U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH

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ADVISORY BOARD ON RADIATION AND
WORKER HEALTH

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WORK GROUP ON SCIENCE ISSUES

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TUESDAY
APRIL 17, 2012

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The Work Group convened in the Brussels Room of the Cincinnati Airport Marriott, 2395 Progress Drive, Hebron, Kentucky, at 9:00 a.m., David B. Richardson, Chairman, presiding.

PRESENT:

DAVID B. RICHARDSON, Chairman*
R. WILLIAM FIELD*
RICHARD LEMEN*
WANDA I. MUNN
GENEVIEVE S. ROESSLER
PAUL L. ZIEMER

ALSO PRESENT:

TED KATZ, Designated Federal Official
IULIAN APOSTOAEI, ORAU Team
OWEN HOFFMAN, SENES
DAVID KOCHER, ORAU Team
JENNY LIN, HHS*
JOHN MAURO, SC&A*
JIM NETON, DCAS
SUSAN REUTMAN, DCAS
DANIEL STANCESCU, DCAS
JOHN TRABALKA, ORAU Team

*Participating via telephone

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

9:02 a.m.

MR. KATZ: Okay. The agenda for the meeting is posted on the website, NIOSH website, under the Board meetings section. And, David, it's your meeting.

CHAIRMAN RICHARDSON: Okay. Well, thanks, everybody, and I'm sorry that I can't be there.

I guess as a starting, I wanted to see if there are additions to the agenda or changes. Ted had suggested there might be some issues with scheduling, but, hearing none -

MR. KATZ: Okay, no suggestions. Nothing in the room.

CHAIRMAN RICHARDSON: Okay. Then what I'd propose doing is starting with the presentation from SENES. I think that will - I had a chance - I received the slides last night. So, I think that will be a really

useful starting point to kind to get us on a common footing.

And then we can move to a discussion following that and work on ideas about how to move forward with this.

MR. KATZ: That sounds good. And let me just note for the other Board Members on the line, I sent to you that presentation just this morning.

So, I sent it to your - whichever email you most frequently use. Mostly personal ones. Okay.

DR. HOFFMAN: Okay, so this is Owen Hoffman and I'd like to introduce our presentation.

The presentation is really in two parts. You've got all the slides together, but what we want to do is to first discuss the role of the low-dose and dose-rate effectiveness factor in IREP.

And then after that, to respond to any of the questions that you have regarding

our draft report on the state of scientific knowledge on uncertainties in the low-dose and dose-rate effectiveness factor.

And so, our presentation is prepared in two parts. One is to introduce how it's used in IREP, and the second is to summarize findings and results within our draft report to NIOSH.

To start the presentation, I've asked my colleague Dr. Iulian Apostoaei to begin. Iulian is developing a case of loss of voice. And if something happens in the middle of this presentation, then Dr. John Trabalka is prepared to step in, David Kocher and myself.

DR. TRABALKA: I will begin.

DR. APOSTOAEI: I think he needs to start right now.

DR. HOFFMAN: You will step in.

DR. TRABALKA: Yes, I am.

DR. HOFFMAN: Okay, go ahead.

DR. TRABALKA: Iulian prepared a

revision to the presentation that he gave to the Health Physics Society meeting in July that covered our work, provided a summary of our work.

By the way, I tend to be soft-spoken. So, if anybody can't hear me, let out a yell and I'll start increasing the volume.

And he was going to give the presentation. But since he's come down with laryngitis, I will attempt to take over.

As Owen said, we're going to kick it off by trying to explain how the DDREF is used in IREP, and then cover some of your questions and talk about what we've been doing.

One question that we heard yesterday is, where is Section 6.3? Well, material in part of Section 6.3, Appendix D, which you did not get, and the last couple of pages in the extended summary, covers pre-decisional information on potential new DDREF distributions for IREP.

Since this material has not gone through an external peer review, it has been withheld at this time.

However, inadvertently Section 6.31 and 6.32 were not included in your package. These cover summaries of the information that we used in developing DDREF distributions, our rationale for choosing them, how we prioritize them, how we waiver them. And I think it would be very useful if those two sections could be made available perhaps even at a later date.

We had to send this draft up to NIOSH in fairly short notice and there are some editorial-type errors as well.

So, we could probably provide a revised copy that has those fixed and these additions, if NIOSH so wishes.

We have been trying to get external peer review prior to a formal peer review through the NIOSH process.

Our report has been shared with an

ICRP Committee that was interested in developing DDREF several years ago.

The earliest version they got didn't have Section 5 or any part of Section 6 - Section 5, by the way, covers epidemiological studies that can be used to estimate DDREF - but I got some very good feedback from Dr. Michael Fry, a radiobiologist emeritus from Oak Ridge National Laboratory.

And so, the current draft reflects some - his feedback and he provided some very useful information for us.

We also had gotten a revised version of our report that included Section 5, and those first two sections of 6.3 was provided at a later date to the ICRP Committee, and also to Peter Jacob who is leading a team that's preparing the German version of IREP and who is also heavily involved in an UNSCEAR effort, and we did get feedback from Peter on the section in our

report that critiques his synthesis of epidemiological studies. The version in the report reflects the version after his comments had been incorporated.

I think it's safe to say that we're still at somewhat of a disagreement with Peter over some of the issues, but that's water under the bridge.

Well, anyway, let's proceed to talk about the use of DDREFs in IREP. That's this slide.

The DDREF is an adjustment factor. It's a divisor that is used to reduce the level of risk based on a hypothesized reduction of risk at low doses and dose rates.

And that's based on an inherent linear quadratic model that is used typically for estimating how radiation produces - for dose responses for radiation.

It's not applied to leukemia, because a linear quadratic model is used for leukemia. So, it's inherent in that dose

response model.

Let's go on to the next slide. Now, this is a flow diagram that you should have received - the first part of the flow diagram that you should have received a copy of.

And at the top of the flow diagram, there are two branches. One branch goes to high-LET radiation like neutrons and alphas. And for those, the DDREF is defined as one.

For low-LET radiation, it branches again. That's covering x-rays, gamma rays and electrons.

Again, if the cancer type is leukemia, we have the dose response model that's linear quadratic that implicitly includes the DDREF. So, none is applied.

For other cancers depending on whether the exposure is chronic or acute, we have two different ways of dealing with it.

We have two different distributions for DDREF in IREP for chronic exposure.

One covers breast and thyroid cancers, and one covers other solid cancers. And I'll have a slide that covers that specifically in just a minute.

Now, on the other side is information that suggests that there is an approach to - basically what happens is, there are a couple of equations in IREP that attempt to take risks at higher doses above 200 millisieverts and produce a smooth transition to a chronic DDREF when the exposures are acute. And the acute exposures have to be less than 200 millisieverts to be considered.

Let's go ahead to the next slide. This shows the DDREF distributions in IREP for chronic exposures.

For breast and thyroid cancers, there is a more limited range on potential estimates of DDREF and there's higher weights to values between one and two.

For other solid tumors, the range is extended up to values of five. You'll

notice this is a set of discrete values rather than the continuous distribution that's often used for DDREF.

MEMBER ZIEMER: Can we ask questions as we go along?

DR. TRABALKA: Anytime. Anytime. Fire away.

MEMBER ZIEMER: Just back up just one minute.

On the 20 millisievert value -

DR. TRABALKA: 200.

MEMBER MUNN: 200.

MEMBER ZIEMER: 200, I always have to convert that.

MEMBER MUNN: I do too. You're not alone.

(Laughter.)

MEMBER ZIEMER: But you're talking about acute exposures above that, and isn't that always a question as to whether you should be in sieverts or grays when you get up to high acute exposures, for example,

exposures at the level of the Japanese survivors?

Because the sievert itself has a quality factor, which it's sort of related here. So - but it's not a dose-rate factor, but I'm just asking about nomenclature here.

DR. HOFFMAN: Basically the -

MEMBER ZIEMER: 20 rads is probably all right, but -

DR. HOFFMAN: The fundamental unit, Paul, that's used for risk estimation in IREP is the gray.

I mean, the dose reconstructionists put together sieverts, but then they - the ICRP W sub R weighting factors are used to divide by whatever sievert is input so that basically, the basic unit that's used for risk assessment is the gray.

MEMBER ZIEMER: Okay.

DR. HOFFMAN: Probably if you've been following the way -

MEMBER ZIEMER: I think in your

paper you use gray. And then when you talked about sieverts, I was wondering if -

DR. TRABALKA: I think mostly in grays myself.

MEMBER ZIEMER: I think you need to go back to roentgens and rads and then we'll understand.

MEMBER ZIEMER: Sorry to interrupt.

DR. TRABALKA: Not at all. Stop me anytime.

If you've been following the iterations of the studies of the Japanese A-bomb survivors, you will notice that they have changed from the use of millisievert to - from sieverts to grays.

MEMBER ZIEMER: Grays, right.

DR. TRABALKA: Because they're not using the quality factor that's applied -

MEMBER ZIEMER: Right.

DR. TRABALKA: - to produce a sievert, for example.

MEMBER ZIEMER: Okay.

DR. TRABALKA: We're not done with that one yet.

For other solid tumors, the bulk of the solid tumors in IREP, this distribution is used. It's got a lower - applies lower weights to values between one and two. And the 90 percent confidence interval is about one to three, for example, the equivalent.

Okay, go on to the next one. This is the approach that is - and you don't need to worry about these equations, because I'm going to show you a figure that shows how this works.

These are the equations and the approach that takes a dose somewhere between 30 and 200 millisieverts and converts it to a chronic DDREF.

And if you go to the next slide, this shows how DDREF changes as a function of dose.

So, when you're at 200 millisieverts, DDREF is inherently one. No

issues.

As you decrease the dose, you begin to increase the potential DDREFs. And this simply shows those discrete values of DDREF that were shown in the previous distribution for other solid cancers and how they approach to the final chronic DDREF as a function of dose. And I think questions were asked about that in the material that we received.

Does this figure answer those questions?

DR. KOCHER: The basic idea behind this is that you - it doesn't make sense to introduce the full DDREF at one dose, and a microsievert above that have no DDREF.

It's just kind of a continuous phasing in. You don't get the full effect until you get to zero dose.

DR. TRABALKA: But on this figure, you can see that at about one to ten milligray you have the full effect of the chronic DDREF expressed for an acute exposure, or for

fractionated acute exposures that are separated by five hours in time.

Okay. Everybody clear on this one?

MEMBER ROESSLER: I think I need to study it a bit.

DR. TRABALKA: It's a lot of information at one time.

MEMBER ROESSLER: If you don't look at the -

DR. HOFFMAN: Something like this is second nature to us, but it may be difficult - here are the values of the DDREF for chronic exposures.

DR. TRABALKA: With the percentiles that are applied in IREP.

DR. HOFFMAN: Yes, with the percentiles associated with that distribution. So, at the fifth percentile it can be as small as 0.5. At the 99.5th percentile it can be as high as 5.0.

Now, for chronic exposures, this full distribution is used in IREP. But for

acute exposures, the distribution used is dependent on dose.

And so at doses above, let's say, 150 milligray, virtually the DDREF is 1.0 or no DDREF at all.

But as the acute dose gets less, for example, here we have a small distribution where what we say is the DDREF is uncertain. It varies about 1.0 with a 99 percent range varying from slightly below one up to about 1.5.

Now, if we brought the dose to 50 milligray or 5 rem, now the distribution increases and it begins to approach that distribution that you would get if you had a chronic exposure.

You get distributions near that for the chronic exposure as you get down towards 10 milligray or 1 rem.

MEMBER ZIEMER: Calculationally, is IREP sampling the distribution for each one of these like it does --

DR. HOFFMAN: The standard run does 2,000 iterations.

MEMBER ZIEMER: Right.

DR. HOFFMAN: And so, there would be 2,000 random samples taken from -

MEMBER ZIEMER: Right.

DR. HOFFMAN: - this distribution. So, if you have an acute exposure at 100 milligrays, you could sample 2,000 times from this distribution. If you had an acute exposure of 10 milligrays, you would be sampling 2,000 times from that distribution.

MEMBER ZIEMER: And that distribution looks almost normal for everything but breast cancer. I mean, just eyeballing it, it looks kind of log-normal for the breast cancer.

DR. HOFFMAN: Breast cancer and thyroid cancer -

MEMBER ZIEMER: Yes.

DR. HOFFMAN: -- where there's a much heavier weight at 1.0.

MEMBER ZIEMER: Correct.

MEMBER ROESSLER: So, then go to - now, I understand the acute, I think. Now, the chronic is just that last -

DR. HOFFMAN: Yes.

MEMBER ROESSLER: That last part there.

DR. HOFFMAN: Right, right.

MEMBER ROESSLER: Okay.

DR. HOFFMAN: And do we have the distributions for the chronic? Can we go back to them?

Yes. So, that y-axis you had before is just representing these distributions -

MEMBER ROESSLER: That's what you had on the report.

DR. HOFFMAN: -- that are used for all solid tumors but breast and thyroid cancer. And as you said, it kind of looks like a normal distribution. And by this, it looks somewhat like log-normal.

MEMBER ROESSLER: Okay.

DR. HOFFMAN: But basically that's what's in IREP now. That's not really what's reflected in our updated report.

Our updated report is basically a critique of these assumptions.

DR. APOSTOAEI: So, we have a figure. This is what we have all the way up. In the figure for acute, we have the distribution on the right. It goes over five.

DR. KOCHER: Now, go back to those. Yes, that one. What isn't clear to me on here, I haven't seen this. I've seen a different kind of figure that displays the same thing.

What doesn't come through to me here is about the uncertainty sub L. How is that folded into these curves?

How is the uncertainty sub L reflected in these curves?

DR. HOFFMAN: The D sub L.

DR. KOCHER: The acute dose at which

you begin to phase in DDREF is an uncertain variable.

DR. HOFFMAN: Right.

DR. KOCHER: And so, that has to be somehow reflected in these curves.

DR. APOSTOAEI: It's already included. This is what happens. If you type in a dose of 200 milligrays, constant dose, the code will verify that this is greater or lower than D sub L, it's uncertainty.

For each iteration, it will sample a sample of DL, it will compare the dose that we typed in with that one sample from the DL.

DR. KOCHER: The point I'm trying to make is the uncertainty, D sub L, is somehow already in these curves.

DR. APOSTOAEI: The uncertainty is already -

DR. KOCHER: Because it's not shown.

(Simultaneous speaking.)

MEMBER ZIEMER: So, if I understand what he's saying, so if your dose is - let's

say it's 150, but it has a distribution, so you're sampling around that distribution.

And then you're sampling around a - doing the same thing. It's like kind of a double iteration, or is it?

MR. HOFFMAN: If dose had uncertainty associated with it, yes, you'd be sampling from the uncertainty and dose. But then there's also uncertainty associated with what is the dose that defines a high acute exposure.

And so, it's not 200 milligray. It's a distribution ranging from 30 milligray up to -

MEMBER ZIEMER: That's what I'm saying. But the 30 part of that when you sample it, is going to assign a different -

DR. HOFFMAN: Right, right. And that uncertainty is reflected in this figure.

DR. APOSTOAEI: Yes, that's all taken into account and folded into those figures.

DR. KOCHER: If you take 150, there's only a certain - the probability is less than one that you'd apply this correction at all.

MEMBER ZIEMER: Right, because the lower ones -

DR. KOCHER: Because it's now 30.

MEMBER ZIEMER: Yes, I got you. And that's how it's doing it in the first one.

DR. HOFFMAN: Yes.

DR. KOCHER: Ready to move on?

MEMBER ZIEMER: Okay. Next one.

DR. HOFFMAN: Okay. Now, basically this was the point at which we thought we would stop, because this answers the question how is DDREF used in IREP.

Now, we thought we'd entertain questions from the Board at this point before there is a follow-up discussion in terms of our report.

DR. APOSTOAEI: Or we can continue the slides.

DR. HOFFMAN: It's the Board's choice.

MEMBER ZIEMER: Well, you've answered some my questions.

MR. KATZ: Any questions on the line from Board Members up to this point?

CHAIRMAN RICHARDSON: Well, thank you. It's very useful to kind of start by laying out what's done. And I look forward to the discussion of the critique of that.

One thing I would - since we've given substantial time to this function for phasing in DDREF for acute exposures, I wonder if NIOSH could comment on the proportion of claimants for which an annual dose is - let's start with proportion of claimants if they have some idea of this, where an annual dose would ever be on the magnitude of 200 milligrays.

So, this is an annual low-LET exposure. An external exposure.

DR. NETON: This is Jim, Jim Neton.

There are some instances of that, but they are few and far between.

I would suspect that where they occur is in the very early years of the AEC activities working with the uranium ores, the Belgian Congo ores, that sort of thing. There was a lot of radium in there. I recall at Mallinckrodt we had some pretty high exposures like that.

But outside of that, I think it's unlikely that we would have exposures, acute exposures in that range.

CHAIRMAN RICHARDSON: Okay. But what about, let's take the lower bound of what's called acute, 30 milligray?

DR. NETON: Same thing.

CHAIRMAN RICHARDSON: Because this is my experience in working with Oak Ridge, Hanford, Savannah River, that those are the magnitudes of career doses.

DR. NETON: Right.

CHAIRMAN RICHARDSON: 30 to 50

millisieverts up to maybe a hundred millisieverts or so.

But when we're talking about an annual dose, we're not talking about any part of this graph in which there's a phasing going on. We're talking about for, I would imagine, for the vast majority of claimants the doses, an annual dose, is going to be on the magnitude of 10 milligray and below, with those types which actually have relevance to the claimants that we're considering about.

Is that consistent with your kind of interpretation of kind of the bulk of the claimants in which we're going to be -

DR. NETON: Yes. Yes, I would agree with that.

DR. KOCHER: Given the limit was 50.

DR. NETON: Yes, right. The limit was 50 for most of those years.

CHAIRMAN RICHARDSON: Well, and operationally, I mean, I've encountered very few workers - I mean, there was the 5 rem

study. But, again, that was the 5 rem study of people whose cumulative doses were 5 rem that was conducted for a while by Oak Ridge.

