Ron Lorentzen
December 19, 2003

Sara Shostak: It is December 19th, and I am interviewing Dr. Ron Lorentzen. Dr. Lorentzen, you know that the recorder is on?

Ron Lorentzen: Yes, I do.

Shostak: Okay. I am going to move this a little bit closer to you. Do you want to go ahead and make the distinction between speaking for the agency and speaking about your own experiences?

Lorentzen: Yeah. In this interview, I will be speaking largely scientifically, but, of course, there is some necessary integration with law and things like that, at least, and these are all my opinion, okay, scientific and otherwise, do not represent any policy -- not that I have one -- insofar as I am working for sandwiches, the food and nutrition part as well as cosmetics -- we have that too -- part. We also have dietary supplements, which makes it interesting. That part of the FDA -- anything I say here could not be construed as representing policy or even inclination of the agency scientifically. Having said that, there are very few people here besides myself who understand transgenics and perhaps not much at all.

Shostak: Well, why don't we start there? And could you tell me how you came to understand transgenics and in what context?

Lorentzen: Well, I won't say that I understand transgenics completely. I mean, I don't

know all of the molecular biology, etc., etc., of all the different strains that have been presented. Okay? So I won't claim to be an expert in that area, mostly because I have not taken the time to learn. I have been interested for many years in carcinogenesis, and I am an expert for the agency in that area. And, of course, this means the use of animal models and making determinations of what does and does not induce cancer, which is sort of the language in our act, in particular, in the *Delaney Clause*, which comes up.

Shostak: Again, just so that I understand how you came to be interested in transgenics, could you tell me a little bit about your background first, and, second, your goal at the agency?

Lorentzen: Well, I have a Ph.D. in biochemistry, but that's a long time ago, and after I did my Ph.D., I was a fellow at Johns Hopkins Medical Institution, and I spent a lot of time working in mechanisms of carcinogenesis and toxicology, and that is where I started to get my expertise, sort of fit in naturally here. And we have had, since I've come essentially 20-plus years ago, we have had a couple of standing committees that are made up of interdisciplinary – they are interdisciplinary committees that all serious organizations use when they have serious choices with serious ramifications. One of these we just call our Cancer Assessment Committee. The other is our Quantitative Risk Assessment Committee. These committees are the best that we have in all the disciplines that make

up these areas, from mathematics to epidemiology, to toxicology, to pathology, and everything in between, and I am chair of that committee. I am chair of both committees. Earlier, I was the scribe for it, which was the really important job, writing up the consensus opinions. So we have laws and particular clauses -- there are three of them -- which, the language in them is, if they induce cancer, they're not safe; that means they can't be allowed for food additives, color additives, and drugs that are used in animal, producing animals, food-producing animals. So, "induce cancer" means everything for these substances which may or may not end up in food. And so the critical decision, "induce cancer" is very critical. It means everything for those substances, and there's other language in the laws, the other language is in man or animals by ingestion, and there are other clause's as well, or by tests which are suitable. I probably have the act somewhere, but we don't need to read it. That's pretty close. In other words, induce cancer, man or animals, by ingestion or by other tests which are adequate or suitable. So we've had these committees for a long time, and when you work with an interdisciplinary group like that, boy, you learn a lot, I'll tell you. I learned more than I ever wanted to know about statistics and pathology, epidemiology, that sort of thing. So that's -- is that what you wanted to know, sort of why I do this?

Shostak: Can you tell me either about when you first heard about transgenic models as testing systems for carcinogenicity or, if it's the better question, when

the issues surrounding those models first came before the committee?

Lorentzen: I don't know what the better question is. They're both . . .

Shostak: Let's do them both, then.

