U.S. Food and Drug Administration

Animal Feed Safety System Public Meeting

Health Consequence Scoring for Contaminants

in Animal Feed

Held on September 12, 2006 commencing at 9:00 a.m.

Location:

Division of Animal Feeds
7519 Standish Place
Rockville, MD 20855

APPEARANCES:

Dr. George Graber, Moderator

Dr. Stephen Sundlof

Dr. Barry Hooberman

Dr. Karen Ekelman

Dr. Phares Okelo

Dr. Delores Beblo

C O N T E N T S

Opening Remarks

Speakers:

Dr. Stephen Sundlof

Dr. Karen Ekelman

Dr. Phares Okelo

Dr. Delores Beblo

(Morning Session)

(Opening remarks by Dr. Graber)

DR. SUNDLOF: Thank you, George. Can everybody hear me?

I have the privilege of welcoming everybody and I see we have a great turnout which is an indication that this is a very important topic.

Just reflecting back on twelve years ago when I came to FDA and started working and learning about feed safety and how things have changed over that twelve year period, at the time most of the issues were about medicated feeds and residues associated with medicated feeds and DSE was just starting to become an issue and we had I think just published a proposed rule about banning sheep in all cattle feed, our ruminant feeds, but since that time feed safety has grown enormously as an issue, not just in the United States but on a global basis.

Now we're seeing it more and more coming up as being dealt with in the international arena, especially with groups like CODEX and others and movements by various countries that will certainly have trade implications and again attests to the importance of feed safety as an issue.

Things will progress and as a result of that, a few years back CVM decided that we needed a more comprehensive overall way of assessing the safety of feed to make sure that we are putting our resources in the right places and that the industry is aware that feed safety is a big concern.

Now today I understand that we have registrants from more than a dozen different countries here today and so that's very impressive.

Feed, of course, is an international commodity, and feedstuffs, and so it is everyone's concern.

Feed safety is one of our core functions at CVM. A couple of years ago, about four years ago we decided we were going to undergo a new strategic planning initiative and one of the reasons for that was because CVM gets pulled in a thousand different directions.

There's always different issues that are putting pressures on our time and resources and as a result of that we felt that the core functions of CVM were not being addressed as well as they should be because we are constantly being pulled in different directions.

Our new strategic plan, I was originally going to call it making the trains run on time but I think that was Mussolini's statement, so that didn't go over too well.

We said we've got to get back to basics, we've got to focus on our core mission. We identified those core things and those core things were drug review function, compliance in enforcement actions, adverse drug reactions, in other words looking at the drugs after they had been marketed

and see if they continued to be safe and effective and the fourth one was feed safety. The feed safety was one of the core functions of the Center for Veterinary Medicine.

Since that time we've been trying to focus on doing the right things, doing the things we think are in the best interest of the public and the interest.

We've started back a few years ago, started looking more broadly, globally at feed safety in general instead of having just specific programs, for instance, medicated feed program versus BSE program versus salmonella program, to try and bundle all of this into a comprehensive overall strategy for making sure that the safety of feed is maintained.

Now, just a few things about what the feed safety responsibilities are and what they are not.

First of all, this is not an initiative to try and shift responsibility away from where we think that the primary responsibility lies and that is the feed industry is responsible for producing safe feed.

That responsibility will continue to rest on the feed industry but there's also responsibility of the regulatory officials both at the federal level, FDA, but also state to provide oversight and guidance and make sure that everybody

is following the rules.

So a stakeholder participation is absolutely essential and and we found that out in our previous meetings.

In 2003 we held the first animal feed safety meeting in Virginia and at that time we got most of the stakeholders together to find out what some of the best practices are. What are some of the best in the industry doing to ensure the safety of their feed and what kind of systems do they have in place?

A lot of that meeting was dedicated to interactions among people so that we could learn from each other.

The second meeting was held in Omaha just last year in which we started the process of laying out a draft framework for putting together this animal feed safety system.

We decided that it should be very much a risk based approach to dealing with this, which is pretty much a theme throughout FDA these days. I really want to focus on what is the highest risk, because we can't deal with everything.

We wanted to present the, in today's meeting, the third of the sequence and there will be at least one more, but today we want to talk about the health consequence scoring, a way of looking at all the various things that potentially are hazards

within the feed system and to start to be able to rank those in terms of their greatest importance so that we can direct our resources and our programs at those risks that we consider to be the most, have the greatest consequence on either public or animal health.

Throughout the meetings we will continue with an open dialog. You will be hearing a lot of presentations this morning but in the afternoon we've allotted time so that we can have a dialog, get questions answered and decide how we're going to move forward.

Again I welcome everybody here this morning. Thank you for coming to this, what we consider to be one of the core functions of our organization here and with that I will return it back to you, George.

DR. GRABER: Thank you, Dr. Sundlof.

The first speaker now to talk about risk ranking and the animal feed safety system, where are we going, is Dr. Barry Hooberman.

DR. HOOBERMAN: Can everybody hear me? Good.

Good morning. This is -- what we're trying to do is present you the bigger picture of what risk is and why we're taking this approach.

We're going to cover basics of risks, what ranking means, how we're applying this for the animal feed safety system and where we're at today.

One of our goals here is to communicate to you guys about what our current thinking is and where we're at.

Nothing you are going to hear is written in stone. We're always looking for input. We have a tendency to slip into jargon a little bit. There are going to be acronyms and abbreviations flying around. If you have questions, please ask them. We're trying to communicate what we're thinking about.

The purpose of the animal feed safety system, the key words are in yellow, supposed to be comprehensive, risk based, preventive and we're looking at risks to both animal and human health.

Just for background, these are some feed contamination episodes just to show that this area needs some attention.

The BSE, the ongoing concern, dioxins, salmonella and this year we had an issue with aflatoxin in dog food.

Why are we doing a risk based approach? Risk assessment really is nothing more than a way of organizing your information and collecting it and analyzing it to help inform the decision-makers what's the best way to go about making their decision.

You can also use a risk assessment

approach to help -- this is part of the present have been nature of what we're trying to do, also helping to organize the information, helps interactions between the speakers, between us and the stakeholders.

What is risk? We can't avoid putting up a formula. Basically hazard, risk is a function of hazard and exposure.

What we mean by health consequences, you've got the terminology here, but what we're really talking about is if you get exposed to the contaminant, the hazard, are you going to become sick and if you become sick, how sick are you going to get?

That's what we're -- severity is going to be how sick are you going to get and the potency would be if you get exposed, are you going to get sick? How much of the chemicals or the hazard do you need to be exposed to if you are going to get sick?

The other half of the equation is exposure. How are you going to get exposed to hazard, what routes and what's the likelihood you are going to get exposed to a level that's going to cause a health consequence.

The focus of today's meeting is on this side and the exposure side will come up at the next meeting.

Just to bring home what we're talking about, we talked about risks and hazards and things like that.

Here is crossing the street. Everybody does risk assessment when they cross the street. They try to cross the street safely. The cars in this scenario are your hazards and the exposure is that you are going to get yourself out into the street, going to expose yourself to the hazards. Of course, the consequences if you get hit are serious, lead to death.

Risk assessment, another way of looking at it poses four simple questions. What can go wrong? We call that hazard identification.

What are the consequences? This is also called the consequence assessment.

Then how can it happen? That's the exposure assessment.

Finally, what's the likelihood everything is going to go wrong and you're going to get an illness or sickness or something like that's and that's the risk estimation.

Just to point out, risk assessment is only part of the bigger risk analysis approach. You are defining the problem, doing your risk assessment, you are going to have a report about that, it's going to go to the risk management.

The goal of a risk assessment is to

help the risk managers make a good decision. They are going to make a decision hopefully and then they are going to communicate that to the public and all stakeholders and that's risk communication. Things that risk management is going to ask are what can be done to address the risk, what's the options, what are the tradeoffs.

You don't want to do something that's going to present a risk in another way. There is a tradeoff in risks and benefits and costs. And then what are the impacts of current management decisions on future options? You always need to be looking forward.

Of course, this is a very iterative process. The decisions are made based on the risk and look at whether they actually worked in reducing the risks and what are the consequences.

Risk ranking. You have an assortment of risks that you get out of your risk assessment and you are going to put them in some sort of order, ranking the worst risks on top in this case.

That's not necessarily how the risk manager is going to make his decision. They are going to look at that and they may have other factors involved. You may have to consider cost, values, a whole number of things. The final risk management decisions may not be in direct order of highest risk.

How are we going to use these risks that we rank? This is, the whole approach is a tool for helping us decide how we can best utilize our resources.

Do we need -- once we identify what the higher risk contaminants are do we need to set limits for them? Which ones?

Can we help implement changes by the feed manufacturers to reduce those risks and then what kind of surveillance sampling programs do we need to ensure that the risks are reduced and that we have a safe feed system?

One of the big concerns, we want to make sure we emphasize that we are not estimating individual risks. We're not going to say the risk of salmonella in feed is this. This is a relative ranking system. I can't emphasize that enough.

We're not trying to make any decisions about individual contaminants in terms of what their risks are.

The framework for our model is basically identifying the hazards up here.

You've got a hazard list identified, preliminary one. And then we're going to follow those hazards as they get incorporated into various feed ingredients, through processing and then what goes to the animals and following that is how humans are exposed to contaminants from consumption of food

animals.

Going back to our four steps of risk assessment, the first one was hazard identification. Karen Ekelman will be talking about that shortly, our proposed hazard list.

Just to give you a little background on that, here is all sorts of source material that go into animal feed, different types of source materials, where the contaminants come into the process.

For grains you get microtoxins, heavy metals, go through the whole list. This is just a way of showing that these contaminants can get introduced into the feed supply by a variety of mechanisms.

The second step that we're going to talk about a lot today is what are the health consequence assessments?

Karen will talk about the chemicals on the hazard list that, hour we're going to deal with the health consequences of those.

We'll talk about some of the challenges of putting it all together.

As I said before, the two factors we're going to be looking at for health consequences are the likelihood of the illness which we're going to call the potency.

If you become exposed to an agent, how

likely is it that you'll become ill?

The second part of that is the severity of the illness. If you become ill, how severe is the illness? Is it just a mild skin irritation, depressed weight gain in animals, is it death, which would be a very serious consequence.

Then we're going to put those two factors together in kind of a format such as this, ranking potency on one side, severity on the other and of course we're most worried about stuff up there, high severity and high potency.

We are not talking about risk at this point in time. We're just doing the health consequence scoring.

The risk will only come in when we put exposure together with health consequence to come up with risk. Now we're just talking about health consequences.

You can see a simple multiplication, 1, 2 and 3 on each side and I just want to point out that while this has got the nine, this may change. You may say anything that causes a high severity ranking here may be elevated, they may all be nines. You've got to worry about that. We may adjust the numerical ranking there.

The third step in our four questions are exposure assessment.

As I said, we're not going to cover

that today. That will be the subject of a future meeting, probably the next meeting.

The final step in the four steps is the risk estimation. That will also be covered in a future meeting.

Some of the limitations in this approach, you could call it semi-quantitative. It tends to push everything towards the middle.

In other words, if you have a high, for example here, you have a high exposure and a low consequence you get the same ranking as a low exposure and high consequence. The same thing you deal with accrual versus mild chronic. How do you rank a severed finger versus a long term respiratory effect? Those are some of the challenges we will face.

The final limitation, of course, is data. It's always nice to have data to fill build your model.

It will be a major challenge for exposure, but we'll cover that in another meeting. We don't have a lot of measured data for many hazards.

We're always looking for data. If anybody has it and you submit it, that would be great, much appreciated and it will help to build a stronger model.

Without data we're going to have a

strong reliance on expert opinion.

Not that there's anything wrong with that, but we have to go out and ask knowledgeable people, experts in the field, about how to rank, help us rank the hazards.

