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U.S. ENVIRONMENTAL PROTECTION AGENCY
FIFRA SCIENTIFIC ADVISORY PANEL

OPEN MEETING TO CONSIDER AND REVIEW
SCIENTIFIC ISSUES ASSOCIATED WITH THE
AGENCY'S ENDOCRINE DISRUPTOR
SCREENING PROGRAM (EDSP)
PROPOSED TIER-1 SCREENING BATTERY

EPA CONFERENCE CENTER
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U.S. ENVIRONMENTAL PROTECTION AGENCY**FIFRA SCIENTIFIC ADVISORY PANEL****OPEN MEETING TO CONSIDER AND REVIEW****SCIENTIFIC ISSUES ASSOCIATED WITH THE****AGENCY'S ENDOCRINE DISRUPTOR****SCREENING PROGRAM (EDSP)****PROPOSED TIER-1 SCREENING BATTERY****MARCH 26, 2008**

MR. DOWNING: Good morning, everyone.

I'd like to welcome everyone to the second day of our FIFRA SAP, scientific advisory panel meeting discussing the Endocrine Disruptor Screening Program Proposed Tier 1 Screening Battery.

I want to just remind everyone that all the documents that have been presented yesterday as well as what will be presented today will be available in the docket for this meeting which the document information identification information is there at the top of your agenda, and that information should be on the docket within just a day or two, actually, certainly by tomorrow, the end of tomorrow, so you can access all of that information in the EPA docket for this meeting.

As well as I would remind everyone that the final report for this meeting which actually will

1 serve as the meeting minutes under FACA will be
2 available within 90 days after the conclusion of the
3 meeting. That will also be posted on the FIFRA SAP web
4 site as well as posted in the LPP docket.

5 And I think, with that, I'd like to turn
6 it over to our chair, Dr. Heeringa, and begin our
7 meeting today.

8 **DR. HEERINGA:** Good morning, everyone,
9 and welcome back to the second day of our meeting of
10 the FIFRA SAP on the topic of the Endocrine Disruptor
11 Screening Program, the Proposed Tier 1 Screening
12 Battery. As Jim just indicated and you probably heard
13 yesterday, I'm Steve Heeringa of the University of
14 Michigan. I'm currently the chair of the FIFRA science
15 advisory panel, and I'm here primarily to assist in
16 running this meeting over the next...balance of today
17 and possibly tomorrow.

18 I'd like to have, again, other members
19 of the panel introduce themselves and their affiliation
20 and a little bit of description of their specialty.
21 Ken?

22 **DR. PORTIER:** Good morning. I'm Ken
23 Portier, director of statistics at the American Cancer
24 Society national office in Atlanta. I'm an applied
25 statistician and a member of the permanent panel.

1 **DR. CHAMBERS:** I'm Jan Chambers. I'm
2 with the College of Veterinary Medicine at Mississippi
3 State University. My area of expertise is in pesticide
4 toxicology with emphasis on metabolism and
5 neurotoxicity, and I'm a member of the permanent panel.

6 **DR. ISOM:** Good morning. I'm Gary Isom,
7 professor of toxicology at Purdue University. My area
8 of interest is chemical induced neural degeneration,
9 and I'm a permanent member of the panel.

10 **DR. BUCHER:** I'm John Bucher. I'm an
11 associate director of the National Toxicology Program
12 at NIEHS in Research Triangle Park. I'm a toxicologist
13 by training with interest in chemical carcinogenesis
14 applications in new models in toxicology.

15 **DR. DELCLOS:** Barry Delclos from the
16 FDA's National Center for Toxicological Research. My
17 research interests are endocrine disruption and in
18 carcinogenesis.

19 **DR. ELDRIDGE:** Charles Eldridge, Wake
20 Forest University, Department of Physiology and
21 Pharmacology. I've been working with steroid hormones
22 receptors, neuroendocrine, and, basically, female
23 reproduction.

24 **DR. DENVER:** I'm Bob Denver from the
25 University of Michigan. I'm a professor of molecular,

cellular, and developmental biology and also ecology and evolutionary biology, and my interests are in developmental neuroendocrinology, steroid thyrocrine action on the brain, and amphibian metamorphosis.

DR. VANDENBERGH: I'm John Vandenberg, professor emeritus of zoology at NC State University, and my area of interest is in hormones and behavior and behavioral endocrinology basically.

DR. LASLEY: I'm Bill Lasley, University of California at Davis. I'm a reproductive toxicologist interested in toxicology and reproduction at the population-based level.

DR. COOKE: I'm Gerard Cooke, Health Canada Food Directorate. I'm a reproductive toxicologist with particular emphasis on male reproduction.

DR. ZOELLER: I'm Tom Zoeller, professor of biology at University of Massachusetts, Amherst, and I work on thyroid hormone action in early brain development and thyroid disruption.

DR. BROWN: Terry Brown, Johns Hopkins University Department of Biochemistry and Molecular Biology, and my areas of interest are in male reproduction, particularly androgens and androgen receptors.

1 **DR. BELCHER:** Scott Belcher, University
2 of Cincinnati Department of Pharmacology. My major
3 interests are mechanisms mediated through primarily
4 estrogen receptor beta and signaling and the role of
5 endocrine disruptors in brain development.

6 **DR. KULLMAN:** I'm Seth Kullman at North
7 Carolina State University Department of Environmental
8 and Molecular Toxicology, and I'm a molecular
9 toxicologist interested in endocrine receptors and
10 comparative genomics.

11 **DR. FURLOW:** David Furlow, Department of
12 Neurobiology, Physiology and Behavior, University of
13 California at Davis, and I'm a developmental
14 endocrinologist interest in thyroid hormones and
15 control of amphibian metamorphosis but steroid hormone
16 control of muscle mass as well in...in mammals.

17 **MR. DOWNING:** Jim Downing, Designated
18 Federal Official for the FIFRA SAP.

19 **DR. HEERINGA:** Thank you very much,
20 panel members. Just a few administrative notes at this
21 point. I want to mention that, as chair, I will be
22 here through the morning. This afternoon, I have a
23 teaching commitment, a regular teaching commitment at
24 the University of Maryland. Ken Portier will be
25 assuming chair duties at that point in time.

1 So, at this point in the process, we
2 have concluded the presentations from the EPA
3 scientists with regard to the endocrine disruptor
4 screening battery, the tier 1 battery, and we have
5 heard public comment from a number of parties. We have
6 written materials.

7 The period of public comment is closed
8 at this point. However, there is...if you have
9 additional materials you would like to provide to the
10 panel, you may do so in writing before the close of the
11 meetings, and I would assume that would carry over into
12 tomorrow as well, to be fair, so that if, again,
13 additional public comments or clarifications, things
14 you would like to bring before the panel, you may do so
15 in writing after this point.

16 At this point, I would like to turn to
17 Gary Timm for some additional comments before we turn
18 to the charge questions.

19 **DR. TIMM:** Thank you, Dr. Heeringa. In
20 listening to the...not only the questions posed by the
21 panel but...but some of the public comments, it seemed
22 to us that it might be useful to clarify a few points
23 before we actually got into the charge questions, and
24 these...these are not point/counterpoint to anything we
25 heard yesterday but just general clarifications.

1 There are about four topic areas, I
2 guess. We would like to take probably 15 or 20 minutes
3 to...to go over these, first of all, updating the
4 battery, quality assurance for...for assays, the status
5 of the OECD fish test guideline, and some illustration
6 of weight of the evidence. That seemed to...to come up
7 a number of different times yesterday, and I think we
8 can give some additional examples to show you how
9 the...the assays in the battery work and how...how some
10 of the...some other cases would be...would be assessed.

11 So, let me start off with a couple of
12 things, and I'll turn to my colleagues for...for help
13 on the others.

14 With respect to updating the battery,
15 there's a lot of research going on in EPA, outside of
16 EPA, but within our own laboratory down at RTP, we have
17 developed and a number of laboratories have already
18 used, probably tested hundreds of chemicals already,
19 some transcriptional activation assays for estrogen
20 binding the...using the MDA KB2 cell line and for
21 androgens using the 247DK blood cell line, and there is
22 going to be probably an effort...we're going to, next
23 week, tell the OECD that we believe that a project
24 should...should be initiated to develop a generic test
25 guideline for transcriptional activation assays for

1 using the estrogen receptor.

2 This will, I think, be very useful
3 rather than going assay by assay. Right now, the
4 Japanese have validated an assay, and there is a test
5 guideline being developed for that particular assay,
6 but I think that this would open up the field by having
7 a generic test guideline.

8 We're also working on an alternative to
9 the existing AR binding assay which, of course, uses
10 the rat prostate cytosol. It would be using the...the
11 chimp AR binding, and that will become an OECD project
12 as well, and we mentioned the status of the H295R assay
13 which is a replacement for the testes assay that
14 the...the EDSTAC recommended, and that assay has
15 completed validation. The report will be submitted
16 next...next month for peer review.

17 So, that's kind of an update on...on the
18 battery. We...we clearly intend to be flexible and to
19 introduce new technology as...as it is validated.

20 And with respect to quality assurance, I
21 know one of the presentations yesterday talked about
22 that. I think it's well to recognize that all of the
23 assays have quality assurance built into them. There
24 are performance standards in them. There are controls,
25 and laboratories must demonstrate, in fact, that they

1 can run the assays correctly before we will accept
2 the...the data.

3 So, I think that that...that certainly
4 has been addressed by...by the existing work.

5 Let me turn now to the...to Les for the
6 update on the...on the fish, a clarification on the
7 fish.

8 **DR. TOUART:** Thanks, Gary. I'm Les
9 Touart, and what I want to do is just...there might
10 have been some confusions with regard to the status of
11 the fish test guideline, at least from an international
12 standpoint, within the Organization of Economic
13 Cooperation and Development. In this light, it may be
14 difficult for folks in the back of the room, you know,
15 to see it, and they may want to get the full paragraph
16 from the summary record of the meeting of the OECD
17 validation management group for ecotoxicity testing,
18 and, basically, first in this, these are
19 recommendations to the EDTA task force. EDTA is the
20 Endocrine Disruptor Testing and Assessment Task Force,
21 and then the working group of the National Coordinators
22 of the Test Guidelines which oversee the EDTA and...and
23 the B and G activities.

24 If you come down to the...to the last
25 bullet, it basically saying subject to the provision of

1 data generated according to the OECD foundation
2 principles, you know, that is the guidance document 34,
3 to integrate fecundity and histopathology into a
4 revised OECD test guideline for fish screening for
5 endocrine active substances.

6 The context here is the...the existing
7 test guideline needs to accommodate new endpoints and
8 those endpoints, in particular, and once these have
9 been demonstrated to be valid, these would be
10 incorporated into the OECD version. The U.S. has
11 completed a...a peer review of the...of the assay and
12 these endpoints. We provided responses to those, and I
13 think the panel has copies of the peer review report as
14 well as the comments to that.

15 These have also been provided to the
16 OECD and will be an item on the agency for the EDTA and
17 the National Coordinators which is scheduled for next
18 week with the proposal that these endpoints now become
19 part of the...the fish screen.

20 **DR. TIMM:** Thanks, Les. Earl, you
21 and...and was Gary going to join you at the table?

22 **DR. GRAY:** I certainly hope so.

23 **DR. TIMM:** Okay, excellent. Why don't
24 you introduce yourselves, Earl Gray and Gary Ankley.,
25 at this time.

1 **DR. GRAY:** I'm Earl Gray, and that's
2 Gary Ankley. What we'd like to do is talk about the
3 ability of the tier 1 screening battery to detect lower
4 potency environmentally relevant endocrine disruptor
5 chemicals. We've talked about a few, and many of those
6 focused on potent pharmaceuticals that have a single
7 mode of action that produce rather diagnostic profiles.

8 What will be the importance of this, I
9 think, is to highlight how the mammalian and non-
10 mammalian assays compliment one another in the
11 battery...they're not necessarily redundant...and how,
12 on occasion, an endpoint that you might think that's
13 not very useful or unnecessary provides useful
14 information, because the purpose of the battery is not
15 only to detect chemicals with EAT; it's to help design
16 the tier 2 testing. So, the information that you gain
17 from this can help design.

18 So, these, as...and we've stolen some
19 slides from Les. These are...this is the tier 1
20 screening battery and the assays that are recommended
21 by EDSP, and this is Les' summary slide of how
22 your...how your potent chemicals would be detected in
23 the screening battery.

24 What...what happens, though, when you go
25 to chemicals with multiple modes of action or when you

1 go to weaker chemicals, in particular, a weaker
2 estrogen, for example? Some of these bright green
3 boxes kind of get a little light or disappear, and you
4 don't have these multiple hits, and it's at this point
5 where a single endpoint can be very useful in the
6 assays. The fish and frog and rodent assays,
7 compliment one another.

8 And...and as...as we all are aware, all
9 estrogens don't act through all of the same...on all of
10 the same tissues, and it's the same with androgens,
11 anti-androgens, and et cetera. You know, the chemicals
12 that interfere with steroid hormone synthesis do so
13 often by inhibiting an array of p450 enzymes that are
14 throughout the body.

15 So, what I wanted to just...we made up
16 these lists on how environmentally relevant chemicals
17 would behave, and...and it sort of gives you a...an
18 idea of the emergence of the weight of evidence
19 approach. If you look down a column, you begin to see
20 with different chemicals, you know, what...what's
21 positives.

22 So, what I have on here, we started off
23 with your potent estrogen. These are, for the most
24 case, environmentally relevant chemicals.

25 And so, ethylestradiol is a

1 pharmaceutical in the environment. It's a classic
2 estrogen. It produces all of the typical responses in
3 the assay, including the hormonal changes in the
4 hypothalamic-pituitary-gonadal axis.

5 But if you look at the...the weakly
6 estrogenic and weakly anti-androgenic pesticide,
7 methoxychlor, the profile is...is a little...is a
8 little different. And...and here, this chemical is
9 really more effective orally which is why I highlighted
10 the...the pubertal female assay in red, because it
11 really provides a really rapid response to this
12 particular estrogen and not necessarily the bisphenol A
13 on the next column which is also an environmental
14 estrogen.

15 And the effects of methoxychlor are
16 complimented nicely by the talogen in the conduction
17 and other changes in fish assays. The...the big no on
18 the pubertal male is there have been issues raised
19 about there haven't been anything run through these
20 pubertal assays that were negative and, in fact,
21 methoxychlor is...is pretty much a negative in the male
22 and in...in this assay. And bisphenol A to the right
23 is negative in the pubertal male and the pubertal
24 female assays with oral exposure.

25 And it's here that the in vitro assays

1 and the uterotrophic assay for bisphenol A and the fish
2 screening show that it's under certain...at least
3 certain routes of exposure, it's clearly estrogenic.
4 And so, you can see that it's profile is quite
5 different than methoxychlor, and the value of different
6 endpoints and different assays is not the same.

7 Tamoxifen was...is an interesting...it's
8 also a pharmaceutical found in the environment. It
9 produced an interesting and expected profile based on
10 we knew that it's a selective estrogen receptor
11 modulator. It accelerated vaginal opening as much as
12 estradiol, but it reduced uterine weight by 60 percent.
13 So, if you say uterine weight's too variable, the
14 animals are cycling, yes, uterine weight is variable in
15 the cycling animal, but these females are not cycling,
16 and there is very little variability in that data.
17 This is a highly significant effect.

18 And it inhibits..tamoxifen inhibited the
19 telogen and...is that correct, Gary? So, I think it
20 provided some really interes...an interesting profile
21 for tamoxifen with dramatic, paradoxical responses in
22 vaginal opening and uterine weight. And...and there
23 are a number of other chemicals where things like
24 uterine weight, ovarian histopathology were useful.

25 This is sort of our androgen page, and

1 we started off with your potent classic pharmaceutical
2 in the environment, trenbolone, and it produces a
3 response almost testosterone or methyltestosterone, the
4 difference being that you're not going to get any
5 estrogenic responses in the...with this with oral
6 administration or subcutaneous administration, because
7 it can't be aromatized, so it's a...a little different,
8 but it...but it's still more of a classic profile.

9 And then you look at the androgen
10 receptor antagonists. The one to the far right,
11 vinclozolin, is...is probably more like flutamide, and
12 it's one of the...maybe one of the more potent
13 pesticides with anti-androgenic activity, and...and in
14 that particular chemical, AR binding is...is positive
15 in some assays and...and not in others, because it
16 requires some degradation or metabolic activation.

17 It's really the Hershberger and pubertal
18 assays that nail that one, and there are positive
19 effects of vinclozolin and other androgen receptor
20 antagonists in the fish assay, but they're not nearly
21 as diagnostic as what you get with the Hershberger and
22 the pu...pubertal assays on multiple endpoints at
23 relatively low doses.

24 And I would add that if you looked at
25 the endocrine profile of the vinclozolin in males, it

1 looks like you would expect from flutamide in that
2 testosterone and LH both go up.

3 Which is not the case for the linuron
4 and DDE, and many of the other xenoestrogens don't
5 affect hypothalamic-pituitary-gonadal hormones the way
6 you'd expect. And the profile of linuron and DDE is
7 much less dramatic than vinclozolin, and...and they
8 have mixed modes of action. Linuron is also a little
9 bit hypothyroid, and DDE really turns on liver enzymes
10 and other things and affects the adrenal.

11 So, you know, and...and if you were to
12 do a toxicology study, you're never sure how important
13 the AR antagonism is, but it will get us a nice
14 vocation.

15 And we call this story genesis and et
16 cetera, and...and it's really...you know, ketoconazole
17 is a nice chemical. It's a potent drug, and...and it
18 shows the characteristic profile that you'd expect
19 would stimulate hormones and inhibits aromatase. In
20 the fish, it was just...it was, what, just testis
21 histopathology?

22 **DR. ANKLEY:** Yeah, what we saw was a
23 Leydig cell proliferation. Essentially, it was a
24 compensatory response to the reduction in testosterone
25 synthesis. It's a rather unique example in the fish of

an endpoint that you would pick up only with this knowledge. I'll come back to that in a minute, though.

DR. GRAY: In the...in the pubertal female what was interesting was that was the chemical where vaginal opening some feel is the keystone endpoint in that assay, and it's really not. Vaginal opening was not affected significantly, but we had every...all of the females...all the treated females had severe lesions in...of ovarian and histopathology. They had atretic corporal lutean follicles, and so...and they also had a 50 percent reduction in uterine weight. So, it definitely had a positive effect but not on vaginal opening.