DR. NETON: I will say, though, that we do, for the most part, especially the early years, the annual dose is considered to be an acute dose if we can't determine what the individual badge readings were, that sort of thing.

CHAIRMAN RICHARDSON: It's considered acute.

DR. NETON: Right.

CHAIRMAN RICHARDSON: But here it's of such a magnitude that you're back down to the part of the magnitude that once you apply this factor, it's essentially --

DR. NETON: The chronic.

CHAIRMAN RICHARDSON: -- getting the weight distribution of the chronic exposure again.

DR. NETON: Exactly. Yes, we do the acute just in case there were high exposures,

you know. We would try to be claimant-favorable, but you're absolutely right.

For the most part, it's going to be treated - the acutes for low-LET will be considered principally as if they were -- well, had a DDREF applied of some magnitude depending on the scale that's used here. That's correct.

DR. MAURO: Owen, this is John Mauro. Just a quick question. I don't have the slide in front of me.

Sorry to interrupt, but is any mention made of organ-specific DDREFs, or are we talking -

DR. HOFFMAN: Yes.

DR. MAURO: Because I don't have the slide in front of me.

DR. HOFFMAN: Yes, if you recall in IREP, John, the DDREF, one, it is not applied for leukemias. We have a different distribution for breast and thyroid than we have for all other solid tumors.

DR. MAURO: Okay. I'm sorry I missed that. Thank you for your answer.

DR. HOFFMAN: Yes.

DR. MAURO: And the only reason it triggered my question was when we were talking about what the doses are and we talk about 1 rem per year, often some organs do get some fairly high doses. Especially the respiratory tract. And that triggered that question.

DR. HOFFMAN: Sure.

DR. NETON: But there, John, you were principally talking, I think, about alpha emitters.

DR. MAURO: That's true. You're absolutely right. You're absolutely right.

(Simultaneous speaking.)

DR. NETON: That's another issue that I'm sure we'll get into.

DR. MAURO: Yes, yes.

DR. NETON: The DDREF actually does get applied to high-LET alpha emitters in a sort of different way.

DR. TRABALKA: As a part of the correction for radiation effectiveness factor for alphas, but there's also an inverse dose-rate effect that more than outweighs that. So, it's a complicated picture.

DR. NETON: Yes, it is.

MEMBER MUNN: As most of this is.

DR. TRABALKA: Yes. Yes, it is.

MR. KATZ: Is that it for questions on the line?

CHAIRMAN RICHARDSON: One other thing I'd like to just point out is there was some discussion about the symmetry of the distribution for cancers other than breast and thyroid. And I heard some comments, but I'm not sure if it was clear.

That apparent symmetry, I guess, is - it was noted the distribution looks normal, but it's looking normal on an arithmetic scale, but it's a ratio measure.

So, a value of 0.5, if there was going to be actual symmetry here, would be

bounded against the value of two, for example.

So, if the DDREF was 0.5, that would say it was half as effective. And if it's two, it would say it was - or vice-versa. Twice as effective and half as effective.

So, here it's actually, when it's going out to values of five and down to values of 0.5, that's - I would mentally imagine that as very skewed in one direction.

MEMBER ZIEMER: You're right, David. As I look at these, these are not linear scales depicted here. They are just numbers. It's a bar graph you're looking at, as I see it.

I was glancing at it and it looked like that, but I realize now that they are not really linear.

CHAIRMAN RICHARDSON: Right.

MEMBER ZIEMER: Although having said that, if you look at the actual values, I think the breast and lung still probably is very skewed toward one. So, probably log-

normal.

I mean, the 0.5 and 0.7 are spread out.

DR. KOCHER: Don't put a great deal into particular percentiles on these numbers.

CHAIRMAN RICHARDSON: Oh, I'm not, but I'm just thinking about the issue of: is it symmetrical around a value?

And it's - I would say it's not, right? It's going towards dose-rate effectiveness factors which you would divide the risk coefficients by a factor of two, three, four or five, and the low probability that you're going to divide it by a value of 0.7 or 0.5, but you would never go down to a value like 0.2, which would be symmetrical around five.

MEMBER ZIEMER: Well, but that may raise the question: does IREP put this in as a distribution, or as a number of points?

DR. HOFFMAN: It's a discrete distribution, exactly as you see it here.

MEMBER ZIEMER: What we see here.

DR. HOFFMAN: And so, I mean, these distributions originally were derived by Ethel Gilbert. And there was no attempt to make one log-normal, normal or - it was degrees of belief based on her review of the literature that would be put on discrete values.

Does that help, David?

CHAIRMAN RICHARDSON: Yes, thank you.

DR. HOFFMAN: Okay.

DR. KOCHER: You can still have symmetry about values other than one. One is not the midpoint of anything. It can be symmetric around two.

DR. HOFFMAN: Well, we are prepared now to continue to change the focus of the discussion into a summary of where we are with respect to our draft - this is a major report. A major draft report on the state of knowledge of DDREF. Probably the most extensive report of its kind anywhere. The

only problem is it's not published. It's still in draft form.

But I'd like to say that John Trabalka of our staff is taking the lead on this work. This is the work now that probably spans six, seven years in the making.

And so, I'd like John to continue with the presentation.

DR. TRABALKA: I will. I'll add one thing to what Owen just said.

At least one member of the ICRP team that was going to develop or at least review the concept of DDREF, expressed the hope to me that our report would be out before theirs was even started so they wouldn't have to do the review and evaluation. They could just critique ours and use as much.

It's so much easier to critique somebody else's work than to do it yourself.

MEMBER MUNN: Always easier.

DR. TRABALKA: Okay. Let's go ahead and talk about where the information for

estimating the DDREF comes from. Go ahead, the first part.

Now, there is information from genetic and cytogenetic endpoints that's used in estimating DDREF - you just jumped ahead to - go back, back, back. First one.

Okay. There is information, as I said, for these other endpoints, but I am going to focus on information that's obtained from laboratory animals and humans for potentially estimating DDREFs.

Much of that information should be characterized as representing low-dose extrapolation factors.

You can obtain estimates of the relative effectiveness of low acute doses, for example, by analyzing the curvature in dose responses for acute exposures like cancer in the A-bomb survivors.

And that's been done very heavily. There's a lot of data. And in our report, we document all of the values that have been

published on that.

You can also estimate it from -- cancer responses from fractionated exposures like from medically irradiated humans. Compare those, for example, with responses in the A-bomb survivors to estimate it, and in laboratory animals where you look at the curvature in the dose response for acute exposures.

Let's continue on to the next one. Also, much of the literature and many of the values are best characterized as dose-rate effectiveness factors, because they compare relative effectiveness of low-dose rates with those at high-dose rates.

Examples are the epidemiological studies of radiation workers compared to the A-bomb survivors, persons exposed in environmental or medical settings - an example of the environmental settings would be folks who were exposed along the Techa River in Russia. Medical settings, the Swedish skin

hemangioma cohorts; these were children who were given exposures with radium applicators because they had blotches on their skin, and of course had developed all sorts of cancers afterwards - and also studies of cancer in laboratory animals.

These particular studies were the ones that were used by the NCRP and also by UNSCEAR in its 1993 report, and were used as part of the basis for the DDREF of two that was selected by the ICRP, for example.

But because of theoretical considerations, when you get down to low doses and dose rates and assuming a linear quadratic model as the basis, which does not always work, and there are a lot of data suggesting the linear quadratic model is not always applicable, nonetheless, when you do that, the two values should converge. The LDEFs and the DREFs should be the same. So, we typically use the term DDREF or a dose and dose-rate effectiveness factor.

Any questions on this before we move on?

CHAIRMAN RICHARDSON: I have one question.

I thought I understood what you meant by LDEF until you suggested that cancer from fractionated exposures compared to an acute exposure -

DR. TRABALKA: Fractionated acute exposures.

CHAIRMAN RICHARDSON: So, you're making a distinction between - so, you're saying for the same total dose if it's fractionated - I would imagine if it's fractionated or protracted, for the same total dose deposited, that that would be - that you would, for the distinctions in effect as those being dose-rate effects.

Why is that?

DR. TRABALKA: Iulian and I have had that discussion. And Iulian would agree with you.

I simply make the point that these are data from fractionated acute exposures as opposed to data from chronic exposures, continuous exposures.

I would agree that that's a moot point.

MEMBER ZIEMER: And fractionated acute in this case, you're still using the 200 millisievert as something above that as being -

DR. TRABALKA: No, no, no. These acute exposures, for example -

MEMBER ZIEMER: When a medical exposure is really high?

DR. TRABALKA: For example, you know, rats. Exposures to look at mammary cancer in rats. They used acute exposures separated in time by 12 or 24 hours.

MEMBER ZIEMER: Yes.

DR. TRABALKA: And down around, say, four milligray, ten milligray, all the way up to maybe a hundred milligray.

MEMBER ZIEMER: Right.

DR. TRABALKA: So, there's a wide range of doses and exposure conditions.

MEMBER ROESSLER: So, to continue on that - this is a good discussion, I think. But in the top category, the medically irradiated humans, they're the ones who are treated for something and they're actually fractionated.

Then when you go down to the second, the DREF, and you talk about medical settings, are you talking about occupational exposures there?

DR. TRABALKA: No, the example I used was the Swedish skin hemangioma cohorts. That was a medical exposure, but what they did is: they put an applicator on a blotch on the skin and left it there for several hours.

MEMBER ROESSLER: I get it. I missed that, yes.

DR. KOCHER: But the doses are well known.

DR. TRABALKA: Yes, reasonably well known or estimated, I should say.

Ready to move on?

MEMBER ZIEMER: Yes.

DR. TRABALKA: Well, I suppose most of us realize why reevaluating DDREFs is important.

The ones used in IREP have a great deal of subjectivity. There has been a lot of information published since IREP was developed.

There are now useful studies of nuclear workers that bear on this issue, some research in the DOE low-dose program. So, reassessing the magnitude and uncertainty of DDREF is important.

And the underlying basis, the LNT model, is heavily challenged. I mean, let's face it. There's a large fraction of the community out there that does not accept it.

There's a wide range of alternative information, also, for developing an improved

basis.

So, our objective is to try and reduce the level of subjectivity, provide better traceability for the information and improve the documentation.

Any questions on that?

CHAIRMAN RICHARDSON: Can you clarify the distinction you're making here between the underlying basis of a linear and a threshold model and your assumption of a linear quadratic model, which you said is your starting point?

DR. TRABALKA: At low doses, the linear quadratic model defaults to a linear no-threshold model.

But the basis for a DDREF is based on the assumption that a linear quadratic model over the entire dose range of your epidemiological information is the proper way to go about calculating it.

CHAIRMAN RICHARDSON: And, see, I've never encountered that, I guess.

DR. TRABALKA: I'm afraid that is the basis, however, for DDREF. It's discussed in Section 2 of the report in detail.

In fact, probably a linear quadratic exponential model fits much of the data better than just a plain linear quadratic model.

Let's not get into that. I'd rather have you read it. I'll be happy to answer any questions you have about it.

CHAIRMAN RICHARDSON: No, I have read your report, but I guess I'm asking for some coherence between the assertion and what I encounter as how epidemiologic data are modeled in radiation epidemiology.

One doesn't start out with a parametric form and fit it to the data regardless of whether it conforms well to the data.

And typically, you would not saturate a model by including kind of polynomial functions if a simpler model fitted

it.

DR. TRABALKA: Well, I agree with that. But if you look at how DDREF, for example, has been estimated from the Japanese A-bomb survivor data, it's based on curvature assuming a linear quadratic model or by comparing risk coefficients from the linear model versus the linear risk coefficient from a linear quadratic model.

That's how the data are obtained if you have an acute exposure, for example.

CHAIRMAN RICHARDSON: No, I don't think that's right, actually.

DR. TRABALKA: I'm afraid it is.

CHAIRMAN RICHARDSON: But, I mean, we can go on.

DR. TRABALKA: Okay.

CHAIRMAN RICHARDSON: I mean, none of the DDREF values that would be shown in this distribution for solid cancers would be - I think you would say that the basis for any of these bars in this histogram are the ratio

of the quadratic to the linear term for solid cancers in the A-bomb data. Values two, three, four, five, right?

I mean, there's curvature for the leukemias, but we've set that aside.

DR. TRABALKA: The basis for those values in the current version of IREP came from data all over the map.

CHAIRMAN RICHARDSON: Yes, exactly.

DR. TRABALKA: It was highly subjective. But if you look in - if you read Section 4 and particularly Section 4.2, look at the Japanese A-bomb survivor DDREFs and you look at how those were derived, you'll see the linear quadratic model or a linear quadratic exponential model was used to derive those DDREFs.

When you get to cancers like breast cancer, thyroid cancer, you have to compare responses in those cohorts to the linear risk - in other words, the linear risk coefficients from those studies to linear risk coefficients

derived from the A-bomb survivor studies, because you don't have the acute exposure component.

You don't have a linear quadratic - enough information to do a linear quadratic dose response. And it would be questionable to use it there anyway.

And if you look at some of the other cancers, that's also true for the lung, bone and skin cancer. You have to compare it typically with - in other words, linear risk coefficients in one case, and quadratic coefficients - or linear coefficients from linear quadratic responses, or just linear coefficients from the A-bomb survivors with those linear coefficients.

When you look at skin cancer -

CHAIRMAN RICHARDSON: Exactly. The last one is, I think, was done in practice.

DR. TRABALKA: Yes, and we've done that in a lot of cases in the report.

If you look, however, at the data

for skin cancer, especially that in the latest iteration, the DSO dose response by Preston and company, they use what's called a linear spline model. Which is a straight line linear, in other words, a linear response at low doses compared to a linear response at higher doses, and you have to take the ratio of those two to get a DDREF.

And you get a different value estimated for DDREF when you do that. It's about six, as opposed to one to two from most of the data for the A-bomb survivors.

I hope that also explains or helps answer the question about whether or not we're looking at cancers other than - in addition to breast and thyroid cancer in our effort here.

Should we go on, David?

CHAIRMAN RICHARDSON: Yes, please.

DR. TRABALKA: Okay. All right. Let's go on to the next one.

So, in our review, we looked at the existing and new classical information. By

"classical," we mean epidemiological, radiobiological, micro-dosimetric data and concepts.

Examples are the new radiation worker studies and what their implications are for DDREF, the DSO2 base dose response for the A-bomb survivors.

But we also felt we had to look at emerging information on other phenomena, because there is such a large part of the community that's pretty adamant that these need to be considered in dose responses.

And these include adaptive responses, bystander effects, induced genomic instabilities, low-dose hyper-radiosensitivity, existence of thresholds and hormetic responses.

Any questions on that?

MEMBER ZIEMER: I have one question, because it's fascinated me and has to do with the bystander.

Is a bystander cell right adjacent

to a cell that is, let's say, hit? I'll use the word "hit." Or could it be somewhere else?

How far removed can a bystander be? I mean, we have in the body, situations where something far removed from a location that's called on to assist a cell.

Maybe the, I don't know, some organ is called on to release something because a cell has -

DR. HOFFMAN: Okay. In other words, what's the distinction between bystander effects and abscopal effects?

MEMBER ZIEMER: Well -

DR. HOFFMAN: Abscopal effects is one part of the body is irradiated, but another part of the body expresses the cancer.

MEMBER ZIEMER: That's exactly my question, because it has great implication -

DR. HOFFMAN: Yes.

MEMBER ZIEMER: We use, in this program, the organ. We take the energy

delivered to that organ as being sort of a cause and effect situation.

And so, it's never been clear to me on bystander, how far away is the bystander? It's sort of what you raised earlier.

Like I'm hitting the line and is my finger is going to suffer for that? I mean, I would think intuitively it's pretty close by, but -

DR. TRABALKA: The tissue models that have been used to study bystander effect suggests that we're talking about distances of millimeters to a centimeter or two.

However, as Owen pointed out, there are - there is evidence of abscopal effects especially in animals.

MEMBER ZIEMER: And what does that word mean, exactly?

DR. TRABALKA: Well, for example, you irradiate the leg of a certain species or strain of rat and it develops mammary cancer. You irradiate the leg of a mouse and it

develops - what's the word I'm looking for here? A kind of lymphoma. Thymic lymphoma.

MEMBER ZIEMER: Yes.

DR. TRABALKA: Albrecht Kellerer has suggested that we have to be very cautious about the Techa River data, because the doses to bone marrow were so high that he suggests that abscopal effects on the rest of the body could be influencing the dose responses in those people.

Some of those folks were thought to have had chronic radiation sickness from exposures. These are extremely high doses.

MEMBER ZIEMER: Yes.

DR. TRABALKA: Especially those closest to the fuel reprocessing plant and the high-level waste storage tanks.

Does that answer your question?

MEMBER ZIEMER: Yes, I just wanted to get a feel for it. It could be, in principle, fairly extensive then.

DR. KOCHER: The problem here, of

course, is that our basic data set is uniform whole-body irradiation.

MEMBER ZIEMER: Right.

DR. KOCHER: So, if these effects are real, they're buried in there somewhere.

MEMBER ZIEMER: They're buried in there.

DR. KOCHER: And you don't know how to adapt that to partial body exposures, if you think there's a difference.

MEMBER ZIEMER: Exactly. Exactly.

DR. TRABALKA: Let me conclude this slide by saying that there is no consensus currently on whether these phenomena really influence epidemiological data. In some cases, they are thought to be embedded in current epidemiologic data.

MEMBER ZIEMER: I understood from your report, at least I thought I understood on the hormetic, you or someone was suggesting that that might even have lower and upper bounds.

DR. TRABALKA: That's right.

MEMBER ZIEMER: And below, it may not exist.

DR. TRABALKA: The more recent studies show that although you might see a threshold effect at one dose or dose rate or a potential for hormetic effect, that at lower doses you actually see an increased effect.

You have to be very cautious about interpreting that information, especially as it applies to humans.

MEMBER ZIEMER: And it could be very dependant on the endpoint in either case.

DR. TRABALKA: Very much so. And so, the precautionary principle has to apply there. We have to use the linear approach.

MEMBER ZIEMER: Right now it seems to me, although it's interesting to look at all of these, on most of them we're pretty far away from knowing answers; is that correct?