That's it. Any questions? That was kind of fast.

DR. GRABER: The next speaker is Dr. Karen Ekelman. Karen is going to be talking about the list of potentially hazardous contaminants. This is a document that's in your packet.

Karen?

DR. EKELMAN: The list is in your folder but we thought it important enough to go over briefly how we developed the list and let you look at it for those of you who haven't had a chance to read it yet.

I don't think I'm going to read it to you but I'm going to go over it.

First I want to give you a couple of working definitions because there's always confusion about what some of these terms mean.

Some of them have dictionary definitions that are very different from their use in risk assessment or toxicology.

The animal feed safety system has a working definition for hazard and by that we mean a

biological, chemical or physical agent in or condition of feed with the potential to cause an adverse health effect in humans or animals.

We also have a working definition for contaminant to distinguish that from any legal definition you might assume we might be using. We mean all potentially toxic or deleterious biological, chemical or physical hazards inadvertently present in animal feeds and feed ingredients.

On the last slide in my talk I'll talk about some of the things that we're not including in this round of the risk assessment model but which we will include later.

The first round we're including what we're calling the contaminants.

The list of potentially harmful feed contaminants should not be considered to be the definitive list of feed contaminants that pose a significant risk to animal or human health.

Identifying a list of contaminants is simply the first step in a risk assessment process. The last step where we rank hazards by their relative risk will be the one that has significant

to the animal feed safety system.

This list was developed in consultation with a limited number of experts and we did not require or ask the experts to provide data to

support their choices.

We simply asked them to give us their opinions about what contaminants might be present or were present in animal feeds that could possibly cause a risk to animal or human health.

Some of the items on the list may in fact, and we suspect they will, turn out to pose very low relative risks to animal or human health and maybe risks that eventually the agency decides not to take any further action on.

We may discover that some items that need to be on this list are not yet on it. It's a working list and it's the first step of the risk ranking process.

Some of the agents that are on this list are biological and for some unknown reason we stuck the BSE on there. Agents responsible for some transmissible spongiform encephalopathies and some evidence of CWD.

We also have some microbiological organisms that have been identified as possible risks to animals or humans from their presence in animal feed. It's a relatively short list but longer than some people thought it might be initially.

We have a longer list of chemicals. We have pesticides and I might say one of the reasons we have this list of pesticides is because the

Center for Veterinary Medicine has a feed contaminant compliance program and for the last 13 or 14 years we've been simply animal needs and feed ingredients for the presence of a large list of the older pesticides.

Many of these have been limited in use or actually banned from use on food or feed in the US but we continue to find low levels or small percentages of feeds either imported feeds or domestic feeds that have some residues of these pesticides.

Here are here of these pesticides. I'll let it sit here for a minute for those of you who haven't seen it before.

As I said, we have data on the level of many of these pesticides in samples of animal feed over 13 years.

We also considered the mycotoxins even though they are caused by an organism because we will evaluate the risks of the chemicals in the way we evaluate other chemical risks and basically we are concerned in the US with five major aflatoxins although we occasionally get reports from other countries that aflatoxins are predominant or may occur in feed in those countries.

Then we asked people just to think about what kind of contaminants might bother them in animal feed. Some of these you'll see belong to a

list of items that we're generally not considering at this point but they were given to us by our experts and will probably be evaluated in the risk model eventually including the chemicals on this list.

Finally heavy metals. We will assess the risk of these very much as we assess the risk for the chemical contaminants.

Radionuclides, these are the same things we are concerned about with respect to human food.

Finally there are physical contaminants. These are mostly of concern with respect to the animals that consume the feeds that have these in them and while we expect to have a relatively simple health consequence scoring methods for these, we haven't yet definitively developed it and won't be discussing it today.

We would like suggestions and any other that you might offer us how we might go about setting that up.

This is what we're not going to talk about in our first round of the risk ranking model.

We know there are other hazardous feed contaminants that could be present in animal feed that we're not going to talk about in this model.

Drugs. If drugs, when a drug is present for an approved species but in the wrong

amount or is present in feeds for unapproved species we will eventually consider those in our model.

The same thing for feed additives. In general feed additives used for their approved use are considered to be safe even though we recognize there is some residual use associated with those.

We will only consider in our model at a later time those ingredients that are in feeds for approved species but in the wrong amounts and those feeds that are in food feed additives in feeds for unapproved species.

Finally contaminants deliberately added to needs will also be added to our model eventually and these are subject to bioterrorism.

Additionally, weeds and/or feed ingredients not declared on the label, when these are not considered to be harmful we're not including them in our risk model although we understand they are an important consideration for regulators.

Many of you have questions about some things on this list and we could have long debates about them this afternoon or short questions about them now.

When I'm done with my talk I believe we have a break and you can get some more coffee but first I'll take any questions you might have.

AUDIENCE MEMBER: Steve Roach, Food Animal Concerns Trust. I was just looking at

biological risks.

Are you considering resistance to salmonella, maybe a higher risk than a susceptible salmonella? I'm just wondering if you are considering that, because there is a different risk. There may be different risks.

DR. EKELMAN: We do have some data on the fact that antibiotic resistance patterns on the domestic feeds are different than imported feeds. At this point I don't think we've considered that factor there.

We're looking more when we consider drugs to use at low levels that might induce antibiotic resistance and that risk will be factored in at that point. If we can think of a way to factor that into the organisms per se that might be useful.

AUDIENCE MEMBER: I think there are some, the salmonella report in the northeast, it could be a different thing than any salmonella that you --

DR. EKELMAN: When you see us talk about salmonella today we're looking generically at it, but they are also collecting data on the various sera types and if they can differentiate among them I suspect the model will differentiate as well.

AUDIENCE MEMBER: I'm Dave Dzanis, American Pet Product manufacturers Association.

I'm just a little confused with the

last slide, regarding the last slide, regarding not considering feed additives and ingredients but then listings likes --

DR. EKELMAN: That was kind of a situation where we gave our experts the ground rules and our experts came back with us with items that we asked them not to include. Eventually we'll look at them anyway.

Eventually they'll be in the risk model anyway. The reason they included selenium is there have been some incidents where animals died in the field.

That's what the experts gave us. Eventually all of those kinds of risks in feed will be part of our model, whether they are part of our model now or later.

AUDIENCE MEMBER: I'm Gregg Sherwood. I'm from Aurora Cooperative Elevator Company.

Is this going to be species specific?

DR. EKELMAN: Yes. When we talk about determining health consequence scores we're going to use the available data.

If we're talking about chemical health consequence scores most of the available data is rodent. Occasionally there's some data on dogs.

When you move to another species you have to extrapolate to that species. Traditionally

you do that in toxicology by using safety factors.

Safety factors will be used to extrapolate between species in which we have actual data to species in which we don't have data unless we have data that defines for us the pharmacokinetic difference between those two species.

Any other questions or we can resume talk this afternoon when we have our discussion group?

Thank you very much.

DR. GRABER: Let's give Karen a break since she is the next speaker. What we'll do is we'll take a break now. Let's get back here at ten minutes after.

(Recess)

DR. GRABER: Dr. Ekelman is our next speaker. She will be speaking on health consequence scores for contaminants in animal feed.

DR. EKELMAN: All right. Can you hear me? If you can't hear me, raise your hand.

This is where it gets full of jargon, full of toxicological information. Feel free to raise your hand and say "what the heck does that mean?" or "you didn't define that," if that's the case, because we want you to understand what we're saying even if you might begin to doubt that half way through this talk.

I'm going to talk a little bit about

how we do our health consequence scoring for chemical contaminants in animal feed.

I'm going to give you a little review of what Barry said earlier, remind where we are and where we're going and then I'm going to talk about how we're calculating health consequence score.

It's very complicated for chemicals in that we have three health consequence scores for each chemical.

We'll have an acute health consequence score, a chronic health consequence score for effects other than cancer and we'll have a health consequence score for cancer.

The goal of this animal feed safety system is to provide a tool for ranking relative risks of feed contaminants to aid the FDA in setting priorities for allocating its resources in a risk based manner.

We expect to make this model and the information that supports it publicly available. The goal is an internal FDA one at this time.

A relative risk score is equal to a health consequence score times an exposure score.

Today we're talking about the health consequence score piece and as Barry pointed out in the bottom line here the health consequence score is going to be equal to a severity score times a potency score.

The severity score again is if you get sick, how sick are you going to get and the potency score often also called a likelihood score is how likely are you to get sick based on a particular exposure level.

The reminders are that the list of potentially harmful feed contaminants are not to be considered as a definitive list of feed contaminants that pose a significant risk.

I summarized before why this is true. They were developed in consultation with a limited number of experts.

They were not asked to provide data in support. Some of these items are going to turn out to be relatively low risk and that means probably of not much regulatory significance and some items may be needed to be added to the list because we may have overlooked some things that have significant hazard associated with them.

Then health consequence scores for contaminants are not relative risk scores, exposure is missing.

So later in this talk when I show you a ranking of some hazards by their health consequence scores, please do not misunderstand and think this is a ranking of the relative risk score. This is for the purpose of this meeting only.

Health consequence scores for chemical

and biological contaminants will be developed for appropriate species.

They will be developed for food producing animals such as cattle, swine, chickens, for pets such as dogs and cats and for humans, though usually by this we mean through indirect secondary exposure from consuming food produced by animals.

And they will be for various specific exposure scenarios such as acute and chronic exposures for chemicals and acute exposures for biological contaminants and Dr. Okelo will talk about that as the next speaker.

First I'm going to talk about one of the three types of health consequence scoring that we're going to do for chemicals, scoring based on acute adverse effects.

An acute adverse effect occurs following a single or short term exposure to a toxic dose of a chemical.

They can be effects that are easily identified by veterinarians or untrained people in the field.

The animal can clearly die or have seizures or begin vomiting or whatever or they can be effects that are only identifiable after laboratory examination of affected tissues and organs.

Once again, this follows an occurrence in the field or following a particular acute toxicity study conducted.

Acute effects may also occur immediately after exposure or they may be delayed.

Most acute toxicity studies treat the animal to one dose of a chemical and then follow the health of that animal for at least 14 days to pick up some of the delayed events associated with that exposure.

It's clear if you have an incident in the field the closer the adverse effect is to the contaminating incident the more likely you are to associate it with the chemical that actually caused the events.

The further away it is the less likely you are able to associate it.

Data on acute adverse effects comes to us from results of accidental or deliberate poisonings in humans and animals such as anecdotal veterinarian or physician reports and also from acute toxicity tests conducted on animals.

The largest amount of acute toxicity test data on chemicals unfortunately, and I'll tell you why later, comes from the LD50 test.

You see a lot of material safety data sheets. You see on the web compilations of LD50 test data for acute toxicity data.

Recently some time in the past ten years the FDA said it no longer requires anyone to submit acute toxicity data to obtain approval for food additives.

If people conduct these tests and submit them to us for evaluate we will use them. The reason we don't condone people going out and conducting these tests because there are other tests that use fewer animals and kill fewer animals to get these results.

The largest amount of data is from the LD50 test and so that's probably most of the data we're going to be using for our risk model.

The LD50 is the amount of chemical given in a single dose that causes the death of 50 percent of a group of test animals.

It can either be directly measured in the study or extrapolated from the result of the study.

Most of these studies are conducted in rodents so results need to be extrapolated to other species including human.

Oral LD50 results are most relevant for contaminants in need but there's a lot of LD50 data from the inhalation and dermal tests as well. If we can, we will avoid trying to extrapolate from that data.

The LD50 is usually expressed in terms of milligram of test chemical per kilogram of body weight of the test animal.

When I talk about LD50 scores today, the units will always be milligram per kilogram of body weight.

Acute health consequence scores consist of an acute severity score times an acute potency score.

