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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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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. MILLER: We will begin the second day's program. At some point later on this morning, depending on how the discussion goes, we will determine the program that we will follow for the rest of day and see how much time we are going to need in order for our discussion and so on. We will see whether we may be able to finish early and those of you who have planes to catch will have a little more time to do that.

Our first speaker this morning is Dr. Sorell Schwartz of Georgetown who is going to talk about animal studies in relation to human health consequences.

Animal Studies and Human Health Consequences

DR. SCHWARTZ: Thank you.

[Slide.]

It is a real privilege to be here. We never had to worry about true-type font. Now, you do because I submitted my slides to the FDA and what was a true-type font on my computer wasn't on

at

theirs, so their computer attempted to make conversions and didn't do very well. So, this morning, we spent some time straightening it out.

However, all the errors are carried on to the printed sheets of the slides that I have. So some of them may be out of format and some of the symbols may be wrong. But welcome to the world of computers.

My presentation does not deal specifically with acrylamide. It really deals with interspecies extrapolation, the extrapolation of animal data to human data, to human use. It can take many forms. It can be rather gross such as in the default options, the false scientific assumptions that are made. If a material is a carcinogen in an animal, it is a carcinogen in a human. Why? Because we say so. That is one form of interspecies extrapolation based pretty much on what someone might say is a prudent public-health policy, or that the human is at least as sensitive as the most sensitive of animals when it comes to carcinogenicity. Again, why is that? Because we

say it is based on just policy matters. But it is hardly a scientific extrapolation.

For noncancer effects, we can have also relatively gross extrapolations taking the no-observable-adverse-effect level that is observed in a rat or a mouse or whatever, dividing it by 100 or dividing it by 1000 as a safety factor, actually an uncertainty factor, again not a very sophisticated means of extrapolation but it gets the job done with respect to doing on harm, or hopefully doing no harm.

But more ambitious attempts at interspecies extrapolation involves some form of scaling the physiology of the experimental animal to the physiology of the human.

[Slide.]

The foundation of interspecies extrapolation with respect to the effects of chemicals on the biological system actually rests on two pillars; pharmacokinetics and pharmacodynamics. Pharmacokinetics, as can be seen, deals with the actions of the body on the

chemical, itself. It deals with the absorption, the distribution, the metabolism and elimination, the so-called ADME, and the output that we get from it is a concentration-time relationship.

The other pillar are the pharmacodynamics which is the action of the chemical on the body. The system we are dealing with is the interaction with biological ligands. It may be a receptor. It may be an enzyme. It may be DNA. It may be some type of adduct formation. The output is, of course, the biological response.

In the interest of saving time, suffice it to say, there are no means to predictively extrapolate biological response across species other than heuristics, other than we have certain things we understand. If we are extrapolating something like some specific organ toxicity like neurotoxicity, we tend to feel that we can extrapolate from animal to man with some degree of reliability.

On the other hand, cancer as carcinogenicity is a bit more iffy, as we have

learned, and teratogenicity, birth defects, are essentially extrapolatable only by guess, recognizing, for example, that the positive control in teratogenicity experiments is aspirin. So it is something that doesn't extrapolate well.

So we are left with really our heuristic understanding of what goes on in extrapolating pharmacodynamics. So that leaves is pretty much with the pharmacokinetics.

[Slide.]

Pharmacokinetic dose extrapolation from animal to man, we essentially say, let's take the area under the concentration time curve that we get for an experimental animal at a particular dose and see what it takes in man to get that same area under the curve, what dose that is.

This action is strictly empirical. There is some computation involved in estimating it, but essentially, we give the dose, we know the pharmacokinetics in man, we know the pharmacokinetics in the animal. We look at the area under the curve of the dose that has caused

the effect we are looking at. What we are looking for--in this case, we have it as an LD_{10}, which we are translating to the minimal tox dose in man, and we try to create the same area under the curve, the area under the curve and the same Cmax, so that the curves look the same.

That is essentially the goal of interspecies extrapolation but it is not as easy as one might think.

[Slide.]

We should digress a minute and look at what can we scale among species. All of us know that a rat is not a small human. Nonetheless, we continue to treat it that way. We give dose per kilogram in a rat and we say, okay, what is the dose per kilogram in a man and, somehow, we make that extrapolation.

But we know, in our heart of hearts, that a rat really isn't a small human. So, we look for some type of proportional interspecies scaling. One is isometric which means that the proportion in the rat or in the experimental animal is the

same as in the human. So, across species, the proportion of the heart weight to the body weight is constant across species. The proportion of lung weight to body weight is proportional across species. And skeletal weight, and muscle weight, and GI-tract weight.

All of these are proportional across species and whatever percentage it is in a rat, you can expect within some error estimate, to be that same percentage in man.

There is one particular organ that is missing here, and that is the brain. The brain does not extrapolate across species. Actually, it does extrapolate across species except one, and that is the human. If you extrapolate across species the brain weight, it works out pretty well until you get to man because, if man is part of that extrapolation, the brain weight would be predicted to be about 275 grams. Actually, of course, it is about 1200 grams.

So this is one departure which we are going to discuss a little bit later but it is of

particular importance. So isometric scaling pretty much covers for organ weight, most organ weights, and blood volume and respiratory capacity.

[Slide.]

That is isometric. Now, allometric scaling essentially says that we can extrapolate across species to some exponent of the body weight. That exponent b, in this case, is the allometric scaling component and a is a coefficient that we get from regression analysis. But is the scaling exponent that is important.

What we spoke of before, the isometric extrapolation, that scaling component is 1 so that we have a direct proportion to the body weight. There are two general categories of scaling exponents. One is at about 0.25 and heart rate, circulation time, respiratory rate, extrapolate at a scaling exponent of 0.25. The other is 0.75, or approximately 0.75.

Basic metabolic-rate blood flow, and we are going to discuss clearance in a little while, can also be extrapolated within a range of some

error of that scaling component. We will discuss it in a little more detail.

Some of you who are familiar with this may say, what would have happened to two thirds, because there a two-thirds scaling component is often used. There is some disagreement with basic metabolic rates should be scaled to two-thirds or 0.75, but the two-thirds scaling is primarily used in scaling body weight to surface area.

It is used clinically in cancer chemotherapy because dose scaling in cancer drugs seems to work best by dosing per body surface area rather than per body weight.

DR. LEE: Ken Lee. Could you just explain how circulation time and blood flow are different?

DR. SCHWARTZ: Circulation time is the time it takes to get from one point to the other at a particular measurement. We know what that is. The blood flow really deals here--I understand your point. Overall, it would seem they should be the same. But it is really scaling the blood flow in a particular organ.

When you look at blood flows in particular organs, the liver blood flow, the pulmonary blood flow, the blood flow through any particular organ, scales at 0.75. The total circ time scales at 0.25.

But I understand your question and it is not clear as it is presented there.

[Slide.]

Now, pharmacokinetic factors that we have to worry about or be concerned about with respect to interspecies extrapolation, and it is the same pharmacokinetic factors we have to deal with clinically, are volume of distribution, clearance and the absorption and bioavailability.

[Slide.]

The volume of distribution is essentially defined as the volume the chemical would be distributed in if it were distributed throughout the body in the same concentration it is in the blood. So you can have, for example, a volume of distribution of 70,000 liters, certain drugs which--certain antimalarial drugs bind very

strongly to all sorts of protein outside the circulation.

So it is an apparent volume, but it is important because, thermodynamically, the system actually behaves as if that apparent volume is a real volume. So it is the total mass of the chemical in the body divided by its concentration in the blood. It describes the distribution of the chemical throughout the body and, ultimately, to the biophase, the site of action.

The greater the volume of distribution, the greater the biological half life. This is scalable based on interspecies composition relationships and physical-chemical factors, what are called quantitative structural pharmacokinetic relationships. This is essentially scalable isometrically. Generally, it is scalable isometrically.

If we think about the body weights, the organ weights, being scalable isometrically, you could understand what the line of distribution might be. It is not absolute, but it is generally

within 0.9 to 1.0.

[Slide.]

The clearance is the volume of blood per unit time from which the chemical is completely extracted. The higher the clearance rate, obviously the smaller the half life. It is the blood flow times the extraction ratio. The blood flow is allometrically scalable across mammalian species, as we said. It is generally to an exponent of around 0.75.

But the extraction ratio may or may not be scalable. Extraction ratio refers to just that, what fraction of the drug or the chemical is extracted by the organ. If the extraction occurs by some process such as filtration diffusion, that is a nonsaturable first-order process. Generally, it will be scalable anywhere between 0.75 and 1.0.

However, if there is metabolism involved, depending upon the saturability of the system, if it remains pretty much first order all the way through, it will be scalable. But you can also expect there will be interspecies differences in

metabolism.

