

are reaching a consensus. I just want to make a point. Yesterday, in the presentation, one of two presentations maybe, we also heard that some of these drugs are effective in animals, horses, perhaps some other animals were mentioned.

I just wanted to hear maybe someone else comment on what sort of overlap might exist in treatments used in veterinary practice versus human medicine with OA.

DR. MILLER: Dr. Cush.

DR. CUSH: Well, there certainly are similarities with regard to degenerative joint disease in animals and humans. Certainly, the analgesics are applied to both. There are differences in the tolerability of nonsteroidal anti-inflammatory drugs in dogs, such they are often not used, because they are unable to tolerate them with severe GI toxicity. Hence, they tend to use either non-acetylated salicylates or they are I think toying with the use of COX-2s.

Even though a lot of the data for some of the drug development has been generated in animals,

there are problems with again extrapolation. For instance, glucosamine is I think widely applied in the veterinary field with great acceptance because some of the studies that have been done in animal models, but again its acceptance in humans is quite variable. It may be based on European versus U.S. differences as far as the interpretation of the data.

I don't know that any of these views are wrong. I think it just shows that there are differences there.

DR. LANE: I would like to make another comment on that. We walk on two legs and most animals walk on four, and I am not saying that to be funny really, it is just that there is a biomechanical aspect of osteoarthritis that you are weighting your joint at the same time, which can set off inflammation and a lot of reactions that, in humans, tends to be more intense than when you distribute the loads onto four legs.

So, sometimes things that work in small animals and we take from the laboratory to the

clinic, just, you know, you see no effect because there is such a strong biomechanical component to our disease.

Does that make any sense?

DR. DWYER: So, we should study kangaroos?

DR. LANE: That's not a bad idea. I mean that's a good point, that's along the same lines. The loads that our joints see are frequently very different than in these lighter, small animals, and that is why so many compounds tend to not be extrapolated or chemical reactions seen in either way.

DR. MILLER: Given what the next question we are going to deal with is, would that make the subhuman primate a better model, say, than the dog?

Is there any evidence to support that idea? Dr. Lane.

DR. LANE: I am not real familiar with all the animal models of OA, but the larger animal you get, the closer, the heavier the bone structure, the weight of the animal, the more it is similar to human OA.

However, if you are looking at it spontaneously, just like in humans, things don't go quickly. So, yes, primate would be the better animal, dog or goat second, but those are expensive studies to do if you are looking at the primary disease.

Any other comments? If not, it seems to me that we have a consensus on this statement that you can't use animal and in vitro models--we didn't talk about those--to demonstrate risk reduction of OA in humans.

The consensus of the committee is you can't do that, you need human data. Agree?
Johanna.

DR. DWYER: Just back to Steve's point, maybe it's covered, but it seems to me it is supportive. We need human data, but the totality of the evidence is what we want to look at.

DR. MILLER: I agree. I think the consensus ought to have a second part saying that it is supportive and useful in determining potential toxicological hazard, et cetera, et

cetera.

DR. LANE: I just want to say where I think the animal and the in vitro data is important is hypothesis generation that we then need to translate.

DR. MILLER: That is a good point.

DR. LANE: It is more the hypothesis idea.

DR. MILLER: That brings us to Question 3(a). What animal models, what types of evidence endpoints should be used to assess risk reduction?

I think this question is a market basket. I am not sure we have the time in the next several days to discuss this issue, but are there some general statements that we can make that would suggest to the FDA what types of models? We have already discussed that, Dr. Lane has already indicated perhaps a conceptual idea of what might constitute a good animal model, and we haven't said anything about in vitro models.

DR. LANE: In terms of a guidance, one might say, you know, large animals, but also utilization of techniques, such as MRI, to monitor

the course of the disease in these animal models, that might have some relevance to human disease. I think sort of the next thing, the MRI needs to go to the primates. Sorry.

DR. MILLER: Dr. Russell.

DR. RUSSELL: Another point with regard to food components is that animal models vary tremendously in their bioavailability for food substances and for their kinetics at disposal, so that the animal model, as just a generalization, should be similar, should handle the compound or the agent of interest similarly to humans.