Acute severity scoring, the scores for chemicals are numerical scores assigned to a chemical based on the types of effects observed in acute toxicity studies or other sources. Most of the severity scores are going to be the score used for death in these studies.

If more than one adverse effect is identified in acute toxicity tests on a chemical the most severe effect observed is in the acute severity score.

This is an example. We can have scores from 1, 2 and 3 for no adverse effect observed, general effects that are considered adverse, neurological or neurobehavioral, and jump to death.

If we are basing almost all the severity scores for the chemicals for which this is being calculated we'll have a severity score of ten.

The second components of a health consequence score for chemicals is the acute potency

score.

The acute potency scores are numerical scores assigned to a chemical based on the measured or extrapolated doses that killed 50 percent of the test animals after administration of a single dose of the chemical, in other words, the LD50 value.

For chemicals with more than one reported LD50 value the lowest value is used to determine the acute potency score for that chemical.

This is an example of how we might do that. This is a generalized example. I'll show you a more specific example later on.

We have scores of 1, 3 or 10. One for a range of LD50 values that where the highest ones which means the lowest potency.

If you have a high LD50 value that means it took a lot of the chemical to kill 50 percent of the test animals.

That chemical had a very low potency and its LD50 score was high. You get a score of ten for the range of lowest LD50 values because those are the ones that it took very little amount of the chemical to kill a lot of the test animals in the study and therefore that chemical had the highest potency.

To incorporate information from acute toxicity studies other than LD50 reports a weight of the evidence approach will be used to assign the

study results to the appropriate potency category shown on the previous slide using information such as chemicals with related chemical and physical properties or information from chemicals with similar toxicity profiles, sort of like an expert opinion with a delineated method of coming to that expert opinion.

Now, this is an example for the purposes of today where I've calculated health consequence scores for the acute adverse effects of 16 chemical contaminants based on their LD50 values.

You saw this before. This is the severity scoring method I'm going to use where ten is equivalent to death. These are all from LD50 data. The severity score for all these chemicals will be ten.

In this case I created a potency scoring ranking from the LD50 values of the 16 chemicals I've used so that the highest LD50 value, in this case they range from 2730 to 5000 representing the lowest potency range, will be given a score of three for three chemicals and the lowest LD50 value which range from 5 to 82 indicating the highest potency range got a score of ten and that was for six chemicals.

If you wonder how we determine which chemicals fall into which potency range, this is simply an example of how you might do that.

I've taken each of the chemicals and given them a number and those are on the bottom.

I've organized them from lowest to highest according to potency and slotted them against LD50 potency.

If you can see, you sort of look here, these three make a natural group. They are the highest LD50 scores, the lowest potency.

These that you can still see above the baseline, sort of the mid-range, and I just arbitrarily allotted these which barely come above the baseline as the highest potency -- excuse me the lowest LD50 and that's how we broke them into categories for the previous slide. That's how I developed those.

Of course, what you would do when you have all your LD50's available, but we're doing it for a limited set of 16.

The next three slides are the name of the chemical that we've used, in this case lindane, the scores here, ten, the LD50 value we found, the potency score given to that LD50 value and the result of multiplying the severity score in this column times the potency score in this column.

We have here, other than aflatoxin, we have all pesticides, we have all pesticides there and here we have all pesticides again on this one.

You can see the severity, the health

consequence scores are not the same for all pesticides.

Finally we see ethoxyquin. I want to remind you for the next slide, this is not a relative risk ranking. This is a ranking of only one of the two components needed to determine risk.

So ten, which is the lowest health consequence score, there were three compounds there up to 100 which was the highest score where there were six.

Are there any questions about the acute health consequence scoring before I go into the more complicated chronic health consequence scoring?

I'm now going to talk about the chronic adverse effects and how we're going to score health consequences for those.

Chronic toxicity occurs when a toxic dose of a chemical is consumed for a significant portion of the subject's lifetime.

Chronic toxicity data can come from long term studies in humans, epidemiological studies and from long term studies in laboratory animals as well.

There is considered by toxicologists to be a set of toxicity studies that you have to complete before you have a full set of data in order to be able to calculate the chronic toxicity of chemicals.

These are chronic toxicity studies usually in two species and we usually ask for one in rodents and one in dogs.

Carcinogenicity studies which are lifetime studies usually in two rodents.

Reproductive toxicity studies, these are studies that look at the reproductive portion of a species's lifetime and we usually ask for those studies to be conducted in two rodent species.

And developmental toxicity studies. We usually ask for two of those to be conducted in different rodent species.

When there are fewer or shorter studies on a chemical that we have to rely upon to determine the chronic adverse effect then we have greater uncertainty about our estimate of that chronic toxicity and that uncertainty will be translated into the risk model in some way.

Just like for acute chronic events we have chronic health consequence scores being equal to chronic severity scores times chronic potency scores.

Chronic severity scoring is a numerical score assigned to a chemical based on the types of effects observed in chronic toxicity studies or from other data sources. A chronic severity score is assigned to a chemical based on the most severe

effect observed.

This is a rather more useful differentiation for chronic effect than for acute effect. Severity scores will range from one to ten, very much like for acute.

One will be that no adverse effects are identified in the particular study.

Two will be adverse effects other than those listed below. Three will be neurological or neurobehavioral adverse effects produced, four, reproductive or developmental adverse effects without maternal toxicity, five cancer, and ten, death.

Unlike acute toxicity studies you will rarely see death as a as a significant outcome of a chronic toxicity studies. There are usually standard ways of setting dose levels for that study and the guidance is generally to set the top dose where you see toxicity but don't see death of the animal.

It's only when you do the study incorrectly or set the doses incorrectly that you see death as one of the significant end points of a chronic toxicity study of the highest dose.

The second component of a health consequence score for chronic adverse effects is the chronic potency score.

Here we're going to have two chronic

potency scores, one for effects other than cancer and one for cancer.

For the purposes of the animal feed safety system risk model, the basis for the chronic potency score is something that we're calling an acceptable exposure level.

We don't want to confuse it with any other regulatory agency's acronym for what they're doing.

We're calling it the AEL and we will calculate these for each chemical contaminants.

The AEL or the acceptable exposure level is an estimate of the amount of a chemical that can be ingested daily over a lifetime without an appreciable risk of adverse effects. In that sense it is exactly analogous to EPA's reference dose, RFD, and the FDA's acceptable daily intake or ADI.

The AEL is usually expressed on a body weight basis so when I talk about AEL I'll be speaking about them in terms of milligram per kilogram body weight per day and the AEL is determined according to standard methods for deriving RFD's and ADI's.

Finally, the lowest AEL calculated from studies used to determine the chronic toxicity of a chemical is the AEL that will be assigned to that chemical.

If you look at a particular study, it's one of the set of studies used to assess the chronic toxicity of the chemical and you try to determine the no observed effect level or no observed adverse effect level in that study.

We usually try to identify a no observed adverse effect level. Sometimes when we're looking at effects that seem to be chemically related we're not able to absolutely say for certain whether that effect is going to be associated with a disease or an injury to the animal in the long term. Sometimes we're forced to use an NOEL as a basis for our AEL instead of the preferable NOAEL.

You determine what the NOEL is and how you do that is if you had three dose levels and you saw as to sick effect as the lowest dose level the next highest dose level is your no observed effect level. It's the lowest dose at which you did not see the toxic effects.

You then divide the NOEL or the NOAEL by appropriate safety factors. Sometimes those are study based and I'll run through the list on the next page.

The resulting number is the AEL for that study.

These are generally accepted and generally used extrapolating or safety factors.

We sometimes use a factor of ten if the

chronic study was done for a limited number of inbred rats.

You know the variability in that population of rats that you studied was not equivalent to the variability in the population as a whole or was not equivalent to the variability in the population you may be extrapolating to and when that's the case you use a safety factor of ten.

If you do not have chronic data and are using subchronic data you need to extrapolate to a chronic effect from that, you use a safety factor of ten.

Sometimes agencies use an extra safety factor of ten based on the severity of effects observed in developmental and/or reproductive toxicity studies and there's a safety factor of ten generally used for interspecies extrapolation but we like to replace with real pharmacokinetic data if we have it.

Chronic potency scores for non-cancer end points are determined by comparing the adverse effect levels for all chemical contaminants and dividing them into three categories, much like I described for determining the potency scores for the acute adverse effect.

Each category is then assigned a chronic potency score. You've seen this before. It's 1, 3 and 10 on the left.

You have the highest AEL's. Those are the lowest potency chemicals. The highest AEL's are chemicals that it took a lot of chemical to induce an adverse effect.

You have a score of ten for the lowest AEL range of chemicals. Those are the ones that it took very little of the chemical to induce the toxic effect so they are the most potent chemical.

We're finished talking about noncancerous effects. Now potency scoring for cancer effects is very similar to what I just spoke about.

One measure of carcinogenic potency is the estimated dose associated with a one in one million lifetime risk which I'm calling an LCR here just for short term.

For those cancer causing chemicals that have LCR doses calculated then those doses will be used in determining the chronic potency score for the chemical's carcinogenic effect using a scale similar to the one established for the non-cancer chronic end point that I just described.

This is how it will be done. You've seen this table the third time now. 1, 3 and 10 based on ranges of LCR scores that are high, the least potent, and low for the highest potency.

For cancer causing chemicals without LCR dose estimates a weight of the evidence approach will be used to assign the chemical to the

appropriate potency category based on analyses by various regulatory bodies, information on chemicals with related chemical, physical or toxicological properties and again this is where expert opinion comes into the scene.

This is my last example. I've taken 14 pesticides and I've calculated the chronic non-cancer adverse -- non-cancer health consequence scores for these.

You've seen this before too. This is what I'm going to use to determine the severity score for these chemicals.

It will range from one to 10. Some of these pesticides are quite old, have been on the market a long time.

Some of them are no longer on the market but we still find them occasionally, residues of them in animal feed but the studies that supported their approval were very, very old. You will see for a few of them the severity scores are ten so occasionally you do find a chronic toxicity study in which you see significant death at the highest dose level.

In this case the potency scoring ranges were set, you set the potency score ranges for the acute toxicity, you look at the range and see where they actually fall.

In this case the high AEL which went from .1

to .01 are five pesticides with the lowest potency, ten, a score of ten will be given to those with the lowest AEL's and they range from .0002 to .00005. There were three chemicals that had this highest potency range.

Once again the next three pages of slides are simply examples of how this works. Pesticides, we have assigned a severity score.

This one correlates to sort of generic severity. It means it wasn't death, it was a cancer, it wasn't a reproductive effect, it wasn't a neurologic effect.

This is the AEL which is similar to the ADI or the reference dose. This is the category into which the potency score was fitted for the ADL and you multiply severity score by the potency score to get the health consequence score.

You can see that both the severity scores now and the potency scores are varying by

pesticides.

There are more of them. Here are a couple here with potency scores in the ten range and severity scores five.

This is the final page. You see a ten here too. Here you see these have significant amount of death in the highest dose group. It's a fairly old study.

Very much like I showed you for acute, this

is what you get when you rank these health consequence scores for these pesticides, they range particular two to 40 and these are the pesticides and where they have them based on the data used to calculate the health consequence scores.

Basically today I talked about how we're going to set the health consequence scores for chemical contaminants in animal feed.

This will also apply to the heavy metals and the radionuclides will use the same method. The health consequence score is equal to a severity score times potency score.

We're going to have an acute health consequence score, a chronic non-cancer health consequence score and a cancer health consequence score for each chemical.

We're now working on the fact that we need to develop a weighting scheme. Maybe the weighting scheme I presented here is the one we'll use, maybe it needs to be adjusted for these acute non-cancer, chronic and cancer ACS scores but the overall score where you combine them is what will be multiplied times the exposure score to get the final relative risk estimate.