Lorentzen: We can do them both. I mean, I'm not sure when I first learned about them… trying to search a faulty memory. Obviously, it's been a -- these ideas have been around for some time. You know, I remember the NIEHS jumping on that one, and always being reasonably enthusiastic about new technology. In fact, we've never really had to deal with -- I can't think of having to deal with the issue directly which impinged upon the fate of some substance that would be additive to other substances. I take it back a little bit. There have been a few instances; it was not the sole source of information. We have more traditional studies, and some of these were sort of ancillary and haven't caused any situations where we had conflicting results that gave us heartburn. So, I mean, I'm very aware that there, of these models, and I'm very aware of what they might, what issues they might raise for us. But other than that, we haven't had to except for in a trivial way so far.

Shostak: When I was talking with the folks down at NIEHS, you were described to me as a skeptic about these models, and that that skepticism, I was told, is rooted in their possible ramifications given the Delaney Clauses. If that is an accurate assessment, could you elaborate on that?

Lorentzen: It's not entirely accurate. I can understand why John in particular would

say that. I would say personally, the concept of using transgenic animals for all kinds of things involved in carcinogenesis or any toxicology or, for that matter, all kinds of other medical research, is, I think, pretty exciting. And I have stated that, but, of course, if you throw a negative note in there, proponents like NIEHS and their program and John and Ray Tennant, who was sort of the head of their development for a while, you know, they're going to remember the negative part of it. And, see, the Delaney Clauses for food additives, color additives, and drugs, I mean, frankly, we've been arguing with our lawyers for a long time about these, and we find ourselves pretty impotent about using scientific judgment for a lot of these. I mean, it has happened, but it's very difficult and the law is written so tightly. So we sort of have a problem, and I told you that important words in the law were to induce cancer in man or animal. I mean, it doesn't distinguish between us being human versus an animal. So, I mean, that's probably a key point here. So, what's an animal? I don't think I have to talk too much more about it; we've always been worried about this. I mean, we've had situations in the past where people and things that we don't quite know how to deal with. While I personally believe that we should have a lot of scientific leeway in deciding what an animal is for these purposes, that's by no means any guarantee at all. The introduction of numerous potential new test animals that have, frankly, don't have a whole lot of validation behind them causes us concern. My concern with

NIEHS and the National Toxicology Program has always been that we're not rejecting any of these models at all, but if there's a… sorry, Ray and John…but if there's a bandwagon, I mean, if there's some political reasons behind having a bandwagon for these or these models, I can understand why they would want to embrace this kind of technology. It may be going too fast for us. I mean, there needs to be some sort of validity to these models, or else we have a situation where we find ourselves doing something that we don't want to do or, alternatively, sort of breaking the law or not enforcing the law, if that's different. That's sort of it. Do you want to ask questions here? I'm sort of rambling on, but, I mean, I'm on a roll, so . . .

Shostak: Why don't you keep going? I'll interject.

Lorentzen: I mean I've been following some of this as well. You know, the pharmaceutical industry got very interested in this. The issue for, the modern way of characterizing… is it faster, is it better, and is it cheaper? Well, the first and the third are pretty clear. It's probably faster, it's probably cheaper. But is it better, of course? And that's a question we didn't have an answer to, and the pharmaceutical industry got very interested and put a lot of money into trying to do some validation of these models. So you're aware of that, the publications . . .

Shostak: This is the ILSI committee.

Lorentzen: Well, I don't know, can't remember now. Is it ILSI? Probably it was done

under the auspices of ILSI. But they published some. And I can remember going to their conferences and those were very, I found them very fascinating. And my understanding that at the end of the day, the pharmaceutical industry was reluctant to endorse any of the models and felt better about some than others but didn't feel comfortable about, in fact, for their own purposes, pulling away from the traditional models that have been used in the National Toxicology Program or in similar ones, namely sort of standard laboratory strains.

Shostak: And also two-year, two species.

Lorentzen: Two years in two species. I didn't get the impression that the pharmaceutical industry -- from all of this, that's still my impression -- till somebody, that they were, that they felt confident to make recommendations about using any of the strings of the regulatory aspects of new drug approval. They do not have a Delaney Clause. Okay? They do not have laws which are restricting them and have much more ability to use judgment, even could use assessment of risk, etc., which can be very important. That's another area that their clauses do not, by and large, allow us to do.