In the case of acrylamide, there are interspecies differences in the metabolism of acrylamide to glycidamide. Also, the acrylamide to glycidamide is saturable. In doses likely to be in contaminated foods, it is not going to be saturable, but, also, the glutathione conjugation of acrylamide and glycidamide which is a means of inactivating both of the compounds is also saturable so that extrapolation from animals can be iffy when you are looking at the metabolism of these compounds.

[Slide.]

As I said, clearance can be flow-limited, meaning we have a high extraction ratio. The clearance is really determined by the blood flow. If we have a low extraction ratio, then the clearance's capacity is limited, that would be a saturable system, what I was just speaking about. Flow-limited clearances, like I said, would be more likely to be scalable than capacity-limited clearances.

[Slide.]

Now, absorption and bioavailability are very important factors to deal with especially when you are speaking of exposures that concern food contamination. The bioavailability, which is the upper case F here, is a function of the fraction that is absorbed, the fraction that gets by GI tissue metabolism--that is why 1 minus f_g is the fraction that gets by tissue metabolism--and the fraction that gets by liver metabolism. That is the same extraction ratio that we were talking about before that is equivalent to an hepatic first-pass effect where a drug is absorbed, when the drug passes from the gut into the liver through the portal vein. Before it gets into the system, it must pass through the liver. In passing through the liver, there is this first-pass effect which will metabolize the drug and reduce the systemic availability.

The problem is that you can have variations in extraction ratios, small variations in extraction ratios, which can greatly affect the

bioavailability.

[Slide.]

In the interest of time, I am not going to go through some of the factors that I was going to go through, but the point that I want to bring out is that, depending upon the size of the extraction ratio, we can have small changes in the extraction ratio and large changes in the effective dose.

Conversely, we can have--this is part of the problem with the formatting. This is not complete, so I am not going to dwell on this other than to say that the extraction ratio variations can have a very profound effect across species on what is absorbed and what the absorbed dose is. It is something that I find, in reading the literature, is not often taken into account as it should be.

[Slide.]

So, for allometric extrapolation, what is likely to be reliable? GI absorption is likely to be reliable, the actual absorption, just the movement. The volume of distribution is likely to

be reliably extrapolatable as blood flow, clearance, where the clearance is flow-limited and the extraction ratio is high, and bioavailability, where the extraction ratio is low.

I am not going to go into the reasons for all of this but it shows you that, in fact, you have a yin-yang between clearance and bioavailability as far as extraction ratio goes; that is, that a high extraction ratio favors the scalability of clearance but not of bioavailability and vice versa, a low extraction rate does not favor the scalability of clearance but does favor the scalability of bioavailability, which shows that life is difficult, which you probably already knew.

[Slide.]

It is less and less likely to be reliable, as I said, as we have just stated before.

[Slide.]

There are certain allometric approaches to clearance, certain variations. One is that the first approach is the one that we were just

describing, just the straight equation.

Another involves the inclusion of neoteny, which is peculiar to humans. Neoteny refers to the juvenilization of humans; that is, it takes human a longer time to reach maturity than it does most mammals. Most mammals reach maturity at about 30 percent of their body weight. Humans reach maturity, puberty, at about 60 percent of body weight and it seems to have some relationship to both the life span, the maximum life-span, potential and the brain weight of humans.

There have been various approaches to include neoteny using, for example, a particular approach, the same equation of body weight to the exponent but divided by the maximum life-span potential, one involving the brain weight and the body weight. But, interestingly, as it has turned out, there is a question of whether the neoteny is as important as really doing some straight-out in vitro measurements of hepatocyte activity in the animal and in man.

[Slide.]

We can, now, get liver from humans. It seems that a way around the interspecies extrapolation for clearance, where metabolism is an important factor, is to take the clearance that is determined in animals in vivo, then take clearance determined from examination of individual human and animal hepatocytes and essentially use that as a correction factor to get the clearance.

This seems not to involve any other assumptions, brain wave or life span. It is just measuring the actual enzyme levels, themselves.

[Slide.]

Another approach to interspecies extrapolation is physiologically based pharmacokinetic modeling. The one problem with allometry, as we have pointed out, is the fact that you can allometrically scale various individual factors in animals, but there is no way to combine all of the factors. We just pointed out, there is a probem of scaling both clearance and bioavailability when the extraction ratio is either very high or very low.

There is the other question of extrapolating various functions that, in fact, may work against each other, like we were discussing with bioavailability and clearance. In physiologically based pharmacokinetic modeling, essentially each organ is modeled by its own flow equation and we establish a model using a series of simultaneous linear and nonlinear differential equations that allow the determination, or the estimation, of concentrations in each tissue, specifically, to estimate what is in the biophase because it is not drug in blood, or chemical in blood, that is active. It is not chemical in the tissue that is active. it is chemical at the site of action that is active.

What is in the blood and what is in the tissue may not always reflect what is at the biophase of the site of action. In the case of acrylamide and its metabolite, glycidamide, dealing with adducts, potential DNA adducts, you could--now this happens to be rate model for drugs, but the pharmacodynamic side of this could be binding

characteristics for adducts so that you could go all the way through and, through such a model, estimate what the binding to adducts would be in the animal compared to humans and extrapolate that and then make some assumptions about response.

[Slide.]

Just to let you know that, in this particular model, you not only can model the parent compound but you can model its metabolite essentially by running a parallel model where one model feeds the metabolite to the other and it goes through its own distribution.

[Slide.]

So physiologically based pharmacokinetic modeling to low-dose interspecies extrapolation, we develop the human physiologically based model using the tissue-blood partition coefficient that can be developed from animals because that is easily scalable, use the value for organ clearance based on human experimental data in vivo or in vitro, or by allometric extrapolation.

[Slide.]

We can use the model to identify daily intake resulting in particular target-tissue concentrations equivalent to the tissue concentration in the experimental animal, and, if there is insufficient information to develop a human PBPK model, we can extrapolate the estimated animal intake associated with an observed response to a human intake using an appropriate allometric relationship.

[Slide.]

Finally, there are a number of applications of the model, of using PBPK modeling. One is interspecies extrapolation. Another is predict the target-site concentration. The extrapolation in cases of nonlinear pharmacokinetics, or pharmacokinetics, where, for example, if you give a dose X, then you get Y blood level. If you give 2X, you expect to get two wide blood 2Y blood level. In nonlinear pharmacokinetics, that doesn't happen. Physiologically based pharmacokinetics allows you to correct for that.

It is especially good for low-dose extrapolation. It is good for route-of-exposure extrapolation. Physiologically based pharmacokinetics can allow you to take, for example, if you had a study, an animal study, that deals with inhalation of, let's say, acrylamide, or dermal absorption of acrylamide, it allows you to simulate what it would have been had it been an oral-dose experiment, a feeding experiment.

It also allows relative risk for multiple route of exposure, which doesn't apply here. So acrylamide, it does apply to such things as benzine. Finally, something here with acrylamide and hemoglobin adducts, it will allow estimations of exposure based on biological markers.

This is going through pretty fast, but to show you the various techniques that are involved in extrapolation. The most important thing that we have to know about models is that we never prove a model is correct. All we do is use it until we prove it is incorrect, which happens, so far, all of the time.

DR. MILLER: Thank you, Sorell.

Questions of Clarification

DR. MILLER: Questions or comments?

DR. BUSTA: Frank Busta. Based on this last summary, what data would you need from our question at hand?

DR. SCHWARTZ: Your question at hand being the extrapolation of acrylamide animal data to human data?

DR. BUSTA: And/or the consumption of acrylamide by humans at low doses.

DR. SCHWARTZ: My own feeling is that--first of all, I should say that acrylamide is not my field but, obviously, in preparation for this presentation, I did look to see what had been done in the modeling.

There have been some physiologically based pharmacokinetic models with acrylamide. I think from the point of view of your problem, that is the only way to go. The reason is that you have, first of all, the problem that you have a number of different routes of exposure--you have a few

different routes of exposure, datasets that can be converted, if you will, by modeling to oral administration datasets which allows you to use the data.

Secondly, the concern about whether or not the amount of acrylamide likely to be taken in would saturate, or the effect it would have on glutathione conjugation. Glutathione conjugation is especially important in the inactivation of electrophiles of which, as you know, acrylamide and glycidamide are both.

I think that is pretty hard to do by straight allometric extrapolation but it can be done, it can be estimated, by physiologically based pharmacokinetic modeling. I think those are the factors.

The real question is whether or not the amount of acrylamide likely to be taken in during food exposure is going to affect how you can extrapolate from animal to man by virtue of -- I guess my question is does the metabolism still remain first order. In other words, do you have

enough to start saturating the metabolic systems or is it low enough that it won't saturate them and you can treat it as first order, which makes extrapolation a lot easier.