DR. MILLER: Dr. Callery.

DR. CALLERY: I am wondering where the biomarker data is going to come from, and the surrogate endpoints, not only clinical. I am wondering if studying the biochemistry in animal models is the place to find a biomarker, and that is really a research opportunity that could provide the biomarker that we have all been looking for.

DR. MILLER: I agree. Actually, I have always thought that that was the value of the

animal model, it told you where to look in human. I just think that an important point that needed to be made, which as I recall, wasn't really made directly in discussions these days, is that metabolic pathways that we are looking at are both kinetically, as well as qualitatively, the same in humans as in the animal model.

I didn't see any evidence to support that, maybe I missed it, but in the discussions that we have had.

DR. LANE: You are right, the metabolic pathways, such as you give bovine cartilage explants, interleukin-1, they are going to generate to the same enzyme processes that human cartilage explants will.

From that perspective metabolically, metabolic pathways, yes, they are similar.

DR. MILLER: But are the kinetics the same?

DR. LANE: That, I don't know, I doubt it, but I don't know.

DR. MILLER: Dr. Harris.

DR. HARRIS: I think in answering the question regarding the overlap here, I think one of the most remarkable findings when the human genome project was completed, and the rat or mouse genome project, was the similarity of the gene structures that were observed.

That seems to suggest that there are a great deal of genes that are expressed in all animal species including humans.

The point I wanted to address, though, was the other part of the question that we are being asked to address, that is, what is the advantage of in vitro models. Just to remind the panel that when we are dealing with the in vitro models, we not necessarily confine ourselves only to animals. We could be dealing with human cells.

Currently, we do have available through a number of agencies, access to human cells that can be grown in laboratories, and chondrocytes and whatever, and perform some very close, careful analyses.

Again, I will also reiterate a point I

made, and that is there are certain things that we can do in cell model cultures that we cannot do in humans, and as I look at the list of the effects of cytokines and the identity of the different factors that have somehow been associated with the onset of disease conditions, I can safely say that I believe all of these have been identified through in vitro models.

That is not to say that we have exhausted our total spectrum of components that have been identified, that are important, in fact, there is probably a great deal of additional components that are remaining to be identified, and I think only through in vitro studies are we going to be able to achieve that.

DR. MILLER: Dr. Zeisel.

DR. ZEISEL: But again, to assess risk reduction, what I think our consensus is, is that all of these models are supportive, but not sufficient for drawing a conclusion as to risk reduction, so that we encourage scientists to use techniques to generate hypotheses and then go test

them in humans, but until there has been at a test in humans, a panel like this, I think we are saying we would be hesitant to accept animal data in the absence of human confirmation.

DR. MILLER: I agree. That is a good summary of what I think is the consensus of the committee. But the question is even in a supportive sense, are there specific in vitro models that would be helpful in attempting to make a determination of whether or not a particular material has a risk reductive capability in a supportive sense.

DR. LANE: I would again state that it is hypothesis generating only, because the mechanical aspects of the disease are such that a few cells in vitro might show you something unique and interesting, but again, because the biomechanical component of the disease, it would only be hypothesis generating.

DR. MILLER: Dr. Callery.

DR. CALLERY: This is going back to your question about the kinetic differences. The enzyme

kinetics, at least the way I read it, was that the glucosamine comes in after the rate-determining step in the process, and that this is apparently the kinetics control probably the enzyme synthesizing the glucosamine is rate-determining in this process, and that probably, and I am not sure of this, but I think that that is the same in humans and in the animals. That is just back to your question.

DR. MILLER: Anybody else?

DR. WASLIEN: Mostly because the committee's role here is to look at dietary supplements, the animal models permit so much variation in dietary intake that if we want to consider that kind of feature of any kind of supplement, I think animal models at least permit that first look at potential role, and even to identify the phase within the disease process, it might be that the animal model at least identifies some processes or some bone changes or whatever that might then lead you into what you are going to look at in the actual disease process in humans.