Shostak: Explain to me what you mean.

Lorentzen: Well, I mean, you know, some substances that induce cancer are more potent than others. In fact, there are eight or nine orders of magnitude in terms of potency, and, of course, you can imagine a rather large difference

in the amount that you might be exposed to. So we have many, many, many orders-of-magnitude difference in the level of risk from one substance to another. So, logically, it seems ridiculous not to be able to consider risk in the regulatory activity. It's unclear to me whether that's going to be allowed in the future or whatever. So, where are we? In other words, the pharmaceutical industry has taken a look and tried -- they spent millions of dollars trying to do studies on known carcinogens, etc., with these, with a subset of these models, and while some seem to be better than others in terms of reliability, my impression still is that they were ready to endorse the transgenics even though presumably they're most cost-effective. Of course, validity is a problem area, too. I mean, valid against what? Most people think about that as validity versus the standard model. Models that are used now have been in the laboratory for the last 20, 30 years, and we all know that those aren't valid with respect to, totally valid with respect to human disease, although quantitation of that is difficult.

Shostak: So you said when you're evaluating a new technology, the question is, the questions are better, cheaper, and faster.

Lorentzen: Yeah.

Shostak: Are there other things that you look at given the Delaney Clause when you're thinking about whether or not a new technology would work for what you do?

Lorentzen: Well, the faster, cheaper, better is just sort of the general standard about new technology these days. The Delaney Clause puts restraints, and makes it faster and cheaper and easier to measure, but better it's not, and that's a problem. Better is what? Better is being able to make a better judgment vis-a-vis obey the law vis-a-vis the Delaney Clause. Even without the Delaney Clause, something that caused cancer would still need to be dealt with on their, without the Delaney Clause, would still be dealt with maybe at least as harshly or, you know, other than general safety aspects of the act that we worked under. So, this would be my opinion -- that would allow us to do risk assessment and make some judgments about using the assessment of risk, some risks are insignificant and could be tolerated, and some are not. But here's another issue that is raised with the transgenics. We don't know how to do -- it's taken us quite a while to understand how an attempt to estimate risk from using rodent models for lifetime studies and estimate lifetime risks for humans. Well, now we have these new transgenic models to test sensitivities for its developing the diseases has changed and life span has changed rather dramatically, and that's . . . In other words, the need to do risk assessment, which we have to do under certain circumstances and which we would have to do more if there were no Delaney Clauses, if you will, would be difficult, very difficult. But that doesn't mean we can't do it, but my -- the objections that John and Ray and others perceived from me were my expressing a

fear of not being able to understand or deal with science with these models, particularly if they were introduced precipitously. I got the impression that that was; there was an agenda to do that.

Shostak: Now, you said something about that earlier, that there seemed to be a bandwagon around these models. What would you, what did you perceive was the impetus for such a bandwagon?

Lorentzen: General enthusiasm for new, improved, technology. I mean, that needs to be demonstrated, but the potential for improved technology; the criticism of the standard models that have been used, they have been using and that we have been using, and the idea that you could, at least in theory, develop models that you could tailor to the kinds of answers that you wanted to get. I mean, just the enthusiasm that was there for that. And also, my perception is the idea that this would show the program was being not stuck in a rut, far-sighted, that had a new answer to some of the problems that were there using the old models.

Shostak: The programming in the NTP.

Lorentzen: Yeah, the [National Toxicology] Program and the NIEHS, I mean, you know, they're joined at the hip, so . . .

Shostak: And is that also what you were thinking of when you said that there were, there seemed to be a politics to this bandwagon?

Lorentzen: Well, I don't want to accuse those guys of politics, but there are . . . You know, you can imagine something as visible and as controversial as the

carcinogen bioassay program might be, just possibly be subject to political interference, if you will, or political . . . And I'm not trying to suggest, far be it to suggest that my friends down there are caving in to anything untoward at all, but the opportunity to come up with new, promising models and new, promising ways to do this, it has to be very alluring. I mean, they see me as a wet blanket, and I really hate being a wet blanket because I tend to be sort of an optimistic person.