So, I would think the latter. I would think that you wouldn't saturate. You can think of all sorts of clinical situation, of someone who is taking too much tylenol or drinking too much alcohol that could have an effect on how acrylamide might respond. But that is sort of an academic exercise.

I think, from a point of view that you are interested in, PBPK modeling would show that you can deal with metabolism pretty linearly--I think. I guess the other question is whether using hemoglobin adducts as biomarkers would be of value. A PBPK model would give you some idea of that.

Does that answer your question or not?

DR. BUSTA: If I followed you, maybe.

DR. SCHWARTZ: I am sorry. I can understand the frustration that people have with pharmacokineticists, but I guess, in summary, we

need to know metabolic data, we need to know physical data, tissue-distribution data. But that has already been determined for acrylamide, as far as I know. There already is a PBPK model. It hasn't worked all that well, but it is not necessarily because of lack of data.

DR. MEHENDALE: I guess one way to approach this is, partly you mentioned, the partition coefficients are generally available and the metabolic constants, kms and so on, should be available. I don't know if, for human tissue, they are available and that might be useful and suppose it can be determined from the human hepatocytes if it is not available.

But, certainly, for animals, I suspect it is available. If it is not, it can be determined. But one area that I think would be useful--generally, we look at the PBPK model as a way of dose extrapolation as you rightly emphasized. But, if there is an enzyme saturation, which, at high doses, is likely to occur--at very low realistic consumption levels, probably not.

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But the issue here is that if there are animal data with high whopping doses of acrylamide, can they be used to extrapolate to humans, and if enzyme saturation is an issue.

Generally speaking, it has turned out to be an issue whether it is the glutathione pathway or the cyp 2E1 pathway. This compound is certainly showing some signs of saturating cyp 2E1 at high doses.

So my comment is whether knowing this data would be useful in trying to determine whether animal data obtained at very high doses can, in fact, be useful unless we establish those issues of saturation and so on in extrapolation with PBPK.

DR. SCHWARTZ: You have brought up what has been an age-old problem--actually, it is an age-old illusion--and that is that somehow or another, that we can get away by taking large doses, taking results of studies with large doses, and extrapolating them somehow back down to low doses without taking into account saturation.

As you know as well as I do, this has been

done time after time after time. It is illusory. If you have a saturable enzyme system and you are giving large doses, it could be illusory in two directions. If your metabolite is this toxic component, you could actually be underestimating the toxicity of the substance. If your parent compound is the toxic compound, you can be overestimating the toxicity by extrapolating to low doses in these.

But you are absolutely right. It is necessary to know, and I think with the availability now of human liver and such, I think it is necessary to know what Vmax is and km for human versus the Vmax and km for whatever animal you are working with.

I think it is very fundamental data to have before you can speak about doing any extrapolation to low-dose exposure from animal experiments.

MS. HALLORAN: I am just trying to make sure I am following the discussion here. This question of extrapolation from the animal studies

to the human situation is, obviously, critical. Do we, at this point, have the necessary data in terms of the pieces of the analysis you were just describing to more or less extrapolate from rat studies to human, or are there critical pieces of experiments that still need to be done to do the best possible reasonably acceptable extrapolation?

DR. SCHWARTZ: I would be deceiving you if I answered your question of how much acrylamide because it is not my area of familiarity that I have, as I said. I am discussing the methodology and I familiarized myself with some of the material that is available, but I do not know all the data available.

I think that what we are saying is that here is what data you need. Whether we have it or not--I know you don't have the human hepatocyte data, but whether you have it or not, I don't know I do know that what data was used in the development of the physiologically based pharmacokinetic model and it didn't have human hepatocyte data.

So, actually, I can't answer your question. But we can pretty well define what it is we need and then you can decide whether or not to go after it. I do have to say some of the reviews, some of the summaries, I have seen on the ADME of acrylamide in the various reports I read and familiarized myself with, have a degree of naivete about them. I don't mean that in a pejorative sense. It is just that you really have to do exactly what you are doing right now, is say, what do we need to really model this.

So the answer to your question is, the only thing I can tell you is it is a good question. But I can't tell you the answer.

DR. DWYER: Just to follow up on Ms. Halloran's question. I think that the thing that I found a little unsettling was your comment that you can only prove that a model is incorrect and then you said that the PBPK modeling that had been done so far didn't come out very well, and then you just said the modeling was naive.

Now, would all of those things contribute

to an underestimation of human risk, an overestimate of human risk or isn't it possible to even say that?

DR. SCHWARTZ: First of all, my response of modeling, it wasn't the PBPK modeling that was naive. I said the discussion of the pharmacokinetics was naive meaning that it didn't deal with the various issues such as interspecies extrapolation and the PBPK modeling was not, by any means, naive. It was very aggressive, in fact.

What is the second half of your question? I'm sorry.

DR. DWYER: I think the bottom line is whether all of this means that the modeling--are we in danger of underestimating human effects or overestimating, or is it like the three bears, just right?

DR. SCHWARTZ: I can't answer the question. We are always in danger of overestimating or understating. From a regulatory point of view, we are always in danger of overestimating, if danger is the right word,

primarily because of the natural instinct to be very conservative.

But I think, from what I can see, and you have to understand, I am speaking really as a novice with respect to acrylamide. My major interest in acrylamide had been to neurotoxicity and some issues we dealt with some time ago. But, from what I see, there is a danger of overestimating the toxicity if the main toxic component is acrylamide and underestimating it if it is glycidamide. That really deals with the issue that, at a very large dose, you are getting less proportion of glycidamide than you would at a smaller dose.

DR. LEE: Ken Lee. What you just said, does that apply to the neurotoxicity as well as carcinogenicity, or are you referring to one or the other?

DR. SCHWARTZ: The neurotoxicity will occur at much larger doses than you are ever going to find in food. I can't see neurotoxicity as being a concern here.

DR. MILLER: The thresholdable phenomenon.

DR. SCHWARTZ: Right. It is not very plausible based on the dose-response data that we know that you really face with the neurotoxicity problem by the type of contamination you are talking about. The acrylamide neurotoxicity comes really from occupational exposure.

DR. MILLER: Other comments? It seems clear from Dr. Schwartz' presentation that there are substantial areas that require research. I think one of the questions that we have to determine is whether or not the modified action plan covers those areas.

Thank you, Dr. Schwartz.

Our next speaker this morning is Dr. Stephen Olin from ILSI who is going to talk specifically about acrylamide toxicity, research to address key data gaps.

Acrylamide Toxicity: Research to Address Key Data Gaps

DR. OLIN: Thank you.

[Slide.]

That discussion was, hopefully, an excellent lead-in to my comments here this morning.

[Slide.]

To give you a little bit of background, where I am coming from, as you know, the Joint Institute for Food Safety and Applied Nutrition, or JIFSAN, and the National Center for Food Safety and Technology convened a workshop in late October to examine current knowledge on acrylamide and food and particularly to identify and prioritize research needs in each of five areas as shown on the slide here.

I had the privilege of co-chairing the Working Group on Technology and Metabolic Consequences with John Doull and I guess that is why I was invited to come here and talk about research needs specifically with regard to acrylamide toxicity for developing a risk assessment for acrylamide.

[Slide.]

The Working Group on Toxicity and Metabolic Consequences identified data gaps and

research needs in these six focus areas. I would say, in general, that recommendations from our working group complement and build on the observations from the WHO consultation last June which, of course, is in your meeting materials.

I also would say, just to let you know, that the full report from not only our working group but the other four working groups at the JIFSAN workshop is available on the JIFSAN web site for you there, for details.

[Slide.]

I think the toxicity of acrylamide, the conclusions that came out, were really very broad and we have heard those reiterated here in various presentations and in the discussion of the committee. First, this research should accomplish these two objectives, first to assess the significance of adverse effects observed at high doses for low-level exposures in human foods, those high doses being in animal studies and, in the case of neurotoxicity, in humans and, secondly, to assess the significance for humans of effects

observed in vitro and in vivo in rodents.

Dr. Schwartz and others before me have sort of laid out that challenge and our working group certainly concluded similarly.

[Slide.]

What I would like to do, then, with you in the next few minutes is to quickly run through the research needs that were identified by the working group and at least what ongoing or planned research that I am aware of that will begin to address these research needs.

As was mentioned, I think, earlier, the Acrylamide in Food website that is being managed for WHO and FAO by JIFSAN is a place where ongoing research is being posted and recorded, so that is certainly one useful resource to keep track of what is going on out there with regard to acrylamide.

First, with regard to this area that Dr. Schwartz and you talked about a bit, kinetics metabolism and modes of action or mechanisms of toxicity of acrylamide. We know that acrylamide can exhibit several kinds of toxicity in animal

models, carcinogenicity, neurotoxicity, germ-cell mutations, others, but to effectively use these data in assessing risks to humans, we need to know more about the modes of action leading to these toxic effects, the critical events along the way and the dose metrics. So that is identified as one of the key research needs.