If you look at the...the other steroid synthesis affecting chemicals, prochloraz and fenarimol inhibit fungal and os sterol synthesis, but their profiles in the mammalian assays and in the fish assays are...are quite different, and, you know, they were...they really had multiple modes of action that are displayed in vivo. Prochloraz is an androgen receptor antagonist, and we don't...we don't...we don't know. It hasn't been run in the pubertal female. It's positive in the pubertal male, primarily for testosterone synthesis. It was very positive in the fish assay, very diagnostic there in the hormone and

1 reproductive endpoints in the fathead minnow assay, and
2 it's very positive in nutria.

3 Fenarimol you might think was
4 the...would be similar. It's the weaker aromatase
5 inhibitor, but it's been reported to be an androgen
6 receptor antagonist, to be an estrogen. You know, it
7 does all things to all people except that it was
8 negative in the pubertal female assay up to a point
9 where there is a significant reduction in body weight
10 beyond the M.D., and it was very positive in the fish
11 screen. So here, the fathead minnow assays results
12 were very important.

13 And then, here...here's chemicals we
14 didn't think much about when we were at EDSTAC, because
15 when we designed the initial battery, we came up with a
16 battery that would have missed the phthalate, and...and
17 EDSP has corrected that omission, but the phthalate
18 inhibit steroid hormone synthesis through unknown
19 mechanisms, and the only assay in which it would be
20 detected would be the pubertal male assay.

21 And so, if you think about on a...take
22 the pubertal male assay out, you're going to miss any
23 of the phthalate that have that activity.

24 And then, this is...I have one chemical
25 that our branch has worked on...on...that affects the

1 hypothalamic-pituitary-gonadal axis, and you can...can
2 see that it's...it's going to be negative in vitro in
3 the uterotrophic and Hershberger, and it's the pubertal
4 male and female where that was detected, and it hasn't
5 been run in the fish, but our expectation would be that
6 it's positive. So, that's a hypothesis, and
7 they...they're not always right.

8 I put thyroid hormone down there just to
9 have an agonist, and as hard as we tried, the frog fell
10 off the bottom. Sorry, Joe. We worked on this to get
11 this on. I'm going to...so, the read for T4, the
12 reason we put T4 on there was to show how it's
13 tyro...this is...produces diagnostic responses to
14 thyroid hormone agonists. If there are any in the
15 environment, this is what's going to detect it, and
16 that was the purpose when EDSTAC put the frog in. We
17 care about frogs, but we really wanted something in
18 there to compliment the mammalian assays for thyroid
19 hormone agonist activity.

20 And our expectation would be that it
21 would be positive in the pubertal assays. I'm sure
22 somebody's run that, but we haven't.

23 The...we should have had one less beer,
24 Gary.

25 What I have on the...there is a

1 polybrominated diphenyl ether. It's...it's an anti-
2 thyroid chemical, and it's an androgen receptor
3 antagonist, and it affects T4 in the pubertal male and
4 delays preputial separation, and it's just a...I like
5 it. You know, the pubertal male assay can detect
6 weakly anti-thyroid chemicals.

7 And then, this is the chemical,
8 diiodinase inhibitor. It's, again, the frog
9 metamorphosis assay is going to give you the diagnostic
10 response about the mechanism and...and detect this
11 effect.

12 And I thought I'd...I'd end with this
13 part on our toxic negative. This was hypothesized from
14 the best available information to be a toxic negative,
15 and it was run for that purpose, and it...it was
16 pointed out and it's quite clear that it wasn't
17 negative.

18 And, you know, that's what happens. It
19 was a hypothesis, and we tested the hypothesis, and
20 that's what happens with hypotheses.

21 And I think it really points to the
22 value of the battery. Here's a chemical that, with the
23 best available information, we thought was going to be
24 negative, and it was clearly positive. And so, in 20
25 to 30 days' worth of evaluation, we learned something

1 important about an unknown chemical.

2 And whether you want to define that as
3 an endocrine disruptor or not is sort of a battle. It
4 clearly affects hormone synthesis indirectly by
5 affecting the Sertoli cells and testis, and it's, I
6 think, important to identify chemicals like that for
7 further testing, whether you define it as an endocrine
8 disruptor or not.

9 And so, I think that the point of that
10 is it's...this is not a deficiency in the pubertal
11 assays that it detects effects other than EAT, if you
12 consider this other than EAT. I think it's...my
13 opinion is it's a benefit. The assays detect...the
14 battery detects EAT, and it also...it's going to pick
15 up these gonadal toxicants. And it's not very
16 difficult to interpret what's happening in that.

17 The last thing I'd like to address, Sue
18 Marty raised some points about the pubertal assays
19 yesterday, and...and I agree with about 99 percent of
20 what Sue said, and what I wanted to do was...was to
21 talk about the pubertal assays and...and highlight that
22 what she said was that there...there are changes in
23 ordinal weights, there's body weight is reduced, and
24 so, there's a difficulty in interpretation in the
25 specificity of the effects, and she said that

1 alternative statistical methods were needed to adjust
2 for this.

3 And my point is that we have the data to
4 develop those alternative statistical methods that will
5 allow us to discriminate the effects of...direct
6 effects of growth on the pubertal assays to do
7 endocrine disrupting chemicals. And so, I was going to
8 show some data from the food restriction studies.

9 These are data from Susan Laws' study on
10 food restriction and what I have top...or this is
11 Tammy's delay...right, Tammy?...delay in preputial
12 separation in the male, and the food restriction study
13 is the line along the axis. You can see that as body
14 weight is reduced, we sort of have a dose response
15 reduction in body weight out to the 20 percent and no
16 effect on preputial separation, and all the little dots
17 on that graph are...are dots that I plotted from
18 different studies run in contract laboratories.

19 So, you can see you could easily put
20 confidence limits around each of those points and know
21 if it deviates significantly from that line, although
22 here, there's no relationship, but we have data for all
23 the other endpoints in the male and female.

24 And so, here's the data from the male on
25 the effects of food restriction on the seminal vesicle

1 weights, and there is a decline there as you go out,
2 and it's more or less linear. But you can see even on
3 those points where you have, you know, an 8 percent
4 reduction in seminal vesicle weight that you can easily
5 discriminate those...those chemicals from the...the
6 line. So, we have...we have the data, the...the
7 relationship between these organ weights and body
8 weight, that can be used to adjust the...and interpret
9 the results of the assay, the pubertal male and female
10 assays, even though there are body weight changes.

11 And then, this is the...just the...all
12 of the reproductive organ weights in the male assay and
13 how they changed with the food restriction. So, some
14 are spared more than others, and each would have its
15 own statistical methodology for adjusting, and I'm
16 sure...there are members on the committee that know how
17 to do this better than I do.

18 This is in the female. You can see
19 there is a delay in preputial separ...in vaginal
20 opening...excuse me...with food restriction out to 80
21 percent. It's...it's not that...it's about a day with
22 a 10 percent reduction in growth.

23 What's remarkable, if you look way out
24 to the...the right there, that little yellow-green dot
25 is a PTU animal where they...they barely grew in the

1 assay from inhibition of thyroid function, and even
2 there, vaginal opening is only delayed a day, so
3 there's not a lot of confounding on this endpoint.

4 Other endpoints in the female...I just
5 show a few are...there is more of a linear relationship
6 decline in organ weight with...with body weight, but
7 the...as I said, these data can be used to adjust and
8 compare your treatment to. So, if you have a, you
9 know, a 10 percent reduction in body weight, you can
10 compare the response of your chemical to these data and
11 see if it really appears to be specific or not.

12 And then, this is just a summary of the
13 effects of those studies, growth retardation. Vaginal
14 opening and preputial separation are relatively spared
15 in the male. Epididymal and testis weights are
16 relatively spared. Reproductive organ weights
17 are...are reduced in the male when you get out to about
18 7 to 12 percent.

19 In the female, reproductive and non-
20 reproductive organ weights do decline linearly with
21 body weight, as Sue said, and...and the female organ
22 weights seem more affected in small reductions growth
23 than the male, but using the data from the Laws and
24 Stover studies as a guide, direct reproductive effects
25 can be discerned from those that may be associated with

1 reduced growth.

2 I thank you for your time.

3 **DR. HEERINGA:** Possibly before we move
4 on, if there are any questions on this presentation?
5 Dr. Chambers?

6 **DR. CHAMBERS:** Earl, on your summary
7 charts there where you've got the pluses and minuses
8 and so forth, were those at the high doses, or how did
9 you discriminate amongst several doses in your summary?

10 **DR. GRAY:** I...I didn't. What I tried
11 to do there was, like with methoxychlor, if the low
12 dose effect in methoxychlor was vaginal opening, then I
13 highlighted it in red to just show that was a very
14 sensitive endpoint. On...on the ketoconazole, some of
15 those effects...many of the effects were invoked dose
16 groups, so the...the trenbolone is across all doses.
17 But they didn't break...you know, most of those run in
18 two or three doses, and I didn't break it down that
19 way, but you could.

20 **DR. CHAMBERS:** The plus...plus on plus
21 doesn't necessarily mean that...

22 **DR. GRAY:** Oh, I put that in...a plus,
23 plus, plus meant it was a really robust response that
24 was quite diagnostic, and then, a plus, some of those
25 were kind of equivocal or small. And so, you know, if

1 you're looking for flags, if you saw...if you see
2 something...if I put something in with multiple pluses,
3 there was...there was no likelihood that that would be
4 missed and misinterpreted.

5 But this...we did this...I wouldn't say
6 hastily, but we, you know, we just...we did it since
7 yesterday.

8 **DR. CHAMBERS:** One follow-up question.
9 Do you have a negative control panel to run through
10 these things?

11 **DR. GRAY:** Well, there's bisphenol A is
12 negative in the pubertal and it's positive in vitro.
13 So, on an assay by assay, there are negative chemicals.
14 Fenarimol was negative in the pubertal female.
15 Methoxychlor was negative in...in the...in the male.

16 And I think the...that points to an
17 interesting...when you're looking at estrogens in the
18 pubertal male assay, one of the things they affect the
19 most is growth, because they interfere with food
20 consumption in the brain. And so, when...you do get
21 delays in preputial separation with methoxychlor in the
22 male rat, but they're above the M.D. of 10 percent.

23 Does that answer your question?

24 **DR. HEERINGA:** Dr. Vandenberg?

25 **DR. VANDENBERGH:** What...what were the

ages of the animals when...when they were dosed? Were these all adult studies that you're talking about here?

DR. GRAY: No, the pubertal studies are the pubertal...

DR. VANDENBERGH: They were...

DR. GRAY: Yeah.

DR. VANDENBERGH: Oh, pubertal.

DR. GRAY: Right? Those are just your...or it's unrestricted there in the pubertal assay as if it was...so it was 20...22 by 42 in the female and 22 to 40...53 in the male. So, I mean, they were directly comparable. They were run for that purpose.

DR. VANDENBERGH: Okay.

DR. HEERINGA: Dr. Bucher?

DR. BUCHER: Earl, do these relationships hold across strains, do you know?

DR. GRAY: Some of these pubertal assays are run in two rat strains. Early on, we ran them in the Long-Evans and in the Sprague-Dawley, and then, other...other laboratories that have run these assays have run other rat strains. I think that most of the ones run by EPA are...are now in the Sprague-Dawley, but I don't...Lianne? I'm sorry. Speak up back there. They know what they're talking about. Many of these are run in the Wistar 2, and I...I...we haven't really

1 seen any evidence of strain differences.

2 And...and, in fact, several...we ran
3 five or six of the estrogenic chemicals back when we
4 were comparing the Sprague-Dawley to the Long-Evans,
5 ethyl estradiol and methoxychlor and tamoxifen, and
6 there was no difference between the...the responses of
7 the females to any of those chemicals at any dose.

8 **DR. HEERINGA:** Dr. Delclos?

9 **DR. DELCLOS:** You mentioned that if you
10 threw out the male pubertal, you would miss the
11 phthalate in the battery. Is that true if you
12 substituted the male adult?

13 **DR. GRAY:** No, I don't think so. I
14 think it's been known for 20, 30 years that the
15 phthalate are much less effective in the adult animal,
16 and you...so, I think there are some studies from 1985
17 where they go up to 2 g/kg and don't see anything. So,
18 I think if you give it chronically to the male, you can
19 see effects, and they're not as robust, but...

20 **DR. DELCLOS:** Decreased sensitivity is
21 what you're saying.

22 **DR. GRAY:** Oh, in the phthalate, that's
23 a...an excellent example of the sensitivity of the
24 developing endocrine system in the pubertal and in the
25 fetal as compared to the adult male.

1 **DR. HEERINGA:** Okay, we'll move on. Dr.
2 Ankley?

3 **DR. ANKLEY:** I just wanted to take a
4 couple minutes. I don't have any slides, but I wanted
5 to take a couple minutes to talk about the OECD fish
6 assay, and as you recall, yesterday, it was proposed
7 that that could be substituted for the 21-day
8 reproductive screen, and I had a couple perspectives on
9 it.

10 First, the committee that Dr. Mahiatch
11 referred to yesterday has been active for a number of
12 years, and it's an OECD committee. Has multiple
13 countries involved. I've chaired that committee since
14 pretty close to its inception, so I have sort of a...a
15 unique perspective in terms of...of seeing how things
16 have developed there, and it's...I think, for those of
17 you that have been involved in international activities
18 of this type, you can relate to the fact that when you
19 have lots of different stakeholders at the table,
20 things don't necessarily evolve strictly along
21 scientific lines.

22 And one of the challenges with the fish
23 assays is that we're, as a rule, interested in having
24 an assay that can be used for multiple small fish
25 species. In the case of the OECD exercise, we're

1 trying to develop a system that would be amenable to
2 fathead minnow, the zebra fish which is the preferred
3 test species of several European countries, and medaka
4 which the Japanese folks prefer in terms of fish
5 testing.

6 So, there's some real biological
7 challenges in terms of developing assay systems and
8 assay designs that would accommodate what...for people
9 who work with rats, a small fish maybe is a small fish,
10 but there are some pretty unique differences with
11 regards to their biology in terms of coming up with
12 a...an approach that would enable you to collect robust
13 endpoints.

14 And...and after some...some amount of
15 testing, it became clear that if we wanted to move
16 ahead quick...quickly, there were a couple of very
17 robust endpoints, and, basically, most of the species
18 that could be used for endocrine screening, and that
19 was induction of vitellogenin in...in males which is a
20 pretty specific and a pretty sensitive indicator of
21 endogenous estrogens, and then also the production by
22 androgens of male secondary sex characteristics in
23 females, another robust, quite sensitive endpoint.

24 And so, the...the decision on the OECD
25 side was that these were good endpoints to proceed

1 with.

2 The question was asked yesterday whether
3 the 21-day assay, the screening assay as described for
4 the EPA exercise, the ESP, and the OECD version of the
5 test would produce the same indicators, and the
6 response was yes. But I think the devil is in the
7 details here. It's yes, sort of.

8 For very strong chemicals, that's
9 certainly the case, that's certainly the case. If
10 you're using estrogen, it doesn't really matter whether
11 you use a 21-day design that is being used by OECD or
12 the 21-day design that's being used by EPA. You
13 produce vitellogenin and the same with trenbolone or
14 methyltestosterone, a strong androgen. They will
15 produce...you'll masculinize the females.

16 But you will miss a number of
17 chemicals...a number of modes of action by using the
18 design that OECD is currently looking at. What's
19 happening with that design at present is that you don't
20 consider fecundity in the assay, and you don't consider
21 histopathology.

22 In not considering fecundity, the actual
23 biology of the test is set up in such a manner that
24 it's not optimized for reproduction in the animals, and
25 that has some consequences when you get to testing the

1 weak chemicals.

2 For example, in the case of the fathead
3 minnow, if you run a 21-day test using the OECD design,
4 because it's not optimized for reproduction,
5 what...what you have is a mixture of an even number of
6 males and even number of females. These are group
7 spawning animals that need a particular design if
8 they're going to be affected in terms of reproduction.

9 So, what you're doing with the OECD
10 design is essentially putting them into a test where
11 you're disrupting endocrine function because of the
12 nature of the test. And so, what you're going to do is
13 you're going to miss subtle changes.

14 A couple of examples that I think are
15 relevant to what Earl presented would include aromatase
16 inhibitors and weak aromatase inhibitors. If you have
17 reproductively active females that normally produce
18 vitellogenin and if you depress steroid synthesis
19 through any of a number of mechanisms, including
20 depression...depressing aromatase, what you do is
21 essentially decrease vitellogenin levels. It's pretty
22 diagnostic. If you don't have the E2 layer to
23 stimulate the estrogen receptor, you're going to
24 depress VTG.

25 Now, what happens when you use the OECD

1 design is because the females aren't reproducing
2 naturally, you'll increase, basically, the variability
3 of that endpoint to such an extent that you can't
4 detect the decrease. You have some females that have
5 very high VTG levels, because they can't dump it into
6 the eggs. Others are actually undergoing gonadal
7 atresia, so they have very low VTG levels.

8 So, as a net result, if you use the OECD
9 design where, basically, you aren't optimizing for
10 fecundity, you would...you would miss a chemical like
11 fenarimol, quite possibly prochloraz.

12 Another example, since the OECD design
13 doesn't incorporate histology, you would miss a
14 chemical like ketoconazole as well where, in a
15 functioning reproductively active system, for example,
16 in males, you'll see testicular changes that are
17 consistent with the males trying to compensate for the
18 depressed testosterone biosynthesis.

19 So, those are just a couple of examples
20 where, although a 21-day fish test may look very
21 similar on the surface, there really are some important
22 differences, and I think that's one of the reasons, one
23 of the critical reasons, why the slide that Les put up
24 earlier that...that talked about why coming back to
25 include these other endpoints is...is pretty important

1 in the overall scheme of things. And...and I think a
2 lot of the folks involved in the OECD process, other
3 countries, by now are...recognize this based on some
4 recent peer reviews there.

5 So, that's all I wanted to say about
6 that.

7 **DR. HEERINGA:** Thank you, Dr. Ankley.
8 Any questions for Dr. Ankley? Do you have something
9 on...

10 **DR. ANKLEY:** I apologize for...

11 **DR. HEERINGA:** No, that's...that's okay.
12 This has been very useful, and, again, it's somewhat of
13 an iterative process here, and there's been an
14 excellent exchange of information, and I appreciate the
15 way it's all been handled.

16 Earlier...Dr. Portier has just reminded
17 me, too. Before we move on to the charge questions,
18 I'm going to give each of the panel members a chance.
19 Is there anything that, having thought about the
20 proceedings of yesterday, last evening, that raise any
21 additional questions that you would like to pose to the
22 EPA scientific group? Yes, Dr. Zoeller and then Dr.
23 Chambers.