Shostak: And just for the record, they never described you that way to me. And when they said you were skeptical, not critical or naysaying. They just said that because of the Delaney Clause, you had a specific set of concerns that would lead you to be more skeptical than other folks.

Lorentzen: I'm not worried. They're my friends and I don't even care if they say bad things about me from time to time. That's the way it goes. I mean, I feel uncomfortable being a wet blanket for things like this because I tend to get -- if I were in their place, I'd be very enthusiastic, too. Okay? But insofar as it can get me in trouble, I suppose. And with these entire tech . . . I mean, I've noticed this throughout my career. I mean, sort of started, when I started out, it was the Ames test. Okay? I don't -- that was going to cure everything, and, of course, it didn't cure everything. And what happened, this is the -- it's, again, my own philosophy on this -- is when you have these technologies and people go in sort of a headstrong way and embrace them without being critical about them, what happens is that

everybody jumps on this bandwagon, and then the bandwagon gets going pretty fast, and then it crashes. It crashes and it reverts to a state, often, that is worse than when you started. In other words, you throw out the baby with the bath water because you crashed. I'm mixing metaphors here, but you know what I mean. I've seen that with all kinds of things. It's happened with [genomic] technology now in the same way. So I would hope people would be a little critical, because enthusiasm goes up for this technology, and then it drops down below, and it takes a while before it comes back up and reaches its proper level in terms of what is its usefulness. So I think that's what has happened with transgenics. I don't know, may be recovering somewhat now and will . . . This has tremendous theoretical potential for doing things.

Shostak: So it seems like there's a distinction between the potential of those models in the laboratory as research tools and the potential of the models as bioassays. Is that a fair distinction to make?

Lorentzen: Well, there's some distinction. It seems to me that it would be easier to develop a transgenic model that would, a laboratory model that would give you some, you know, whatever we introduce. When you try to do this now by going around and looking for strains of whatever that are deficient in this or that or doesn't have this and that, and that's just sort of my luck to be able to do that, at least theoretically at your own whim. Wow, it sounds wonderful. And you could say the same for a model for testing or a more

general bioassay type. One could say the same, but it's a little bit more difficult to reach. Bioassays are really very complicated, incredibly complicated experiment. It runs two years. That's the in-life phase. And now whether you have you have an in-utero phase or not, and that's more, and if you don't. Then, of course, there's the after stuff that you do and whatever experiment and is done. It's very complicated experiments, runs for two years, and you have all kinds of different people. Some of the people aren't the same at the beginning and the end of the experiment. Can you imagine how one does one of these perfectly? It's not possible. In fact, it's a huge experiment. And when you talk about a bioassay for cancer, well, cancer, even in rat or mouse, we're talking about 50 diseases or so or more, that we see commonly, and so it's a bioassay for not one big disease, it's for all these different ones. And since any one of these diseases, whether it be of the liver or the lung or the spleen or whatever, can trigger a violent action in terms of public response or otherwise, they all need to be good. And so this multiple-comparisons issue in the bioassay means it's much more difficult to come up with a model that people can be comfortable with.

Shostak: I know on the pharmaceutical side, there's ILSI, there's an International Conference on Harmonization that issued guidelines on transgenics. There seem to be a number of multi-actor organizations. Is there anything similar to that on the food safety, cosmetics, nutrition side?

Lorentzen: No, not quite at the same level. You know, there are international organizations, but, by and large, they have chosen not to, as far as I know, which is they have not addressed these issues very thoroughly. You know, there's the WHO agencies influencing IARC, which I'm sure you're very familiar with. There's also something called JECFA. It's the Joint Expert Committee on Food Additives. They're a committee; they're a WHO committee which does what the title sounds. They sort of set standards for the world. Nobody is, I don't think, beholden to them, but particularly all of the developing countries are using these. They have their own capacity, too. They may keep document here or there, whatever. I'm talking about transgenics, but they have not faced it. They have chosen not to face it, and that's sort of what our position has been too. And I'm just this guy who is knowledgeable of the law that affects us and expressed concern, so there's not been any example in the area outside of drugs where this has been addressed to any extent.

