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UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON NUCLEAR WASTE AND MATERIALS

(ACNW&M)

188th MEETING

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TUESDAY,

APRIL 8, 2008

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ROCKVILLE, MARYLAND

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The Advisory Committee met at the Nuclear Regulatory Commission, Two White Flint North, Room T2B3, 11545 Rockville Pike, at 8:00 a.m., Michael T. Ryan, Chairman, presiding.

COMMITTEE MEMBERS:

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| MICHAEL T. RYAN | Chairman |
| ALLEN G. CROFF | Vice Chairman |
| JAMES H. CLARKE | Member |
| RUTH F. WEINER | Member |

ALSO PRESENT:

MARY HELEN BARCELLOS-HOFF, Lawrence Berkeley Laboratory

BERNARD LE GUEN, Electricite de France

VINCENT HOLAHAN, RES

CHARLES LAND, National Cancer Institute

KENNETH MOSSMAN, Arizona State University

JEROME PUSKIN, EPA

THOMAS TENFORDE, NCRD

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P-R-O-C-E-E-D-I-N-G-S

(8:05 a.m.)

CHAIRMAN RYAN: I guess the staff is sweeping the lobby, so I'm going to take care of a couple of preliminaries, if I may, and read our opening statement.

I would like to ask participants to please come to the table to their name tags, and I would like to ask everybody else to take their seats.

This is the first day of the 188th meeting of the Advisory Committee on Nuclear Waste and Materials. During today's meeting, the Committee will conduct a working group meeting on the effects of low radiation doses. At the end of the day, the Committee will consider discussion of ACNW&M letter reports.

This meeting is being conducted in accordance with the provisions of the Federal Advisory Committee Act. Neil Coleman is the Designated Federal Official for today's session.

Regarding today's session, we have received written comments and requests for time to make oral statements from two members of the public, Dr. Ted Rockwell, Vice President of Radiation Science

and Health, and Mr. Lynn Ehrle, Senior Biomedical Policy Analyst for the Organic Consumers Association. Should anyone else wish to address the Committee, please make your wishes known to one of the Committee staff.

It is requested that speakers use one of the microphones, identify themselves, and speak with sufficient clarity and volume so they can be readily heard. It is also requested that if you have cell phones or pages that you kindly turn them off or place them on mute at this time.

Feedback forms are available at the back of the room for anyone who would like to provide us with his or her comments about this meeting.

I have two items of interest regarding personnel. Ms. Sanari Chay, who has been with the ACNW&M staff for almost five years, is leaving on April 14, 2008, to join the Office of Nuclear Reactor Regulation in the Division of License Renewal. During her tenure with the ACNW&M staff, she has provided outstanding support to the Committee and the Committee staff. Her dedication, professional attitude, hard work, attention to details, and willingness to assist others are very much appreciated.

Sanari, thank you very much, and good luck

in your new job.

Ms. Carol Brown, who has been with the PMDA staff for almost two years, is also leaving on April 18, 2008, to be closer to her family in Central Virginia. She is joining the staff of the University of Virginia in Charlottesville. During her tenure on the PMDA staff, she has provided outstanding support to the Committee in areas of travel, scheduling, and support for letter reports. Her professional attitude, dedication, hard work, attention to details, and willingness to assist others is also very much appreciated.

Carol, thank you very much, and the best of luck to you in your new job.

Let's see, I think we'll have a few folks that will be coming in late, but we'll go ahead and get started. I'd like to introduce our first speaker. Commissioner Peter B. Lyons is here to share his views on communicating risks at low doses. Without further ado, Commissioner Lyons, the floor is yours.

COMMISSIONER LYONS: Well, thank you very much, Mike, and thanks to ACNW and the other folks who are joining you here today to discuss this topic.

This whole area of low-dose radiation effects has been a subject of great personal interest

to me for many, many years. And now that I have the opportunity to be here at the NRC and see -- and perhaps get a better direct understanding of how our, I would say, extremely limited scientific knowledge of effects at low doses, to see how that limited scientific understanding drives major elements of public policy, including a few areas that I'll touch on in my brief remarks. It's truly something that I find very, very frustrating.

I'm very hopeful that the discussions that you're going to have today I'm at least very hopeful will shed additional light on this very complex area of health effects at low doses. Hopefully, particularly through the DOE program, and other discussions that may well go on here, that all of you may be able to provide some feedback to the Commission on ways of better understanding the science of risk at low doses, and perhaps guiding us in directions that might be better supported by science than the paths that I think we're on now.

To the extent that this group today can propose new approaches, that to me would be a measure of success for the workshop's activities.

In an ideal -- in anything resembling an ideal world, I would look forward to being with you

throughout today. Unfortunately, the Commission is meeting with FERC, and I will have to get out of here right at 8:30, jump in a car and go downtown and spend the rest of the day with FERC.

Members of my staff -- Steve will be here, and certainly I am looking forward to Steve's report back, along with Mike's and other of you discussing with me what transpires during the day's discussions.

In addition, as I'm sure you are well aware, NCRP has another major meeting coming up devoted to this subject very soon. Again, in an ideal world, I would be there. However, in this case I will be in Japan, a different part of that ideal world. So I'll have to miss that one, too. But certainly my absence doesn't reflect on my interest in these very, very important areas.

If I could have that next slide.

A large part of your discussion today is I'm sure going to involve the linear no-threshold model. And I would like to just share in the next few slides some of the reasons why I'm particularly frustrated by the use of this model, not that anything I'm going to say is going to be the least bit surprising to any of you. You are even -- you are far better aware of the literature and the issues than I

am.

But at least from the perspective of just one member of the Commission, and just one regulator, the concern I have is that we deal with the LNT, which -- the linear no-threshold model -- which is no better than a hypothesis. And I think that -- I think that most scientists would agree with that.

But we treat it as essentially fact. We frequently use the word that it is a prudent way of managing risks. From a regulatory standpoint, I'd much rather know the right way to regulate risks. And, again, another word on this slide, the word "conservative," is applied frequently.

But I'd like to at least suggest that it may well not be conservative to be -- to be using a model with very limited scientific foundation, if any, and a model that drives very, very large expenditures of public funds. And as I'll note on my last slide, I think also is one of the main drivers of public fears about this unknown quantity of radiation.

So to me there are very, very real public impacts of the so-called conservatism that we use in this area. And I hope that your workshop today will consider and discuss some of the impacts of that conservatism.

And, again, I hope out of this you can provide some guidance to the Commission that might allow us to take alternative approaches, at the same time that I, and I would guess all of you, are going to be cheering on further scientific research that will I hope nail down with greater confidence exactly what the effects are.

If I could have the next slide.

This is just -- well, this is -- I was going to say this starts a series of quotes, but it actually doesn't. This is just the standard sound byte that you hear relative to LNT. It's repeated in any number of ways for -- sometimes it's just the statement that all radiation causes cancer. This statement certainly has nothing to do with an understanding of risk.

It does use the word "risk," but it's certainly not placing that risk in any sort of a context. And most of the quick sound bytes that you hear that derive from LNT are relatively or completely devoid of any risk-based statement by -- such statements, unfortunately, can and do increase the public fears of radiation.

It would be probably equally accurate to say that the simple fact that all of you showed up

today had a risk. You might have gone on the Metro. You might have walked across the street. You might have driven in a car. That's all -- those are all activities that introduce risk as well.

And I personally have been very frustrated by the difficulties of trying to communicate both the uncertainty and the knowledge of low doses, of what the risks may be, and then trying to place those risks in terms of perspective, in terms of the risks that we experience and accept as part of modern life.

The next viewgraph, if I may, starts the series of quotes which, again, all of you know. But just to make my point that for virtually any of the careful studies on the linear no-dose threshold, the LNT model, there is -- there are statements in there recognizing that it is a theory, that it is a hypothesis, statements like you're seeing here -- assumed proportional to dose; or the second one, a prudent basis for practical purposes; or the third one, scientifically plausible. Again, those are all accurate statements I think, but then -- let me go on to the next slide and make a few more points on this.

The National Academies, evidence consistent with the hypothesis, and the Committee judges it is unlikely that a threshold exists. Those,

to me, are not scientific statements. Those are all hypotheses and certainly best guesses, and they are carefully worded statements. But they all reflect the dearth of scientific knowledge.

If I could have the next slide.

The Department of Energy -- Ray Orbach -- responded to the BEIR VII National Academy report, and made a number of points from the work, or based on the work, that is ongoing within the Department of Energy's low-dose radiation effects program.

And, again, I'm sure you've seen these, but Ray Orbach -- and this was back in 2005, there is even stronger statements that have come out since from this program. But even in 2005, Ray was able to state with high certainty that significant elements of the assumptions under pending LNT are simply not correct. Plus, Ray also was concerned that BEIR VII, in his view, and I would say in my view, as he says in the first point, did not have adequate consideration of recent scientific advances, particularly those in the DOE program.

Could I have the next slide?

Coming in from the other side -- did we lose it, or maybe I just lost it on this screen? Coming in from the other side is the excellent work of

the French Academy, and I certainly appreciate your presence here today, sir. That should be most useful to again share the French perspectives with the ACNW.

But the research in France and the views in France are really quite different than those professed by the National -- our National Academy here. And the last statement that the LNT is not based on valid scientific data I absolutely agree with. Certainly, I have not seen data that would led me to say that LNT has a strong scientific basis. We're, again, back in this mode of, well, is it prudent or is it conservative?

May I have the next slide with the Health Physics comments?

And the Health Physics Society again makes the point about the LNT being an oversimplification, rejected for a number of different cancers, and making the point that there is a number of effects that have been well documented in the DOE program that can simply not be accounted for by the linear no-threshold model.

And the next one.

The NCRP -- again, and I hate to be belaboring this, but again making the points that the data are inconclusive. When I see a statement like,

"No alternative relationship appears more plausible in LNT," that's hardly a ringing scientific endorsement for LNT.

And the next one.

No conclusive evidence to reject the assumption. As a scientist, and now as a regulator, statements like that I find very frustrating, and I think all of us would be very, very well served if we can complete enough research to better understand the effects in that range.

And if we go to the next slide, perhaps the most frustrating aspect of LNT to me is the way that it is used in applications of collective dose. At least to me mathematically, if you believe LNT, then you have to believe collective dose, even though groups like ICRP and others make a statement like you see here that tries to argue against the use of collective dose for projecting radiation effects on large populations.

I very much agree that collective dose should not be used, and I agree with the first statement from the ICRP on this slide, but to me is -- when at the same time ICRP is saying, "Well, let's use LNT," I don't see how you accept the use of LNT and then argue that, well, we don't really mean it to be

used for collective dose where collective dose is used to calculate actual risks to real people.

I have no problem with the bottom suggestion from ICRP that it's an instrument for optimization. But as you are all well aware, collective dose is frequently used in far, far broader context.

The next slide shows the Health Physics Society, which, again, makes exactly the same point. And, again, this isn't going to be news to anyone.

And if I could go to my very last slide before I run out the door to head for FERC.

I started with the question on the LNT. Certainly, my very strong view, and I think the view supported by any of the scientific organizations is that it is a hypothesis. There is not adequate scientific data to say that LNT is a fact.

I discussed earlier my frustration on the words "prudent" and "conservative." And from a regulatory standpoint, I think one has to truly question whether using a model that is so-called conservative is the wisest course when it has substantial implications. And I've tried to list some of those implications.

I think we would all be very well served

if we could move towards a stronger scientific basis for radiation effects at low doses. And I think if we had that we would be able to address each of those implications that I have down there. Instead of taking a conservative view, we could perhaps be -- I think we could be much more confident that we are adequately stewarding the use of public funds. I'm thinking here in the cleanup and the decommissioning aspects.

I think we would do a far better job of discussing where it's appropriate to use collective dose and where it's not appropriate to use collective dose. And in particular, it's my very strong belief that improved science would only confirm the statements that have already been made, by Health Physics, by ICRP, and others, that collective dose should not be used to estimate risks to large groups.

And I think the public's fear of radiation would certainly be addressed by -- partially addressed at least -- by a better understanding of what those effects truly are. We may find that we -- I don't know which way we need to go on LNT. Is it more conservative or less conservative? But to me, the important point is that we should be using better scientific information, trying to strive for that

information, and trying to use the most scientifically accurate models we can for risk estimates.

I should stop there. You have a fascinating set of presentations planned for today. And, again, I wish I could be here for the day, but I will be 10 miles away.

There may be time for a question, Mike, or maybe I should just head out.

CHAIRMAN RYAN: Sure. I think, Commissioner, we certainly appreciate your views. And as you've noted, we have an excellent panel of experts to explore the questions that you've outlined, including a discussion of the LNT in light of current science, and then some of the implications that that science might have on policy. So we're pleased to have them.

I want to thank everybody with you here that has given of their time and expertise to participate today. It's, I think, going to be an excellent panel and a rich discussion for two days.

On topics like this, we tend to try to explore the range of views, and our report to the Commission will certainly try and document the views that we hear today, and then provide you with our analysis of those views.

COMMISSIONER LYONS: Very much appreciated.

CHAIRMAN RYAN: We thank you very much for your time, and good luck in the rest of your day.

Is there anybody on the bridge line? Is the bridge line open? It's open. Okay. We have a bridge line for folks that want to dial into the meeting. We have not had anybody dial in, but we'll hear them. And if I may just beg your indulgence, we'll need to interrupt and have them identify themselves for the Court Reporter. So as they do that, we'll have them announce themselves.

MR. EHRLE: I'm on the bridge line I guess.

CHAIRMAN RYAN: And you are, sir?

MR. EHRLE: Lynn Howard Ehrle, Senior Biomedical Policy Analyst, Organic Consumers Association, and chair of its project, the International Science Oversight Board, a 41-member worldwide group.

CHAIRMAN RYAN: Thank you, Mr. Ehrle. We do have, as I mentioned in my opening remarks, time for you to make comments, and that will come up a little later on -- let's see, a little later on this afternoon at 3:15. So we'll look forward to your

remarks then. I'm glad you're able to participate throughout the meeting. Welcome.

MR. EHRLE: Thank you.

CHAIRMAN RYAN: It might be helpful -- I don't know if your phone is capable to have a mute button, but sometimes the mute button is helpful, because if you don't have one we'll hear whatever you -- you know, whatever happens on your end of the phone.

Okay. Without further ado, I guess I would ask our keynote speaker, Professor Kenneth L. Mossman from Arizona State University, to open the meeting. Dr. Mossman?

DR. MOSSMAN: Thank you. Thank you very much, Mike. First, as a start-off, I want to applaud the efforts of Chairman Michael Ryan and also Commissioner Lyons for putting this meeting together. I think that the timing of this meeting is very important.

It's interesting that the NCRP is holding its annual meeting next week and will be talking about many of the same issues that we will be discussing here. So hopefully -- I'm not going to be able to make the meeting, but hopefully many of the other people here will be able to, because in my view what

is absolutely critical is we get as many perspectives on the table as is possible.

LNT is a -- to say the least -- an emotional issue, in addition to a scientific one, an economic one, and a social one, and a political one. And over the past several decades, the primary focus has been on the social -- I'm sorry, has been on the scientific issues. But over the past 10 or 15 years, I have come to believe that, really, science is not the driver. The driver in the LNT debate is going to be --

CHAIRMAN RYAN: Did you want your slides up, Ken? I'm sorry.

DR. MOSSMAN: I'm sorry?

CHAIRMAN RYAN: Do you need your slides up?

DR. MOSSMAN: Yes, I do. I will need my slides. Thank you.

Over the past 10 or 15 years, I have come to believe that the major drivers are the social implications and the economic implications of using LNT.

In fact, could we have the next slide, please?

So I want to take just a few moments of

your time to go over what I think are the major issues, and at the end pose a number of questions that hopefully we can address and may lead as a springboard to other kinds of questions as well in trying to resolve the LNT question.

And what this workshop is about is a broad exploration of the LNT question. It will focus primarily on science, but we have speakers such as Professor Jim Hammitt from Harvard School of Public Health who will be able to address important issues about economic questions as well.

CHAIRMAN RYAN: Again, forgive me, Dr. Mossman, but Dr. Hammitt has a personal issue he has to take care of today that came up suddenly. So he will be here --

DR. MOSSMAN: Oh, okay.

CHAIRMAN RYAN: -- either late today or tomorrow.

DR. MOSSMAN: Okay. All right. But hopefully his talk will --

CHAIRMAN RYAN: Is tomorrow, yes.

DR. MOSSMAN: Okay. Very good.

CHAIRMAN RYAN: I just wanted to let you know he's not here.

DR. MOSSMAN: Thank you. Thank you.

This is not a policy discussion, because policy is the province of the Commission, and we are not here to set policy or in any way to provide policy input, although hopefully the products of this workshop will be very helpful to the Commission -- to Commissioners and their staff.

So what we do want to talk about is: what is the state of the science? What is it that we know and don't know, from am epidemiologic perspective as well as a radiobiologic perspective? What are the uncertainties and risk estimates?

I find it very interesting that we use LNT down to doses of the order of one millisievert, two millisieverts, and calculate a risk. Well, what does the risk mean? Because the risk really is anything from zero all the way on up. And if we are making decisions on risk, it's beyond me how we can make any kind of decision when the uncertainty is so large. So uncertainties and risk estimates are really a critical issue.

And then, of course, there is the whole question of how we balance science and policy, and that is considered with the economic, political, and social issues. Even if LNT is right from a scientific standpoint, do we still use it? And the reason why I

ask that -- are social and economic factors such that it would be -- preclude its use?

The science is such that we cannot exclude candidate theories. In other words, there is no robust, statistically significant, scientific data at low dose that will allow us to distinguish alternative scientific theories. And, therefore, one can really say with some degree of confidence that every theory that is currently on the table -- linear no-threshold, quadratic, linear-quadratic, hormesis -- is to one degree or another scientifically defensible. That means anything works.

And the real question then becomes: if the science cannot eliminate candidate scientific -- candidate theories in favor of one versus others, then the decision really is going to very much depend on economic as well as social considerations. And that is why I said at the beginning of my presentation that science may not necessarily be the major driver. What will be the driver, in my view, is going to be economic considerations as well as social considerations.

I think it's useful at this point -- if I may have the next slide, please -- to talk about what LNT is used for, what it's not used for, and, perhaps

more important, what it shouldn't be used for. What LNT is used for, obviously, is its federal policy. And whether you like LNT or not, that's federal policy. And it's endorsed by the ICRP, it's endorsed by the National Academies through their BEIR reports. It is also endorsed by the National Council on Radiological Protection.

It is used as a translator of dose to risk. It establishes a dose floor of zero, where we consider the structure of radiation protection as a top-down mechanism, where the dose limit is the ceiling, and the LNT theory establishes the floor as zero. And what we try to do in radiation protection is to keep doses as low as reasonably achievable, never above the dose limit, but as low as we possibly can, given that there are social and economic constraints in trying to do so.

Unfortunately, as Commissioner Lyons pointed out in his opening remarks, sometimes LNT is often misinterpreted, and that means we have to go to zero. So the goal of radiation protection is zero dose, zero risk, when in fact that may not necessarily be the case.

What ALARA tries to accomplish is to achieve a rational, quantitatively-determined

acceptable risk. How is a risk acceptable? It's acceptable when we have applied all of the economic and social resources necessary to the situation, to reduce the dose as low as reasonably achievable.

Once we've done that and we're satisfied with it, that residual risk is then acceptable. If it's no longer -- if it's not acceptable, then we go back and we apply additional resources -- social, economic, whatever it is -- to get the dose and the risk down to an acceptable level.

Next slide, please.

What LNT is not use for. It is not used for setting dose limits. I have followed the BEIR reports quite closely over the past 30 years -- no, I'm sorry, it would be 25 or 27 years -- no, is it more than that? '72 was the first report, so it would be 35 years, or thereabouts.

And it's interesting that special interest groups argue that BEIR VII is going to establish dose limits via its adoption of LNT. And their argument against LNT, therefore, is that the -- is that dose limits are not restrictive enough.

But, in fact, when you look at the history, when you look at the data, LNT has really not been used in any way in setting dose limits. And the

little chart that is shown on the slide, and presumably everyone has a copy of that, shows the history of occupational dose limits from 1940 to 2005. And there has been a steady decrease with no change since 1960. And BEIR VII risk estimates, of course, have been all over the place since the first report in 1972 through the most recent report in 2005.

I should say -- all over the place -- in retrospect, they are pretty good numbers. We probably know more about radiogenic cancer risk than we do about any other agent -- carcinogen -- in humans. And, in fact, although the numbers look like they are varying wildly, they are all within an order of magnitude, which is pretty good.

And, in fact, I was struck by the fact that the first numbers that came out in 1972 are not that different from the current estimates in 2005, even though we have much more epidemiologic data, including incidence data, we have far more sophisticated modeling capacity, and just the back-of-the-envelope calculation, puts you well within an order of magnitude of what the numbers are that we are currently using, and the nominal risk now is roughly about five percent per sievert. In other words, five in a -- five percent lifetime cancer mortality risk.

Next slide, please.

What LNT should not be used for -- it shouldn't be used for estimating individual radiogenic risk. Why is that? Because the risk estimates that all of the authoritative bodies use in developing their recommendations come from studies of large populations. So they are really population risks.

The real question is: how do you translate from population risks to individual risks? And we really don't know how to do that very well, because we fully don't understand what the nature of the risk factors are for these diseases. At very small doses of the order of a few millisievert per year, radiogenic risk is a very, very small contributor to the total cancer risk in any one individual.

If the individual smokes cigarettes or has a particular diet that would enhance risk, these factors tend to be far more important than any radiogenic risk. And how we factor in these individual risks, how we structure an individual risk profile, is problematic, but it's obviously something that we would need to do, if in fact we're serious about going from population-based risks to individual risks.

Estimating public health impacts from collective dose, as Commissioner Lyons had pointed out, is inappropriate in a number of ways. I would disagree with the Commissioner that collective dose should never be used, and I apologize if I am paraphrasing incorrectly.

There are instances in which collective dose may be meaningful -- when you're dealing with a population that is very well characterized, doses are high, and for which we have some confidence in risk. Under those circumstances, collective dose may be reasonable.

But the way collective doses used routinely is -- is inappropriate, and the NCRP, in its report 121, the ICRP in its most recent report, 103, clearly discuss the limitations of collective dose. And we need to be very careful about how we use it in trying to estimate public health impacts.

I'm always reminded of the comment that when individuals are exposed to very, very small doses, and the associated risks are small, if the risk to the individual is small, then the risk to the population is small, too. And simply because you have a large population, millions of individuals, and you multiply the individual risk, which may be of the

order of one in a million, and you get some number, doesn't make it a public health problem.

And we need to be -- and that's -- and that's a key part of the collective dose constraint is that we should be cognizant of the fact that we're not dealing with infectious diseases where individuals can affect the probability of other people. We are all autonomous units, if I could use that expression, in the public. And the fact that I got one dose and Dr. Land got another dose doesn't impact his risk any more than his risk impacts me.

Let me turn quickly now to a recent history of the LNT debate, because I think it's useful to see where we've been and where we might be going. And those of you that have been following LNT for a while know that it has been a concern ever since LNT was introduced into the radiation protection philosophy several decades ago.

But it is only within the last 20 or 25 years that there has been a systematic effort to really look at LNT and determine what the basic of the -- what the scientific basis is for supporting LNT and the like.

As I best can gather, in 1988, Leonard Sagan at the Electric Power Research Institute was one

of the first people to convene a workshop that looked at ionizing effects research, and particularly opened up the question about whether the science really did support the LNT or whether we need to look more closely at it.

The ICRP recommendations, in 1990 and 1991, and the BEIR V report also looked very closely at the LNT question.

In 1998, the Health Physics Society convened the Wingspread conference, which looked -- and some of you may have been there -- looked at the conflicting scientific views in the LNT question. And we had representatives from all camps, including hormesis, LNT, quadratic, linear quadratic, etcetera.

We have a followup conference in 2000, again supported by the Health Physics Society, the Airlie House Conference, in which at this time we began to look at linking some of the science issues with policy. And then, of course, in 2005 and 2006, emerged the first really serious, serious debate by major authoritative bodies -- the BEIR VII report and the French Academy of Sciences.

Both panels are -- both reports were written by arguably the top people in the world on low-dose radiobiology and understood the problem.

They essentially looked at the same data and came to diametrically opposed conclusions.

The heart of a scientific debate is honest difference of opinion. And I think that the differences between the BEIR VII report and the French Academy report highlight what we really don't know about the science, and how much more it is that we need to learn about.

And then, this year, the ICRP 103 report came out. EPRI is currently revisiting its issue that it introduced back in 1988, looking at economic as well as social implications of the LNT debate, in addition to science.

This meeting, of course, is going to be doing much the same thing, and then, of course, next week the NCRP is also going to be looking at these questions.

So, in summary, the debate has transitioned from a purely scientific argument to one which includes both social and economic factors.

Next slide, please.

The LNT problem -- there are three basic elements to the problem, as I see it. One, scientific questions. There is new radiobiology, which has -- it's not so new now. There's -- some of the data is

10, 15 years old. But there is new stuff coming out all the time questioning the assumptions of LNT.

There is lack of conclusive scientific evidence at low doses below 100 millisieverts to eliminate competing theories, and this I think is very important.

Now, I've gotten arguments before. Yes, there is data below 100 millisievert. And if you believe that data, you know, that's -- you know, that certainly adds to the debate. But I think when you look at the majority of the data, at low doses below 100 millisievert, there is a paucity of statistically significant risk information there.

Economic costs -- there are enormous costs to reducing dose when the benefits are uncertain. We are confronted with this with waste management -- a very, very serious problem. I worked with the National Academies on the waste isolation pilot project and -- or the waste isolation pilot plant, and the costs to isolate waste there, characterize the wastes, are just absolutely incredible.

And you asked, "For what end? What's the benefit of doing that?" And it's unclear.

The social costs -- the notion, as Commissioner Lyons had pointed out, that any dose, no

matter how small, is associated with the risk. That the general public concludes from this that there is no safe dose. And, again, because it's federal policy, then the conclusion from the Federal Government is that the Federal Government doesn't believe that there is no safe dose, and that any dose is potentially harmful.

Next slide, please.

The low-dose problem is interesting. I sort of like to draw the analogy from cosmology where cosmologists talk about the singularity. And the singularity is essentially all about what happens to laws of physics as we know them when you hit the event horizon. And essentially at the event horizon physical laws tend to lose meaning.

Well, I like to draw the analogy that when you get down to very, very small doses of ionizing radiation on an LNT, or even a curvalinear model, when you get down very, very close, are we approaching a radiobiologic singularity? In other words, the kinds of events that are occurring really cannot be predicted or understood in any way based on what it is that we know at higher doses.

So it's an interesting concept. When the dose approach is zero, we have a problem understanding

what is going on. Now, there is a lot of research, primarily funded by the Department of Energy low-dose program, which I might add Commissioner Lyons was instrumental in helping secure this funding through Senator Domenici's office back in I think it was about the year 2000 or 2001. So he has played an important role in getting research dollars available for this kind of research, but we are learning more and more about what is going on at very, very small doses.

And what we can say with a high degree of certainty is that what is happening at low doses is different than what is happening at high doses. And that causes a problem in terms of how we use LNT, because what LNT -- the theory would predict -- is that mechanisms ought to be the same, and that the only thing that is varying is the dose, and that's what the predictor of risk is going to be.