24 **DR. ZOELLER:** So, this is kind of a
25 general question. When I think about Tier 1, there

1 are...there are things that come before, and there are
2 things that go after. And so, in order to...and I
3 guess this, in part, goes to the concept of weight of
4 evidence, but...but this...first of all, in concept, I
5 remember at the end of EDSTAC, there was a lot of
6 debate about how to prioritize chemicals.

7 Can we go into how these chemicals might
8 be prioritized? To what...to what extent will previous
9 information...there are some chemicals about which we
10 know a lot. There are others about which we know
11 almost nothing. What...what kind of front loading is
12 occurring before it hits the tier?

13 And, secondly, once it goes through the
14 tier, especially from the thyroid point of view,
15 because there are very few...certainly, thyroid
16 endpoints are not captured in the same degree to which
17 estrogen and androgen endpoints in the...in the
18 proposed tier are being reviewed, are being captured
19 here. So...so, how is weight of evidence going to be
20 used for that?

21 **DR. TIMM:** As you know from what we said
22 yesterday, the...the 73 chemicals really have been put
23 on the list with...without any review of existing
24 information at all, and we...we have thought about
25 doing so.

1 We looked...we conducted, actually, a
2 pilot exercise looking at about 30 pesticide chemicals,
3 and we found that as you got into really old
4 information, that it...that it was not very helpful.
5 And so, we...we went ahead and...and since we did not
6 have the high throughput screens optimized to help us
7 select, as EDSTAC had recommended, we just went ahead
8 with the exposure approach.

9 Clearly, before...before testing begins,
10 we will look at the information. People will...will be
11 given the opportunities. One of the responses to
12 the...the test order is to...to submit data that they
13 believe satisfy the...the requirements. So,
14 that's...that's one opportunity for...for looking
15 at...at...at data.

16 In the future, however, there are a
17 number of...of efforts going on. There's the Computox
18 program where they're developing QSARs which would be
19 helpful as priority setting tools, and we have not
20 really thought much...we've been busy. We have not
21 really thought much beyond the 73, and as you know, one
22 of the things that before we plow ahead with...with the
23 program, we...we will reflect upon what we have
24 learned.

25 So, it's really premature to get into

1 speculating very much on...on how that will...will take
2 place. The one thing we did say to...to people is that
3 gee, we really wish you would have taken into account
4 hazard information, toxicity information, in making
5 your selections. We said clearly, we recognize that
6 there is the desire to do that, and that would be done
7 in the future, so we won't have a pure exposure list,
8 in all probability, in the future. There will be other
9 ways to...to prioritize.

10 **DR. HEERINGA:** Dr. Chambers?

11 **DR. CHAMBERS:** Two questions. I think
12 one of them is a follow-on to Dr. Zoeller's. I'm still
13 a little confused about the weight of evidence. So,
14 are you saying that if...if there is existing
15 information or QSARs predictions and all that exist
16 before the screen is initiated, then that data could
17 supply some of these lines of tests?

18 **DR. TIMM:** Q...QSAR information, I
19 think, is proprietary. I don't see QSAR information,
20 at this stage of the game, really substituting for
21 any...any test results, but QSAR information would be
22 useful for...for prioritizing in the future.

23 I think, though, we're looking at
24 functionally equivalent information for...we obviously
25 do not want people to repeat tests where...if it

1 already exists. I think that is a clear principle that
2 the statute indicates, that...a principle EPA has...has
3 embraced, and it's certainly one of the recommendations
4 of EDSTAC.

5 **DR. CHAMBERS:** The other question is the
6 bioassay that was presented yesterday, Lumey cell, was
7 that considered, and if so, why was it rejected?

8 **DR. TIMM:** The Lumey cell assay
9 was...was not considered and not rejected. It's...it's
10 an ongoing exercise. I...I understand from the status
11 of things that there...a lot of the...I think all the
12 prevalidation work is...and correct me if I'm wrong in
13 this...prevalidation work's been done.
14 They're...they're going into the interlaboratory work
15 on that.

16 But I believe that it is about a year
17 away before they will complete that process and go
18 through peer review. So, obviously, it's coming along
19 too late, but that's where it would hook into our
20 initiative with OECD to develop a generic test
21 guideline for...for these kinds of assays.

22 And a generic guideline gets around a
23 number of problems. One thing we...we really...OECD
24 will not, regardless of the U.S. position, OECD will
25 not allow a proprietary system to be required, so there

1 needs to be a generic approach with a proprietary
2 system which would mean, basically, it's a performance-
3 based test guideline, and so, probably using data from
4 similar systems, the Staray system in Japan, the Lumey
5 system, the assays that we've developed.

6 What we are going to propose is that an
7 expert group get together and use those data to try to
8 develop a performance-based test guideline that we
9 could use the model for...for future such work.

10 **DR. HEERINGA:** Dr. Denver?

11 **DR. DENVER:** Yesterday, there was a lot
12 of discussion of specificity and, you know, general
13 effects, general toxicant effects, and clearly,
14 the...the assays can...are intended to identify modes
15 of action that are endocrine in nature, but it seems
16 that they are...they're also going to identify, as was
17 stated this morning, reproductive toxicants or general
18 toxicants. And I'm curious how the EPA responds to
19 those criticisms and whether it is, in fact, an
20 intended goal to identify these more general toxicants
21 or if it is an acceptable goal.

22 **DR. TOUART:** I get the palmer. This is
23 Les Touart. I can provide a little bit of a response
24 and...and Gary may have some...some follow-on.

25 But I think that the context...and,

1 again, the recommendations are that the...the EDSTAC
2 were that...that we should stress more sensitivity than
3 specificity. I mean, specificity is fine. It...it
4 assists, but the...the goal of the Tier 1 isn't to
5 confirm a mechanism of action. It's to be able to
6 detect, you know, the potential for, you know,
7 mechanisms to...to be involved.

8 In some cases, the more summary or
9 apical, you know, endpoints would be downstream of...of
10 other endocrine potentialities, but, you know, there
11 are possibilities that...that these could be affected
12 by...by non-endocrine, you know, bases, but some of
13 these summary endpoints, in and of themselves, you
14 know, on growth, development, or reproduction in
15 particular, you know, these are endpoints of concern,
16 you know, to the Agency. So, an assay, especially an
17 in vivo assay that identifies that as a potential
18 effect, whether it's endocrine or non-endocrine, we
19 need to evaluate it in a longer-term more definitive
20 study to understand, you know, what the adverse
21 consequence is, but the more definitive endpoints or
22 variety of endpoints will help understand whether it's
23 really operating through endocrine or non-endocrine
24 type mechanisms.

25 And...and part of the feedback on weight

1 of evidence...and I think Earl pointed to this fact in
2 kind of just his little talk earlier...is the context
3 of the assays themselves in play and the endpoints, you
4 know, in play so that...that it helps us to kind of
5 understand whether the...the strength of the
6 information leads us to a conclusion that...that it's
7 more likely an endocrine-active material than it's not,
8 but we want to make sure that if...if an endocrine, you
9 know, activity is present, that we have assays in place
10 that would be able to detect, you know, that, you know,
11 activity.

12 Whether we capture a couple of other
13 things, you know, these are, you know, are true but a
14 concept of what's really a false positive. If we have
15 a positive, you know, reproductive active material or a
16 developmental active, you know, material, you know,
17 that's a positive, and it would be positive in the
18 long-term, you know, test.

19 It just may be positive for other
20 reasons, and that would be clarified in the Tier 2, and
21 it's only after we've completed the Tier 2 would the
22 Agency be in a position to say, you know, this compound
23 is determined to be, you know, endocrine disruptive,
24 you know, in...in nature, and so, it would be, you
25 know, identified in...in that kind of context, but the

adverse consequence would be what the Agency would
utilize in terms of risk management or risk assessment
practice.

DR. HEERINGA: Dr. Delclos?

DR. DELCLOS: I just have one question.
I guess about a legal definition. I may be the only
person confused here, but representing assays as
validated...and some of the public commentators are
saying these assays were not validated...for instance,
if you did not have a...a demonstration of a chemical
which you would expect to be negative and it's not
demonstrated to be negative in these pubertal assays,
could you go forward with that program in August as
you, as you plan, or do you have to stop and...and do
that? Is that a legal requirement for the validation?

DR. TIMM: I think it's...it's clearly
necessary to show that...and we wouldn't want
everything to...to light up positive in the assays. I
mean, as somebody mentioned the other day, you don't
have an effective surrogate if everything's going to go
through it. We don't think that that's the case.

Now, whether others are as convinced as
we by the fact that when you look at the...the...some
of the other modes of action and you find that you
clearly have thyroid active chemicals, you clearly have

1 estrogen active and you have androgen active and they
2 don't...they don't act by the other modalities,
3 if...some people, obviously, are not persuaded. Some
4 people would like to...and we would like to,
5 actually...have had a clear negative. We...we...we
6 didn't choose well.

7 I don't think that that means there
8 isn't one out there. It just means we...we didn't make
9 a very good choice.

10 So, we would...we would...we're now
11 reflecting upon the peer review comments...we...we
12 certainly may amend it...initial cut of peer review
13 comments, but I suspect that...that...we're pretty
14 convinced that we do understand how these assays work.
15 I think that's the real test of validation, is do you
16 understand the performance of the assay, the
17 limitations of the assay, the trends of the assay.

18 **DR. HEERINGA:** Dr. Brown, do you have a
19 question?

20 **DR. BROWN:** I had a question, I guess,
21 related to the transferability of these various tests,
22 and I...you know, I sit here, and I listen to Earl and
23 Gary who are certainly experts, I mean, at the top of
24 the field in these areas, and I wond...and...and
25 I...I...I hear them expressing, you know, some little

1 thing that they found here or there, like Earl's
2 Sertoli cell toxicity and Gary's concern about some of
3 the...the fish reproduction assays. I just wonder
4 whether, you know, the endpoints that we're really
5 concerned about here are really going to be
6 transferable from laboratories like theirs to the more
7 routine laboratories that might be conducting these
8 tests.

9 **DR. GRAY:** Let me...let me talk first to
10 the Hershberger, because I...and Gary Timm was involved
11 in the OECD validation of that. I mean, that's
12 a...that's an old and fairly simple assay, and...and
13 all of the endpoints are organ weights, and the only
14 one that was really new to the tox community in general
15 was the leather anions. So, I think there was no
16 difficulty in transferring that technology to 17 or 18
17 laboratories.

18 I think, in the pubertal assays, there
19 is not much new for endpoints in those. The assays, as
20 they are constructed, are...are new, but the...even the
21 vaginal opening and preputial separation are part of
22 the 1998 multi-generational reproduction guidelines.
23 So, I think the...some of the...much of those
24 endpoints, there wouldn't be any difficulty in
25 transferring.

1 I think you do run into
2 different...different problems with some of the in
3 vitro assays, clearly, and there's where we talk about
4 having very strict performance criteria to make sure
5 that a laboratory can run the assay and sort of self-
6 validate before they run it, so we can validate an in
7 vitro assay in ten laboratories and...and give it to
8 somebody and they just can't do it. So, we...I think
9 there needs to be that.

10 You want to talk about something?

11 **DR. ANKLEY:** Yeah, I think that's a...a
12 very fair question, and in the field of ecotoxicology,
13 primarily what's been used over the years are whole
14 organism tests and whole organism endpoints, and so,
15 it's not a lot of concern to me whether a lab's going
16 to be capable of rearing frogs or fish and doing an
17 exposure, but some of the endpoints are endpoints that
18 have traditionally not been used in the types of
19 consulting situations any way that these sorts of tests
20 would be used in.

21 A good example here is vitellogenin
22 measurement which is typically done within ELIZA, and
23 ten years ago when...ten years seems like a long time
24 now, but when we first started all this, there weren't
25 a lot of labs that were really proficient in measuring,

1 for example, vitellogenin in the fathead minnow. Now,
2 over that time, commercial kits have become available.
3 People have become familiar, more familiar, with the
4 concepts of ELIZAs, and labs, a lot more labs now, can
5 do that.

6 And so, there's going to be a learning
7 curve for some of these endpoints just because the
8 assays, by the nature of looking past apical endpoints
9 to some of the more mechanistic responses, a lot of
10 labs haven't been familiar with these, but in the case
11 of vitellogenin, for example, there's been a fairly
12 rapid evolution, and, you know, quite frankly, one of
13 the reasons for that is people see the potential to
14 profit from doing this, and so, it's really spurred the
15 competition, for example, to develop commercial ELIZA
16 kits. There really wasn't anything years ago, and
17 there's three or four now that could be used.

18 **DR. GRAY:** Let me...let me comment on
19 what I said a little bit. I mean, I'm not...I'm not a
20 specialist in the thyroid, so I don't think of that. I
21 think those are...in the assays, those are probably the
22 newer endpoints, and some of them are more difficult
23 than others, and there just...there will be need...need
24 to be more guidance there, I think, but I think that
25 the people like Tammy or Susan who have worked on this

1 or Tom Zoeller could address the difficulty in
2 transferring those endpoints.

3 But I wanted to clarify what I said,
4 mainly on TS agents not routinely measured, and the
5 histo...thyroid histo path is going to require some
6 help.

7 **DR. HEERINGA:** Dr. Denver?

8 **DR. DENVER:** You know, a very important
9 endocrine axis that has not been mentioned here is the
10 hypothalamic-pituitary-adrenal axis and
11 corticosteroids, and I'm just curious why and
12 whether...I mean, you must have thought about
13 these...these hormones and...and the fact that they
14 could cause or influence many of the endpoints in these
15 assays if they are disrupted.

16 Is there any thought among the EPA of
17 including down-the-road analyses of corticosteroids
18 in...in these assays, levels of stress that are...I
19 mean, many of these toxicants can alter, you know,
20 activity of the stress axis that could then lead to
21 many of the effects that we see in the assay.

22 **DR. HEERINGA:** Dr. Touart?

23 **DR. TOUART:** This is Les Touart. I'll
24 try to respond a...a little bit.

25 I think yeah, there have been

1 considerations in terms of what other assays and...and
2 things to have considered, but we were, you know,
3 following more of the...the EDSTAC recommendations in
4 terms of...of considerations that they have, and,
5 again, at the time, it was felt that estrogens,
6 androgens, thyroids have the...the broader availability
7 of...of assays and specific, you know, endpoints that
8 would be, you know, relevant. And so, we kind of
9 focused more on them in terms of identifying assays
10 that would work and in going through validation, you
11 know, processes.

12 In context of the in vivo apical assays,
13 you know, clearly, HPA would be a component of the
14 pubertals, you know, fish and even in frogs in terms
15 of...of the axis, you know, being there, how much it
16 would contribute. We just don't have specific
17 endpoints that are...that are also being measured.

18 In terms of something like the fish
19 assay, there's a limitation in...in the number of
20 things that one might be able to look at in terms of
21 sera. You know, you might be able to...like
22 vitellogenin, you may be able to do, you know, an
23 androgen or an estrogen in...in the sera, but to add
24 other component, you know, parts would be difficult,
25 for instance, if your...your sample would have been

1 completely utilized.

2 So, those are, you know, considerations.
3 I think if...if there are some endpoints to...to be
4 considered and if these could be done without
5 disrupting the, you know, other core endpoints, I think
6 we'd be interested in...in those, and there may be
7 technologies that exist that others might be aware of
8 of some of these.

9 **DR. GRAY:** You know, adrenal weights are
10 included in these, and that seems rather primitive, but
11 they are actually remarkably responsive to some of
12 these chemicals, actually, quite a few of these
13 chemicals, and...like ketoconazole tripled adrenal
14 weight in the male and female in the 20 and 30 ages
15 based study without any obvious toxicity in the
16 animals.

17 The fungicides like vinclozolin increase
18 adrenal weights, and I think the modes of action of
19 those are completely undefined and definitely not the
20 same. So, I think it's...it's interesting.

21 **DR. DENVER:** I mean, measuring plasma
22 cortisol is a fairly straightforward thing to do that
23 could potentially be included in these assays, but
24 I...actually, I was more interested in whether these
25 effects were being recognized or, at least, appreciated

1 and then considered down the road, you know, beyond
2 August, 2008, because I think it's...it's not just
3 another endocrine axis. It's a very central, critical
4 axis that could influence all of these other endpoints,
5 you know.

6 **DR. HEERINGA:** At this point, I...oh,
7 Mr. Gray...Dr. Gray?

8 **DR. GRAY:** I agree, and it's unexplored,
9 and I think there's a fairly large database on things
10 that affect adrenal, but it wasn't...it hasn't
11 been...it's not part of the program now, as are many
12 other endocrine modes of action that may be very
13 important.

14 **DR. HEERINGA:** Okay. At this point, I'd
15 like to take a 15-minute break, and when we return, we
16 will turn to the charge questions, the first charge
17 question. At 10:25, we'll reconvene.

18 (WHEREUPON, a brief recess was taken.)

19 **DR. HEERINGA:** Okay, welcome back,
20 everybody, to the second half of our second day morning
21 session on the meeting of the FIFRA Science Advisory
22 Panel on the topic of the Endocrine Disruptor Screening
23 Program proposed Tier 1 Screening Battery.

24 At this point, we have gone through our
25 series of presentations, had clarifying questions, and

1 also heard public comment, and we are about to enter
2 the period where the panel will formally respond to the
3 charge questions posed to it. So, I'd like to ask Dr.
4 Touart to...to read the first charge question into the
5 record, and I think Dr. Belcher is going to read all of
6 the subpoints, but then, we can organize our response
7 point by point.

8 **DR. TOUART:** Okay, I thank the chair.
9 And the first charge question directed to the panel is:
10 Please comment on the ability of the proposed Tier 1
11 Screening Battery to provide sufficient information to
12 determine whether or not a substance potentially
13 interacts with the estrogen, androgen, and thyroid
14 hormonal systems based on the modes of action covered
15 within the battery.

16 And we have seven modalities that
17 are...that are listed in subsets. I don't know if you
18 want me to read those, too, or...

19 **DR. HEERINGA:** You just read the
20 modalities, yes. I don't think you have to read the
21 descriptive part.

22 **DR. TOUART:** Okay. The modalities being
23 estrogenicity, anti-estrogenicity, the androgenicity,
24 anti-androgenicity, steroidogenesis effects, the
25 hypothalamic-pituitary-gonadal effects, and

1 hypothalamic-pituitary-thyroid effects.

2 **DR. HEERINGA:** Our lead discussant on
3 this will be Dr. Belcher, and I think that you've
4 indicated that you would like to have a discussion sort
5 of mode of action.