DR. TRABALKA: That's correct.

MEMBER ZIEMER: Okay. Well, we can

leave that.

DR. TRABALKA: Yes.

MEMBER ROESSLER: As I look at this slide and the things you're talking about, especially the emerging information, this is a huge amount of data.

I've been to NCRP meetings where they talk about all this stuff and it is new. It just seems like this is a huge amount of work that nobody else is really doing that you've done, and you've put in a number of years on this.

So, my question is, who's funding it and where will it be published?

DR. TRABALKA: It's in our report in Appendix B of our report.

MEMBER ROESSLER: Okay.

DR. TRABALKA: And in Section 3.

DR. HOFFMAN: And the answer is, NIOSH is funding this effort. And when and where will it be published is partly at the discretion of NIOSH.

DR. NETON: In the TBD.

MEMBER ZIEMER: But you're funding the pulling together of the information, the research itself.

DR. HOFFMAN: Yes, but we recognize, I mean, we have the pleasure and honor of being charged with doing this work and it's put us at the forefront of the group.

MEMBER ROESSLER: This is a huge contribution that is being made to this program.

I think one of the early ones was David's work on REF. It was published. There's a lot that's been published.

This is something very scientifically important to be doing this.

MEMBER MUNN: It is.

DR. TRABALKA: Ready to move on?

GROUP RESPONSE: Yes.

DR. TRABALKA: Okay. I just want to briefly touch on information on DDREFs that we can obtain from the genetic and cytogenetic

endpoints like cell transformation, chromosome aberrations or point mutations.

The range of values is quite large, typically in the one to 12 range, but also values much less than one of infinity are out there from threshold or potential hormetic responses that are shown in the literature. The central estimates are around two to six.

These dose responses are complex, often difficult to interpret, and they represent only one of the many steps that is required to take a radiation-induced lesion up to a cancer. So, you have to interpret these with a grain of salt.

There was some information early on suggesting that the DDREFs might be LET-dependent for endpoints like chromosome aberrations and cell transformation suggesting that they might decrease with decreasing photon energy, for example, but more recent information suggests that that probably is not an issue.

It is, however, still an issue for RBEs and radiation effectiveness factors. In fact, this is still, in other words, the suggestion that for photon energy you might have - when it decreases, you might have an increase in RBE.

That is the subject of a current NCRP Committee effort that David is involved in. And so, whatever results from that committee effort, assuming it comes out before our report gets out, we will factor into our report at some future date.

Okay. Shall we move on?

This rather busy slide is a summary of the animal data. Most of it is animal cancer data.

There is one data point at the bottom for mice for life shortening. And the reason there's only one is that life shortening typically doesn't - data don't typically distinguish between leukemias and lymphomas and solid cancers.

This particular set of data on mice does that, and you get a DREF of about one from that data set.

The other data come from - in one case, there are combined malignancies, mammary cancer in mice and rats, lung cancer in mice, beagle dogs, non-melanoma skin cancer in mice.

A number of these endpoints have infinity either as the best estimate or the upper bound, because they represent potential threshold data.

These show up typically when you get exposures to single organs like the lung or the bone.

A lot of the bone data comes from exposures to animals from strontium-90, for example.

There are also some data on pituitary tumors. Harderian gland, for some reason harderian gland DDREFs have been fascinating for some of the radiologists.

But for us, they're not

particularly useful because they only occur in animals with a third eyelid. And since none of us seem to have third eyelids, they're not typically useful.

If you look at the data, most of the values, most of the point estimates range from about one to ten. Actually, most of them fall between one and six, except for the threshold data.

And we've attempted to estimate what the lower bounds for DDREF might be on some of this threshold data, and we typically get values between ten and 20.

And other investigators who have used alternate models for that same data, come out with values on the order of, say, 20 or more. So, we think we're in the right ballpark.

In other words, despite the fact that there are what appear to be apparent thresholds in this data, there could very well be concealed linear quadratic responses in

these data that still have a finite, but quite large DDREF.

And what it really suggests is that for bone cancer, the linear risk coefficient could be much lower than it is for carcinomas and other cancers.

Okay. Any questions on this before we go on?

MEMBER ROESSLER: What are Long-Evans rats?

DR. TRABALKA: Just a strain of rat that's favored in some research.

MEMBER ROESSLER: They just kind of fall out of the picture here.

DR. TRABALKA: Well, these were used in a study comparing the effects of x-rays, localized x-rays and iodine-131.

And if you assume that there is no higher effectiveness for x-rays, the value moves up to about double, about 1.2.

If you use the information that suggests that the radiation effectiveness - or

the RBE for x-rays should be about twice that for iodine-131 beta and gamma radiation, you get a value of 0.6, but the uncertainties are great enough in that information that still overlaps one and the upper bound is close to two.

These are mostly 95 percent confidence intervals, but some represent ranges of data.

Where there are bars on the end of the lines, those represent confidence intervals. The rest of them are ranges. For example, data in mice and rats on mammary cancer typically fall between two and three. Something like that.

Should we move on?

MEMBER ZIEMER: The life shortening on this particular one, there's no bars there.

DR. TRABALKA: No.

MEMBER ZIEMER: What did you say about that?

DR. TRABALKA: The information to

provide uncertainties in that data isn't available.

This is based on work that was done at Argonne National Laboratory in the pre-JANUS studies over a significant period of time.

The dose rates in this set of studies extend down to 0.002 milligray per minute, which is 50 times lower than the dose rate at which a chronic DDREF is applied in IREP, and significant life shortening was being observed even at that lowest dose rate.

And of course it didn't go any further, but still it was linear down to that range.

MEMBER ZIEMER: Significant life shortening at low dose rates but high total doses?

DR. TRABALKA: Well, at 0.002, it would be over the entire life of the mouse. So, we're talking probably several hundred days in this case.

We have to convert that to per day and -

MEMBER ZIEMER: In my memory bank somewhere, there are some mice studies where you actually get lifespan increases -

DR. TRABALKA: Oh, yes.

MEMBER ZIEMER: -- because of the fact that the mother mice have, at higher doses, have smaller litters. And that's less wear and tear on the mice and they live longer.

DR. TRABALKA: That issue is discussed in Section 4.3 of our report. You have to be kind of careful about how you interpret these apparent beneficial effects.

MEMBER ZIEMER: Exactly.

DR. TRABALKA: If you look at the one case that you mentioned, the study by Storer and his colleagues at Oak Ridge National Laboratory, it used the largest number of mice in any study on life shortening.

And they still saw between two sets of controls, a 30-day difference in lifespan, which is on the order of what's typically observed in these studies that show apparent lifespan increases, and that's just in controlled.

It simply shows that in animal studies or any kind of research, you can have variations in your controls that are hard to explain.

MEMBER ZIEMER: Yes.

DR. TRABALKA: You've got to be very cautious about how you interpret that data as, for example, representing a real effect on lifespan increases or something like that.

Shall we proceed?

MEMBER ZIEMER: And that's just an animals where you - they're all alike. Can't go to humans.

DR. KOCHER: John, is this kind of information that UNSCEAR used to come up with their two to ten range back in the day?

DR. TRABALKA: The NCRP. Most of it is what NCRP used. Not all of it, because not all of it was available.

NCRP came up with the two to ten range, but ICRP came up with their DDREF of two.

They used the lower end of the range of animal data, because it was more consistent with what they thought the A-bomb survivor dose-rate response represented.

CHAIRMAN RICHARDSON: I have a couple questions, if I could.

DR. TRABALKA: Sure. Yes.

CHAIRMAN RICHARDSON: The first one was just an issue of understanding the presentation of the data.

The scale on - the X scale. I was imagining, if you would move to the right from one, that that next line represents two.

DR. TRABALKA: That's correct.

CHAIRMAN RICHARDSON: And that if you move to the left from one, you're moving

to 0.9; is that correct?

DR. TRABALKA: That's correct. It's a log scale.

DR. HOFFMAN: So, you have arithmetic numbers on log scale.

DR. KOCHER: I think his point is there's a few ticks missing.

CHAIRMAN RICHARDSON: I'm trying to find what's balanced. Where would you get -

MEMBER ZIEMER: I think the nine is at the edge of the green.

MEMBER ROESSLER: The blue line.

(Simultaneous speaking.)

CHAIRMAN RICHARDSON: Okay. So, I'm sort of understanding it. Just maybe there's - it's not easy to see. Is that the -

DR. TRABALKA: A very complicated data set.

DR. HOFFMAN: Yes, but it's a log scale and so all the ticks should be there.

CHAIRMAN RICHARDSON: Okay. But the experimental design for the - there's one

circle - well, there's two circles.

I'm trying to imagine an experimental dosing design that conforms to DDREF as opposed to the other two categories you have there.

I can imagine an experiment in which we apply an acute dose to animals of different magnitudes and we study the shape of the dose response with an acute exposure.

And I can imagine a dosing experiment in which we aim to deliver to the animal the same total dose, but under different periods of protraction.

What's the experimental design that conforms to the DDREF?

DR. TRABALKA: Actually, I think that symbol should be a square, because these were continuous exposures at varying dose rates. We just have the wrong symbol up there.

MEMBER ROESSLER: So, you switch the DDREF and the DREF?

DR. TRABALKA: No, no. On the life shortening data point for the square.

MEMBER ROESSLER: Well, within the figure there's around -

DR. TRABALKA: Oh, okay. The reason why the DDREF is shown for lung is that when they - this particular data set they were able to fit to a linear quadratic model and to show that you got the same answer as you would get if you were giving individual acute exposures.

So, it is both a DREF and an LDEF. So, that's why it's called a DDREF in this case.

So, they were able to show that the data, a theoretic linear quadratic model and what you got from extrapolations down to low doses and dose rates was the same.

CHAIRMAN RICHARDSON: I would frame that as interpretation of experimental evidence as opposed to an experiment which estimates DDREF.

DR. TRABALKA: That's reasonable.

CHAIRMAN RICHARDSON: I guess for me, it gets to a fundamental issue of typically in, for me, I would like to be able to imagine the experiment in which I could test the question.

And I can imagine the experiment in which I can understand differences in response under different magnitudes of exposure and the experimental design that conforms to that.

And I can imagine the experiment that conforms to understanding the effect of protraction of the exposure over time and answering the question given the same magnitude of exposure when it's protracted, does the effect vary.

The DDREF, I believe, is a - kind of a concept that was put forward for administrative purposes. To me, it's conflating those two thought experiments and, you know, for better or worse.

So, I was just curious as to whether there existed an experiment like that.

DR. TRABALKA: Unfortunately, data are limited even for all the animal studies that have been done. And the Department of Energy terminated their animal studies before all such questions could be addressed.

I would agree with you that it would be great to have that set of comparisons, but they simply don't exist. And so, we're left with trying to represent the data we have as best we can.

And as I pointed out for that set of data for lung cancer in BALB/c mice, we have both acute exposure information and chronic exposure information. And the linear risk coefficient obtained from comparisons between the risk coefficient from the linear quadratic model and that from the low dose-rate information agreed with one another. Hence, this term "DDREF" can be applied to that data set. It's both a DREF and an LDEF.

CHAIRMAN RICHARDSON: It's an experiment that conforms to a -

DR. TRABALKA: A hypothetical linear quadratic representation of the data.

CHAIRMAN RICHARDSON: Yes.

DR. TRABALKA: Right.

CHAIRMAN RICHARDSON: But there's not an experiment that proves that it -

DR. TRABALKA: No, no. No, no. I would be the first to say that the animal data don't prove the existence of a linear quadratic dose response.

CHAIRMAN RICHARDSON: Yes.

DR. TRABALKA: I would also say the animal data for leukemia don't prove the incidence or the existence of a linear quadratic dose response.

And if you read that section of our report, you'll see that that is in fact what we said.

CHAIRMAN RICHARDSON: Very good. Thank you.

DR. TRABALKA: Okay. Should we move on?

Okay. Prior to 2009, some of the conclusions we had reached were first and foremost that the DDREFs in IREP didn't represent the uncertainties in the data, a lot of new information that was much greater than is represented in any current distribution at the time, including BEIR VII, and based on the limited information available, we suggested that both the LDEF and DREF data should be combined simply because of limitations.

And at that time, we were leaning toward using both human and animal data and quantifying DDREF distributions, but things have changed since 2009.

One of the things that's happened is that we've gotten the updated epidemiological studies of worker - nuclear workers in the UK, a study published by Colin Muirhead and his colleagues.

We now have results for cancer incidence and mortality. We have ERRs for combined solid cancers, in this case, all

cancers other than leukemia that are now statistically significant.

We have the first comprehensive results of cancer incidence, and this adds to the results that came from the 15-country study of nuclear workers, which, despite some of the criticisms, is still valid, we think, if you include the entire Canadian cohort as we have done in your deliberations.

That study suggested that the risk to workers exposed to low doses and dose rates was at least comparable to those in the A-bomb survivors and could, in fact, be somewhat higher.

And the UK study suggests that risks in workers are comparable to those in the LSS cohort. And we talk about that in the next slide.

No, no, you missed a slide. Oh, I guess you - we have a slide out of sequence here - no, we're missing a slide. What happened to the slide on DRFs for solid

tumors?

MEMBER ROESSLER: We have it in -

DR. TRABALKA: You have it in your handout, but I guess it went missing from here.

Anyway, if you look at the page, the following page in your handout, if you look at - try to estimate a dose rate - there it is. That's it.

Okay. If you estimate a dose-rate effectiveness factor for the UK workers compared to those in the LSS cohort, values are on the order of 1.0 to 1.4. 1.0 for the cancer mortality endpoint, and 1.4 for the cancer incidence endpoint. And of course there's considerable uncertainty in these data because of their origin.

If you look at the 15-country study and try to do the same thing for cancer mortality, again emphasizing that we included the entire Canadian cohort, you get a DDREF estimate - point estimate of about 0.55 with

considerable uncertainty.

If you look at the data for some of the Chernobyl remediation workers papered by Ivanov and his colleagues in 2006, there's also cancer incidence data available from this cohort.

In cancer mortality, you get a DDREF of 0.15 for the point estimate, which suggests that the risks for these people are much, much higher than the A-bomb survivors.

However, if you look at the data for cancer incidence, they're about an order of magnitude lower. So, you get a value that's very close or even - I mean, the estimated DDREF would be either equal to or slightly higher than - greater than or equal to one. Let's put it that way and I'll stop there.

All right. However, there are problems with those data. And the reason why we say not to be used, is because there are serious issues of cancer ascertainment as is

obvious when you compare the results for cancer incidence and mortality, and also uncertainties in the doses for these folks and a host of other problems.

The paper by Ivanov that was published in Health Physics in 2004, goes into detail on some of these issues. I would recommend that you look at that paper if you're interested.

MEMBER ROESSLER: It's in your report in -

DR. TRABALKA: We discuss it in our report, yes.

MEMBER ROESSLER: That's a 2004 -

MEMBER ZIEMER: This is from the 2006 -

MEMBER ROESSLER: Sure.

DR. TRABALKA: Can we continue?

If we look at the data for responses, dose responses in the Techa River cohort, and try and estimate a dose-rate effectiveness factor for both incidence and

mortality, and these data don't include bone cancer, you get a value of about 0.6.

However, both of these papers provide the caution that these are preliminary estimates, should be interpreted with caution. There are all kinds of uncertainties especially in dose reconstruction, releases, confounders.

The population along the Techa River is a very difficult one to use in comparing with any Western or Japanese cohort.

We're talking about people who lived in abject poverty, had no medical care prior to the releases that occurred in the early 1950s. Only half of the 27,000 or so people had medical checkups from the Ural Center for Radiation Medicine after that point until -- they really didn't get interested in this until about the 1980s to 1990s.

The attempts to dose - the problems with dose reconstruction are quite difficult.

I would commend reading Mira

Kossenko's report, her DTRA report. It's referenced in our - it's in the bibliography that we provided.

She goes into great detail on this. And she's been involved in this effort from day one.

She and one of her colleagues visited Oak Ridge when we were there. They brought some members of the Techa River cohort. So, we had the opportunity to find out firsthand some of the problems that are involved.

In 2008, I was asked to review the revision of their release - radiation release study and there were major problems with it.

It was just published in Health Physics this year. It was not - it was published too late to be included in our report.

But one of the things that they have noted is that there is an order of magnitude spike, increase, over previous

estimates in the last quarter of 1951 in the releases.

None of this has been factored into these studies thus far. So, we have to be very cautious about this data.

Another problem is that in the cancer incidence study, they were able to fit the data with either a linear model or a quadratic model. They couldn't choose between the two. And at, say, doses of ten milligray, there's a factor of 34 difference in the risk estimates.

So, again, the long-term study of this cohort may provide some useful information, but we prefer not to use it in our DDREF calculations at this point.

MEMBER MUNN: You're not ever going to have a viable baseline though.

DR. TRABALKA: Well, that's another issue. I agree with you.

Shall we continue?

MEMBER MUNN: Sure.

DR. TRABALKA: Okay. Now, also in 2009, a rather influential paper appeared by Peter Jacob and his colleagues and it was a synthesis of 12 occupational environmental exposure studies.

They compared risk with the LSS cohort attempting to match the ages at exposure and attained - they attempted to do this. It's rough, but I think they did a good job on that part of the study. And rather than calculate DDREFs, they calculated risk ratios.

In other words, comparing risks in the worker cohort or the Techa River study, for example, with those in the A-bomb survivors, but flipping it using the inverse of DDREF.

And what that does is helps you avoid infinities that occur in calculations, because you have dose responses where the ERRs, for example, are so wide that they go below zero on a lower bound of the confidence

limits. They applied an inverse variance approach to weighting the values. The equivalent DDREFs in the 12 studies range from 0.05 to infinity.

But when they do their inverse variance weighting scheme, they come out with risk ratios of greater than one that convert to DDREFs of 0.5 to one. 0.5 to one. Inverse of one is one.

So, anyway, what they did is they developed three groupings of occupational and environmental exposure data for either cancer mortality or incidence.

They had one group where they had seven sets of data on cancer morality, another group where they had four - a different group with four sets of data on cancer mortality, and then one group that had three sets of information on cancer incidence only.

