what I meant, like NIHS.

DR. TROXELL: Right, we will work on that but, again, that isn't in our control. We can control the agency's dollars and where they go. We can work through the Department to try to get additional funds focused on this and, hopefully, we will be successful in that.

DR. MILLER: Have you had discussions with NIHS on this issue, or any of the NIH institutes?

DR. TROXELL: Well, they are definitely interested in looking at the neurotox. and the germ cell part of the work so that is in progress.

DR. MILLER: Dr. Lee, yes?

DR. LEE: Terry, since we are on this subject of "Troxell-cology" I would just like to ask perhaps philosophically what is the long-term

outcome? Do you think we will ever get to a point with acrylamide that no more information is needed?

[Laughter]

DR. TROXELL: Well, in the sense of good "Troxell-cology" as with all toxicology, we always need one more study.

DR. LEE: Right.

DR. TROXELL: If we can nail down those essential needs of bioavailability, the high dose/low dose and so on, that is going to really help us get a handle on what the potential human impact is. Again, trying to understand high dose/low dose is going to depend on some pretty sophisticated chemistry trying to measure adducts. This is science and, as you know, you never know exactly where science is going to take you and how far you are going to go with it, and we are going to push it as well as we can and certainly some of the best researchers in the country are measuring adducts and you will hear from one of them later, Dr. Fennell, on adducts and we will see how far they can go with this work.

DR. MILLER: Johanna?

DR. DWYER: I am concerned a little bit though about singing from the same hymn issue of all the government agencies working on this. I know you are trying very hard to coordinate the work, and so forth, but I am just concerned that we don't sit here in a year or two and hear three different agencies, all telling us different things about the exposure assessments they have done, and so forth. And, what kind of guarantee is there that this isn't going to happen? I am also concerned about Dr. Miller's question of the time frame. How do we know if the time frame has been revised if we don't know the time frame to start out with?

DR. TROXELL: Well, as far as the exposure assessment, the FDA is responsible for the exposure assessment I believe so we will be doing that. We are doing our best to coordinate the work and all I can say is we are working very hard at it. We had an interagency meeting. We are going to go back and have further meetings to try to ensure

coordination. There have been meetings along the way on the neurotoxicity. Dr. Canady attended a meeting that had a session on acrylamide in November. We will be doing a meeting at some point this spring, I believe, on the germ cell toxicity, and so on. So, we are making every effort to coordinate the actions and we hope, you know, that it pulls together. I don't want to provide any absolute guarantees because obviously it is not all under the control of FDA but we will work our best to keep it coordinated and on track.

DR. MILLER: Have you made an attempt to develop some kind of a consortium of those people who are working in this area? Because if you just have meetings periodically there is always a delay in this thing but a consortium with different groups given the responsibility of coordinating information on different aspects of the problem might be a way of getting the data distributed much more rapidly.

DR. TROXELL: The closest thing to a consortium is the work of JIFSAN to coordinate the

efforts.

DR. MILLER: Coordinate which efforts?

DR. TROXELL: They are basically coordinating all aspects and gathering the information together on all aspects internationally to make sure that all information is available to everyone. That is more of an information exchange kind of system. So, I guess I would have to say, no, we don't have an explicit consortium to work on this. The FDA, because this is a problem in FDA regulated foods, is basically taking the leadership to coordinate the efforts among the agencies and to do what we can to leverage the academia and industry. So, in a sense, we are the head of the consortium to explore acrylamide.

DR. MILLER: Yes, Dr. Mehendale?

DR. MEHENDALE: I was pleased to see that you mentioned the high dose/low dose bioavailability studies as being very critical. I was hoping that there was a timeline on those studies. But it seems like the results of those studies would help us to at least get the direction

of the larger issues I think.