6 **DR. BELCHER:** Generally, what I'd like
7 to do is to take each of the sub-components, the mode
8 of actions, and address each of those in order as
9 listed. The first mode of action will be
10 estrogenicity, and there are five assays proposed that
11 address estrogenicity. They include the ER binding
12 assay, the human ER alpha transcriptional activation
13 assay, the uterotrophic assay, the pubertal female
14 assay, and the fish screen.

15 At this point, based on the diverse
16 amount of data that goes into each one of these, I
17 would like to open up for comment to the SAP to carry
18 on and discuss each of these mode of actions
19 individually and how they fit into the battery to
20 address estrogenicity.

21 **DR. HEERINGA:** I think what I would like
22 to do is to go through the associate discussants for
23 their specific. Do you have anything yourself that you
24 would like to...

25 **DR. BELCHER:** General comments based on

1 this is that there is strength in the multiple assays
2 that inform on estrogenicity. Many of these assays are
3 quite robust and reproducible.

4 One of the major comments that I might
5 want to come back more on is the potential for ER beta
6 in playing a role. As a major role, there is focus on
7 ER alpha-mediated mechanisms, and the potential for the
8 combined effects of ER alpha and ER beta to produce
9 false negatives in this assay is apparent to me, and
10 if...it's difficult to see how, with the important in
11 vivo assays, how this may be resolved in a general...as
12 a general comment.

13 **DR. HEERINGA:** Dr. Denver, associate
14 discussant, your comments on the estrogenicity mode of
15 action charge question.

16 **DR. DENVER:** Well, clearly, this...this
17 mode of action is, I think, best addressed by the...by
18 the Tier 1 screen, and this could be, in part, due to
19 the historical reasons, that is, estrogenic compounds
20 in the environment were recognized very early, and so,
21 there was a lot of focus placed on means to detect
22 them.

23 I think that the...there are five
24 different assays, and each one...each of the assays has
25 their strengths and their, you know, their weaknesses,

1 but taken together, they provide a very overall
2 powerful test of the hypothesis that a compound has an
3 estrogenic action.

4 So...and I would also add that, you
5 know, even the amphibian metamorphosis assay would
6 potentially find an estrogenic compound, although it's
7 not designed to do that, because estrogens can, in
8 fact, slow or block metamorphosis.

9 So, those are all general comments. I'm
10 going to defer to the other panel members who are more
11 expert on estrogenic modes of action to comment
12 specifically on the assays.

13 **DR. HEERINGA:** Dr. Delclos is the next
14 associate discussant on estrogen...estrogenicity as a
15 mode of action.

16 **DR. DELCLOS:** Barry Delclos. I agree
17 with what Bob just said in terms of this being probably
18 the strongest of endpoints. There's certainly a very
19 good strength in the battery for detecting ER alpha
20 nuclear receptor mediated effects with the uterotrophic
21 assay, the binding assay very strong. The other assays
22 are comparable to that.

23 I think the one case...I don't know if
24 maybe Scott, later in his comments, will discuss what
25 might be appropriate in the in vivo assays for picking

up the ER beta ag...agonist, but there's also...there could be a number of effects, other effects, and I think this would be argument for...there's certainly arguments against including apical endpoints.

I mean, apical...inclusion of apical endpoints really has to be done in order to pick up some of these other mechanisms that might...that we know there are and may come up later. It's going to be difficult to...to adjust the battery to adapt to each new mechanism that might be identified in...in the molecular biology labs.

I have a few comments. There was some discussion with the uterotrophic assay here and the...and in the Hershberger later, there's a choice given between the route of administration. We discussed that a little bit, I think, yesterday, the questions, but I think it's...the EPA's approach of using, at least for compounds in which there is sparse information on metabolism and so forth, there...I agree with using the subcutaneous injection for...for one of the in vivo assays and oral for another would be valuable in those cases.

For example, in the bisphenol A case, there's clear, very clear difference in the...in the activity with route of administration, and so, while

1 using the...suggestion of using the relevant route to
2 human exposure is a good one, any time...is necessary
3 any time you're going to do a risk assessment, these
4 data are not being used for risk assessment. They're
5 being used to identify potential for action. So, I
6 think that was a...a good point.

7 I really think that's about all I had to
8 say at this point.

9 **DR. HEERINGA:** Dr. Cooke, the next
10 discussant.

11 **DR. COOKE:** In terms of estrogenicity,
12 we would pretty much agree that there's a sufficient
13 number of tests to be able to say whether something was
14 estrogenic or it wasn't estrogenic or maybe it's
15 estrogenic for both the in vitro and the in vivo
16 approaches. That's...that's a good thing in one
17 aspect.

18 Maybe in a more general discussion, we
19 can discuss whether you need all of those. It's
20 designed to give you a maximum amount of information.

21 So, in common with the other people on
22 our panel, that's pretty much all I would have to say.

23 **DR. HEERINGA:** Thank you very much, Dr.
24 Cooke. I think the issue of complementarity and that
25 potentially redundancy is...charge question 2 covers

1 that as well. So, we'll certainly get to that.

2 Dr. Furlow?

3 **DR. FURLLOW:** Thank you. So, again, in
4 thinking about these charge questions, often, I tend to
5 drift into thinking about the second one in my
6 comments, so I'll try to be careful about that.

7 **DR. HEERINGA:** Well, there's no need. I
8 think we're just going to make sure that what...the
9 point is that something gets covered, not necessarily
10 when it gets covered.

11 **DR. FURLLOW:** Absolutely, absolutely,
12 because I was actually going to make a comment about
13 VPA, for example.

14 Again I think, as Dr. Denver pointed
15 out, the estrogen...estrogenicity assays are...are the
16 most mature. They're the best validated, in...in my
17 opinion. There's a combination of biochemical,
18 molecular, genetic in terms of transactivation,
19 although we haven't seen the validation yet. Right?
20 That hasn't been fully completed, but...but I'm
21 optimistic that will be a good online assay, and the
22 uterotrophic assay is...is...is quite...is quite nice.

23 I'm also happy to see the fish screen
24 included, not just because they're fish, but I think
25 there are things that, in terms of the low background

1 of vitellogenin synthesis in the male is a particularly
2 nice, sensitive screen.

3 The...the...the...well, the coverage and
4 multiplicity of different assays in covering
5 estrogenicity I do think is...is, in fact, also
6 important. I was thinking in terms especially about
7 bisphenol A. If you just looked...if you just, say,
8 used the pubertal assay, you might say okay, it's a
9 general toxicant, it's not an endocrine disrupter.

10 There has been...I was also concerned
11 about...and this has been addressed a little bit about
12 strains, but this is something maybe we can talk about
13 in the next charge question, but I think that if the
14 argument that's been made that Sprague-Dawley rats are,
15 say, relatively insensitive to bisphenol A...this has
16 been something that's been talked about a lot,
17 actually...the fact that you have the fathead minnow
18 assay, I think, helps.

19 You'd say, you know, by weight of
20 evidence, you'd say okay, well, it didn't show up in
21 the pubertal assay. That was a Sprague-Dawley. But
22 you've got these other assays, estro receptor binding,
23 transactivation, and the fathead minnow, to...to help
24 cover that and...and something...but the, you know,
25 extreme differences, I think, still is something that's

1 extremely important, should not be ignored by the EPA,
2 but that my concerns are somewhat mollified by the
3 redundancy and the different mode of actions
4 incorporated in the estrogenicity assays.

5 So, I guess, those are my...those are my
6 main comments. So, I'll stop there.

7 **DR. HEERINGA:** I'd like to turn now to
8 other members of the panel on the estrogenicity of mode
9 of action and the Tier 1 battery. Yes, Dr.
10 Vandenberg?

11 **DR. VANDENBERGH:** John Vandenberg. I
12 had some concern about the assay, the female puberty
13 assay, in the sense that if one is looking for a
14 measure of female puberty, the vaginal opening is,
15 obviously, a good one, and the onset of first estrus
16 is, but it goes on and measures cyclicity, and there
17 are some real problems with...associated with that.
18 Some have been brought up by the public comments that
19 we've had, written and oral, that a lot of other
20 factors can influence that cyclicity, the social
21 conditions of the animal, nutrition, and on and on.

22 So, I just wonder how essential it is
23 to...to do that part of it. You can get the puberty
24 information by measuring vaginal opening and then
25 smearing for a week or ten days, at most, and you

1 should get the first estrus cycle.

2 **DR. HEERINGA:** Other contributions from
3 panel members on this mode of action? Again, we can
4 return at any point in time if you have something else
5 that comes up, but I think that covers. I'll turn back
6 to Dr. Belcher. You want to wrap this up or move on to
7 the next mode of action, please?

8 **DR. BELCHER:** If there's no other
9 comments, we can go ahead and move forward to anti-
10 estrogenicity. That is covered through the estrogen
11 receptor binding assay, the human ER alpha
12 transcriptional activation assay.

13 However, their using this as a reporter
14 for inhibition has not been validated to this point.
15 There is some information from the pubertal female and
16 the fish screen. My feelings in...with this are...are
17 in line what was presented by the EPA in the technical
18 document, is that this is actually a rather weak...weak
19 coverage of this mode of action, and, essentially, the
20 strongest component is through the ER...the ER binding.
21 However, there is no information beyond that a compound
22 is a binder.

23 There are some...some potential
24 information from the pubertal female assay and the fish
25 screen. I'm not in a position to comment on how

1 increased vitellogenin in female is that robust of an
2 endpoint for detecting these sorts of changes.

3 **DR. HEERINGA:** Dr. Denver?

4 **DR. DENVER:** I would just concur that
5 this mode of action, the assays are not well developed
6 to detect that, and that was stated by the EPA. And,
7 obviously, we need to encourage further validation and
8 development of the ability to detect that mode of
9 action.

10 **DR. HEERINGA:** Dr. Delclos?

11 **DR. DELCLOS:** Well, I agree with what
12 the previous commenters and with the EPA in saying that
13 this is one of the weaker modes of action, really, in
14 the battery. And, again, as with the...the
15 estrogenicity assay, this focuses more
16 on...specifically on ER alpha, and at the other end, at
17 the binding assay, I'm...I'm not competent to comment
18 on fish assays at all, but other than the ER binding, I
19 think that the...there's weak coverage.

20 I was wondering if it could be
21 considered to...to the relevance in value with the
22 uterotrophic assay, consider adding in, the anti-
23 estrogen component of that into that battery to...to
24 complete things. That's all I had to say.

25 **DR. HEERINGA:** Dr. Cooke?

1 **DR. COOKE:** I don't really have anything
2 to add to them.

3 **DR. HEERINGA:** Dr. Furlow?

4 **DR. FURLOW:** Yes, I want to actually
5 amplify on Dr. Delclos' comments. I do think that
6 there...there can be robustness in the uterotrophic
7 assay and some of the transactivation assay in terms of
8 developing and validating an anti-estrogen screen. I
9 think...I think there's real potential there, and we've
10 talked about how that has been done, and if it...if
11 it's validated to EPA's satisfaction, I think those can
12 be very powerful assays.

13 Vitellogenesis in the fish is the issue.
14 One issue is that yes, it's a quite specific to
15 estradiol or estrogens in the fish, and so, it can
16 interfere with that by making aromatase or something
17 but also anti-estrogenic activity at the receptor can
18 actually serve as a...as a good assay for anti-
19 estrogenicity.

20 That said, interference with thyroid
21 hormone actually, you know, also interferes with
22 vitellogenesis by unknown mechanisms, but you need
23 thyroid hormone, adequate levels of thyroid hormone in
24 order for estrogen to induce vitellogenesis. So, if
25 we're...if we're concerns about the precise mechanism

1 of action, there may be some softness there anyway in
2 the...in the fish vitellogenin assay, although I still,
3 again, think that can be a good assay for
4 estrogenicity...anti-estrogenicity, but, again, that's
5 another opportunity. If you have the male fish, give a
6 low dose of estradiol, and then introduce a battery
7 of...screen for various anti-estrogens
8 Again, in parallel with the transactivation assay and
9 the uterotrophic assay, I think you can develop a good
10 validated anti-estrogenic assays, but I...but I...the
11 discussion in the presentation made it feel like we're
12 really not there yet, but we should get there, and I
13 think we can get there.

14 Just one other point. The...the point
15 has been made about the pubertal assay, then, is
16 serving as one of the endpoints, and I...I guess
17 I...I'm more comfortable with accelerated vaginal
18 opening as an estrogenic endpoint.

19 With delayed vaginal opening, I'm less
20 comfortable with as an in vivo anti-estrogenic endpoint
21 just due to the specificity of the assay that's been
22 brought up by a number of speakers, that you can delay
23 and interfere with the activation of the HPG axis in a
24 number of different ways. So, as a...as an anti-
25 estrogenic assay per se, I don't...I don't think it

1 serves that purpose.

2 **DR. HEERINGA:** Thank you very much, Dr.
3 Furlow. Comments from any of the other panel members
4 on the anti-estrogen? Dr. Brown?

5 **DR. BROWN:** Well, I may be speaking a
6 little bit from my bias as a research bias, but...

7 **SPEAKER:** That's appropriate.

8 **DR. BROWN:** It just seems to me that the
9 maximum effort and the maximum gain would be from
10 developing the estrogen receptor transcriptional
11 activation assay as...as kind of the premier or the
12 primary in vitro assay. And I say that because it's a
13 system where I think you have much more control over
14 the conditions, and it's also a...it's an assay that
15 even though it's not indicated for antagonist
16 screening, it has...obviously, has the potential to
17 screen out...to screen for antagonists also. And it
18 also can measure estrogen receptor binding for these
19 agents.

20 So, it has the potential both for
21 measuring estrogen binding to the estrogen receptor
22 and, in this case, the estrogen receptor alpha, but it
23 also has the ability to...to look at...at activation
24 of...of...of...at a target gene. And the potential
25 there is also that it could be modulating gene

1 expression through other means in addition just to
2 direct activation through the estrogen receptor genomic
3 traditional DNA binding modalities.

4 So, I'd like to kind of put in a plug
5 for...for that assay, you know, rising up the...up the
6 level of...of priorities, and, I mean, it also then
7 addresses a number of things that came up yesterday,
8 and that is, you know, it takes care of the three Rs,
9 too.

10 And there's also the aspect of
11 developing an assay that could be high throughput, in a
12 way. Also could be developed potentially as a non-
13 radioactive assay that does away with the...the
14 radioactive waste and...and exposure potential, too.

15 So, I think I'd like to see that kind of
16 put up as a higher priority maybe.

17 **DR. LASLEY:** Yeah, I'd like to amplify
18 on that point. Clearly, the transduction assay is
19 already...has already been shown to be useful in
20 discovery in finding new types of endocrine disruptors.
21 So, I think this is not only a good screening assay for
22 what we know, I think it's going to be a good assay for
23 what we want to learn.

24 And in addition to that, I think it has
25 promise across some of the other categories of...of

1 endocrine disruption. I can see that thyroid and other
2 hormones would benefit from...from this technology.
3 So, I think that's one that will satisfy a lot of
4 needs.

5 **DR. HEERINGA:** Thank you, Dr. Lasley.
6 Dr. Bucher?

7 **DR. BUCHER:** Yeah, I would agree
8 with...with those comments, but I think you have to
9 remember that it goes in tandem with the problem of
10 metabolism. So, one might want to consider, in some
11 instances, when data come in from Tier 1 screenings
12 that don't make sense that, in that regard, there be
13 some thought given to testing major metabolites in...in
14 these in vitro assays.

15 **DR. HEERINGA:** Yes, Dr. Kullman?

16 **DR. KULLMAN:** I want to go back to
17 vitellogenin for a second, as I think it's well agreed
18 that vitellogenin induction is a...an excellent
19 mechanism for looking at estrogenicity. Vitellogenin
20 or lack of induction or a decrease in vitellogenin has
21 some inherent problems when looking at generalized
22 toxicity. Certainly, a compound that is a general
23 anti-toxicant will significantly reduce vitellogenin
24 activity.

25 And so, it's like, you know, it may be a

1 decent indicant. I don't know that it's as robust as
2 the vitellogenin.

3 **DR. HEERINGA:** Yes, Dr. Eldridge?

4 **DR. ELDRIDGE:** Yes, at the risk of
5 sounding over redundant, the endocrine system is, by
6 definition, a signaling system. It's...it's endogenous
7 chemicals that make things happen.

8 So, looking for antagonism of that using
9 a generalized in vivo model is inherently much more
10 difficult than looking for an appearance of an effect.
11 So, it...it puts much further emphasis on having
12 specific kinds of tests looking for an antagonist, for
13 a true antagonist of a system, and it's...there's a lot
14 of risk of what we might call false positives from a
15 chemical causing something to disappear which is
16 completely unrelated to the hormone action.

17 **DR. HEERINGA:** Thank you, Dr. Eldridge.
18 What I'd like to do, since we have general comments
19 from the panel on both estrogenic and anti-estrogenic
20 activities is maybe turn to Gary Timm and Dr. Touart
21 here to see if...if there are any confusions or
22 clarifications, anything that comes to your mind from
23 the panel's comments. There's no need, but if you feel
24 satisfied with what you've heard, then...

25 **DR. TIMM:** Yeah, I've been taking notes

1 vigorously, and I think I understand.

2 **DR. HEERINGA:** So, I think we'll try to
3 check back, because, obviously, we want to make sure
4 that you feel comfortable that you understand what you
5 heard, whether you agree with it or not. I guess
6 that's...so, okay, let's...let's move on.

7 Dr. Belcher?

8 **DR. BELCHER:** Moving on to the
9 androgenicity mode of action there are one in vitro
10 assay, the AR binding assay from rat prostate cytosol,
11 the Hershberger assay, the pubertal male, and the fish
12 assay.

13 In general, my comments are limited to
14 that the AR...the AR binding study is, again, a
15 reasonable and classic approach to finding...binding.
16 The Hershberger assay is...was quite impressive
17 and...and is an important assay for this component of
18 it.

19 And, in general, my feelings were that
20 this was a...a...had good predictive abilities, and I
21 thought that the pubertal male assay with the oral
22 administration and the...the ability to discern
23 metabolic activation was also a good component of this.

24 **DR. HEERINGA:** Dr. Denver?

25 **DR. DENVER:** So, I think that this is

1 the second most robust or complete set of assays
2 following the estrogenicity assay, and among these
3 assays, the...the androgen receptor binding assay is
4 probably one of the best developed of...of the assays
5 in the tier, although it does...it does have some
6 issues. It can't distinguish between agonist and
7 antagonist, but that was recognized.