DR. MILLER: Good. I think we have reached--unless there are any further comments--Johanna?

DR. DWYER: Just to follow up on Dr. Russell's point, we know there are some animals that are not suitable for dietary-related factors, and could those be specified more precisely as one of the criteria for what models?

In other words, if we are talking about dietary supplements, we want to make sure that the animal is similar in terms of its metabolism, and so forth. I don't know if some of those animal models that are mentioned in the Biorheology or other articles would be inappropriate.

DR. MILLER: Any response to that? Are there any animal models that should not be used, or have, let's say, less credibility?

DR. ZEISEL: From the nutritional point of view, ruminants are going to be very different in their absorption metabolism from the gut of dietary substances, so it would be very hard to imagine you would want to use a model of osteoarthritis in a

ruminant and then ask whether an oral manipulation makes a difference to them.

DR. MILLER: That is a good point. A lot of these comments that you are making won't necessarily show up in the conclusions of the committee's reports, but they will be in part of the record, and they will be available to the FDA for them to use as they put together their paradigms for evaluating these things.

I just tell you this ahead of time, so that if you don't see them in the conclusions, they are in the report.

Dr. Downer.

DR. DOWNER: So then maybe from Johanna's question, we should include those animals that should be included rather than looking for that exhaustive list of those who ought not to be included in the studies.

DR. MILLER: I think the important point is that there are some animal models that have less credibility than other animal models. I don't know that we can sit and make a list of these things

here. We have an example of a ruminant, I think, and that is good enough to give the people what we are trying to do.

Question 3(a). Again, to the extent that animal or in vitro models of OA may be useful, what animal models, types of evidence and endpoints should be used to assess risk reduction of OA in humans?

DR. ARCHER: I think I heard Dr. Lane answer that question before in terms of coupling, if possible, animal studies with better imaging or looking for the magic biomarker, if that is the kind of speculative answer that is of any kind of use to the agency.

I mean the way I read the question, we can answer it several different ways, but I think that is it, what is desirable, what would be good.

DR. MILLER: Dr. Harris.

DR. HARRIS: To the extent that one reads the literature, and it seems to be impressed with the fact that a necessary condition that will develop into eventual cartilage deterioration, and

so forth, is the death of the chondrocyte.

So, that would be my suggestion, that an animal model or actually an in vitro model, forget the animal for a moment, would study the programmed cell death and factors that would cause it, and somehow correlate these factors that could be present in the joint.

I think this would be highly beneficial in deciding an initial course in the progression, or even the progression of the disease. Apoptosis, I think you know is what we are referring to here, and that is programmed cell dying, and this is now very clearly defined and how it correlates with this condition we are talking about, that I think would be very interesting to find out.

DR. MILLER: Yes, Dr. McBride.

DR. McBRIDE: I think if the question is what animal endpoints or what in vitro endpoints should be used to assess risk reduction, that we are really saying there aren't any.

DR. MILLER: Well, that is a good point. The issue is do the same caveats apply to the

animals models that are based on experience with them, that are those that we have identified for looking at risk reduction in humans.

Is there any data to suggest that there is a point when there is no joint degeneration or cartilage? Nobody?

DR. LANE: I am sorry, I didn't hear the question.

DR. MILLER: The question is does the same caveat apply to the animal models that applies to humans in terms of not being able to really look at risk reduction because we can't define a point at which there is no disease or precursor of disease?

DR. McBRIDE: I think that is true, we have to study, you know, a careful study of an animal model must be done, at which point we might be able to assess where we go from health to disease, where that critical point is, that hasn't been done.

DR. MILLER: I think the point really is, though, in thinking about this, that the value of the animal model is, as you say, it's hypothesis

development, that is where its real value is, and I think we have already said that the animal model can't replace human data in looking at this whole problem, and I think that is specifically true more so for the question of risk reduction.

DR. LANE: I agree.

DR. McBRIDE: I agree with that. I mean actually, I don't think we really even need to have the definition of when does the disease begin if we are talking about risk reduction at any point before the development of symptoms of osteoarthritis in human, can we jump from animal data or in vitro data? No.