I apologize for the jargon. For those of you who are not toxicologists it must have been a very difficult talk. I thank you for waiting through it. Any questions?

I'm glad it was so completely understandable but if you come up with some questions, we're going to have a panel discussion later and you can ask them then.

DR. GRABER: The next speaker on the program this morning is Dr. Phares Okelo and he will be discussing the health consequence scoring for microbiological contaminants in animal feed.

DR. OKELO: Good morning. Can you hear me back there?

I'm going to be talking this morning about the health consequence scoring for biological contaminants in animal feed.

As you have seen in previous presentations, the model that we have selected for health consequence scoring has two components, the potency scoring and the severity scoring which is the biological potency score, measure of the likelihood of illness, and the biological severity score which is a measure of how severe the adverse effect will be.

In potency scoring we are looking at the likelihood of illness.

The question we ask is if a person or animal is exposed to a hazardous biological agent what is the likelihood of illness.

The following factors are what we could

use to quantify the factors that we would use to predict the likelihood of illness.

Median infective dose is the factor that we would, one of the factors we were considered to be.

We are talking about the location of the peak of these two curves. If this is the illness which a dose is given to a population of animals, then the median that occurs at the dose lower than the second, that would be more potent.

So if you are considering two different organisms with two different curves than the one that shows the same level of adverse effect and a lower dose would be more potent than the one that shows the same level of illness at a higher dose and the one that shows illness at the lower dose would be assigned a higher score.

Infective dose range is another factor we would use to predict the likelihood of illness and by infective dose range we are talking about the difference between the lowest dose that causes illness and the highest dose that causes illness here and this is a hypothetical case again, but we have a second distribution that has a tighter range and by range here again we are referring to the difference between the minimum dose that causes illness and the maximum dose that causes illness in that distribution.

In this case we consider the one that

has a tighter range to be more potent for the following reasons.

If we start at the dose level where a known proportion of illness occurs in the population and we increase that dose level to the median value and in this case these two divisions have the same median then we would notice that for the same change in dose that we would get a small change in the adverse effect for the distribution that has a wider range as compared to a large change, when you compare that to the large change that you get for the same change in dosage moving from that level to the median.

We see from this example that distribution that has a tighter range is more potent and therefore we would assign it a higher score.

Now I show you an example of how we go about scoring the median infective dose.

We have empirically assigned the range of one to the biological agent to small dose and the large dose when we have 10 to the power of 5 units and greater and the larger dose gets the lower score because it defects a large amount of the agent to cause illness and therefore is less potent.

Now I show you -- the median infective dose is based on the colony forming unit, the range and the range is formed in a similar model where in this case we consider the smallest range, that is

that tight range, having a higher score compared to the larger range.

Now we'll describe to you how we go about scoring the severity of the effects. The question that we ask is if a person or animal is exposed to the hazardous agent and becomes ill, how severe will the illness be? Will it be something like loose stool, in this case caused by salmonella or would it be something more severe or less severe than that.

In severity scoring we have empirically selected the major signs and symptoms as the factor for quantifying how severe the illness will be.

In the major signs and symptoms we start by looking at the list of signs and symptoms that are obtained for contaminating pathogens under consideration and we have seen in the previous presentation agents that are likely to be found in feed.

We base that list on the signs and symptoms that are caused by those pathogens. Then we look at the signs and symptoms and assign them a severity score, again, this is relative to each other, for an animal species under consideration.

This now will be an example of how we go about doing that.

In this example we considered a list of signs starting with abortion at the top and these

are just major signs that are exhibited when three organisms were used, in this case salmonella, E. coli and clostridium. We start with abortion and the dots there indicate many more signs and vomiting being the last one in there.

We start with, based on the list of contaminants that were shown before, with that list shown before and we used multiple experts to assign a score based on how severe they think the sign is and that again is relative to the other signs that are on the list.

These are means of the scores that are obtained from each expert.

Now that we have talked about the potency scoring scheme and the severity scoring I want to talk about how we combined the two to get the overall health consequence score.

This is an example of how we have done it in swine. The data is not complete but it's to illustrate the concept relative to each one of these agents, salmonella, E. coli and clostridium.

The score was gotten by summing up the signs and symptoms, signs for salmonella, the score was 50, E. coli was 39 and 58 for clostridium. The median scores were assigned based on the median scores that caused illness in populations of animal species.

In this case we are talking about

swine. The infective dose range were assigned as you see there giving the final health consequence score, the product of the severity score and the potency score which is a product of those two areas and in this case we noticed that the E. coli got the highest score relative to clostridium which came in second.

Relative to one another, we can determine which one has the highest health consequence. We can also use these kind of data to see relative to each other how much greater E. coli causes health consequences relative to another, in this case comparing salmonella and E. coli, we noticed that E. coli, the health consequence score is more than six times as great as the health consequence caused by salmonella.

Looking at the three organisms, severity score of 40 for salmonella, the same amount for E. coli and much smaller for clostridium.

The median infective dose scores were obtained as follows and the infective dose range in the same way, giving a final score again, E. coli coming up with the highest health consequence score followed by salmonella and clostridium.

For future considerations we continued to give it other data and to review that data and we obtained those from published literature as well as such as published data and we would use those to

refine the scoring systems.

The two factors that we use are the potency score and we would consider that, the subfactors that we use for potency score, so far we have only use the median infective dose and the infective dose range for the potency score.

We may need to look at other factors, other subfactors for predicting the potency scores and for the severity scores we may also need to look at other factors other than just the major signs and symptoms.

We would also use the data that we gather and review to refine the ranges of the subfactors that we have considered.

MSS here refers to the mean science symptom score and we would need to refine the ranges.

So far the examples that I gave considered only three organisms on the list of about seven. So when we add, we add the data from the other organisms, we would need to refine the ranges. When we look at all the other organisms that may need to come on the list or be taken out we would adjust the ranges accordingly.

In summary, we have identified the need for using health consequence scoring to address the relative hazards that are caused by different biological agents.

So far we have considered two factors for the health consequence scoring. That's the severity and the potency scoring system.

We looked at many other factors for severity and potency scoring but we, to illustrate the concept, the mean sign and symptom scores, the median infective dose for potency scores and then the infective dose range in addition to the median infective dose for potency scoring and based on published data that we have looked at, it appears that the approach that we are taking is reasonable.

We will continue to assess and to modify our modeling according to the data that we come across.

Thank you. Any questions?

DR. GRABER: There will be plenty of time this afternoon to get into some of these issues in more depth.

There's been a lot of coffee consumed. It's about ten minutes after. Let's take a ten minute break and we'll finish up with the last speaker.

(Recess).

DR. GRABER: Our last speaker this morning is Dr. Beblo. She will be covering challenges in developing a risk ranking model for the animal feed safety system.

Dr. Beblo.

DR. BEBLO: Good morning. I'm Delores Beblo and I'll be talking about challenges we face in developing a ranking model for contaminants.

It would be nice if we could just look into a crystal ball for the answers to our public health questions but, alas, assigned space approach is likely to provide the most help and best return when making feed monitoring decisions.

The current plan is to generate a relative risk ranking of various contaminant feed ingredients for feed pairs. This would comprise a framework for organizing information on feed contaminants, feed production, processing, distribution and consumption.

It could be used to compare and evaluate different exposure scenarios and identify where along the production to consumption pathway might affect the rate of benefit.

It will identify what data gaps exist for estimating and optimizing mitigating interventions. Ultimately the goal is to better understand the interaction between contaminants, feed, animal illness, food animal products and human illness.

The risk ranking model is comprised of four components, the first one being hazard identification and Dr. Barry Hooberman mentioned

previously.

This addresses the question of what can go wrong. The second component is the hazard characterization and this includes the health consequence scoring that was discussed previously.

The third component is the exposure assessment. How can the consequence happen? And finally the relative risk estimation. What are the relative likelihoods that things will go wrong?

Data sources for hazard identification include investigational sample data collected as part of the FDA feed contaminants program. Also the FDA surveys of feed ingredients and feed and finally, the USDA Food Safety and Inspection Service, National Residue Program sampling data for pesticides and environmental contaminants where investigation indicated a feed source.

Experimental studies confirm that animals given feed artificially contaminated with non-type E salmonella enterica develop infection with that organism.

There are also numerous examples of salmonella, numerous examples of outbreaks of salmonella outbreaks in animals that were traced to contaminated animal feeds.

It is well established that the consumption of infected or colonized food animals

and their products result in human illness. However, there are only a small number of cases of human food borne illness that have been traced to contaminated animal feed, as few investigations traced the source of contamination back through the food supply to the farm of origin.

Some factors both currently under assessment and potential that contribute to the hazard characterization or influence the outcome of contaminant exposure are listed here.

Drs. Karen Ekelman and Phares Okelo just presented a health consequence scoring procedure for chemicals and biological.

Additional factors that could be considered include physical and chemical properties, strain virulence, feed composition, factors related to conditions of ingestion. It's been reported that food may provide protection against the acidity of the stomach for pathogens, animal and human host factors and sensitivities of animal and human populations.

A challenge for the health consequence scoring regarding the probability or likelihood of consequence from ingestion involves identification of a reference amount of contaminants. For chemicals standard procedures and various reported exposure reference levels are available whereas for microbial hazards limited data are available on

infectious doses and there is no widely acceptable procedure for estimating an acceptable exposure level.

Another model challenge is combining different factors for chemical and biological contaminant classes and assigning relative weights to factors across the classes and to different factors within the class.

For example, in the biological health consequence scoring the relative weights of the median infective dose and the infective dose range warrants a decision.

Age and human immune status are host factors that we are considering in the model development but others are beyond the scope initially.

Data sources for the second component of the relative risk ranking model include the scientific literature and the battery of chemical toxicity studies.

We will also review epidemiological surveys. However, data gaps exist because there are limited pathogen dose response data in animals and humans.

Incomplete epidemiological information, there's difficulty in extrapolating from animal data to humans or other animals and there's a lack of mechanistic models of contaminant toxicity.

I should also mention that industrial surveys and production monitoring data, although usually kept confidential, would be valuable data sources and I encourage interested stakeholders in the sharing of information that could be used to improve animal feed safety for all to benefit.

Just to review, the third component, the exposure assessment addresses the question what is the probability of consumption of contaminated need and what are the likely numbers of microorganisms or amounts of physical or chemical contaminants in the feed at the time of consumption?

I list here some factors contributing to feed contaminant exposure along the production to consumption pathway.

We need to rely on external sources for data level in raw feed changes and changes in particular types of production processing. We have two dedicated animal safety feed members compiling dietary and feed consumption data for different species.

The USDA food and nutrient database for dietary studies provides human food consumption data.

For pesticides, industrial chemicals, elements and microtoxins, quantitative residue level and prevalence data from our feed contaminant

program and consumption survey data may be used to

estimate exposure.

Currently our feed contaminants program includes only collection of prevalence data for microbe samples and quantitative microorganism count data may be identified as an important data gap to address in the future. Also not all feed contaminants of concern are included in current feed sampling programs.

I would like to once again encourage industry participation with the sharing of any available data, working together efficiently toward data gap reduction.

Model development is an iterative process. My vision is to create a tool that connects to an active FDA surveillance database. New feed sample data would provide additional training data for model refinement which could then be used to help this side on future surveillance planning.

In the development of this framework or model for application in feed production, processing, distribution and consumption data are coming from many different sources. Two issues arise. First, what data should be included within the model such that the essentials for safeguarding animal feed are captured? And second, how to combine such information.

Drs. Karen Ekelman and Phares Okelo

have discussed factors they are currently considering relating to health consequence of chemical and biological contaminants. We have also identified other risk factors that I mentioned previously that may be included.