The second point I wanted to make is I didn't see anything in what you mentioned, if you are considering any special populations. A couple of them I can think of, You know, just last week we had an issue of Science devoted to obesity and I know lots of people are considering diet restriction or caloric restriction. One of the things that happens with caloric restriction is induction of Cyp 2E1. That is a special population or special physiological condition. Diabetes is also thought to be associated with some induction of Cyp 2E1, and there may be other special populations. I wonder if you have any comments on that aspect. I think considering these populations might also be helpful when you are looking at more sensitive populations and, therefore, it might be helpful in arriving at safe levels.

DR. TROXELL: Number one, I don't have any further information personally on timelines, other than to expect that the toxicology on the short-term studies, which can give us some insight

on high/low dose bioavailability, are going to take one to two years. Do you have anything further, Rick?

DR. CANADY: With regard to the toxicology studies, we have already got some results. For example, work on adduct formation, DNA adduct formation has already been developed. Bioavailability and studies along those lines with regard to toxicokinetics, some of the initial findings I guess we will have within the next six months to a year. We have proposals that we are currently reviewing on the specific studies but some of the studies as you can imagine, for example bioavailability, are relatively short-term studies comparing area under the curve for different routes of exposures and that is something that can be done fairly quickly. So, those studies with regard to toxicokinetics we can expect to see, as Terry was saying, in the next year or two but probably some of the initial results will be in the next six months to a year. Again, some adduct studies are already available.

I am not sure how else to give a more specific deadline or specific timeline, other than to say we have proposals and we have specific information on modes of action we are evaluating within those timelines. Is there more detail you would like with regard to that? It is not like we can give you that the bioavailability studies will be done by June or--

DR. MILLER: I think the question was in terms of priorities, what is being done and what is going on. I think you have done that.

DR. CANADY: Good. With regard to the special populations, clearly in considering the prospective studies that is a very important determination, very important source of confounding or a way of designing the studies. Glutathione transferase, Cyp 2E1, polymorphism with regard to those inductions are things that are clearly important to consider when thinking about how you might go about doing those studies, and we are well aware of that.

With regard to specific animal studies,

NIEHS has already initiated some studies with Cyp 2E1 knock-out mice to look at the conversion of acrylamide to glycidamide and looking at the mechanistic interpretation of that information with regard to neurotoxicity, germ cell toxicity and also DNA adduct interactions. NCTR and NHANES are working together to develop that line of mechanistic research. Specifically, NCTR will do the DNA adduct work for that set of experiments.

The NHANES studies, as you know, sampled some specific populations but they weren't designed to specifically look at acrylamide issues so maybe others can comment more specifically with regard to how NHANES would be used to look at specific populations. You would have information that would be relevant to intake but whether it is specifically relevant to caloric restriction, probably not. Whether it is specifically relevant to foods that are high in acrylamide, that is something we need to evaluate still. But the bloods have been set aside to do specific adduct work, the bloods that were taken earlier this year,

in fact, for NHANES so that information would be worked into the study design to the degree it could.

Results of separate studies being considered by CDC and CEH are intended to look at sort of add-on acrylamide dosing or foods that have acrylamide and through that we could evaluate some of the questions that you are talking about.

DR. MILLER: I think this issue of stress populations, particularly for something as ubiquitous as this is, would seem to me important enough to mention as part of the Action Plan. I am not exactly sure how it would be done but it seems to me it needs to be considered, and more general stress situations where we know there are metabolic changes and inductions that occur in response to stress.

DR. TROXELL: See, it makes a difference when you have a real toxicologist instead of a "Troxell-cologist" to provide the answers!

DR. MILLER: Any other comments or questions? Yes?

DR. RUSSELL: Jumping ahead to risk communication because I don't see any other time to really comment on this, I think it is a good idea to have the dietetic nutrition associations in concert with you in communication efforts, but you will have to cast the net pretty wide for these nutritional organizations. It is not that you can just pick one or two or them. There is a whole group of them that have different kinds of missions, if you will, but they have very important audiences and very important journals, a couple of them, even though the societies are pretty small. So, you need to really cast the net pretty wide there. You have mentioned one very big one, the American Dietetic Association, and one very small one but you need to go much beyond that.

DR. TROXELL: Thank you.

DR. MILLER: Yes, Johanna?