But if at high dose we are seeing certain radiobiologic effects that are different than what is going on at low dose, it makes interpretation of risk rather difficult.

If we can go to the next slide, please.

I have a -- I'm anal, let me put it that way. I'm anal about definitions, and particularly about definitions of theory, models, and hypothesis,

and as they pertain to LNT. And the reason why I think this is important is because we can't advance the debate unless we have a clear understanding about what LNT is and what it isn't.

LNT is not a model, and LNT is not a hypothesis. LNT is a theory. Hypotheses are questions that we ask about theories. In other words, you can ask a whole array of hypotheses or questions as hypotheses that question the LNT theory. For instance, one could ask a question about: is the data consistent with linearity? Is the data consistent with a threshold dose? And these all go back ultimately to asking the question: can I support LNT as a theory?

On the other hand, models -- and there was a recent National Academy report on this -- models are conceptual or actual physical constructs that describe some type of theory. But the model operates on the basis that the theory is there. So when we talk about climate models or the like, the underlying theory is energy processing, Second Law of Thermodynamics, things of that nature. There is lots of different models that one can use to support the Second Law of Thermodynamics. There's all sorts of different models that one can use to support the LNT theory.

So what I'm saying is that we need to think about LNT as a theory, because then we can begin rationally to talk about, well, how do we begin to discuss the appropriateness of LNT versus hormesis versus linear quadratic versus quadratic? Because ultimately what we're trying to do -- in the utopian view, what we're trying to do is eliminate everything else and come up with one theory, whatever that is.

You can't do that if you're talking about hypotheses. You can't do that if you're talking about models. What we need to do in the Popperian sense is that we need to collect data that will not necessarily prove a particular theory, but it will be used to disprove candidate theories.

And Popper, who was a very well-known philosopher of science and his treaties on falsification of theories, and what not, I think is worth reading for anyone who is interested in the LNT question, because it's the nature of the scientific data and how it can be applied to candidate theories that is going to help us answer the particular question.

Can we go to the next slide, please?

I'm not going to spend any time on this, but here is just a little schematic of the different

kinds of dose -- the different dose-response theories that we took -- take a look at. The take-home message here -- we have lots of data at the high-dose end. That doesn't help us because all of the candidate theories essentially converge there.

So the data are really very -- are not very helpful in helping us distinguish one theory from another. Where we need data, and where we don't have a lot of statistically significant risk data, is at very, very small doses, whereas you can see at the origin now you have divergence of the theories, and we can better take some -- a clear path as to determine which theories are acceptable and which theories can be eliminated.

Next slide, please.

I'm sort of running out of time, aren't I? How much time do I have, Mr. Chairman?

CHAIRMAN RYAN: You have to 9:15.

DR. MOSSMAN: Through 9:15. Okay.

CHAIRMAN RYAN: Leaving time for questions, please.

DR. MOSSMAN: Okay. Fine, thank you.

There are some data from -- just to illustrate how you can fit various theories to scientific data. This is data from the Radiation

Effects Research Foundation, the life span study. It's not looking at cancer; it's looking at non-cancer disease. But the point still -- is still valid, is that at very small doses there is some difficulty in trying to determine which theories are acceptable and which ones are not.

And, obviously, depending upon which theories you choose, the risk estimates that you are going to predict at small doses are going to be very, very -- are going to be very different. And I might add -- in looking back at the BEIR VII report, it is too bad that they didn't follow the model that was used in the BEIR III report.

And the BEIR III report, which was published in 1980, came under a lot of criticism, because they couldn't focus on a single dose-response theory. What they did was they provided risk estimates for a linear no-threshold theory, for a pure quadratic theory, and for a linear quadratic theory, and they provided risk estimates.

In retrospect, what a beautiful thing to do, because that's what the policymakers need. You know, we can't -- we can't provide the science that is going to distinguish one theory from another. But what the authoritative bodies ought to be doing --

like the BEIR committees, like ICRP, like NCRP -- they are staffed, and they have sitting on their councils the top people in the world, who know more about this stuff than anybody.

What they ought to be able to do is provide a pallet, if you will, of options that are each scientifically defensible, and allow the policymakers to work with that.

And, in retrospect, I wish BEIR VII would have done that. They didn't. But if there is to be a BEIR VIII, or a BEIR IX -- and I don't know whether there is or not -- I hope that they will revisit the BEIR III model and ask the question: do we want to go back to this? Because that's really what the policymakers need.

And, frankly, the BEIR VII report and these other reports are written in part for policymakers. They are written in part for people who are going to be making some decisions, in addition to regulators in various government settings, radiation safety officers, other people who actually manage risk, and things of that nature.

Next slide, please.

The collective dose problem I have already mentioned. And, again, I focus on my -- on my last

bullet. If the individual isn't harmed, then the population isn't either. Collective dose has utility. Its utility is not in determining public health impact. Its utility is in establishing trends analysis of doses in a particular occupational environment.

So in trying to determine whether a particular ALARA program is effective not, it is useful to calculate collective dose, the sum of doses in the exposed population at various times, and look at what is happening to the collective dose, without inferring anything about risk. That's a useful way to utilize collective dose. But because population risks are poorly defined, particularly at small doses, there are significant limitations.

Some of you may be familiar with a recent paper by David Brenner and Eric Hall that appeared in New England Journal, I think it was in October or November of last year, where they were looking at CT doses. It received a lot of public press, and I don't know about your local papers, but in our local papers in Arizona there was a good deal of fear that was engendered about whether I should get a CT exam or whatever.

No question, doses are too high. I can

tell you that the American College of Radiology has been looking at this problem for a long time. In fact, they put out a very important white paper in their journal, I think in May or July -- May or June of last year -- that essentially recognized the problems that we're having with high-dose CT, the problem with multiple studies, and whether these are appropriate or not. That's the problem.

Calculating risks, where for the most part the risks are very small, and engendering fear because they are calculating a total cancer mortality burden of something of the order of two to three percent in the U.S. population, is, in my view, an inappropriate application of collective dose, and does nothing to advance what the fundamental problem is. And the fundamental problem is: how do we deal with large doses in CT studies? So collective dose is an issue that we need to be cognizant of.

Risks are uncertain at doses below 100 millisievert, although as I mentioned before there are some studies. The most important one perhaps is the Oxford childhood cancer survey that was begin in the mid-1950s that shows, or purports to show, that at doses of the order of one to five rad there is an elevated risk in children who are exposed in utero.

Those studies have been the subject of very careful analysis. It's unclear to many epidemiologists what the nature of causality is, but there are still others who believe that this is a very real effect. It has stood up the test of time. It is an important study. To my mind, it is unclear to me what the relevance is of an exposure in utero to an exposure of an adult in a powerplant situation. But, you know, that kind of issue needs to be I think fully resolved.

So down to 10 -- to 50 millisievert may be an area where we need to look much more closely, and hopefully the DOE low-dose program can provide us with some useful scientific information at that level.

Next slide.

Let me look -- next slide, please. Sorry. Thank you.

Let me look very quickly at the economic impacts, and this is from a very, very narrow view -- one study. And I'm looking forward to Professor Hammitt's discussion of the economic questions when he is here tomorrow.

This is some data from the General Accounting Office from 2000. And, again, I applaud Commissioner Lyons and his boss at the time, Senator

Domenici, who commissioned the Government Accounting Office to look at questions about economic impacts of LNT.

Senator Domenici recently received an award I think from the Health Physics Society, and it is well deserved, because he is a member of Congress who really, really does understand the science and knows what questions that need to be asked. And, certainly, the economic question is an important one.

And here I illustrate the -- at the Nevada test site, the costs of cleanup -- and these are data from the General Accounting Office -- where we -- where we limit the dose down to about .15 rem -- 15 millirem a year, .15 millisievert per year.

As you may recall, there is an ongoing controversy between the U.S. Nuclear Regulatory Commission and the EPA as to what the appropriate cleanup should be. Should it be .25 millisievert, as the Commission would argue? Or should it be .15 millisievert, as the Environmental Protection Agency would argue?

As a classical radiobiologist, frankly, from a public health and environmental perspective, there is no difference between those numbers. However, there is a very, very significant economic

difference, and that is what's illustrated -- that's what's illustrated here on this slide. That once one gets down to doses that are very, very close to natural background, you're cleaning up to natural background, and the costs are extraordinarily high.

And one needs to ask, when you are going to allocate public funds in this way, what is the benefit? You know, I'm the first to say, if there is a need for cleanup, absolutely, let's allocate the money. But then, we need to look very carefully at the cost-benefit equation and at what point are we just throwing away money for very little return.

I would strongly recommend Associate Justice Steven Breyer's little book that he published in 1993 called Breaking the Vicious Circle on regulatory law, where he talks specifically about getting down to very, very small doses of anything. And when you regulate down to those levels, the costs can be enormous, and you need to very carefully look at what the benefits are from these large expenditures.

The social impacts -- of course, radioactive -- next slide, please.

Radioactive waste disposal, well-known "not in my backyard" philosophy, there are significant

questions. Particularly now at Yucca Mountain the Commission is likely to receive an application from the Department of Energy any month now for the Yucca Mountain facility. And the Commission will be looking very carefully at public health and environmental risks.

And no doubt there will be many special interest groups that will also be challenging the Department of Energy to be sure that if this facility is to be licensed that environment and public health questions are completely and thoroughly answered.

Mammography and CT imaging continues to be a problem. We have now reached a point -- and I think at the NCRP annual meeting last year Fred Mettler made a very -- a very important presentation on where medical exposures now sit in the grand scheme of exposures to the U.S. population. And medical exposures now are by far the vast majority of sources of exposure.

To give you an example of how serious the problem has become -- in 1980, there were only about three million CT scans that were done in the United States. And last year there was something like 60 million. And I'm not going to sit here and argue that these weren't justified, because I'm not a physician

and can't tell you that.

But whatever the justification question was, the enormous increase in numbers has got to give us pause, particularly when doses are very high. And that's why I made my comment about the Brenner and Hall study, that we need to be very careful about what we saw about public health risk, although they were right on the nose when they said -- and they have repeated things that have been known for decades -- that doses from CT are high, and that we need to take care of that.

So the social impacts are considerable, and what we want to avoid is in the medical arena patients declining radiographic examinations because of fear of radiation, where declining such examinations may have a significant impact on disease diagnosis and treatment management.

So with that, let me turn to my last slide, and then I will open this up for questions. I'm sure you have many.

And here are a few questions that I would like to challenge the group with. One is -- is the LNT question even answerable? In other words, are we ever going to be able to -- and what I mean by "answerable" is, are we going to be able to get enough

robust, statistically significant scientific data at small doses that we can in the Popperian sense falsify candidate theories, so we're left with one, whatever that theory is.

It could be hormesis, which means that there is a threshold somewhere. It could be LNT, and all of the -- all of the scientists in the establishment have been right all the time. Or it could be curvalinear, or it could be something else. I mean, what muddies the water, of course, is that we already know from epidemiology that for several cancer types the dose-response curve is different already. I mean, if you look at certain kinds of leukemias, it's curvalinear. If you look at breast and thyroid, it's linear. If you look at bone, it's threshold.

So we already know from a substantial amount of epidemiologic data that there is already difference in models -- in theories. So one of the questions that I think we are going to need to answer, certainly in terms of the scientific questions: is it even answerable?

Now, I may sound pessimistic, and to a degree I am, but that doesn't mean that we shouldn't go after the studies and do them anyways. We still need to understand what's going on at low doses from a

scientific perspective.

I'm a health physicist. Some of the other people around here are health physicists, too. We essentially manage small doses. We are professionally better if we understand better what is going on at small radiation doses.

So if, in fact, we don't get anything resolved with regard to the LNT debate, nonetheless the more information that we have about what is happening is going to be very, very useful. So I would certainly strongly encourage we do that.

What is the lowest dose associated with statistically significant radiogenic cancer risk? Current debate. The Health Physics Society put its foot in first, said it's 100 millisievert, and then there has been arguments ever since. Why is this important? Because I think it's an important trigger in resource allocation.

I mean, once we understand -- what are the significant risks? There are some epidemiologists who would say -- and I don't necessarily ascribe to this in this case, but they would argue, if I can't measure the risk, is the risk worth even worrying about?

Well, I don't know that that's necessarily a philosophy that I would want to follow, but

nonetheless that's a view that's out there. So how we -- what triggers that we use to allocate resources depends on how well we can measure the risk. Because otherwise, if we can't measure risk very well, then we are almost blindly allocating resources to try to reduce risks that we can't measure. And that, I think, is a significant problem.

Can low-dose radiobiology answer the threshold question? Well, I think that that goes to the heart of the LNT question as to whether it's arguable, but certainly the threshold question is at the heart of whether hormesis has any validity. There are arguments that even if there is a threshold, does it really impact the way we do radiation protection? There are people that would argue, no, it won't.

What are the economic and social costs of using an LNT-based system of protection? The GAO report in 2000 was certainly a good start, but I think we need more such reports. We need more efforts to determine, what are the economic impacts? What are the social impacts?

And what does this mean? That means we need to recruit economists, we need to recruit cultural anthropologists, we need to recruit psychologists, we need to recruit risk analysts, other

people who we normally don't converse with, other people who we don't normally get involved with, to help us learn a little bit more about what some of these issues are, because, again, my view is that the economic and social costs are actually the key drivers in the whole debate.

And then, finally, it's an issue I have -- for those of you that are unaware, I have a book that I published last year, Radiation Risks and Perspective, in which one of the big issues that I promote is this notion of abandoning the risk-based system of protection and going straight back over to dose-based system of protection.

The Commission is essentially doing that anyways. You have a dose limit, and you measure doses, and you determine whether, you know, you are sufficiently far enough from the dose limit that you don't have to use administrative controls and things of that nature.

I used to be a radiation safety officer. Not one time in my 15 years of doing it did I ever calculate risk, because I didn't need to. What I needed to calculate was dose and look at my ALARA program in terms of dose. So in terms of my own operational situation, I didn't have to measure risk.

What I really needed to know was dose, and that's what really was important.

So it's an interesting -- it's an interesting idea, because then the LNT question goes away, because then we don't have to worry about calculating risks. Then, we don't have to worry about explaining to people what the risks are when we don't know what the risks are at small doses. And it certainly might help ameliorate the social and economic questions.

So with that, I stop. I thank you for your attention, and I'm more than -- I will turn it back over to the Chairman.

Thank you, sir.

CHAIRMAN RYAN: Thank you, Dr. Mossman. We'll have a panel discussion of all presenters at 9:30 this afternoon, so we'll maybe save interactive question and answers for that time.

Just one comment. I want to clarify a point that this Committee has written on regarding collective dose. We have I think stated that collective dose for the purpose of work planning is a very useful tool, and I want to emphasize that, that for example, in our work practice 1 versus work practice 2 or 3, for a group of individuals conducting

an assignment may, in fact, be a very good way to judge work practices, tools, equipment, whatever it might be, and the Committee has stated that.

And I think you implied it, but I wanted to be explicit about --

DR. MOSSMAN: Yes. Thank you for clarifying that.

CHAIRMAN RYAN: -- is an excellent way to sue collective dose, but it's a relative comparison of one activity versus another. It's not an absolute estimate of risk, but I want -- and I'm pretty sure you agree with that.

DR. MOSSMAN: No. Absolutely. Absolutely, thank you.

CHAIRMAN RYAN: That's one thing I wanted to make sure that we're clear on the record.

We do have just a couple of minutes, if there are any comments from the Committee at this point. Or do you want to just press on?

PARTICIPANT: Jerry has got a question.

DR. PUSKIN: Can I ask, what do you mean by dose-based standard versus --

CHAIRMAN RYAN: Jerry, if I may, I'm going to defer questions to Ken individually until we get to the panel discussion, if I may, because I want to make

sure we get all of the speakers in. If we start, we might not get through too much in five minutes, if that's all right.

Yes, Dr. Tenforde.

DR. TENFORDE: May I make just one comment and amplification of Dr. Mossman's calculation of economic impact versus cleanup target doses at the Nevada test site. And that is, NCRP published Report 146 in 2004 that deals with very specific issues on differences in target doses for remediation of contaminated sites.

And it is extremely interesting to compare the underlying assumptions in the NRC recommendation of .25 millisievert versus the EPA recommendation for cleanup of .15. The EPA's recommendation is largely based on a resident farmer who eats produce from the site, drinks the water, etcetera, whereas the NRC goal is based on a suburban resident, 30-year suburban resident.

Those are very different underlying assumptions, and lead to some different conclusions on target doses for cleanup that actually, when you look at them from the higher level, really are not very different, because they are driven more by the underlying assumptions on land use, ultimate land use.

So I think that is a very important factor to keep in mind, and I highly recommend to those of you interested in this issue to look at NCRP Report 146.

Pardon me for doing that --

CHAIRMAN RYAN: That's okay. That's fine, Dr. Tenforde.

DR. TENFORDE: I wanted to point that out.

CHAIRMAN RYAN: We appreciate your comment.

Jerry, if you do have one quick question, maybe we could fit it in now.

DR. PUSKIN: I just wanted to know what you meant by dose-based regulation versus risk-based, since I think all regulations that I know of are risk -- are dose-based in the sense that they are defined as a dose limit or concentration limit or some exposure limit. And I don't -- I just wonder what you mean -- what would be the change? I guess --

DR. MOSSMAN: Well, in part, it's not -- the NRC dose limits are not really dose limits, because you are factoring in weighting factors that are based on risks. So, in other words, the tissue weighting factors are a portion -- are fractions of the total risk that can be applied to a particular

tissue.

So, in fact, they do include risk information in the dose limit calculation. When you say -- when you say one millisievert a year, or 50 millisievert a year, the fact that you are using the millisievert is a dose -- as a measure of dose includes the weighting factors, which are risk-based. So those are risk-based.

What I'm saying is we should eliminate that and use just straight dose to the absorbed organ or to the target organ. If it's the whole body, then it would be the whole body. So don't factor in risk at all there.

DR. PUSKIN: Let me just ask one question, then. Let's suppose the dose were entirely in the lung. What would you allow? How much would you allow, just in the lung, as compared to the whole body?

DR. MOSSMAN: Well, I wouldn't change the dose limits, because as I pointed out earlier in my talk, the dose limits don't have anything to do with risk anyway. The way I would manage the system is that I would use -- I would use some reference level, either from natural background or whatever, as a basis for comparison to the dose that was actually received

in the occupational setting or whatever it might be.

DR. PUSKIN: So you would allow just as much to one organ as you would allow to the whole body.

DR. MOSSMAN: No, I didn't say that. No, I didn't say that. All I'm saying is that the limits -- the limits are not based on any information that we have on risk. I mean, all -- the limits were established before we had any really good handle on risk estimates as we do today.

CHAIRMAN RYAN: Let's pick up that discussion, if we can, when we have the general panel discussion.

Dr. Le Guen, did you have one quick question?

DR. LE GUEN: Yes. No, it would be a quick comment. Of course, about collective dose, I would agree with you, because the problem is not to use or not to use a collective dose. Of course, we -- in a nuclear powerplant we monitor the collective dose.

The problem is when you want to predict the future risk for this group, and particularly to assess the number of cancer. So the problem with the LNT now is management of risk.

I would like just to take an example about CT scan. From my point of view, if today we have a large decrease of the dose received by nuclear workers, it is because we have a good ALARA approach. For CT scan, it is exactly the same approach.

The problem is because we must take into account two other parameters -- medical benefits and age of patients. So from my point of view, the good question is how to avoid to the most sensitive populations, for the children, to avoid non-useful radiation? And I think the best way is then to try to assess and try to have a lot of faith to the population with this kind of approach.

That's all.

CHAIRMAN RYAN: Thank you, Professor.

With that, we're at the point of inviting Dr. Tenforde, President of the National Council on Radiation Detection and Measurements, to provide us with his insights.

Dr. Tenforde?

DR. TENFORDE: I'll bring this a bit closer, so that I project.

CHAIRMAN RYAN: You don't have to move it. It will be just fine where it is.

DR. TENFORDE: I see.

CHAIRMAN RYAN: It's high tech.

DR. TENFORDE: Very high tech. Thank you.

Well, let me begin by thanking Chairman Ryan and Neil Coleman and the other organizers of this working group meeting for inviting NCRP to participate. I think this is a very important subject, and I think this is a very timely workshop that you're hosting.

Next slide, please.

What I would like to cover are several issues that do relate to the theme of the workshop. First, let me just say a few words about the role of NCRP, and I will ultimately describe some of our current and future activities related to understanding low-dose radiation effects.

I will briefly talk about the rationale, some key research issues that I feel need to be addressed, and the public policy and regulatory implications of having a better science base for judging models of --

CHAIRMAN RYAN: Dr. Tenforde, excuse me. Have we had somebody join the bridge line?

MR. BRUCEMAN: Yes. This is Carl Bruceman.

CHAIRMAN RYAN: Carl, thank you for

joining us.

We'll return to Dr. Tenforde's presentation. Excuse me, Dr. Tenforde.

DR. TENFORDE: That's quite all right.

And then, I want to give you an overview of NCRP's near-term and longer-range plans in the area of evaluation of low-dose radiation effects and models, and then, finally, make a few concluding remarks.

Let me say at this point that although this presentation is based on my own slides, I have built very much on several months of strategic planning by NCRP. We have just issued our triennial strategic plan for 2008 to 2010. Much of what I say is consistent with the scientific goals and thrusts described in that plan. It is also consistent, I believe, with the content of next week's NCRP annual meeting on low-dose and low-dose rate radiation effects and models.

And I believe, also, much of what I will say is consistent with the current thrusts and themes of the DOE low-dose program, which I think is a very important, new -- well, not so new, but a very important research area. And so that will be largely the basis of my comments.

I will state at this point that at this time NCRP does not have a firm position on the LNT model or theory as Dr. Mossman has described it. We are, I would say, very open-minded in terms of alternative models of radiation response, and a major thrust of our future work will be in analyzing scientific information and building a framework upon which hopefully we will be able to better judge appropriate models of radiation dose response, including of course LNT.

So that's somewhat of a disclaimer. I will mention LNT at a number of points during my presentation, but more in the context of scientific issues that must be addressed in order to more appropriately and adequately assess LNT.

Next, please.

Well, NCRP, in brief, was originally formed in 1929 as the U.S. Advisory Committee on Radium and X-Ray Protection, and in 1946 became the National Committee on Radiation Protection and Measurements. The change was largely driven by the many new types of radiation, such as neutrons that had to be considered after the A-bomb detonations.

And then, in 1964, under Public Law 88-376, NCRP was formally chartered as a non-profit

organization to provide national guidance on radiation protection and measurements. In the Public Law, there are four primary elements of NCRP's mission -- first, provide information and recommendations on protection against radiation and radiation measurements quantities and units; and, secondly, to develop the basic concepts of radiation protection that underlie these recommendations.

We are also in our mission mandated to facilitate effective use of the combined resources of organizations, both in the U.S. and worldwide, that are concerned with radiation protection issues. I put the first two in red because they are particularly relevant to some of our current and future thrusts in the area of low-dose radiation effects.

Next, please.

Now, I think there would be little argument that there are several main drivers that underlie the need for a better understanding of low-dose radiation effects. First of all, as has already been said, our current knowledge is largely based on higher dose laboratory and human exposure data. And the conclusions that can be drawn from epidemiologic data on low-dose exposures, let's say less than 100 millisievert, or some people will say 50 millisievert,

are rather limited.

And, of course, with human populations you have confounding factors, such as diet, lifestyle, smoking, etcetera, that complicate the interpretation of the data that's available. There are a lot of studies on individuals that have been exposed to low doses -- occupationally, medically, in the subset of A-bomb survivors who were in relatively low exposure areas, and a variety of other populations have been studied. But it has been very difficult to draw conclusions.

Yes?

CHAIRMAN RYAN: I'm sorry. Is somebody dialing a telephone? Anybody new join the bridge line that hasn't signed in?

(No response.)

Sorry.

DR. TENFORDE: That's quite all right.

Third, it is important to understand low-dose effects. Obviously, through improved work practices, especially over the last couple of decades, the radiation exposure under occupational conditions is generally quite low. And largely the regulations are based upon extrapolation and models or theories that are based on information obtained from high-dose

exposure situations in the laboratory or in human populations.

And there is clearly, I think we would all agree, a need to close the gap in scientific knowledge on low-dose versus high-dose effects, and evaluate the implications of this improved knowledge base for radiation exposure practices and policies.

Next, please. Next? Thank you.

Let me now, just in a few slides, give some fairly high-level perspectives on key areas of research related to low-dose radiation effects and trying to develop this improved scientific framework for evaluating dose-response theories and evaluate effects and implications.

Clearly, the continuing and ongoing efforts in characterizing damage, repair, and misrepair mechanisms, and consequences of both cellular and integrated tissue levels, are extremely important, and at lower and lower doses.

Second, I can't emphasize strongly enough the importance of the work that is going on in characterizing so-called non-targeted effects. These include bystander effects, where say a single cell is hit but neighboring cells are influenced or killed as a result of the radiation of the individual cell. And

genomic instability is another non-targeted effect.

It has been argued by some that these could enhance the overall radiation effect and damage at very low doses. And these are being characterized at progressively lower doses. There are, of course, alternative effects, such as adaptive responses, that can counteract any adverse effects of non-targeted effects such as bystander effects or genomic instability. So it will be very difficult to analyze the tradeoff of these.

And I might point out, as Dr. Brooks, who headed the -- well, he was a consultant to the DOE research program and has argued very effectively that, as you get down to lower and lower doses, you do encounter signal to noise issues of extracting from the scientific data the true biological signal versus the background radiation in which the experiments are conducted.

So this is a very difficult area of research, but extremely important, because there may be some major implications in terms of dose-response theories and analysis of effects.

There are many modifying factors, and these are extremely important. It's not just DNA damage, but we know that there are a number of

mechanistic factors that come into play that influence the ultimate expression of damage, and that includes, of course, repair enzymes and antioxidants, humeral factors such as hormones, and regulatory factors, and the extracellular matrix interaction with cells influences integrated tissue responses. We know that now very well from work that has recently been done.

And so we need to bear in mind that analysis of radiation damage and repair or misrepair really can be modified by a number of biological factors, as well as the physical damage to DNA and other cellular structures.

And then, extremely important is the analysis of dose and dose rate on exposure outcomes, and the differing effects of low and high LET. We know that in terms of relative biological effectiveness, high LET is generally much more damaging than low LET radiation.

These are modifying factors, physical factors, that must be taken into account in evaluating radiation damage and repair mechanisms.

Next, please.

Moving to laboratory animal studies, it's very important to use the wealth of data that has been acquired over the years, with support from DOE and

many other sources, on various toxic effects. Not only cancer but non-cancer effects are getting more and more attention, such as cardiovascular effects, cataracts, nervous tissue influences.

And the relationship of these measured outcomes, adverse outcomes, to radiation sensitivity, genetic factors such as genetic susceptibility of the irradiated animal, or in the human case obviously the human organism, and then the damage mechanisms studied in vitro need to be taken into account in evaluating the results of animal studies.