This brings us to the question of too much or too little detail, are the data representative of real feed scenarios, whether scientifically and statistically sound sampling and test methods were used in the collection of data and how best to allocate resources.

Data collection is likely the most resource intensive part of the exposure assessment in modeling.

We understand that the rationale and process for risk selection, risk factor selection and combining data must be transparent. Combining chemical and microbial contaminant data remains a challenge and we welcome further discussion on this topic.

Because of very limited dose response data our current strategy for hazard characterization makes assumptions in this area and these assumptions would benefit from further reflection and discussion.

Assumptions will also need to be made about processing, distribution and storage conditions for feasible implementation.

The model will be most beneficial, most useful if it accounts for inherent variability in residue sampling in manufacturing and distribution phases.

Factors that will introduce variability include location and regional feed ingredient availability, seasonal effects, different procedures followed by different procedures, differences in processing facilities, characteristics of the distribution chain and consumption patterns.

For pesticides, industrial chemicals and elements, the feed compliance program guidance manual calls for an original and a check analysis to support regulatory action. These could be used to define bounds of a uniform probability distribution for reflecting data variability in estimating exposure.

For microbes in feed, two samples, an official sample and an investigational sample, are collected and analyzed and these may be used to define bounds for a uniform prevalent distribution.

Adequate data may not be available for all contaminants. A way of dealing with this is to use expert opinion.

This introduces the consideration of how to combine information from different experts. During his presentation of health consequence

scoring for biological contaminants Dr. Phares Okelo discussed one method for eliciting and combining information.

We understand that factors that may be variable or uncertain need to be identified and their influence on the relative risk ranking outcome transparent.

Considering the production to consumption exposure pathway and the inherent uncertainty in variability increases the complexity of the model but provide the most information for its managers when implementation of intervention strategies may be considered at any point along the chain.

It is our hope that we can overcome the challenges I have mentioned and our efforts will culminate in a valuable user friendly decision-making tool for addressing safety issues in animal feed beneficial to all stakeholders.

Thank you for your attention. Any questions? Thank you.

DR. GRABER: It's a little after 11:30 now. We were scheduled to break around noon.

We thought either we would be more longwinded or you would, but apparently neither one of us were. So we're ahead of schedule.

I think what we will do is we'll break now for lunch and we'll come back instead of at 1:30, we'll come back at 1:00 and we'll start at 1:00.

(Luncheon recess).

DR. McCURDY: Dr. Gebreyes has some interesting comments here and I'm going to try to paraphrase.

Variation of health consequences among different animal species. This needs to be of prime importance in computing or compiling the final document.

This is for Okelo. The significance of the infectious dose range in biologic data in questionable. Infective dose is sufficient. Infective dose is sufficient once the minimum effective dose is achieved, any dose above that remains infective. So no range.

You want to address that? We talked about that when we had our practice session.

DR. OKELO: Well, we are not looking at the minimal infective dose. We are looking at the median infective dose.

We are not saying that above the minimum infective dose that you will have a problem but below the minimum infective dose you will not have a problem because it is possible to have disease happening even below the minimum infective dose because with biological agents it's possible to have the bacteria, the bacterial numbers increasing above the minimum infective dose.

So we need both of them because we are

measuring different things, the minimum infective dose and the infective dose range. They are different parameters.

We think they are characteristic of the organism.

DR. McCURDY: Any further dialog?

AUDIENCE MEMBER: Thank you.

Definitely I agree that a median value will be important but if you already have that median infective dose, what does range, what is additional -- what does it add, because you already included that in the factors, if I understood correctly.

That's my question.

DR. OKELO: So far it looks like it would add something but we will look at the data.

We have not extensively looked at the data yet but we think that it would add some value. If it does not, we will drop it. As we say, we are considering other factors. In the end we will use the best factors that we'll need to make the prediction.

DR. McCURDY: You want to continue on with the rest of your questions?

We'll continue on. He also asked the issue of negative data that do not end up in

publication could create not only a data shortage but also lead to bias.

Any further discussion? You and I discussed something like that the other day.

Any comment? Unpublished data may lead to data shortage and bias.

DR. EKELMAN: It's absolutely true that we cannot include in our risk model data that we don't know anything about which is one of the reasons why we're asking people to contribute information or data to this project so that we can all have the best model that would be useful for the agency and anybody else that wants to use it, but given that, we can't estimate or even predict what the data are likely to be.

We believe also that there is positive data out there that we don't know anything about and we can't include that either.

Yes, this is a problem with data and we're just going to have to live with it.

DR. McCURDY: Any further comment, discussion on that point?

Some data is not appearing, negative data may not appear in the open literature or publications here and there that would cause a data shortage.

DR. HOOBERMAN: It might appear once the results come out.

I suspect that data might appear once the results come out and people don't really agree

with the results or they think it's not accurately representing the situation and then we might get some data in but we would hope that it would come in as soon as we can get it or as soon as possible.

DR. McCURDY: Anything further? Dr. Gebreyes's next question, do some food animals such as swine and poultry (indiscernible). In essence what he's asking is cancer, chronic diseases, can that be measured as a health consequence.

DR. EKELMAN: You are correct.

If an animal doesn't live for the majority of its lifetime it's unlikely to get the chemically induced cancers.

We think pets, we want them to live their lifetime so we are concerned about cancer causing chemicals for health feed.

If the animals are going to go to market, greatly reducing their life span we wouldn't worry about those animals developing cancer although some cancers can occur relatively soon. We do worry about residues of these chemicals being in the food derived from these animals and contributing to cancer incidences in humans that consume these products.

Those are the contexts in which we would be concerned about cancer.

DR. McCURDY: Any other questions?

We do have a set of regulations that

speak to cancer causing agents, causing residues in meat, milk and eggs.

It's in the beginning of our regulations that speak to sensitivity of method and tissue residue.

We can continue on that line how that is going to be affected by the animal feed safety system and the particular questions that we (indiscernible).

This last question has to do with extrapolation from one species to another species and to humans particularly, from rat, mouse, what have you, data and to human beings and that this could be a problem.

Since Karen has had a lot of experience in that and Barry, would you like to speak to that issue about extrapolation across species?

DR. EKELMAN: Of course, it's a lot of uncertainty in doing this.

There are some post hoc studies that show how accurate it is to include safety factors and I guess those studies have shown that most of the standard safety factors reliably account for most of the risks associated in extrapolating from animals to species.

We're pretty comfortable that there's a generally accepted method in the toxicological world for extrapolating from rodent and animal data to

humans.

What we find most problematic is extrapolating from animal data in rodents to a huge range of animals that will be consuming animal feed.

Very seldom are there studies in the animal species that we're interested in and so we have to make assumptions about how to extrapolate between species and it's not always easy because there are lots of different variabilities in their digestive systems, et cetera.

We're going to have to use safety factors and we're going to have to also search for data that allows us to bound those safety factors reasonable.

There are a couple of cases in which we know there's chronic toxicity data in a particular species like cats. We'll use that instead of an extrapolation from another species.

There is some pharmacokinetic data to inform our extrapolations on occasion but we find the biggest problem is not going to be extrapolating from rodents to humans because that's pretty well established you can do that with safety factors and not be off too much at the time, you won't miss any risk at the time but the issue is how successful that's going to be extrapolating from rodents to other animal species.

DR. McCURDY: That's the list that

Dr. Gebreyes had to ask the panel on this comment.

Are there any other questions? You've got to ask your questions now. There are your targets up there. Throw your barbs. I hope they hit dead center.

AUDIENCE MEMBER: I'm Steve Roach from the Food Animals Concerns Trust.

My first question is there are substances that if you look -- sorry. There are substances where you really can't find no effect level. I'm most familiar (indiscernible).

I think with your system it's just going to move to the top but it seems like there are some things that have a different magnitude of risks, or the risk is very different than other things where you actually have an effect level and I was wondering do you have any way to actually address that?

I'm just concerned because you are going to end up with things that I would believe there should be no tolerance for and I just wonder how you address that. I know you can just put a ten on that factor but I think that might miss something.

DR. EKELMAN: I guess as we continue to evaluate substances we'll start running across some of these and we'll have to decide how to deal with them.

Certainly it would be good to deal with them in a way that would allow them to rise to the top.

If there were, indeed, for instance -- some people believe that lead is a substance for which the impact on intelligence has no known effect level should one let that rise to the top considering the effects in humans, so I don't think we've yet decided how to do that.

We run across chemicals like that. We certainly consider it important. One model we could use is the way we're doing the cancer process, we're calculating a linear to low dose.

Most of those are calculated -- one in a million are calculated in a linear to low dose basis.

So you could use something like that, and so follow the cancer model for that but we'll have to think of some way to factor that in. That's an important question. The examples we've run across, we haven't yet found one that we can't effect a no effect level or a benchmark, something like that.

AUDIENCE MEMBER: A fairly related question, there seems to be at least in the list you had orders of magnitude difference between (indiscernible) your results actually end up with a couple of orders of magnitude.

Again, it seems like you might have

things where if you combine that with an exposure you are going to have something where if you had actually just gone ahead and done a quantitative risk assessment you are going to have to come out with a different ordering and I wondered do you see that as a problem?

I'm concerned about it. Things that are active at very low doses, they might not be addressed very well.

DR. EKELMAN: We talked about the fact that we're going to the ranges is because we anticipate that for exposure we're not going to have data for many, many substances and the best we're going to be able to do is get experts to commit to a range.

It's hard to have a risk number that's more accurate than your least accurate component.

However, we're also talking about the fact that since we do have the AEL's calculated and the minimum effective doses calculated that we will go back and explore the question of whether we should just use those calculated numbers rather than assigning them to a range and reducing the distribution among them.

That's something we haven't decided yet. We can assign them to the ranges as we showed you or we can still choose to use them separately. We haven't decided.

DR. HOOBERMAN: Let me just pull up that slide.

I think you're talking about this and the fact that these are grouped in one category and we're not differentiating among the three.

AUDIENCE MEMBER: I'm not sure. Basically from what I saw you go from, you may have five orders of magnitude of difference but in your results you are at two orders of magnitude. If you do the -- if you had done qualitatively you may have something.

DR. HOOBERMAN: Yes. The weakness of a qualitative approach but one of the things we will do is as we get more and more chemicals and we look at this kind of a distribution we may have more than three categories, low, medium and high.

We may expand to ten in order to better differentiate among the distribution. We may be able to handle this has a separate category. We have to see how the distribution falls out of these kind of scores.

AUDIENCE MEMBER: I just have one final question which is quite broad.

I'm just considering, you are doing a bunch of risk assessments but is there any -- before finishing all this are you considering are you going to try to set risk management triggers, okay, this amount of risk is unacceptable or are you just going to wait until you are finished and do risk management afterwards? I'm curious about where it

actually fits into that.

DR. EKELMAN: Am I going to leave this one to George? Do you want me to --

We are doing a risk ranking exercise. The only factors that will go into our ranking, the result of this model will be science based risk factors.

However, how we use that, we anticipate to use that internally to help us set priorities for dealing in a regulatory fashion with the greatest risk to animal and human health from animal feed, but if management is then going to use this for another purpose they would, of course, incorporate factors other than risk like cost, like feasibility, like controllability, things like that. If they do that we're going to encourage them to be as explicit about those factors as we've been about these. That's not the point of this exercise.

AUDIENCE MEMBER: I'm still not clear on that.

You all do not anticipate proposing risk management steps? You all anticipate saying these risks, this is a high risk, therefore it's an acceptable risk? I'm not sure.

DR. EKELMAN: We are developing a risk model.

Other people are going to decide what to do with that model, including George and other

people at CVM but this is about how we're going to develop that model and the end result is going to be a rank order of risk and not a decision what about to do about those risks.

AUDIENCE MEMBER: Somebody else is going to decide what to do about the risk.