We also have quite a lot of information about metabolism and kinetics in rodents, as has been suggested here, but the working group really felt that we needed to make the link now with the metabolic fate and kinetics in humans. Those data, frankly, are lacking.

To pull all of this together, then, the group felt that we really need a good physiologically based pharmacokinetic model as discussed by Dr. Schwartz that will allow us to calculate dose to target tissue or dose to specific receptor or cellular component that may be a risk as a function of dietary intake for rodents and humans.

So how are we doing on these research

needs in terms of ongoing or planned research?

[Slide.]

We hope that FDA will be able to gather some information on critical events and dose metrics for the postulated modes of action for the various endpoints in conjunction with the NTP bioassays. I think there were some hints of that in the draft action plan that would certainly support that.

We know that NIEHS has beginning studies with this special mouse strain that has been discussed already here in which the gene for expression of the cytochrome P450 2E1 has been deleted, the so-called cyp 2E1 null mouse. These studies certainly will help to distinguish between modes of action that, in critical events involving *glycidamide and those that bypass glycidamide.

There are also some industry-sponsored studies that will contribute to our understanding here.

You heard yesterday from Dr. Fennell about the ongoing RTI work on metabolism and kinetics in

humans. CDC, apparently, is planning studies of the relationship between intake and biomarkers of exposure prior to the next round of NHANES and that was discussed briefly yesterday. Several other groups are looking at this problem from various perspectives, the group at Stockholm University in Sweden, at Kaisersalutern University in Germany and others.

With regard to PBPK models, there actually was a fairly extensive PBPK model for acrylamide and glycidamide in the rat and it was published just a few weeks ago by Kirman et al. The authors of that paper note that additional data is still needed to refine model parameters for metabolism and tissue binding, particularly, in the rat and they reiterate the need for a human PBPK model for acrylamide.

I would just add that that human model also should consider variability in kinetic determinants across different life stages. We are beginning to see some models that attempt to do that and I think that would be important for

acrylamide.

[Slide.]

With regard to genetic toxicity, the genotoxicity of acrylamide and, to a lesser extent, glycidamide, has been studied in a number of traditional assay systems over the years. I think the consensus at the moment is that the results for acrylamide, itself, are a bit of a mixed bag whereas, for glycidamide, we seem to have a classical DNA-reactive mutagen.

The working group identified as priority research needs in this area the identification and characterization of adducts of acrylamide and/or glycidamide with DNA and with significant nuclear proteins including the biological relevance of these adducts and their dependents on species and dose both in vivo and in vitro. You heard a little bit about ongoing planned research in that area, again, from Dr. Fennell yesterday.

The working group also pointed to the importance of the investigation of mechanisms of specific genetic effects that have already been

reported such as various chromosomal effects, cell transformation et cetera.

[Slide.]

As we have seen in the draft FDA action plan, NCTR is planning DNA and protein-adduct studies including dose response in vivo to be coordinated with the rodent bioassays. Industry also is sponsoring some DNA adduct studies.

Mechanistic studies at NCTR, perhaps including in vivo mutagenicity and transgenic models such as the Big Blue rat and the thymidine-kinase heterozygous mouse as well as industry studies looking for indirect effects mediated by certain chromosomal motor proteins, kinesin-related proteins, for example, should also help to define the likely shape of the dose-response curve at lower exposures for genetic effects. So those are felt to be key research needs in that area.

[Slide.]

With regard to developmental and reproductive effects, the effects of high doses,

relatively high doses, of acrylamide on reproduction in rats and mice has been well-documented. The primary effect seems to be germ-cell toxicity related to dominant lethal mutations.

The research need, however, here is for dose-response data for this germ-cell toxicity, probably in rodents, to assess the risk at lower doses for information on whether the toxicity is a direct effect of acrylamide or due to its mutagenic metabolite, glycidamide. If they had to put their money on it, they would guess glycidamide, but that does need to be defined.

The potential for developmental neurotoxicity also has not been extensively studied and the working group felt that, given the dietary exposures that we are seeing to acrylamide, more work was needed in this area.

[Slide.]

In terms of ongoing or planned research in this area, NIEHS has indicated that they will include a study of dominant lethal mutations in

their work on the cyp 2E1 null mouse which will, again, test the hypothesis that glycidamide or a subsequent metabolite, perhaps, of glycidamide, is responsible for these effects.

I am not really aware of other studies on germ-cell toxicity that are planned or ongoing at the moment. NCTR is interested in doing some work on developmental neurotoxicity under the NTP program and also the ongoing academic studies on mechanisms on neurotoxicity may shed some light on this question. So this developmental-neuro area, I guess, could go on developmental or it could go in neuro and I put it here. So now you have seen it.

It is my understanding that acrylamide and glycidamide also will be evaluated in the NCTR neonatal-mouse assay system. That certainly will be a valuable addition to our understanding of effects of early life exposure.

[Slide.]

Carcinogenicity; obviously, this has been highlighted, I guess, in much of the discussion of

acrylamide that we have heard recently. The working group meeting in October was aware that the National Toxicology Program already was considering conducting a new carcinogenicity study in rats and mice at NCTR to confirm and clarify the results in previous studies.

The group noted that this could also provide an opportunity to develop enhanced data for cancer dose-response assessments, to assess the effects, if any, of perinatal exposure on carcinogenicity and, with ancillary studies, to gather useful information on the mechanisms of induction of key tumors, their modes of action, that might provide insight on their relevance to human cancer risk.

[Slide.]

So, in terms of ongoing and planned research that we are aware of, you have heard, now, the presentation of the draft action plan that plans are moving forward for the conduct of well-designed two-years studies of acrylamide in rats and mice at NCTR under the NTP program.

The neonatal-mouse studies, I believe, will require about a year or so to complete once they have been initiated and the full two-year studies in rats and mice, of course, will require several years. So another recommendation of the working group was that,in the meantime, an expert working group of pathologists be convened to look at the critical slides from the previous rodent studies all together using current diagnostic criteria with the intent of developing consensus views on some of the key neoplastic lesions.

NIEHS, as part of its efforts under the National Toxicology Program convenes these so-called pathology working groups or PWGs routinely. However, it has not been determined as yet as to whether this would be possible for acrylamide.

We also heard that FDA's draft action plan calls for mechanistic studies to complement the rodent bioassays and contribute to their utility for risk assessment and that is certainly important. Industry also has studies under way

that should contribute to our understanding of the tumors that have been reported in rat thyroid, brain and the role of induced cell proliferation in various target tissues and so on. So there is quite a bit of work under way in that area.

[Slide.]

Neurotoxicity; as you all know, neurotoxicity is, in fact, the only toxic response of acrylamide that is well documented in occupationally exposed humans. The neurotoxic effects of acrylamide have been studied in the laboratory for years and years. Nevertheless, most of what we know about acrylamide's neurotoxicity is at high doses relative to our current understanding of dietary exposures in the range of tens of milligrams per kilogram body weight.

So, understanding of where our dietary exposures are, the working group concluded that we really need a better definition of the relationships between dose, duration of exposure and effect levels and the onset of neurotoxicity including a determination of the effects, if any,

of low-level, long-term dietary exposures.

It is not that the group believed that we would see an effect there, but there is an information gap that may be important given the fact that we know that this can exhibit neurotoxicity in humans at high doses.

The working group further concluded that this research needs to link effects observed at the cellular or tissue level, the functional changes, to allow an assessment of the significance of the cellular responses.

It also became apparent in our meeting that several mechanisms of neurotoxicity have been proposed for acrylamide and that further work is needed including understanding the role of acrylamide versus glycidamide versus other metabolites or adducts and bridging of the studies in animals to effects observed or postulated in humans. So, where are we in that area?

[Slide.]

With regard to the area of dose duration and effect onset, there would appear to by an

opportunity to gather some pertinent data in rats and mice in conjunction with the anticipated NTP studies at NCTR, although it is certainly true that the design of these studies may not be straightforward. For example, in the selection of the critical endpoints or effects to be monitored is not obvious but, perhaps, could be identified with an appropriate working group of neurotoxicologists familiar with this area. These studies also may be resource-intensive.

Mechanistic studies are continuing in academia at several universities and NIEHS will be using various approaches to look at the role of acrylamide and its metabolites and acrylamide's neurotoxic effects. Also, the proposed NIOSH study in exposed workers will examine markers of exposure and effect that should help with the animal human bridging part of that.

[Slide.]

Let's skip the next slide and just go directly on to ongoing and planned research in epidemiology.

[Slide.]

As noted before, the NIOSH study proposed to examine biomarkers of exposure and look for effects including neurobehavioral changes, also markers of reproductive effects, sperm motility, chromosomal changes, reproductive hormone levels and so on. There is also a report on the acrylamide and food website of planned industry review of the design and sensitivity of published epidemiology studies.