8 There was also issues related to the
9 performance of the assay, that is, the generation of
10 rat ventral prostate cytosol among different labs, and
11 there was a lot of variability there, and so, that was
12 a concern among reviewers, and the thing I would say to
13 that is I would recommend considering, at least, moving
14 to a recombinant AR binding assay as soon as possible
15 to avoid some of those issues.

16 The Hershberger assay is strong,
17 reliable. It's a validated assay. It's been around
18 for a long time. It can detect AR-dependent processes.

19 It may be worthwhile to develop an AR
20 transactivation assay to...to compliment this to...to
21 round out the set of assays, at least in the future,
22 similar to the estrogenicity assays.

23 The fish short-term reproduction assay,
24 as an in vitro assay, is a...is a strong assay in terms
25 of male secondary sex characteristics. Those are

1 robust endpoints that can be monitored readily.

2 And, finally, the pubertal male assay
3 is...is necessary. An in vivo rodent assay is a
4 necessary assay to detect androgenicity. However,
5 I...I don't think I'm the one to comment on whether
6 it's a better assay than the adult male assay, and so,
7 I'd like to hear comments from my colleagues on the SAP
8 on that matter.

9 **DR. HEERINGA:** Dr. Delclos?

10 **DR. DELCLOS:** In general, I agree with
11 the previous comments. It's a strong...strong coverage
12 of the AR receptor binding, and the Hershberger assay
13 also, with the...as with the estrogen receptor, a
14 transactivation assay might be useful.

15 I...I think, for this particular
16 endpoint, I don't know that the pubertal male is
17 a...has the strength relative to the Hershberger assay.
18 I might be wrong, but I think the pubertal male still
19 has...has advantages down the road for the HPG axis,
20 certainly.

21 **DR. HEERINGA:** Dr. Cooke?

22 **DR. COOKE:** Yes, the...it's the opinion
23 of most that development of a transactivation assay for
24 the androgen receptor would...would be beneficial. In
25 terms of answering the...the question, does the rat

1 prostate cytosol test tell you whether it's likely to
2 interact, then I guess it does. It's just probably not
3 the best system to use.

4 In terms of the others, obviously, the
5 Hershberger, the animals are castrated so in...in
6 terms of telling you from the point of view of
7 potentiating androgen action, and maybe it comes up
8 into...into the next one more so.

9 Pubertal male, that should...that should
10 give you some indications of potentiation with respect
11 to preputial separation, and the fish reproduction, I
12 would defer to Dr. Furlow. He's much better acquainted
13 with that system than I am.

14 **DR. HEERINGA:** Dr. Furlow?

15 **DR. FURLOW:** Well, I've seen fish, but I
16 haven't worked with fish, so I...I teach about fish,
17 remarkably even though I don't...I don't work with
18 them.

19 So, again, while not, I think, quite up
20 to the standard of the estrogen ass...estrogenicity
21 assays, androgenicity assays have some value. I would
22 echo the recommendation to get away from the rat
23 ventral prostate cytosol and to get to a recombinant
24 system quickly, because that...again, that would spare
25 animals when I think we...we do need animals for the in

1 vivo tests. If you can get away from them in the
2 beginning, I think that would actually be quite
3 beneficial but also much more reproducible.

4 Transactivation assays, I, again, I
5 think they would help quite a bit, almost more, maybe,
6 for the anti-androgenicity than the androgenicity, in a
7 sense, because the Hershberger assay does appear to be
8 quite robust. Despite having to cut off the tissues I
9 don't get to see very often and...and weighing them,
10 that's the assay. It's remarkably robust.

11 And regarding the secondary sex
12 characteristics in fish, I also think has an impact,
13 quite...quite additive value.

14 The...again, the pubertal male,
15 accelerating puberty, I guess, has more value than
16 delaying it in the sense of general toxicity. You can
17 be a little bit more...a little bit more certain about
18 something being an androgen if it accelerates some of
19 the pubertal endpoints, but, again, that's a...that's a
20 tougher deal.

21 I think in terms of just essentially raw
22 androgenicity, if you will, the binding
23 transactivation, if it can be developed...and I would
24 urge that the Hershberger and the fish have...have good
25 coverage.

1 The question was just brought up about
2 potentiation. I do think that's an issue, and the
3 pubertal male could help you with that or the 15-day
4 male could help you with uncovering hormones that could
5 potentiate the actions of androgen...of androgens.
6 That's something that is becoming much more apparent.
7 Maybe Dr. Lasley can talk a little bit about that, too,
8 but I guess in...well, we'll talk about the pubertal
9 male and the pubertal female in a moment, but I...I
10 think those are a little bit less well validated.

11 So, in general, just for straight
12 androgenicity, I think sticking with the binding and
13 developing transactivation, the Hershberger, and the
14 fish assays are actually quite...quite useful.

15 **DR. HEERINGA:** Okay, at this point, I'd
16 like to open it up to other panel members who'd like to
17 contribute on the androgen...androgenicity. Yes, Dr.
18 Lasley?

19 **DR. LASLEY:** I...I think the
20 transactivational assay for the androgens, particularly
21 for the anti-androgens, is...is not only feasible, I
22 think that we really should talk about it in terms of
23 validation, because there's at least four or five
24 stable transvective cell lines that are in the
25 literature that work, and I think every...everybody

1 appreciates that...that those are on line in a number
2 of labs and...and could be validated and probably will
3 be validated, and that will fill an important niche
4 in...in this area of screening.

5 **DR. HEERINGA:** Dr. Lasley, I would...not
6 to do any advertising, but we will cite...can we cite
7 those examples in our minutes? Dr. Vandenberg, yes.

8 **DR. VANDENBERGH:** Maybe I'll just
9 comment a minute about the male pubertal assay in
10 comparison to the 15-day adult. It does concern me
11 that the only developmental period that we're dealing
12 with in this is puberty. We're not dealing with the
13 intrauterine or the early post-natal, because that's
14 been eliminated by another study, unfortunately.

15 And so, I think it is important to
16 maintain that. The other thing is the 15-day male
17 doesn't tell you about female puberty, and so, you
18 would still have to do the female puberty, and it would
19 seem much more reasonable to, if you're going to study
20 puberty, to study it in two sexes. I mean, both of
21 them need to go through that experience. So, we need
22 to stay with that.

23 **DR. HEERINGA:** Thank you, Dr.
24 Vandenberg. Additional comments on androgenicity?
25 Yes, Dr. Cooke?

1 **DR. COOKE:** In...in response to Dr.
2 Lasley's comment about the different labs, we, in fact,
3 produced one several years ago. Please don't include
4 it in the list. It doesn't work anymore.

5 **DR. HEERINGA:** Obviously, not a self-
6 promoter. Yes, Dr. Brown?

7 **DR. BROWN:** Yeah, I'll speak to that
8 transactivational assay, the in vitro assay, too. I
9 think there's too little appreciation, probably, for
10 the intricacy of handling the rat prostate cytosol
11 preparations.

12 I mean, I think it was partially
13 demonstrated in the validation proc...peer review that
14 was done, but the prostate is nothing but a bag of
15 enzymes, proteolytic enzymes. When you homogenize that
16 tissue and try to make a prep and stable...stabilize
17 the androgen receptor in that prep, you find all kinds
18 of things that can affect it, pH, buffer, temperature
19 specifically...particularly, and a number of other
20 things. It's a very crude preparation, and it really
21 needs to be handled with a lot of care and a lot of
22 knowledge of what the...that the potential problems are
23 in handling it.

24 And I think that led to some of
25 the...the validation issues in...in the peer review, is

1 that, you know, for instance, one of the labs that was
2 commissioned to do this couldn't make a...a viable rat
3 prostate cytosol prep, and other labs, I think, had
4 probably issues in relation to the stability of it, and
5 it's an overnight incubation assay which isn't really a
6 nice, quick assay which you can actually do in these
7 transactivation systems.

8 You can do those relatively quickly, and
9 you can also measure androgen receptor binding in
10 those. You have a lot more control over the system, I
11 think.

12 **DR. HEERINGA:** Thank you, Dr. Brown.
13 Dr. Belcher, want to wrap up or move on to anti-
14 androgenicity?

15 **DR. BELCHER:** I have no further comments
16 on it, so moving on to anti-androgenicity, it is
17 informed on the...the same four assays, the AR binding
18 assay, the Hershberger assay, the pubertal male, and
19 the fish screen.

20 To make a general comment about the
21 binding assays and the transactivational assays, I
22 would recommend that there would be additional effort
23 of integration of the design and development of these
24 lines. There are, in many cases, both for the ER and
25 the AR assays, the ability to use similar initial cell

1 lines and to be swapping out using a standardized sort
2 of...of cell lines, and if there could be future
3 consideration and thought put into designing that, it
4 may streamline the ability to look at different
5 configurations and different variants of these
6 receptors for...for the future.

7 The...in the anti-androgenicity, what
8 has been brought up previously is there is a little bit
9 of weakness because of, for example, looking in the
10 pubertal male assay, looking at delays of puberty, and
11 in the fish screen, the attenuation of male secondary
12 characteristics was identified as being a rather weak
13 endpoint, so there is some loss of the ability to
14 detect effects relative to the...the androgenicity
15 battery as a...as a whole.

16 **DR. HEERINGA:** Dr. Denver?

17 **DR. DENVER:** So, the same issues hold
18 here regarding the andro...anti-estrogenicity assays,
19 that is, the ability to identify antagonists, and that
20 is a weakness in the...the overall panel of assays that
21 we have.

22 So, the only thing I would add is to
23 advocate for developing the AR transactivation assay's
24 potential to screen better for antagonists.

25 Currently, I guess the...the best...the

1 best that we have is the...the AR binding where
2 something is binding to the AR, because that could
3 potentially be an antagonist. So, if that were then to
4 move on to a transactivation assay, that might help to
5 clarify that.

6 **DR. HEERINGA:** Dr. Delclos?

7 **DR. DELCLOS:** Well, I think this
8 endpoint is covered a little better in the anti-
9 estrogen series. I think the Hershberger is a very
10 sensitive and effective measure, together with the
11 androgen receptor binding and...and transactivation
12 assay that's added eventually.

13 And also, there seems to be coverage
14 with the pubertal male as well. So, I think this
15 endpoint is...is better covered than the anti-
16 estrogens.

17 **DR. HEERINGA:** Dr. Cooke?

18 **DR. COOKE:** Yeah, I haven't anything to
19 add to it at this point.

20 **DR. HEERINGA:** Dr. Furlow?

21 **DR. FURLOW:** I would tag...echo again
22 the transactivation assay being extremely useful for
23 anti-androgenicity, and the use of the Hershberger for
24 anti-androgenicity appears to have merit and,
25 therefore, you know, the uterotrophic assay could be

1 used the same way for anti-estrogens.

2 Delays in the onset of puberty, et
3 cetera, again, we'll...I will talk more about that in
4 the HPG axis, I think, but as a...as a pure assay
5 independently of other assays of anti-androgenicity, I
6 don't think it has great value, but I think it's
7 important to look at.

8 Other than that, I...I don't have
9 further questions...further comments.

10 **DR. HEERINGA:** Additional comments from
11 panel members on the anti-androgenicity? Dr. Lasley?

12 **DR. LASLEY:** Parading the
13 transactivation assays as much as we are, I think it
14 needs to be pointed out that although there are several
15 in the literature, they're all slightly different in
16 their format, and...and I think we...we have to be
17 aware that these differences lead to performance
18 differences, and before we jump on the train, I think
19 we need to make sure we're headed to the right station
20 in terms of which format we're going to choose, and
21 this is something that, I think, needs to be considered
22 early in the development and validation of these.

23 **DR. HEERINGA:** Maybe just to stimulate a
24 little further discussion, with regard to both
25 androgenicity and anti-androgenicity, several people,

1 Dr. Vandenberg's touched on the pubertal assays and
2 their potential role there. We touched on the fish
3 assay with regard to androgenicity. Is there a little
4 more discussion about the pubertal assays with regard
5 to the anti-androgenicity mode of action or the fish
6 assay? Something that you'd like to defer?

7 **DR. FURLOW:** I guess I would ask Dr.
8 Vandenberg about that, I mean, maybe...maybe in a
9 greater discussion about the pubertal assay versus the
10 adult male assay. So, in terms of anti-androgenicity,
11 the 15-day male would tell you general things about how
12 androgens are working, but if it...if it is true that
13 the pubertal male, that...that period, pubertal period,
14 is, in fact, more sensitive, then that is something we
15 ought to...we ought to consider, and maybe as part of
16 the limitations, et cetera, talk about whether or not
17 the specificity is...is there.

18 But I guess...I guess related to that,
19 something we didn't talk about in the estrogen assays
20 as well...and maybe Dr. Vandenberg can have some
21 particular input on this...would be, say, behavioral
22 endpoints, so organizational versus activational
23 effects of...of estrogens or androgens. And these are
24 not at all addressed in any of the assays.

25 And so, either in utero or peripubertal

1 exposure to these...to these hormones and maybe
2 behavior effects is...could be something that they
3 ought...that the EPA ought to consider. Maybe you can
4 address that one.

5 **DR. VANDENBERGH:** Let me address the
6 behavioral aspect first. I didn't bring it up,
7 although I have talked to people at the EPA about it,
8 because there are behavioral measures that are quite
9 reliable. Lordosis in the rat, for example, is an
10 excellent...is well worked out, and...but we're not
11 here to add more procedures to the program. So, that's
12 something that could be considered in the future.

13 The other thing about the behavioral is
14 that they're truly an apical test, because behavior
15 summarizes a whole lot of things that occurred before
16 that time, and so, you can detect differences. The
17 hard part is identifying which of those variables that
18 we know affect behavior is the one that's important
19 here, and you can control for those, but it's
20 difficult. So, I didn't go into the behavior aspects.

21 Your other point about organizational
22 versus activational effect is absolutely right. I
23 don't see anything in here that really deals with the
24 organizational at all. It's almost all activational.

25 That's why I said the only developmental

1 aspect that we have at hand here is the puberty, and we
2 don't think of puberty so much or that period of
3 puberty as being the time when act...when
4 organizational events occur. It's usually much
5 earlier, often in utero.

6 But there is evidence that, I think,
7 there are differences in the response of the animals to
8 testosterone when they're pre and early puberty than
9 they are when they're old and gray like...like I am.
10 So, there are changes over time, and that's why I think
11 it's essential to keep at least some semblance of a
12 developmental inquiry in this battery of tests.

13 **DR. HEERINGA:** And the role of the fish
14 reproductive screen? Maybe Dr. Furlow can pick it up.

15 **DR. FURLOW:** That's fine, and he should.
16 So, the...most of that's focused on the...on the
17 secondary sexual characteristics, and I think...I think
18 there is some value. I think, like the estrogen
19 assays, though, if you have...it might be a cleaner
20 system in some sense if we decide on how we want to do
21 a transactivation assay and then titrate in inhibitors.
22 The same principles, perhaps, ought to be employed in
23 the fish or the Hershberger assays, and I think they
24 are complimentary if you have either a pre-pubertal
25 fish and add androgen and then take it away. I think

1 this may be a more controllable system to try to
2 understand anti-androgens, say, than just taking the
3 intact animal and then titrating and hoping something
4 happens.

5 And...and so, that's...that's the idea
6 with the Hershberger, is that you have a castrate
7 system, and then you put in a little androgen and then
8 try to...try to inhibit its action. That same
9 principle, either in a...in a...in a mature fish or
10 even a castrate fish might...might...might be useful as
11 well.

12 Thank you.

13 **DR. HEERINGA:** Additional contributions
14 on androgenicity or anti-androgenicity? Dr. Brown?

15 **DR. BROWN:** I'd just like to make a
16 comment on the...on the assays of the hormones
17 themselves with measuring testosterone, estradiol, LH,
18 FSH, that are incorporated into some of these assays.
19 I think this is really not necessarily a trivial
20 matter, either.

21 I know we broached the subject yesterday
22 of, you know, whether there should be a...a
23 standardized lab that would conduct these tests or not,
24 and, you know, obviously, that's not what you want to
25 do, is condone, you know, a commercial lab to...to do

1 all these tests, but I think there's been a lot of
2 discussion in the literature lately that all these kits
3 that measure these...these various hormones are not
4 created equal, and you've got a lot of variability
5 depending upon which kit you use and, particularly, I
6 think, in terms of the sensitivity of some of
7 these...these kits in actually detecting the hormones.

8 And then, the other matter is, you know,
9 measuring these hormones at a very distinct time of day
10 under very controlled conditions, because stress adds a
11 lot of influence to the...to these hormones in vivo.

12 In addition, they...they vary over
13 the...over the diurnal variation of...of the daytime so
14 that it's...it's critical to really make the
15 measurement of these very much a standardized condition
16 for the collection of the blood, it's processing, and
17 then also in...in relation to the acts...actual assays
18 that are used to...to perform the measurements.

19 **DR. HEERINGA:** Dr. Zoeller?

20 **DR. ZOELLER:** So, to follow up on that a
21 little bit, it seems to me that clinical labs that
22 do...that do radioamino assay or other hormone assays
23 have, for a long time, figured out ways to standardize
24 across labs across the country, and there are...there
25 are a lot of, I think, good ideas or good ways of

1 ensuring that a...a laboratory that's performing a
2 specific radioamino assay or hormone measurement in one
3 contract lab is getting the same answer that another
4 contract lab might get.

5 And these assays have been around for 30
6 or 40 years, and ways of...you've got ways of
7 standardizing results across clinical labs seems fairly
8 well worked out, and those could easily be integrated
9 into this program without compromising principles of
10 making recommendations for specific kinds of assays, et
11 cetera.

12 **DR. HEERINGA:** Maybe I can turn back to
13 Gary Timm and Dr. Touart to see if you have any
14 questions. Is there anything in this...yes, Dr.
15 Touart?

16 **DR. TOUART:** Just on...a clarification
17 just for your information purposes based upon some of
18 the comments Dr. Furlow made in terms of the fish assay
19 and anti-androgen...anti-androgenicity and some of the
20 considerations that are going on in terms of how to
21 improve or better address, if I could call Gary Ankley
22 up and if he can take a little bit of time to talk
23 about some of the efforts and how the assay is being
24 adapted for that.

25 **DR. HEERINGA:** I think that's

1 appropriate at this point.

2 **DR. ANKLEY:** This is a great segue,
3 because I'm doing...a paper I'm just finishing talks
4 very much about an assay along the lines that you
5 describe. Essentially, what you do is you take female
6 fish. We've run trenbolone which is an androgen, quite
7 latinal, so you can induce tubercles in fish, and
8 what you can use...what you can do is block the
9 production of tubercles in the fish by treating them
10 concurrently with anti-androgens.