The main result was based on the seven studies of cancer mortality and the risk ratio was 1.2. And then when you invert it,

you come up with a DDREF of roughly 0.8 with confidence limits of 0.53 to two.

Now, there are a number of issues with that study. And I won't go into all of them, because there's a whole section of our report that covers it.

I found several more issues with it in getting ready for this meeting. So, those will have to be included at a later date.

There are many who thought this was the answer when it came to DDREF, but then there were a lot of people who thought that the BEIR VII report was the answer, and there were a number of people who thought that the French National Academy study was the answer, and none of these studies agreed with one another. And certainly the DDREF estimates they produced would be very, very different.

Before we move on, are there any questions about this?

MEMBER ROESSLER: What section of your report is it in?

DR. TRABALKA: I can't give you the exact section right now. It starts on Page 149.

MEMBER ROESSLER: That's good enough. It's such a big report.

DR. TRABALKA: A mighty tome.

MEMBER ROESSLER: Yes, it is.

DR. TRABALKA: And as some of my colleagues would say, opaque.

(Laughter.)

MEMBER MUNN: Nicely done.

DR. TRABALKA: Are we ready to continue?

DR. KOCHER: Could you allude to some of the problems with that study, maybe?

DR. TRABALKA: Well, one of the problems of course is that they used - despite the fact that most of these studies did not have normally distributed confidence limits and they assumed that they were normally distributed and estimated a standard error, and then they - so they have ratio - and this

includes the A-bomb survivor data.

So, they have ratios of two normal distributions, which produces a Cauchy distribution, which has an undefined mean and variance.

The median is well-defined, but a Cauchy distribution has very long tails. Their results were given as 90 percent confidence intervals.

And if you look at the results and you start looking at 95 percent and 99 percent confidence, you see that they've ballooned. So, there's some issues related to that.

I'm not going to hit them over the head with that part because, you know, they were trying to come up with a better way of looking at the data to estimate what DDREFs or risk ratios might be.

Data selection is a bigger issue. We think that more consideration should have been given to weighting the studies according to their value and their - as I pointed out,

there are problems with the Chernobyl worker studies, the clean-up workers, the Techa River studies.

They also were limited in some of the studies that they used. For example, they left out the nuclear power plant worker study by Howe and company, they left out the Cogema Nuclear Power Plant worker study by Rogel and company, and the Idaho National Laboratory study by Mary Schubauer-Berigan and her colleagues from NIOSH.

In the 15-country study, all three of those cohorts were assigned a negative risk. Of course if you would put those back into this deliberation, I think you're going to change the results somewhat.

Also, the - well, that's enough for now. I would rather that you read that section. And then if you have any questions, I'd be happy to answer them. Written responses, or just talk to you on the phone.

DR. KOCHER: Yes, there have been a

lot of studies of various kinds that have done this inverse variance weighting scheme. And that just always raises a red flag in my mind, that's a way to deflate uncertainty and -

DR. TRABALKA: I don't like to deflate uncertainty unless I have a really good reason for so doing.

Should we move on?

MR. KATZ: I thought David Richardson had some questions.

David, did you have some questions or points?

CHAIRMAN RICHARDSON: Yes. Well, there were two questions.

Right now you're reviewing literature, if I'm correct, which is focusing on dose-rate effects. These are the Jacob and the workers compared to the LSS, and public and environmental exposures compared to the LSS.

You're focused on investigations in which an estimate under a linear model for the

magnitude of excess risk per unit dose is compared between populations where you're presuming the exposures are protracted over time, to populations in which there's an acute exposure.

DR. TRABALKA: That's correct. And linear risk coefficients are being compared in both cases.

CHAIRMAN RICHARDSON: Right. So, this is one - as I'm trying to map this out to my thought experiment and to - this is a focus on the category of solid cancer risk estimates when we have protraction over time and exposure.

DR. TRABALKA: That's correct.

CHAIRMAN RICHARDSON: And we're not looking at leukemia here, because the thought experiment is that the acute exposure response shape is - does not have a magnitude - the magnitude of that relationship is not affected by whether the dose rate is higher or lower. Which, to me, is an empirical question, but

it's an assumption that's built into that.

I would like to separate out the categories of the shape of the exposure response curve, where you can do a dosing experiment and for a given magnitude of dose we see that the response varies as a linear quadratic function, and then we protract that exposure over time and we might ask whether the response is insensitive to the protraction of exposure over time.

DR. TRABALKA: Right.

CHAIRMAN RICHARDSON: That's off the table here, right?

DR. TRABALKA: Well, specifically for leukemia for chronic exposure, what is done is to take the linear risk coefficient from the linear quadratic model and apply -

CHAIRMAN RICHARDSON: I understand. I understand that. I'm pointing out that -

DR. TRABALKA: But the issue of whether or not there is also information that would suggest that you need to apply, let's

say, a DDREF to that is still an issue.

And I think at the moment, we simply don't have enough information to be able to answer that question.

CHAIRMAN RICHARDSON: I think we have all exactly the same information, actually, as we do for the solid cancers. There are leukemias in the A-bomb data, and there are leukemias in all of these epidemiologic cohorts.

DR. TRABALKA: But what we don't have is the latest iteration based on the DSO2 dose response for leukemia in the A-bomb survivors. That has yet to be published.

CHAIRMAN RICHARDSON: For what outcomes are you considering?

DR. TRABALKA: Leukemia, multiple myeloma, lymphoma -

CHAIRMAN RICHARDSON: You mean for mortality?

DR. TRABALKA: No, no, incidence. Remember, IREP is used to estimate cancer

incidence.

CHAIRMAN RICHARDSON: But we've just been reviewing a set of comparisons most of, for example, Jacob's work, I believe, is mortality data, right?

DR. TRABALKA: Yes. And for cancer incidence, the DDREF is about one, for example, based on the three studies that they included.

I think if you take out the data for the Techa River studies and then redo it, you get a DDREF that's close to one and a half, but that's for the future discussion.

CHAIRMAN RICHARDSON: Yes.

DR. TRABALKA: That's not covered in our report.

CHAIRMAN RICHARDSON: And you said that the French Academy came to a different conclusion than the, what I would call a meta-analysis by Jacob.

Did they do their own meta-analysis of these empirical data, or did they derive

their conclusions some other way?

DR. TRABALKA: They weren't looking specifically at DDREF. They were looking at the - or reviewing dose response model information.

So, they were reacting to the BEIR VII report that suggested there should be linearity in the low-dose response. And their conclusion was that phenomena such as hormesis and thresholds were very highly likely at low doses and dose rates.

And so, the issue was on the dose response, of course that has a tremendous effect on potential DDREFs.

CHAIRMAN RICHARDSON: So, it wasn't derived from, let's say, observational data from epidemiologic studies and -

DR. TRABALKA: They included epidemiological studies in their evaluation, yes. But it was mostly based on animal studies, laboratory studies and things like that.

CHAIRMAN RICHARDSON: Thanks.

DR. TRABALKA: Okay. Ready to move on?

So, anyway, as I said back around 2009 we thought probably it would be best to combine human and animal data. But now, our current approach focuses on human epidemiological data for combined solid tumors to estimate a DDREF.

We have attempted to estimate DDREF distributions for thyroid and breast cancer and we've compiled information on lung and bone cancers.

And we're going to use animal data - or have used animal data as a check on our results, but not in quantitative derivation of the DDREF distribution.

And we concluded from our review that separate distributions for thyroid and breast cancers are not warranted, because there's much more uncertainty in the dose responses than formerly considered.

The EPA in its 2011 revision of the blue book, basically came to the same conclusion. They're using common DDREF for all solid cancers.

Now, there was another point I was going to make here, but it's flown away. So, I'll wait and respond to questions.

(No response.)

DR. TRABALKA: Oh, okay. That's good. Go on. Let's go on to the next slide.

This slide summarizes some of the information, but the information that we did involves studies where we have combined solid cancer data available for estimation of DDREF.

Comparing the results from the UK worker study, the updated worker study with the LSS cohort gives us a DDREF. And these are 90 percent confidence intervals shown on this slide, I should point out.

The next two values are LDEFs that were obtained from the latest iteration of A-bomb survivor data, basically the DSO2-based

dose response information sets.

BEIR VII and Preston and company in a 2007 paper, produced results that are very similar. The uncertainties are different, but the point estimates are identical of DDREFs - or LDEFs at 1.3.

Continue on. The next set of data are those on cancer mortality from a variety of studies. There's only one DS86-based data set there. That's the one from Linda Walsh and her colleagues published in 2004.

A variety of estimates obtained from the RERF folks typically for mortality, the point estimates are between one - are closer to two than one.

The linear quadratic exponential model that Little and his colleagues developed for the UNSCEAR report has very wide confidence limits. It was reported to fit the data better than linear quadratic model, but it has extremely wide confidence limits and its point estimates are slightly greater than

two.

If we look at the comparisons between the 15-country study including the entire Canadian cohort and that with the UK workers using mortality, you get values as I mentioned earlier from 0.55 to around one.

Now, what we did is we assign a much higher weight to values based on cancer incidence, because IREP is -- the endpoint in IREP is cancer incidence.

We assign essentially equal weights between the A-bomb survivor data and that obtained from comparisons between worker studies and the LSS cohort.

That can be argued as, you know, it should be looked at, but we applied a wide range of sensitivity and uncertainty studies to our result.

We even looked at assigning a higher weight to a fixed value of one. We assigned a 25 percent weight for that.

In another case, we assigned a 25

percent weight to a threshold which is the value of infinity and we did that in combination. And what you find in doing that is that the point estimates don't vary all that much.

The upper bounds on the DDREF distributions of course vary tremendously. If you put a value of infinity in there, your upper bound is going to be infinity, but the lower end of the confidence limits and the point estimates don't vary by much with a result that it's that region of the DDREF distribution that drives the 99th percentile of PC in IREP.

So, you don't - in fact, most of the distributions we came up with would probably produce - will produce higher estimates of PC than in current distribution in IREP.

Well, let's continue on.

DR. NETON: I want to explore that a little bit. You're saying you did sensitivity

analyses.

DR. TRABALKA: Right.

DR. NETON: Explain that a little more to me.

DR. TRABALKA: We looked at different weights, the assignment of different weights, for example, to the incidence data versus the mortality data.

We ran a case where the - all of our results were done using Monte Carlo simulations.

DR. NETON: Right, yes.

DR. TRABALKA: And we did - and we ran cases where we did attempt an inverse variance approach to the data to try and reduce uncertainty.

But with all of the ones we ran, as I pointed out, we didn't have a big - the point estimates varied from 1.1 to 1.6, with a center probably around 1.3.

DR. HOFFMAN: In an attempt to come up with a state of knowledge distribution

representing uncertainty on DDREF, we looked at multiple approaches. This is what's called their sensitivity analysis.

DR. NETON: Right.

DR. HOFFMAN: So, we have our preferred approach, and then the report - I don't know if that section has been delivered or not.

So, this is the section of the report that hasn't been delivered, which would show the outcome of the sensitivity analysis and how many different iterations were used to not only express our overall state of knowledge, but to look at the impact of these various distributions of DDREF on the upper 99th percentile of the Probability of Causation for specific diseases.

DR. NETON: In hypothetical cases?

DR. HOFFMAN: In hypothetical cases.

DR. NETON: See, my concern is that the central estimate really is what's going to drive a change in PC, because the

distributions are so tight compared to the other uncertain distributions in IREP.

Any incremental change in the central estimate of the DDREF will result in a corresponding incremental change in the PC calculation.

So, the central estimate really - I don't care how much wider you make your uncertainty bounds on that distribution, it's not, I don't think, going to have much of an affect on the overall PC change.

What will change is probably a change in central -

DR. HOFFMAN: But what we're saying is central estimates don't change much. Nor does the lower bound. But the upper bounds change dramatically.

DR. TRABALKA: But what Iulian and Brian discovered in looking at what was driving PC from DDREF distributions, was that values between the fifth and the 40th percentile were driving the 99th percentile PC

estimates.

So, it is the lower end of the distribution.

DR. NETON: I don't know if you tried it with real cases or not.

DR. TRABALKA: Well, no. Obviously we couldn't.

DR. NETON: You can only do so much in a hypothetical situation.

DR. TRABALKA: That's correct.

DR. NETON: I think if you try real cases, you might see something different.

DR. TRABALKA: And you could argue that we need to do additional sensitivity analysis. That's a fair statement.

CHAIRMAN RICHARDSON: So, have you ended up with a histogram?

DR. TRABALKA: Actually, we have developed continuous distributions, not histograms.

CHAIRMAN RICHARDSON: And when you were describing the upper tail, I'm imagining

a distribution that has a long tail on the right.

DR. TRABALKA: Well, for example, I'll give you an example of how it might look. A point estimate, let's say, of around 1.3, fifth percentile at 0.5, and 95th percentile at five.

That's just one, you know, that might represent our preferred distribution at the moment. That could change with future analysis.

You can compare that with what you get when comparing the studies - or the study of Jacob of the history cases and with the distribution that's currently in IREP for the combined solid cancers and that from the BEIR VII DDREF distribution.

Both of those have tighter confidence limits.

MEMBER ZIEMER: Could you clarify on the third -- or the second study by Little, what does that say at the low end of that?

DR. TRABALKA: It means that the confidence limits were wide enough they would have extended below zero for a DDREF when you do a Monte Carlo simulation.

MEMBER ZIEMER: Oh.

DR. TRABALKA: They provided parameters for a linear quadratic exponential model with uncertainty.

And when you run a Monte Carlo simulation, what that represents in terms of a DDREF, that's what you get.

MEMBER ZIEMER: Is that a minus 13?

DR. TRABALKA: Minus 13, that's correct. That's correct.

MEMBER ZIEMER: All right.

DR. MAURO: This is John. Quick question.

When you get a minus, would that be interpreted as a hormetic effect?

DR. TRABALKA: It could be, or it could just be representing noise because of the wide uncertainty.

DR. MAURO: Okay.

DR. TRABALKA: I would interpret it as a hormetic effect. And of course in IREP since values less than zero are - or the risk distributions are truncated at zero, we probably should have truncated that right at zero ourselves, but we just wanted to show the entire data set.

DR. MAURO: One follow-up question on that.

In the 95 percent confidence intervals that you have been discussing, do any of those intervals include negative values if you propagated the distribution without truncating?

DR. TRABALKA: Which distribution? These are all 90 percent confidence intervals.

DR. HOFFMAN: He doesn't have slides.

DR. TRABALKA: Oh, sorry. These are all -

DR. MAURO: Yes, unfortunately, I

don't have slides.

DR. TRABALKA: No, in our preferred distribution, we have no negative values.

DR. MAURO: Okay. Thank you.

MEMBER ROESSLER: Can I ask a question on this?

CHAIRMAN RICHARDSON: It seems to me you'd be more concerned about values of zero than even negative values.

You take the risk coefficient and divide it by zero and get infinity.

DR. TRABALKA: Yes.

DR. HOFFMAN: None of our distributions have zero.

DR. TRABALKA: Go ahead.

MEMBER ROESSLER: Yes, just looking at this figure and looking at your central estimates, I don't totally understand all your sensitivity analysis.

But it seems like if you, for the time being, kind of set the Jacob studies aside, that you're putting a lot of emphasis

on the Cardis or the 15-county data, you know, compared to all those other sets that appear in kind of a grouping there.

DR. TRABALKA: Well, actually I should have given you some more details of how we did all this.

DR. KOCHER: The answer isn't shown here.

DR. TRABALKA: Well, I know.

MEMBER ROESSLER: Okay.

DR. TRABALKA: And of course there's a reason for that.

But when we pooled the data, we first pooled all of the LDEF information from the A-bomb survivors, ran a Monte Carlo simulation that applied roughly equal weights to each one of those values that's represented by a solid triangle, slightly lower weight to the value for Walsh and company's value simply because they didn't provide a lower confidence limit and we had to estimate it.

Once we got that answer, we pooled

it with the information obtained from the comparison of the 15-country study and the UK study, but those two sets were given equal weight.

So, the 15-country study is not dominating at this point.

MEMBER ROESSLER: Okay. Then another question. The French Academy study, you mentioned that earlier. And you're not considering that, and can you give me some reasons why that was not part of your evaluation?

DR. TRABALKA: Well, we evaluated that information. ICRP evaluated it in their 2005 report, and we just don't think that there's enough credible information in that report to use.

DR. NETON: That wasn't really a DDREF study.

DR. TRABALKA: No, it wasn't a DDREF study.

DR. NETON: It was really a

commentary on LNT. That's my recollection.

DR. TRABALKA: Exactly. Exactly.

DR. KOCHER: And one of the things that I try to remember in this whole business is that we're starting with an LNT model. That's a given.

And so, we're trying to estimate if DDREF would apply to that model, warts and all.

MEMBER MUNN: And I think that we challenge that concept.

DR. KOCHER: Yes, but that's not - the rules of the game have been fixed.

DR. TRABALKA: I should also point out that a brand new study of the A-bomb survivors, cancer mortality in the A-bomb survivors has just been published in 2012.

And the DDREF estimate we've obtained from that set of information is 1.8. And so, it falls within the range of all these other values.

However, there were some other

interesting ramifications to that study that suggest that you have to be cautious in writing off super linearity at low doses.

So, that's why values less than one cannot be eliminated from DDREF distributions. We have to be very, very cautious right now. We have plenty of indications of supralinearity in some of the human data.

MEMBER ROESSLER: And this new study is by whom?

DR. TRABALKA: Ozasa et al. I think it's the first one that I've seen where Donald Pierce and Dale Preston haven't been involved.

MEMBER ROESSLER: And where was this published?

DR. TRABALKA: In Radiation Research.

MEMBER ROESSLER: Okay. Okay.

DR. TRABALKA: I think it may be January. Somewhere in the January to March frame.

DR. HOFFMAN: So, fairly recent.

DR. TRABALKA: Yes, well after the draft date of our report.

MR. KATZ: Do folks want to break? We've been going at it for an hour and a half or more.

DR. TRABALKA: There's one more slide, but it's just a quick wrap-up.