Finally, this was an area that was discussed some by the committee yesterday. As noted in the draft FDA action plan, there is a need to consider the feasibility and design criteria for studies in populations that are not occupationally exposed to acrylamide.

A case-control study of patients with enlarged bowel, bladder and kidney cancer and their dietary exposures to acrylamide appeared last month in the British Journal of Cancer. I believe Dr. Acheson is going to say something about that. There will undoubtedly be more such assessments of

acrylamide exposures in existing populations for which health-effect ascertainment is already available.

The CDC NHANES database in the U.S., the EPIC dataset in Europe and others may be looked at prospectively over the longer term. Yesterday, we talked about the Women's Health Initiative, the Framingham study and others as possible for resources. Again, FDA has recognized the need to explore these opportunities in its action plan.

[Slide.]

So, what do we make of all of this? In conclusion, I think that it is clear that the ongoing and planned research, particularly the proposed FDA and NCTR efforts, will, indeed, address many of the most important toxicology research needs for acrylamide. Some of this work will be completed within the next few months or years, or within the next year, whereas some of it will require several years as we have seen.

It will be important to monitor the ongoing research and assemble the picture of

acrylamide's risk assessment like a puzzle, as the pieces become available, perhaps modifying research priorities as we go, depending on what we are learning.

As a closing thought, though, it seems to me that, at present, our key objectives must include creating a robust PBPK model for acrylamide in humans and developing an understanding of the significance of high-dose carcinogenic effects in rodents and neurotoxic effects in humans and experimental systems for low-level exposures to acrylamide in foods. That, I think, is our principal research challenge.

Thank you.

DR. MILLER: Thank you.

Questions for Clarification

DR. MILLER: Comments or questions?

DR. RUSSELL: Thank you very much. I had a question about cancer sites. In the rat, I gather there is--you mentioned thyroid and brain and some mesotheliomas, I think, that are reported but, in the epidemiology studies, you just mention

the sites. I haven't seen that report, but you mentioned large bowel and kidney in the human.

So is there some evidence that the site specificity is different in the animals versus humans?

DR. OLIN: No. The Mucci et al. study that appeared last month in the British Journal of Cancer was using an already existing cohort of patients with large-bowel, kidney and whatever the third cancer site was and then going back and looking at what could be ascertained with regard to dietary sources of acrylamide. So it wasn't specifically selecting those as likely sites, but those sites were actually available.

DR. MILLER: For clarification; is it true that the tumor types that were found in the animal studies were relatively rare types in humans?

DR. OLIN: Well, you know, that begs the question of site importance.

DR. MILLER: I am trying to clarify that.

DR. OLIN: There are some that are relatively rare. For example, the testicular

tumors of the tunica vaginalis is not a common tumor in humans. The astrocytomas, we do see brain tumors, occasionally, in humans. The thyroid follicular-cell tumors, the question there, really, with the rat being the model, is are we looking at a rat-specific phenomenon that has been well-documented. That can be examined and I think that is being examined now to find out whether that is a relevant endpoint for human risk assessment.

DR. MILLER: The reason I asked the question is not because it is necessary for the same tumor site to be the endpoint in the species but to emphasize the possibility of important species differences not only in the site specific for the carcinogen but also in terms of metabolism.

We already know that rats and mice metabolize differently, so we already know there are species differences.

DR. MILLER: Dr. Mehendale?

DR. MEHENDALE: I know NIEHS is planning, I guess, this cyp 2E1 knockout, studies with knockouts. I wonder if anyone has considered some

studies with mice that overexpress cyp 2E1. There may be some populations that would overexpress cyp 2E1 even if they drink alcohol or not. There may be other conditions for overexpressing cyp 2E1. Just a question to see if someone is considering those studies.

DR. OLIN: I am not aware of any such studies that are planned at the moment. The studies in the knockout mouse, of course, are really to try to sort out acrylamide versus glycidamide as the active intermediate.

DR. BUSTA: Frank Busta. I fully agree with your last conclusion there that the key objectives include those of developing a PBPK model, et cetera. When I listen to the research proposals that you put forward, it sounded like we wanted to really learn how to develop and care for rats. I know we know rat nutrition very well, so we have got that better than in humans.

It seems like a tremendous amount of work on high dose and on rat metabolism and not very much on low-dose exposures in food even though the

whole workshop was titled Acrylamide in Foods.

DR. OLIN: If that impression came through from my presentation, that certainly was not the impression I wanted to give. The focus of all of this research, really, is trying to take what we already know at very high doses and assess the relevance of that for low-dose human exposures. That is, as you well know, easier said than done. But that is where we need to go with all of this.

DR. MILLER: Towards that same end, was there much discussion concerning dose selection?

DR. OLIN: Not really, other than the fact that it is the low-dose region that we need to understand better. But, in terms of the details of what specific dose-level studies need to be done, no. The neurotoxic rodent studies and, actually, a primate study as well, the carcinogenicity studies, and so on, generally have shown effects down to the level of around 1 milligram per kilogram body weight per day.

DR. MILLER: What kinds of effects? Carcinogenicity?

DR. OLIN: Carcinogenicity. I think for neurotoxicity, the WHO consultation, if I am not mistaken, estimated that the no-observed-adverse-effect level would be around 0.5 milligrams per kilogram body weight per day. So that is kind of where the animal studies have gone so far.

DR. MILLER: That would be the quasi-MTD?

DR. OLIN: The NOAEL, the no-observed-adverse-effect level. So the question, then, is how do we assess the shape of the various dose-response curves, and there are a lot of them, at levels below that down to the 1.0 microgram per kilogram body-weight level where we are seeing dietary exposures in humans. That is a long distance from a milligram to a microgram.

DR. MILLER: Right.

DR. DWYER: Now that you have seen the draft FDA plan, I wondered if you could give us your observations on areas where it might be further strengthened.

DR. OLIN: I think it is good. I really

do. I am not being paid to say that. I mentioned a couple of areas along the way. This area of trying to gather neurotoxic data in conjunction with the bioassay studies may be a challenge. Those studies certainly haven't been designed. I don't have proposed designs, but I think that would be useful.

We need to get a better understanding of potential effects of chronic low-level exposures in rodents and we just don't have that data yet. I think continuing work in bringing all the pieces together for a human physiologically based pharmacokinetic model is an important goal.

DR. MILLER: Jean?

MS. HALLORAN: Hearing all this, I am impressed by the degree to which science has progressed in this area in the last year or so. It seems as though the questions have been fairly well defined and there are approaches to getting answers to them. I wonder if you could say how long--I know you can't always predict science, but here we have got very specific questions we are trying to

get answers to.

How long will it take before the work has been done and the answers are in place to have a pretty good idea of whether you can extrapolate from high-dose rats to low-dose humans, or have the data in place to assess the risk to the low-dose humans?

DR. OLIN: I wish I could answer that. I can't say that I really know. I think there is some low-hanging fruit, as they say, that we can get answers to in a fairly short term. I think a lot of the answer to that really will depend on what data become available from some of this low-hanging fruit over the next six months to a year. I think we will have a better idea of what the critical issues really will need to be, what additional data might be needed for an appropriate risk assessment.

So that is why I think it is really important for the community at large to have in mind a framework for a risk assessment for acrylamide and to monitor the pieces as they fall

in place so we can see how it is developing.

DR. MILLER: Again, as a matter of curiosity, was much thought given to the endpoints for the neurotoxicity studies, the functional endpoints that are going to be used, any suggestions that were made, because you get terrific differences depending on which model you use.

DR. OLIN: No; there was not a lot of detail given there. I think what was recommended was that the neurotox community come together and look at that and provide some consensus recommendations on what these studies should be. There has been some work on that. Dr. Canady cochaired a meeting at the neurotox meeting in Little Rock in November and there was some discussion of that issue then.

DR. MILLER: Any other questions or comments?

We are going to take a break now. If you would all be back by 10:20.

[Break.]

DR. MILLER: Our next speaker is Dr. David Acheson of CFSAN. He is going to talk about implications of this work.

Potential Implications

DR. ACHESON: Thank you, Dr. Miller.

[Slide.]

What I want to do in the next fifteen minutes is just to talk about some of the implications of a lot of the science that we have heard about in the last day and a half.

[Slide.]

I am going to divide the talk into three main parts. The first part is just to go over some of these current areas of scientific interest that we have been hearing about and then really to try to address this issue of what we know about these scientific areas in relation to the current impact on health risks, which I think is a critical question, and then finally to at least bring up the issue of whether the consumer message should be altered based on the current state of knowledge. I want to emphasize the word "current."

[Slide.]

To begin, I just want to repeat the overall goal that we have in this regard, "Through scientific investigation and risk-management decision-making, prevent and/or reduce potential risk of acrylamide in foods to the greatest possible extent."