And it's very important to expand the investigation of biological markers of radiation damage and recovery. Traditionally, we have used endpoints such as chromosome damage, but there is more and more focus on alternatives that have a lot of sensitivity related to protein and gene expression, molecular markers, gamma-H2AX, foci, near DMA, damage sites, and other powerful tools can be brought into play in this molecular biology that can be good markers of radiation damage and recovery patterns.

Next, please.

A very important direction that's being taken more and more is to look at damage in integrated tissues, organs, and whole organisms, using systems'

biology approaches to understanding radiation risk.

We know now that damaged individual cells, although an early event can be propagated through an integrated tissue, it can either be moderated in terms of enhanced or diminished and often diminished through mechanisms that are induced in an integrated tissue. And there's some excellent examples of this that have been worked through in laboratory systems and I think that the use of system biology concepts and approaches is becoming increasingly important.

And then again, it's very important to emphasize the need to evaluate injury and recovery from radiation after exposures to radiations of differing dose and dose rates and differing qualities.

Next, please.

Human health studies are on-going and important in the low dose regime. Of course, it is very important in the view of NCRP to attempt to use the wealth of information from laboratory animal studies for projection of risks in humans at the tissue and whole body levels. NCRP published, a few years ago, Report 150 on exactly this subject.

It turns out that in many cases the extrapolation of risk from laboratory animal models to humans can be done very well; mammary cancer, for

example; hematopoeta cancers, and other end points in humans can be related quite well to appropriate laboratory animal studies. And I think this is a powerful tool that should be applied in analyzing low-dose effects.

And then interpretation of the outcomes, based on laboratory-based studies as they grow in number and wealth of information, I think it will be coming increasingly important to use this information to evaluate health outcomes in humans, including of course, as I mentioned before some of the new biological markers of radiation damage that are being developed through laboratory-based studies.

And then ultimately, of course, evaluation of modifying factors influencing radiation damage, repair and ultimate health outcomes is very important. These are not only physical factors such as uniformity or non-uniformity of exposure, partial body or whole body, but of course, as I indicated earlier, in the human case you have to deal with confounding factors such as diet and lifestyle and other things that can significantly modify risk to radiation injury.

Next, please.

I think that as the scientific database

grows, there will be more and more need for critical risk modeling and dose-response modeling at tissue, organ, and whole-body levels. And again, I want to emphasize the very important analysis of factors that relate to dose, dose rate, and radiation quality on health outcomes.

Next, please.

Now where does all this ultimately lead us? In an ideal sense, we will be able to improve risk modeling, reducing uncertainties, and I think that this will be a very key application of the improved and greatly expanded scientific basis and framework, including again, I keep saying this, but it's very important to include the factors of radiation quality, dose, and dose rate. And the application of the results of laboratory-based studies and extrapolations to humans in establishing acceptable levels of exposure in both occupational and public settings will become, I think, more and more possible and more and more important as the database grows.

Next, please.

I think I've already said this basically that we need to use this improved scientific knowledge and framework to reduce the uncertainties in risk

estimates and improve radiation protection policies and practices, if indeed that proves to be an important thing to do. It's not absolutely clear that's necessary at this point, but as our knowledge grows, I think we will begin to understand better the limitations and possible need for improvement of our current policies, practices and regulations.

And ultimately, we want to resolve the question of whether, in fact, general conclusions can be drawn and predictive models developed for optimization of health protection in individuals that are in many cases chronically exposed to low doses of radiation that at or close to background levels.

Next, please.

I'd like to just now turn to some of the work recently done by NCRP that relates to low-dose radiation effects and then tell you about some near-term and longer-range plans that we have. I have already mentioned this important report published in 2005 on Extrapolation of Radiation-Induced Cancer Risks measured in Experimental Systems to Humans.

Statement 10 looked at applications of NCRP public dose limits that were published in 1993 in various settings including, for example, the use of radiation in homeland security applications where

members of the public could be irradiated.

We've published the report that was mentioned by Commissioner Lyons and I believe also briefly by Dr. Mossman on evaluation of the linear-nonthreshold dose-response model for ionizing radiation. That was published in 2001 and I must say that this report has a very different character than BEIR VII 7 and other reports that have been published that relate to LNT, because basically the conclusion was drawn in this report that the evidence available through the late 1990s, that database was not sufficient to reject LNT.

On the other hand, it didn't form a strong basis for accepting LNT as a sort of a general theory of dose response. So this leaves the issue more or less up in question and really points to the need for a significantly expanded scientific database for drawing conclusions on LNT and I think that that's -- that was a very appropriate conclusion at the time this report was developed under the chairmanship of Art Upton.

I believe that what we're seeing in the last few years is the evaluation of some factors that can modify dose response characteristics including, as I mentioned, non-targeted effects that need to be

taken into account and these were really not studied very much at the time this report was developed. So there's a need for re-evaluation in this area.

We've also published report on fatal cancer risk estimate that are used in radiation protection.

Next, please.

Research needs for radiation protection was published shortly after Report 116 which is perhaps one of the most cited -- undoubtedly one of the most cited NCRP reports on limitation of exposure to the public and occupationally-exposed individuals to ionizing radiation. Report 115 lay the groundwork for this report 116 in estimating risk for radiation protection and some uncertainties in those risk estimates. And then earlier, we had published an important report on RVE for radiation of differing qualities.

Next, please.

Now moving to some near-term activities after about a year and a half of planning, we have scheduled for next week a very exciting annual meeting on low-dose rate and low-dose radiation effects and models and that will be here in North Bethesda, literally across the street at the North Bethesda

Marriott Hotel, rather convenient location for those of you located in the Washington area because the Metro stop is right across the street. And those of you who have not yet registered or planned to come to the meeting, I would encourage you to do so. I think this will be a two-day meeting and we have many experts from the U.S. and internationally discussing important issues in low-dose and low-dose radiation effects, including an interesting dialogue or debate, if you will, between representatives of the BEIR VII report position versus the French Academy position. And that will be a debate moderated by Eric Hall. It should be very fascinating.

The program is available at this website and the sessions, in brief, will include discussions of molecular cellular tissue and animal radiation responses, human epidemiological studies. Dr. Land will be a speaker, thank you very much. And there will be a full session devoted to low-dose radiation effects, regulatory policy and impacts on the public. I think many of you will find that to be of great interest.

And then, of course, as always, we will develop peer review proceedings and they will be published the following year, hopefully early in the

year in the Healths Physics Journal.

Next, please.

Now on the path forward, we have in our strategic plan a very ambitious plan to develop a definitive report on Biological Effects of Low Radiation Doses and Implications for Human Health and Radiation Protection.

There is in an early stage now the development of a detailed outline of the report and we will be submitting proposals to potential funding co-sponsors for this report with an anticipated starting date in 2010 and we do anticipate because of the complexity of this effort that it will be a four-year effort. And we want to go well beyond the simple analysis of existing information and drawing conclusions. We want to create a framework for using this scientific information in moving forward in radiation policies, practices, regulatory issues and it's a very ambitious plan.

Next, please.

And we anticipate that this will involve a relatively large committee. At NCRP, reports typically have drafting committees with 10 to 12 scientists. We expect in this case we may have as many as 10 to 15 or even more scientists involved in

all major aspects of basic radiation research, epidemiology, operational public health radiation protection and public policy and regulatory issues. We want to cover all these bases with the depth of expertise in the scientific committee that will draft the report. And we will, of course, reach out and consistent with our charter, we will engage experts from the international arena and we would like for the report ultimately to be one that can be placed in both national and international context.

Last slide, please.

Finally, these are some general concluding remarks. I think everyone here would agree that understanding the biological and human health effects of low-radiation doses is a major scientific challenge and a frontier that must be crossed.

I think that commitment has been made and it's very excellent to see the commitment of government agencies, DOE, NRC, NASA, and others in improving the scientific database on which to cross this frontier. And as discussed in our recently issued program plan which you can read and download from the NRCP website, NCRPonline.org, the analysis of low-dose radiation effects is a major strategic area, a focal area of long-term effort by NCRP and as

always, we welcome input on our plans and our activities from interested scientists and regulators in the United States and worldwide.

And with that, I'll conclude my comments and would welcome any questions that you might have.

I believe I've left enough time.

CHAIRMAN RYAN: Plenty of time. We've got 15 minutes.

Dr. Mossman.

DR. MOSSMAN: Thank you. Dr. Tenforde, I was interested in your comments on laboratory animal studies and the use of systems biology. I think that that's clearly a path in a number of areas of life science where system biology and engineering concepts are used and I trust what you mean by that is working in the context of cells as networks with feedback controls and the like.

But another area which I think is just as important is to explore emergency biology. If you think of cancer as an emergent property of cells, then a whole vista opens up, if you will, in terms of understanding cancer not so much as a cellular problem, but as a much larger reflection of complexity. For instance, the classic example is the brain where we essentially define emergence as that

property where you can't predict brain function like thought processes, ideas, language, by looking at individual nerve cells. What you have to do is look at nerves in their collection in the brain. That emergent property, where you have these connections of individual units, that's the driver. And I think emergence becomes a really interesting concept that goes to the heart of this issue and I applaud the NCRP for taking this approach. I think it's very important.

DR. TENDORDE: Thank you, and I, in turn, will applaud DOE for supporting some very enlightening studies. I mean there's some excellent laboratory models now, for example, release of TGF beta from a few select radiated cells and the enhancement of kinase activity in the organized tissue and the resulting effects in terms of radiation response of the integrated tissue.

In a way, it's like propagation of signals and can be in many cases protective. Tissue responses may be collectively lower than individual cell responses studied in a petrie dish, for example. So I think and I like the term emergent biology because it does capture this idea in a very good way.

CHAIRMAN RYAN: Any other questions or

comments?

MEMBER WEINER:: This is -- I'm going to save most of my questions for the panel at the end, but several people have mentioned the DOE low-dose responses, low-does response research facility. And perhaps this is a question for Dr. Barcellos-Hoff and not for the two panelists, but how do you get DOE to talk to each other and to bring these scientific facts into their other activities? And maybe that's a question that the panel can speak to.

DR. TENDORDE: Well, actually, there's a member of the audience who could probably best answer that, but let me give you my 20,000-foot level view. I think that DOE has been very open in their communications. For example, in January, they held their seventh investigator workshop which was open to everyone and I think a number of you attended that. It was very enlightening. I mean all the investigators presented the results of their work. There were some overview presentations. I thought it was very open and very informative and from the statements made by Dr. Orbach, the head of the Office of Science, I think ultimately as the data base grows the intent will be to integrate that information into DOE policies and practices and the communication, I

think, with other organizations such as NRC has been very good and so hopefully this wealth of information that's being acquired in the DOE low-dose program will have a very broad effect across many government regulatory activities and policies and practices in the private sector, as well as in government.

So that's kind of my view as somewhat of an outsider, but I think two people here are better equipped to answer that and one, of course, is Dr. Barcellos-Hoff and the other is Dr. Noelle Metting, who is the manager at DOE of the low-dose radiation research programs. So I will leave it to these two ladies to respond.

DR. METTING: I'll just comment.

CHAIRMAN RYAN: Could you come to the microphone and tell us who you are?

DR. METTING: Hi, I'm Noelle Metting. I run the low-dose program. I'm in the Office of Science. And I think -- I'm not sure about your question, but I think you were also maybe implying that DOE doesn't talk to each other. And I talked with Health, Safety and Security all the time who is Andy Wallow and Ed Renier and I think that Office of Science, we're very interested in the excellent research which you will hear about when Mary Helen

gives her talk after the break. And I think that our health protection part of things, I think we're all trying to keep the communication open.

Thank you.

CHAIRMAN RYAN: Thank you very much. Well, with that, we're just a few minutes ahead of schedule, so everybody can enjoy a leisurely cup of coffee and we'll start promptly at 10:15. Thank you very much. We'll take a break.

(Off the record.)

CHAIRMAN RYAN: Everybody take their seats, please. Come to order, please. All right. Thank you.

Next on the agenda is Mary Helen Barcellos-Hoff. Dr. Barcellos-Hoff, welcome. Thank you for being with us.

DR. BARCELLOS-HOFF: Well, thank you very much for the invitation to speak today. I apologize for my tardiness this morning. I went to the wrong place, always pleasant way to start the day.

I'd like to begin by introducing myself just a little bit so you have a little bit of a notion of my background. I'm a Senior Scientist at Lawrence Berkeley National Laboratory. I've been there for over 20 years doing basic research in radiation

biology and breast cancer. I'm currently the Deputy Director of the Life Sciences Division, as well, which consists of about 50 investigators. And in 2007 or 6, Noelle Metting asked me to be the Chief Scientist for the Low Dose Radiation Research program, so I acted in an advisory capacity to Noelle, and to the program in organizing some of the research efforts. So what I'd like to do today is give you an overview of some of the research that's going on in this program.

Now, obviously, this is going to only be a snapshot because there are something on the order of 80 different projects currently funded, multiple investigators, and very interesting areas of research. And what I've decided to do today is to highlight some of the aspects of Radiation Biology that are probably considered to be a little bit newer. In fact, one of the things I'll do is highlight the publications that have occurred in the last couple of years in the very low dose region.

So with that, I'll try to operate everything. It's important to recall the goals of the DOE Low Dose Radiation Research program, was initially to, and remain, to understand the mechanisms action for low doses of radiation, to provide a scientific basis for radiation standards for the low dose region,

and to supply up-to-date information on low dose effects for researchers and the public. So one of the components of this, research program has always been communication, and many of you know Tony Brooks, who has operated in that capacity for nearly the entire reign of the program, which has been essentially nine years at this point in time. So I'm going to -- Tony also supervises the website for the program, so you can find a listing of all the projects that are currently funded projects, as well as publications and summaries.

It's important to recognize that over a nine-year period, the program has evolved. The initial focus was on low dose studies using single cell systems, which are essentially the standard of the science at the time. But what the low dose program stimulated was research on many previously studied underfunded phenomena; for example, adaptive responses bystander effects and genomic instability. And, also, initiated the use of new technology, which brought a new aspect to the biology of radiation effects.

One of the most fundamental ones that was initiated very early in the program by Sally Amundson and Al Fornace, as well as Nat Coleman and Andy

Wyrobek was the use of expression profiling in single cell systems, as well as in vitro, I'm sorry, in vivo by Andy Wyrobek. And you can take this expression profiling, where you're looking at 20,000 different genes at one time, and you're looking at snapshots as a function of dose, or as a function of time, and ask the question how do low doses and high doses different in their ability to change the transcriptional program of a given cell type. And so these are very complicated data sets, and I've summarized them very succinctly here on one slide, which is what I'll try to do with the other research studies.

At low doses, you can look for transcriptional profiles, look at the transcriptional profiles, and look for genes that are unique to those very, very low doses. And I believe in Sally Amundson and Al Fornace's work it was 2 centigrade was their low dose, 400 centigrade high dose. In Andy's work, he had a larger dose range. But you can ask this question and essentially make little Venn diagrams, and very simple analysis shows you that there are unique low dose genes that do not overlap with the high dose genes. There are genes in common, so these transcriptional profiles that change even response to a few centigrade.

These pathway analysis that you then take the gene transcriptional patterns and classify them according to what they have been recognized to regulate or be involved in processes for; for example, apoptosis or metabolic pathways. Suggestion that the transcriptional programs are differentially affected at low doses and high doses. And although there's some overlap across species or cell types, endothelial cells versus epithelial cells, transcriptional programs are differentially affected in vitro versus in vivo. So this tells you, to begin with, that low doses do elicit a different biological response than high doses at the very same instant as -- well, very shortly these are usually on the time course between one hour and twenty-four hours post radiation, and that the cell is able to respond to that radiation stimuli.

The research funded in these simple systems, mono layer culture, have motivated challenges to the biophysical paradigm of linearity because there is good evidence now from a variety of researchers that low dose radiation exposure alters the subsequent response to high dose. Now, I think, as pointed out by Dr. Tenforde, this is actually follow-up on work that was done in the 1980s at UCSF, but there's now a

better understanding of what that adaptive response might actually mean for the cell, and how it's executed.

We've also investigated how cell-cell communication is affected by exposure to radiation, so the fact that an irradiated cell can send signals to a non-irradiated cell has been extensively studied using the microbeam facilities at Columbia, as well as some work by Ellie Blakely at LB and L using the advanced light source.

Those radiation elicit heritable phenotypic responses because, of course, one of the aspects of radiation biology that we're concerned with is what are the persistent effects of radiation? What actually could have consequences when we think about the time frame under which cancer actually occurs, which is usually years in the case of Leukemia, to decades after radiation exposure in the case of many solid tumors, so we need to understand heritable. In this case, I don't mean generational, transgenerational, but just that a somatic cell can pass on a feature, a phenotype to its daughter cells. Genomic instability is a very good example of that, this occurrence of genomic instability in the daughters of irradiated cells. And there's a new

interest in epigenetics.

And, finally, one of the things that the program has initiated is a movement away from these 2D culture to understand how multicellularity modulates radiation responses and consequences. And there's a variety of different models systems in which now there's multicellularity, even between cell types, like fibroblast and epithelial cells can be used to now understand long-term consequences of radiation.

So as Tony Brooks likes to put this, he's a much more classical radiation biologist than I am, targeted -- essentially, we have to deal with this question of targeted versus non-targeted effects. In terms of targeted effects, we're thinking about the production of damage. Linear processes due to energy deposition, because we know that energy deposition is linear under most circumstances that we're considering.

In this case, we think the critical sensor is the DNA. And as a transducer into that heritable consequences, we're thinking about the genetic changes that occur, mutations that will then modify the behavior of cells for many -- for an extended period of time post irradiation.

In terms of non-target effects, one way to

characterize it, it's like a processing of this damage. These non-linear process, these tend to be non-linear because it's due to a signal cascade that's propagating an effect. We don't really know what the critical sensors are here, but we think they are proteins, could be lipids. Leave that question open. That should be a question mark after proteins. And the transducer here is the genome, not genetic sequence change, but rather how the genome is expressed. So change that are really epigenetic in terms of what we've characterized as modifications that affect the way the cell expresses its individual genome. And those can actually have -- those two aspects of the radiation biology need to be incorporated into our thinking.

So one of the ways I discuss this is to say, okay, there are radiation phenomena, like bystander effect, genomic instability. There are effects, so consequences that we can really read out in our measured assays, and then there's cancer risk. And that's, of course, what regulatory committees, and regulatory institutions are interested in, what is the cancer risk due to these effects. So another -- I'm just going to -- because there's a basis for the rest of the talk, I wanted to just make sure we're on

the same page for targeted versus non-targeted effects.

I showed you Tony's description, and my description is slightly different. One of the things I think of targeted effects are those that affect the irradiated cell, so this can be an autocrine effect, like apoptosis, the induction of apoptosis. That is occurring in the cell that was irradiated, or it can be a paracrine effect, so signals that are sent out to adjacent cells are bystander, what we call bystander phenomena, is, in effect, occurring in the irradiated cell, is sending out a signal that you can then measure responses to that signal in adjacent cells.

Targeted effects are thought to generate mutations in the progeny, and this is the mode of action by which you effect long-term consequences in a tissue or an organism.

Non-targeted effects I think can be classified as those that affect the progeny by altering daughter cell behaviors that affect, for example, genomic instability, or stability, or phenotypic stability. I'm going to give you some example of what I mean by phenotypic stability.

These are really through the perpetuation of persistent signaling cascades that mediate a

variety of different -- that are mediated by a variety of different types of signals, reactive oxygen, ROS, cytokines, lipids can be signals that can be perpetuated in a tissue. And these signals can affect surveillance for - and I'll get a little bit into that - phenotypes or cell-cell interactions. And these are thought to then modify epigenetic modifications of the genome versus the genetic change.

So I guess my take-home message from this overall talk is that radiation elicits complex biology, and it's probably not something anybody wants to hear, because it really is very complex biology. And for the biologists who are in this program, I think they've done a fabulous job of really digging into the underlying mechanisms. But what we really want to get at is how does this actually mediate carcinogenic risk? So these heritable non-mutation effects of radiation mediated through dynamic signaling, directed perhaps towards maintaining homeostasis, now can induce a variety of effects, including something I'm going to describe in more detail, selective apoptosis. And, as a consequence, this kind of biology may actually suppress or eliminate abnormal cells. And radiation is actually a very good tool for getting at this underlying biology

of a system of a tissue. And I'm going to give you a couple of examples of how this works, and then we're going to go into the more complex models.

So protection by selected deletion of aberrant cells. This is actually a very interesting phenomena, and it suggests a whole higher level order of organization in the tissues. But I'm going to briefly give you a summary of four studies that suggest that this actually does occur, and occurs in the cells of interest. So in Les Redpath's work, he's published a very recent paper on radiation research which shows that low doses suppress the transformation assay that he's used over the last 20, 25 years to demonstrate the linearity of transformation at high doses, but that low doses suppress th is transformation.

Georg Bauer, who participates in the program via his collaboration with somebody whose name just escaped me, who's co-funded by NASA. His name will come to me, I'm sorry, has shown that transformed cells can be selectively deleted by signals from normal cells, and that low dose radiation actually augments the efficacy of the normal cells in doing this. This was a paper on cancer research in 2007< Portess was the first author.

We have work in my laboratory that shows that radiation TGF Beta mediates the surveillance of genomically unstable cells, and Pam Sykes has shown in vivo that low dose radiation can suppress an endpoint that she uses for genomic change recombination in vivo. So how does this work? Essentially, what the little diamonds are supposed to represent are normal blue cells. Of course, I'm from California. That's a reference to Democrats, you know.

(Laughter.)

DR. BARCELLOS-HOFF: And abnormal red cells in the middle, and the idea is that the signals from those normal cells can actually cause those cells to selectively die.

Now this is some of the kind of data that supports that idea. Here's from Les Redpath, his transformation frequency, where you can see that, first of all, there's a J-shaped dose response curve, and these are very -- Les being a classical radiation biologist with a lot of experience with this assay, these are actually very extensively done studies, showing that at doses of lower than 10 centigrade, you definitely see a decrease over the baseline frequency of transformation in this assay. He suggests that there are three mechanisms that actually contribute to

this. One is a low dose radiation sensitivity possibly of G2 cells that may operate at above 10 centigrade, the induction of DNA repair, and up-regulation of antioxidants. And, interestingly, he has done this with very, very low dose rates, a few milligre a day, and shown that actually over the -- exposing the cells for a few milligre a day actually suppresses the transformation frequency overall in this assay.

So this very complicated slide represents the accumulation of mechanistic understanding of how normal cells can suppress or cause apoptosis in transformed cells that has been the work of Georg Bauer, and the fellow's name that just won't come to mind. The reason I show this slide is to show that, indeed, we're getting a more detailed understanding of how this actually operates. And that then leads us to understand why antioxidant levels are going to have a major impact on whether we see or don't see aberrant cells in a population, so I'm going to leave at this, but I recommend Georg's papers in this area.

So this carcinogenic risk is mediated by this complex biology, which you can actually show deletion of aberrant cells. But we can also show in the program that there's altered cell-cell

communication displayed by the progeny of irradiated cells that disrupts cell-cell interactions and corrupts these cell signaling networks. And this actually may promote abnormal cell phenotypes and genomic instability. So an example of this is work from Zhi-Mingh Huang, who published a paper in cancer research in 2006, that showed that small doses of radiation induced fibroblast phenotype called senescence.

Now, senescence is an interesting phenotype, and it's not that senescence is part of aging, where you -- the cells actually revert into a non-proliferative viable state. So what do I mean by a viable state? They're metabolically active, but reproductively inactive, something you all may be familiar with from the 1980s feeder cell layers in clonal assays were essentially senescence cells. So what Zhi-Min showed in this case was that this top dose, this is incidence of senescence using a beta-Gal marker, and here you can see that it's much more efficiently induced by single fraction, or fractionated exposures, 5 centigrade every 12 hours, versus a single dose of radiation. But both were able to elicit it, so this is very interesting in and of itself. But what he showed is that these senescent

fibroblasts alter the signals that send out. They alter, and particularly induce matrix metaloproteinases. This is just RTPCR showing that the senescent SF fibroblasts actually have more of these various and sundry matrix metaloproteinases, and then when you then mix these fibroblasts with epithelial cells, in this case MCF10As, you alter their growth properties. So here's a traditional monolayer where the epithelial cells are growing -- I'm sorry, this is a 3D culture, and you can see this is the normal way epithelial cells grow. And then in this 3D matrix, and if you put in these fibroblasts, senescent fibroblasts, and they grow in these kind of arborized fashion. And, indeed, if you do this now using confocal microscopy and immunoforescence, you can see the very different morphology that the cells, the epithelial cells assume when they're out with the senescent fibroblasts.

So you would think well, that doesn't look good. You know, you've changed the matrix, you've changed by the induction of matrix metaloproteinases. And, indeed, in our own laboratory we showed a variety of different effects that suggest that when you irradiate cells, human mammary epithelial cells, these are non-malignant epithelial cells, you can

alter the way the cells undergo morphogenesis when you expose them to another cytokine. Now, this is a cytokine TGF beta which we showed years ago was induced by radiation, so the question was well, how does an irradiated cell differ in its response to TGF beta versus a non-irradiated cell? And what we show in these 3D images here is that the normal appearance of these cells should be a nice little hallow sphere. And when they're irradiated, in this case with a dose of 2 Cy, which is a high dose, they undergo disruptive morphogenesis. But what's interesting about this is these are the progeny of the irradiated cells. These are ten days out post irradiation, and yet they remember the fact that they've been irradiated, and now response to TGF beta in a quite different fashion.

As it turns out, they also, when you expose irradiated epithelial cells, and we've done this with three different cell lines. And, in fact, we've also done it with non-cell line, cell strain, normal epithelial cells, we find that radiation predisposes these cells to now acquire mesenchymal cell markers. And that, actually, is a feature of EMT, epithelial to mesenchymal transition. This is a physiological event that occurs during development, but has also been linked to carcinogenesis. It's a

way of cells beginning to acquire motile capacity as they break away from their normal association with each other, and then begin to behave independently. And, indeed, when we measure motility, we can see a significant increase in the motility of these cells when they've been irradiated and then treated with TGF beta.

And, again, the important thing about this is this is the progeny of the irradiated cells, and that it persists for up to several passages in culture. So we're quite interested in well, okay, this is a negative, I would assume a negative effect of radiation. Now, I don't have on here is the dose response. What's fascinating about the dose response here, does it make any difference whether I irradiate them with 2 centigray, or 200 centigray. If I then expose them to radiation -- to TGF beta, they all undergo EMT, so that is a classic indicaci of a non-targeted effect.

So we have these negative effects and these positive effects, deletion, how might they play out? There must be some interaction. I think Tom Tenforde alluded to this in his review, so we can induce these abnormal cell phenotypes and genomic instability. Radiation can reduce signals that

counteract these events, which is actually going to prevail? So, again, taking these non-malignant mammary human epithelial cells, I wanted to show you an example of this.

Here we're using again two epithelial cells, and we're looking for an indicaci of genomic instability aberrant centrosomes. Centrosomes are the organelles that allow your chromosomes to segregate at mitosis, and if you don't have two, you begin to disperse your chromosomes in odd fashions, and develop very quickly, and then genomic instability. And we see here that radiation is actually -- appears to be acting in a very targeted fashion in inducing these centrosomes aberrations. It's a dose response that goes down to 10 centigray, but that's a significant different down there at 10 centigray, going up to 500 centigray.