Very important data in helping our understanding and in designing studies, but we can't then use that data to suggest that we have evidence of risk reduction in humans at any point in the pre-symptomatic phase.

DR. MILLER: I think we have got agreement on that.

Jack.

DR. CUSH: We heard yesterday from the

petitioners and from the public hearing, from Dr. Arnot and Dr. Theo, you know, what sounded like a wealth of evidence that made this sort of a slam dunk.

I would say that the wealth of evidence in the animal field, as has been suggested, is useful and interesting, and tells us about maybe some of the mechanisms by which this works, and the possibility that it works, but this in no way implies that it would work in this instance when applied to a normal population.

Hence, it is deficient in that requirement, and that if we are looking to make that connection, we require better data. I think that a lot of the data presented by the petitioners were compilations of studies that were more likely to be sponsored. Positive reports are more likely to--you know, whenever you do research, if it's a negative report, it doesn't get published.

Whenever a company sponsors a line of research that has a positive outcome, it always gets reported, so there is a bias in the

literature, and then when one goes to do meta-analyses of small, uncontrolled trials, it makes it look even better, and then we do meta-analyses and meta-analyses, it looks even better.

So, it is an amplification of the same simple suggestion that it might work, or in Texas, we say might could work. So, I think it is all well and fine, but again the standard that we should demand is much higher, and while such in vitro and animal data is useful, it is not the end answer that we need to apply this to a general well population.

DR. MILLER: Good. Any other comments?

DR. DWYER: It is slightly off topic, but I just wanted to say that I really enjoyed those presentations yesterday, I thought they were fascinating, and for what they did, which I agree was not exactly what we need, still the petitioners should be commended for the kind of work that they were doing with respect to the disease models. I thought they were very good.

DR. MILLER: I guess what we are saying is that exceptions of general rules, that two-legged animals are better than four-legged animals, and that animals that have metabolism more similar to humans, other than the example of ruminants being an example of an animal that is not a good--otherwise, the elephant would be big, has a lot of--but it is a ruminant.

We didn't deal with endpoints, but I think that the basic issue is the same as we dealt with No. 3, that animal studies can't replace human studies, that the gold standard are the human studies, and that animal studies alone are not useful in attempting to determine whether a substance has risk reduction capabilities.

Okay. We go to the last question, I am not sure how to approach. But if limited human data are available, what data should be based on human studies and what data should be based on animal and in vitro studies to determine whether the overall data are useful in assessing reduced risk of OA in humans?

I guess this is a question of trying to determine how much power the data package has in supporting a conclusion that the substance has risk reductive capabilities.

DR. ZEISEL: I think this question is trying to ask us that given that you have some human data, how much can animal and in vitro data be used to supplement and strengthen that conclusion in lieu of multiple replications of human data.

So, you could argue that one human experiment is never enough. Two could be enough if there were a big supporting base of data that showed in other model systems that it worked, you wouldn't need a third replication to believe it. I think that is sort of the issue we are dealing with here.

I think to put something on the table, that strong animal and in vitro data can indeed help to augment and supplement existing human data to reach a level of certainty that is greater than the human data alone might generate.

DR. MILLER: How would you define strong animal data?

DR. ZEISEL: Well, I think that, as said and I think quoted by Johanna, that if you have evidence of an effect in humans, and you then have a body of data, either that preceded or came after, that supports that approach and delves into manipulations of dose and mechanism that you can't do in the human, that it would be strong supporting data, that in the absence of the human data, the animal data in itself could not be used to reach a conclusion.

But if it is a model that corroborates and extends our understanding of the human study as presented, it could give it enough strength that you would move forward with it when, on the human data alone, you might feel hesitant to believe that you have reached the closest to the truth that you might have reached.

DR. MILLER: Are you saying that you would have to demonstrate that the animal model--

DR. ZEISEL: Is valid.

DR. MILLER: --metabolically and mechanically the same as in the human model?