Dr. Troxell already went over this, but a subgoal of that in relation to consumers is to, "Inform and educate consumers and processors about potential risks throughout this process as we go through it and as knowledge is gained.

[Slide.]

Consumers who are having to deal with this are having to address a multitude of questions and many of them are not easy to answer. I just put some of them on this slide which, from a consumer perspective, may raise questions such as will eating certain types of food cause cancer. What is safe to eat? Should I stop eating certain types of food in this context? Should I be cooking foods differently? What should I be doing differently to

protect myself and family?

Although these are not particularly put in a scientific perspective, I think these are the sorts of questions that our goal is to try to come up with answers for.

[Slide.]

So our current consumer message is to eat a balanced diet that heeds the advice in dietary guidelines. I think one of the questions on the table is should this be any different based on current knowledge.

[Slide.]

So, where are we in terms of the science? You have heard a lot in the last day and a half about a whole variety of issues that relate to our action plan and the science that goes around it. I just want to go through some of these in a little bit of detail.

First of all, the whole question of the formation of acrylamide. We have heard a lot about that and with two great presentations yesterday in relation to looking at ways to diminish formation.

Obviously, understanding the way in which the acrylamide is formed, what its components are, asparagine and reducing sugars, we will begin to open pathways to allow us to develop mitigation strategies.

So, formation is an important and ongoing area of scientific interest. There is ongoing work looking at the levels of acrylamide in food. Ever since this problem developed from last April, there has been an increasing number of publications related to the levels of acrylamide in food.

But this is ongoing. We already have generated a lot of information but there are more questions in terms of variability. You heard, through the talks yesterday in relation to using dietary intakes of various foods, and there was some discussion around that, of the limitations of intake data, two days, three days, fourteen days, when we are really dealing with the need to understand chronic exposure.

The exposure assessment, about which I will say a little bit more about in a subsequent

slide, you heard about that yesterday and how that will also evolve. Then, finally, the epidemiology. The critical question, which I believe is what is the impact of all of this exposure at various levels, at various ages, on human health.

[Slide.]

So, understanding formation and developing mitigation strategies could certainly lead to a reduction of levels in food. Some of the preliminary data that you heard yesterday is very exciting and very encouraging.

But there is still a key need to understand the health implications from these levels. I keep coming back to this because I think this is a key issue.

[Slide.]

The exposure assessment that we heard about yesterday was based really on a relatively small number of foods, but the data clearly showed that a small number contribute most to the total daily acrylamide exposure. Yet, there was no single food that contributed the majority. As Dr.

Robie pointed out, there were seven or eight foods that accounted for more than 5 percent of the intake, so we are talking about a fairly large spectrum of food, but no single food that was a primary culprit.

The overall mean acrylamide exposure is generally in the range of 0.3 to 0.5 micrograms per kilogram per day and those numbers seem to be becoming more solid in relation to what we have found and what others have shown.

[Slide.]

But there was a wide range of exposure and this clearly depended on the diet. Generally, diet that is high in certain types of foods such as fries, chips, et cetera, will have higher acrylamide intakes than diets of equivalent caloric intake that are lower in those types of food.

To me, I am essentially stating the obvious, but I think it is an important point, is that diet does have an impact. For example, 100 calories of raw apple is clearly going to have less acrylamide than 100 calories of overbaked fries.

We already know that.

But, again, coming back to this issue and the mean levels and exposure assessment, what is the impact on human health?

[Slide.]

This is a key need. In the last two talks, you have heard a lot about the ongoing research, the planned research, in relation to trying to understand this issue of the human consequences as it relates to neurological issues, whether they be developmental or whatever, the effects on germ cells and acrylamide's role as a potential carcinogen.

[Slide.]

So where are we in terms of trying to put this in place and to look at the evidence that indicates that these levels of exposure are, indeed, harmful to health. Well, I think, as we have already determined, there is still work to be done. But you heard a lot this morning in relation to animal studies and the complexities of translating studies using doses in the milligram

per kilogram range, 0.5 to 2.0 milligrams per kilogram, down to the microgram per kilogram range that we are seeing from human exposure and the complexities of making that extrapolation which are clearly considerable.

In terms of human dosing studies, there are some single-dose kinetic studies that are under way but, as yet, that data is not yet available but will clearly play a key role in helping us understand these issues.

Turning now to the epidemiological studies which, again, we have heard are an important part of this endeavor to try to understand the human health risk, but are clearly very complex and very cumbersome. There are data out there on occupational exposure which has been already discussed which are linked with neurological consequences as, as far as I am aware, there have been no links with cancer in relation to occupational exposure but it is clearly an area that could be examined.

The key question, what about exposure via

food. As has been discussed during the course of the last couple of days, there is one study that has been done to look at that.

[Slide.]

In relation to trying to make these links and looking at human epidemiological studies, there are a number of factors to consider. Dose is one of them. The length of exposure, the age at which exposure begins and the levels in relation to age, whether there is some genetic susceptibility. I am just throwing that out there as a possibility.

We certainly heard about issues in relation to cytochrome P450 and whether there is some genetic susceptibility in relation to that. Maybe there are synergistic factors in terms of the metabolism of acrylamide, and, certainly, as was mentioned by the previous speaker, variation in the types of tumors that we should be looking for.

[Slide.]

In the next two slides, I am going to summarize the data from this study that was published in the British Journal of Cancer just

about a month ago by Mucci, et al. First, to state the purpose of this study, and that was to analyze data from a population-based control study in Sweden to investigate whether higher intakes of certain food items with a higher acrylamide content increases the risk of large-bowel, bladder or kidney cancer.

They only looked at three types of tumor in this study. Again, as was mentioned before, this was because they already had the dataset available.

[Slide.]

In summary of the study design, they have 538 controls, 591 cases of large-bowel cancer, 263 cases of bladder cancers and 133 cases of kidney cancer. They ascertained dietary consumption through questionnaires and they went back five years prior to the submission of the questionnaire focusing on the foods that were high in acrylamide.

Most high acrylamide foods were included in the questions. I want to just underline the word "most" because one of the issues with this

study, acknowledged by the authors, is that it did not necessarily cover all foods which may have contained acrylamide but certainly most.

[Slide.]

Based on the data that they received, they then stratified the acrylamide exposure into quartiles and then looked for associations. The conclusion of the study was that there was no positive association between dietary exposure to acrylamide and the risks of bowel, bladder or kidney cancer.

[Slide.]

These are limitations as acknowledged by the authors. There was a limited sample size. This was a cohort of patients that they already had and I think the authors should be congratulated on at least looking at this and raising the questions. But it was a limited sample size.

As I have already mentioned, not all acrylamide-containing foods were captured in the questionnaire and I think, importantly, they only looked at selected cancers. So it is critical not

to extrapolate these data too far.

[Slide.]

So this brings us back to the current implications. Again, we are coming back with this question of the strength of the link between the animal-tox studies in the milligram-per-kilogram range with human exposures in the microgram-per-kilogram range and what exactly does that mean and how do we extrapolate that. A lot of effort is going in to understand that.

Human data indicating that this level of exposure poses a significant health risk I believe is currently lacking. There is a lot of work ongoing to try to fill that gap but, as far as we can determine, that direct link is not there. That clearly needs to play into the consumer message.

We also know that consumptions of certain types of food will increase exposure to acrylamide. But, in view of all of this, what should the advice be to consumers?

[Slide.]

This is clearly a complicated

risk-management problem and we certainly do not want to create one problem by solving another. Where I am going there is specifically the issues in relation to cooking, and this was mentioned yesterday by Dr. Troxell, and the dangers of getting an inappropriate consumer message over of "cook food less" could certainly raise problems in terms of undercooking certain types of food that do need adequate cooking to kill pathogens.

A second issue is in relation to nutrition. We do not want to get out a message that could have nutritional consequences if people stopped eating certain types of food. One of the observations in the Mucci study was that, in the large-bowel-cancer group, there was a trend towards protection against cancer in those in the higher quartile with acrylamide.

Now, I say a trend. This was not statistically significant. But it simply raises the question of what were these people getting in their diet potentially that was protected. There are certainly data out there to say high fibers are

protected against large-bowel cancers. So I think all it is just illustrative of simply reducing the foods containing high acrylamide could have unforeseen consequences. This needs to be thought through very carefully.

Really, what I am coming to is that maintaining objectivity and a balance is a critical part of managing this risk.

[Slide.]

Currently, our advice is to follow dietary guidelines which I have listed here and I am not going to read through all of these. They are on your handouts. These essentially are the federal guidelines for diet.

[Slide.]

So where are we going in the future? I think it is important to emphasize that we are going to review our consumer messages as new information is obtained during implementation of the action plan. The message that we have right now is good for February, 2003. As new data comes in, we are constantly looking at it and attempting

to integrate the science into the message and should we change it.