MR. KATZ: That's fine. That's fine. Why don't we do that? That makes sense then.

DR. TRABALKA: Well, basically our own conclusion is that we can develop a distribution of DDREF that represents the current state of knowledge, it has wider ranges, a central estimate closer to one.

It contains also most of the point estimates from the animal data. It's just that they're not given the highest priority as they have been in the past in some of the estimates.

However, our conclusions are preliminary until selection and interpretation

of our data and our choices of alternative distributions have been vetted. That has not been done.

We've tried to get some comments from the ICRP Committee on Section 5 and our approach to doing DDREF distribution estimates, but we have not been successful thus far except for the comments from Peter Jacob.

However, one thing that Peter Jacob did that was very useful, was the idea of using risk ratios where you invert -- it's the inverse of DDREF to avoid infinities in calculation.

So, in future it might be better to try and do calculations that way and it would simplify calculations. At least give consideration for doing that in the future. And that's it.

MR. KATZ: David, before we go on break, David, Bill or Dick, do you have any questions you want to raise before we break?

CHAIRMAN RICHARDSON: No, I suggest we take a break.

MR. KATZ: Okay, good. So, we'll rejoin in 15 minutes, maybe, which will be about 11:00.

(Whereupon, the proceedings went off the record at 10:48 a.m. and resumed at 11:01 a.m.)

MR. KATZ: Okay, everyone's back in the room, but let me check on the line. Do we have David and Bill and Dick?

MEMBER FIELD: Bill is here.

CHAIRMAN RICHARDSON: David Richardson, yes, I'm here.

MR. KATZ: Okay. I don't hear Dick, but I think we can restart. So where are we?

DR. TRABALKA: We're done with our component, except for questions that folks still want to ask.

MR. KATZ: So, I don't know if you could hear John. He's offering up if there are questions people want to raise, they're

finished presenting.

CHAIRMAN RICHARDSON: Maybe we could start with a question about the timeline that NIOSH is imagining for kind of finalizing and releasing a draft of this report for the Committee on those final sections.

DR. NETON: Good question, David. This is Jim. I think that we need - NIOSH would like to submit this report for external peer review very much like we did the radiation effectiveness factor work, or that SENES did.

We would solicit at least three subject matter experts, up to five, to provide comment on the full report, including the conclusionary sections.

We're willing to move forward with that very quickly as soon as, I think, John wants to make a couple changes to some errors that he's noticed in the report.

But that process is not probably, from my experience, going to be real quick. I

mean, we have to allow - we have to first identify the experts, get them to agree. It's a fairly lengthy report. I would envision that in the three to six-month time frame is where I would go.

But I think at this point, sufficient information, it's been consolidated, put together, that it's got to go out for review.

And until we get that input, I don't know that we can release the - I would not feel comfortable releasing a full report.

CHAIRMAN RICHARDSON: No, sure. I was just wondering how -

DR. NETON: And once that occurs, though, I think then we would open this document up for -- essentially, I would think at that point.

And I need to work this through the process, but I would assume that we would open it up for public comment, which would include the Working Group, and at some point the full

Board as well, with our recommended path forward.

We would take the subject matter experts, respond to their - working with SENES, respond to their comments, concerns, and then adopt a position.

We're treading somewhat cautiously here, because this is a major, major change to IREP. We've done other changes in the past that were minor, in my opinion, compared to this.

And I'm struggling with the idea of our charge to rely on consensus science for our scientific approaches. And at this point right now, we have our contractor's opinion as to where things are and we'll move forward with the subject matter expert reviews, and then full public comment.

So, it will be three to six months, I guess, is the best I can -

MEMBER ROESSLER: So, you think you can get the subject matter reviewers

accomplished in three to six months?

DR. NETON: Well, probably closer to six months.

MEMBER ROESSLER: Yes.

DR. TRABALKA: With some arm twisting.

MEMBER ZIEMER: That's at the 40 percent confidence level.

(Simultaneous speaking.)

DR. NETON: I would say six months is doable. I mean, if we could identify folks, we have a fairly quick mechanism. We don't - we will essentially do this like we do other documents of this type.

We would offer an honorarium. We don't hire people to do this. We offer an honorarium to review it and it goes quicker.

And then it's just a matter of finding someone with the time to read almost a 400-page report, which maybe six months is a little bit optimistic because it's a tome.

MEMBER ROESSLER: So, you at NIOSH

pick the reviewers.

DR. NETON: Yes, that's the way we've worked it in the past. I think it's incumbent upon us to do that.

We certainly accept input from anyone as to what potential reviewers would be available or might be appropriate because we would want to get a spectrum of reviews, not just one-sided.

MEMBER ZIEMER: Is SENES done with those missing sections or close to done?

DR. NETON: Oh, they're done.

DR. HOFFMAN: The missing sections are complete.

DR. NETON: Yes, I just - it's been my holdback or at my request that they be held back because I'm not comfortable releasing their conclusions given the document had not really been reviewed externally.

MEMBER ZIEMER: Gotcha.

DR. KOCHER: The business about consensus is tricky. I mean, I can't sit in

your seat politically, but the REF work was certainly not any kind of consensus thing because it was new and a consensus -- consensi take time to develop after new stuff comes out.

Now, this is not a new concept, but the approach to doing it is, in my judgment, pretty new.

DR. NETON: Well, to the extent there are other consensus organizations out there that have a different opinion. I mean, the BEIR VII report, it differs from that. I guess what else is - does UNSCEAR have their own distribution? I think that they -

DR. TRABALKA: UNSCEAR uses a linear quadratic model for cancer mortality. So, they don't apply DDREF. It's inherent in the model.

And for cancer incidence, they just said, hey, it's close enough to linearity, we're not going to worry about it, we're just going to use the value of one, just assume

it's one.

DR. NETON: So, to some extent, this is groundbreaking, I mean, what we're doing here. And I'm, like I said, we're moving cautiously.

But I would be comfortable going out and getting three, hopefully up to five, independent reviews that we would solicit, get those reviews back, work to address the concerns.

And then I'm reasonably certain that we would go out for public comment in some kind of a Federal Register Notice to say, here is our intent. Once we formulate and come to a conclusion based on the report, the revised report, this would be our intent.

Or, I mean, that's presuming that we came to conclusion to revise the DDREF. I mean, I don't want to presume that all the comments that we see come back, you know, and say, yes, this is the greatest thing to do and proceed down this path.

It's also possible that a conclusion could be made that now is not the appropriate time. I don't know. I don't want to comment either way, I guess.

MEMBER MUNN: Well, "consensus" is a dangerous word.

DR. NETON: Yes, it is.

MEMBER MUNN: And certainly human history has not shown it to be always the wisest choice with respect to scientific endeavors. So it would be wise to be cautious with that.

MR. KATZ: Yes, I think just to clarify what we said up front in the regulations about new science was that as authoritative groups and so on, consensus groups produce new findings, recommendations, those would be taken into account and serve as drivers for the program to reconsider its science, but that doesn't limit the program to only awaiting, BEIR reports, etc.

MEMBER ROESSLER: So, as a Work

Group, what is our - I guess David maybe knows the answer to this. But as a Member of the Work Group, what is our responsibility at this point?

Just to follow the development as it goes and be prepared to present to the Board what we've observed and -

MEMBER ZIEMER: I think we have to help the Board with whatever comments the Board is going to make.

David actually had drafted some sort of straw men comments which I think will have to await the review of this, David, until, you know, but I think that's the nature of what we would do, because I think our Board, the full Board, is going to depend on us coming to them with a recommendation as to what the action should be.

So, we can do the - we could develop the recommendation and wordsmith it and get it ready for eventual adoption, but it seems to me we're going to have to await the

outside review.

Because perception-wise for this to look like some sort of independent consensus in a sense, I mean, it would be different if an international group or NCRP had come out with some - that you guys are ahead of them on this, it appears to me, and there's even the possibility that they would end up adopting whatever the endpoint is here.

But in any event, if we have good external reviewers that are seen by the public as not having a vested interest in the outcome would be very important.

People of recognized stature, it's true you have to pay them a stipend. But I think even on the CLL thing, we had different views on that. And then we made a decision, but we want to get the pros and cons on this and then go from there.

I mean, even SENES will be seen as having a vested interest here because you guys have a contract to do this and, you know.

People, their perceptions are you're getting paid to produce what the government wants.

I mean, that's how people look at these things. We see that all the time. So, we get these independent reviews and we can go from there.

David, I wasn't trying to preempt you, because you've done a straw man thing which I think is the sort of thing we need to provide for the Board in fleshing out the detail.

This is much more complex than I anticipated it was going to be at the front end.

CHAIRMAN RICHARDSON: Yes, the task that you suggested, I think we'll end up having to do of when NIOSH makes their - or puts forward something to be able to comment on. And I think it would be very useful to be able to comment on it and the reviewers' comments as well.

That's sort of - it makes it

somewhat unusual for the kind of list of issues that the Work Group has before it, because it's something that NIOSH is moving on independently and is relatively far ahead on.

But the, you know, when we started out laying our scope of task, it was to identify issues that would be impacting the risk models and suggest or raise questions that would be kind of at least necessary to think about for moving forward on the issues and report just back the status of these scientific issues.

It would be possible for us to do that in sort of a modest scope, or we can hold off and sort of table the issue and wait for NIOSH to put forward their opinion. So, that would be either.

I mean, many of the issues that I think in the long run we'll be dealing with are not going to be like this.

MEMBER MUNN: I should hope not.

CHAIRMAN RICHARDSON: But like this

in a sense that NIOSH may be considering or reacting on it while this Work Group is really not supposed to be - I don't think is supposed to be proposing distributions or something like that for parameters that NIOSH uses, but rather kind of looking at broader issues.

MR. KATZ: Yes, I mean, David, I mean, I think the Work Group is free to comment as it will. I mean, it sounds like the comment on technical matters really needs to await the peer review and so on.

But to the extent that there are already points of view or whatever that they should take into account before sending it off to the peer reviewers, I mean, I think that would be valuable.

So, I don't think the Work Group is restrained or the Members from providing whatever kind of comments they might - or point of views they might have up front here.

MEMBER MUNN: But by the same token, it's sometimes wise for groups especially like

this Work Group, I think, to take a step back and reevaluate precisely what our responsibilities are in this regard.

It's not our responsibility to identify the science, I think. I haven't seen any indication of that in our instructions.

CHAIRMAN RICHARDSON: To identify the science, did you say?

MEMBER MUNN: Yes. It is -- I believe our responsibility is to assure that the agency is performing the best science available in their activities, and our oversight role is one of oversight as I have interpreted it.

Perhaps my interpretation is simplistic. But if that's the case, then the results of the developments in science that occur during the period of time that this program is operable may have results that a Work Group such as this one probably should consider in our deliberations before we go too far in our involvement in the development of

the science itself.

CHAIRMAN RICHARDSON: I guess I have a different view of that. I think the Science Issues Work Group has a responsibility for identifying scientific or technical issues that impact on the risk models.

So we do, we should identify where we think there are either issues that relate to validity, clarity or the scientific basis for the compensation decisions that come through the program.

MEMBER MUNN: Well, yes, I don't see that as conflict with what I said, David.

CHAIRMAN RICHARDSON: Okay. Maybe I wasn't understanding you.

MEMBER MUNN: No, no. I'm just saying -

DR. KOCHER: You're not wanting to tell NIOSH which data set they should use to solve a problem.

MEMBER MUNN: Exactly. Exactly. But I certainly think that we are charged with

the responsibility of taking a look at it and saying, yes, this is good science.

CHAIRMAN RICHARDSON: Right. So, this is where kind of going back to the slides, the very early slides that showed what's currently done with IREP. There's a flow diagram, and then there's a set of histograms.

And where I, you know, what's sort of been discussed right now relates to the histogram.

I find the whole thing a little bit mind-boggling, the flow diagram and kind of the - I find that there's a level of complexity there and a set of varied assumptions. And then a lot of judgment that to me if I was going to point to NIOSH about places to think about this aspect of the compensation program, I would say this - I find this unsettling.

I mean, it's not that it's unique. There are other organizations which have made

a set of similar assumptions, but there - I mean, it's, you know, as the kind of justification, well, this histogram was drawn by Ethel Gilbert based on her judgment about those parameters, it's broken out for some disease entities and not others, you know, there's a whole series of things here which I, you know, I think we might want to think about as pointing out as technical issues.

At least I would. I would lay on the table as a series of issues moving through the whole flow diagram.

MEMBER MUNN: Certainly anytime we address something like as complex as IREP, we are going to be faced with innumerable technical conflicts both in terms of opinion and in terms of what data is reliable.

That's one of the reasons why I said it is more of a burden than I believe could be intended for the Work Group or even for the Board to undertake to -

CHAIRMAN RICHARDSON: But IREP is,

in fact, far less complicated than a lot of the dose reconstruction that's going on. I mean, it's the application of a set of risk coefficients and a few modifying parameters.

I mean, we're working with lots of technical issues that are -- in which we evaluate uncertain scientists -- science with the reliance on subjectivity for, I mean, for lots and lots of aspects of the exposure reconstruction program that's going on. And this is another one of those.

MEMBER ROESSLER: As a Work Group Member -- well, what David said about this being mind-boggling really hit home.

But I think as a Work Group Member myself, I don't have the time and I don't have the expertise to go into all the details of this. But I think as Work Group Members, we can evaluate the experts that NIOSH selects and that's where I think we weigh in.

If we have confidence in the experts who will put in the time and we know

they have the expertise, I think that's a big factor.

MEMBER MUNN: It would be.

MEMBER ZIEMER: Dave, another comment. It seems - this is Ziemer. I think it would be appropriate for the Work Group to report to the Board some, in a preliminary way, number one, that we've reviewed the current use of the DDREF in the IREP model with the help of SENES and the NIOSH staff; number two, that we're aware that there's a lot of new biological data out there that SENES has been evaluating it and they are preparing a report for NIOSH and perhaps indicate that, and this could be a Work Group conclusion that, for example, that we agree that these parameters need an update - or not an update, but need a closer look for potential update and modification of the IREP model and that we agree with the direction being taken here. Which is to have the review, to have it independently evaluated,

and then to have the opportunity to look at the potential changes. Something along those lines.

I think we do owe the Board some sort of status information on what we're doing with this.

CHAIRMAN RICHARDSON: Yes, I think that sounds reasonable.

MEMBER ZIEMER: We don't have to reach any conclusion at this point other than to say we recognize that here's what's being done now, and there's a lot of new biology that could impact on this. Not that it necessarily will, but that it may or something along those lines.

We can't reach a conclusion at this point in any event.

CHAIRMAN RICHARDSON: I would like to reserve the -- kind of the option or the opportunity that this Work Group does - expects at some point that it will tackle issues that are difficult that may require

time or resources.

I feel hesitant to say, well, these aspects of the program are complicated and technical and we can't be expected to dig into them. They're as technical and complicated, from my perspective at least, as much of the other exposure reconstruction and other aspects of the program.

And I guess coming onto the Board, I felt like there were a number of technical issues that relate to this side of the program that are, you know, haven't been given nearly the attention that the exposure reconstruction aspects have, and yet, are part of the program and will take some time to get up to speed on, but are really important as well.

MEMBER MUNN: David, I think you're amplifying what I was trying to say earlier and perhaps did not say in a very concise manner.

Really, what I was trying to say is, first, my apologies for not having been on

the teleconference when you were making an effort to set the Work Group up. I was traveling and was on airplanes at the time.

But it - there's some question in my mind as to whether we as a Work Group have adequately defined our charge ourselves. And I didn't see just reading quickly through the transcript, I didn't see that the conversation that was had came to a logical conclusion in that regard.

And I think perhaps you and I are saying very much the same kind of thing, except that I'm asking that the Work Group perhaps devote some time before we go too much further with very many of these scientific issues in better defining for ourselves exactly what our responsibility, what our charter is, and what our boundaries are going to be with respect to how we address these issues that have been placed before us as starting points.

I don't know whether today is the

appropriate day to do that, but it would be worthwhile from my point of view if we did spend some time trying to be very clear with each other about what our responsibilities are and how we're going to address those.

CHAIRMAN RICHARDSON: Yes, we had some discussion of that the first time, and I think it would be worthwhile to kind of go back and review those. We had talked about some issues regarding scope and kind of process and deliverables and how that would happen.

Maybe we should set some time at the start of our next meeting to revisit those, and maybe I can circulate something ahead of time as kind of a starting point for that discussion.

MEMBER MUNN: I think that would be wise. It would be very helpful from my perspective to have the views of the other Members of this Working Group as to how they perceive their responsibility on this group to

be.

Yes, I would like very much if we would set aside some time at the beginning of our next session to do that and perhaps even have some exchanges by email and try to come to some general conclusion with respect to limitations of what our expectations are and what the Board's expectations are of us.

MEMBER ZIEMER: One of the philosophical things I think might be worth discussing is the issue of use of current science and what happens when it changes. And this is a practical thing.

For example, when we change a method of reconstructing dose, and there I'm talking about some usually modeling where NIOSH has some early models, and then there's - and we have some sites that are in this category now where the models get changed simply because we get new information about the site and that sort of thing.

But here if the science changes,

for example, a dose-rate factor changes this issue, and I'm not sure how the regs read or the legal ramifications, but does it mean you go all the way back to ten years or 15 years where you were using the best science at the time? Because science is always going to change.

Ted, you might help us out, but one of the things that is sort of a concern is that do you go back and redo everything that you've done for a decade because the science has changed.

MR. KATZ: And to speak on that point, and we wrote the regs with an eye to the fact that the science would change and to accommodate that by, whenever necessary, because the science dictates better methods, incorporating those new methods.

And integral to that is that cases that were already completed that would be affected by those improvements, would take into account those improvements that would be

affected.

I mean, honestly for cases that are already compensated, it's a nonissue. But for cases that are not compensated -

MEMBER ROESSLER: Not to reverse -

MEMBER ZIEMER: Well, you can't reverse.

MR. KATZ: No, there's no reversing cases that are compensated. But I'm saying for cases that are not compensated --

(Simultaneous speaking.)