DR. ZEISEL: No. What I was saying is that suppose we find an effect in humans, we then can replicate that effect in animal models, and that that animal model can be argued to be valid, that it becomes a support that allows you to have greater belief in the human study without multiple replications.

I still think you would want to see a replication in another human study before really believing it, but you might not need three or four or five replications if you have a very strong panel of in vitro and human that go with it, while you may need more than one replication if it didn't have that panel of supporting information.

DR. MILLER: Does everyone agree with that? Dr. Nelson.

DR. NELSON: I guess I have a question, Steve, about the strength of the human data. I mean if we have 1,000 anecdotal comments that I have taken this substance for 10 years and I don't

have any symptoms, what amount of animal data would make us all satisfied that we have got a preventive effect here?

DR. ZEISEL: I think that we all agree that a randomized, controlled trial is the information needed. Perhaps very strong population-based data could act as a replication for a randomized, controlled trial, but that what the animal data might let you do is say, well, I have evidence in a prospective nurses health study, let's say, that people taking chondroitin sulfate have half the risk of osteoarthritis, and then I have a randomized, controlled trial where we did that, and indeed, in 300 patients I could show the effect.

That, in addition to a animal base of understanding of the mechanism and the properties involved might lead you to make a recommendation for a health claim that you wouldn't make without that supporting information. You might ask for the second randomized, controlled trial.

DR. MILLER: Just to make sure we don't

forget we are dealing with risk reduction issues now.

DR. ZEISEL: Right.

DR. MILLER: And we first have to figure out how to do a risk reduction study in the first place.

DR. ZEISEL: Right.

DR. MILLER: Before we did the animal study.

Dr. Krinsky.

DR. KRINSKY: It would seem to me that all of the animal and in vitro studies in the world, regardless of how positive they are, would not be adequate to come up with an assessment of a reduced risk of OA in humans.

DR. LANE: I agree.

DR. KRINSKY: That the studies that you described, Steve, you know, RCT, and a population study, which could be very powerful studies, if, in fact, they were sufficiently powerful to convince us, we wouldn't need the animal data.

The animal data is wonderful, and the in

vitro data, in terms of understanding the mechanisms, and in terms, as Dr. Lane said, of hypothesis generation, but for assessing a reduced risk of humans, we have got to use the human data.

DR. LANE: In fact, just to echo that, observational data in humans doesn't hold up to the RCTs either, Women's Health Initiative, as prima facie evidence, so we have to be ever so careful.

DR. MILLER: Steve.

DR. ZEISEL: Again, let me take the converse, let's try to get away from the concrete to the more abstract to help us think a little. Magnetism, a randomized, clinical-controlled trial comes out, one of them, reporting that applying magnets to a joint makes osteoarthritis better.

I would put it to you that in the absence of a compelling animal base, an in vitro base for a mechanism and understanding, a committee like this would be loathe to accept one randomized clinical trial, and would ask to see a repetition, replication of that as normal size.

On the other hand, with a large number of

rat or horse or guinea pig study showing that they can identify a mechanism, they can apply the treatment and get the effect, we might accept a randomized clinical-controlled trial that is well done in humans to say okay, we have reached a level of certainty that we are willing to make a recommendation.

So, I see the animal as never being sufficient, but that sometimes giving you the base and the kind of structure and mechanistic understanding that we need to feel comfortable with a single or a double trial, and that is my only point.

I don't think you can ever substitute, but I think there is a legitimate use for mechanism in helping make us feel more secure in acting with limited data because, as scientists, we would always like another experiment and we can always find a flaw in any randomized, controlled trial that says maybe it isn't true, let's do it again.

So, I think that base is where the animal and in vitro studies can be useful, and should not

be abandoned in any big study, because I think they can supply support.

DR. KRINSKY: I didn't mean to suggest that the animal and in vitro studies should be abandoned. I think that they contribute to the totality of the evidence.

But the example that you gave and of RCT of using magnets, I can't conceive of that taking place without a series of preliminary experiments that were not RCTs, but there was some indication that magnetic treatment could, in fact, be a modality for improving OA, and that that led ultimately to an RCT.