And, furthermore, that's at the first passage. If we now take irradiated cells, clone them and look for instability in the clonal progeny of these cells, we can see that is occurring at doses at least above 10 centigray. Ten centigray didn't seem to persist in inducing this instability. And here we're measuring centrosome aberrations, and here we're using spontaneous DNA damage, these foci that occur in

pre-malignant lesions. You can see it's quite increased in this case. So that's a negative effect of radiation, but, again, here's another -- this goes back to this complexity. If you add TGF beta to these cells, then you can suppress those -- actually, you don't suppress the instability. You actually still generate the aberrant centrosomes, but three days after radiation, you begin to see an increase in apoptosis, so TGF beta induces this apoptosis, it induces it in p53 dependent fashion. And I can go through the details of this if anybody is interested in the experimental. But the important thing about this is that TG beta is actually selectively inducing apoptosis in the aberrant cells. And so when we look at the TGF beta treated population, we can actually see the genomic instability disappearing from the population, very similar to the effect that Georg Bauer, and Portez, and it will come to me showed in selective deletion of transformed cells. So you can have this operational, even in the same population. Right?

So there's been a significant interest in how you would incorporate these kind of processes into how we think about modeling radiation effects at low doses. Bobby Scott has probably been the foremost in

doing these kinds of modeling, putting all the pieces of information together. And he has a number of papers suggesting that you can actually model this protective apoptosis mechanism as an inhibitor of neoplastic transformation.

So while the evolution -- so I wanted to go back to this. So it's evolving, and the real current emphasis is to find these mechanisms that I was just talking about in the in vitro studies, and to integrate these single cell responses into complex multicellular systems, tissues and organisms.

So I think it's important to recognize that this is not unique to radiation biology, that tissues as a modifying influence on oncogenic events is quite well-established in the cancer biology community. Carcinogenesis, you can show with experimental systems that carcinogenesis is suppressed by normal tissues, that's promoted by remodeling tissues, like in wound healing, that malignant genotypes can be reverted to normal phenotypes by modifying the extracellular signal so you actually suppress their malignant features. That's pioneering work by Nina Bissell at Lawrence Berkeley Laboratory, who's been funded by the DOE for her entire career, practically. And that the micro environment, and here

we're being very inclusive, inflammation, neovasculargenesis, immune system, stroma is paramount to facilitating this neoplastic progression. So this was pioneered by Beatrice Mints, Barry Pierce, Judah Folkman and Nina Bissell, but recent studies appearing in cancer cell and in nature have shown that even oncogene models where you've deleted a primary immediate of genomic stability like p53, or you've treated with large T antigen which takes out p53 and RB at the same time. Even in those model systems, what you really need for cancer to occur is the cooperation of other cell types, so the oncogenic event occurs here, but it's the other cell types that actually allow that cell to express its neoplastic potential.

So what's important to recognize about radiation, that it affects the pathways by which tumors actually develop. It's not identical, necessarily, to spontaneous radiation. This is work from Alan Balmain's laboratory at UCSF where he showed the genomes of high dose radiation induced tumors are different than those of spontaneous null tumors. And, indeed, the genomes of these high dose down here, this is a comparative genomic hybridization which is showing you loss of regions of the genome versus gains

in the region of the genome. And here, the preponderance of the irradiated, the tumors from the irradiated animals incurred in this mix bag of amplification deleters and scrambled genomes.

Interestingly, even though the genomic changes were very different in these tumors, there was no difference in the latency of the tumors, so it didn't predict which tumors were going to come up early or late, an interesting aspect of this biology.

So what this is says is that radiation affects the pathways by tumors develop. Radiation actually altered tissue context and progression. In our system, we took mice and irradiated them, and then -- with a high dose here. And this is a published study in "Cancer Research 2000", that showed that if we irradiated with high dose 4 Gy, and the transplant a non-irradiated, non-tumorgenic epithelial cells, we, indeed, got tumors very rapidly in this model system. And we could extend the period between irradiation and transplantation out to 14 days, and still saw this increase in tumor frequency.

We've now expanded that study to ask, okay, that's a huge dose, what does it mean for low doses? And we essentially take advantage of the mammary gland, which develops post-natally. If you

come in and surgically remove that epithelium, you can transplant new tissue, it will grow out into a normal mammary epithelium, or you can use a genetically modified tissue, like p53 null mammary epithelium which has a propensity to develop into tumors. So we remove the epithelium at three weeks, we wait until the animals are 10 weeks old, and then we irradiate them now with 10, 50, and 100 Gy, we transplant them with this p53 null tissue, and then we wait for tumors to develop.

Under normal circumstances, these tumors develop in the mammary tissue develop at a year of age, and they're quite similar, actually, to humor tumors. They undergo DCIS type lesion, and genomic instability. And what we found, very surprisingly, was that a dose of 10 Gy at 10 weeks of age increased the frequency of tumors at a year of age, quite significantly, and interestingly, with no dose response, 10, 50, 100.

Now remember, we're not irradiating the epithelial cells. The epithelial cells have their own innate driver here. But what we're seeing is this drive promotion of the carcinogenic effect. More importantly, though, we can say we now have a better understanding about how that actually operates,

because if we now do this in a TGF beta compromised mouse, based on all the biology that we've done in the past, we can see that we can significantly decrease that effect of radiation. So we begin to understand the mechanisms that are operating to drive this carcinogenic potential.

It's even more complicated because one of the things David Boothman's program has shown is that radiation, very low doses of radiation, 10 Gy actually induces the expression of a protein called clustering, which is a pro-survival factor that suppresses TGF beta signal. So, obviously, as we get into this more complicated biology, we're going to have to begin to understand how these phenotypes and the genotype of an individual actually cooperate to initiate cancer susceptibility. So we, obviously, think cancer susceptibility is this complex array of different components, inflammation, immune response, stromal cells, metabolism, but that those then are affected by genotype, and they all interact. So how are we going to pull this apart?

Allan Balmain and Zhi-Mingh Huang have proposed a systems genetic approach for studying radiation carcinogenesis, where they now take a series of animals that they've created genetic diversity in,

and then they track a variety of different features so they ask this question down here, which is a network analysis to identify susceptibility genes, and these contributions from environmental factors, like lifestyle, or diet in the case of the mice. They don't have a very elaborate lifestyle. And they've shown, actually, that when they do that, they begin to see these phenotype networks that are associated with tumor resistance. And it's very interesting because it begins to pull out different contributions of cell types in terms of the ability of given tissue to develop a tumor. And what they have found is that if you look for lung cancer versus skin cancer, these phenotype networks shift, and so that again gets to one of the fundament questions in radiation protection is why are some tissues different than others in terms of their susceptibility to radiation?

So, obviously, we need new tools to describe this complexity that I've just dazzled you with, I hope, using systems biology. There's a genetic basis of sensitivity. This is looking for genetic basis, hindered by looking under the lamp post. You look for things that you know about, and then you say ah-hah, or you say oh, didn't work, so there are other ways of doing that where you have a

systematic analysis of diverse phenotypes in the context of genetic diversity, which you can have multiple outcomes, increases and decreases in susceptibility.

Then you use data integration of all these things, molecular phenotypes, genotypes, and biochemistry and functional phenotypes to actually pinpoint mechanistic contributions. So in our approach at the DOE Low Dose Program, is to initiate - to think about organisms using these excess haler endocrine, paracrine, juxtacrine signals to orchestrate damage responses of cells, and that actually it's a system, i.e., the tissue or the organ, or the organism that responds to the damage by radiation at the molecular level. So we have to better understand what the system control is of this cancer. And so appreciate the good words about systems biology, because that is an area that the DOE program has initiated actually two years ago in collaboration with the European community. We initiated the first set of workshops in systems radiation biology. Everybody has a different -- well, it's one of those new fields, so there are a lot of different definitions of systems biology, but I think Dr. Mossman and I agree on what makes systems biology

the most interesting, is this idea that what distinguishes a complex system from a merely complicated one is that some behaviors emerge as a result of altered relationships between the elements. And you can actually ask that question, is cancer an emergent phenomena?

And believe it or not, I had this slide in there before Dr. Mossman's comments, because this is an example that I always use. I study TGF beta, but this is a fascinating thing. Here's a mouse in which the TGF beta receptors were floxed in fibroblasts, only in fibroblasts. That means that there's a loss of TGF beta signalings in the stroma. And, as a result, you got epithelial cancer at six weeks within birth, and two different types, prostate and squamous carcinomas of the forestomach occurred in these mice so rapidly, just by deleting, and actually not even abrogating because this in a subset of fibroblasts, the signaling from TGF beta in a non-target tissue.

I think that suggests that cancer really is about the relationship between cells, and not a feature of the individual cell, per se. So we've put this together as integrative cancer biology, cellular events such be placed in a multicellular and organismal context, systems are maintained by

information, in which space, and time, and location are a factor. Radiation may actually give rise to emergent phenomena, i.e., small perturbations and many things that result in big changes like cancer. In order for us to actually then predict cancer risk, we have to understand how these actually intersect. And, if so, then dose rate may actually alter this in a non-linear manner.

So my final slide, and I apologize, I talked really fast, which I know I have a habit of doing, to try to cover the breadth of this program, and I haven't left very much time for questions. So what does it tell us about LNT? We think that responses to low dose radiation are different from high doses, and probably have different sensors and elicit different biology. Non-targeted are a mode of radiation action whose actions may prevail in carcinogenesis, and that's something that we need to understand better how they actually intersect with those targeted mutational mechanisms of carcinogenesis. And that predicting radiation effects actually needs to integrate biology occurring at different levels of tissue organization, so we understand how cell-cell interaction, cell communication across tissues and across organs

actually affect cancer in the organism, the human. Thank you. I'll take questions, and thank you.

CHAIRMAN RYAN: Thank you very much. Any questions? Dr. Mossman.

DR. MOSSMAN: What are the aspects -- I read this somewhere, and I can't recall who I should give this credit to, but there's on school of thought that says everybody's got cancer, but relatively few people have disease.

DR. BARCELLOS-HOFF: Right.

DR. MOSSMAN: And what they're referring to is this notion that in prostate cancer in males, in males who die 85, 90 years old, almost all of them have cancerous lesions, but they don't develop into overt disease. And my question is, in the context of emergent biology, what does this say about to what extent do the cells have to acquire emergent behavior in order to make the leap from just in situ disease to overt disease? Is cancer of the prostate, cancer of the breast where you would see similar kinds of epidemiologic data, are these model systems that you would want to look at in-depth, in terms of understanding emergence? The question that I've always had in the back of my mind, at what point does emergence occur? I mean, I'm sure it's not just a

discrete phenomenon, that it's something that's gradual, but at some point you ought to be able to see a tipping point, if you will. Any comment?

DR. BARCELLOS-HOFF: I think that's a very pertinent question, and it's something that's only beginning to be better recognized in the cancer biology field. We've been in a paradigm of reductionism where we're thinking about the oncogenic changes, or genetic changes that occur in the cells, and that's been very, very informative. It's pointed us in the direction of a lot of intrinsically interesting biology, and looking at those mutated cells. But, again, all these models I referred to, and I can give you the reference list where it shows large key antigen, oncogene doesn't actually operate to induce cancer of the skin unless there's a b-lymphocyte cooperation, and doesn't induce cancer in the pancreas unless there's macrophage cooperation. And you can eliminate those cell types, and you eliminate cancer incidence, so emergence is actually the key feature of cancer biology.

I started with the idea that my research group, we all walk around with initiative cells. It's just a function of breeding, breeding and inefficient repair mechanisms. But what actually drives clinical

disease is the ability to escape that normal tissue control, and so the studies that you're referring to, there was a -- there are autopsy studies published in Lancet, and, essentially, if you look at breast, if you look at prostate, if you look at thyroid cancer, 90 percent of all -- well, I would say just about everybody in this room has incipient thyroid cancer, yet, the incidence of clinical disease in a 50-year old plus population is one in 4,000. So it's very interesting biology, shift in our paradigm about what we're thinking about cancer.

CHAIRMAN RYAN: Allen, you have a question?

VICE CHAIRMAN CROFF: Yes. A question on, I guess, definitions. I think you clearly defined low doses on the order of a few centigray early on. What do you define as a low dose rate?

DR. BARCELLOS-HOFF: Oh, do we have a functional definition of low dose rate, Noelle? So our low dose is 10 centigray and below, low dose rate, I think anything delivered in less than the standard 100 rads a minute or thereabouts is maybe a little bit lower than that.

DR. METTING: Yes. Just for fun, I say one gray and one day is what, 1,000 times background

radiation, something like that.

DR. BARCELLOS-HOFF: But there's not a standard definition in the program. A lot of people use different --

VICE CHAIRMAN CROFF: Okay. But in the terms of dose rate, low is high.

DR. BARCELLOS-HOFF: Okay. Well, yes. We don't do our experiments on the order of human exposures.

VICE CHAIRMAN CROFF: Okay.

CHAIRMAN RYAN: One follow-up question to your discussion with Dr. Mossman. So where do we fit -- this is a novice question, so forgive me. Where do we put our emphasis then? We put our emphasis on the thing that keeps the thyroid cells from not expressing a cancer, or do we think about cells and what triggers the --

DR. BARCELLOS-HOFF: Well, let me put it this way. I've written a couple of proposals, I haven't had any luck with funding yet, but I'm going to persist in this idea. A really interesting thing about the non-targeted effects is epigenetic effects that are modifiable. Mutations you can't do anything about. Once you've been irradiated, you've got a mutation, you got it, but I don't know what your's is

versus mine, versus the person next to you. Right? And if we understand how normal tissues suppress carcinogenesis, then we can really support that under the circumstances that you're treating clinically, or if you have an accidental exposure to a population that the NIAID is interested in. But understanding how these two components intersect in terms of radiation I think actually, something I'll talk about in my NCRP talk next week, is the way I think about this, and I didn't put it in here because I'm trying to represent the program, is that the non-targeted effects actually do cooperate, and radiation acts as a carcinogen, primarily because of that cooperation. But we don't know how the non-targeted effects actually operate in the dose response fashion in intact organisms, other than to say they seem to act more switches. Right? On and off, like my 2 centigrade versus 200 centigrade, which is on or off. And, therefore, then it becomes critical as to what turns the switch on, so what is the threshold.

CHAIRMAN RYAN: Thank you. Good luck with your proposals. Thank you very much. Without further ado, I'll introduce Dr. Bernard Le Guen, who is the President of the Commission on International Relations, and President of the Research and Health

Section of the French Radiation Protection Society.

DR. LeGUEN: Well, just before to begin, I would like to have a comment. You know, radiobiology is a long story, and before about the explanation on cancer, we talk about cells disease. Today, we talk much more on tissue disease or body disease, and that's why -- and beyond your question, there's another comment. It's the problem of extrapolation from in vitro study to in vivo study. That's why it's so difficult. So thank you for your invitation.

So I will try to explain to you in 45 minutes the estimation of the carcinogenic effects on low doses of radiation, and particularly about the French Academie reports, because I am one of the co-writers of this report.

Over the past 20 years, the French Ministry of Research has asked the Academie des Sciences to carry out a critical review of the available data regarding the effect of low doses of radiation has. And in 2003, the two Academies, the Academie of Science and also the Academie of Medicine decided to join the effort for an update of two main topics. So those carcinogenic effects relationships, and the carcinogenic effect of low doses. So a working party was set and a report was accepted after

a few modification, and continue, today we are in 2008, and continue to work on these topics, I'm sure in next years we'll continue, too. So this report was released in March 2005.

So another remark about the Kenneth Mossman presentation this morning. The main problem for both medical and non-medical uses of radiation is a possible carcinogen risk associated with small doses of ionizing radiation. And these eventual risks are also of great importance with regard to natural irradiation. We are today in the ACNW meeting. For example, it would be of great value to assess the risk of lung cancers caused by various radon concentrations in the air at home, or at work, and whether there is a practical threshold below which the risks become negligible. Because a narrow estimation of the risk associated with exposure to radon at home could lead either to overlooking serious public health problems given the number of people exposed, or conversely, to insuring considerable pointless expense in order to limit such exposure. So, again, the problem of management of risk.

So the assessment of carcinogenic risk associated with doses of radiation from 0.20 to 50 is based on numerous epidemiological data. However, the

doses which are delivered during medical x-ray examination, or the dose received by nuclear workers, or in regions of high natural background radiation are much lower, from 0.1 mSv to 20 mSv. So the evolution of the cancer risk of low dose is of great importance in medicine, but also in nuclear.

Here you can see the radiation of more than 50 person over 10 years of the average individual dose in mSv. So nuclear energy delivers about 1 mSv per year to each person in France, in the vicinity of stations so dose can reach 50 mSv per year. People working in the nuclear industry receive an average of 1.5 mSv per year, with a large increase over the last 10 years due to CLR process. So the impact on health varies widely, depending on how it is estimated between zero impact, and several dozen cases per year for the entire French population. And between zero and a few little cancers per year for workers. Next one.

Well, following small doses, no excess of cancer has been detected with epidemiological studies. However, the lack of an increase does not excludes the possibility of a small concentration of cancers. Solid tumors, and leukemia have spontaneous incidents and varies according to lifestyles. Possible increase

in this incidence following irradiation is relatively low, so the study must have sufficient statistical power which requires large cohorts. But in large population, confounding factors are present, and they must be taken into account by appropriate statistical measures, because their specific affect can be much greater than the effect of radiation. Of course, you know tobacco consumption, but here you have also an example. With the increase of the incidence of cancer simply due to the aging process. Next one.

All the difficulties must be taken into account with epidemiological studies, cosmic radiation, external exposure due to earth radiation, but also internal exposure due to drinking water. Next.

Following exposure to low doses, epidemiological studies have no evidence any significant effect, because either there is no effect, or the effect is too small to be detected by such studies. These results, which are sometimes described as negative results, are useful because they help to assess the upper limits of the potential risk, and can be included in meta-analysis. Next.

Moreover, some important new facts have emerged, such as feasibility and value of studies

comparing the morbidity and mortality in regions with high and low levels of natural irradiation, but similar lifestyle. Next.

So the question is what is a good relation between dose and effect? At low doses, you know, and we talked a lot about different possibilities, and you know that the regulator has taken the LNT curves. Next. Continue. And it's always interesting to have a look at the long history of radiation protection.

The LNT model was used in 1956 by Russell to evaluate the radio induced mutations germ cell line in the mouse. It was introduced between 60 and 80 for the purposes of regulation in radiation protection with regard to all mutagenic and carcinogenic effect in humans.

In the 60s, the International Commission of Radiation Protection introduced it because it alludes to the addition of second shell irradiation delivering low or high doses of radiation received by an individual, whatever the dose rate and the fractionation. Tests which really simplifies accounting in radiation protection. However, gradually LNT was interpreted as a meaning that the carcinogenic risk is proportional to the dose, and that even the smallest dose induces a cancer risk.

Next.

So the LNT has been used for assessing the effect of low and very low doses. This procedure has become the norm in many radiation protection cycles, but the validity of the LNT has been challenged over the past decade for two main reasons, and we talked about that. We talk about the meta-analysis of the animal data have shown the absence of any carcinogenic effect of doses below 100 mSv. And, also, with Mary Helen, about scientific progress as reveals the complexity of carcinogenesis, and the diversity of effectiveness of the responses of a cell to radiation.

Indeed, a cell is not passively affected by the accumulation of lesions induced by ionizing radiation. It reacts through several mechanisms. The LNT model postulates that the cell reacts the same way regardless of dose rate, and dose, which implies that the probabilities of death and mutation per unit dose, and the contribution to carcinogenesis of each physical event remains constant irrespective of the number of lesions in the cell, and the neighboring cells. This consistency amid several hypotheses -- you can see it's a different hypothesis here, and these hypotheses are not consistent with current radiological knowledge which shows that cells do not

remain passive when they are irradiated, either by solar UV, or by ionizing radiation. Moreover, intercellular communication system inform cell about the presence of neighboring cells. Next.

So using recent molecular approaches radiation impacts -- so DNA lesions in cells and tissue has been measured down to very low doses below 1 mGy, and this allowed to get important new insight in the effect on cells and tissues that was formerly inaccessible in that range. It is not surprising some results obtained change our understanding of ionizing radiation induced effects at low and very low doses. Next.

So radiation risk evaluation are concerned with radiation effects that lead to long-term genetic effects such as genetic alterations or mutations, general stability, malignant transformation, and cancer.

In the case of low inner transfer radiation, such as photons or electrons, when the whole body is exposed to 1 mGy, each cell is on average grows by one electron. Each electron induces in average, two DNA lesions. This initial effect is proportional to the dose, and is direct or indirect consequence of a high transfer of energy within or

alongside a DNA molecule. Oxidative stress stimulate enzyme systems that detoxify active spaces of oxygen and induce synthesis of enzyme that destroys them. In parallel, oxidative stress also activates neural signal pathways, so about DNA damage, it is not the initial physical chemical events that change, but their outcome. So defense mechanism is induced in a cell depend on the degree and the nature of the cellular damage.

The defense mechanism induced in a cell depend on the number and nature of cellular damages. The number of double-strand breaks caused by 1 Gy dose has been estimated to be between 30 and 40. In contrast, the number of double-strand breaks of endogenous origin produce in each cells by the oxidative metabolism remain controversial. It has been estimated to be eight per day and 50 per cell cycle by Vilenchik who estimates that about one percent of single-strand break turning to double-strands breaks, and there are about 3,000 single-strand break per day. It's interesting to note that the double-strand break caused by natural irradiation of 2 to 25 mSv per year only seems to correspond to a very small fraction of the total number of double-strand breaks, less than 1 per 1,000. Next.

In recent years, some new findings have alerted radiation biologists, K-shell activation by low LETs ionizing radiation, the emission of two energy Auger electrons can induce complex DNA damages, like DNA double-strand breaks. Also, very low energy electron, below 10 electrovolt can give rise to double-strand breaks, and high LET and low LET radiation can give rise to locally multiply damaged sites in DNA.

In the light of theoretical considerations and in vitro experimental studies, it has been proposed that ionizing radiation could induce multiple localized lesions consisting of two or more DNA lesions form within one or two helical turns of the DNA molecule at the end of the single radiation track located within a distance of less than 20 base pairs within the DNA. These very complex lesions are considered to be responsible to a large extent for the genotoxic effect of radiation.

LMDS are thought to be responsible for most genotoxic effects such as lethality, mutations, chromosome aberration, cell transformation, and cancer, said BEIR VII. However, the number of such lesions induces in a cell and their impact have not yet been clearly established. Much work has been done

in recent years to better define and quantity these lesions in irradiated cells, and to determine their biological consequences. However, LMDS are difficult to quantify human cells, and their number, if present, is quite limited. Most of cluster lesion make consist of complex double-strand breaks. In most cases, cluster of lesion are found refactory to repair. But those lesion are lethal, and non-mutagenic. That is unlikely to contribute significantly with mutagenic and carcinogenic risk of ionizing radiation for humans. So differences in the efficacy of the protection system are supported by various experimental and clinical data, but with equal doses the mutagenic effect varies markedly with dose rate. When the dose rate increases, the mutation frequency after having passed through a minimum increases strongly.

On this figure, you can see indication of double-strand breaks is reduced after exposure at low dose rate, so 0.5 Gy/min, as compared to exposure at high dose rate, 3.5Gy/min, so another definition, we talked about that before. You know, at equal dose, when the dose rate is low, the number of lesions simultaneously present in the cell is limited. Conversely, a high dose rate leads to the simultaneous

presence of a large number of lesions, which interferes with the coordinated action of repair systems, and also increases the probability of error-prone endjoining due to the presence of several double-strand break in a restricted volume.

Conversely, a limited number of lesions induces reversible arrest of the cell cycle, which enhances repair. A high amount put on to cell cycle average which can lead to apoptosis. And that's very interesting to note that in this slide you can see the induction of double-strand break in the repair-deficient Chinese hamster ovary shows an absence of dose rate effect on the induction of double-strand break due to the absence of repair in the cell line. So the effectiveness of DNA repair systems is evidenced by the lack of any reduction of the mutagenic and lethal effect as the dose rate decreases in the cell line, in which the DNA repair system are impaired. This lack of repair is also observed when yeast or mammalian cells are exposed to gamma rays at zero degrees Celsius, a temperature that inhibits the repair enzymes. The number of DNA double-strand breaks is identical at high and low dose rates, whereas, at room temperature it is much smaller at the lower dose rates. So the dose rates determines the

average time interval between physical hits. It has a major effect on the cellular response, so biological effects of irradiation lethality, mutagenesis, chromosomal aberration, and so on decrease as the dose rate decreases. So biological effect of irradiation depends on two distinct factors, the greater efficacy of the DNA repair at low dose rates, and the probability of damaged cells to be eliminated by death.

DNA damage signaling via ATM protein and H2A phosphorylation was found to be absent at a very low dose rate, 1.5 Gy/min, and associated with lethality but present at a slightly higher dose rate, 4.16 Gy/min, and at high dose rate 750 Gy/minute. So Collis and collaboration has shown that at a very low dose rate, double-strand breaks are recognized by detector proteins, but not repaired, because of an absence of activation of ATM, so an absence of DNA damage signaling. So signaling of DNA damage double-strand break depends of dose rate. At higher dose rates, DNA damage signaling is taking place. There appears to be a tracer for ATM dependent signaling and DNA repair.

Dose rates changes affect genes of radiation induced apoptosis but not genes of cell

proliferation, because exposure at very low doses levels of chronic radiation may cause more cell killing than that estimated from extrapolation at higher doses. Next.

For some cell types, mortality is very high per dose unit as the onset of irradiation during the first 200 mGy, then falls to a very low level before increasing again. This low level hypersensitivity is observed in many cell types leading to a high mortality rate per dose unit for doses of less than a few hundred mGy of low LET radiation. This variation in the mortality rate per dose unit indicates that the cellular defense mechanism against lethality, which initially show little efficacy become more effective during irradiation. And this initial hypersensitivity eliminates damaged cells with mutagenic potential after low doses of radiation. Next. So variations in DNA repair efficiency, different for dose rate, but not only, depend also on genetic background, depend on the different status of cells and tissue, and depends on age. Next.

So DNA damage signaling is necessary for DNA repair. Deficiencies in DNA repair are associated with cancer. Deficiency in DNA repair are

associated with individual hypersensitivity, and may cause premature aging neurodegeneration, and immunodeficiency. Next.

Well, I didn't prepare my slide with Mary Helen, but I have exactly the same example with another publication. Let me present to you an example with normal human skin cells. Specific molecular responses are triggered in cultured primary keratinocytes from adult skin at low doses, 10 mGy, or at high doses, 2 gray of gamma rays. Using DNA microarrays, it is shown that among 850 modulated probes, the expression of 214 are specifically modulated by low doses, 10 mGy, and 370 genes are specifically modulated by high dose 2 gray exposure. Low dose specific genes, 140 known genes, include mostly genes of homeostasis, cell communication, signaling, membrane, cytosketelon, RNA and protein synthesis, chromatin, energy metabolism, stress, cell death and transport but rarely DNA repair genes. Conclusion, the radiation response at low dose is rather specific, and quite different from that obtained at high dose. Next.