Shostak: Okay. One of the things that I know about, again on the pharma side, ILSI and the International Conference on Harmonization is that they're places where folks from industry and from CDER and from NIH and NTP end up having conversations about new technologies. Where do those conversations happen on the food safety side? In what context do you interact with NIH or NTP?

Lorentzen: Well, that's intergovernmental, so, I mean, we interact at all levels. You

know, the National Toxicology Program is administered through NIEHS, and the executive committee is made up of primarily, set up by Congress, by NIH, including the NIEHS and the NCI, the FDA, and I believe -- I forget -- NIOSH.

Shostak: NIOSH, EPA.

Lorentzen: Well, EPA is on it now, but they were not originally a part of it, and that's only been, as I understand it, that they've been brought in by the executive committee to weigh in, I guess, on these probably Consumer Product Safety Commission. You know, anybody who has to deal with these issues of toxicology in the government, you know, sit in on the executive committee. But the three major ones were from the Department of Health and Human Services or whatever it was when they put this together. So, ostensibly, they interact with the NTP that way. They have that kind of connection. I mean, it's more formal.

Shostak: And I realize this is a personal question, but do these friendships develop at meetings or at conferences?

Lorentzen: Meetings, conferences. I mean, the tough things which may affect us, I go down to their peer reviews about that. We have an interagency agreement with the National Toxicology Program to do research on NTP issues. The NCTR -- do you know NCTR?

Shostak: Yes.

Lorentzen: Good. So I'm not sure I know how to count the ways where we interact.

We talk on the substantial level.

Shostak: From a historical perspective -- and you spoke to this a little bit when you were talking about the Ames assay -- are there lessons to be learned from the introduction of other, new technologies about how technologies become useful to regulatory agencies?

Lorentzen: Well, that's a big philosophical question, and I think I already sort of addressed it. I mean, my view of how these things happen is I'm suggesting it has not been ideal, and it has -- the overenthusiasm has led to sort of temporary setbacks. And I think that happened with Ames tests for sure. I believe it's probably happened with transgenics, but it's probably happening also with toxic genomics. I could be enthusiastic about all of these, but, predictably, there are people who have, there are many people who will turn out to have interests in these technologies, and they, of course, will oversell the capabilities, and that makes people cynical. That's the philosophy. I don't know how you stop it or how you change it or modify it, but it seems to happen that way. When something really is good and really is promising, it almost always gets oversold and doesn't realize its real potential perhaps ever, or later.

Shostak: Is there anything about the history of these models and your perspective on them that we haven't touched on that I should have asked you about?

Lorentzen: Well, I could tell you a story.

Shostak: Great.

Lorentzen: And it would be -- and I apologize to John for this, but he knows -- it would be an example of how not to do things and how, which probably turn people seriously off. There's a high-intensity sweetener, artificial sweetener. It's called Aspartame, which you may probably use. I don't know.

Shostak: I ingest quite a bit of it, yes.

Lorentzen: It was an agonizing approval, and they had to bring in a board of scientific inquiry. It was political reasons, in my opinion. And as these peer review groups, they're dangerous.

Shostak: Tell me what you mean.

Lorentzen: I mean this has been our experience, peer-review groups, and you bring people from the outside who are not ensconced in the real environment, regulatory environment or otherwise, they end up making conclusions that make it very difficult for us, and they did. There was an issue that is still around today of brain cancer associated with Aspartame. It never was a serious issue, and it's one we looked at very, very carefully. But this group, which was a board of inquiry of some academic people from the outside, this group was primarily chosen to look at issues of neurotransmitter issues with aspartic acid and phenylalanine. But the brain tumor issue was thrown in there for them to deal with, and they weren't equipped to do it. They weren't pathologists and they didn't have a lot of expertise. But they felt like they were somehow on this end and should