DR. DWYER: Specifically, I would suggest that you go to the American Society for Clinical Nutrition, the American Society for Nutrition Sciences and certainly IFT. I believe Dr. Russell

is currently the president of the ASCN.

DR. TROXELL: Thank you.

DR. MILLER: Have you made a commitment, Robert?

DR. RUSSELL: Well, that journal reaches a large audience.

DR. MILLER: Yes?

DR. SCHERER: I wonder whether there has been any thought or discussion about the potential problems that the agency faces in terms of release of information? I certainly support the idea of open communication but given the nature of the wide range of studies that are being done, it is likely, it seems to me, that at least one of those studies at some point will have implications for serious health concerns, whether that is eventually supported or not but the possibility exists. So, the challenge, it seems to me, for the agency is how do you respond to that information that is likely to be picked up by the media and, as we all know, perhaps be exaggerated? But the idea of trying to put it in perspective of the wide range

of studies that are going on, whether there has been any thought given to that process?

DR. TROXELL: Well, for every one of our meetings we do a lot of thinking about how appropriate the message is about acrylamide, and we will clearly bring a lot of energy and information to bear from our people who do consumer messages, and so on, in the chain who understand risk communication we bring that kind of to bear.

I think also, as you suggested, it is important for us to think about how we are going to communicate what would reach consumers, and I think that is a valuable comment.

DR. MILLER: Actually, that is an issue that really needs special emphasis because I have been trying to think if there were any other materials that I could remember that are so ubiquitous in diets everywhere in the world so any culture that produces a dough baked product is going to be exposed to some level of this material and how do you deal with that? That is going to be a big problem, it seems to me, as a research issue

and it needs to be emphasized. I think maybe it requires going back and looking at it again to reemphasize it again.

DR. TROXELL: Thank you. I think these are valuable points.

DR. MILLER: Any other comments or questions? We are caught between a rock and a hard place in terms of timing. We are substantially ahead of time and I was thinking of going on to our next speaker.

DR. TORRES: Maybe I could ask one more question.

DR. MILLER: Please, do.

DR. TORRES: On the subject of cooperation with different groups, one thing that really caught my attention was the message that the U.K. had done analysis on 4000 food items. That seems to be a lot of work. Could you explain to me why there is a difference between 100 in the U.S. and thousands in the U.K.?

DR. TROXELL: Well, I don't think the Central Science Lab of the U.K. has done 4000.

They have compiled 4000 from industry and around Europe, as well as their own analyses. It is just the level of progress we are at in different areas.

DR. TORRES: Thanks.

DR. MILLER: Terry, there is another question that I meant to ask before, given the different methods--well, let me ask you this question, how many different methods are being used by the different laboratories?

DR. TROXELL: That is a good thing to dwell on for a minute because even with the most elegant methods, like the LC/MS/MS method, it is pretty easy to mess up and get erroneous results. But there is LC/MS/MS; there is GC/MS; there is GC after bromination. Well, if you brominate your extract and then run it through GC with electron capture detection you get pretty good results. We are trying to look at this LC/UV as more of a screening method. I mean, we are looking for something that people can use as quick and dirty to screen their products, to help fuel their research, for developing countries to be able to use, and so

on, and also maybe as a quick screen for us although we will probably end up as an agency, when we get into the screening mode, using something like the GC/MS.

Surprisingly, when you look at the cost, and they did this at the JIFSAN meeting, the costs are--what?--$200 or something per sample for the LC/MS/MS and you are still talking about $100 or so per sample for some of the GC/MS. So, this is very expensive work and you can imagine that developing countries wouldn't have the capability to be doing much of this work.

Of course, some countries have quite different foods, different fried products and so on that can reach the high temperatures. So, for the world to get its arms around the distribution of acrylamide in foods is an interesting point, and also for us to understand if the analyses that are being put into the database are valid is also another interesting question. We are going to have to be very careful, based on the information they provide, to understand if the results are good. I

mean, there are many methods that give good results but, again, you have to perform the analyses correctly and it is very easy, initially particularly, to have problems. Therefore, people are circulating proficiency samples to try to make sure that the results that other labs are getting are going to be accurate. That is one of the efforts that is going on, to get proficiency samples in different types of foods to help improve the credibility of the results.