DR. GRABER: This really, this exercise is one of science based, just to get relative risk among the potential hazards in animal feed.

This is not an absolute determination of risk or an estimation of risk. This is basically looking at relative risk.

Obviously at some point in time when you have something that's at a higher risk in a relative sense you have to come to some confusion about does that risk for this hazard present an issue for the center, the agency to work on, but that will be a separate exercise.

AUDIENCE MEMBER: I'm Richard Sellers with the American Feed Industry Association.

We really applaud what you are doing here, to take the time to go through these steps. We appreciate that.

One of the reasons -- I think my blood pressure went down about 30 points when you said you'll use this for internal determination. That's a good point.

We know you do this on a regular basis. When you go through exercises, you can adopt those crazy numbers from the European Union which really their scientists turned down as not insufficient samples, not adequate risk assessment, a whole bunch of factors and we're watching what EPA is going to do with the draft docs and I have a series of questions.

One of them is are you aware of the OMB circular regarding risk assessment coming down from the executive branch and is this an exercise in that?

DR. EKELMAN: We're aware of the circular and we're aware that we're going to have to adhere to what the requirements are but those requirements didn't drive this exercise.

Our real desire to have a sensible scientific way of separating the higher from the lower risks relation to animal feed was what drove this exercise.

Everybody has opinions but sometimes the end results of the scientific analysis show us the opinions we've held for years were just not right.

None of us have any, have prejudged what this is going to turn out to be in the end. I don't have a clue which is risks are going to be higher than the other but it was driven by an

internal need to know.

AUDIENCE MEMBER: That's an excellent answer.

That's what we like to hear, that it's a transparent process and that you are planning on holding -- our largest angst issue is frequency of occurrence of these hazards and how you picked this huge laundry list of pesticides that we very rarely see any type of residues and lindane being a banned pesticide for 30 years, who keeps spraying these bags of lindane over the farmland? Questions come up about that.

The other issues that we've harped on in a number of our public letters is Dr. McChesney referred to, gut reaction of experts and I heard Dr. Goober man say there's nothing wrong with that.

We have a lot of, lot of heartburn in making design specific decisions based on the gut reaction where there really aren't any data and we would like to know how that's going to proceed and who were your experts who helped you making these determinations adding a couple of food additives that are okay for use in feeding.

DR. EKELMAN: I'm going to let Barry answer the second part of that question because when he answered that question for me he reduced a lot of my angst about that very issue.

There's actually standard procedures that let you anchor expert opinion --

DR. McCURDY: Save your voice and let him answer.

DR. HOOBERMAN: There are a lot of procedures.

There is a way to kind of control the gathering of expert opinion to make it into a more reliable and less variable process.

Up to now the experts that we've employed are basically internal CEM scientists and I think as we identify data gaps to a better extent we will be going out to others, academics or possibly industry people --

AUDIENCE MEMBER: Can (indiscernible).

DR. HOOBERMAN: As we identify the issues we could identify which experts we would like to come in or what expertise we would like from the experts to address these questions. We could certainly do that.

It's not a single expert, although we said the term gut reaction of an expert, you know, and as you gather more experts you can get a better handle on what is a more realistic opinion from the experts.

It's not just one person. As you get more people, a higher sample size, theoretically you get a more accurate response has to what may be really going out there.

Does that sound right?

AUDIENCE MEMBER: We could probably agree to that.

We know a lot of about gut reaction. The ones that bother us are the ones that you make regulatory decisions based on limited amount of data.

More importantly, regulatory policy issues where you are going to establish, heaven forbid, reference doses or something that you referred to them as AEL's.

DR. HOOBERMAN: It's got another name because we are attaching no regulatory significance to these AEL's. That's why we didn't call them that.

AUDIENCE MEMBER: Touche.

MR. HOOBERMAN: That was a big concern of ours. We tried to find a name that has not been used.

AUDIENCE MEMBER: Touche. The largest category of these hazards that gives us the most angst is we've had a lot of conversations with the center director's office is the microbes and absent some kind of national risk assessment we hope that there's not any regulatory policy made to determine that salmonella in that regulation, 535, just point blank is going to be a hazard that has to have a zero tolerance.

I think the agency learned that that really didn't work from, say, 1990.

I hope that you're going to work down that road. We're willing to work with you on that and we've identified some experts and I know CODEX has taken this on and also OIE has taken this on and we recently named Dr. Paula Cray to that and the Secretary General accepted that so she is going to be the US representative on that task force in trade and animal health and issues in animal health. You might want to watch that. I don't know if you are aware on that.

Comment?

DR. HOOBERMAN: We're staying abreast of those kind of developments and it is a consideration that we will follow up on. In the face of no data we're going to have to go out to experts who have knowledge out in the field of what's really going on.

AUDIENCE MEMBER: Finally, data. We have wrestled with supplying data to the agency over a wide range of issues for a number of years. We cannot find a mechanism to do that without some type of civil liability attached to it.

If I pick one or two ingredients of which there may be one or two ingredient suppliers in the US that supply you data it's going to become apparent not only to the feed industry manufacturing side but also to anybody in the public that requests

that data or finds out about it and I don't know how.

If you are expecting any kind of industry data from us you need to create a mechanism to protect that data or we can't supply it.

We've got a wealth of docs and data which is extremely positive but help us, Karen, you heard this from me.

DR. EKELMAN: We are not going to be able to keep anything you give us secret because you saw we're going to make everything we use in our model publicly available.

However, if you group into larger groups, for instance you have three ingredient suppliers which fall into a larger category, say some esoteric wheat protein that they supply.

Group them into the larger category of wheat byproducts and give us all the data on that. Group it in a way that individual firms aren't identifiable.

We don't need individual firms identified. We don't need every individual product identified.

Categories, large, broader categories of products would be fine. It would be a good starting point for some of the data we don't have. That's one way to make that data sort of non-identifiable, if that would work.

AUDIENCE MEMBER: I don't know how

that's going to work.

For instance, in fish meal, I can't put it in marine products because there are two suppliers in the United States and you'll know where that information came from.

With perhaps plant protein products or something we might be able to do that but we still have a concern about giving you that type of data and looking like we're out of control when in fact I heard at the US Animal Health Association meeting one year in the feed safety committee that a large integrated poultry company came up with about 200,000 samples of poultry carcasses and feed and no correlation between those two and that's a significant finding but that's all they are willing to say.

DR. EKELMAN: Maybe by the time we're asking for data on dioxin we'll have published a couple of papers that indicate where our interest in dioxin levels lie and maybe if the data you have are data that lie below that level you'll be more comfortable providing it under the circumstances. Lots of things can happen that might make it more possible.

Keep an eye out and look at ways to give us partial data. If you can't give it for those industries that we can't identify the actors and group them and given us for people that we can't

identify, we would appreciate that.

AUDIENCE MEMBER: We would like to continue to talk about this. We'll give you the seven's and nine's.

The last thing I'd like to say is congratulations on your centennial of protecting public health.

I have a lot of respect for the scientists working with this and the ones I work with. You do a stellar job in a risk uncertainty basis on trying to help us, so kudos.

DR. McCURDY: Yes, sir?

AUDIENCE MEMBER: My name is Fred Angulo. I'm with the Centers for Disease Control in Atlanta, Georgia where I work in the Division of Foodborne and Bacterial Diseases in the National Center for (indiscernible). My comments relate to microbial contaminants.

As you know, the charge of CDC is to conduct national surveillance for foodborne diseases and we're very excited about the recent news in foodborne diseases with important declines in the last couple of years in E. coli. (indiscernible) and the cattle industry reducing the contamination of ground beef with eke coal he (indiscernible).

It demonstrates when there's a commitment by the industry voluntary actions by the industry can result in remarkable declines in human illness.

I think one of the critical foodborne disease problems in the United States currently is the stagnation of the incidence of salmonella infections in the United States.

In fact there has been no decline in salmonella infections incident to human salmonella infections in the last decades I didn't think initiatives to reduce the incidence of human salmonella infections and it doesn't look promising that we will achieve our national health goal which was to reduce salmonella by 50 percent by the end of the decade.

The failure to make progress with the salmonella incidence has led the USDA food safety inspection service to launch a new initiative on salmonella in the food supply and we support that initiative.

One of the fundamental questions that's asked when we discuss surveillance data in salmonella and particularly in a setting such as this is what is the contribution of the animal feed supply to human salmonella infections. It's a very difficult question to provide a quantitative answer and largely it's because we do not have national surveillance for salmonella contamination of animal feed.

We have robust surveillance for human salmonella infections. We have, with the NARMS program we have robust (indiscernible), salmonella

isolated in processing plants from animals and also from humans and because of the FDA retail food study we have also information about salmonella in grocery stores but we don't have national surveillance of salmonella contamination of feed and it's very difficult to have a risk based approach with that huge data gap and if resources are available, one of the important places to put those resources is to gather salmonella islettes from animal feed upon which we could do comparison approaches and show the similarity of the salmonella islettes in animal feed to human salmonella islettes.

There have been a few limited studies that FDA CVM has recently done. With that background we certainly impose efforts throughout the food chain to try to reduce salmonella, the human health burden of salmonella.

The human health burden of salmonella is recognized to be over a million people infected each year, 10,000 people hospitalized, an estimated 500 people dying each year of salmonella infections.

We applied the efforts here in this discussion about trying to improve animal feed safety and I applaud your approach.

I find it quite exciting to see the similarities of this approach to the recently developed FDA CVM guidance 152 approach for dealing with the hazard of antibiotic resistance.

In that approach guidance 152 approach

you follow a similar paradigm of hazard identification, consequence assessment, exposure assessment. So I endorse these first steps you are taking.

Allow me then -- let me comment on what you've presented today. First with the hazard identification, I understand the need to have a comprehensive list of the possible microbes that might contaminate animal feed.

I also recognize when the model is completed most of those microbes listed there will fall out because there is no exposure from those microbes.

The list that you have, bacillus and mycobacterium pseudomonas and staphylococcus, it's hard to understand what the human health consequence of those organisms would be although perhaps there's an animal health reason that they are on the list.

What will happen -- first, you do need to classify the E. coli shikatoxin toxin producing E. colis. I don't think you mean generic E. coli.

At the end of the day the two pathogens that will be of greatest concern in terms of human health will be shiga toxin E. coli producing toxin and then, of course, salmonella.

Clearly the microbial hazard of concern is salmonella. CDC has recently, although it's been a couple of years now, has recently published a manuscript that describes our concern about the role

of the animal feed supply in human salmonella illness.

Besides the hazard identification, turning to the consequence assessment that you conducted. I think first commenting upon the severity score which makes complete sense that there's a need to have a severity score.

All pathogens are not the same. If the only microbe of interest turns out to be salmonella not all sera types of salmonella is equally virulent and they do result in different likelihood of causing serious illness.

I do think the way you try to prioritize the severity score is not adequate. It doesn't make sense to just get a catalog of all the symptoms the patients have and then give a category score for a variety of symptoms and if something causes diarrhea and vomiting, you get so many points, but I think the better way to do the severity score is getting a likelihood of having a severe infection.

Salmonella type B would have a very high severity score, very high likelihood of having a blood infection with a salmonella type infection.

I think the problem, my judgment, the problem with your consequence assessment is the potency score. The problem with potency score is that essentially is a proxy for dose response and

we're dealing with microbes and microbes multiply, especially in this matrix.

In animal feeds salmonella will multiply and if you find a certain quantity of salmonella in animal feed today, it won't get higher or lower depending on how it's handled. The quantity is not static.

I don't understand how you can do a potency score, essentially an infectious dose quantification based upon a measure of single points in time, particularly, when as I say, there can be degradation or increase in concentration of salmonella.

I actually see no reason to have a potency score. I think that the entire human health consequence assessment can simply be based upon severity and that would capture the discrimination that you are hoping to gather.