So, the RCT doesn't exist in isolation, it has a foundation beneath it that permit it to--because who is going to fund it if it doesn't have a background?

DR. LANE: And frequently in medicine, there are anecdotal reports, and there may be some in vitro and small animal data supported, then the RCT is from that point on.

DR. MILLER: It's a question of the

strength and credibility of the data you are dealing with. I don't think we can or should get into the question of how much human studies are sufficient to enable some animal and in vitro studies to carry on, we can't quantitate that.

Jack.

DR. CUSH: The analogy in drug development would be, of course, that in vitro and animal studies are done prior to randomized, controlled trials and those confirmed, and often one needs large numbers of appropriately powered trials, and several of them, to get a drug approved for use in a disease population.

Instances where you can get one clinical-controlled trial is when you basically take the same compound which has been approved for another indication, now apply it to a new but similar disease state, and now just one appropriately controlled trial, for instance, going from rheumatoid arthritis to ankylosing spondylitis, the same kind of drug. If it is a well done trial and we have prior evidence of

safety and efficacy, then, it is all well and fine.

I don't think we should hold these standards or minimize these standards when applying natural products to a healthy population. I think the same sort of demands for safety and efficacy should be there for these claims to be allowed, and I think that your analogy of one trial being alone sufficient, I think would be poor and I would not accept that, but if there were several well done controlled trials, that were appropriately powered, then, to go further may not be necessary if there was a totality of evidence in the animal or in vitro world to support that.

But again, it needs to be done in the right target population.

DR. MILLER: Dr. Waslien.

DR. WASLIEN: As my colleague next to me said, unfortunately, we have a law that says we can't enforce the same requirements for a dietary supplement that we do for drugs.

So, I think we might look, though, at a different model, and that is the RDA requirement of

kinds of support that you need for setting nutrient requirements, and that wording and that kind of support statement that comes out particularly for some of the newer nutrients might be something that we can look at instead of a drug model.

DR. LANE: A point of clarification on that. In some ways the RDAs have a pretty high bar, too, don't they?

DR. WASLIEN: For some of the newer, you know, the chromium, the cobalt, and some of micronutrients that are being looked at.

DR. MILLER: I can tell you that the standard is very high. It is very difficult to increase the list of nutrients, et cetera, I can tell you from experience.

It's not to say that the dietary supplement issue that is being discussed here it shouldn't have the same standard. Irrespective of whether we are dealing with a food or a drug, the major standard has to be safety and efficacy. It has nothing to do with what we are discussing here per se, it is not being asked to make that

judgment.

Steve.

DR. ZEISEL: Again, I think we have some consensus that human data is absolutely essential and that there is some utility and use of animal data as supporting framework for the understanding of that human data and our utilization of it to make a decision about a health claim, that right now we are not presented with adequate human or animal data to reach conclusions about any compound that has been presented to us, and we are not required to, but that there is a role for animal data as a supporting framework for the human data, but not to substitute for it.

I think that is what we have been saying and gives the answer to be.

DR. MILLER: I would agree that is the point. I think one of the things that we don't have to do or shouldn't be doing is putting together a matrix how much animal studies will replace how much human studies. I mean I would object violently to any attempt to do that.

Johanna.

DR. DWYER: Just back to Dr. Kale's point. I think he pointed out that those animal data might be very useful in terms of safety.

DR. MILLER: Yes, and we noted that. It is certainly one of the essential components of the thing, and you can get a substantial amount of safety information based upon experience, but I think with a dietary supplement, it seems to me that you have to be even more careful in that it is conceivable it could be used throughout the entire population, and not limit it to a specifically identifiable patient population.

That is the difference between dietary supplements and drugs.

I think we have come to a consensus here that in vitro studies and animal studies are useful, again as we said earlier, in a supportive sense, that the basic credibility of the relationship must be based on human studies, but animal studies could be used to further strengthen the relationship between them.

I think that is the last issue, am I right? Let me see if I can very quickly and very shortly--I am not going to try to summarize the discussions.