Another experiment on yeast at very, very low dose, studies carried out with the DNA micro array techniques, and yes, show that continuous irradiation

at a dose rate of 20 mGy/h so lower than the level of irradiation that causes a detectible (lethal, mutational) biological effect is enough to change intercellular signaling without modifying the genome to activate or inhibit numerous genes involved in the general metabolism, and in defense against ionizing radiation. Such mechanism bring into play defenses at dose of the same order as those due to natural irradiation. It's possible to reduce or prevent its potentially harmful effect. Next.

So when we compare repair double-strand breaks it depends ionizing radiation dose, and the answer is not linear, and you can see an absence of repair at 1.2 mGy in this experiment. When a large number of cells in the same tissue are killed or damaged, repair and proliferation mechanism are triggered, which are intended to protect the integrity and function of the tissue. By means of intercellular communication system, the reaction of the cell to irradiation, therefore, seems to be influenced by the number of cells affected. Some DNA repair system are activated by low doses of ionizing radiation, but associated with apoptosis. So the disappearance of damage cells seems to result from the rate of activation of repair system, which leads to an absence

of repair, and to cell death, and from high fidelity repair from constitutive systems. When only a few cells are damaged, this elimination strategy seems to be optimal because repair system are sometimes error-prone and can potentially lead to the emergence of pre-cancerous and subsequently cancerous cells. Next.

So to summarize with another publication, low dose radiation increased phosphorylation of proteins involved in the more general biological processes, and not specific genotoxicity-related responses. And high dose radiation increase phosphorylation of proteins involved in the cells signaling pathways and apoptosis. Next.

So the cell response, therefore, seems to depend on the dose, the dose rates, and the cell type, and without doubt on the concentration of damaged cells. So extrapolation from high dose effects to low dose effects do not respond to the actual rate of living cells to ionizing radiation.

DNA damage or modification of the chromatin are detected by signaling proteins. The activity of these proteins is modulated by the number of lesions, and by messages from neighboring cells. These protein activate phosphokinase transmitters, in particular, the protein encoded by ATM gene and the

ATR genes. In turn, these transmitters modulates the action of proteins involved either in cell cycle control, so the interruption of which promote repair, DNA repair, or in triggering apoptosis. So, hence, the cell reacts to irradiation by a global and integrated response that involves several enzyme systems which governs the efficacy of DNA repair, and the probability of cell death, of senescence eliminating damaged cells. DNA induced damage is constant per unit dose, the probability of mutation is modulated within a framework of what could be called a strategy of least cost.

Consequences of the tissue level cells are usually embedded in tissue. At very low ionizing radiation doses ionizing radiation damaged cells do not survive, and are eliminated. Tissue function are not compromised. At higher doses, a substantial fraction of cell damage, tissue function cannot be any more assured except if cellular damage is repaired, and cells are allowed to survive even if mutation and fulfill some of the tissue function. This, however, may also allow genomic instability, malignant transformation, and cancer to occur. Next.

So all the radiobiological phenomena which contradict LNT hypothesis, and we saw that before with

bystander effects, low dose impaired sensitivity, adaptive radiation response, I tried to win some time because Mary Helen showed that before, so tried to respect my time. Next.

But I would like to talk about adaptive radiation response. The existence of an adaptive response is now well established. The first low dose of radiation leads to a reduction of the mortality of organisms in vivo. The number of mutation and the rate of neoplastic transformation caused by a second irradiation carried out during subsequent hours or days. This inducible and transient protective effect seems to occur also in humans, and appears to result from a stimulation of cell defense and DNA repair system. At the cellular level, an increase in lethality may be observed as a result of apoptosis and delayed mortality due bystander effect. One hypothesis is that Genotoxic physical agents, UV and ionizing radiation, were present when life appeared on earth, and very likely at that time irradiation was generally more intense than today. Recent work has revealed the efficacy and multiplicity of defense mechanism which developed during evolution, many of the systems are targeted against reactive oxygen species produced by irradiation. Next.

And that's very interesting, and also Mary Helen talked about that. Recent works shows that low doses selectively remove transformed cells in co-culture by stimulating intercellular induction of protective pro-apoptotic process mediated by reactive oxygen and nitrogen species and TGF beta that eliminates cell with genomic instability. These may relate to positive effects of low dose ionizing radiation, radiation hormesis, showing a reduction in transformation frequency after low doses. The low dose saturation of radiation induced apoptosis in pre-transformed cells as potential implication for the effect of low doses of ionizing radiation on the naturally occurring anti-cancer defense mechanism. These effects are not compatible with the LNT model. Next.

Also, non-targeted effects of ionizing radiation might be interrelated and possibly have a protective role under in vivo consideration by promoting differentiation. This effect might relate to adaptive responses because of increased non-targeted differentiation in irradiated samples. Based on this experimental data, Berlyakow and collaborators proposed as a main function of non-targeted effects, the decrease of the risk of carcinogenesis in a

multicellular organism exposed to oxidative damage. Next.

About bystander effects, bystander effects can be beneficial or detrimental depending on the cell type and the range of doses analysed. So it is possible that bystander effects play a role below one to 5 mGy where few cells are actually damaged by irradiation. Are there bystander effect in vivo and in radiation therapy? I don't know. What about abscopal radiation effect? Yes, they may arise, but they need to be fairly defined before assuming that bystander effects radiation induced carcinogenesis. Next.

Well, a new concept in radiation biology emerge. Cells respond even very low radiation impacts. The response to ionizing radiation involves activation of defense mechanism, maintenance and death pathways. Cell react differently at high and at low doses, or dose rates of ionizing radiation. The ionizing radiation response involves activation of signaling pathways, and different genes families are activated. At low doses and dose rates a multitude of parameters influence the cellular fate, whereas, at high doses, and doses rates cellular responses are more directly channeled towards survival, genomic

instability, and malignance transformation of cell death. Next.

Radiation induced carcinogenesis is considered a multi-step process, and is initiated DNA damage and genetic alterations in somatic cells which after stepwise promotion and progression will cause cell transformation, and the development of cancer. It is strongly dependent on the cell and tissue microenvironment. These interaction are ongoing, and play a crucial role in tissue transfusion during embryogenesis, growth, and the repair of damaged tissues. The conventional model acknowledges that by a series of stages modification of the genome confer a selective advantage on the cell during carcinogenesis. We know now that this phenomena cannot be described by a linear process during which successive genome damages accumulate at random. Carcinogenicity is a phenomenon that cannot be reduced but to a series of mutations due to independent stochastic lesions occurring in the same cell. Indeed, it affects all aspects of genome function. The association of genetic and epigenetic mechanism is now well-established. The process leading to the transformation of the normal cell into a tumor cell is interpreted as a Darwinian selection process

determined by a series of genetic or epigenetic events, each or which gives the initiated cell a selective advantage in terms of survival or proliferation within the tissue to which it belongs. The cells, the tissue, and the body all have defenses against carcinogenic processes, and these must be successively overcome for carcinogenesis to occur. Cell death, therefore, appears to be a main safeguard mechanism, in particular programmed death or apoptosis. Next.

So cell tissue and body defenses against cancerization, so we saw all together the intercellular system and cell proliferation control is important. Death of initiated cells which has escaped to a safeguard mechanism, apoptotic response, are also important. Control by neighborhood cell, secretion by neighborhood cells and stroma of regulation factors, inhibitor of proliferation, bystander effects, exchange of signalization, and regulation molecules by intercellular gap junction are also important.

And I would like to focus on the last one, mechanism of immunosurveillance. Perhaps, this is the answer to the question of Kenneth Mossman before. Because at the whole body level, escape of the immune surveillance responsible for eliminating tumor cells

is based on selection of cells that are capable of escaping from it. For instance, by the low self expression of the competence of the major histocompatibility complex. Carcinogenesis may be facilitated by a reduction in human defenses when a large segment of the body has been irradiated. So, in conclusion, next -- why LNT may be useful for the administrative organization of radiation protection. It's used for assessing carcinogenic risk induced by low doses, such as those delivered by diagnostic radiology, or the nuclear industry, is not based on valid scientific data. All the data shows the lower effectiveness of low doses, and dose rates. Moreover, the quantitative discrepancy between the results of the various epidemiological and animal experiment studies supports the view that there are several dose effects relationships rather than only one, and perhaps would be the answer to your question before.

Their parameters depends on the type of cancer, the type of ionizing particle, radiation dose, dose rate, fractionation of irradiation, species breeding line within the same species, target tissue, volume irradiated, age, and individual sensitivity factors. Epidemiological and biological data are compatible with the existence of a threshold but

cannot today demonstrate its existence, or assess its value somewhere between 10 and 60 Msv. The concept of collective dose can be used for alleviating the cancer risk in a population. So my last slide, to say if you are interested by those topics, you can find an English version of the Academie Medicine and Science report on the web line. Thank you for --

CHAIRMAN RYAN: Thank you very much, Dr. LeGuen. Any questions or comments? We have five minutes. Let's see. We'll start with Dr. Puskin.

DR. PUSKIN: Thanks. That was very interesting. I would just like to be a little bit of the devil's advocate here. One of the things you cited was the Lobrich and Rothkamm study, which showed a threshold below which there was no repair. I'd just like to mention that a lot of people question that study in terms of the methodology, the assay that was used, that it was unreliable. And also, when they did a later study with patients who had been -- humans now had had CT scans at somewhat higher dose than where the threshold was, but not very high, on the order of 1 centigray, they found there was repair in the human body. So there's a lot of questions to the importance of that study.

Then a second thing I'd mention is that -

and it's also something in Mary Helen's talk, that there's a difference in how cells react to high doses versus low doses, it's certainly true. But we already know that cancer is caused at 10 centigray. What we're really interested in is the difference between lose doses and very low doses. And my understanding is that Dr. Lobrich's study, he didn't find any difference there that he could show. And then the immuno surveillance, I'm not sure exactly what you're -- I missed exactly what your point is, but it's pretty clear that immuno surveillance may not be perfect, even at the lowest doses, or at least it does -- we know that people get cancer without any excess radiation, so whatever -- no matter how low the dose, it appears that the immuno surveillance is not able to pick up all these pre-malignant cells, and stop them from becoming cancer cells, unless it somehow works for radiation differently than everything else. But maybe your point was that radiation could stimulate the immuno surveillance.

DR. LeGUEN: You know, I'm a radiation oncology physician, and one of my masters was Georges Mathe, and Georges Mathe during the 60s was thinking a lot about the link between cancer and the human response. And at this time he has no tool to -- but

he was his idea. In fact, I'm very happy to see now a lot of experiment with new molecular biology. It's a new tool. To be -- we believe a lot in the immuno surveillance. I think one of the response to the question to Kenneth Mossman, if you take prostate cancer, and we know that some people will have a very aggressive cancer, and others not, one of the explanations is to say well, one moment, there is something in the body that we have - I don't know - a cell, will become much more aggressive because it's not under control, under pressure of the immuno surveillance. And we know when we have a deficit, when you have a disease, and immunological disease, we have much more risk to have cancer than if we have not this kind of disease. So the human pressure is very important. It's one of the parameter, it's not only. That's why I say, it's different parameters, and with those natural sensitivity, with also the different tissue sensitivity, the neighboring cells, the tissue. That's a wall response, not one response.

DR. PUSKIN: I mean, it's unquestionable that the body, including the local environment could suppress a cell that's mutated from becoming a cancer cell. The question is, is the probability of it becoming a cancer cell any different at very, very low

doses, compared to 10 centigray, and --

CHAIRMAN RYAN: Let me get Dr. Land's question before we break for lunch.

DR. LAND: Oh, I was just going to comment that in your conclusions, your sum-up, it seemed to me you make a very good argument against use of high dose excess relative risk, or excess actual risk per gray being applied at very low doses. But it's not an argument -- it doesn't seem to me that it necessarily leads to a threshold, it leads to a DDREF. And the DDREFs are used routinely, it's accepted the idea. And so the question, it seems to me, is more like what is the DDREF, rather than --

DR. LeGUEN: That's it. That's a very good question. You're right. I agree with you. So the problem is the assessment of the risk and the DDREF. I fully agree with you. And one of the -- the question for the future is this, if we can assess at the very low dose, the real risk associated with DDREF more precisely than today. That's the problem. You're right. You're right.

DR. LAND: You know it's higher than two, though.

DR. LeGUEN: Yes, yes. Yes, I know.

CHAIRMAN RYAN: All right. With that, we

will close our morning session and reconvene promptly at 1:00.

(Whereupon, the proceedings went off the record at 11:50:08 a.m., and went back on the record at 1:05:05 p.m.)

CHAIRMAN RYAN: Come to order please.

All right. Thank you very much. We'll open our afternoon session and the first speaker this afternoon is Dr. Charles Land from the National Cancer Institute.

Dr. Land, welcome and thanks for being with us.

## OVERVIEW OF UNCERTAINTIES IN THE ESTIMATES OF LOW-DOSE EFFECTS

DR. LAND: Well, I guess this will be fairly self-explanatory.

The background for this particular talk is ultimately quantitative uncertainty analysis which I discovered as a well-established field of study and it is the really basis for what follows. And NCRP Commentary No. 14, "A Guide for Uncertainty Analysis and Dose and Risk Assessments Related to Environmental Contamination" I think is where the NCRP first became involved and basically it's the evaluations of risk are based on a combination of statistical and

subjective sources of uncertainty. That's the -- of it.

And then where I came in working with Warren Sinclair and Andre Bouville on NCRP report 126, "Uncertainties in Fatal Cancer Risk Estimates used in Radiation Protection" I think it was very illuminating to me. I didn't know anything about this before from the side of a statistician. But it really does develop into what I think I call a "New Paradigm" for expression of radiation-related cancer risk and for dealing with what we don't know well but can't ignore, things you just can't leave alone.

Some examples of New Paradigm examples, there is the report of the NCI-CDC Working Group to revise the 1985 NIH Radio-epidemiological Tables in 2003. There's ICRP Report 99, "Low-Dose Extrapolation of Radiation-Related Cancer Risk" and then something I wasn't involved in which was BEIR VII.

All of these used this general approach. The way it works is first you do statistical analysis of epidemiological data and the new wrinkle is that they are corrected for dosimetric uncertainty in the data that underlie this analysis. And it yields, this analysis yields, estimated excess per Gy if linear with confidence limits or statistical uncertainty

distribution. And then takes a quantitative uncertainty analysis approach to necessary, but uncertain, assumptions needed to apply the statistical information to risk analysis.

And I'll just make a couple of technical notes which are kind of dry, but in all this risk is an actuarial concept. I'm not talking about personal risk. I'm talking about the thing that you can actually estimate and verify on the basis of population rates and you apply to an individual, if you do, as a property of a population to which he or she is assumed to belong. Okay. I don't know what anybody's, any individual person's, actual risk is.

Excess risk can be expressed in relative terms as a multiple of baseline. That's Excess Relative Risk. Or absolute risk as an addition to baseline, that's Excess Absolute Risk and they are related to -- Excess Absolute Risk is the baseline to sometimes the Excess Relative Risk and Excess Relative Risk is the Excess Absolute Risk divided by baseline.

Actually, the age-specific graphs for EAR and ERR are essentially the same. There's just a difference in scales. So I'll use them interchangeably.

This is an example of statistical

uncertainty. It's a long normal uncertainty distribution for all solid cancers from the life scan study population, all survivors. This sex-average excess relative risk for GY at age 50 after exposure at age 30 allowing for dosimetric uncertainty and I'll be building on this particular example throughout the talk.

Other sources of uncertainly, one is transfer of risk estimates between populations which is not a big problem for all solid cancers combined which is the subject of the previous slide. But it can be a big problem if the baseline cancer rates differ greatly between populations. I think stomach cancer is probably an extreme example. The stomach cancer rates in Japan are about 12 times higher than those in the U.S. Though it makes a great deal of difference whether you transfer the excess relative risk per Gy to U.S. or the excess absolute risk per Gy from Japan to the U.S. It's a 12 fold difference. It's a big deal.

There is surprisingly little information on how to do it because you need data on radiation-exposed populations in both countries and there's very little on stomach cancer, radiation and stomach cancer in the United States. There's some, but not very

much.

And one approach to this problem might to treat everything in between these two extremes as equally likely and incorporate the uncertainty into the estimation process. Take the excess relative risk times probably (p) plus (1-p) times the additive transfer where p is uniformly distributed between 0 and 1. That's what we did. Well, actually we did something a little bit different, but I'm just going to use it for example.

And here you see this one is what you would get if you took the multiplicative transfer to the U.S. population. This is what you'd get if you took an additive transfer. In your handouts, I did all this in log scale, but I think I wanted to save some time here. So this is arithmetic scale and this complete ignorance is somewhere between multiplicative and additive is this distribution here. It treats everything as equal.

For all solid cancers combined, the Japanese rates are a little lower than the U.S. rates. The difference is far less than for stomach cancer, but it still requires some adjustment.

And so again, I'm going back to this example of statistical uncertainty for all solid

cancers and this is a Monte Carol stimulation of the uncertainty distribution for all solid cancer with an excess relative risk at 1 Gy after transfer to U.S. population using essentially the same method as I used before in the stomach cancer evaluation. And it's -- You get a shift a bit to the right. The mean is a bit larger and the -- Oh, sorry. It's shift to the left. This is the mean of this distribution and it's error range and this is what you had before. So it's a shift to the left and a wide distribution.

Here's another thing that's an uncertain DDREF for low-dose extrapolation and, for example, this is a subjective uncertainty distribution that was used in the Radioepidemiologic Tables Program. It's just an example, but when you divide by this uncertainty DDREF for low doses you get a distribution that looks like this. Again, it's approximately low normal and you have a mean of 0.17 compared to 0.25 before making that -- and again the range with the 90 percent probability limits broaden. Again, you're exchanging uncertainty. You're folding in this uncertainty. But it becomes part of your information.

So the "New Paradigm" approach uses objective and subjective information about radiation-related cancer risk. And I think a real advantage of

it is that the approach is transparent. It highlights crucial uncertain factors and requirements for more information. That is more research. But it also provides an interim and non-arbitrary basis for making decision. If you don't like the assumptions, you change them. You can argue about them. But anyway, this is what you get if you make this particular assumption.

Radiation protection, okay. It's really a political process with stakeholders. They feel threatened by radiation exposure and concerned about the worst case or they value certain benefits that involve radiation exposure to themselves or to others and I think most of us belong to both of these groups. We don't want to really be exposed to radiation unnecessarily, but we do derive some benefits from it.

And it's useful to address the stakeholders' concerns from their particular viewpoints. For example, for some of you, how bad could the risk plausibly be? So that's addressing their concern. What actual or potential benefit to you or to others is associated with the exposure? And what is the highest acceptable risk level, if there's a benefit or if there isn't a benefit? And I suppose the answer would be different.

The methodology can provide a considered average value of risk and the highest plausible risk and the lowest plausible risk and that allows comparison of these risks with other risks that a stakeholder may tend to disregard or they would strenuously avoid and with a known or uncertain benefit. So you can fold all these things in together.

Now a little about linear, no-threshold theory which is currently the radiation protection practice, the basis of radiation protection practice. The theory states that at low doses excess risk is proportional to dose and it doesn't require linearity of dose response over the entire dose range, just at low doses.

And I actually don't need to spend any time on this. We've already done this. This is collective dose of how we get the implications of LNT if we take it literally. Estimated risk, if we have the estimated risk, to 10 mGy to 10,000 people would be one excess cancer than the estimated risk from 1 mGy to one million people who would be 10 excess cancers which we would never be able to prove by studying the million people if that indeed were the risk now would we be able to prove that the risk is

much lower, if indeed it is. It might be helpful though to show that, if we can, we can be reasonably confident that the risk isn't as high as, say, 1 per 10,000 which is the industrial standard that is what is considered to be acceptable in industries and usually considered to be safe.

Now the low-dose threshold theory, if we could agree that there is no radiation-related cancer risk associated with doses below, say, 2mGy, then the million people could relax. And it might be cheaper and easier to protect than it is today. I'm not sure that's true. But a low-dose threshold at, say, 2 mGy would be difficult to prove, very difficult to prove, for the same reasons that make it difficult to demonstrate the opposite.

The experimental and epidemiological evidence does not preclude tissue-specific thresholds. But also it doesn't support, no at least, existence of a universal threshold operating in all or most tissues which is I think what you want to influence radiation protection policy.

So what would be the implications for radiation risk assessment of assuming some likelihood of a low-dose threshold?

Let's go back to this Monte Carlo

simulation of the uncertainty distribution for low-dose excess relative risk per Sy after division by an uncertain DDREF and this simulated distribution is roughly lognormal.

And here it is made nice. So it is really lognormal. So I can work with it. The mean 0.17, 95 percentile 0.36.

Now here is the cumulative form of that distribution and if you want, this is how you get the upper 95 percentile. You just go over from -- Well, I didn't do that. You just go over from here over to there and you drop down and you get this 0.36. There isn't a way to do that with the mean, but here it is just for comparison and this is the lower 95 percent interval limit.

Now suppose we allow for the uncertain possibility of a threshold at some dose greater than the one we're interested in now. Suppose that for doses below some assumed threshold value, we accept that with 20 percent probability there is no excess risk. That's what an uncertain threshold would be. And with 80 percent probability, the previous cumulative graph applies.

So you start with this. Then we assume a 20 percent probability of a threshold. So 20 percent

of the probability goes into zero and the rest from there is distributed 80 percent over this way. So you get a difference calculation. You have a mean that's -- Well, the mean is actually 80 percent of the previous mean because 20 percent goes to zero and the 95 percent limit is obtained this way and it's slightly less than before.

Now let's suppose a 50 percent threshold probability. Okay. The mean is now half of the original mean and the $95^{th}$ percentile of the distribution is shifted over a little bit more.

And now let's assume an 80 percent probability of a threshold. Now the mean is 20 percent of the original and the 95 percent limit is shifted over quite a bit more, but it doesn't disappear. Neither does the mean.

And here is a graph that summarizes the previous four. We have as a probability as the mean value decreases proportionately to 1 minus p where p is the assumed probability of a threshold. The upper 95 percent confidence probability limit is more complicated, but it actually remains quite high relative to the mean value until p approaches 0.95 when it disappears.

Now the implications of an uncertain

threshold for radiation protection, well, for any given threshold probability the effect on the mean of increasing p is like dividing the excess relative risk per Gy by a fixed DDREF value which is equal to 1/(1-p). The 95 percentile limit decreases with increasing p but remains relatively high until p approaches 0.95, just what I said before.

The epidemiological and radiobiological information available does not suggest a high value for p at any threshold dose level high enough to matter. Thus, allowing for the possibility of a threshold should make very little difference to radiation protection.

Conclusions. Probably most people would object to exposure unless the potential benefit clearly outweighs the potential risk or they judge that the risk is truly negligible. Information on risk and its upper probability limits, in particular, are important to this process. If the scientific consensus were that a threshold is very likely, we should take that into account. But otherwise, I think, the threshold possibility is mostly a distraction and can be largely ignored in risk protection.

And that's my talk.

CHAIRMAN RYAN: Okay. Thank you very much. Questions? Comments? Ken.

DR. MOSSMAN: Charles, you and Warren Sinclair authored that excellent report. I think it's NRCP 121 or --

DR. LAND: 126.

DR. MOSSMAN: 126 which essentially reviewed in a good bit of detail the sources of uncertainty in risk estimates and I was struck by the -- Well, you reported in some detail on uncertainty related to dosimetry, population, transfer and also DDREF. But there seems to be one other factor that wasn't included and I wonder if you could comment and, that is, if we assume LNT to be right, what's the uncertainty in dose extrapolation? In other words, to get down to doses that are typically involved in nuclear power plant operations --

DR. LAND: That's the DDREF.

DR. MOSSMAN: All the DDREF is doing is changing the value of the risk coefficient, changing the slope. Right?

DR. LAND: Yes.

DR. MOSSMAN: But what I'm talking about is the actual extrapolation of extrapolating from almost two orders of magnitude. You know, if we say

that we know risk at 100 mSv, many nuclear power plant workers are getting doses closer to 1 mSv. So that's hundred fold reduction in risk and that's a substantial extrapolation and my question is what's the uncertainty in doing that dose extrapolation. I mean, is that a --

DR. LAND: That really is what the DDREF is about. You can make a DDREF more complex and have it be dose dependent so that it goes down. You can if you can justify it. But that's how you would handle it.

DR. MOSSMAN: I don't --

DR. LAND: The DDREF takes into consideration what we think we know about this extrapolation.

DR. MOSSMAN: I mean, the DDREF really isn't a dose extrapolation. It's a dose rate extrapolation. You're accounting for repair and other kinds of radiobiologic phenomenon that ultimately result in a reduction in radiobiologic effects that you see when the dose rate is reduced.

DR. LAND: You know, if you can only deal with what you know or you have some familiarity with and I think that what you're -- It's again I do think that the way to handle it is with DDREF. The DDREF

have this one real bad -- probably there's a disconnect and it goes down and then you go down like that. Well, actually, in the radioepidemiological table stuff we put in a kind of segue in a curvilinear thing and I think that once you get down to really low doses that dividing the dose by another factor of 10 probably doesn't make much difference, at least, as far as the theory are concerned. That if the difference between a one and 100 chance of having a traversal and a one and a 1,000 chance of having a traversal, it shouldn't make that much difference, I mean, besides dividing by ten, of course. And if your question involves something else, I don't understand it.

DR. MOSSMAN: Yes, I'm just -- The dose extrapolation --

DR. LAND: That's the whole thing. That's what we're talking about is the dose response function. We're talking about the shape of the dose response function. We have a linear model and then we're modifying it by a DDREF.

DR. MOSSMAN: I guess what I'm really trying to ask is there is a difference in uncertainty if I'm extrapolating by a factor of ten or a factor of 100. I mean, the closer I get to zero, do I see any

more uncertainty in the dose extrapolation? I guess that's the question I'm asking.

DR. PUSKIN: I would say that the approach that was in there, there's a hidden assumption in there that the dose response is a linear quadrate and therefore and extrapolating down --

DR. MOSSMAN: Not at low dose.

DR. LAND: Not at low dose. Well, dose squared is --

DR. PUSKIN: Dose squared. As you extrapolate to low doses and low dose rates that there's a single function like that that describes it. But the real question is what's the chance -- Is there some mechanisms that come in between where we can observe it epidemiologically and zero that change that dramatically.

So the uncertainty in this that's in that report presumes the only uncertainty is in this single factor that the dose response is of that form. If that's the case, there really isn't much uncertainty about radiation risks. But I think the question is is there something below that kicks in.

DR. LAND: Right.

DR. PUSKIN: And you considered that when you put different percentages on thresholds or

something where that whole function no longer describes things. So something else might -- The dose response would be something else.

So that's the question. As you go down, I won't say where we have the data at this point, go down from where we have data to where we don't is what does the dose response look like at those doses, those dose rates.

DR. LAND: The DDREF is uncertain. It has uncertainty built into it.

DR. MOSSMAN: Right.

DR. LAND: And I suppose with more you actually might have a more sophisticated evaluation of the DDREF as a function of dose or dose rate. But it isn't. We don't. So far we just have what was handed down.

DR. MOSSMAN: If DDREF is a function of dose, then does that preclude LNT as a -- Again, DDREF is -- The way it's used is simply an external correction to the LNT theory because all you're doing is multiple the risk coefficient, the slope, by some factor.