11 And so far, we've tested vinclozolin and
12 flutamide with Soperton acetate in that system, and
13 it's a very effective way of picking up anti-androgens.

14 Now, it's probably a...a little far off
15 to try to imagine that would be ready for an August
16 time frame, but just to follow on to your suggestion,
17 we do...we are thinking very much along those lines
18 and...and we do have some promising data that...that
19 would enable the fish to...the fish system to actually
20 handle that particular mode of action.

21 **DR. HEERINGA:** Additional? There will
22 be opportunities later, too, but I just want to make
23 sure that as we go through these modes of action
24 systematically, there's a chance for you to make sure
25 that if there's anything that's confusing or needs to

1 be developed...yes?

2 **DR. TIMM:** One point. When we were
3 talking about the transcriptional activation assays and
4 the constructs, when you write your report, if you
5 could give us more detail on the...the types that you
6 think would be most profitable, that would be helpful.

7 **DR. HEERINGA:** We'll definitely do that.

8 So, Dr. Belcher, you want to continue on
9 with steroidogenesis effects?

10 **DR. BELCHER:** Sure, let me go down to
11 steroidogenesis. There are five...five assays that
12 were in the tier, the H295R cell line, the aromatase
13 assay, the pubertal male, pubertal female, and the fish
14 screen.

15 My comments are going to be primarily on
16 the in vitro assays with the H295R assay.

17 There...there really isn't enough
18 information to be able to comment on the utility of
19 this assay, and the endpoints that are being measured,
20 the estradiol and the testosterone content in the cell
21 supernate would be a, actually, a very good assay,
22 although I think premature at this time as...as
23 suggested in the technical document to...to replace the
24 aromatase assay or any of the other steroidogenic type
25 assays.

1 The strength, to me, in the battery does
2 come from the in vivo assays and the abilities to
3 detect, in a general way, the...the influence on
4 steroidogenesis. The aromatase assay is...is a
5 straightforward and validated assay that does have
6 utility in this, and I tend to be rather strong in
7 supporting the inclusion of the aromatase assay through
8 the indirect impact of aromatase on some of the earlier
9 developmental effects that may be occurring through
10 aromatasation that are...aren't really directly
11 addressed by any of the...the sensitive period of not
12 being...having the in utero or the earlier components
13 in there.

14 **DR. HEERINGA:** Dr. Denver?

15 **DR. DENVER:** This mode of action, while
16 important, is...is relatively weak right now in terms
17 of assays that can address it. The...the strongest is
18 the aromatase assay which, admittedly, addresses only
19 one point in the steroidogenic pathway.

20 It...it appears to be well designed
21 and...and could be a robust assay. It cannot account
22 for compounds that will change aromatase expression
23 which is another potential...potentially important mode
24 of action.

25 The H295R cell line based assay is

1 potentially a valuable addition to this in that it
2 could address multiple points in the steroidogenic
3 pathway. However, this has not been peer reviewed, so
4 we can't really evaluate that fully at this time.

5 The in vivo assays, the pubertal and
6 fish assays, although they are potentially capable of
7 picking up disruption of steroidogenesis and could
8 potentially signal this as a mode of action,
9 they...they really cannot define this as a mode of
10 action at this point, and it would be difficult to
11 decipher that type of action in...in those assays.

12 **DR. HEERINGA:** Dr. Delclos?

13 **DR. DELCLOS:** I have nothing much to add
14 to the previous comment except to say that on the last
15 point that in the technical review document, there's a
16 lot of focus on the use of the cell line data, the,
17 that's undergoing validation in interpreting the
18 changes in the in vivo responses as far as their effect
19 on the HPG axis for steroidogeneis, but I think that it
20 really may not be that easy because of the lack of
21 metabolic capability of that cell line. And so, that's
22 just something to keep in mind.

23 **DR. HEERINGA:** Dr. Cooke?

24 **DR. COOKE:** Yeah, I have a...a few
25 things. I was sort of glad to see that the minced

1 testis idea was being put aside, because I can attest
2 to the variability of that, but then, that does leave
3 us with the...the cells and the recombinant aromatase.

4 One of the criticisms of using the
5 recombinant aromatase was that you couldn't see
6 potentiation in terms of expression which was already
7 mentioned, but presumably, it could pick up any other
8 steroid activation of the enzyme activity, and I...I
9 haven't come across a chemical that...environmental
10 chemical that does that, but I presume it would. And,
11 obviously, it would be good for inhibition.

12 To look at the...the cells, I have
13 questions. I don't really have comments; I have
14 questions. I'm presuming that the cells, according to
15 the...the literature I read, are very happily producing
16 testosterone and estradiol, and then, in fact, the
17 suggestion to use the cells as an aromatase assay
18 substitute would be a possibility. I...I'd like to see
19 that developed a lot more, because how...how efficient
20 is the steroidogenic process in those cells in
21 comparison to a normal aromatase activation...activity?

22 The...the other question...maybe two
23 other questions relating to the cells. One, I
24 don't...I don't see any mention of 5-alpha reductase
25 which is a quite important enzyme, and I don't see

1 how...how the cells, if they have 5-alpha reductase,
2 could then be used as an aromatase assay, because you
3 would have two draws on the...on the testosterone and
4 the estradiol in the precursor.

5 The...the...the other two comments that
6 I have are related to the comment that the...the cells
7 would be good, because then you could look at the
8 transcription of the steroidogenic enzymes. So, my
9 question there is when you're doing the validation or
10 the peer review, one of the questions they asked was
11 are the enzymes in these cells regulated by
12 steroidogenic factor 1, because that would be sort of
13 the normal process that would regulate the
14 transcription of those enzymes?

15 And then, on the other side, some of the
16 criticisms of the assay, some of the assays were that
17 they would not detect chemicals that promote the
18 degradation of the proteins, and I would imagine that
19 the cells, you would be able to, at least at the
20 expression, although maybe at the Midwestern blocks,
21 find whether the...the effect on the steroidogenic
22 pathway was at the level of protein degradation.

23 And my last comment refers...and I would
24 defer to the fish experts on this...is that the
25 androgens in the fish, as I understand it, are 11-keto

1 derivatives. They're not the same androgens as would
2 be found in a human or a rat.

3 And so, from the point of view of using
4 the fish assay as a mechanism...mode of action leading
5 to this chemical affects steroidogenesis, I'd...I'd
6 like to get some feedback on how...how you would
7 determine that in relation to the rodent or the human
8 mode of steroidogenesis when the...the active androgen
9 is not testosterone or dihydrotestosterone.

10 Thank you.

11 **DR. HEERINGA:** Thank you, Dr. Cooke.

12 Yes, okay, let's do that. Dr. Ankley, please, and then
13 we'll...Dr. Ankley and Dr. Furlow after that.

14 **DR. ANKLEY:** It's correct that in the
15 fish, the...an active androgen is 11-ketotestosterone
16 which is derived from testosterone, but up...up to that
17 point in the steroidogenic cascade, all biosynthetic
18 enzymes are the same. In fact, both males and females,
19 have fairly...fairly high level of testosterone, and
20 what you see in males is a...a correlation between
21 testosterone and ketotestosterone.

22 The ketotestosterone is only found in
23 the males, not in the females, and the biosynthetic
24 pathway in the female fish is exactly the same as other
25 vertebrates. So, really, what you have is an

1 additional biosynthetic step where before that, it's
2 essentially the same set of enzymes.

3 **DR. HEERINGA:** Dr. Furlow? Thank you,
4 Dr. Ankley.

5 **DR. FURLOW:** So, before Dr. Ankley gets
6 away too far, so how...I guess one question to follow
7 up, if I may.

8 **DR. HEERINGA:** Sure.

9 **DR. FURLOW:** How low is the enzyme
10 between the 11-ketotestosterone? It's a liase or it's
11 a blood or whatever it is, and how well is that
12 characterized in terms of inhibitor spectra and that
13 sort of thing? I mean, has anybody...are there...are
14 there known inhibitors of that testosterone, 11-keto
15 conversion?

16 **DR. ANKLEY:** We haven't found any in our
17 studies. What we have seen consistently, both in
18 control fish and in fish that have been treated with
19 all the sort of chemicals we've used to characterize
20 the system, is this continued correlation between T and
21 KT. The actual KT levels, abs...on an absolute basis,
22 are higher than T about four-fold, but the results seem
23 to be correlated.

24 So, we haven't found a specific
25 inhibitor. That's not to say that they wouldn't exist,

1 and so, what we have been doing in the assay is

2 measuring both T and KT in the plasma of the fish.

3 It would be very interesting to find an
4 inhibitor, but we haven't see it yet.

5 **DR. FURLOW:** Okay. All right.

6 **DR. HEERINGA:** Dr. Kullman?

7 **DR. KULLMAN:** I think you probably know
8 this, is the...the potency of the 11-keto versus the
9 testosterone would be AR.

10 **DR. ANKLEY:** The relative binding
11 affinity?

12 **DR. KULLMAN:** Right.

13 **DR. ANKLEY:** They're actually pretty
14 similar. In fact, that's why one of the...I...I don't
15 want to get too far afield, but it's been quite a
16 challenge in the area of fish endocrinology to try to
17 sort out exactly how KT works, what it's key roles are,
18 partly because you have both androgens there at the
19 same time, and they both have affinity to the receptor.
20 There doesn't appear to be a KT receptor. It appears
21 to be a common androgen receptor.

22 **DR. HEERINGA:** Thank you, Dr. Ankley.
23 Dr. Furlow, your general comments on the
24 steroidogenesis?

25 **DR. FURLOW:** Okay. So, just in...in

1 general, then, yeah, I...I agree that the...the steps
2 in the fish, the steps up to 11-keto are identical, and
3 they...and...so, the effects of ketoconazole, et
4 cetera, should be...should be expected. There may be
5 something that...that comes up, and that would be of
6 great interest to the field if there was, in fact, an
7 11-keto inhibitor.

8 Just to actually, then, in terms of
9 steroidogenesis and the effects of potential endocrine
10 disrupting chemicals on that, to echo Dr. Brown's
11 comments on standardized tests, I mean, you know,
12 standardized radioamino assays or ELIZAs, I mean, these
13 really have to be reproducible, reliable, and if...and
14 if I was...you know, if you can't, do what I said which
15 is do it yourselves or...or have one designated
16 contract lab that...I still want to echo Dr. Brown's
17 point. That has to be very tightly controlled so we
18 can...we can make some...some kind of guess about what
19 might be going on if you do see an effect.

20 Otherwise, in terms of the
21 appropriate....the appropriatess...appropriateness of
22 the assays, et cetera, I'll defer to Dr. Cooke's
23 comments on that.

24 **DR. HEERINGA:** Comments from other
25 members of the panel on steroidogenesis mode of action?

(No response.)

DR. HEERINGA: Before we move on to the endocrine pathways, Gary or...you're okay? Again, we can revisit this again if questions do come to mind.

Dr. Belcher?

DR. BELCHER: Next mode of action is interference with the hypothalamic-pituitary-gonadal system, and that's covered by the pubertal male, pubertal female, and the fish screen. I am going to defer my comments to my colleagues at this point because of being a little bit further afield from my area of expertise.

DR. HEERINGA: We'll turn to Dr. Denver.

DR. DENVER: And I'm going...I'm going to make, really, just a few general comments.

I think that, together, these assays have...have the ability to identify disruption of the HPG axis. Individually, they have weaknesses. For example, there are concerns about quality control, repeatability among laboratories, you know, time...timing of puberty, things like that that...that could...could represent some real concerns in terms of evaluating the data.

The in vivo assays suffer from issues of specificity, and that's been raised a number of times.

1 However, I recognize that such apical endpoints are
2 really necessary to identify compounds that can disrupt
3 hormone-dependent processes such as reproduction and
4 growth.

5 The challenge is going to be to
6 understand the modes of action and to distinguish
7 endocrine modes of action from general reproductive
8 toxicity which, presumably, is going to be addressed
9 further in the Tier 2 assays, but I think that's going
10 to be the real difficulty at this level at these apical
11 endpoints.

12 **DR. HEERINGA:** Dr. Delclos?

13 **DR. DELCLOS:** I think that the EPA has
14 made a strong case with their experience over the years
15 that these assays in term...to detect effects on the
16 HPG axis, and, again, there is the problem of
17 specificity which was mentioned by the last commenter.

18 I think that there...there were some
19 problems with validation studies with transferability
20 between labs, differences in endpoints, but the...the
21 conclusions came out to be the same even though there
22 were...there were some differences, and...and the
23 validation issue that I asked about earlier is...is
24 still a concern to me, but that's really, I think, out
25 of our...our purview and up to the EPA to make a

1 decision on that.

2 **DR. HEERINGA:** Dr. Cooke?

3 **DR. COOKE:** Yes, thank you. I just have
4 a...a couple of small comments to make.

5 The...the aspect of steroidogenesis
6 should...should also give you some indication as to
7 whether your chemical of interest is likely to affect
8 the HPG axis. If you...if you know what inhibitor of
9 androgen production or estrogen production, then
10 you...you've got a good...you've got a likely candidate
11 for affecting feedback loops and things like that. So,
12 in...interpretation of the steroidogenic data could
13 help you with that.

14 The other thing re...refers to
15 the...getting back to the question of whether you're
16 going to get a yes or no answer regarding the
17 production of hormones in gametes, and the pubertal
18 assay seems to be...both pubertal assays seem to be the
19 more contentious assays around the room, if I could say
20 that.

21 So, because they're pubertal, you...you
22 don't have the...the gamete question answered to...to
23 the maximum, because while you're measuring vaginal
24 opening and...and preputial separation and you can
25 measure the hormones, admittedly at a single time point

probably, the...the gamete question, I don't...I don't see that being answered as best as it could.

DR. HEERINGA: Dr. Furlow?

DR. FURLOW: So, I guess my comments, again, are more general, and...and, actually, my comments on...on these assays are...are clearly more relevant to the second charge question in terms of are they...are they appropriate, are they sensitive enough, et cetera.

Do...do these assays detect changes in the HPG axis? Clearly, they can. Right? So, I think that's...that's clear.

How they do it is...is another story, and whether they're endocrine related or not is another story, and whether or not that's the purview of this...of this screen is something that...that we should...we should take up. I...I personally believe that if something is, in fact, active in the HPG axis that isn't specifically endocrine related, that that is important, however. Right?

If reproductive tox..toxicity is something that the EPA ought to be concerned about, then regardless if we know exactly how it works, if we know exactly it's inhibiting trnH release or...or changing sensitivity at the...at the pituitary, et

1 cetera. So, that's my...that's one general comment.

2 So, the other...well, and that relates
3 to the question of not having a negative control in
4 the...in the pubertal female assay. I mean, it
5 certainly doesn't look good. Right? So, it certainly
6 doesn't give...give one confidence that the assay can
7 be specific enough.

8 But, again, I actually do tend to agree
9 with what was presented this morning, that that...that
10 may not be a terrible thing, that that may, in fact,
11 have some utility. It just may not specifically tell
12 us what...what hormones may be...may be being affected.

13 The other...the other issue was if, of
14 course, they stood alone, they wouldn't be completely
15 satisfactory, and I point again to the BPA issue, that
16 it would not necessarily have been scored as an
17 endocrine disrupting chemical in the pubertal female
18 assay, and that may be strain dependent. That may be
19 just how it works in that particular assay. I don't
20 know, but...but as a...as part of a battery, it may
21 have utility, but, of course...and we're not
22 considering it by itself.

23 Whether or not, again, we need them
24 relative...the relative utility versus the 15-day male
25 assay, I think, we'll take up again.

1 The issue...I guess I'm unclear as to
2 whether or not statistics can really help you in terms
3 of body weights and tissue weights and if they're
4 endocrine related or not. That, to me, isn't
5 convincing, and I think the fact that drops in body
6 weights can, then, affect the HPG axis, that...that's
7 even a more general toxicity that...that...that you'll
8 have to...you'll have to resolve.

9 I...I guess I don't...maybe some of the
10 statisticians can weigh in on that. I don't...I don't
11 know if the al...these alternative statistical methods
12 are appropriate and can be used to sort out what might
13 be going on there.

14 And then, finally, I guess I would urge,
15 although alcohol does seem to be negative in the 15-day
16 assay, maybe you ought to run that through the...the
17 pubertal assays and see if that gives a negative
18 result, and I think that would strengthen EPA's
19 position that these are, in fact, useful assays for
20 determining effects in the HPG axis.

21 In addition, I guess I also agree with
22 Dr. Vandenberg's comments earlier. I mean, we...we
23 don't have an assay other than the...the metamorphosis
24 assay that deals with earlier development, a
25 particularly sensitive developmental time point, since

1 the inter...intrauterine to lactational is out.

2 And so, despite a lot of the concerns
3 about the sensitivity and specificity of the HPG or the
4 pubertal assays which are...which are really mostly
5 what are being used to test effects in the HPG axis, I
6 guess my...my major comment is that if they could be
7 tightened up, if they could be made more specific,
8 maybe not use weights, per se, as the assay but...but
9 have very tight...the vaginal opening and the PPS looks
10 okay, to use those rather than the weights and to have
11 a negative control, that these things would make me
12 feel a lot better, and I think...I think they are
13 important to include, actually, in...in a battery. We
14 shouldn't just throw the baby out with the...with the
15 bath water in that sense.

16 **DR. HEERINGA:** Other general comments on
17 the HPG pathway and the effectiveness of this test
18 battery to...

19 **DR. VANDENBERGH:** Right, I...I agree
20 with Dr. Furlow's comments about a better negative
21 substance to test. I think that...that would be very
22 useful.

23 I had one brief clarification from Dr.
24 Cooke about that the puberty assays don't answer the
25 gamete question, and I think that's true. They don't,

1 because they...they're not being measured.

2 I think I, from what I hear from the
3 EPA, this would be done in a second tier where you do
4 multi-gen rather than in the first tier, because to add
5 that to the first tier would make it a second tier.
6 Right?

7 **DR. HEERINGA:** I think maybe between Dr.
8 Portier and I, we can touch on the statistical
9 question, I think, on the body weight versus organ
10 weight relationships. Essentially, that winds up being
11 a calibration problem in the design.