MR. KATZ: -- better science would be employed again if it would affect their results.

DR. NETON: And since DDREF is in every single case -

MEMBER ZIEMER: Well, that's exactly my point. And then ten years from now you'll have something else -

MR. KATZ: That's an argument for taking due diligence in revising the science, I think. It's not a question of whether the

science should be revised when it should be, but it just is an argument for doing this in a very deliberate, diligent way.

DR. MAURO: This is John Mauro. I also have an observation that I'd like to put out. The DDREF operates off the excess relative risk, which is really the rock that IREP stands on. And I realize SC&A does not get involved in reviewing any IREP work, but I'm on the phone and I'm listening and I'm very interested with a strong background in radiobiology.

If the day comes when a judgment is made that some change will be made to the distribution for the DDREF and incorporate it into IREP, I would say the only caution I would advise is that that be done in concert with any consideration on the excess relative risk, which is even more fundamental and which is also a subject undergoing considerable reevaluation.

They sort of go hand in hand and

you really wouldn't do one without the other.

DR. NETON: You raise a good point, John. This is Jim. But there's a continuing dilemma as to where you draw the line in the sand and move forward.

I mean, we've talked about this in the past and -

MEMBER ZIEMER: Or do you wait for something to -

DR. NETON: Do you wait for something else to catch up? And then all of a sudden, as you saw, the change between our 2009 concept that SENES has outlined versus the one today is even different.

So I don't know how you realistically do it all at one time. It just would be very difficult because the data aren't available all at the same time. But you raise a very - that's a very good point.

MEMBER MUNN: Well, since we have no sunset clause for the operations that we're involved in here, one can question how long we

wait for the science to mature and change.

I'm not sure science ever matures, but as it changes as we go -

DR. NETON: It's a little different with this particular issue because it was sort of an in-house developed science -

MEMBER MUNN: Yes, it is.

DR. NETON: -- that is commenting on the change versus something that's, in my mind, a little more clear-cut if you have a new ICRP lung model that came out, for example.

And we would probably adopt that fairly readily because it's consensus science and it's put out there for general use. This is a little different.

MEMBER MUNN: It is.

DR. NETON: That's why we're moving cautiously, but I think the plan is valid to move forward with a review by experts and see where they land.

But I don't disagree with David

Richardson though. We would welcome any general comments on the DDREF itself and its employment in the program. I mean, that's certainly fair game for, I think, the Working Group.

CHAIRMAN RICHARDSON: Well, thank you very much for the presentation. I didn't say that at the start, but it was really very useful for me in understanding both what's been done and to kind of hear about the review that you've undertaken.

And I think a lot of the points in your conclusion correspond to some of the streamlining that I was imagining and hoping that NIOSH will take both in kind of trying to lean more on an empirical basis for the distribution for this factor - I think the idea of stepping away from separate distributions for different tissues is probably a sensible one.

I appreciated the way that you handled a number of the points as I tried to

in my own thinking, kind of separate out low-LET from high-LET radiation.

It's still not quite clear to me what I - the point that you made, I believe, is that the inverse exposure rate effect, which in my world would be a dose-rate effectiveness factor, is, in fact, incorporated into IREP someplace else; is that correct?

DR. TRABALKA: Within the radiation effectiveness factor, yes.

CHAIRMAN RICHARDSON: Which is interesting why that's the way it is, I guess, but it is there. Because there's right at - if I look at this flow chart, you're implying full certainty about the dose-rate effectiveness of high-LET radiation. But what you're saying is that there's a distribution someplace else capturing that side of the -

DR. HOFFMAN: Yes, there is quite an important distribution associated with the uncertainty and what's called the radiation

effectiveness factor.

And especially as that is applied to high-LET radiation, namely neutrons and alpha radiation, both neutrons and alpha radiation have this inverse dose-rate adjustment.

CHAIRMAN RICHARDSON: Which is a DDREF less than one.

DR. HOFFMAN: Yes.

DR. NETON: At what point does that kick in though? It's pretty high. The dose?

DR. KOCHER: No, it's always there. Certainly for alpha particles it's always there. For neutrons, I have to go back and think about it.

DR. NETON: Even for very small alpha doses?

DR. KOCHER: Yes, see, I argued that it shouldn't be in there, but I lost.

DR. NETON: I don't remember that argument.

DR. KOCHER: Yes, I do. You and I

had at it.

CHAIRMAN RICHARDSON: As long as this is a topic, at some point it may be something that I guess I would suggest again the Work Group may want to think about. Because it would fall - for me, it falls under the rubric of a dose-rate effectiveness factor, and it's fine for us to start by looking at low-LET radiation.

But if there's been apparent disagreement among the people in the room about how it's implemented for high-LET radiation, then I think this is where there is probably, I don't know, BEIR VI, for example, has a strong opinion about high-LET radiation and inverse exposure rate effects. So it might be worth us at least -

DR. KOCHER: Let me clarify the situation for neutrons since we raised it. This inverse dose-rate effect is applied only in cases of chronic exposure to neutrons. The acute dose response is assumed to be linear at

any dose. So that's how it differs from the low-LET.

For alpha particles, the inverse dose-rate effect is always applied because all the internal exposures, the alpha emitters, are assumed to be chronic, reasonably enough. So it's always in there.

And you and I had an argument about whether it should be in there, and I lost.

DR. NETON: I completely forgot that.

DR. KOCHER: Well, over lunch or at a meeting this afternoon we can revisit that.

DR. NETON: That's fine. Because my thinking was as long as we're talking on this subject, the DDREF is built into the calculation for excess relative risk for alphas.

DR. KOCHER: That's to adjust the photon risk.

DR. NETON: Right, adjust the photon risk. Because we have gone - it was my

thinking early on that the change in DDREF would not affect many of our cases because we don't have very high external exposures, as we talked about when the meeting started, except in the very early years.

But what happened since that DDREF is built into the adjustment of the photon dose when you have an REF for alphas, we have - as a major effect, we've done some analyses internally that will majorly affect people with exposures to alpha, which is probably the majority - a large majority of our cases have exposures to plutonium, uranium. Those are the cases that have high PC values, and it's going to affect those.

And it was a surprise to me to find that out that this DDREF embedded in the adjustment factor because of the way the REF was developed. So it's not really accurate to say that the DDREF does not affect high-LET radiation, especially alpha - it does.

DR. KOCHER: It affects alpha

particles but not -

DR. NETON: As much. At least from our analysis, that's true.

MEMBER ROESSLER: Perhaps the Work Group needs a little review of the REF. Because I'm thinking back to that, and what you've just said, yes, that's an impact and I think we need to look at that.

DR. NETON: That would be an interesting - I don't think we've ever gone over it with the - actually, we have.

MEMBER ROESSLER: He did a presentation.

DR. KOCHER: There were two presentations to the Board -

DR. NETON: Early on.

MEMBER ROESSLER: But we weren't thinking -

DR. KOCHER: Well, it was all new.

MEMBER ROESSLER: Yes, yes. And we weren't thinking of the impact that -

(Simultaneous speaking.)

DR. KOCHER: - snowstorm.

MEMBER ZIEMER: Well, as a minimum I'm wondering if we could revisit that and just update our own memories on that. I don't recall the details of it at all.

MEMBER ROESSLER: I mean, that's a publication, but it's pretty hard to get through. It's pretty heavy stuff.

MEMBER MUNN: Yes.

DR. TRABALKA: Well, if I -

(Simultaneous speaking.)

DR. TRABALKA: -- longer and less dense.

MEMBER ROESSLER: It was easier to understand when he presented it in person.

MEMBER MUNN: A man after my own heart.

DR. NETON: Well, we certainly would not be against having a presentation in the future as long as we can get SENES -

DR. TRABALKA: That's something we can talk about this afternoon, if you want.

DR. NETON: Yes. And it is, in my opinion, integral to the DDREF issue because of this incorporation of it into the adjustment of the photon risk model -

(Simultaneous speaking.)

MEMBER ROESSLER: It appears to be.

DR. NETON: Well, yes. I mean, this equation -

MEMBER ROESSLER: How can you -

DR. NETON: To prepare for the meeting, Daniel and I were going over the Health Physics publication. Which, by the way, if anybody doesn't have a copy of this special edition that we put out, we have about 300 in the closet back at work.

DR. KOCHER: Please take one.

DR. NETON: Please take several. But specifically Equation 26 in that article is the one I'm talking about with the adjustment. And it's pretty clear. And that's why we ended up testing, Daniel with Iulian and -

CHAIRMAN RICHARDSON: Now, for alpha particles and neutrons, let's set this aside and say for neutrons, the DDREF for neutrons applies to both acute and chronic neutron exposures? Was that what you said? But at different threshold levels?

DR. KOCHER: No, the dose response for acute exposure to neutrons is assumed to be linear with no adjustment at any dose. The inverse dose-rate effect is applied to neutron exposures only in case of chronic exposure.

DR. HOFFMAN: And DDREF is not applied at all for neutrons.

DR. KOCHER: The way this separation that you pointed out has been made, there's no DDREF anywhere for neutrons. But there is this inverse dose-rate effect that's embedded in the REF for neutrons that's applied to chronic exposure only. And for alpha particles, the inverse - there is no DDREF for alpha particles, per se.

CHAIRMAN RICHARDSON: So there

you've made a distinction between the shape of the exposure response relationship for neutrons and the effect of inverse exposure rate effects, the protraction effect of the exposure.

And you've said that the energy deposition for neutrons results in cancer risks which are proportional to dose and they're linear on an excess relative risk scale.

But when there's protraction, the effect varies; is that right?

DR. KOCHER: When it's protracted, it basically changes the slope of the entire dose response for chronic exposure. It just shifts the slope because it's applied independent of dose for chronic exposure.

The same distribution applies at any dose. It's a little different than this phasing in of the DDREF for the low-LET. It's just a single correction that's applied to any dose as long as the exposure is chronic or

protracted. So you're just changing the slope of the linear dose response, basically.

CHAIRMAN RICHARDSON: And someone characterized what the recent UNSCEAR report did for solid cancers with exposure to low-LET radiation, which was they said, well, with the cancer incidence data the effect looks proportional to dose. The shape of the exposure response is well-modeled by a linear model.

And that, I mean, I don't want to go too far there except to say it remains for my thinking that what's been done, for example, in modeling the effects of inhalation of radon and other places, is to separate out the question of the shape of the exposure response function from the effect of protraction or the exposure rate effect.

And that's - there's a lot of clarity to be gained there.

DR. KOCHER: You can't do that for radon because there's no such thing as an

acute exposure.

CHAIRMAN RICHARDSON: They've modeled the shape of the exposure response function and the exposure rate effect.

DR. KOCHER: Yes, based on an observation in some studies that the risk was higher the lower the dose rate at the same dose.

CHAIRMAN RICHARDSON: Yes, exactly.

DR. KOCHER: But the difference between radon and gamma rays is you don't have acute exposure to radon.

CHAIRMAN RICHARDSON: I mean, we talked through the experimental setups in which you could consider the effect of different types of dosing experiments, right?

And all of those thought experiments involved separating out the shape of the exposure response function from separating out questions about the effect of protraction.

We're all aware of the effects of

priming exposures, for example in radiotherapy, in which the response is mitigated by fractionating the exposure and giving the priming dose.

That would be an example where even if we're talking about leukemia, as I read it, the shape of the exposure response may be linear quadratic. And yet, a priming dose, fractionation or delivering the same total dose over periods, is going to yield a different response.

The argument that they're somehow intimately embedded by the linear quadratic shape of an exposure response function for a single exposure doesn't conform to experimental evidence in medical practice.

So I'm sort of looking at like a lot of complexity laid out in this flow diagram for scenarios where I would think we could question a series of these decision points. And I think what's been done has started to simplify them, but it's -

DR. KOCHER: Yes, my reaction to your comment about the flow diagrams is that I suspect it's fairly transparent what has been done if you stare at the flow diagram for a little while because there's not that many decision points. But what you're raising is certainly something that we would be interested in knowing more about, and that is problems that you have with these decision points and how they're made.

That's a whole other area that if you have different thoughts about the validity of these decision points, I suspect NIOSH would like to hear about that.

MEMBER ZIEMER: All you're saying is this is what you're doing now.

DR. KOCHER: Yes.

MEMBER ZIEMER: So the interesting question is what would the decision points look like in your new proposal, and are they the right ones?

CHAIRMAN RICHARDSON: Right, yes.

No, I - yes, I agree. So it's great to know. I mean, as I said, there have been a series of these questions about what was currently being done that weren't as clear in my mind as they are now after your presentation. And I really appreciate that. And I'm still, I guess -

DR. KOCHER: Your comment about leukemia I thought was also well-taken. My sense is that, okay, we have a linear quadratic model in IREP for acute exposure. And the assumption that only the linear term applies in cases of chronic exposure, that's probably a judgment.

I doubt that that's written in concrete somewhere. Charles might disagree with me, but I suspect that falls in the rubric of an assumption.

MEMBER ZIEMER: Have you thought about a similar diagram for the new things you're proposing or -

DR. APOSTOAEI: This is Iulian

speaking. One point that will change in the flow diagram is that we will have the same distribution and be applicable for all solid tumors. So that decision point to separate thyroid and breast will go away. So, that's one example and -

DR. NETON: The histogram goes away. I mean, it's a continuous function, right?

DR. APOSTOAEI: Right. So, but we have two distributions; now we're going to have just one.

DR. HOFFMAN: We'll have one distribution also where we are proposing different ranges for the definition of what should be considered a lower bound for the acute dose. That would determine when a DDREF needs to be considered for acute exposures.

DR. KOCHER: Other than that change, it really - I don't think we've thought about any changes in the decision diagram, per se.

MEMBER ZIEMER: You're proposing ten millisieverts when you lower the bar. And

it's currently 30, okay.

CHAIRMAN RICHARDSON: You know, as the histogram you're imagining becomes - has more mass at one -

DR. HOFFMAN: Yes, and it becomes essentially a piece-wise uniform distribution, continuous. And the reason for this is that numerous data sets that are then weighted in terms of degrees of plausibility are then combined.

And so the final state of knowledge of distribution that we are recommending that replace these histograms, is a continuous distribution, but it can only be approximated by the - it is not exactly - does it conform to a named statistical distribution.

CHAIRMAN RICHARDSON: Right. I'm imagining though -- so we've got a decision point here with - you've got on the left and right-hand side of this figure - on the right-hand side of the flow diagram, there's a complicated function which moves you from one

to a distribution which you're imagining which has mass - the majority of its mass around one.

And as you get to this threshold, you're smoothing the transition between a value of one and a value which has its modal value around one. So you're moving from certainty about the shape of the acute exposure response relationship -

DR. HOFFMAN: To uncertainty.

CHAIRMAN RICHARDSON: -- to one where there is uncertainty about it.

DR. HOFFMAN: Right.

DR. KOCHER: Which increases as the dose goes down.

CHAIRMAN RICHARDSON: Yes, but it's - it does that as a function of the magnitude of the acute dose.

DR. HOFFMAN: Yes.

CHAIRMAN RICHARDSON: So it's saying that's the - as you get into the low-dose range, there is greater uncertainty about the

shape of the exposure response function.

DR. HOFFMAN: Yes.

CHAIRMAN RICHARDSON: Is that what you - maybe that is what you think of as the DDREF.

DR. HOFFMAN: Well, the way you said it in plain English is exactly what's happening. As the acute dose decreases, the amount of uncertainty in the risk associated with that dose increases. But the central value, given our proposed revisions, would be closer to straight linearity or closer to a DDREF of 1.0 than it was previously.

CHAIRMAN RICHARDSON: Right. I mean, previously as it got down there, you divided the linear excess relative rate model by a factor which had its modal value around 1.5?

DR. HOFFMAN: That's right.

CHAIRMAN RICHARDSON: Which to me, was sort of, you know, it's surprising if you would say that to most people when they would

be thinking about, you know, saying we're starting off with the assumption of a linear no-threshold model. And yet, implicit in this is that there's non-linearity. There's a curvature to the exposure response function as you get to lower doses.

I guess one of the questions is we know there's uncertainty about the exposure response function as you get to lower doses. And why isn't that captured already by the variance of the risk estimates?

Why are we adding another factor in to say that there's uncertainty of our essential estimates -

DR. KOCHER: The uncertainty in the ERR per sievert is independent of dose, is the reason why. If there were no DDREF, the uncertainty would - in the ERR would be independent of dose.

CHAIRMAN RICHARDSON: So if you just wanted to answer that question, the best way to do it, the most logically coherent way to

do it would be to derive point-wise confidence bounds using the lifespan data for the risk, for all the risk models.

You already have - you have preferred data sets you want to use to derive the dose response coefficient, you've fitted a model to it, and now you want to reflect the fact that there's variance in a point-wise fashion as you're moving along in the model.

So this would be like a very complicated exercise to get around to something - I'm not saying our best estimate is from the fitted model, but the uncertainty increases as you get to move along the datas.

DR. KOCHER: The DDREF is really kind of an artificial construct that -

CHAIRMAN RICHARDSON: Absolutely.

DR. KOCHER: -- attempts to make things a little easier, but of course it's a complicated problem.

CHAIRMAN RICHARDSON: No, but if you would show this to somebody and they've got

this weird assumption about a very complicated function smoothing in an uncertainty distribution that's going to move from one to a bound around one with a distribution that's going to be around modal and it's to capture uncertainty in the exposure response function at the lower doses where we've extrapolated to where all the exposure is occurring for the workers, then maybe what you just want to do is just take the point-wise confidence bounds from the data sets that the risk estimates are coming from.

DR. KOCHER: So you would say that the ERR per sievert should have an uncertainty that's a function of dose?

CHAIRMAN RICHARDSON: Well, you would use the empirical confidence bounds for the risk estimates. You're already doing that. I mean, you've already got one. You're just - it's not point-wise right now.

I mean, I'm still, you know, I'm trying to work through what all is wrapped up

in this. And there's a lot of things wrapped up in it.