DR. LAND: Right. Of course, yes

DR. MOSSMAN: But then -- And we're assuming dose independence when we apply DDREF. But

if, in fact, --

DR. LAND: We are now.

DR. MOSSMAN: I'm sorry.

DR. LAND: We are now.

DR. MOSSMAN: Yes. Right. But if, in fact, DDREF is dose dependent, then that argues against LNT theory as the approach theory because then the degree to which you are modifying the risk coefficient changes with dose and therefore it's not linear anymore.

I'm not -- I don't mean to -- I'm not making any astounding kinds of things. I'm just saying that it's my observation that LNT is no longer valid under that circumstance, but it requires dose.

CHAIRMAN RYAN: Tom, you had a comment.

DR. TENFORDE: Well, yes. A question related to the interpretation of the results of the life span study on A-bomb survivors. As you know, the curves generated by Preston and his colleagues showed some very intriguing features in the population exposed to relatively low doses, let's say, 20 mSv to 50 mSv and yet the statistical analysis that I've seen presented in papers and the radiation research and elsewhere suggest that you can't really discriminate dose response models in trying to fit this data with

different models.

DR. LAND: The low dose data, yes, that's true.

DR. TENFORDE: And I'm just wondering if with different uncertainty analysis assumptions you might arrive at a somewhat different conclusion.

DR. LAND: You know, I honestly don't think so and it's not -- it's a sort of a psychological thing, but the first thing we do when we're calculating things is we do straight lines.

DR. TENFORDE: Yes.

DR. LAND: And then if there's evidence that it's not a straight line, then you make it more complex. Well, actually when you're down at that low doses --

(Conference calling center.)

DR. LAND: -- There just isn't the information there. You can't --

CHAIRMAN RYAN: I'm sorry. I think we're getting a phone.

(Conference calling center.)

CHAIRMAN RYAN: I'm sorry.

DR. TENFORDE: Could I extend my --

CHAIRMAN RYAN: Please, yes.

DR. TENFORDE: Just to my related

question. As you know, there have been some very ambitious dog life span studies with various kinds of radiation and again, in the extremely low absorbed dose region, there are some intriguing features in terms of life span shortening and carcinogenesis, etc., and some people have even interpreted some of the data on life span to be supported of the idea for hormesis because some of the big old dog studies do show a dip in the dose response of low doses that would be suggestive of increased life span, not shortened life span, and this has been a subject of great debate and proponents for hormesis, of course, have seized on this as one of the central pieces of information from laboratory-based research in support of their theory.

And I'm wondering if you have applied uncertainty analysis to the interpretation of the data at low doses from many of these very ambitious, large scale animal studies, dog studies primarily.

DR. LAND: Maybe I could trade somebody to do that.

DR. TENFORDE: It might be a very good PhD thesis project or at least a Masters degree thesis project. Now a trivial thing to do, I'm sure, but it would be interesting to bring the full power of some

of these techniques you had described to bear on reinterpreting some of the data published in the literature you using fairly conventional statistical models and maybe not reaching exactly the best conclusions. Just a suggestion.

CHAIRMAN RYAN: All right. Well, thanks, Dr. Land.

PANEL DISCUSSION ON SESSION 1

CHAIRMAN RYAN: Again, we're at a point in the discussion where we have a panel discussion on this first session to discuss. Dr. Mossman, you've been taking copious notes. Maybe you could lead us off and again, this is kind of an open forum. Anybody that has any particular comments about any other paper or wants to offer some general comments or additional information, please don't hesitate.

So we'll start with the panel and then I'm going to ask could we get a few minutes if Members have particular questions of the first session to speak because we'll go through that and then we'll come to more discussion and hopefully finish up at or before 3:00 p.m., I'm sorry, at or before 3:00 p.m. We'll have some short break in there and then we'll have Stakeholder Participants who I believe are on our conference call or some are in the audience. I'm not

exactly sure where but we'll manage between 3:15 p.m. and 4:00 p.m. or so or if we're running ahead of schedule, we'll close at about 4:00 p.m.

So with that, Mossman.

DR. MOSSMAN: How did you want to proceed?

CHAIRMAN RYAN: What have we learned so far?

DR. MOSSMAN: I haven't gotten the foggiest idea except it's all very, very complicated.

Let me just take a moment if I can just to sort of summarize what I think are the salient points and please the other speakers jump if I say something that's incorrect.

I thought that Commissioner Lyons set the stage very nicely. He obviously has serious reservations about LNT, but he is open to a serious dialogue among scientists to try to better understanding what's going on at low dose and it's understanding the science that I think is going to be key in determining whether we have a threshold or whether dose response is curvilinear or whether the problem is indeed intractable and so I thought he opened the conference with that idea and that was very useful.

In my own talk, of course, I tried to set

the stage without getting into any detail to identify what I think are the key issues in the debate and the science is the topic of the day. Tomorrow we will have a talk from Professor Hammitt who will get into some nonscience issues.

President Tenforde, of course, from the NCRP talked about some of the reports that the Council has put out on the issues of LNT, risk estimates and the importance of, for lack of a better phrase, the new radiobiology, understanding non-targeted effects, things of that nature. And that's -- We need to look at the NCRP and the ICRP and other learned organizations for guidance in terms of where we need to go scientifically. So I think that the work that the Council is doing is critically important in many ways to lead the way.

That's not to say that Dr. Barcellos-Hoff and the other radiobiologists that are doing work in the DOE low dose radiation program aren't doing things appropriately. They are. But, of course, that's laboratory stuff and I think the NCRP, in many ways, provides a perspective, an additional perspective, which is very critical in terms of putting all of these pieces together.

I was struck by Mary Helen's presentation

in terms of the complexity of the data, not so much that we're talking about systems biology and that the systems are complex, but just the complexity of the findings and how we make sense out of all of this. And it seems like it's becoming as we answer more and more questions, additional questions continue to come up in a positive feedback loop, if I can use that, in a way that makes the problems even more difficult.

And understanding these various non-targeted effects, one of the issues that is of interest to me is what do these non-targeted effects mean with respect to our idea or the concept of dose where we've always thought about absorbed dose, the fundamental quantity that's of interest to radiological detection where we've always thought about that as deposited energy in some tissue and that that was the metric that was important in determining what the risk is.

Well, what the radiobiology is now telling us is that maybe that's wrong or, at least, maybe we need to start looking at it in another way, that the target, the radiation deposition target, is different than the radiation effects target. The radiation effect target or the radiobiologic target is much, much larger and maybe very different. So I was

particularly struck by Mary Helen's talk in that regard.

Dr. Le Guen's talk about estimating the carcinogenic effects from low doses from the perspective of the French Academy of Science's report was extremely enlightening. If there was really a take-home message for me, it was not even a science message. What the message was is that we can all look at scientific data through honest interpretation of the data come to diametrically opposed positions. I mean, the French Academy of Sciences says one thing. The BEIR VII report says something else.

We can argue about who's right and who's wrong. I'm making the assumption that everybody is professional and everybody is making an honest interpretation of the data and yet we have these very, very different interpretations of what's going on and that's what we're faced with in this entire LNT debate is we're looking at bunch of data. People are looking at the data through different lenses and I was particularly struck by the differences in the reports in that way.

And then finally Dr. Land provided a very useful overview of some of the biostatistical questions, the uncertainties in risk, whether in fact

we have a threshold, whether in fact a threshold can even be detected or measured or whether it's something that has a high probability of occurrence or has a low probability of occurrence and even if it does, does it mean anything and these are obviously key questions particularly in considering hormesis where you obviously have to assume that there's a threshold. But if we -- Depending on how you look at the threshold question hormesis either goes away or becomes a very, very serious alternative.

That's the way I saw things. Obviously, everybody else has different views. But I thought the session this morning was excellent.

CHAIRMAN RYAN: Thank you.

DR. MOSSMAN: And I applaud the speakers for excellent clear presentations.

CHAIRMAN RYAN: Let's start in the order we went. Next is Dr. Tenforde.

DR. TENFORDE: I'd like to echo what Dr. Mossman just said in terms of congratulating all of the presenters. I felt I learned a great deal today and you generated some interesting ideas and thoughts in my mind as well.

Let me more or less follow the procedure used. Dr. Mossman, first, with regard to your talk, I

think after reading some of your papers and hearing you speak today, I certainly understand your concerns about using risk as a basis for setting guidelines and regulations.

I want to mention an activity that NCRP is about to embark upon and that is we have been told that we have funding for a report on uncertainties in radiation risk estimation and that will be a committee that will be chaired by Julian Preston who I think is probably a familiar name to most of you and we have a number of ideas of the candidates for the committee. But that committee in the scope of work that has been developed will address some of the issues on uncertainties in radiation weighting factors and tissue weighting factors. And you didn't mention this, but, for lack of a better word, the frailty of the tissue weighting factor and the ICRP effective dose system is that there are such large uncertainties as evidenced by the fact that in 2007 the tissue weighting factor for breast was increase two and a half fold and for testes decreased two and a half fold and those are rather large shifts and has some impacts on, of course, estimation of effective doses. So I share some of your concerns and I hope that a contribution from NCRP through this new committee

effort will be to try to pin down a little better what some of these uncertainties are and give a little better estimate thereby of effective doses.

With regard to Dr. Barcellos-Hoff's presentation which I thought was very elegant, you've I think made the case very well and I congratulate as well the DOE program for the importance of looking at integrated tissue responses and not just focusing on single cells because obviously there are so many modifying factors that come into play in an integrated system that moderate in one direction or another radiation responses that we've probably ignored them too long and it's great to see some of this new and very elegant work underway especially using some of these new three dimensional tissue models which I think are very interesting.

One thing I would like to comment on in a broad sense is that using acute radiation, there have been some differences that have been fairly well characterized between response as to high and low doses as more or less defined within the context of the DOE program. But I think when you look at human exposures particularly, for example, in an occupational setting, you're really dealing with fairly low dose rate exposures and I think it's

extremely important and I hope this will become part of the DOE research program to a greater extent than it is today to look at dose rate effects in a practical sense, dose rates comparable to the dose rates we experienced from occupational or public or background exposure which is very low dose rates basically. And I think it's going to be necessary to sort that out in relation to low acute dose phenomena because we may begin to see -- issues enter in in a way that might not even expect. So there are some, I think, candidate model systems that would be good for those studies and I'd like to encourage that.

Also one thing that I talked with you about during the lunch break is very intriguing to me and has been for years. It's very well known that endogenous oxidative damage creates about 10,000 strand breaks in DNA per day per cell. It's a lot. And so because we have placed quite a focus on oxidative interactions and damage from radiation and some in cases at very low doses, it brings to my mind the question of extracting the signal of oxidative damage from the radiation insult from the background endogenous oxidative damage that cells are coping with day in and day out. And that may actually be part of a survival mechanism for cells because it may enhance

oxidative damage control mechanisms, anti-oxidant levels, etc. So I think it would be interesting with the very low doses, centi-Gy and below, that are being used in many of the oxidative damage studies to try to somehow segregate the endogenous oxidative effects from the imposed oxidative effects of radiation and I wish I had some really good suggestions on how to best do that. I'm sure that there must be some approaches that can be taken.

And then another thing that has intrigued me which I don't -- We again talked about this at noon and that is we live in the background radiation on the average in the U.S. about 3 mSv per year and one question that intrigues me is supposing we had some laboratory test systems where we could shield the target tissues or cells or even animals. It's been suggested deep salt mines or places where the natural background fields are greatly reduced and then look at very low dose radiation effects.

When I was speaking earlier, I mentioned that one of the real challenges, of course, in going to very low doses to try to discriminate dose response characteristics is extracting the signal from the experimental system from the background radiation noise and that is a huge challenge and maybe this

would be one approach to take. It's not an easy experiment to do but there have been suggestions of how to do it and possible places where it could be done.

I also was very intrigued by the report largely based on the conclusions of the French Academy and again I'll echo Dr. Mossman that it's very interesting that two groups of scientists looking at pretty much the same worldwide database should reach different conclusions about the LNT theory and I find that intriguing. I think that it would be of great interest to have a small subset of the BEIR committee and the French Academy committee try to ferret out what are the elements that have driven this difference in some of the final conclusions.

As I said of next week's NCRP meeting, there will be an interesting debate between Dave Brenner and Dietrich Averbeck from the French Academy group and I'm very anxious to hear the results of that and hopefully some things will come to light on the basic reasons for the final differences and conclusions. But again, I think that some of this may be driven in part by the type of studies that have been done comparing higher dose responses to lower dose responses, both from the biological perspective

and the physical energy deposition aspects of radiation. I think that needs to be looked at very carefully.

And then finally, I thought that Dr. Land's presentation was very informative. Obviously, the role of uncertainty analysis has probably been understated over the years and I think we are really beginning to appreciate how important that is in estimation of risk and so I was very interested in your discussion of uncertainty analysis with differing models' response. I think that was very informative and hope that we'll see more and more applications of that in some of the studies that exist in the literature like the ones I mentioned, the life span study, which I think you've probably already looked at and some of the animal model studies, the dog life span studies, etc. So there may be some jewels to be mined there by doing a little more in-depth uncertainty analysis of the data and the way that it has been fit with varying models. Again, I think that's a very informative presentation.

I think that's about all. I'm pleased to be here today. I think there's been a lot of very enlightening discussion of low dose radiation effects and models. So thank you again for inviting me to be

here.

CHAIRMAN RYAN: Thank you, Tom. Again, more to come this afternoon and more tomorrow.

Next, Mary Helen. First let me say that I'd like to add my thanks too for a very enlightening presentation. It was -- For the first time, it put together a picture of a biological model and a physical model of radiation dose, energy deposited, pre-heated mass. I won't think about it as mass anymore. I'll think about it as a system of biology that I have to think more carefully about. So that insight I think is one of the most important things that if we can take away a message. It's not dose per unit mass. It's dose per biological unit whatever that unit might be.

Yes, Dr. LeGuen.

DR. LE GUEN: Just I don't know if you know that we have a lot of slides that are close.

CHAIRMAN RYAN: Yes, very much.

DR. LE GUEN: Because the metric of the slide prepared for this morning was on publication raised after the French report.

CHAIRMAN RYAN: Right.

DR. LE GUEN: And in fact we have not the same result but the same approach in that we are very

close because I was much more on ATM and she was much more on TGF beta. But the conclusion of the different publication was not different, I think.

DR. BARCELLOS-HOFF: Yes.

CHAIRMAN RYAN: And again, just from a health physicist's point of view, we take a physical absorbed dose and we multiply it by factors, all kinds of factors, to get into a biological system. Maybe we ought to just change the fundamentals, the way we think about it a little bit, and think about what's the biologic system to which we are imparting something, whether it's energy or chemicals or information or whatever it might be.

So with that, I ask you to offer your comments on today's panel.

DR. BARCELLOS-HOFF: It's quite a lot to digest.

CHAIRMAN RYAN: It is.

DR. BARCELLOS-HOFF: For somebody who is not used to thinking about so many different sides of the problem. But I'd like to just start with a couple of general comments and actually keep them very brief.

I think it's actually one of the unique aspects of radiation biology as a community, radiation sciences as a community, is that we are really the

original systems biologists. We start from physics and go all the way to disease and that's something that we don't give enough credit to our own field of research in trying how difficult that task is, how difficult it is to actually move through those different levels of molecular, cellular, tissue, organismal populations and that's something that we should actually acknowledge the difficulty of that problem.

Right now, biology is finally coming out a wave of reductionism to try to put these pieces back together and essentially systems biology is just that. How do you extrapolate from one level of organization to the next which again is a problem that radiation biology and sciences has been trying to grapple with for many decades. I think that's something that we should kind of give ourselves a little breathing room in that, yes, it's a difficult problem.

I think that I completely have been reeducated in terms of what kind of implications are the fundamental radiation biology that I came into the field to do has in terms of understanding health consequences in humans and I really appreciate Dr. Mossman's comments of how -- radiation protection is not about the science at some fundamental level. It

has so many other layers again of input in society, economics, regulatory paradigms which we went to a meeting in Helsinski organized by the European Union that really brought this in terms of how I think about communicating the results of our very interesting radiation biology. And we can go on and on. I really truncated a lot of the details, I think, biologists get so enamored of that we forget, we lose sight of this bigger picture.

I think one of the things that I think this meeting is particularly important is getting that communication opened up and just trying to discuss it from the different perspectives. I thought that our discussions this morning on the science were very complimentary and it was remarkable to see how many overlaps we brought to the table and without any preparation in that regard because I made my talk yesterday on the plane.

So I think this is the important thing to recognize. I'm probably repeating myself at this point. So essentially it is a complex problem and we should give ourselves a lot of credit for even attempting it. And I see that the implications of the biology and the understanding of the biology have many more ramifications that we tend to think about at the

biological level and that this is a really good venue to educate each other and to perhaps elaborate on this discussion productively.

CHAIRMAN RYAN: Great. Thank you.

Dr. Le Guen.

DR. LE GUEN: Well, I was really impressed today because for different reasons. Me, too, I really appreciate your point of view about economic approach and science approach not only based all on sciences. I fully agree about that.

I was also very surprised about a lot of overlaps that we had together because I promise I didn't have your slides before and you can say exactly that you didn't have mine before. We are really different of this. Because in fact from my point of view the best way is to have an open mind for the future, to say if you know one conclusion, that's why in fact I don't like so much to say to try to compare BEIR VII and French Academia report.

I think the most important is to try to have a good approach of the management of risk, of risk management. And I would like to this morning, in fact -- When I prepared my slides, I was thinking about is there a better understanding on the effect today than before when we used the LNT approach. And

I said, yes, we have a lot. It's much more sophisticated today than before.

And my first point was to say, well, we must keep in mind that when we decide to take the LNT approach it was the next calculation from high to low to this and today we can say that it's not exactly like that and we know exactly that it's a different mechanism at low dosage than at high dosage. So on this point, we know.

But the other question is is there trouble if we use the LNT approach. From my point of view, there is no problem because for every day and we saw that also today that LNT is very convenient. But it's very important to not -- that be careful about LNT because it's not universal. If you want to have all the answers with LNT approach, you will make a lot of mistakes.

If we need to use LNT for managing, for -- for population and so on, okay. But it's very important to education the population on this. If you don't educate -- Because the problem is that when we introduce Sv a long time ago, we introduced Sv as a unit of risk. So if you have a dose in mSv, in mSv, I can assess my risk easily. But it's not true.

That's why today we have trouble because

time has changed that shows that today is much more complicated than before. But it's not a problem. I think it's -- I'm very excited about the evolution of science today because, of course, I said during lunch it's like Lancet. Do you remember in 1993 the first pages on Lancet was p-53 the molecule of the year because all was based on cell. And with time, we've -- the molecule tool, we've observed that, of course, there is reaction into the cell. But there is also reaction on the tissue and on the body, too.

And that's why that's amazing and that's why I say also today it's not so easy to extrapolate from individual measurement, individual experiment, to in vivo because there is a lot of connection in vivo that it's not possible to see if we are only in vitro experiment. But that's not the problem.

So please let free the science and we will see and don't try to mix a political problem with science. I think science is a part of the problem, not only this, and perhaps I'm sure that with time and you know just three years ago we were not alone, but we were a little bit alone in Europe and it was amazing the presentation of Mary Helen's this morning to say now we have a great power to exactly the same approach and with a different experiment and perhaps

about my dialogue, about my sentence, that I said before. Perhaps we will have no sentences on the paper and I think with this we will have perhaps one day, you know, other connection with epidemiology.

You know, I'm also a scientific advisor and I give grants and subsidiaries to other French research team and we have begun to have molecular epidemiological approach. I believe a lot in this because this is a link between molecular science and epidemiological studies and I'm sure that alone for science it's not possible to have the answer. But also from epidemiological approach due to natural background and so on, about all confronting factors. As I said before, it will not possible to have the answer. But perhaps if we have a great link between the two approaches, perhaps we will see.

CHAIRMAN RYAN: That's interesting. Thank you.

Dr. Land.

DR. LAND: Well, I would like to just get something a little off my chest here that it's about purpose of radiation protection. And the idea that it is people have to agree what we tell them. They have to accept it.

And I think that, of course, there is an

education process involved but generally if we decide if we can agree on a general approach I think probably it's going to be accepted.

But I'm just thinking of something that happened to me a couple of years ago. I was giving a talk on radiation related breast cancer to a group of breast cancer survivors in New York and I gave my speech and was asked a question about isn't there a better alternative than mammography. And I said, "Well, there probably is some small risk associated with mammography, but we don't think it, we don't see how it could be very great and when you look at the risk compared to the benefit it really generally in most situations where it's used the benefit clearly outweighs the risk" and there was this rustling in the room and then somebody stood up and said, "You just don't understand. We don't want risks. We just want benefits."

(Laughter.)

DR. LAND: It's a very reasonable thing to say actually. But the fact is that really you do have to accept risks in order to get benefits and how to get that across in this whole essential political nature of the radiation protection. I just don't think that you can make it fly and to say there isn't

any risk at really low doses just isn't going to work unless you have enormous agreement among all sides.

So I think the problem is a difficult one, but I think it's actually solvable by emphasizing the tradeoff and again addressing people's concerns and being seen to address people's concerns. That's it.

CHAIRMAN RYAN: Thank you. Great. Thanks for sharing that story. That's an epiphany of sorts, I guess, to hear that message.

With that, I'd like to -- I'm sorry. Yes, Dr. Le Guen.

DR. LE GUEN: Yes, just a reaction because you mention a very good question. We have exactly in front exactly the same trouble today about women with BfCR1 and BfCR2 mutation and about the different exam and between mammography and echography and IRM, MRI. Okay. IRM in French, MRI. And it's not so easy because, of course, there is a risk/benefit and we have to take into account the risk of exposure with mammography and because we are physicians we must propose monitoring for these women because it's of a great important to be sure to see the concern as a very small step, as a very small concern.

And the question is we need to propose mammography every year, every two years, every five

years and we know if we wait too long, if we wait a long time, it's a risk for the woman. But if we propose mammography every year, we have a risk of concern due to the radiation, to the mammography, to X-ray and that's a real problem.

And today we have not found an consensus on this point. That's why it's not so easy to answer. And we know that in fact it's not only one exam and we must take into account it's three exams, mammography, echography, and MRI.

CHAIRMAN RYAN: Very good. With that, I'd like to ask if the ACNW&M members have any questions and start with you, Allen.

VICE CHAIRMAN CROFF: I have a couple. First, thank you for some very interesting presentations. After a couple times around, I think I'm starting to understand at least some of it.

I'd like to note Dr. Tenforde's mention of background which I thought was appropriate and use that to segue into my first question. I come at this whole issue from, I guess, let me call the perspective of a regulator. This committee doesn't regulate, but we advise the Commission on technical issues related to regulation.

And from that perspective, we sort of in

my view start at a dose of about, let's say, 200, maybe 300 mSv over a lifetime. That's a natural background and that's sort of a floor. This Agency and nobody else can do anything about it. We all get this kind of a dose, some people more, but that's an average for natural background. And let me preface my remarks also by saying I'm going to focus on low dose rate situations. But if we're starting at a floor of about 200 mSv it seems to me from the perspective of this agency we're interested in regulating and interested in dose response in the range of, say, 200 to 500 mSv for most situations. Occupational can run you up a little bit. There's variability in there, but it's that kind of a range we're interested in.

Now going back to what I've heard around the table from a number of you as to at what point the uncertainties in dose response start to get to the place where you really just don't have much confidence and you can't tell what's going on. In various talks, I've seen numbers that seem to be around 100 to 200 mSv, again low dose rate and my first question to the group is did I hear that right and is there some reasonable degree of confidence in the dose response curves in the 200 to 500 mSv range?

Don't all jump in at once.

DR. LAND: I think there is. I think there is very definitely evidence of excess risk in that range.

VICE CHAIRMAN CROFF: That's the impression I took away from what I heard from more than one of you as a matter of fact. But I wanted to make that explicit. Does anybody think that's not the case?

DR. PUSKIN: I think it's more complicated because it really depends on what time period you're talking about the dose. If you're talking about dose per year or dose per day.

VICE CHAIRMAN CROFF: No, I'm talking about low dose rate. On the order of background dose.

DR. PUSKIN: We don't have -- I'd say we don't have any data at that range.

DR. LAND: I take it back.

DR. PUSKIN: That's -- It has to be extrapolated. We don't have any data at low dose rates really.

VICE CHAIRMAN CROFF: With my definition of low, if you will.

DR. PUSKIN: Yes, right, unless --

VICE CHAIRMAN CROFF: So you're saying the complicating factor is that the dose rates where we do

have data are more what you're currently defining to be -- I've heard numbers like 10 centiGy, I'm sorry, 1 Gy a day and something on this order.

DR. PUSKIN: No, much lower than that.

VICE CHAIRMAN CROFF: Lower than that?

DR. PUSKIN: Certainly 1 centiGy, less than 1 centiGy in a day.

VICE CHAIRMAN CROFF: Okay.

PARTICIPANT: Is there data at that point for less than 1 centiGy a day?

DR. PUSKIN: A little bit less, yes.

DR. LAND: If there's a risk at 50 mGy, then it's not much of a stretch to say that there's a risk at 2 or 1. That isn't a stretch.

And the question that I wonder about is when you're talking about really fractionating doses spread over a long time, how are you going to get that kind of data?

VICE CHAIRMAN CROFF: Okay. That's the other --

DR. HOLAHAN: One of the places I think we're going to get some information in the future is going to be with our occupational workers and our occupational workers if you look at the IARC study on average they've had about 20 mSv. Now keep in mind

those workers generally men have gotten a background of cancer incident rate probably over 40 percent, cancer mortality rate of about 20 percent. And those exposures even over a ten year period are probably going to take another 30 or 40 years to manifest themselves so that you see an excess over background. And we haven't gotten to that point yet.

The early indications and I'm going to call them early indications from the 15 nation IARC study said that among those workers that were only exposed to external radiation, anyone who had internal radiation was pulled out of the cohort, their average exposure being about 20 mSv, about one percent of their cancer was associated with that occupational exposure. Now that was primarily biased by Canadian data and I think that's going to be corrected and rescinded. But that's going to be a source of data in the future to look at because generally those workers were 40 years of age and have clearly not had enough time to express an access.

The second set of data that we're going to see are probably going to be the resident along the Techa River because of releases from the Mayak Production Association. There we have data that probably extends over 50 to 60 years. We're looking

at access cancers in that population. There were exposed to very low compared to the occupational and some of the other stuff exposures. But again, the problem there is reconstructing the doses and assigning some dose to their background. Again, that's going to be complicated by a lot of other factors, too, socioeconomic being one. It's the food, what they drink, what do they smoke compared to a reference population.

But there I think in the next 10, maybe 20 years, we might be able to extract some information and again the latter program is supported by DOE. DOE is putting a lot of money into that as well as NIH.

DR. MOSSMAN: I think the Techa River study will be very informative because doses are fairly high there. Now in the 15 country IRAC study I'm not sure how to interpret that data because I get to see any stratifications of the data according to dose.

I mean, you say, and correctly so, that the average was something like about 20 mSv. But what we don't know is among the groups that received the highest doses what's their cancer rates versus the populations that received much lower doses. So we can't -- Until we stratify the data according to dose

intervals, we really won't understand in that population what the magnitude of the risk is.