The other discrimination in terms of differences between the strains can be captured in the exposure assessment. I know you didn't present on exposure assessment.

There was one, at least one comment made on exposure assessment and that was the comment that at least I think it was implied that the likely exposure route that would be of most interest would be ingestion but I caution that direct contact with animal feed products such as pet treats, pig ears, the recent salmonella outbreak we had that we shared

with Canada was a consequence of families, largely children handling pet treats and -- or you should also consider direct contact with animal feed products as well as indirect food supply ingestion.

Sorry I talked so long. I'd be happy to clarify any comments I might have made.

DR. OKELO: Thank you.

AUDIENCE MEMBER: Do you have any questions on my comments?

DR. McCURDY: Anybody in the audience like to comment? Our friend from Ohio State?

AUDIENCE MEMBER: I know for good --

A VOICE: Dave, wait up. We'll bring you a microphone.

AUDIENCE MEMBER: I'm Dave Wagner.

I think the value of the group for our use, probably the best thing for you to do would be if you could provide those comments in writing.

You sort of had several ideas that you expressed. It would be good if you would provide that information to us.

The other comments about some of the organisms on the list, I would agree. I think they are only tenuous at best.

Some of them were provided with sort of a circuitous logic. Pseudomonas, for example, that would be for multi-(indiscernible) widely disseminated in the environment. It's also one that

survives wells in refrigerated conditions. So there are other rationales as to why those things are on that list.

AUDIENCE MEMBER: Isn't this meeting being transcribed? Just to be clear, I didn't mean to sound so disjointed but the fundamental single criticism is largely positive. Thank you for doing such a great job.

The specific criticism is I don't understand the consequence assessment and I don't understand how you are going to manage the infectious dose of a microbe that multiplies in the matrix that you are measuring.

The consequence should simply be the severity of human illness.

DR. McCURDY: Anybody else?

DR. HOOBERMAN: One alternative if we believe that the potency score is not as important as severity score in coming up with the health consequences we can weight it lower. There's no reason to have equal weight.

If we feel that it's going to help in drawing a distinction between biological agents, we'll give it some more thought whether the infectious dose is a good representative of the health characteristics of a biological agent.

There's no reason it has to be weighted the same as the severity score. We just have to see if we have enough to distinguish between biological

agents.

AUDIENCE MEMBER: I agree. Because my comments were largely based on microbial concerns and it is largely salmonella, there is no such thing as a nonpathogenic salmonella.

Any salmonella fed at a high enough dose will cause human illness. Our understanding of the epidemiology and biology of salmonella is they all are pathogens. Even salmonella Kentucky which is very prevalent in poultry at processing in fact causes human illness fed at a high enough infectious dose.

DR. HOOBERMAN: What you just said --

AUDIENCE MEMBER: At a high enough exposure.

The whole infectious dose can be captured in your exposure assessment but you are going to be doubling, double counting exposure by having an exposure component and an infectious dose component that's in your consequence assessment.

DR. HOOBERMAN: No, I don't think so. What you said is at a high enough dose.

That would mean that perhaps biological agents have different or even different strains of salmonella have different doses that would cause a disease.

That's what we're trying to get at. You don't need as much to cause an infection with

one as with another.

AUDIENCE MEMBER: The problem is you cannot -- it's not like a toxin that's stagnant. It multiplies.

DR. HOOBERMAN: I understand. One of the struggles that we're going to have when we get to the exposure side is what does the exposure data look like and that will have to be part of our considerations and whether we can do a potency score on the health characteristics side.

A VOICE: Can you expand a little bit more on the exposure number?

DR. HOOBERMAN: No. We're trying to not get into exposure.

In my opinion, I think all of our opinions, exposure is going to be a much more difficult challenge based on the amount of data we have available.

For instance, Karen knows more about -- for instance, the salmonella data, what it looks like. I'll let her speak.

DR. EKELMAN: We've had a contractor for a while trying to gather data for us because we knew that there was a tremendous dearth of data on when feed is contaminated with salmonella, how many organisms are there per unit and there's very little data on that.

We are at fault ourselves, in fact, in that when we get sample feed for salmonella we just

do positive or negative. You can say it has to be above a certain level to test positive but that doesn't give us much help.

For microbial data remember we said that we wanted the two pieces to be there. Delores has said you want the -- or the likelihood that the meat is going to be contaminated with the agent that you are looking at and then you want to know how contaminated it is and it's possible that for some contaminants we might only have one part of that.

We might only have how likely the feed is to be contaminated and then we might have to have some structured expert opinion to get an opinion on what they suspect the contamination will be.

For chemicals, it's nothing like the scale of the absence of data for microbes and that's going to be a big problem.

I think what Barry was trying to say is whatever we decide or figure out that we can use for exposure calculations for the microbes we'll go back and decide if we've used the right thing for the hazard consequence scoring so that we don't double count.

We don't know yet for sure what we're going to be able to use. We keep hoping for more data than I think we're going to be able to get.

AUDIENCE MEMBER: I'm Greg Sherwood again.

Are you going to look at specific point of contamination, the most possible point of contamination is?

Frank brings up a great point about salmonella but we all know that you can swab salmonella out of the mouth of every bovine animal in the country.

DR. EKELMAN: Let me just briefly explain what our model is going to look like. I think there was a slide to this effect at one point. Do you want to put that back up, Barry?

We're going to look at feed ingredients. We're going to take our list of hazards and try to figure out based on data and based on reasonable guesses which ingredients are likely to be contaminated with which hazard so that we'll then have hazard ingredient pairs.

Then we'll look at the data that all house us to come up with a quantitative estimate of the level of hazard in that ingredient.

Then we're going to use information we have on manufacturing to track that ingredient into feed for all of the relevant animals and to track what happens to that ingredient in that feed when the feed is processed by various methods.

In other words, is the method you are using to process the feed likely to increase, decrease or not change the level of contaminant in the feed?

Then we will adjust the exposure of contaminant to the animal based on the amount of the ingredient that's likely to be consumed by that animal.

So we're going to start at the ingredient and track it all the way through. Sometimes we have data on the level of contaminants in complete feed so that will be a check to us on our system for doing this.

Yes, we're going to track it all the way through. We'll be able to say well, I'm out in the middle of Iowa and I'm making feed for hogs and I use these three procedures and if I just adjusted this procedure to have one with a different temperature I would significantly reduce the potential for having these microbial hazards in my feed so I guess I will do that.

It's a kind of a process where you can say if you substitute alternate methods of manufacture, when you change the ranking of the hazards that could be in that feed, so it's sort of like going to be a story from the beginning all the way down through and track what really happens.

AUDIENCE MEMBER: Mel Van Denberg with ABC.

We know that exposure to these pathogens isn't exclusively or cannot always be associated with feeds.

My question is do we really know that priority should be placed on feeds rather than some other potential exposure such as those areas outside of the feed industry?

DR. EKELMAN: Our model is not going to answer that question but we hope our model will answer the following question either on the basis of data or expert opinion.

How often does human salmonella illness result from salmonella contamination of animal feed?

I'll tell you there's really no data that we can find that leads directly from one to another but we hope to get an estimate that may be many or most people can live with in our risk assessment.

The issue for us isn't where it's best to control. The issue for us is is feed a reasonable place to put control.

DR. McCURDY: Any other comments or questions?

AUDIENCE MEMBER: A question about the acute adverse effects --

A VOICE: Your name?

AUDIENCE MEMBER: I'm David Johnson. I'm with the Canadian Food Inspection Agency, the feed section.

When you are using LD50's to assign acute potency this doesn't take into account the

dose response relationship.

Would you be using something like that, I notice for the microbial pathogens, you began (indiscernible) response relationship with the, not the median dose but the other (indiscernible) adverse factor that, the median infective dose.

DR. McCURDY: Let them answer the first question first.

DR. EKELMAN: If you use LD50 you don't get ranges, you don't get a gradation of effect and yet that's the most prevalent kind of data available for us to use and in a sense for chemical contaminants we think the most important factors we're considering are the chronic exposures because it's highly unlikely that we're going to get enough of a chemical in the feed to actually kill animals out in the field.

You are far more likely to get a very low level of contaminant in the feed that will contribute to a chronic lifetime adverse effect of an animal and those low level of events we're trying to capture, we have to look at both, we'll factor both in but we're spending a lot more time and attention on the chronic than we are on the acute.

AUDIENCE MEMBER: If there are data available from the dose response to develop the LD50 you need to have some (indiscernible) in the first place, then having the (indiscernible) may be useful in that regard.

DR. EKELMAN: It will also be useful

in us using other than ten as the bad effect because some of the LD50 studies, they get LD50 but no animals died during the study. If we can get the data and look at the actual studies we would be able to do something more.

Some of them we may be able to get the data and some we may not.

AUDIENCE MEMBER: Are there any data that you are looking at for acute toxicity studies which provide nonlethal adverse effects and how is it going to be used?

You haven't transferred like an acute toxicity value. Sometimes if you have a concentration that causes an adverse effect and it was nonlethal at the same time, those data are available.

DR. EKELMAN: If you go and look at the end of 14 days, for example, it would be possible to use those and we would be able to score those, decide how to score those and factor those in.

It's better to get the most data you can, most information rather than just limit it.

AUDIENCE MEMBER: When making the, putting the AEL's, I'm not sure, you mentioned you are using the same types of methodology as RFD's and AEI's. In NOEL's, they rely heavily on (indiscernible). Are you actually using

benchmark --

DR. EKELMAN: Let me tell you. We're trying not to reanalyze the data from scratch.

For example, pesticide data we go to EPA and we look at what they've done to each of the relevant studies and they usually identify the level and they identify an oral limit dose, sometimes based on the no effect level and sometimes based on benchmark dosing.

Whatever they use, we use what they used for that. If you went to JACKFA and they analyzed it we would use what they use.

In our database we would specify where we got the data and how it was analyzed. We're not going to reanalyze from scratch well analyzed data from other agencies.

There may be small discrepancies in how things were done but we thought it best not to re-do good analyses.

AUDIENCE MEMBER: I hope as far as drug residues, when eventually these are added to the list we're looking forward to seeing those sorts of things.

We're trying to develop, we're in the process and we've been reviewing submissions other people have given us to review.

We're trying, we're really interested in seeing how you guys are going to be handling

those in the future ourselves.

DR. EKELMAN: We haven't actually developed a method but we do assume if a residue is where it shouldn't be that it was there because they used an improper dose and in a species for which it was approved or improper withdrawal period or something like that or they gave the drug to a species that wasn't supposed to have it, kind of animal that wasn't supposed to have it. Those would eventually be part of our model.

AUDIENCE MEMBER: The chronic exposure, I notice you have a ranking, you are giving a value of five for carcinogenicity and also a cancer ranking too. Is that double counting?

DR. EKELMAN: No, because the severity would be the cancer. Maybe a little double counting, bad cancer here, bad cancer there, but not potency-wise.

AUDIENCE MEMBER: Thank you.

DR. McCURDY: Anyone else? Randy, you're next.

AUDIENCE MEMBER: Randy Gordon with National Grain and Feed Association.

I too want to thank on behalf of our association and I'm sure a lot of others here, thank you for this opportunity for the transparency of the discussion.

One quick question. With the missing

component on physical hazards, do you have a timeline for which you anticipate to fill in that blank in your paper.

DR. EKELMAN: Couple of months at the most. We were almost there but we weren't enough there to tell you what we are going to do. It would be a relatively simple method.

AUDIENCE MEMBER: As you -- I'm interested in how you plan to call out these discussion papers, if I can call them that, if that is a proper terminology for some of the hazard assessments that you are going to be doing as part of this exercise.

Specifically, the transparency with which you are going to be talking about, where the science leaves off and where the expert opinion begins and the rationale that you used to make certain decisions in your internal deliberations on this.