One of them is the shape of the exposure response function. One is the kind of confidence you have in the estimates in the low-dose range. And it's, I mean, I guess -

DR. HOFFMAN: Yes, I mean, if we were to think about a major revision to IREP, then there are several ways one could proceed. One is a revision update of DDREF and how it is applied to linear risk coefficients that have been published. Another is to forget the DDREF and apply confidence bounds to the epidemiological data as they are extrapolated down below limits of epidemiological detection.

DR. TRABALKA: There's some extremely large uncertainties on low-dose data.

CHAIRMAN RICHARDSON: Right. Well, I mean, that's - I'm just not - introducing a shape parameter as - which appears ad hoc, a

dose limit which is some transition value, a complicated kind of logistic function, I guess, sort of shaped thing to smooth - to transition into that to capture the fact that we're uncertain about the low-dose risk coefficients.

I mean, it seems to me like lots of parameters and decisions about parametric forms introduced - I mean, there's already - I mean, from my point of view the risk estimates are already highly imprecise. I'm not sure there's actually any value in any of it.

You could just say, I mean, if you wanted to do that, you would say these risk estimates are - these are our best empirical risk estimates. We have a linear model that we fit to solid cancer data. It has an estimated variance around it which captures uncertainty, and it leverages some form of precision through the parametric assumption that as exposure increases, cancer risk increases. And that's the best we can do.

I think, I mean, from my point of view, that's what's done in epidemiology right now.

DR. KOCHER: But yet all the published risk coefficients using a linear model are dose independent.

CHAIRMAN RICHARDSON: No, what's done - exactly. What's done right now is you say the best we can do is to make a parametric assumption that cancer risk varies as a linear function of dose and we estimate it.

And that's where we're leveraging our confidence. That's where we're leveraging the precision about the low-dose range is by the parametric assumption that there's a linear exposure response function.

And that's, you know, so that's the best estimate. That's one simple parametric assumption. And what's being - if my characterization that moving from the left-hand side to the right-hand side of this flow diagram is when we're going to - if we're

going to have modal values centered around one, it's just adding in greater uncertainty about the low-dose range where you've just stepped away from the kind of, you know, the foundational kind of parametric assumption that we had that, well, we can get some sort of best estimate by just saying the risk - the average risk changes apportioned to the dose like we do with almost all risk assessments.

DR. KOCHER: Well, it would be a way of representing greater uncertainty at the low doses where you really can't see anything.

DR. TRABALKA: It would make adjustments based on DDREF look like pikers. Because, remember, the A-bomb survivor data and the risk coefficients in IREP, these are driven by doses between 0.5 and 4 gray.

The question then becomes how does the risk change from the risk estimates made derived by the - apparently these higher doses, down at very low doses?

And the only theoretical way to do

that is to assume a linear quadratic model could be there in the data. It's just submerged in the uncertainty.

It really should be a linear quadratic exponential model that covers the whole dose range, which adds even more uncertainty in the three parameters to deal with. Everything blows up.

Right now the DDREF is probably the best we can do, and we simply don't have enough information to separate data on LDEFs and DREFs to do what you're suggesting, which would be excellent, you know, in your hypothetical approach here.

But it's a compromise approach and there's no getting away from it, but that's just the state of our knowledge.

MEMBER MUNN: The question is is it the best approach? That seems to me to be our responsibility as a Work Group. Is it the best we can do? Our only responsibility, as I see it, is to judge whether or not this is the

best science available.

DR. TRABALKA: And speaking for the SENES group, we would welcome any input on that topic and any specific comments you have on the report recognizing that people like professors are very, very busy and they don't have time to do all this, and others.

MEMBER ROESSLER: Can I make a comment - two comments, actually.

Jim Neton mentioned Equation 26 in the publication by NIOSH. And I just found it and I think everybody should look it up, because it very clearly -

DR. KOCHER: Also in the REF paper.

MEMBER ROESSLER: That is the REF paper, I think.

DR. KOCHER: No, that's the IREP paper.

MEMBER ROESSLER: Yes, it very clearly shows the relationship between ERR, REF and DDREF in dose, weighting factors. It's just right there.

Now we know what the real impact is going to be, even on high-LET, which is - I'm glad David brought it up.

The other thing I noticed when I was looking at that issue -

DR. KOCHER: The key is that Equation 26 applies to alpha particles as well as low-LET. So, you end up saying, I thought there was no DDREF for alpha particles, but this is a DDREF for photons.

MEMBER ROESSLER: The other thing in that same issue and I haven't looked it up, is a paper by Paul Ziemer. And I haven't reviewed it, but maybe we should look at that on the responsibilities of the Board.

And so, Wanda, you brought that up and we should maybe reread that.

DR. NETON: Which paper, I'm sorry?

MEMBER ROESSLER: The issue of the journal that you have there. There's a paper by Paul Ziemer talking about -

MEMBER ZIEMER: I don't remember it

myself.

DR. NETON: I remember it being in there. I haven't read it in a while -- oh, the responsibilities of the Advisory Board.

MEMBER ROESSLER: Yes.

DR. KOCHER: You make good points, David, but we're basically playing by the rules of the game as conventionally accepted today realizing that DDREF is an artificial construct that covers all kinds of sins. If you had the right -

MEMBER ZIEMER: Well, David may be saying, go and sin no more, I think is what he -

(Laughter.)

DR. KOCHER: I mean, if you knew the correct dose response down to zero dose, you wouldn't use it.

CHAIRMAN RICHARDSON: Well, one of my concerns is suppose we take the empirical data for solid cancers. We take the empirical data for the leukemia, we fit a model, we have

a parametric model and we stop there.

We take the empirical data for the solid cancers, we have a model which fits reasonably well, and we say, but under different exposure conditions, we think the data should look - should have curvature to it, and it doesn't.

Then you were sort of, you know, I'm at a loss as to why we don't look at protraction effects for the exposure response for leukemia or vice-versa.

Why are we - why would we divide the risk coefficient by DDREF that has an X percent probability of being as large as four saying that there's a real nonlinearity below something as large as 200 millisieverts - and are either of those consistent with a reasonable model for the observed data?

DR. KOCHER: Well, that was kind of the BEIR VII's conclusion that they just can't - you just can't find much curvature in that dose response.

So they came up with a small DDREF with low uncertainty bounds.

CHAIRMAN RICHARDSON: Yes.

DR. KOCHER: But that's a different data set than what Ethel Gilbert would have based her judgments on.

CHAIRMAN RICHARDSON: So I kind of fall back on Occam's razor here of saying we're positing factors to describe departures from a simple model and that I find hard to be consistent with the empirical data.

DR. KOCHER: They're not in the data at high doses, but you don't know, you know, the uncertainties are so big at the -

CHAIRMAN RICHARDSON: Below 200 millisieverts, it's possible in the LSS data for solid cancers to describe - it's consistent with a DDREF of five?

That's not my recollection of those data.

DR. TRABALKA: The problem is that the risk coefficients are based on doses from

zero to four gray.

CHAIRMAN RICHARDSON: No, but there's a whole series of papers on restricted analyses. You get like 80 percent of the LSS cohorts below 200 millisieverts, I think.

DR. TRABALKA: But a DDREF has to account for differences in risk at high doses above 0.5 gray to 4 gray, and doses below 0.5 gray.

CHAIRMAN RICHARDSON: But the simple model for solid cancers fits the line across the entire range of observed data.

DR. TRABALKA: Right.

CHAIRMAN RICHARDSON: A reduced model fits the slope over, let's say, a range of zero to 200 millisieverts. And we're saying there is X percent probability that the slope over that restricted range is five-fold lower than it is over the full range.

My question is is that at all compatible with the observed data for the lifespan study?

DR. TRABALKA: It is.

CHAIRMAN RICHARDSON: My recollection is that that -

DR. TRABALKA: It is for skin cancer.

CHAIRMAN RICHARDSON: Yes, but -

DR. TRABALKA: Look at the figure for skin cancer.

CHAIRMAN RICHARDSON: -- this is not a model primarily for skin cancer, is it?

I'm talking about, I mean, I would use if I was going to make a judgment, I would look at solid cancers as a group.

DR. HOFFMAN: I think your question is a good one. And it's certainly something as we move forward into this next phase of peer review and revising our report we need to keep in mind. Because one avenue of attack is to look at various values in our distribution and say are these values even plausible given the epidemiological data at low doses.

And if the answer is, is that

they're not plausible, well, then that speaks towards a revision of our proposed distribution.

DR. KOCHER: I think BEIR VII kind of faced the same dilemma. And they ended up, if I remember it correctly, they ended up inflating their uncertainty to account for animal studies. And you may be able to argue that their bounds of uncertainty don't fit the LSS data.

DR. TRABALKA: Just the opposite, David. They used animal data to reduce the uncertainty in the DDREF. The epidemiologists then inflated it back so that the uncertainty represented that and the A-bomb survivor data.

Because they said it was just - the exercise was just too uncertain.

DR. HOFFMAN: And to find all that out, you need to read the fine print in the report. It's not easy to find.

DR. TRABALKA: I'd like to make two final points, and then I'm going to shut up.

I like your idea of looking at parametric models. I think the whole exercise of looking at alternate models of the dose response is a very good one. It's something that really hasn't been done up till now and needs to be done.

It's being done in conjunction with the development of the German IREP, for example.

And the other is that even though we have a bias, let's say, to certain values of DDREF, if our data sets contain uncertainty such that we have a range, let's say, from 0.5 to 5 and we have information that suggests we can have values less than 1, and we have other information that suggests we can have values as high as 5, in fact we have some data that suggests, for example, mortality from lung cancer in tuberculosis fluoroscopy patients that would suggest a threshold even though we all have questions about the meaning of that data.

The UNSCEAR used a quadratic model to fit the data for bone cancer in the A-bomb survivors. That's a very different one. It produces a risk at low doses that's very high. It produces a DDREF that's very great.

And your point about, yes, if we lump all the solid cancers together and we get what looks like this interesting straight line, is that model representative of the data all over the entire four-sievert range.

If we fit a model that had to accept all of the data from zero to four sieverts, would it have the same linearity as the data from zero to one and a half sieverts or two sieverts that's currently being modeled?

No, because you'd have to have a cell-killing component that would affect the curvature at the low end and the low doses. It's going to change it.

The A-bomb survivor data had not been adjusted for effects of smoking. What

would happen if we took out lung cancers and related cancers?

The data for the A-bomb survivors for digestive cancers are clearly different in terms of the incidence of those cancers from Western populations and other populations.

What would happen if we took those out and then remodeled the data? Are we going to get such a perfect straight line?

These kinds of uncertainties are still inherent in the A-bomb survivor data. It's the best data set we have, but it's not perfect. We have no perfect data sets.

That's why I'm saying is we have to be very careful not to restrict uncertainty unnecessarily because of some preconceived assumptions that we have. I would rather -

CHAIRMAN RICHARDSON: I'm not talking about restraining uncertainty.

DR. TRABALKA: No, I know you're not.

CHAIRMAN RICHARDSON: There's

actually been quite a bit done on assessment of confounding by smoking.

DR. TRABALKA: That's not -

CHAIRMAN RICHARDSON: I'm saying if there's uncertainty in the risk coefficient and there's already been uncertainty factors added into the risk coefficients to deal with transporting risk coefficients from a Japanese population with different baseline rates to another one, there's uncertainty coefficients added in for dealing with potential confounders, but there's - if you want to add in more uncertainty, then just increase the uncertainty.

The kind of - if that's what this is about, then just make it much simpler. Just take the risk coefficient and increase the uncertainty at the low-dose range.

DR. HOFFMAN: And, in fact, that's exactly what's being done at this point.

CHAIRMAN RICHARDSON: Okay, maybe that's it.

DR. HOFFMAN: I mean, it's not that there's something magical in this DDREF. The fact that the central value is moving closer towards one, but then as the dose goes down, we increase the uncertainty, but the overall functional effect is exactly as you say.

CHAIRMAN RICHARDSON: Okay, that's great then. What I would suggest is we can say, you know, previously what was done was we divided the risk coefficient by a value that was not unity and we had an uncertainty distribution about it, which had lots of implications.

What we're suggesting is extrapolation down to low doses implies uncertainty. So we're going to increase the uncertainty on the risk estimates.

DR. HOFFMAN: Yes.

CHAIRMAN RICHARDSON: That's a very straightforward story. I found that 400 pages of arguments about kind of biological processes really was obscuring something.

What you're talking about is uncertainty due to statistical and precision in risk assessments as you extrapolate the low doses.

That's a one-paragraph -

MEMBER ZIEMER: But I don't think they're describing it that way. Maybe the -

DR. NETON: The distribution is closer to one, but it's not one in the central estimate.

CHAIRMAN RICHARDSON: It's not, exactly. So we've introduced something more complicated. And I'm asking, you know, I'm still not satisfied with the description of the etiology of the complication.

DR. TRABALKA: Well, if you have suggestions for alternate choices of data and approach, we certainly welcome them.

DR. KOCHER: Yes, I have some misgivings about saying that the dose response for all solid cancers combined defines DDREF because that -

CHAIRMAN RICHARDSON: Well, I do too.

DR. KOCHER: That implies that every - IREP is interested in individual cancers. And you kind of have to bear that in mind.

DR. TRABALKA: You know, and there's a page that has a set of figures from Preston's report, the dose responses for the individual cancers, and there's also another one that - another page that shows the dose response for skin cancer and those data are all over the map.

CHAIRMAN RICHARDSON: You're talking about the estimate of the magnitude and shape of the site-specific cancer risk; is that right?

DR. TRABALKA: Let's look at -

CHAIRMAN RICHARDSON: Yes, and again I would say as you get to site-specific cancer risk coefficients, they have larger uncertainties than the analyses in which you pool categories of either cause of death or

types of cancers.

DR. TRABALKA: That's right.

CHAIRMAN RICHARDSON: I mean, again, this is by definition.

DR. TRABALKA: Right.

CHAIRMAN RICHARDSON: Statistical imprecision and uncertainty.

DR. TRABALKA: The figures on Page 136, for example, from Preston and Company's report, if you compare the parametric - nonparametric fit, for example, with the linear extrapolation, you get to see some rather interesting variations that are, in part, statistical in nature and give you some idea of what the uncertainty might be.

Looking at the one, the figure for thyroid cancer on Page 136, Preston and Company made the observation that doses below about half a gray or roughly in that region, that there appeared to be a pattern of perhaps super linearity in the response.

So and you look at lung cancer, you

can see something similar to that. So there are all kinds of ways you can interpret the low-dose response in these data.

But I think looking at alternative models like you suggested is an interesting exercise that should be done.

DR. HOFFMAN: And, in fact, in other work that we're involved with, with Dale Preston, Charles Land and Peter Jacob and his colleagues in Germany, they are developing approaches whereby the uncertainty on site-specific cancer risks will include modeling uncertainty accounting for multiple models that plausibly fit the data.

This is something that up until now, no international group has undertaken to include the effect of model uncertainty above and beyond the selection of one model and including simply statistical uncertainty on the fit to the epidemiological data.

CHAIRMAN RICHARDSON: I certainly agree that as you move to risk coefficients

for site-specific diseases, there's greater uncertainty in the risk estimations and there is greater sensitivity to model selection.

I mean, that, you know, again you'll end up with a model best estimate and an estimate of the variance of the risk coefficient.

So I think that the suggestion that we provide a brief report maybe talking about the awareness of new data, SENES' efforts to evaluate that and report to NIOSH, and I mean, I agree this is a really important and not straightforward issue.

I would hope that the - as we move forward, I mean, maybe, I mean, NIOSH seems like they're going to have an important role in moving this report out to kind of a broader discussion in the scientific community about DDREF.

And as they do that, I mean, maybe we could have some comments about the utility of kind of clarifying and hopefully

streamlining what has the appearance of being in many cases, a very subjective kind of approach to handling this form of uncertainty.

I think that there's probably more that can be done. I mean, what do other people in the Work Group think? Would you like, I mean, as a first step, that we follow something along a brief report to the Board along the lines that Dr. Ziemer suggested?

MEMBER ZIEMER: Well, of course I like my own idea, but I would amend it a little bit. Some of the concerns that you raised, I think we can raise those as well that we hope that these issues are looked at.

It's always appeared to me that to some extent we get driven into fiddling with these models because they have gotten accepted like the BEIR VII. And you end up with, okay, this is the accepted model. So, now how do we adjust this so it fits what we're doing here?

If we go back to the logical simplest case, which is just a linear model,

which from a physics point of view is what you can strive for, the simplest model is what you'd like, and then everything else particularly at the low end is uncertainty, even if it makes sense, it's going to be harder to sell simply because of the way these things have developed over years.

And, in part, because of attacks on the linear model, which I suppose reflect some different worlds. One is the epid world, which is -- it certainly makes sense. And the other is the health physics world where we have, to some extent, run into problems with going as low as reasonably achievable and then saying, yes, but there's still risks there and arguments about the risk being greater at the low doses and all of those kinds of things we've gone through those gyrations over decades now. And we find ourselves in this kind of dilemma as to what does it look like, what's the model.

So to some extent we end up - and

I'm not arguing that we shouldn't do this, but you sort of end up fighting the scientific establishment for how you model dose.

But I think it's worth raising the issues and maybe SENES goes back and can think about some alternatives to - well, you can accomplish the same thing by this in this simple way. That may be worth looking at too. I don't know.

But I think David's raised some interesting points for us to think about.

MR. KATZ: Just from a process standpoint, I'm just also wondering, I think raising these questions might be very useful for the peer review context as well.

I mean, why not put those -

MEMBER ZIEMER: Yes, you can ask the reviewers to think in terms of as those questions even if you - even if they are not explicitly raised, maybe could you accomplish this just as easily in this other manner. I don't know.

DR. HOFFMAN: Well, I think we're going to take these seriously one way or another. And as we work through this report, I mean, if it turns out that for acute exposures there is a more transparent straightforward way of handling the increase in uncertainty in risk with decreasing dose, I would like to recommend that that be adopted.

But right now, this is the best we've been able to do.

MEMBER MUNN: From my perspective -

MEMBER FIELD: This is Bill. Can I just make a comment or two?

MEMBER MUNN: Please.

MEMBER FIELD: Yes, I've just been listening to this and I'll tell you my learning curve has been at a high rate here.