The doses that we're typically seeing now which is under a half of -- Well, it's under 5 mSv per year, well under that in many instances. So I think the jury is still out in terms of the 15 country study. It's a very important program because there's, what, 400,000 nuclear workers involved.

DR. HOLAHAN: Actually, it's closer to 600,000.

DR. MOSSMAN: Is it 600,000? Yes. But I think until we understand the stratification according to dose it's going to be difficult to really understand what the magnitude of the smaller dose is. All of the cancer we may have been seeing may have been those that were exposed very early and at very, very high doses.

DR. LE GUEN: Of course, it's very important to have a meta analysis study in order to have a large cohort. But one of the problems that we have about large cohort is the uncertainty. About the 15 country, there was problem about the uncertainty due to the Canadian cohort and if you exclude this Canadian cohort it would be better.

And a similar point, this is very

important to continue this study. Why? In fact, I'm involved in the French cohort of nuclear workers and this French cohort is too young for the moment. And that's why it will be very important to continue during the next 20 years to follow this population because you remember my relation between age and concern and you increase the number of concern with age and, of course, if your cohort is too young, it's not -- you are not able to see a small excess of concern.

So we are decided in France to continue to support because, of course, for the future if we want to assess a risk at low dose this is very important to take into account these nuclear workers. But also perhaps medical examination, don't forget this because we have a broad population because we are all involved in this cohort and perhaps it's also of great importance to AP epidemiologists, AP epidemiological studies with medical examination.

DR. MOSSMAN: But it's also -- To follow up, it's important to look at leukemia as a sentinel disease. I mean, we ought to be able to see that in increase before we see anything else and that ought to -- We should be seeing increases in leukemia 10, 15, years, even earlier than that, following exposure. So

I think we ought to be getting indications of what the risks might look like by particularly paying attention to the leukemia because in general they're latency is shorter.

CHAIRMAN RYAN: Just go there and then --

DR. PUSKIN: There are several other studies on chronic exposures like the Taiwanese apartment dwellers, people who lived in apartments that had cobalt-60 contamination steel. We had quite a range of doses. The epidemiological follow-up is very short now. So there's data that's pretty preliminary on that. There's -- I think there's some --

There are some old studies where we really don't know the dose, but we know the chronic dose did elevate cancer rates in radiologists back when they didn't control the doses very much or medical technicians. There is --

CHAIRMAN RYAN: Relatively small groups though. Not huge numbers.

DR. PUSKIN: No, but another one that's very worth looking at is the clean-up workers at Chernobyl whose doses were over a few months at least and there is one study so far that they have not, I don't think, seen leukemia where you might have

expected to see it. That's an interesting group.

CHAIRMAN RYAN: Allen.

VICE CHAIRMAN CROFF: Vince, did you have something?

CHAIRMAN RYAN: Vince, sorry.

DR. HOLAHAN: Leukemia has been observed in -- It wasn't picked up in the IARC study because if you received any internal exposure, the reprocessing activities or even up in Canada having gotten exposure to tritium, they were among the 200,000 that were pulled out of the cohort. So you have to really watch the methodology of the study and how the protocol is set up.

VICE CHAIRMAN CROFF: Okay. I had a second question if I could and going back to Commissioner Lyons this morning who expressed some degree of frustration over the collective dose issue which I share and let me try to pose the question like this. For the purposes of regulation, let's say, the policy has been LNT and, as Commissioner Lyons said, if that is the policy, collective dose immediately follows. You can do very simple math. There it is in front of you.

But yet the ICRP, for example, on one hand says use LNT, but on the other hand they say you

shouldn't use collective dose to produce risk to populations.

And what I'm leading up to given that this is a technical body here. In other words, we don't do social factors and not really economics, is there any technical reason the panelists can come up with why such use of collective dose is not or should not be done or is inappropriate. Let me phrase it that way.

DR. LAND: I can't think of any technical reason why you shouldn't use collective dose.

DR. PUSKIN: I think it's just important when you use it that way to put in context --

CHAIRMAN RYAN: How about a 10 millirem a year per person in addition to background?

VICE CHAIRMAN CROFF: On what basis?

CHAIRMAN RYAN: I'm just saying. Ten millirem in addition to background should be treated as just a multiplication and it's the added risk. But I struggle with any addition dose that's within -- I don't know. Pick a number. One segment of the average of background in the U.S. and saying that's added risk.

DR. PUSKIN: I would say you should put it in context. Two things. One is that it's based on the assumption of LNT and that we're not positive

that's right. And the second is that the individual risk is for individual probably down -- if it's like a dose as an individual, you probably would not be concerned about.

VICE CHAIRMAN CROFF: I fully agreed it needs to be put in the context of the background collective risk and other risk people get and also it needs to be done properly.

CHAIRMAN RYAN: I say you could miscommunicate the risk. That's my problem with it.

DR. PUSKIN: It could also be -- I think the misuses come in to trying to apply to populations you really don't know their background rates, for example, populations -- months from now.

VICE CHAIRMAN CROFF: It's interesting that the IRSP in the separate report in an appendix to it gave what I thought was some pretty good advice on sort of how to do uncollected dose. You have to apply it to homogenous groups with similar lifestyles and this kind of stuff and, of course, if you're looking at a very large population, release Krypton-85 or something that persists in the atmosphere, that can get to be a real chore.

But I just wanted to make sure and I also recognize that there are other balancing factors, the

economics and social aspects and would the use of the collected dose result lead you to spend a lot of money on something that doesn't make any sense is very valid as a policy issue, but not necessarily --

DR. PUSKIN: I do have a problem though if you say don't use. I think there's a danger that people think you're hiding something. In other words, some scientist is going to come along and use it because there's, I would say, pretty good evidence for LNT and it's not all conclusive, but there's a scientific basis for it. Somebody is going to go out there and calculate it and they're going to put out the number and if you're going to say "I'm just not going to look at that."

CHAIRMAN RYAN: No, no. I think you can do whatever you want as long as you recognize its limitation. Very often, what you say is true, people use it and never site the limitation.

DR. PUSKIN: Right.

CHAIRMAN RYAN: That's just as bad as not leaving it silent.

DR. BARCELLOS-HOFF: And essentially what you touched on is how do you communicate information about risk.

DR. LE GUEN: Absolutely.

DR. BARCELLOS-HOFF: And one of the things that people -- If you just listen to risk communication discussions, you were just exposed to 1,000 mSv, 1,000, and that number impresses people. If you say you were now exposed 0.0001 whatever it is which I can never do it just loses any impact and I think one of the things that we tend to, and I think probably what you're alluding to, is how you communicate risk to regulatory bodies or to the public and we don't do a very good job of that.

One is we have all these different units which is impossible to keep track of even as a radiation biologist in terms of --

CHAIRMAN RYAN: -- bilingual in the U.S.

DR. BARCELLOS-HOFF: But there's also the same that you could ask the other question. Why use collected dose? Why do you use it? Under what circumstances do you use it? And what does it convey --

DR. LAND: Just a higher smokestack thing.

DR. BARCELLOS-HOFF: Yes.

DR. LAND: You know, you get -- you spread it out more and you think it isn't going to go away. It's sort of reasonable to think that maybe you're just causing just as many cancers only they're spread

out over a larger area. So nobody will ever find out and that seems to me that's morally not such a good thing to do.

DR. MOSSMAN: Yes. It's equivalent in insurance to spreading the risk and I'm not sure that there's really any value and you're right, Mary Helen. It's a question of communication. If the idea is communicating risk, collective dose is not the way to do it. I think that there are ways in which you can frame risk that uses appropriate analogies that helps people understand what the magnitude of the problem is and I think that that needs to be the approach.

But to me, collective dose is really its true value is in looking at trend analysis, evaluating job scenarios, things of that nature. I think that's where it's very, very useful. You do not calculate any kind of risk from that. You're just using a --

CHAIRMAN RYAN: It's a relative measure.

DR. MOSSMAN: Yes, it's relative measure. That's right.

(Simultaneous speakers.)

CHAIRMAN RYAN: -- dose than this way of doing it.

DR. MOSSMAN: Right.

CHAIRMAN RYAN: And that's a good tool to

use in the -- I agree with that.

DR. MOSSMAN: It's a good tool. Yes, it's --

DR. LE GUEN: That's a good word. It's a tool.

DR. MOSSMAN: I mean, dose -- There's nothing wrong in an ALARA situation to establishing dose targets in which the dose target is expressed as a collective dose and then your idea is then in the population that you're managing to make sure that that trend analysis meets this dose target and you might want to say 300 millirem per person, mSv, of whatever it is for the large population and you evaluate your ALARA program based on that. That's fine.

DR. PUSKIN: I think take a couple more controversial uses of collective dose and one would be after the Chernobyl accident dose to the European population result in roughly 10,000 cancer deaths. That would be one. Right? Another one would be the latest one about the dose from CT scans that there are so many cancers.

Now I know I'm going to be in the minority here. I would say those are both legitimate uses of collective dose in terms of looking at the population impact of an activity. Now from an individual risk

standpoint, the people need to understand that there is, first of all, that there is an uncertainty about that and, secondly, that particularly in the medical case, that this risk is balanced by a benefit that is larger in almost every case.

CHAIRMAN RYAN: In whose judgment?

DR. PUSKIN: Well, I think the --

PARTICIPANT: It's a personal judgment.

DR. PUSKIN: I think we could -- I think the medical community --

CHAIRMAN RYAN: I got your point.

DR. PUSKIN: Assuming LNT is correct you could say that the benefit is greater than the risk for those exams unless the exam is unnecessary.

CHAIRMAN RYAN: But that's -- You know, the hard part to me, Jerry, is not that I agree or disagree with you. It's that's your assessment and a reasonable person could come up with exactly the opposite assessment and that's to me the flaw in LNT as a tool or as a metric or whatever you want to call it for the purpose of making the assessment. If, in fact, it's a dose based way of thinking, if, in fact, all that we've heard about biology tells us it's not that simple then we're sort of, it seems to me, backing up just a bit to keep waving it as the flag

we're going to rally around.

Just for the sake of the discussion, I offer that to you. It's really easy and comfortable and familiar. That doesn't mean it's right.

DR. PUSKIN: I don't understand how else you can examine the question as to whether CT scans are a good thing or not unless you look at the projected risk that you might incur and look at the benefits of it. If you're going to say I'm not going to calculate it because the risk is too low --

CHAIRMAN RYAN: Calculating it is fine, but the real proof would be in the epidemiologic study that examines that question, not in the estimate of what it might look like when we're done with the study.

DR. PUSKIN: I don't know if that's true. I think if it really came out that the calculation showed that based on LNT CT was a bad thing for a whole slew of purposes I think there would definitely be resistance using CT for that purpose. I don't think you'd wait 30 years and see if there's a bunch of cancer showing up.

That's the old way. That was the old way they used to regulate the environment in the 1800s, but I don't think that's --

DR. MOSSMAN: The alternate -- the flip side of that is also true. If you look at coronary angiography which has associated with very, very high doses, can be anyway in a complicated case. You can make the argument that there isn't probably a person alive who would not accept such a procedure if they told you, if the doctor told you, "This is a critical procedure for us to diagnose your condition. We need to be able to do this in order to save your life", and under those circumstances you accept the risk.

The bottom line then is that risk and how one perceives it, is very much dependent on the context in which the person is in. I mean, you know, if it's something for which you derive personal benefit, suddenly the risk acceptability goes way up. You know, and I think that we to keep that kind of stuff in mind. I'm done.

CHAIRMAN RYAN: Okay, thanks.

DR. MOSSMAN: Thank you.

CHAIRMAN RYAN: Ruth?

MEMBER WEINER: Thank you. First of all, just following up on that discussion, I'd like to thank Dr. Mossman for making the statement on the slide that if the individual isn't harmed, the population isn't harmed either. Thank you for that.

But my question to the -- an individual. That wasn't what was on your slide. I'd like to ask a question though and that is something that was not really addressed. And that's the question of accumulation of damage with dose and it's something that those of us in another life -- I deal with Environmental Impact Assessment and projections of doses to populations. And the common way to do this is to say, you have a population exposed to a dose of X from one event.

Now, if you have 100 of those events over a period of 25 years, you are -- you are exposing that population to an accumulated dose. Is that a valid concept?

CHAIRMAN RYAN: Those would be the imaginary doses.

MEMBER WEINER: The imaginary doses, but this is very commonly done. Every DOE Environmental Impact Statement does it. And I am asking the group, is that a valid construct? Can you say that a group of individuals, a population, exposed to a particular dose from one event if that event is repeated, you have 100 similar -- 100 events of the same type which exposed that population to the same dose, and those 100 events take place over a period of let's say 25

years.

DR. LE GUEN: This is the definition of the natural background.

MEMBER WEINER: But is -- this is above the natural background. Is this a valid way to accumulate doses?

CHAIRMAN RYAN: Well, the real question, Ruth, is you use those numbers to assess the appropriateness or inappropriateness of some activity.

MEMBER WEINER: Yeah, and --

CHAIRMAN RYAN: So it's only in that context you can ask that question.

MEMBER WEINER: Well, it is used to assess the appropriateness of --

CHAIRMAN RYAN: Something, it doesn't matter what it is.

MEMBER WEINER: -- something and I'll even say what it is that I'm thinking of. The transportation of radioactive materials, you go by a population that lives along the side of the road. You're exposing them to a very low dose, it's a very low individual dose. I mean, it's like $10^{-5}$ sieverts per -- as the average dose. You're exposing this population and then you have 100 shipments and then you take that 100 shipments are spaced over 25 years

say and you calculate and dose.

CHAIRMAN RYAN: So what's the nature of the background you're talking about 10 to the minus nothing?

MEMBER WEINER: Okay, yes, that's the answer to the question, but I ask, do the doses accumulate?

DR. MOSSMAN: In fact, what you do in the Environmental Impact Statement is you assume that they do.

MEMBER WEINER: Yes, exactly.

DR. MOSSMAN: And as -- to establish an upper limit of risk, now, then you can begin factoring in DDERFs or whatever to determine dose rate in all of that but in the impact statements that I've been involved in, just assume the dose has been received all at once. It's not been received over 25 or 30 years. You receive it all at once. You do the calculations to determine what the cancer risk is to the population and that's the worst case scenario.

MALE PARTICIPANT: But that didn't answer her question.

MEMBER WEINER: Thank you, Ted. It did not answer -- the question, is that a valid procedure? I know that we do it. But what is that procedure

communicating?

DR. BARCELLOS-HOFF: That procedure is communicating that you have a biophysical -- is the biophysical model of radiation damage. In other words, any increment of dose is going to have some increment of damage and that is cumulative. It doesn't have to be cumulative in the same cell. It can be just cumulative across the organ or across the organism.

And I think it is based and I wanted to say something along the lines of there's an elephant in the room, okay, that nobody has actually raised, which is that we have a linear no threshold radiation protection policy that has -- or was established many decades ago consistent with ALARA, but in the last 20 years there's been a scientific argument for linear no threshold based on biophysical considerations of energy distribution, targets, DNA and the ocogene driven model of cancer.

And that's where we see this disconnect, now between the biology of targeted effects versus non-targeted effects. Using the biophysical model of cancer risk and what I have a hard time with is we have policy and we have models, you know, and then we have scientific rationales or support for those models

and they go back and forth and back and forth and you know, you lose track of which one you're talking about when we talk about LNT.

So let's just say there's the policy, there's linear threshold biophysical modeling and its application then back to policy. But that is exactly what you're talking about. It's a cumulative because there's a biophysical event. There's a persistent of that event and all I was -- one of the contributions of the DOE low dose program in getting people to work at the very low doses and looking at non-targeted effects is there's another component, another mode of action beyond the biophysical which is -- are these non-target attacks, these signaling cascades, interactions between cells that can both suppress and promote complicated biology that needs to be worked out. But that's the part that we don't take into account and I would say if it was me, I wouldn't worry about it.

But that's my risk assessment, right, my personal risk assessment, not yours.

MEMBER WEINER: Thank you. That's very -- that clarifies it a great deal. To answer Dr. Le Guen's comment, background is something that is experienced on a continuous basis. I'm talking about

discrete events. And my question is really and you've answered it in part, Dr. Barcellos-Hoff. My question is really do those discrete events have a -- does the damage or punitive damage or benefit done by one discrete event, is that accumulated in the next discrete event?

DR. LE GUEN: You remember this morning I told you that this is not the physical event that is important but the outcome, the consequence and due to natural background but also a lot of stress because you are talking about transport which we can leave closed to the reader and we have a chemical agent. We eat a lot of -- a lot of chemical product and so on and we live in the stress.

And if we have planned a good mechanism in your cells we have some trouble. And, of course, that's why it's not, for us even this is modern, but our reactor cells and particularly not the cells, the tissue in the body. And so a dose is always a dose. If a dose is very small and close to the natural background, if we -- it's not possible to make a difference between a very small dose due to transportation with the natural background. That's not possible and it was one of the comments of Thomas Tenforde this morning to say how it's possible to make

a difference between the natural background and the very small dose rate with an experiment. It's not so easy.

DR. TENFORDE: Let me address Ruth's comment. First of all, 10 micro-sieverts is defined by NCRP and it's agreed upon almost worldwide that that is a negligible individual dose. Now, that doesn't mean if you get a lot of repeated exposures to 10 micro-sieverts, let's say you have a truck driving by every minute or something, that you wouldn't see some cumulative effect.

However, we do know that the critical issue is distribution of dose over time. And there's a vast literature on animal carcinogenesis, for example, and Bob Ulrich's many elegant studies and others that show either dose protraction or dose fractionation creates lesser outcome in the long run than single acute exposure. So there are recovery processes going on and to estimate the extent of the recovery processes, you really need to have a clear understanding of the distribution of dose over time and so you know, in a random situation, it's very difficult to achieve that.

And that's why in EA's and EIS's as Dr. Mossman said, quite often the starting point is the

worst case analysis where you take the maximum possible dose even if it's protracted over time or a fractionated exposure, and use that as a basis of estimate of risk and I mean, that's the nature of an EIS or an Environmental Assessment is you want to know what could happen in the worst case typically, but that isn't the proper scientific approach to take.

You really need to understand distribution of dose over time and in your situation if this person was exposed let's say once a day to 10 micro-sieverts, I'd say, well, they got a negligible individual dose every day, you know.

MEMBER WEINER: That answers the question. One very quick one, and that is we mentioned -- epidemiology was mentioned in many cases but there are a number of uncertainties in epidemiology and it's very uncertain and I wonder, Dr. Land, if you have looked at the distribution of epidemiological fact parameters.

DR. LAND: That's my job. That's what I do.

MEMBER WEINER: That's great.

CHAIRMAN RYAN: So the answer is yes.

MEMBER WEINER: The answer is yes. Do you think it's adequately considered the -- in drawing

conclusions from epidemiological studies about the effects of ionizing radiation? Do you think that the uncertainties are adequately included?

DR. LAND: The ones you can deal with, yeah, the ones you know about, you can -- if you don't have any measurements, then you can't do it then.

CHAIRMAN RYAN: Jim?

MEMBER CLARKE: Thank you. Let me join my colleagues in saying I think this is a wonderful day so far as well and thank all of you for some very interesting presentations. I have kind of a basic question but I need to give you a little background and frame it a little better.

If we start out with -- by the way, I come from the chemical side. I'm a risk analysis person, slowly gaining an appreciation for dose and was engaged for many years in the conduct of investigating and so-called remediation of contaminated sites beginning with chemicals and moving into chemicals and radionuclides and have some familiarity with the process that the EPA uses to do risk assessment as embodied in the Superfund guidance.

And if we start with -- Dr. Mossman had a nice slide early on of the dose response curve and showing that at high doses all the different

extrapolation approaches pretty much come together. I remember a similar chart for DDT where many of the models that you could use really converged at the high doses but as you went down to the low doses, they started to diverge.

And you know, that divergence on the chemical side, this case up before, can be considerable. I mean, it's many orders of magnitude. I guess we could force them all to come back together again and look at them as linear, very low doses, but we find, at least for those kinds of analyses or if you wanted to use that process say to estimate a so-called maximum contaminate level for the chemical in drinking water, you could essentially do that same thing, pick an exposure scenario, get a slope factor, risk coefficient and calculate a number.

But I think we find that we have to operate at least for those objectives in that area where there's just a great deal of uncertainty. So the question arises to me is, is there -- and by the way, the EPA removes the mystery by telling us what model they've used and give -- and they give us the slope factors so the calculation is actually pretty straightforward. You just calculate what's called a chemical intake through an exposure scenario and then

you multiply it by a slope factor and you get a risk.

Also it strikes me that every time we do that, we get into trouble, so that I'm gaining an appreciation for more of a semi-quantitative approach to risk analysis which I think is coming out of the merits of using collective dose, if you're going to use collective dose at all, more of a relative kind of assessment.

But I guess my question is around this area of great uncertainty where we find we have to operate and I'm wondering given the cellular work that Mary Helen described and some of the other studies, is the work that's coming out of the laboratory investigations at that scale, is that going to position us to better select one model we might use for -- on the chemical side it would be for a certain class of chemicals, I guess.

In other words, is that going to help us with this ultimately? And I didn't mean to --

DR. BARCELLOS-HOFF: That's an interesting question. Now, but I guess it depends on how much the regulatory policy is set on the science and what the scientific community considers the weight of evidence. I think there is one -- in my view, one community of scientists who value really the observational data

that you can get from epidemiology as being the evidence of what will happen in humans.

In the biological studies, the experimental research, you always have the question of expectation either to dose rates or across species or across organs. And that is a complicated question. I think where the science, the basic research comes to bear is in asking -- is coming down to this question of what does the science support in terms of if you have alternate models, can you provide a biological rationale to LNT?

MEMBER CLARKE: That's my question.

DR. BARCELLOS-HOFF: We can certainly provide a biophysical rationale for LNT but can you -- is there sufficient biological evidence to support LNT at very low doses and I think that's where the whole field is looking.

MEMBER CLARKE: I guess I'm going a little beyond that because I'm going into a region where you might have multi -- single hit, multi-hit, all these different models and saying you're operating in that region and you want to -- you just want to say, well, I'm going to pick a model, you know, I'm going to calculate a risk, you know, what's the best way to do that.

I guess if I had my druthers, I wouldn't do that, you know.

DR. MOSSMAN: To me the Karl Popper philosophy becomes very important and the reason why I say that is what we try to do with the science is to discredit competing theories. So really what we're doing is collecting data that hopefully will allow us to say that there's -- that what we want to say is that there is no threshold or that there is a threshold with a high degree of confidence.

If we can make statements like that, if we can make statements like yes, the dose response at very low doses is linear or it's curval linear, then we can begin to make rational decisions about whether certain candidate theories are scientifically defensible or not. I am not so sure that we're ever going to come to that. I don't think we're ever going to come to the situation where we're going to have rigorous scientific data that's going to allow us to exclude certain candidate theories in favor of other ones. Therefore, I think science is very important to establish -- to defend particular theories but the decision to use one theory or another would be an economic, political and social determination. And what's key is, is that whatever economic, social and

political determinations you make. It has to be based on scientific defensible information which we have, frankly, for all the theories.

I mean, we can -- there are people out there who can point to data that says, yes, Hormesus (phonetic) is right. We've got lots of data to support that. Same thing with threshold, same thing with curval linear, same thing with LNT. And of course, what the Bureau 7 report says is the preponderance of the evidence, an interesting rule for making decisions, but the preponderance of the evidence is in support of LNT.

Okay, that's fair enough. That's their -- that was their determination. So I'm not very convinced that the science will ever come to the point where we're going to be able to disqualify theories.

MEMBER CLARKE: Let me respond to that. I appreciate that and again, just to put my question into perspective, we are using a process that estimates risk and we are using that process to evaluate the current state of the contaminated site and we are using that process to evaluate certain alternative approaches through remediation technology and remediation strategy and we are spending billions of dollars with this process.

So my question simply is there -- if we have to operate in these regions, we have to do these calculations, and again, I'm much more comfortable with risk when I'm using it on a more relative semi-quantitative comparative basis, but if we have to operate within a certain risk range, which the CIRCA (phonetic) regulations specify, and if we have to use this tool to make these decisions, is the work that is being done at the -- and I believe the EPA is doing the same thing for chemical carcinogenesis, they're looking at in vitro and cellular. They're looking at everything they can. Also a lot of the data that we use for chemicals came from very high human exposures as well, for example, arsenic, and we have the same extrapolation problem.

So is this helping us get to that area that we have to operate in, I guess is my question and I probably answered it.

DR. MOSSMAN: Well, I mean, the way I see this thing going and I'm probably wrong but I'll say it anyways, is that someone or some group of people will say this is costing us too much money. Is there another way that we can manage risk using a scientifically defensible underlying theory that will cost us less money and still protect the public health

and the environment?

CHAIRMAN RYAN: Ken, one element of that is back to this idea of bounding case.

DR. MOSSMAN: Is what?

CHAIRMAN RYAN: Bounding case. Bounding case is an admitted overestimate of risk.

DR. MOSSMAN: Well, LNT in some ways is that --

CHAIRMAN RYAN: Well, leave that aside for the moment.

DR. MOSSMAN: Okay.

CHAIRMAN RYAN: As John Garrick, who was my predecessor in this chair would say, "You can mask risk by using bounding analysis". Actually, you don't know what it is because you haven't done a credible job of trying to assess it. Now, sorry, Jim?

MEMBER CLARKE: I'm sorry.

CHAIRMAN RYAN: So if -- you know, if you think about the way we reach those decision tools, particularly if we use bounding analysis so use this, well, we assume, you know, all sorts of goofy assumptions, for example, low level waste. You know, you have to have a farmer who lives on top of a waste site and he has to grow his food in exhumed waste, which I challenge anybody, show me how that can be

done.

But you know, we do it anyway and then we come up with a dose calculation and say that's -- you know, that which we do on concentrations. Is it safe or is it bounding? Well, you know, I guess so but does it really tell you what the risk is from disposal of the waste, no. So I struggle a little bit with you know, this idea of you know, the premise for some of the decision making are these sorts of bounding analysis that really don't tell you what the risk is. It's a convenient way to calculate stuff and say, well if we're there we're okay. It has nothing to do with risk. Nothing.

That's my point is that if you use some of these extreme cases, you don't learn anything about the risk. You just have made a decision based on an absolute. So that's kind of a strategy for how to assess risk I wish we would get away from.

DR. BARCELLOS-HOFF: I just wanted to raise that in terms of strategies for managing risk, I also work in -- for NASA's program for space radiation exposures where, of course, you're never going to have a population in our lifetimes or next couple lifetimes to actually evaluate risk of sending people into space and you have a very complex space radiation exposure

on top of your biology.

CHAIRMAN RYAN: All the quality factors are well worked out, I'm sure, yeah.

DR. BARCELLOS-HOFF: An RV is a lovely concept. And their strategy has been to try to attempt, and I think attempt is about where we are, a molecular mechanistic based model of cancer risk. Now, what does that mean? It essentially at one level says identifying every single step and the possible interactions in this hugely complicated human body which consists of $10^{14}$ cells. And so you say, well, that will keep us busy longer than getting to Mars, right? But there is some element of reality there and because what it says is, what you need to know are going again to systems biology is the critical cuts, the really -- and we've been working under that paradigm for many years thinking that the critical nature was a genetic sequence. And you know, putting -- and you know, that that was it and that we could extrapolate everything from changes in the genetic sequence. And now, we're trying to incorporate more of this and I think there will be this better defined process of what it takes to become a cancer.