DR. HOOBERMAN: I think what we originally envisioned was a collection of one or two page summaries for each hazard that describes the background for the hazard, why it's on the list, how we came up with the scores, methodology that went into it.

It's not an exhaustive document but it will reference how we made our decision.

I envision a looseleaf full of these,

one for each hazardous agent.

You'll just have a collection so you can just go to a list and look up in the index where a particular hazard is and see how we came up with the score.

DR. McCURDY: Here you are.

AUDIENCE MEMBER: Could I have clarification on a comment that you had?

You expressed that the goal of the AFSS is to know the -- how many human illness is a consequence of examining animal feed which is, although very lofty goal circumstance a very lofty goal and very desirable, it's a very different goal than what I thought I heard earlier.

I thought this model was largely going to be a risk ranking approach and I think there is data at hand and the approach you have at hand will get to that outcome of having a near term risk ranking but if your near term goal is this attribution that you just described, we're not giving the -- there's actual a lot of momentum in our agency on attribution that we need to make you aware of.

I just caution you that that will be a much longer term goal.

DR. EKELMAN: I was speaking about exposure.

It's easy to figure out how to calculate exposure to animals that consume

contaminated feed or otherwise are exposed to contaminated feed.

Another one of your comments, it's true that some humans, and I'm excluding all workers, some humans in the home are directly exposed to salmonella contaminated feed and the rest of us are indirectly exposed as well because we eat food from animals that ate salmonella-contaminated feed and may have had some of the contamination and for that the exposure assessment you need to have a sense of what percent of human salmonella is attributed as a first cause to salmonella present in animal feed.

You need to have some estimate of that to be able to arrive at what the human risk is, even the relative risk, and so that's where that's at,

but if you are working on that we would love to have whatever information you have on that.

AUDIENCE MEMBER: We presented models to several of the industry groups and several of the umbrella professional groups.

These are efforts that we and others call attribution, trying to partition the human illness to the specific commodities so instead of saying there's this much salmonella.

Each year we say there is this much salmonella infections attributed to chicken or whatever and it would be an additional step to do the attribution to the component in the chicken

inputs, et cetera.

DR. EKELMAN: That sounds like a good approach, one we could use in building our model.

AUDIENCE MEMBER: That was my question. Is that what you are trying to do in the near term or are you trying to do risk ranking? Risk ranking I can see you doing with the current data.

DR. EKELMAN: How would you estimate the number of humans that become ill every year from salmonella that derived from feed as opposed to having derived from other sources, because we see that as -- you have to answer that question to get to the exposure piece which is part of the risk piece.

If you don't think we need to answer that then we'll talk more.

AUDIENCE MEMBER: You are just ranking the relative risks among each other.

DR. EKELMAN: We're not ranking the hazards. Risk ranking is not hazard ranking.

We need exposure. We'll continue this dialog. We'll call you and talk to you more about this.

AUDIENCE MEMBER: It's a great question. The feedback of the earlier discussions of what you were trying to do, I understood you were doing risk ranking, trying to compare risk and not

doing the attribution.

If that's going to be picked up in the exposure discussion then I think we could -- we would like to provide input on that.

DR. EKELMAN: That would be wonderful. That would be great.

DR. McCURDY: All right.

AUDIENCE MEMBER: Dave Dzanis, American Pet Products Manufacturers Association.

I just had a discussion on how some of the scoring was done, specifically with a microbiological severity scoring.

I notice there was, abortions 3, anorexia 2, et cetera, then you go to the example of specific organisms and you've got scores of 10, 30, 40, 60.

How is that? Is it just a summation of all the signs or a multiplication?

DR. EKELMAN: You really need to go to the spreadsheet.

DR. OKELO: You were wondering how we came up with the numbers for the severity scores? Is that what the question was?

AUDIENCE MEMBER: Yes. How is the severity score calculated?

DR. OKELO: As you can see here, we have the three experts scoring the different signs. This is for the swine.

The three, vomiting for example, the three scores are 1, 4 and another 1. That gives a mean of two.

In this case vomiting is not shown in salmonella, when swine is exposed to salmonella. Therefore, that means (indiscernible) it's either zero or a one.

It's zero if it's not -- if that sign does not appear and a one if the sign appears. That multiplication is done for all of them, for all the signs.

It's either going to be a two followed by a zero or a one and 2.7 multiplied by whatever the score would be there. Then those are summed up. That's how the 49.7 is obtained.

DR. EKELMAN: Go ahead and move it up to show the range.

DR. OKELO: This is just to illustrate the concept.

AUDIENCE MEMBER: Are there 20 or 30 different signs.

DR. OKELO: Yes, that number may vary depending on how many organisms you are looking at. We start out here with abortion and go down to vomiting and in this case we are considering the three organisms, salmonella, E. coli and clostridium.

If we increase the number of organisms

we are looking at, this list of signs might change.

AUDIENCE MEMBER: Thank you.

DR. McCURDY: Any other questions, comments? No other questions or comments?

Let's have a ten minute break so you can go back and think.

(Recess).

DR. McCURDY: Some interesting discussion going back and forth earlier.

Do we have any other questions, any other comments, any other thoughts? Take your best shot.

Now I've got a question or two that I can ask. How many people here right now that are still left submitted data to the FDA? Just one?

How is this going to affect my evaluation of an FAP or my evaluation of an AFCO product that's coming before us for an AFCO definition? Is this going to affect how I review my data?

DR. EKELMAN: This is a relative risk ranking so that model won't tell you what you need to know for determining the safety of the feeding ingredient coming before you.

DR. McCURDY: Will this have any effect on the final specifications for product X?

DR. EKELMAN: Not being a chemist, I have no idea what you mean by that question. If you

mean --

DR. McCURDY: Materials like arsenic, lead.

DR. EKELMAN: If we identify a component of a feed ingredient that has a potential adverse effect then we decide on a specification that would make that ingredient safe and I don't see how that would change what we do in terms of evaluating the risk of feed ingredients.

DR. McCURDY: It's been hinted out and mentioned in certain ways but what effect will this animal feed safety system have on something that has a maximum residue tolerance?

Will this have an effect on those already existing tolerances?

DR. EKELMAN: We're going to close our eyes to the maximum residue limit and do the risk ranking because you know some of those maximum residue limits are based on the basis of safety only and others in addition to safety. The two exercises are somewhat different, although the data that inform the setting of residue limits can certainly help us.

You are right, there are regulatory term implications.

DR. McCURDY: That's all I have.

AUDIENCE MEMBER: I just had one last comment. I think I heard you all the way through

hearsay (indiscernible).

If somebody like Dairyland or something like that, if they want me to do Pennsylvania with them, they send me out these bags, they are self-addressed, stamps on them, all I have to do is pull a sample, drop it in the bag and it gets mailed to them and I get my results back via e-mail.

If you want that, if you send me some bags with self-addressed stamps and all I've got to do a pull a sample once in a while and I'll send it to you and you can do your own data.

It will be an easy way to get to you what you need.

DR. EKELMAN: There are people that suggested various scenarios that we can follow and we're interested in all of them. We'll be thinking about at of them.

Thank you very much.

AUDIENCE MEMBER: Dennis Snow, the European Commission.

It strikes me as a hazard assessment is a hazard assessment no matter where you are. (indiscernible) means that this is very relevant also at the international level and I was wondering if you had any plans to introduce it at the international level or to use it in prioritizing products. I'm also wondering if you are using internal FDA (indiscernible) to check the validity of your approach.

DR. EKELMAN: If we're using real FDA what?

AUDIENCE MEMBER: Real FDA risk assessments where you have the ranking already.

DR. EKELMAN: There aren't as many internal FDA risk assessments on these substances as you might imagine so we would -- we use whatever ones are there to check the validity just like we are going to start out with a level of contaminants, hazards in feed ingredients and predict what will happen to them as they become feeds but we'll also look at the data we have on feeds to validate that system.

I think you were asking if we wanted to use our hazard assessments to do some comparisons with EU and other countries and the answer is no, we do not because we don't think that the name of the game is comparing hazards.

We think the name of the game is comparing risks. Those are two very different things. This is a risk ranking model, not a hazard ranking model and anybody will be able to pull out of it the hazards but we're interested in ranking the risk.

AUDIENCE MEMBER: I was more interested in the CODEX, prioritizing the work, say of the CODEX because there the exposure side will vary from country to country but the hazard is something that we all share.

DR. EKELMAN: By making the kind of data we're using, the sources of the data explicit, any differences in hazard score or hazard assessment between one regulatory body like JACKFA and another like EPA will be readily apparent when you look at things like which study did you use, what safety factor did you use and as long as those are consistent and reasonable and we all understand each other then we would have a common starting point for that piece, yes, that seems reasonable.

DR. McCURDY: Any other comments, disagreements, agreements?

DR. GRABER: This part of the program, we said we would throw out any opportunity for any comment or questions about animal feed safety system projects.

Can you hear me? Use the remaining time we have for any comments or questions that people have might with regard to the animal feed safety system in general, not just the risk ranking health consequence aspect of it.

In your packet, as I mentioned before, there was a framework document that we put in after public consideration back in February of 2005. It's in your packet.

I know it's been a long day.

AUDIENCE MEMBER: I have a question. It's a logistical question from Nancy.

Thank you very much for providing the slides, all those documents today, we really appreciate those.

Are those available on the FDA website? Can we link to those for the folks that couldn't make the meeting who would like that information and thanks again to the group for providing this opportunity to hear what you think.

DR. GRABER: We are planning on putting all the documents into the document. We'll consider about putting them on the website. I'll have to talk to my boss.

AUDIENCE MEMBER: They are public

already and it would be nice if they were available.

DR. GRABER: They will go into the document, as well as the transcript of the meeting.

Hearing nothing, for those of you who are left, there's an evaluation form in your packet.

It's just one page, just a few questions. We've got a biased sampling now. The best have stayed, I guess.

If people would fill out that form and leave it in the back of the room, there's a box for it, we would really appreciate it. It will help us in future meetings.

Speaking of future meetings, as numerous speakers have said, we do plan on having at least one more meeting of the animal feed safety system dealing with the exposure component

specifically and if we're far enough along in that, also bring in the risk ranking aspect of it.

If not, we may do a subsequent meeting in which we put both the health consequence scoring and exposure component together and discuss the risk ranking model.

As you could tell from the speakers today, there are a lot of uncertainties about this particular process. There are missing data.

We're going to use expert opinions. Barry says it's okay so I assume it's okay but the fact of the matter is that's -- the truth of the matter, that's the way things work.

You don't always have the data set that you need to operate and that's true whether you are doing a risk ranking model or you are dealing with an absolute case where you are just trying to assess the safety associated with a particular contaminant in feed.

You don't always have the data that you need. We're always looking for more data. So there are always uncertainties in decisions that you make and this one is no different.

This is work in progress. What you heard today is not going to be the final product.

We're looking for as much input as we can into this process. Sitting in Rockville behind our walls sometimes lead you to one conclusion.

You might come to a different conclusion if you had a broader set of eyes, broader set of minds involved in the process.

We encourage everyone who has not offered an oral comment to provide comments in writing.

Without your input the process will not be as robust as we would like it to be and I'm sure as robust as you would like it to be.

Barry has a comment.

DR. HOOBERMAN: Nobody asked how we're going to compare biological hazards to chemical hazards and how we're going to fit them into the same ranking scheme so we're looking for ideas.

There is an assignment. That is a real challenge, how to put them on the same scale. That's something we're looking on if anybody has any good thoughts on that. We would greatly appreciate that.

DR. GRABER: Thank you. I think that's it. I appreciate everyone coming. I know some people came from a long distance. I wish you a safe trip home.

Thank you.

(Meeting concluded at 3:00 p.m.)