comment on it anyway, and what they did was they made it equivocal. They said, there might be something here, blah-blah-blah, whereas we had previously taken every scientific avenue that we could to make sure that this was not a real issue. But this has been with us for 20 years that Aspartame has been approved. So it's sort of out there. This issue is floating out there that there is an approved food additive that people use extensively that might have an issue of cancer. And I don't know how to say this other than, with artificial sweeteners, you entrap every kind of [unintelligible] that you can. I mean, you wouldn't believe some of the things that have been sent to us as adverse reactions. But, at any rate, this board didn't do us any favors by making an issue that we felt we had resolved by raising it again, frankly, with their incompetence. But this issue is out there, and it wasn't John, but, I mean, there are some people in the National Toxicology Program or NIEHS decided that they wanted to study Aspartame and perhaps throw a couple other sweeteners in there as well and we talked. We had them up here, we had Ken Olden, we had everybody, and we had some very strange meetings on that.

Shostak: Why strange?

Lorentzen: Well, I'm sorry. I'd have to say strange in that it wasn't; we weren't talking well to each other. And at the latter part of our, almost some estrangement between our agencies because they were suggesting perhaps they might do some transgenic animal studies, and we said, oh, my God,

we're dealing here with an issue that there's some ambiguity to begin with, throw in a new model. What is that going to cost to the world? This is something used worldwide. We objected to that strenuously, but, for reasons that I'm privy to, we decided to use a new transgenic, the p16, I believe, a new transgenic at that time, which was developed to be sensitive to brain tumor issues. And, I mean, even -- I'm pretty sure we're on record objecting to this. But they went ahead and did this within the NIEHS. I don't know whether it took place in the extramural or intramural. I'm not sure. But this was a place, a murky area. And so they studied, I believe, sulfide potassium, which is another sweetener, and I don't know, maybe saccharin. But they studied in this model at least Aspartame, and even though we objected that this, in particular, this model hadn't even any level of validation at all. Very little was known about it as opposed to the p53 knockout, which there's a lot known about it. I mean, this one, there's not much at all. And here they were taking a very prominent food additive. It's prominent worldwide, and they were going to study it. Sure, you can rationalize that if you really think there's a problem. And we tried to tell them that, tried to elaborate to them how much we'd looked at this issue over and over and over again. At any rate, so they did that.

Shostak: What year was this about?

Lorentzen: It was recent. The results in the file somewhere, you know, they just had a

peer review last, sometime this year. I mean, John has said to me more than once they should never have done that. At any rate, fortunately, I'll say fortunately; it's my bias -- fortunately, nothing came out of the studies that were cause for concern. In fact, John said flippantly to me, well, we can now use them as our controls. We can use Aspartame as negative controls for this test species. Well, that's a nice joke. But here's an example of -- I'm not going to name any names, but I know who they are -- of somebody who had influence deciding that this was going to be done over our objection. And this is, I mean, this is using a new technology. Can you think of a better way to create doubts about the use of a new technology for purposes of deciding whether something is or is not a carcinogen? I don't know if I'm clear on that, but it was.

Shostak: Could you elaborate the last sentence -- could I think of a better way of creating doubts about new technology?

Lorentzen: Discouraging, creating doubt about the use of such technology as transgenic models, okay, that could do something like that.

Shostak: I guess what I'm unclear on is . . .

Lorentzen: That's a rhetorical question.

Shostak: Okay.

Lorentzen: I'm saying that I can, I think, divorce myself from the politics and keep the science separate, but I still think of potential, great potential properly developed. But it's made all the more clear that you can go, instead of

doing these, using these studies. I mean, we've got a public now that's skeptical enough of models that have been used for decades, to go off half-cocked, so to speak, and use these models to potentially make declarations about safety of substances without knowing much about them.

Shostak: Any other stories?

Lorentzen: No. That's good enough.

Shostak: All right. Thank you for talking with me.

END OF INTERVIEW