And maybe that's something that will eventually used but again, I have no real appreciation

of what you actually do. So -- but I think from the biology side, that's the goal.

CHAIRMAN RYAN: With that, we're kind of at the hour where we need to take a 15-minute break. We have some other stakeholders as I mentioned this morning, that have asked for time to participate and so we'll start promptly at 3:15 with our two requesters starting first with Dr. Ted Rockwell I see here in the audience, and Ted if you want to go up and get yourself set up that will be fine. And also, Mr. Lynn Ehrle, are you still with us on the phone, sir?

MR. EHRLE: Yes, sir.

CHAIRMAN RYAN: Okay, well, thank you for being with us. And just for the record, would you tell us who you are at the microphone? And we've got a third request.

DR. COCHRAN: I'm Tom Cochran with the Natural Resources Defense Council and I would like to speak as well.

CHAIRMAN RYAN: Dr. Cochran also has some time to speak after the break. So we'll reconvene promptly at 3:15.

(A brief recess was taken.)

CHAIRMAN RYAN: Could I ask everybody to take their seats please, and reconvene. Come to

order, please. Dr. Rockwell.

DR. ROCKWELL: Mike, I have to congratulate you on a tight ship you're running.

CHAIRMAN RYAN: Well, you know, we've got a lot of speakers and a lot of views, Dr. Rockwell, and we certainly want to have appropriate time for our stakeholder comments this afternoon. And without further ado, right on the appointed hour, if you'd take it away, Dr. Rockwell, you have about 15 minutes.

DR. ROCKWELL: Thank you. Well, I've been in the nuclear business for 64 years now from when I was in Oak Ridge during the Manhattan Project and the explaining the thing is very complicated and we always get tripped up. Every item you want to talk about turns out you can't talk about that one until you've talked about the other one first kind of thing.

My objective in putting the material into the record is a small one and maybe a bigger one will follow with that but the smaller one is that we in the nuclear community, authoritative people in the nuclear community, are saying opposite things day after day. We're telling them over and over again there is no such thing as a safe dose of radiation and the other day the Chairman said in a big public meeting, the public needs to understand that here is such a thing

as a safe exposure. You know, and it goes on.

We're completely repeatedly told that collective dose can't be used and yet, as you've heard, we have procedures in which the Government is requiring people to use collective dose to make evaluations. So I would like to see if I could contribute a little bit to resolving that. I find that there's a lot of information out there that people don't really want to hear and it's amazing how fast they can forget data. And when you put a number of these things together, one after another on a piece of paper, it's really quite a shocker and that's one of the things that I've tried to do.

So what I've put into your record here with the little memory stick and it's on the web so anybody can get it if they click this thing. They can get the whole package of stuff we have here.

CHAIRMAN RYAN: Now, this is your packet, I believe.

DR. ROCKWELL: Yeah.

CHAIRMAN RYAN: And we've made copies available in the back of the room for other participants as well.

DR. ROCKWELL: Yes, that's right.

CHAIRMAN RYAN: Okay, very good.

DR. ROCKWELL: There are two things here. One is this info paper that I've just mentioned and I threw in at the last moment in response to the idea that gee, there really isn't any good low dose information and therefore, we have to make a lot of assumptions we wouldn't have to make otherwise. And that simply is not true, that there's no good radiation -- low dose radiation information. And so what I did just hurriedly is show you that -- mine is in color because this is the original one but since I'm paying for this out of my own pocket, the black and white -- you're getting black and white copies of it.

But this is an outline of the material in the Radiation Science and Health website. This is data, scientific data, at low dose that refutes the LNT that shows that low dose radiation is not harmful and is, in fact, beneficial in most cases, Just as is stated in NCRP 136, it is important to remember that most populations exposed to low dose radiation are not harmed and as a matter of fact, most are benefitted. That should have been the bottom line. They should have said, that's the question you asked me and here's the answer.

But they come to the opposite conclusion

in the report, as you know. But this thing is five pages of outline and after each line in the outline, and this is eight point typed single spaced and we've got five pages of it here, just of the outline. And after each line in the outline is how many reports. There are 29 on this line, there are 106 reports on that line and so forth.

This is just to show and if you want to see how substantive those papers are and how legitimate they are, go to the website because there it is, but the basic document here is in three pieces. It's a one page that says what it is and that's what's on the website that you start clicking on to get the rest of it. And what -- on the printed copy we give it to you, it's a one-sheeter. And then there's a four-page executive summary that goes through the arguments and doesn't have two many links on it and then we have the scientific attachment which is 26 pages showing some actual stuff.

Now, even this 26 page thing does not have any figures and doesn't have very many pieces of actual data but what it does have is some links and citations to reports that are really solid and those, in turn, have a lot of citations of their own. So this is the information on which decisions can be made

and pulling in a lot of stuff that hasn't been used before and which should be. Now if these reports are legit, they ought to be used. If they are not convincing, then they should be repudiated, but they are ignored. They just don't get into the reports.

So that's what's the package in there that you can use. Now, the -- there's a couple of points I want to make and that is that in addition to the fact that this good data that is not being used, there is bad data that is being leaned on very heavily. There's some really terrible reports that are cited over and over again in favor of preserving the LNT. And some of them have just very basic scientific flaws in them. The work of Cartiss, et all, for instance on those things that -- did some terrible stuff of data selection. There were seven little data bins and three of them were -- showed some damage, net damage and four of them showed benefit. So she never mentions the four that showed benefit, just quoted the others which was 70 percent of the data. She ignores 70 percent of the data. So she ends up with only 30 cancers out of the whole thing. That's not enough to get good statistics.

So she builds a computer model of 500 cases to represent the 30 and then goes for there.

And on top of it all at the beginning, she says, that since there's no reason to believe that radiation could be beneficial any radiation effect will assume it's damaging when used just one-sided -- one-tailed curves. Really bad stuff.

So let me tell you about what I think is some of the myths of this game that ought to be examined and fixed. One is that there is a debate going on between people who favor the LNT and people who don't. There is no such debate. I don't know anybody that will stand up and defend scientifically the basis for the LNT. There are people who say that although there isn't good data to support it, nonetheless, it's the best we have and it's prudent to assume and so forth and so on.

I've been trying to get a debate between the pro and the non-LNT people. We tried to get -- when Charlie Meinhold was Chairman of the NCRB, tried to get him to chair a debate and lead a debate of people, we could pick on either side and here's some of the scientific efforts. And you know, he wouldn't do it. He wouldn't get involved. He says, "Gee, we're in the middle on the thing," he says.

On one side you have people like Sternglass and Radford and who was the third one, oh,

Coldecott (phonetic) and on the other side you have Cohen and Polycove, who was the other one, Cohen, Polycove and -- the idea that -- and he says, "We're right in the middle so we're not in a position to do a debate. You know, we must be doing something right because we're right in the middle".

So I have not seen, and I would like to see a good open discussion of the scientific story as to where we are on the thing. Now, I've heard a lot today about the fact that there's more than science involved but Mike opened the meeting with a very important statement. He says, "We don't make policy here, we're here to talk about science". And I think it's important that we act on that and the policy people will decide what they're going to do with the science.

But if we can't give them a straight story from the science, how can we expect them to do their job. So I think it's misleading, I think it's dodging the issue if we pin too much on the fact that there are factors other than science involved here. It seems to me, if I understood Mike and I certainly agree with him, that our job is to talk about what is the best scientific story and right now, as I say, we're talking out of both sides of our mouth and we

can't blame that on the press and we can't blame it on the anti-nukes, we can't blame it on Tom Cochran. He didn't invent the China Syndrome and he didn't put out reports telling people that we're killing people every day at normal radiation levels. When what's his name, the guy from New Mexico was -- Bill Richardson, when he was head of the Department of Energy, he put out this report, calculations showing they're going to kill so many people, 250 people, whatever it was, in the plants and 98 percent of this will fall within the tolerable limits. I don't know how in the world anybody would ever calculate that, you know, it's an impossible thing to say, but then the DOE proceeds to run out and send people to all the old people's homes, retirement homes and things like that and tell them, "Don't you feel sick, you know, you were a visitor or a participant in one of the bomb tests", and so forth.

So we're really -- we have created this problem, we in the nuclear industry have created this problem all by ourselves. The scientists and the contractors and everybody else, we've created this fearful thing. We're going to have to build a 323-mile highway for a billion bucks so that we don't send Ruth's trucks be the churches and schools. If they sent them by churches on weekdays, I suppose it would

all right but you know, we've created this thing and so I think it's really important that we clarify that if it is not true, that there is no such thing as a safe dose, then we ought to quit saying that and we ought to tell people that that's what it is. And I've heard the argument that says that we should, you know, not look as if we're trying to downplay the danger, that if we say something like that, we'll be considered that we're speaking in our own behalf.

Why shouldn't we? Who else is going to do it for Pete's sake? So this is a document, I hope you'll look at. I hope you'll look at the radiation science and health thing here. There are hundreds of good reports here and I was told that what I should do is get the facts out and let people draw their conclusions on the thing, but I've got a bunch of letters in here quoting from different people with bitter complaints that they have sent data in, whether it's NCRP or whether it's DEIR, I've done it myself, testified, gave them the data and it's never mentioned, never mentioned.

You say these are flaws in the draft that you sent around and they send the thing, and they're still there. And that's not a narrow group of people. That's the thing. So that I think that we've got the

power and in an advisory committee like this, you are freed from any obligation to have to implement these policies, so you're set up this way solely with the idea so you can speak truth to power. That's your job. You don't have to live with it.

You know, you don't have to live with it, but you ought to tell them what you think honestly the science says and if they have some trouble dealing with that, they'll have to take that responsibility but they won't be able to say, "Gee, my advisory committee told me this was what the science said". That's my time, I think.

CHAIRMAN RYAN: Thank you very much for your comments. Just for everybody's benefit, Dr. Rockwell's material will be part of our written record and your comments today a part of the transcript for this meeting. So it will be part of the record.

DR. ROCKWELL: Thank you very much.

CHAIRMAN RYAN: Thank you very much. Next, I believe we have Mr. Lynn Ehrle on the phone.

MR. EHRLE: Yes.

CHAIRMAN RYAN: Mr. Ehrle, the floor is yours and I think we can hear you quite well. We have a very good speaker phone here. So you have the next 15 minutes, sir.

MR. EHRLE: Thank you. Lynn Howard Ehrle, I'm a retired consumer economics and social studies teacher who happens to have been studying radiation effects at low dose for the past 40 years. I became interested in this field initially because I began to be concerned about the whole issue of nuclear power and shortly thereafter, I was a founding member and was the Vice President of Consumer Alliance of Michigan for a 10-year period during the `70s.

Did all of their testimony in the Public Service Commission and was even nominated twice for a post but unfortunately the Governor didn't want to have a consumer advocate setting utility rates so that was that. The -- there's several concepts that I am curious to see if we can get our hands around. A statement was made by one of the panelists that there's an elephant in the room. Unfortunately, you haven't even tweaked its trunk. There are issues that will not be discussed by neither the Commission nor NCRP nor the ICRP. Those organizations are basically closed unions.

They're self-appointed, self-perpetuating, and there's no way that all stakeholders can get a foothold in those organizations. And it's very simple. A statement was made by Dr. Le Guen who

indicated that science and politics should remain or be separate. My observation is, is studying the sociology of the issue, science since Hiroshima and Nagasaki, has been inextricably interwoven with politics.

Classic example, the Atomic Energy Act of 1946 locked up radiation research. In fact, it stayed locked up all through the Cold War, under its restrictive data label, RD, and in the Act, it, of course, was interpreted to mean that all radiation research relative to weapons was borne secret. In fact, the book "Atomic Audit", done by Brookings Institution that estimated $5.8 trillion has been spent on nuclear weapons and the system between 1940 and 1996. The Department of Energy, they stated, had at least 280 million pages under lock and key.

And so you can see the enormity of the problem for those of us who had a concern about risk as it related to the exposures from nuclear power, from the embryonic nuclear power plants that were coming on line. By the way, for several months I tried to search out studies dealing with shoe fitter salesmen. You know, there isn't a study around. Well, I love to stand under that periscope and see my toes wiggle. And one day about 1952 they took them

out and I asked the salesman where did they go. He said, "I don't know, they just came and took them out". I said, "Why"? He said, "Well, we were never told". Well, obviously, those salesmen are all dead because those were low doses over time, protracted and scatter gun fluoroscope. So we can look at events.

For a classic example, what is it that was kept under the rug after Hiroshima? Indeed, it was not until 1950 that the American Bomb Casualty Commission began to do its work. And so there was a long period where Japanese physicians were told to report their findings on health effects to the agency that was coordinating their efforts with the Army. And indeed, that whole process, that super secret process, was set in motion by Leslie Groves, compartmentalized so that nobody could know what the other hand was doing. And that had serious consequences scientifically as you might well imagine.

And so as the situation developed from the Atomic Energy Act, we began to see that some of the scientists were treated as Pyrrhus. They were made -- subjected to scientific shunning, as it were. They were closed out because they were too independent, because they may challenge the conventional wisdom and indeed they tried to but they could never get a

hearing.

Take the case of John Gofman, Gofman was a brilliant scientist. He is my mentor. Over a 12-year period I conversed with him frequently. He sent me all five of his radiation books. The first one "Radiation and Human Health", over 900 pages, a brilliant book, but as one doctor said in complaining about it, "Well, that was published by the Sierra Club", as that somehow case a pall over the science. It really is even now very current in terms of what was presented.

And yet as the Atomic Energy Commission gave Gofman a grant, Associate Director of Lawrence Livermore. Well, before that, he had distinguished himself as a cardiologist. I've interviewed several cardiologists. They don't even know Gofman's name. He wrote the book. In 1974 he was designated as one of the top 25 cardiologists of the past quarter century by the American College of Cardiology.

And as far as radiation effects, he could run circles around some of these people that pontificate about the fact that there's no low dose data. It's ridiculous. It's all over the place. When Klausner was head of NCI, he spoke out in 1996, I recall at Nancy Pelosi's town hall meeting in San

Francisco and he said, "We don't have any data on low dose". I sent him a list of 71 low dose studies that were all peer reviewed and never got a response. There's plenty of evidence. I'm looking at John Gofman's book right now, "Radiation Induced Cancer from Low Dose Exposure". Two top flight medical physicists reviewed his book along side Beard 5 (phonetic) and concluded that persons concerned about radiation risk should read both of these excellent studies.

And it seems as though Gofman had already established himself as an anti-nuclear advocate and so his studies were uniformly dismissed and so you wonder why I have a tone of anger in my voice. When you see people like Albert Einstein that was trailed, read the "Einstein File", a brilliant book that summarizes what the FBI did in copious detail to hound him and cause him and other scientists to be on the defensive and the same thing happened to others as well.

And so they either caused them -- well, take the case of Heuper. Here was a man, who in 1948 became the first director of the Environmental Cancer Section of NCI. They put a collar on him because he worked at Dupont. They sent his studies to Dupont for them to review. If you haven't heard some ridiculous

stuff there, read it in the book "Cancer Wars", by Proctor, who goes through the case of Heuper. When he retired in `64, the NCI disbanded his project and shipped his large library, broke it up and sent it elsewhere. And so that was the treatment that people who dared to challenge the conventional wisdom would get. So you can see why I make the conclusion that one of the impediments to low dose radiation and effective science is because the people have come up with new science.

For example, here's a classic one for you, the Health Physics Society, Ken Mossman former President, they came up with a report, and I'm looking at it right now that said below 5 to 10 rem that "risk of health effects are either too small to be observed or are non-existent." Well, I should refer you to the TNAS paper. Brenner was the lead author, 15 top flight cancer experts were on that study and they concluded that there was risk, good epidemiological evidence, that low dose risk from 10 to 150 milli-sievert and protracted dose of 50 to 100 milli-sievert.

Well, that certainly goes against what Mr. Mossman has said in the past relative to statements that he has made that -- in fact, one of the articles

that I had from -- that he had written related to a statement that he said that these doses of -- at those levels are diminimus. So here we have people who supposedly are experts in the field and yet you go to either ICRP or NCRP and none of the people that I'm dealing with and right now, I'm -- for the past two years was appointed Senior Biomedical Policy Analyst for the Organic Consumers Association that basically is trying to keep food safe and I worked with the director in the early `90s to try and keep Monsanto from putting rBGH in the food but unsuccessfully and so he appointed me to this post because he wanted to see this project that I put in front of him, the establishment of an international science oversight board. We don't have a dime, that's the problem with all the non-profits. They don't have time to travel to Washington. They don't have time to get involved in these conferences and they're certainly not going to get any grants from the NIH or the NCI to deal with these conflicts of interest that so bedevil our science today.

So here we have this huge problem and in Gofman's book, "The Radiation Effects of Low Dose", he points out the genetic risk factors and if you go back to H.J. Muller who, of course, only won the Nobel

Prize for his fruit fly study, drosophila, the treatment he got at first, doctors walked out of his lectures. They didn't want to hear it. He was uniformly criticized, of course, until he won the Nobel and then was called the Father of Human Genetics. But in -- and that was 1946. In 1955, he went to give a talk at an international body and the Atomic Energy Commission -- he had just won the Kimber Genetics Award, the first one from the National Academy of Sciences and he, in that particular award, indicated that one of the accounts he pointed out the tremendous damage, autogenic (phonetic) damage, that is caused by radiation and then in the talk that he was about to give in `55 at the International Conference of Peaceful Uses of Atomic Energy, he was called up for this, sponsors of the meeting were called up and said, "Muller can't speak. He's not designated as a technical advisor by the Atomic Energy Commission".

Can you believe the treatment of a Nobel Laureate and a recipient of the Kimber Genetics Award being told that by any government agency? That shows the tremendous power that we're up against and now we have Chernobyl. And three of the members of my International Science Oversight Board, 16, by the way

out of the 41 are low dose experts, three of them from Russia, and if you go over, it's very interesting to note that the World Health Organization and the ICRP and the IEA have had the Russian studies in their files for years and have refused to translate them. There is a book that I reference in my study that I passed out there that apparently you must have in front of you. That book is called "Chernobyl 20 Years On". It can be viewed full text at euradcom.org. That is the European Committee on Radiation Risk.

The editors, Chris Busby, a UK physicist and Alexey Yablokov, a Russian biologist are on my oversight board. And they distinguish themselves by Yabolkov actually translated some of -- enough of these studies to compile something that nobody else has ever bothered with. As you know, the Beer studies deal with cancer mortality. This book has a whole long list of what is equally as dangerous and that is the non-cancer effects and they are all from low dose.

Of course, you look at -- with the exception of the liquidators, of course, that worked around the reactor and were subjected to very heavy doses, but the fall-out was basically low dose. And what is it that could cause low birth weight in many countries to spite, after Chernobyl? What other

event? You say we have to measure dose. Why do you have to measure dose? Look at the effects and then tell me what other events took place concurrently with Chernobyl that would cause a spike in low birth rate, which by the way is the single most important cause of infant mortality.

CHAIRMAN RYAN: Mr. Ehrle, excuse me. First, we do have your materials, but second, I'd like to ask you in the next couple of minutes to finish up.

MR. EHRLE: Okay.

CHAIRMAN RYAN: We do have another speaker that we want to include.

MR. EHRLE: Understand, and I appreciate the time.

CHAIRMAN RYAN: Thank you.

MR. EHRLE: The book that I mentioned on that website is one that everybody can read and should read if they're concerned about the non-cancer effects. As you might recall, and I have the three volumes of Unsteer 2000 (phonetic) that basic problem that they said with the survivors at Chernobyl is that they're suffering from psychosomatic problems.

Well, guess what, that's radiophobia. Isn't that something to us that are concerned about the radiation risk at low dose that by the way studies

now indicate are more dangerous in protracted doses over time than in a single acute dose, but you will not hear that discussed at the NCRP conference. You will not hear discussed the bystander effect or gnomic instability to the effect of the Hsu study (phonetic) with Tom Hay at Columbia and others that I have right here that indicated that a single hit, a single track of radiation can actually, through a process of gap junction communication effect other cells at far distant site and they predicted that this would mean that we have to reorient our theory about the Japanese A-bomb study.

CHAIRMAN RYAN: Mr. Ehrle, I'm going to have to ask you to finish up.

MR. EHRLE: In fact, the obvious is that there is an excess risk. It's super linear at low dose and I thank you for the time.

CHAIRMAN RYAN: Thank you very much for your participation. Our next speaker is Dr. Thomas Cochran. Dr. Cochran?

DR. COCHRAN: Mr. Chairman, thank you for this opportunity. For those who don't know me, I'm Thomas Cochran. I'm retired as the Director of Nuclear Program at the Natural Resources Defense Council and I'm on the Senior Staff there. I was an

Atomic Energy Commission Health Physics Fellow in the `60s and have been a member of the Health Physics Society since `64.

I've several short items. First, the announcement says you plan to prepare a letter to the Commission. I wasn't here for your opening remarks. I don't know what that entails but I would caution you that this agency is not under Executive Branch guidance, not the agency responsible for setting general policy on radiation standards. That's the purview of the EPA so be careful what you ask for.

CHAIRMAN RYAN: We're -- our letters are consistent with our charter and we provide advice on the scientific aspects of what we hear. So we're not here to give policy advice. We made that very clear at the outset.

DR. COCHRAN: Okay, thank you. Secondly, this is just a plea on the use of the term "low dose" and "low dose rate". I'll pick on Dr. Le Guen because you quoted Collin's with reference to 94 milligrade per hour as a very low dose rate and in some quarters that might not be viewed as a very low dose rate. And I just think in these discussions the more one focuses on the numbers and not sort of use low dose to mean almost any dose depending on which exercise you're

involved in the better.

Next, I think Allen mentioned, of course, all of these sources that are regulated by this agency are added to background radiation and therefore, really the interest is in the range of background radiation and somewhat above. And that I think a lot of these problems that people have about arguing what the meaning of collected dose and so forth would be lessened if people would -- now that we have computer models and they're easy to do these calculations would plot a cumulative risk, number of people at risk versus the risk. So it would be a cumulative plot and then people can make their cutoff and either do that as a dose, cumulative dose, versus dose or cumulative risk versus risk and then don't put yourself in the position of trying to be the arbiter of what the -- whether there's a threshold or not and let people look at the data and judge what the individual risks or the collective risks are.

The -- another sort of plea is on discussing extrapolation, we're not -- this whole debate is not about extrapolating dose but it's about extrapolating overdose rates because if you look at, for example, the Oxford study, somewhere in the 1 to 5 rem or I use the old terms 10 to 50 mSv, that's the

dose one gets from natural background radiation over 10 years, 15 years. So we're not extrapolating dose. We're extrapolating dose rates, to ask the question of whether the risk is still the same or lower or higher at the lower dose rates.

Couple of minor points, Dr. Le Guen, in your slide, in your conclusion, you have a statement, "All data show lower effectiveness of low dose and dose rates". I would advise you to take that out. I think that's in error. All data don't show that. Some data show that. The -- there's another statement, I believe, of Dr. Mossman that I think is in error when he said dose limits don't have anything to do with risk. I know that you're implying but in fact, from the very beginning, dose limits were based to minimize the risk. In the early days they were based on radium exposures and the risk of radium exposure.

Just an observation in the discussion of effects at low dose, the concept of dose itself already averages vast differences in energy deposition across tissue and across organs and so forth. So this is just my personal view, it's hard for me to reconcile the concept of a threshold. I don't believe -- I personally believe the linear model -- the

preponderance of data is that in a Beer 7 report supports the linear model and that's the best estimate today given all the uncertainties. And I have difficulty when I recognize that for a single hit of a gamma or even a high LET radiation, you get vastly different amounts of energy deposited in local areas depending on whether it's Compton scattering and what kind of Compton scattering or whether it's some other photoelectric absorption or whatever and when we talk about dose we average that over an entire organ. And so then turn around and talk about threshold as if there's a threshold in energy deposited below which there's no effect, it just doesn't make a lot of sense to me.

Lastly, I want to say just a word or two about collective dose because there was some discussion of that toward the end. I think the concept of collective dose is extremely important in some applications. If you're talking about individuals, a lot of individuals want to know their individual risks, either their average risk or what the maximum likely -- maximum possible risk is but if you're talking about weighing benefits and costs of a technology or process when proving safety, you've got to weigh all the benefits against all the costs. And

even that doesn't factor in the issue of justice. That implies that the same people are gaining the benefits as receiving the costs or risk. But you can't weigh the benefits and cost even if you don't sum up all of the costs. And only collective dose, if you accepted the linear model is the best estimate of the effects at low dose, given the uncertainties, then you've got to add in even those small risk to large populations.

And I would -- maybe some people would believe that this is -- should be repealed but I would point out that we do have, as in 40 CFR 190, I believe it is, standards set in this case for the amount of noble gases released from commercial reprocessing facilities that are based on a collective does assessment of the dose to the -- all equal in the Northern Hemisphere from krypton-85 releases.

And I think that's valid. I was on a NRC Citizens Advisory Committee that was asked to give advice on whether to release the krypton-85 from the secondary containment in Three Mile Island and I said, it ought to be released but that's based on a collective dose assessment. So I do think it is important. It's certainly important for me and I would hate to see some other body or the Commission

tell me that it's misleading for me to see the collective dose. Put it out there and those of us who want to use it, will use it and if you don't want to use it, you don't have to use it. Thank you. I'll be happy to answer questions.

CHAIRMAN RYAN: No, I think thank you very much for your comments. We appreciate it.

DR. COCHRAN: And I don't want to be critical of what your -- I just -- there were a couple of things I disagreed with.

CHAIRMAN RYAN: Thank you. With that, we are at a point in our agenda for closing remarks. I guess my closing thought is that I think we've had a very rich discussion during the day from a wide variety of views and subjects and topics and I appreciate everybody's participation. I'd like to take the last minute or so and preview tomorrow.

We'll start with two presentations, first with Dr. Puskin from the EPA and Dr. Holahan from the NRC's Office of Nuclear Regulatory Research, with I believe the US EPA agency views and the NRC staff view. So we'll start with those presentations and again, starting up with. I'm sorry, the first presentation, we'll start just with opening comments and the opening statement at 8:30 and then of course,

Dr. Hammitt will be here from the Harvard School of Public Health to offer his views on the economic perspective and then we'll go into Dr. Puskin and Dr. Holahan. So that will take care of our morning, and then we'll have a similar panel discussion on those issues and bringing in any other thoughts we might want to share from today's discussion and again, we have an opportunity for stakeholder views. At this point, I don't know that we have anybody who has requested a slot in that time period but we'll certainly have that available if anybody would like to make additional comments in the same time period as we used today, and with that, we'll close the working group somewhere around 4:00 o'clock and then we'll be onto other business with the Committee. So thank you very much. Have a pleasant evening and we'll see you promptly at 8:30 tomorrow morning. Thank you very much and we'll close the record here for the day, thank you.

(Whereupon, at 4:05 p.m. the above-entitled matter recessed to reconvene at 8:30 a.m. on April 9, 2008.)