We are very interested in the methods that will be involved in reducing levels as I have already discussed whether these be related to industry and at home, and there is a lot of ongoing work in relation to the action plan of trying to understand the formation and methods to mitigate acrylamide formation.

I think the bottom line of all of this is the key need to better understand the risk to human health with the doses that we are now beginning to understand people are being exposed to.

With that, I will finish and will be happy to take any questions.

DR. MILLER: Thank you, David.

Questions of Clarification

DR. MILLER: Comments or questions?

DR. DWYER: David, I wonder if you could comment on the Nurses Health Study and that analysis that has been in all of the newspapers I have been reading?

DR. ACHESON: I am not familiar with that one. Which one?

DR. DWYER: I thought that they had done a study in the Nurses Health Study that suggested the risks were not large.

DR. ACHESON: Is that the same study I am talking about, the one from Sweden, the Mucci?

DR. DWYER: No. I thought it was the Nurses Health Study. Am I wrong?

DR. RUSSELL: Yes. I think that was one that was mentioned as the possibility of planning it. But it has not been carried out. The one that was was the Swedish--

DR. DWYER: Oh; I mistook it.

DR. TORRES: Antonio Torres. One question I have, yesterday we saw some estimate of what would be the reduction in the exposure if we brought down to zero certain foods. That is just a guessing game of trying to look at what would be the impact of doing some measures.

The question is has there been some effort, since this is such a broad-spectrum

exposure, at looking at the way we prepare certain foods in terms to see what would be reasonable reductions without getting into any risk situation; for example, we know that if we cook too much potato chips, then we will have higher acrylamide concentrations. Could we think about what would be reasonable levels and see how much the exposure would be reduced?

DR. ACHESON: Yes. I mean, part of understanding that is to understand the formation, how much cooking leads to how much acrylamide. Only by knowing that, can you come up with advice in terms of don't overcook something. But the obvious question is, how much should I not overcook. That is complicated.

Linked in with that is obviously gaining an understanding of what the health consequence is of reducing the level from X to Y. Without that, it is difficult to know where to pitch that. So I think the answer to your question is that we are looking at the ways to reduce it. Then the question is going to be is that enough, does that

get us to the point where we are having an impact on human health?

So it is evolving. But, yes; those kinds of deliberations and discussions occur.

DR. DICKINSON: Annette Dickinson. We have been focusing, as we should, on extrapolating the animal data to the human situation. I wonder if you, or perhaps some others of our speakers who are still here, would characterize what, in your view, is the strength of the evidence on the animal carcinogenicity of acrylamide as compared to other things that you might have looked at. Is it weak? Is it strong? How specific is it?

DR. ACHESON: I think that is a hard one to answer. It is what we have. I do not profess to be a toxicologist. If there is somebody who wants to--maybe Dr. Canady can specifically address that, if that is all right with the chair.

DR. MILLER: Yes; it is okay.

DR. CANADY: There are two rat studies, two chronic rat studies, that have clearly shown increased tumors with exposure to acrylamide. So

the evidence, at least in the rats, is fairly clear and widely accepted.

DR. DICKINSON: Are they benign or otherwise?

DR. CANADY: It is a mixture. Perhaps Dr. Olin will want to speak more specifically to that. But it is a mixture. That is really all I am going to say. The doses that showed tumor went down as low as, I think, 0.5 milligrams per kilogram per day in the rat studies. The route of exposure was drinking water, not food.

MS. HALLORAN: I have two questions about your consumer message and whether you have considered alternatives. One was to have a message to follow the dietary guidelines is really not a message. We are constantly told to follow dietary guidelines. It seems like a non-answer or possibly even an evasive answer.

Has FDA considered an alternative message which would be, to my mind, more direct like, "The FDA does not yet feel it has enough scientific data to answer the question on whether there should be

any special dietary advice as a result of knowledge about acrylamide." Have you considered that sort of message?

DR. ACHESON: Reviewing of the consumer message is an ongoing process. I think that the feel was to try to say something positive about diet. What you are proposing is certainly something that we should think about as making that statement.

But, in effect, without stating it, it is implicit in what I am saying here is that the science is not yet at a point where we can make any other determination. But it is not explicitly said.

MS. HALLORAN: I actually think it is not implicit. It is certainly not obvious, I think, to the average consumer. I think, to the average consumer, they see a bee-hive of activity. They are aware in the press that there is tremendous research going on this and then, when you go to FDA for advice, they say, "Follow the dietary guidelines." It seems nonresponsive.

DR. ACHESON: We can certainly consider that; yes.

DR. MILLER: That is one of the questions we are going to have to deal with in our discussion in our advice to the agency.

DR. LEE: Ken Lee. I just wanted to follow up a little bit about the message and behavior. If you came out with a very direct message, hypothetically--I know we are not going to do this--and said people should avoid foods with acrylamide, what, in your opinion, would be the actual behavior? Would people change the way they eat? Would it spike for a few weeks and then go back to the way it was? What is our track record in that regard?

DR. ACHESON: I think, like dealing with any nutritional issue, the general population does not necessarily follow advice. That pertains not just to this but many, many other significant problems. I think our goal would be to give the best scientific advice that we can and couch it in such a way as a consumer message that it was not

complicated and easy to understand.

I think those two things, to me, are critical. Whether people heed it, I don't know. That is somewhat beyond my control, but our goal would be, certainly, to try to get a simple message that was clear.

DR. LEE: Certainly, that has been studied. There must be some data on how dietary recommendations are actually affecting consumption patterns.

DR. ACHESON: I'm sure there are. I am not personally familiar with those, but there will be. Obviously, we would need to try to get that right.

DR. DWYER: I think it is like the Ten Commandments. There is quite a bit of slippage. Two questions. One is have you done any focus groups to see if consumers do feel it is a slippery statement or whether they feel that it does answer their concerns. Secondly, would your message be the same if the Mucci study had come out with relative risks of 1.3 or 1.5 for one of those

various cancers?

DR. ACHESON: The answer to your first question is not yet. I think, obviously, with any consumer message, couching it, developing it and then going out with it to test it is a critical part of determining whether it is going to be successful and whether it hits the target.

The Mucci study? You are right. What if? Clearly, that would have played into the science and the message. It may well have been a little different but you would have to look at the science. If they had come out with an odds ratio that was significant, then you are starting to say what is the power of the study, is it enough, do we believe it, et cetera, in terms of moving forward with that.

DR. DWYER: The reason I ask you that is because the agency, yesterday, I guess it was, made available a larger database. Scientists tend to look at what they can look at and now you have a large database. I would suspect, in the next several months, there will be ten or fifteen

case-control studies. Everybody who possibly can look at it will.

So one of those studies, even if there are a hundred studies, even if there is nothing there, you would have three or four or five that are going to be significant; right, just by the law of odds?

DR. ACHESON: Yes. I think that that would play into it. Right now, we have one. The second one may be negative or it may be positive. I think you are building it up as you go along and each one would need to be looked at in terms of its scientific merit, its design, its power, in terms of making consumer messages which, I think, could have a big impact.

That was another part of where I was trying to go is that, even though we are focusing on acrylamide, dietary messages have impacts on many other things in terms of telling people to eat and not to eat certain things.

DR. DWYER: Did you consider telling people not to smoke? Isn't there acrylamide in smoke?

DR. ACHESON: I think that message is already out there.

DR. DWYER: It seems like it might be tied into the dietary guidelines, too.

DR. MILLER: Smoking?

DR. DWYER: Say, "If you are going to follow the dietary guidelines, don't smoke."

MS. HALLORAN: I know the new FDA Commissioner and others in FDA are interested in reevaluating health claims on food with the thought that the use of health claims on food could promote beneficial consumption patterns. Are you considering how to integrate that effort with any message you might have on acrylamide or concerns about acrylamide? For instance, I suppose french-fry makers could promote potatoes as a source of Vitamin C.

DR. ACHESON: I think that would all have to be looked at in the context of what the message was and what the health claim was.

MS. HALLORAN: Do you have a mechanism for integrating your work with the health-claim work at

FDA?

DR. ACHESON: Yes. That is all part of CFSAN is to look at the big picture.

MS. HALLORAN: I have one more question. In the FDA action plan, it says, "As messages are developed and refined, FDA will consider working with diet, nutrition and home-economics organizations and the Ag Extension Service to get its message out to consumers."

Is there any reason for not including consumer organizations and the general media?

DR. ACHESON: Absolutely not. I think that was one of the points that was made yesterday when Dr. Troxell gave his talk was that the potential there was a little narrow.