Concluding Comments

They were interesting and wide ranging, and all of these discussions, there will be a verbatim transcript that will be available on the internet, and a summary report will be put together, which will be shared on the internet, but also will be shared directly with the members of the committee.

In terms of Question 1, which was concerning the question whether joint degeneration or cartilage deterioration are modifiable risk factors for OA risk reduction, I think the committee reached a consensus in saying that joint degeneration is too nonspecific and cartilage deterioration is and could be used as a modifiable risk factor.

Nevertheless, we had a broad and I think important discussion concerning how one defines a

non-affected population, and I think we all agreed that that is possible to do, but we don't have the data at the moment to be able to define people that are not subject to OA from those that are.

The next one.

I think we all agree that the data doesn't support the idea of using information gathered in experiments on OA patients to interpolate the effect of these materials in a healthy population as individuals without OA, again, not that you can't do it, we just can't do it now.

Next question.

The third question, I think we answered that in general, that animal studies and in vitro studies cannot replace human studies and that the value of animal studies is in hypothesis generation and in getting a better understanding of the mechanisms that might be involved in interaction between various materials and the processing of OA.

I think, unless there are any further comments--yes, Dr. Blonz.

DR. BLONZ: Would it be possible to make

some sort of a statement that the safety and efficacy of glucosamine and chondroitin sulfate for the treatment of osteoarthritis was not the issue here, and that is not being debated at this point?

DR. MILLER: We have made that point several times, but you can make it also.

DR. BLONZ: Thank you.

DR. MILLER: Well, you already made it, it's in the record.

Dr. Krinsky.

DR. KRINSKY: As a member of the Food Advisory Committee, I just appreciate the fact that the FDA has had the wisdom to bring the collection of rheumatologists to this meeting, because I think in their absence, we would have floundered helplessly, so this has been an immense help to me.

DR. MILLER: Thank you. I agree and you have anticipated my final comments.

DR. LANE: We appreciate your kind comment.

DR. MILLER: If everyone is anticipating my final remarks, I am not going to recognize you.

DR. DWYER: Can we get free consults after the meeting?

DR. MILLER: I want to thank the committee. I especially want to thank the temporary voting members and rheumatologists. They really made this I think an informative, as important, advisory activity.

I also want to thank the entire committee for their discipline and for their being able to maintain their focus when it was really a complex study. Complexity, I always felt is a fact made up of 90 parts, ignorance and only 10 parts knowledge.

I think that the main part coming out of this is how much more research is really needed in order to begin to understand and to begin to come to some predictive conclusions for these activities.

With that, in the absence of hearing any objection, I am going to close this part of the meeting having to do with glucosamine and chondroitin, and adjourn until we meet later on. The temporary voting members and the members of the

Supplement Subcommittee are excused, and you can go home. The rest of us will have to stay to deal with the furans this afternoon.

We are scheduled to start at 2 o'clock on furans, if we can get people together, we may start a little earlier.

[Whereupon, at 11:12 a.m., the meeting was adjourned.]

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4:00 PM

June 8, 2004

**Statement before the
FDA Food Advisory Committee
Contaminants and Natural Toxicants Subcommittee
Meeting
June 8, 2004
by
Richard Jarman
Vice President, Food and Environmental Policy
National Food Processors Association**

**NATIONAL
FOOD
PROCESSORS
ASSOCIATION**

Good afternoon, my name is Richard Jarman. I am the Vice President for Food and Environmental Policy at the National Food Processors Association (NFPA).

NFPA is the largest trade association representing the food and beverage industry in the United States and worldwide, serving as the industry's voice on scientific and public policy issues involving food safety, food security, nutrition, technical and regulatory matters and consumers affairs.

NFPA has closely followed FDA's initial examination of the presence of furan in a variety of foods and drinks and our efforts have included the development of analytical methods, which have been compared with FDA's method, for measuring furan in various food matrices. I will touch on the analytical issues we have encountered in a moment.