MEMBER MUNN: Is it bent?

MEMBER FIELD: I think I have previous knowledge about some of the aspects of the report. But, boy, the scope of the knowledge you need to understand the report in

its totality with all the possible interactions with the topical areas has been a bit challenging for me.

And this whole process I think would be a lot easier, obviously, if there was somebody else that had some sort of report that was considered a consensus.

I think what we're running into is that the report as presented is very pushing the envelope as far as what's known. And we don't really know what the consensus will be on this report from content experts or the public or others.

So I think at this point, I think content experts, to me it's very critical to really see where the points of agreement lie or where the points of disagreement lie that we can explore further.

And I think considering that, it's going to be very important to figure out which five people you ask to review it. Because as you know, you can pick five people that you

know a priori will probably consent on it or probably say, this is pretty good stuff.

So I think getting a diverse group of reviewers would be good. And I would favor five as opposed to three. And I think once that process is done, then I think it would be interesting then to come back together and see if they found some of the similar problems that Dave has brought up or some of the similar concerns, to see if they also are sharing those concerns.

MEMBER MUNN: Thank you, Bill. This is Wanda, and this - Bill's comments bring me back, I think, to my original question which may need to be deferred until after we've had our discussion that we mentioned earlier at our next meeting.

And that is, is the purpose of this group to help define the science, or is the purpose of this group to report out that we feel that the agency is or is not pursuing the proper effort to assure that the best science

is being used?

It's a fairly basic question, I think, and one with which I think the Work Group needs to come to grips very clearly because there's an enormous difference in whether or not we will immerse ourselves in the science of this process as it goes forward, or whether we will make a judgment call as to whether or not the agency is pursuing the best science. Two entirely different questions.

MR. KATZ: Can I say something to this?

I mean, I think -

MEMBER MUNN: Can I stop you?

MR. KATZ: You can if you want to, but I think the Board can do both in a sense. I mean, I think the Board is welcome particularly when the agency invites it, to provide counsel along the way, as well as at the end of the day provide advice, counsel on what it thinks about the results that the

agency thinks it's going to take.

So, I don't think there's really necessarily an either/or here. And the agency is clearly asking for advice along the way. And I think as deep as you are able to go on that question is being welcomed.

So it's really more a matter of your capacity to provide such advice, but I don't think you're constrained. That's my point of view.

MEMBER MUNN: Well, it's a point I think we need to come to some agreement on as a Work Group.

CHAIRMAN RICHARDSON: Again, we did have a discussion about scope and process. And I think what I'll do is recirculate the discussion of the scope and the points that were laid out there, and then we can talk about that again.

I would view the scope as something larger than saying is the process NIOSH is taking sufficient. I hope that we can talk

about the substance of the issues as well. That's, I mean, the way that we talk about the substance of other technical issues, which is to provide some form of evaluation and comment on them.

MEMBER MUNN: Well, it would be hard for us to take a position as to whether or not the process is appropriate without spending some time looking at the nitty-gritty. There's no question about that. We have to know what is going on and what the issues are if we're going to weigh in on whether or not it's appropriate.

CHAIRMAN RICHARDSON: Yes.

MEMBER ZIEMER: And I don't think we will, as a Work Group, come up with sort of the decision on whether a linear low-threshold model is the preferred one over - but we want to make sure the questions are asked and that the scope of what's being done is being fully considered in going - I mean, I'm going to rely on the experts because that, you know, we

work, you know, some of us even teach about there being a no-threshold model, but we're not, you know, the experts on the biology or even the statistics of it.

MEMBER ROESSLER: That's one whole lecture on the various models.

MEMBER ZIEMER: Oh, I can stretch it into two if necessary.

(Laughter.)

CHAIRMAN RICHARDSON: I think there's - I get the sense that there's agreement that there's going to be a lot of value in seeing what Bill was calling the content experts, seeing what they come back with. And I think that makes a lot of sense.

I think it would be worthwhile for us to maybe at the next meeting at least whether it's in written form or orally, at least, to update the Board on what we're doing.

Does that make sense?

MEMBER MUNN: Yes.

CHAIRMAN RICHARDSON: And then to kind of move forward with kind of keeping an eye on the process that NIOSH is going to take with their external review and hopefully have an opportunity to read over the comments that come back from the content experts. And expect that we'll take it upon ourselves to at that point, provide a follow-up discussion maybe in a little bit more formal sense based on their comments in the report.

MEMBER ROESSLER: David, with regard to the selection of the content experts, and I think we're wanting to do it fairly soon, do you see that the Work Group would ask to be involved in the decision on that at some point, some soon date?

CHAIRMAN RICHARDSON: I don't know. I think NIOSH usually has a fairly formal process laid out for that, don't they?

MEMBER ROESSLER: NIOSH just went out for a minute.

MR. KATZ: Jim Neton stepped out. I

mean, they have a process for selection, but, I mean, I think they are open to suggestions. I mean, I think they start with a pool and a number of factors as to what they end up with, including willingness to perform.

So, I would just say to all of you here, I mean, on the Work Group that certainly if you have people in mind that you think should be considered, NIOSH will be glad to hear that.

MEMBER ZIEMER: Yes, I wouldn't want us to review names -

MR. KATZ: I'm not saying -

MEMBER ZIEMER: -- as a Work Group, but individually -

MR. KATZ: Yes, that's what I mean. And it's NIOSH's decision, but certainly any advice, suggestions you have I think will be helpful to NIOSH in this next step.

MEMBER MUNN: We could always ask NIOSH about it after lunch.

MR. KATZ: NIOSH being Jim Neton who

stepped out, you mean, right?

MEMBER MUNN: Lunch being -

MR. KATZ: I don't think he'll tell you anything much different.

MEMBER MUNN: Lunch being the operative word.

MR. KATZ: I understand that lunch is on your mind.

MEMBER ZIEMER: David, do you plan to give sort of an interim report at our teleconference? At least report on this meeting. It's coming up in two weeks.

CHAIRMAN RICHARDSON: That sounds like a good idea.

MEMBER ROESSLER: What date is the teleconference?

MR. KATZ: April 26th at 11:00 a.m.

MEMBER MUNN: Correct.

MR. KATZ: The question was, when was the Board teleconference, for those folks on the phone who -

MEMBER ZIEMER: April 26th.

MR. KATZ: Right. So do we have a - Wanda is almost making the motion for lunch.

MEMBER MUNN: Yes, I am.

MR. KATZ: But let me just ask, because it's not clear to me, do we have an agenda for after lunch?

MEMBER MUNN: Guess I thought we did. Don't we have several other items?

CHAIRMAN RICHARDSON: My sense is that on this topic, we're at a stopping point with DDREF unless there are clear ways forward aside from providing kind of a report on our status and the status of NIOSH's activities and then holding this topic until we see back kind of the external review.

MR. KATZ: So then the only question that I think I'd raise in an email - hope I didn't - maybe I didn't - was whether the Work Group wants to at this point, and you may not, to discuss the rest of the agenda other than this of this Work Group, whether you want to - whether you need any discussion of what other

items are on that agenda and their path forward, etc.

MEMBER ZIEMER: Well, what were these other slides that were in our packet that you sent out? Were those from NIOSH path forward?

DR. NETON: You mean the - there was an agenda that was sent out.

MEMBER ZIEMER: No, there were two sets of slides you sent us.

DR. HOFFMAN: That other thing, get rid of it because that's supposed to be an internal discussion between us and NIOSH.

(Simultaneous speaking.)

MR. KATZ: So everyone in the Work Group, just to be clear, what I sent forward this morning to the Work Group was what I received from SENES.

MEMBER MUNN: Can someone please tell me what SENES stands for? Nobody knows?

DR. HOFFMAN: Yes, to give you the story -

DR. KOCHER: Just give them the answer. It's lunchtime, Owen. Define the acronym.

DR. HOFFMAN: Yes, but I have to get warmed up into it. It's Scientists -

DR. KOCHER: No, it's not.

DR. HOFFMAN: Specialist - okay, you name it. I can't remember.

DR. KOCHER: Well, it's the specialist part. And then N is nuclear and S is sciences. And then the two Es are either energy and environmental or vice-versa.

DR. APOSTOAEI: No, it stands for Specialists in Energy, Nuclear and Environmental Sciences.

MEMBER MUNN: All right.

DR. HOFFMAN: We get asked that question so seldom.

DR. KOCHER: The N stands for nuclear. And the two Es stand for environmental and energy.

(Simultaneous speaking.)

DR. APOSTOAEI: Specialists in Energy, Nuclear and Environmental Sciences.

DR. HOFFMAN: Specialists in Energy, Nuclear and Environmental Sciences.

MEMBER MUNN: Thank you.

DR. HOFFMAN: It goes way back to the Canadian firm in Toronto that wanted to name their firm Energy Nuclear and Environment, and someone else had ENE already coined. So, they put Ss on either side of it.

And then later people said, what does SENES stand for? What does SENES stand for? Specialists in Energy, Nuclear and Environmental Studies.

MR. KATZ: So let me just return to the question so that we can decide whether we're adjourning or we're breaking for lunch.

David and the Work Group, do you have any discussion, do you want any discussion at this point about other agenda items of the Work Group?

CHAIRMAN RICHARDSON: Well, I think

at the next Work Group meeting we would return to the topic of scope and process. And then one of the suggestions as another topic was something that's going to parallel this very closely was issues of RBE. And I believe SENES has a report as well on that, which if it's available, we may want to ask for that and kind of follow a similar line.

Is Jim back?

DR. NETON: Yes, I'm back. Sorry.

CHAIRMAN RICHARDSON: Does that - would that be possible, and is that -

DR. NETON: Yes, I'm trying to remember if there is actually a standalone report, or is it just the Health Physics publication? I think there's a NIOSH report.

DR. KOCHER: There's a huge paper on your website that was put up in 2002.

DR. NETON: You're right. You're right. So, yes, that's out there available now.

DR. KOCHER: And that represents

what's in the program, what's in the code. There's nothing like this DDREF report about what might come next.

DR. NETON: No, no. There's not been any additional work on our radiation effectiveness factors. The report that's out there is what we're using - intend to use, but it could be summarized on a presentation. Because as we pointed out or discussed, some of the high-LET distributions are affected by DDREF applications.

MEMBER ZIEMER: We did have a list that we prioritized at our previous meeting of the issues that we'd look at. I don't recall the top five, but -

CHAIRMAN RICHARDSON: I believe RBE was number two.

MEMBER ZIEMER: Okay.

CHAIRMAN RICHARDSON: There was also issue - the third one on that list if I'm recalling correctly, it was the adjustment of Probability of Causation based on other

factors.

There was interest in reviewing smoking and radiation joint effects.

MEMBER MUNN: Yes, there was that.

CHAIRMAN RICHARDSON: And both of those would be, you know, again, meaty topics to get into and report back on.

MEMBER ZIEMER: Well on RBE, is there anything active going on in the agency there? And I guess my question is are there particular issues that we would need to address on RBE versus smoking, which I know we adjust for smoking in part of the model for lung cancers, but is there additional smoking information that's available that should be looked at? Anything new there?

CHAIRMAN RICHARDSON: There were some questions about how joint effects were being handled. And this has come up several times, I think, at the full Board meetings. And some interest in asking that there be some evaluation of kind of time friendliness of

those -

DR. NETON: Yes, I think Dr. Lemen raised an issue some time ago.

MR. KATZ: Yes, I think that's right.

DR. NETON: That sort of was the genesis, I think, of the Science Work Group being put together, was a question that was raised on smoking and interaction, I believe.

CHAIRMAN RICHARDSON: Right.

MEMBER MUNN: Yes.

DR. NETON: Susan Reutman, our epidemiologist, is working on that issue now doing some pretty extensive annotated -- searches and stuff to build up an annotated bibliography of -

MEMBER ZIEMER: Well, would it be of value just to have sort of an update on what -

DR. NETON: We could describe what we currently do and how it evolved and what's maybe out there.

MEMBER ZIEMER: And what's out

there, what the issues are. And we obviously aren't in a place where we would do anything to -

DR. NETON: Correct. Because, you know, we've always maintained as the science evolved, we may revisit that issue.

CHAIRMAN RICHARDSON: Yes, there was, you know, RERF had a report either in 2011 or very early 2012 on fitting some new joint models for smoking and radiation with lung cancer, which went a good ways beyond what had been done previously with those data. So that would be useful to kind of also consider.

MEMBER MUNN: But also based on the notes from your last meeting before you go away from the idea of the RBE issues, even though that does not seem to be a burning issue or one that's of as much interest as the smoking and PoC questions, since SENES has done a recent update of where we are with that, it would seem only logical that we would

want to at least hear about that.

And as you suggested last time, David, report back to the Board on the status of the assumptions that are made in RBEs, our assertion that they are or are not good science.

DR. NETON: Well, I'm a little confused, Wanda. There is no update by SENES on the radiation effectiveness factor.

MEMBER MUNN: Oh.

DR. NETON: It stands as it was, and we currently have no plans to revisit that.

MEMBER MUNN: Okay.

DR. TRABALKA: Wanda may have been referring to what I said that David's involved in an NCRP committee that's looking at those.

MEMBER MUNN: No, I was just reading from that from the transcript from last time. Led me to believe that a study that SENES has recently done is an update of all the information on the RBEs.

That's all right. Forget it.

CHAIRMAN RICHARDSON: And switching the order so that we deal with the PoC and then maybe come back to the RBE might also be useful because the NCRP is looking at this issue. They may be further along. Maybe they won't be.

MR. KATZ: So just to remind you all as well because these - seems like these are all IREP-related matters, but there are some -- these would have been termed differently, cross-cutting or whatever, science issues related to dose reconstruction that also have been suggested might be considered by this Work Group. They were in the lineup, I think, as I understand it.

DR. NETON: I thought the decision was made early on not to include those because they're handled under a different format like the Procedures Work Group handles those cross-cutting issues.

MEMBER ZIEMER: You mean like the resuspension factor?

DR. NETON: Resuspension factors and that sort of thing, yes.

MR. KATZ: There have been a variety. And I've shared - I've sent, I think, to the whole Work Group, as well as to David, emails including some transcript material that was suggested by the Procedures. But the Procedures Subcommittee had sort of expressed -

DR. NETON: But I think if you go back and read, I think that was all sent out. And I think at some point when the Work Group developed their charter or mission statement, I thought that they agreed to focus primarily on risk model issues. I could be wrong.

MR. KATZ: No, that was never explicitly discussed, I don't think.

DR. NETON: Really?

MR. KATZ: If it was, I missed that.

DR. NETON: Well, David's the chair. He can -

MR. KATZ: David, what's -

CHAIRMAN RICHARDSON: That was early on kind of in the discussion of scope, science-based issues impacting on risk models used by the program and that the group would focus on risk model issues.

So are there - Ted, you're pushing for scope creep?

MR. KATZ: I'm not pushing at all. So let me make that clear. But there were a number of items that were more dose reconstruction, but sort of fundamental - or cross-cutting dose reconstruction matters, more science than sort of particulars related to sites or what have you, things that have arisen that a number of sites and caused concern and never been really properly put to bed.

And there certainly were at least suggestions on the Procedures Subcommittee that these might be matters best taken up by the Science Issues Work Group versus the Procedures Work Group.

So that's the discussion that arose. And some of these items were, I think, in the list that sort of was the -

DR. NETON: Well, there were two I think.

MR. KATZ: Anyway, of this Work Group produced by Jim Neton. So those weren't - those items weren't prioritized when the Work Group first met, the Science Issues Work Group first met, but they were raised in an initial paper that I gave to the Issues Work Group.

And then since then, I have, like I said, I think shared some transcripts and other materials with you, David, when the question arose in the Procedures Subcommittee.

So it's clear that no one is ready to take that up right now, that issue. But I think maybe at the next meeting you might want to just consider those issues and whether they deserve to be addressed by this group or rest with other groups.

Procedures is the only sort of generic group there is to otherwise take them up, but it's constituted very differently than this group. I mean, you have a lot of scientists on this group that are good for some of these issues, I think.

MEMBER MUNN: We perhaps can shine a little light on that by next time.

CHAIRMAN RICHARDSON: That sounds good.

MR. KATZ: Okay.

CHAIRMAN RICHARDSON: Well if - I know Wanda is hungry.

MEMBER MUNN: You bet your bottom dollar.

CHAIRMAN RICHARDSON: So I would suggest adjourning at this point if that's acceptable.

MEMBER MUNN: If we have nothing more to discuss, then -

MEMBER ZIEMER: I move we adjourn.

MEMBER MUNN: Second.

MEMBER LEMEN: I'll second it.

MR. KATZ: It's good to hear your voice, Dick.

MEMBER LEMEN: Well, I'm still here. I've learned a lot today.

DR. NETON: Just to clarify, I'm looking at the Science Issues Work Group mission statement on our website.

(Simultaneous speaking.)

DR. NETON: It says is responsible for reviewing the status and number of risk model issues that have been identified as important for the EEOICPA program. These include incorporation of epidemiologic studies, DDREF, cancer, age-at-exposure. the Work Group will review the status of the current work and report back to the Board.

MR. KATZ: I'm familiar with that, but that was generated after the first meeting where we just came up with this initial priority list and some of the things just really weren't addressed in that discussion.

DR. NETON: All right. I thought it was the other way around.

MR. KATZ: No, it wasn't. We actually it took a while to clarify that charge. We started off thinking we knew the charge. And then we readdressed it and came back to the Board.

DR. NETON: Okay.

MR. KATZ: Anyway, it's -

DR. NETON: Okay.

MR. KATZ: We can resolve it at the next meeting.

MEMBER ZIEMER: Well, I think the Work Group can look at those overarching issues and see if there are science issues in there that we need to look at.

MR. KATZ: Right. I mean, the scope can be changed. So the important issue is where is the best place to address those issues, not whatever scopes are specified currently for these different Work Groups.

Okay. So I think we're -- thank

you, everyone. David, thank you.

CHAIRMAN RICHARDSON: Sure. And I look forward to seeing you soon.

MR. KATZ: Yes. Take care.

(Whereupon, the meeting was adjourned at 12:52 p.m.)