12 In some ways, if you were to design
13 this, you would integrate...you'd essentially integrate
14 the diet restriction component as an arm of the study
15 and sort of capture interlaboratory and interexperiment
16 variability, but you're...you're really throwing in
17 another comparison group, and I can't do the numbers in
18 my head, but I can tell you that if that is going to be
19 a requirement to...to utilize this to determine
20 effects, I think power considerations, now that you've
21 got this calibration, even if it's brought in
22 externally, it has variability. I think it's going to
23 drive up...it's essentially going to drive up the
24 number of subjects per arm in this particular assay.
25 And so, I think that'll...that'll be a critical issue.

1 I know the people in ORD could certainly
2 look at that issue for you and try to assess just how
3 much that would affect, but you clearly will have to
4 take, I think, what would amount to, if there is that
5 calibration step, to determine effect in the presence
6 of body weight reduction, I think you're going to have
7 to be looking at increased size for each of these
8 assays in terms of numbers of animals per dose, and I
9 guess that's something we've been trying to avoid, but
10 it's, I think, statistically, that's the general
11 implication as I see it.

12 Dr. Portier, weigh in, too.

13 **DR. PORTIER:** I'm not often hesitant to
14 jump in on these things, but I guess what I'm
15 hesitating about is that from what I'm hearing, body
16 weight is both a covariant and a response at the same
17 time, and that's what...I hesitate to think about it
18 that way, because you're basically saying the effect of
19 the drug...the chemical might be to decrease body
20 weight at the same time affecting the HPG axis.

21 So, is body weight being affected
22 because HPG, or is HPG being affected because body
23 weight? And I don't think you have the data to pull
24 those two out.

25 So, adjusting for body weight may

1 actually weaken the strength of the test to determine
2 HPG effects. I'm going to have to think more about
3 this over lunch, but I...I think it's not a
4 straightforward answer. It's not a just simple kind of
5 thing because of that tight multi-connection that's
6 going on here.

7 **DR. HEERINGA:** I think because of that,
8 essentially, you're not sure whether this variable's on
9 the right or the left-hand side of the equation. I
10 think that introduces this uncertainty.

11 And I think my point that whatever
12 happens is going to drive up the demands on the data in
13 terms of sample sizes to either calibrate or to
14 untangle this effect. So, we can work a little bit
15 more on this, too, but I think it was an important
16 issue that affects the general nature of what...what
17 this will require for these relationships between body
18 weight and organ weight that we saw demonstrated, in
19 fact.

20 Additional comments on the HPG axis?
21 (No response.)

22 **DR. HEERINGA:** Dr. Belcher, if we could,
23 turn to the HPT axis.

24 **DR. BELCHER:** Yes, turn to the HPT axis.
25 The pubertal male, pubertal female, and the amphibian

1 metamorphosis assay are all informative on these
2 points.

3 Generally, my comments will be limited
4 to there is a strong reliance on the amphibian
5 metamorphosis assay for integrating these components.
6 That leaves this component with some weakness in the
7 reliance, that it is relying on this one assay, and
8 there's some concern with the actual portability of
9 transfer of this assay to...to the...to the general
10 spectrum of investigation.

11 **DR. HEERINGA:** Dr. Denver?

12 **DR. DENVER:** So, it appears that the
13 only assay that was specifically designed to address
14 thyroid is amphibian metamorphosis and that, you know,
15 addition of thyroid measures in the rat pubertal assay
16 is...is sort of an add on.

17 These assays have the least, in my
18 opinion, have the least power in addressing specific
19 modes of action, and that's due, in part, to the...the
20 limitations that we have in the number of assays that
21 are addressing this question. In the...the pubertal
22 assay, the major measurements are serum thyroid hormone
23 levels, TSH, and thyroid histology, and, you know, it
24 was pointed out yesterday that there is...there is
25 perhaps overlap or redundancy.

1 I wouldn't use the term redundancy in,
2 you know, looking at thyroid dysfunction between the
3 amphibian metamorphosis and the pubertal assay, but,
4 really, the only overlap there is at the level of
5 thyroid histology which is really only one measure of
6 thyroid axis function and would indicate, you know,
7 perhaps a...perhaps a direct action on the thyroid,
8 perhaps disruption of thyroid hormone synthesis.

9 There's a well known syndrome in humans.
10 It's called sick thyroid syndrome that results in...you
11 know, it's...it's associated with non-thyroidal illness
12 that results in changes in...in measures of thyroid
13 function, and virtually every human illness results
14 in...in some as...some changes to the thyroid system.

15 And it was pointed out yesterday that
16 many of these compounds did, in fact, lower plasma T4.
17 And so, without other assays to really look at mode of
18 action, one concern is that you find lowered plasma R4
19 in many, many instances that are not directly related
20 to disruption of thyroid function per se.

21 Another issue is, you know, when you get
22 a lowering of plasma T4, you've got a change in THS,
23 you know, what is the nature of that compound that is
24 causing that...that change? And that's something that
25 can't really be addressed from these assays.

1 One of the best known and best
2 characterized mode...modes of action in thyroid
3 disruption is the disruption of binding to serum
4 transthyretin and, also, clearance of thyroid hormones,
5 and that's not addressed at all in this assay. In
6 fact, you know, in...in terms of going forward and
7 developing other tests for modes of action, looking at
8 binding to transthyretin, looking at thyroid hormone
9 clearance, gluteoronidation, sulfation, things like
10 that would be obvious points to...to...to follow up on.

11 In terms of the only assay that was
12 developed to specifically look at thyroid function, the
13 amphibian metamorphosis assay, that is the only assay
14 that specifically addresses compounds that act as
15 thyroid hormone mimics, that is, thyroid compounds that
16 would accelerate metamorphosis perhaps.

17 So, that...that is a deficiency in the
18 screen, that there...there's...there's a real
19 limitation in being able to...to address the...the
20 diversity of modes of action that are possible in
21 disruption of the thyroid axis.

22 The amphibian metamorphosis assay is
23 generally the only assay. It's actually...it's a
24 fairly good assay for addressing thyroid mimetics. I
25 think, given that, you know, the tadpoles depend, you

1 know, entirely on thyroid hormone for metamorphosis and
2 it's well known that thyroid hormone will cause
3 metamorphic changes, there are also limitations in that
4 assay in that being able to distinguish acceleration of
5 metamorphosis by scoring some of the endpoints, for
6 example, to focus on hind limb development as opposed
7 to other measures of...of...of metamorphosis.

8 Staging can be complicated among
9 laboratories, so transferring the...the assay among
10 laboratories could be a challenge, as was mentioned
11 earlier.

12 The most sensitive part of that assay is
13 the thyroid histology, as was pointed out in the peer
14 review, and, you know, that can detect very low dose
15 effects of glutrogenic compounds on the thyroid, but
16 it, you know, it's remarkable that those effects were
17 not seen at the higher levels, the apical endpoints.

18 And, really, what that...what that
19 indicates is just the biol...the underlying biology
20 which is that you really just need very little thyroid
21 hormone to move this process forward. And so, in order
22 to use it as some....as a screen for compounds that
23 would decrease thyroid activity, you really do
24 need...need to rely on the...the endpoint which is the
25 thyroid histology.

1 So...so, I think it's fairly strong as
2 a...an assay for thyroid mimetic in terms of looking at
3 the apical endpoints. It's fairly strong as a...an
4 assay for disruption of the thyroid axis and its
5 inhibition if one looks at the thyroid histology.

6 The other point that was made is it
7 could potentially signal disruption of diiodinases
8 through asynchronous development, and this may be true.
9 However, this could...so, this is based largely on the
10 studies with IOP, iopanoic acid.

11 Now, there are three different
12 diiodinases that come into play during metamorphosis,
13 potentially three, at least two, that can convert
14 thyroid hormones to an active form or inactivate it,
15 and so, using asynchronous development could be an
16 indication of disruption of diiodinase or something
17 else. So, at this point, I'm not convinced that that
18 is going to be an definitive test for disruption of
19 thyroid function.

20 But, you know, as I said, it's the only
21 assay in the screen that is directed specifically at a
22 thyroid hormone act...thyroid hormone action.

23 **DR. HEERINGA:** Thank you, Dr. Denver.
24 Dr. Delclos?

25 **DR. DELCLOS:** I have nothing to add on

1 this.

2 **DR. HEERINGA:** Dr. Cooke?

3 **DR. COOKE:** I don't really have much to
4 add except because it is the only one and it should
5 give you a yes or no answer to...to your question, it's
6 sort of a fait accompli, you know, at this present
7 time, but from the point of view of developing other
8 assays that could detect thyroid interference, like an
9 in vitro test, histocyto, those sort of things, thyroid
10 effects on Sertoli cell number in the testis, just that
11 are ideas, but other than that, I don't have anything
12 to add to Dr. Denver's points.

13 **DR. HEERINGA:** Dr. Furlow?

14 **DR. FURLOW:** So, there were comments
15 yesterday about, say, redundancy and that the amphibian
16 metamorphosis assay, what it gives you is covered in
17 the pubertal assays, and I do disagree with that.

18 The metamorphosis assay, as Dr. Denver
19 said is...and Dr. Zoeller actually mentioned
20 yesterday...is the only one that can look at disruption
21 of thyroid hormone in peripheral tissues, and
22 everything else, both the pubertal and then even a
23 central aspect of the metamorphosis assay, really has
24 looked at thyroid...has really focused on thyroid
25 histology. And then, at least in the pubertals, is TSH

1 and T4 levels but not...but not directly at action.

2 And because metamorphosis is
3 such...is...is...is completely dependent on thyroid
4 hormone for progression and the assay is started before
5 there are circulating thyroid hormones in the animal
6 but there are already expressed thyroid hormone
7 receptors, it is, in fact, an assay for looking at
8 thyroid mimetic compounds and has been...has been very
9 useful for that.

10 You know, that said, but it...that said,
11 with that background, it puts quite a lot of pressure,
12 actually, on the amphibian metamorphosis assay then,
13 because, you know, I look at iopanoic acid, and,
14 really, there wasn't a good response in the pubertals.
15 Right? There was only a response in the metamorphosis
16 assay.

17 Now, to me, who really likes and loves
18 dearly metamorphosis, I wonder if things that are
19 weakly active in the metamorphosis assay but not at all
20 active in the pubertal assays, whether or not that
21 would trigger your weight of evidence response. I
22 mean, that's something that...that...that can be
23 addressed, because, again, there's...there's nothing in
24 the pubertals that addresses action at all or, in fact,
25 the...the activity of the diiodinases per se.

1 So, I think, for the future...I don't
2 think this will happen before August, but I think for
3 the future, it would be incredibly desirable to have
4 both binding assays for thyroid hormone receptors. I
5 know in the EPA's analysis, there was no evidence for
6 direct binding, but, in fact, there is, and Dr. Zoeller
7 and I can...can provide references on that and enter
8 them into the record. So, there is evidence for direct
9 binding of...of various compounds with the thyroid
10 hormone receptors.

11 A. ...a transactivation assay would also be
12 extremely useful, both for agonists and antagonists.

13 And there are other improvements to the...to
14 the metamorphosis assay that I...that I will actually
15 wait until we discuss the limitations and...and
16 improvements in...in the next...the next part of this.

17 So, again, in the absence of any other assay
18 to detect peripheral effects, I think you have to
19 include the metamorphosis assay, and I have to say I'm
20 actually quite impressed at the, at least within,
21 within lab, progression through metamorphosis. I think
22 that the labs in Duluth and in Germany that...that
23 really put, to...to my knowledge, the lion's share
24 of...of work into developing this assay really are to
25 be commended, because before they got started, we were

1 all over the board in terms of trying to have
2 reproducible progression through metamorphosis as...as
3 a...as an endpoint.

4 And so, so that part of it is...I think
5 should be particularly noted.

6 Finally, just some general comments. It's
7 the only amphibian assay, and I think the EPA is to
8 be...is to be commended on including amphibians in...in
9 their assays. And it is now, without the intrauterine
10 to lactation assay, the only one that looks as
11 development, as has been noted, at least morphological
12 development or...or development through organogenesis,
13 and I think that is, in fact, extremely important, an
14 underappreciated aspect of the endocrine system.

15 There are limitations in terms of interlab
16 variability, practicality, these things, cost, length
17 of time. These things have been brought up, and...and
18 we will...I think we will revisit many of them.

19 There...I think there can be some
20 improvements to the assay, and I will...I will address
21 those then, but...but I think that just relying on the
22 pubertals for effects on...on thyroid hormone system in
23 general is...is clearly not sufficient. If there are
24 ways of really improving the metamorphosis assay
25 and...and allow it to achieve its full potential, I

1 would...I would certainly strongly...strongly encourage
2 that.

3 **DR. HEERINGA:** Comments from other
4 members of the panel on the HPT axis? Yes, Dr.
5 Zoeller, please.

6 **DR. ZOELLER:** Just one small comment is
7 that there are known instances where gender differences
8 in metabolism of compounds can greatly influence the
9 ability of those compounds to impact the thyroid
10 system. So, if you were to replace the pubertals with
11 a different assay or get rid of one of the pubertals,
12 you would really miss chemicals or potentially miss
13 chemicals that...in which there are...there are
14 significant gender differences in metabolism.

15 **DR. HEERINGA:** Turn to Gary Timm and Dr.
16 Touart to see if there's any questions of
17 clarification.

18 **DR. TOUART:** This is Dr. Touart, and
19 it's not necessarily a question, more of a comment back
20 on...on some of the points that Dr. Furlow had raised,
21 and this goes back to some earlier, you know, points in
22 terms of the context of HPG or even HPT axes, you know,
23 being affected and the...the generalized nature or
24 these non...non-specific context that that
25 would...would have and whether we should get concerned

1 about that or not.

2 And I think that, in general, the
3 endocrine systems, it is built on...on homeostasis and
4 whether we have a disruption on homeostatis or, you
5 know, just a compound that overwhelms, the ability of
6 the...of the endocrine system to compensate, and these
7 would be of concern, so that's the perspective that
8 they would be, you know, utilized in determining, you
9 know, the nature of an effect.

10 It wouldn't...wouldn't necessarily move
11 on to, you know, to want to be able to compensate, but
12 I think I would...would urge the in common
13 considerations and...and I think Dr. Furlow alluded
14 that there may be some suggestions in terms of
15 improvements in...in, you know, in particular endpoints
16 or endpoints that could be added that would assist in
17 the specificity, you know.

18 You know, I think the Agency's
19 perspective, you know, the battery overall and part of
20 the strength of the battery is to help us focus on a
21 variety of endpoints that we...that we consider
22 reasonably valid to include and approach, but then the
23 consideration of...of what more we might be able,
24 because as was pointed out, in some things, especially
25 like maybe amphibian metamorphosis, you know, it's

1 maybe weak in terms of...of compounds that are weakly
2 active in terms of how we're going to be able to
3 interpret if that's the only assay or the only endpoint
4 that might have been affected. So, any help in...in
5 trying to buttress or, you know, assist in...in
6 improving that ability to...to resolve as well as to
7 detect and identify would be helpful and appreciated.

8 **DR. HEERINGA:** Comments?

9 (No response.)

10 **DR. HEERINGA:** Okay. What I would...5
11 after 12:00. What I would like to do is I'd like to
12 adjourn for lunch, but we're going to start a little
13 later than we normally would. We'll start again at
14 2:00 p.m., and the reason there is that the group
15 that's responsible for charge question 2 which has some
16 very important issues, I think has...needs a little
17 more time to prepare some explanatory materials and
18 power point. So, we'll provide a little extra time and
19 start again at 2:00 p.m.

20 And, again, Dr. Portier will...will
21 serve as chair when you reconvene. So, see everybody
22 at 2:00 p.m.

23 (**WHEREUPON**, a luncheon recess was taken.)

24 **DR. PORTIER:** Okay, we'll continue with
25 the panel discussion. Sounds like the panel has had a

1 productive lunch. They produced their slides, and
2 they're ready to begin the discussion on the second
3 question. So, I'll have...ask the EPA to go ahead and
4 read the second question.

5 **DR. TOUART:** Jerry, I...this is Les
6 Touart again, and I'll...I'll go ahead and...and read
7 for the record the...the second charge question that
8 we'll be discussing this...this afternoon, and it
9 reads: EPA proposed a Tier 1 screening battery that
10 includes many assays that are complimentary in nature
11 and that coverage of the estrogen, androgen, thyroid
12 hormonal systems. The strengths of one assay offset
13 the limitations of another, albeit by different taxa,
14 life stages, endpoints, exposure, and use of in vitro
15 and in vivo methods executed at different levels of
16 biological organization. Example, cytosolic receptor
17 binding, cell-based assays, whole organisms.

18 The subparts to the question, a) please
19 comment on how well the proposed battery minimizes the
20 potential for false negatives and false positives;

21 **b) are there any unnecessary redundancies for mode of**
22 **actions across the battery; and**

23 c) please comment on whether a different combination of
24 validated assays would be more effective in
25 achieve...achieving the purpose of the battery than

1 that proposed by EPA.

2 **DR. PORTIER:** Dr. Lasley?

3 **DR. LASLEY:** Yes, I'd like to introduce
4 this part of our response with three caveats. First of
5 all, we recognize that the conversation here represents
6 the work that is in progress, and we really now need
7 what is a stop frame on a moving target.

8 And we understand, the second caveat,
9 that some, perhaps many, of these assays will be
10 extended. There will be additional transactivation
11 assays and assays that will see different mechanisms.
12 Clearly, there will be new endocrine disruptors
13 revealed in the near future, and these new endocrine
14 disruptors or...or discovered endocrine disruptors will
15 require additional assays to be developed and
16 validated.

17 Our approach to addressing charge 2 is
18 we're going to divide the work up into three groups,
19 and questions 1 and 2 are going to be answered by way
20 of a grid which is going to allow us to first talk
21 about false positives, false negatives by looking at
22 the redundancy of the assay as applied. In that same
23 grid, we'll look at complimentary assays to see if we
24 can see if there's any additional requirements or what
25 the benefits are of...of the complimentary assays.

1 Then, finally, in the third category,
2 we'll...we'll go back to our whole group and talk about
3 combinations that might do better or as well.

4 But first, I want to start with Dr.
5 Kullman and Dr. Eldridge who are going to talk about
6 the estrogen assays and how they feel. So, with the
7 first slide, Dr. Eldridge will introduce.

8 **DR. ELDRIDGE:** What we did here was to
9 try some linear thinking to try to break down the
10 system in terms of its different components in a
11 somewhat more linear fashion, that is to say, starting
12 with overall control of...of gonadal function, either
13 gonad, and then moving to the gonadal products and what
14 they do to produce their responses, and what we've
15 done...where's the list of the nine...of the
16 eleven...those numbers...

17 **DR. PORTIER:** Go to the next slide for a
18 minute and then come back.