In May, when FDA announced the results of its exploratory work on furan, important information for understanding the implications of the preliminary findings was provided and the need for additional work was clearly and appropriately indicated. NFPA believes FDA was and is justified in stating that consumers should not alter their diets based on the Agency's initial findings and that until more is known existing federal dietary guidance should be followed. NFPA applauds FDA for its efforts to explain available information about furan and furan in foods in a manner that does not create an unnecessary and unjustified "food scare." We urge FDA to continue to help consumers understand that finding very low levels of furan in a variety of foods and drinks does not in and of itself mean there is a dietary risk and that consumers should continue to follow established dietary guidelines and eat a healthy, balanced diet consisting of a wide variety of foods in moderate amounts.

It is also important that consumers understand, as indicated by FDA, that the exploratory findings related to furan in foods and drinks should not be interpreted as the risk associated with eating any particular food or individual brand. FDA appropriately explained that the fact that certain types of foods or brands are included in this study does not indicate an Agency concern about these particular foods and that more information must be collected and evaluated to determine if there is any public health significance to finding low levels of furan in many different foods.

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provided by adequate thermal processing are not compromised to address hypothetical risks determined through the application of limited toxicological evidence from animal models.

The risk posed by low levels of furan in foods and drinks needs to be assessed and put into perspective before concluding risk management steps must be taken.

Again, we applaud FDA for the open and thoughtful approach being taken in developing a meaningful, scientifically-based plan for dealing with the finding of furan in foods and for providing appropriate and reasonable guidance to consumers.

We recognize that furan is one more of what may be a growing number of compounds that can be found in foods due to accepted food preparation practices. Now may be the time for finding an alternative approach for dealing with naturally produced compounds in foods that pose no or insignificant risk to public health. It is clear that for compounds like furan and acrylamide current risk assessment approaches may clash with advances in science and risk management decision-making needs. We urge FDA to take a lead role in developing a new framework for assessing risks, risk/risk tradeoffs, and comparative risk/benefit tradeoffs for exposures to low levels of naturally occurring compounds in foods.

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I would like to briefly make several points in the time available:

First, analyzing for furan in foods poses a significant challenge and attention must be given using methods that are both standardized and validated. A study of methodology involving three laboratories, including NFPA and FDA, using three different methods applied to analyzing four foods, gave results that were generally in agreement. However, we also found a relative standard deviation of 30-43% between laboratories and about 20% repeatability within a laboratory. Clearly, any data on the level of furan in food must be considered in terms of the analytical method used and care should be given not to attribute undue precision to analytical results when considering differences in reported levels.

Second, more information is clearly needed on the mechanism of formation. Preliminary research indicates temperature is an important factor with "boiling" temperatures not appearing to generate detectable levels of furan, while temperatures reached in "browning," pressure-cooking, and microwave cooking all appear to produce furan. Also, both carbohydrates and proteins appear to be involved as precursors.

Third, more information on the the range of furan in foods as consumed is needed. FDA's exploratory research focused on commercially prepared jarred and canned foods. A thorough characterization of possible exposures should include consideration of commercially processed and foods prepared at home and in restaurants, including reheated foods. The effect of home cooking, restaurant cooking, and reheating on possible furan formation and subsequent levels needs to be better known and understood.

Finally, and perhaps most importantly, it is critical that FDA establish a solid basis for evaluating the risk from low levels of furan in a wide range of foods and drinks. NFPA commissioned a food intake analysis using the results of FDA's preliminary work. This assessment performed by the firm Exponent indicates that 97% of the US population is exposed to low levels of furan from foods representing 20% of the dietary intake of protein or calories. Clearly, the determination of what, if any, risk furan poses will have huge implications for diets and, possibly, food preparation.

As the Committee and FDA know, furan represents one more naturally occurring substance in food that is receiving attention as the result of targeted analysis for the presence in food combined with toxicological evidence obtained from animal bioassays using high levels of exposure. We urge the Agency to carefully consider furan, and other like substances associated with accepted food preparation practices, in terms of risk-risk tradeoffs. We must be certain that the benefits of food safety