DR. MILLER: Looking at the developing world, is FAO doing anything to try to collect some samples?

DR. TROXELL: Not that I am aware. As I said, we have proposed an informal workshop and FAO/WHO were behind getting that together. Of course, FAO and WHO were behind the consultation and also will be working on gathering information for the next meeting.

DR. MILLER: Someone has to do those samples.

DR. TROXELL: Right, and if you look at

the JIFSAN info. net you will find, I think, there are samples in there from South Africa and I think there might be some samples from Egypt. People are sending data. That is not the JIFSAN info. net; it is the WHO/FAO information network that JIFSAN is operating for them. Anyway, these data are coming in; the databases are growing and there are criteria for methods. There are many fields to fill out--what is your methodology, and so on--so that in the end, hopefully, we will be able to understand what these results look like and how valid they might be in different foods.

DR. MILLER: I imagine a lot of these populations that consume flat breads might get a little higher exposure.

DR. TROXELL: Yes.

DR. MILLER: Johanna?

DR. DWYER: Back to the issue of the quality ratings of the values that are coming in, I don't have any knowledge of this particular compound but certainly with flavonoid in food, where there are a lot of advantages for industry

and others to try and find out what is in there because there are possibly positive health effects, there are quality rating systems already in place that can be used and adapted for determining whether a value is adequate or not adequate. I believe Dr. Beecher and others at the Ag. Research Service, right over in Beltsville, developed those methods some time ago. I wonder whether you are using those methods, adapted for acrylamide, to screen your values so that the database is as inclusive as possible, at the same time meeting quality criteria for analysis, sampling and so forth.

DR. TROXELL: Clearly there are performance criteria one can apply to analytical methods, and the GEMS database at WHO has many data fields which list out what is your method, what is your limit of quantitation and how you establish it, and so on. I believe an awful lot of information is requested of submitters so probably it is more than adequate and, in fact, if anything, there is so much information requested that it kind

of inhibits people from submitting data because they have to put so much energy into providing the data. So, yes, I think we should be able to distinguish between the good data and the questionable data. Clearly, when it is questionable we won't use it.

DR. MILLER: Any other comments or questions? If not, we are going to adjourn for lunch and return at 12:45 for the afternoon session. Thank you.

[Whereupon, at 11:15 a.m., the proceedings were recessed, to resume at 12:45 p.m.]

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

Mechanisms of Formation

DR. ZYZAK: April 24, 2002, this is a shocking date to many people in the food industry as Stockholm University, in connection with the Swedish NFA, revealed acrylamide presence in a variety of foods. As many organizations began to develop analytical techniques with a capability of analysis of acrylamide in foods it came out that the data released at this time was accurate.

[Slide]

We, at P&G, did our own product survey and here is a sample list of that. As you can see, we also found acrylamide present in a variety of foods such as toasted bread products, roasted asparagus, corn chips and potato chips.

[Slide]

What is acrylamide? Acrylamide is a conjugating e-amine molecule. It has a high boiling point and it is also very hydrophilic or water loving. I think this is probably why it took a while for us to detect it in the food system.

Typical analytical techniques in the food industry involve head space which is dependent on the boiling point or extraction of organic solvents and in this case acrylamide would tend to stay more in the aqueous phase.

[Slide]

Now that people have accepted the fact that acrylamide is present in foods, the next issue is how is it formed. Some initial mechanisms that were proposed from the Food Research Institute were based on equivalence formed in the frying process so there are lipid oxidation products which could be precursors, and some of these have similar structures to acrylamide. You can see acrylamide here and this is acrylic acid. The only difference is we need an amide bond here and acrolein, another lipid oxidation product.

However, this formation of the amide bond is not a very favorable reaction in typical food conditions and subsequent research in this area has shown that this is not occurring under typical cooking conditions. Again, the trouble came in the