DR. TORRES: If I could learn a little bit more about the message impact, could you tell me a little bit about what is the difference between when you say a specific message like, "Don't smoke," which is under my control versus, "Eat more vegetables," which is--well, maybe not that. Let me think about it. "Don't eat food that has too

much cholesterol." If I am going to eat meat, or I am going to eat stuff like that, I have no control over how much cholesterol that food has. So it is harder for me to become a vegetarian, which I don't want to be.

The difference between things that are much more under my control than things over which I have no control. What is the response of consumers when they say, "Don't eat food because it has acrylamide," but you look and every darned food has some acrylamide. So what do I do then?

DR. ACHESON: I think you have just put your finger on the problem. It is very complicated as to how do you deal with that? The smoking message is clear. You can say, "Don't smoke." This is much more complex because, as you just pointed out, acrylamide is present in a lot of foods. It is present in foods that are important for nutrition, for fiber. So how do you couch that in terms of education and a message?

That is part of where we are trying to go here is to get a really good handle on the science

so that whatever message we come out with is going to have a significant health impact in a positive direction.

DR. DICKINSON: It sounds to me like a great deal of what you are saying and what many of our other speakers have said is that the evidence is really not strong enough at this point to recommend that anybody avoid any particular food or class of foods and that you are going to try to refine that evidence in case something would actually emerge from it.

But, if I am reading Dr. Robie's presentation from yesterday, and also other presentations, that indicated that potatoes, because of their amino-acid content and because of their sugar content, may have a unique propensity to form acrylamides when they are exposed to excessive heat or to drying heat, and if I look at Dr. Robie's tables, it seems to me that between 34 percent and 40 percent of the cumulative exposure in her tables is accounted for by french fries and potato chips, while I think it is certainly

scientifically correct if the decision is to say, "We don't know enough about the risk to say that you should restrict anything," at the same time, if you were to decide there is a risk that would suggest restricting something, it does seem to me that the intake projections, and I realize they are models and not real-life samples, do suggest that there may be a limited number of foods which a person might choose to restrict which would not likely have a negative impact on nutritional content or on other cooking practices.

DR. ACHESON: Yes. We are not at a point where I think we can make that statement. As you have pointed out, those data are being developed. Part of the reason for stating that the best advice is to follow guidelines is that, if you do follow the guidelines, you will limit intake of some of those high-fat, fried goods that have been--that come out repeatedly on the list.

Obviously, it doesn't cover everything. But, to some extent, it does address that in terms of if you follow the dietary guidelines. But, your

final point is that as data is developed, then I think the strength to go with more force down a certain track will, hopefully, develop or you will learn, "No; it is not worth it." It is all couched in the context of the human health risk.

I think if the advice were, "Don't eat potatoes," then there could be some significant consequences of that that have got nothing to do with acrylamide that need to be considered.

DR. DICKINSON: But there are potatoes and potatoes.

DR. ACHESON: Right. So, again, complex consumer message. But, before you even go down that road, you really need to know what is it going to be, what is the health benefit from that message and what is the science behind it.

DR. MILLER: I think the issue is, partly, from a communications point of view and Cliff can comment on this better than I can, the difference between a positive message and a negative message. There is a story this morning on the news concerning acrylamide. The reporter went and

interviewed some people at a local diner. Uniformly, the people he talked to just pooh-poohed this negative message about avoiding things. They said, "They are always telling us not to eat something."

The differences in terms of the dietary guidelines, for all its problems, is that it is a positive statement, in a sense. As you said, if you follow the guidelines, you are going to reduce some of the high acrylamide products but it is a much more complex analysis, if you will, about what you are talking about.

It seems to me, and this is something we will have to talk about later, that, if it comes to Draconian measures that have to be taken, they better have the data to support it. Short of that, it is going to be a much trickier situation to deal with. It seems so easy to say, "Don't eat french-fried potatoes." It may turn out to be not only french-fried potatoes. It may turn out to be asparagus.

MS. HALLORAN: We are obviously starting

to get into the discussion about policy. I had one more question about--you have said a couple of times that you have a concern that somehow, if there was a message about cooking, that the result would be that people would undercook things with pathogens, which is basically meat.

I wonder if you have any data or focus groups that would suggest that people would get confused in that way. To me, it is not necessarily apparent that a message about cooking potatoes and grains would be confused with a message about cooking meat. After all, people routinely thoroughly cook chicken and pork but eat rare beef.

DR. ACHESON: The specific answer to your question is no, we do not have data on that. It is simply an area that I think needs to be taken under consideration of ensuring, maybe through focus groups, that, if a message goes out, don't overcook one product, that it is not interpreted as, don't overcook, or adequately cook, everything else.

But it is just simply another concern that needs to be considered in a broader picture.

DR. DICKINSON: To go back to the flip side of the same point that we were just discussing a moment ago, I have been somewhat concerned in these couple of days to hear it continually mentioned that one of the reasons we don't want to give specific food advice, even if we got to the point that you thought specific food advice was necessary, is that it is ubiquitous in the food supply.

The other side of my comment about the cumulative effect of specific foods is that I am concerned that people get the idea that it is ubiquitous, that it is in virtually everything, the implication being that it is in approximately equal amounts in virtually everything and that, therefore, I am doomed, there is nothing I can do about it when, in fact, the evidence would appear to suggest that there may be some things that could be adjusted without an impact on the overall consumption of a variety of foods if, indeed, the evidence suggested that that was reasonable advice.

DR. ACHESON: I think that is a very good

point. Part of the dilemma here is trying to come up with consumer advice based on inadequate data, that this is where we are now. This is what our consumer advice is now based on what we know now. But, within that context, as we develop more information about types of cooking, types of potato, which just isn't there yet, then, yes, I think you are right, a focused message, because don't also want to give over the notion that it is hopeless and that there is nothing you can do if, indeed, it turns out to be a significant health risk.

I think that is part of the problem, in the midst of trying to understand all this.

DR. DWYER: Back to Annette's point. I think it is important, in your plans, to plan for worst-case as well as a best-case scenarios and to begin to think of what the message would be if, in fact, this did prove to be a major problem. So you can't wait until the day you get on television, or wherever, to have a message that hasn't been thought out very carefully ahead of time.

The other thing is this whole climate that we are in right now where we have a lot of people saying all sorts of sometimes true and sometimes not true things about foods and supplements and whether there is an equivalence here among the messages that consumers are receiving. I leave that to my betters, but it is rather a vague message at this point. Maybe it needs to be that vague, but I agree with Annette that I think we know a little more than that.

MR. SCHOLZ: We are not ready to give advice, or you say we are not ready to give advice, on food and how we are going to cook it and what products but, yet, we are listing a lot of products here. Aren't we, in a sense, implying some of these are bad just by the amount in the parts per billion that they have. We kind of joked yesterday there was at least one brand of potato chips we might have a problem eating when we kind of checked to see what the amount was.

Aren't we implicating some of these products now and is that the right thing? Is that

what we intend to do?

DR. ACHESON: I think my take on that is that one is struggling with the need to be transparent and keep the public informed of progress, and, with just that, we are not overinterpreting the data. The assumption that the high levels are bad, and what does that mean in the context, that the levels are higher in one product versus another product.

But, again, back to what I was trying to get over is what is the impact of that as a health consequence? That is where we are trying to take this.

MS. SCHOLZ: Are you doing enough, though, to say we are listing these products, because you are listing them by name. It is not just generic categories. So we are listing it by name. We are implicating that when one has a much higher incidence, we are, in effect, saying we think it is bad, we just don't know it is bad.

Take that, then, into a consumer warning. If we are going to show this and we are going to

list this, should you, in fact, be doing a consumer warning now before you know?

DR. ACHESON: I think, right from the beginning, we have been saying that this is pilot, preliminary, exploratory. The action plan, by its very nature, is saying that there is more to come. Comparing one brand versus another brand, the n's are just not there yet, I think, to make those statements.

DR. TORRES: I had two questions. One was, looking at the data and to kind of follow up with the same question, is why wasn't--since we know there is so much variability between lot-to-lot and batch-to-batch within the same food, et cetera, why wasn't there more effort and time to keep the data to generic rather than very specific brand names.

I find it a little bit concerning that we may be sending messages on data we really don't know. We are saying, Product XXX has so much, and we really don't know whether the product effect. So, I am sure that the food industry must be very

concerned.

Also, talking about the industry point of view, consumers, when they see this kind of information to specific brand names, they would like to know what are you telling the food industry to do. So one message is the message to the consumer and the other message is what FDA is going to tell industry to do.

DR. ACHESON: In answer to your first question, that is essentially a policy of FDA to give that level of detail. In terms of what the FDA tells industry to do is, as you have heard, there are a variety of industry groups that are trying to understand formation and mitigation strategies.

Again, it is a point of really trying to understand the science behind this problem before anybody is capable of saying this is what you should do, either to the consumer or industry, and I am using the word "should." I think it is very encouraging that there are so many groups who are taking this seriously to try to understand it.