19 **DR. ELDRIDGE:** Yeah, I think so. So,
20 those numbers represent 11...the 11 basic assay types,
21 and you can see them. Right? Where it says key. And
22 what is does is start from the most direct basic. 1
23 and 2 are hormone receptor binding on up to hormone
24 synthesis, fundamentally, to the Hershberger
25 uterotrophic being tests, essentially, of hormone

1 expression, and...and then, 8 and 9 are...are whole
2 system integrity tests, and then, 10 and 11 are the
3 amphibian and fish assays.

4 And so, what we then tried to do was to
5 take each of the tests in the battery and see which of
6 these components they apply to, and that would give us
7 an indication of how much redundancy there is, whether
8 there are significant gaps and holes, and, you know,
9 what do we think about it from there. Okay.

10 **DR. KULLMAN:** Seth Kullman. Since we're
11 on the grid, we'll...we'll kind of go through it step
12 by step just to give you an idea of how these break
13 down. If you look at the x axis, you can see that
14 we've listed a number of the components that we think
15 represent different types of mechanisms of actions and
16 different responses of an organism or systems. Along
17 the...the top there, you can see the numbering, 1
18 through 11. Those are referring to the different types
19 of assays that have been included in the Tier 1
20 battery.

21 And so, the way we worked this out was
22 we went, basically, from column C down through the
23 different types of responses that we're going to see.
24 You can see in column C there that the estrogen
25 receptor binding interacts specifically with the

1 target, and it really does not involve signaling or
2 cell response or any of the other components. In this
3 particular instance, let me reiterate that
4 we're...we're looking at an estrogen response, and
5 thyroid and androgen will be reviewed subsequently.

6 So, number 2 is AR binding. We have no
7 response for AR binding in any of our assays when we're
8 looking at these estrogens.

9 Number 3 is the signal transduction such
10 as the transcriptional activation assay, and we're
11 going to assume here that that will interact both with
12 the target binding and interact with cell signaling
13 such as transcriptional activation.

14 Row 4, aromatase. Aromatase, at this
15 point, is providing information regarding enzyme
16 activity alone.

17 Row 5, or column 5, sorry about that, is
18 the H295R cells. At this point in time, we put down
19 enzyme activity. We do understand, however, that these
20 cells provide a fair amount of additional information,
21 but no data has been validated at this point in time,
22 and I think we're still awaiting peer review of that
23 particular assay, but we've all seen this cell line as
24 providing a significant mode of assays and
25 opportunities to assess estrogenic activities here in

1 addition to looking at steroid and estrogen production.

2 6 is the Hershberger estrogenic
3 activity. Would be null there.

4 7 in uterotrophic assay. We have, for
5 both receptor and target binding and cell signaling A's
6 in these position, A standing for an assumed response.
7 We're not measuring receptor binding, and we're not
8 measuring receptor transactivation in these assays, but
9 this is assumed.

10 However, the caveat to that is that with
11 new mechanisms of action for various endocrine-acting
12 compounds, such as membrane receptors, G proteins,
13 tyrosine kinase receptors is such that there may be
14 alternative mechanisms besides estrogen receptor
15 binding that may elicit a similar type of response, and
16 this is why we put in the target binding here as well.

17 So, in this, we are looking at both
18 cellular responses, organ level responses, and female
19 system integrity responses.

20 As we continue on, 8 is the male
21 pubertal assay. We don't expect any activity with that
22 with the estrogenic compounds.

23 9 is the male pubertal assay. Again, we
24 have our A is assumed ligand binding and
25 assume...receptor binding and transactivation, but

1 also, we have here cell responses, organ responses,
2 female system integrity responses, and complimentary
3 system integrity where we can use these for complete
4 HPG and/or partial HPG and make comparisons to the
5 other assays in the battery that do have HPG
6 components.

7 With the last two being the fish and the
8 frog, you can see that we have positives in the organ
9 system response through the comparative system
10 integrity.

11 The take-home for...essentially, for all
12 of this is that we're able to then tally up the number
13 of redundancies for the different types of processes
14 that we see and also the number of compliments that we
15 have for different types of assays. So, if we look at
16 redundancies for receptor target binding, we can see
17 that we have three additional redundancies that include
18 7 and 9 in this.

19 And then, the same as far as you go down
20 the chart here. For cell signaling, two redundancies.
21 Cell response, one redundancy. Enzyme activity, one.
22 Organ response, three. And so on and so forth.

23 On the bottom row is the number of
24 compliments that we...you can see, and the first thing
25 I'll point out is that the compliments are heavy on the

1 right-hand side which showed the in vivo assays, and
2 they're rather light on the left-hand side which are
3 the in vitro assays. We believe that making this type
4 of tally provides us with a mechanism to ask the
5 questions about both the redundancy and the possibility
6 of creating false positives and false negatives.

7 When we look at the compliments again,
8 the in vivo,...in vitro assays provide probably a
9 greater degree of specificity than some of the in vitro
10 assays, but when you begin to look at the balance of
11 them, I think we...we begin to extract for a balance
12 between both specificity and sensitivity which the
13 battery of assays may provide.

14 With that, we'll move on to the next.

15 **DR. PORTIER:** I would like to open it up
16 for discussion on this part, and then we'll go to the
17 androgen component and then, finally, to the thyroid
18 component. Any discussion? Comments?
19 (No response.)

20 **DR. PORTIER:** Dr. Lasley.

21 **DR. LASLEY:** All right, then, I'd like
22 to ask Dr. Brown to do pretty much the same thing with
23 the next slide which is...is the testosterone grid, and
24 it follows the same format. It's a...Terry?

25 **DR. BROWN:** Okay, we're using the same

1 format here, so the slide that's up there now just show
2 where the different components that Seth just described
3 that we divided this up into, y on the...on the...on
4 the integrated axis that includes the...the
5 hypothalamus, pituitary, and gonad, producing the...the
6 steroids in terms of either estrogen or androgen
7 and...I thought it was going to be...

8 Okay. So...so, what we're dealing here
9 with is, you know, the CNS, the hypothalamus,
10 pituitary, labeled the HPG axis, including the gonad
11 where the steroids are produced. The steroids then,
12 either androgen or estrogen in our cases, affect the
13 target tissue, and they do so either through a
14 combination of receptor binding signal transduction and
15 cellular response. So, the numbers that are shown on
16 here are the numbers that...that Seth just referred to
17 in terms of the...the different assay components that
18 comprise the different responses that are en...entailed
19 in...in looking at this full complete axis of...of
20 activities. So...

21 Yeah, slide 3. Okay, so as Seth did for
22 estrogen, we took the same approach for androgen,
23 using...using testosterone as our...as our potential
24 test substance. Okay? So, that's shown here.

25 Here are the different levels of

1 responses that we could get at the receptor target
2 binding, the cell signaling level, cell response,
3 enzyme activity measures, organ response measures,
4 whether...and then, whether the assay includes, you
5 know, looking at the integrity of the male system, the
6 female system, the...the entire axis, whether it looks
7 at development related to thyroid or to the compar...in
8 the amphibian system or the comparative system
9 integrity such as with the...shown by the fish assay.

10 So, those are all represented down here.
11 So, then across the top, we have the...the 11 different
12 assays that are envisioned here, and then we have the
13 different types of...of measures that we will get
14 from...from those 11 different assays. So, if we're
15 dealing with the androgens and testosterone, obviously,
16 column 1 which looks at estrogen receptor binding, we
17 don't really have anything there. That's going to be
18 essentially a...a non-complimentary assay. But looking
19 at receptor target binding in the androgen receptor
20 binding assay under column number 2, the androgen
21 receptor binding assay would be the...the single
22 component here.

23 In column number 3, we're looking at AR
24 signal transduction, again, obviously, that doesn't
25 apply to androgens.

1 In column 4 where we're looking at
2 aromatase, effects on aromatase, the...this would be a
3 compon...the component here would be to affect enzyme
4 activity.

5 And, again, in the H295R cell line,
6 again, in column number 5, we'd be looking essentially
7 strictly at enzyme activity.

8 Then we go on to column...in the in vivo
9 assays, captured by...first by the Hershberger assay,
10 and that's represented in column 6 where, if we have an
11 androgenic substance, chemical, we would assume that we
12 would have activity at the receptor target binding
13 level through cell signaling, through cell response,
14 potentially an enzyme activity, and we would really
15 actually be measuring in these...in the Hershberger
16 assay an organ response and also the overall integrity
17 of the...of the male system.

18 And if we have an androgenic response in
19 the Hershberger assay, we would essentially expect that
20 that would be reflected in the...in the comparative
21 fish system, that we would also have an androgenic
22 response in...in that assay also.

23 Obviously, in the uterotrophic assay, we
24 wouldn't expect any response to an androgenic
25 substance.

1 In column 8 where we have the male
2 puberty assay, again, we would assume that an androgen
3 would be acting at one or more steps through receptor
4 target binding, cell signaling, cell response, effects
5 on enzyme activity, certainly, at the organ response
6 level where we would be looking at effects on various
7 organs and also on the integrity of the...of the HPG
8 axis.

9 If we go to the female puberty,
10 obvious...here we would expect that an androgen might
11 have an effect on the female system in its integrity
12 through some other...some mechanism not reflected here.

13 In the frog metamorphosis
14 ass...amphibian metamorphosis assay, if we have an
15 androgenic substance, we would expect that it would
16 also be reflected in the developmental aspects of...of
17 amphibian mor...metamorphosis through responses at the
18 organ and system level and...and throughout development
19 and...and also would be seen in the comparative system
20 integrity.

21 And then, in the fish comparative
22 system, again, if we have an androgen, we would expect
23 to see these responses.

24 Okay, so then, if we...if we address the
25 question of do these systems have...assays have

1 redundancy, we've summed those up over here on...in
2 this...on the right-hand side of this slide where,
3 obviously, if we have...if we have responses in three
4 different assays at the receptor target binding level,
5 then there would be a redundancy of two. If we have
6 responses in cell signaling at...in two of the assays,
7 we would have a redundancy of one, and so on down
8 through the...the various assays.

9 And then, the complimentary, the assays
10 that would be complimentary to each other are summed up
11 down on the bottom. Again, as Seth mentioned, we see
12 that the in vivo assays contribute to complementarity
13 between the various responses in the test systems,
14 whereas the...the in vitro assays over here are kind of
15 stand-alone assays where we have a single readout and,
16 therefore, there's really no complimentary assays
17 within the...within the battery that actually can lend
18 credence to these.

19 So, in this case, we're...we have
20 specificity and we have a...a...a single response
21 readout, whereas in the in vivo assays, we have
22 complementarity combined with redundancy, and,
23 therefore, this is where weight of evidence
24 would...would probably enter into the...into the
25 judgment of...of evaluating these assays more...much

1 more so than on the side of the...the in vitro assays.

2 **DR. PORTIER:** Any additional comments?

3 Does everybody agree with this? Okay, Dr. Furlow.

4 **DR. FURLOW:** Yes, I just had one
5 clarification, I guess. Right? So, Dr. Denver
6 mentioned earlier that estrogen can affect
7 metamorphosis. Right? And that...so, you could have
8 an outcome there.

9 I guess I'm interested why you have...I
10 guess maybe I'm not understanding this correctly. So,
11 you think that metamorphosis could be a scorer for
12 androgenic properties because...so...so, gonads aren't
13 being looked in that...at in that assay. Actually, one
14 of the reviewers pointed that out. So, sexual
15 differentiation, yeah, it's just kind of progressing
16 through metamorphosis.

17 So...so, there might be something on the
18 estrogen side, but on the androgen side, I'm not aware
19 of any interactions. Maybe Dr. Denver might know. But
20 I guess I want a clarification of why that was in
21 there.

22 **DR. BROWN:** Okay, this may...

23 **DR. PORTIER:** Dr. Brown?

24 **DR. BROWN:** This may have been our
25 naivete on one...on one side of things. On the other

1 side of things, we...we were...we looked at this
2 as...as these ass...both the...the amphibian
3 metamorphosis assay and the...and the fish assay
4 included both sexes in...in...in the assays. They
5 weren't...they weren't defined by male or...and/or
6 female separately, and, therefore, if we had an
7 estrogen or if we had an androgen in the system,
8 we...we thought maybe that would in some way affect the
9 development, but that may be a naive assumption on our
10 part. I don't know.

11 **DR. PORTIER:** Don't...don't forget to
12 identify yourselves when you make comments. Dr.
13 Lasley?

14 **DR. LASLEY:** Yeah, Bill Lasley. Yeah,
15 we're being as optimistic as possible here, because the
16 question is what is the possibility of false positives
17 and false negatives, is the first question, and any
18 information you get would guard against getting the
19 false information. So, if there is the possibility of
20 seeing it would...a...a redundant assay, that it might
21 not be there, it...it might prevent accepting a
22 false...a false positive. It might avoid a false
23 negative. So, we were being as optimistic as possible,
24 but I agree it's not necessarily going to...to have a
25 lot of weight.

1 **DR. FURLOW:** Yeah, David Furlow. Yeah,
2 I just wanted some clarification. I mean, I guess the
3 other point is that it is truly the only developmental
4 assay. Right? So, there is a lot of weight there, but
5 it...it's a...it's an aspect of development, not global
6 development.

7 **DR. PORTIER:** Since we don't have
8 printouts of this in front of us, would it be possible
9 to slide this sheet down so we could look at both of
10 them from here? Maybe one of you can slip over and see
11 if you can do that. Minimize this one. Yeah, the
12 second...that...the other one, the next box. Not
13 minimize but shrink it and try to show both at the same
14 time, so we can see...there you go. Click on that and
15 drag that one down so we can see both of them at the
16 same time.

17 So, that's the estrogen one. If you can
18 put the...the testosterone one at the bottom, then we
19 can kind of...you don't have to cut and paste.
20 Charlie, you know what I want. And just drag that
21 down. You don't even have to split it. Just drag it
22 down. Just drag that one down a little bit. Now you
23 can see both of them.

24 There you go. Yeah, so you can see most
25 of it. You can just see the...I just wanted to look at

1 the...the complementarity of the two. Look on the
2 front one. There you go. Good. There we go.

3 So, why don't we have cell signaling for
4 the testosterone?

5 **DR. LASLEY:** That's the transactivation
6 assay.

7 **DR. PORTIER:** Oh, that's the TM. Okay,
8 any further comments?

9 (No response.)

10 **DR. PORTIER:** Dr. Lasley, continue.

11 **DR. LASLEY:** I'd like to have Dr.
12 Zoeller now to present a similar approach with the
13 thyroid.

14 **DR. ZOELLER:** Okay, so I'm going to
15 start out with a similar construct and point to or kind
16 of illustrate the similarities and differences between
17 the thyroid axis and the HPG axis.

18 So, again, we're running out here.
19 Like...like the APG axis, this axis is neural endocrine
20 axis with the hypothalamus controlling pituitary,
21 pituitary controlling thyroid gland. Thyroid hormones
22 are secreted, travel through the blood bound to various
23 proteins, and can act on target glands. Also, there's
24 the negative feedback effect of thyroid hormones on the
25 hypothalamus.

1 Now, there are also some important
2 differences here that aren't maybe so well illustrated
3 in this diagram, but one is that thyroid hormones
4 themselves have to be taken up selectively in the cells
5 and tissues which is a little bit different. And this
6 is a point of likely interference.

7 Also, thyroid hormones have to be
8 metabolized. So, a T4 has to be converted to T3, and
9 the enzymes that do this are selectively expressed in
10 different tissues, like the type 2 diiodinase is
11 expressed in the pituitary gland, and if you knock it
12 out or if you inhibit it, thyroid hormone levels
13 change, because they do not...they don't effectively
14 exert a negative feedback as well.

15 Can I go to the next one? Now, there's
16 an issue that I want to talk about very specifically,
17 and that is one of the main mechanisms by which thyroid
18 hormones can be suppressed by chemicals, and that's
19 by...can we go back one? And that's by activating
20 enzymes in the liver to cause clearance of thyroid
21 hormone, and this is...this is a mechanism, for
22 example, of phenobarbital, and phenobarbital was used
23 as the positive control in a couple of these assays.

24 So, in this case, these enzymes can be
25 activated in the liver. Thyroid hormone level...or

1 thyroid hormone clearance is increased, so the half-
2 life is decreased. As a result, T4 levels decline. In
3 this...in this example, TSH is increased. Cell
4 proliferation in the thyroid gland is increased, and
5 thyroid tumors can be...can occur also.

6 And this is what the histopathology
7 would capture. You'd be able to see those histological
8 changes in the thyroid gland that would be secondary to
9 TSH increase that would be secondary to thyroid hormone
10 reduction.

11 Can we have the next slide?

12 So, here's an example from Kurt
13 Klausen's lab that was published in 2001, and what he's
14 looking at is the number of these microsomal enzyme
15 inducers that have similar effects on activation of
16 these enzymes in the liver and can all cause a
17 reduction in T4, but they don't all increase
18 circulating levels of TSH.

19 So, if you look on the left-hand side
20 here...I'm not sure that this is working, but if you
21 look on the left-hand column, you can see free T4, free
22 T3, and TSH, and along the bottom are phenobarbital,
23 and there's two other enzyme inducers in PCBs.

24 You can see that T4 levels are reduced
25 by all of these microsomal enzyme inducers, but TSH is

1 not increased by all of them. On the right-hand side,
2 he's looking at labeling index. So, this is kind of a
3 marker of cell proliferation in the thyroid gland.

4 He's also got thyroid histopathology in
5 his paper as well, and you can see that thyroid
6 histopathology is altered by these enzyme inducers that
7 increase TSH. So, there's link between TSH and changes
8 in...in thyroid histopathology.

9 Next slide.

10 Okay, so now, if we look at the assays,
11 and, in fact, the thyroid gland isn't represented here.
12 Can we fit this...so the point is...the point from
13 this...from this slide is going to be I've changed
14 these...these points at which chemicals can interfere,
15 in principle, with thyroid hormone action at the
16 hypothalamus-pituitary-thyroid hormone synthesis and
17 release, and so, this is kind of a direct pituitary
18 effect.

19 Circulating levels of thyroid hormone is
20 going to be central to all...to most or all of these
21 modes of action, serum binding proteins, tissue
22 responses, liver metabolism.

23 That's not the entire...we need 8, 9,
24 10, 11. Well, that's...this kind of illustrates a good
25 point about the Tier. Yeah, so...

1 So, there are essentially three assays
2 that...that touches on thyroid disruption or measures
3 thyroid hormone, and that is the two pubertal assays,
4 male and female pubertal assays, and...that's not very
5 visible...and the frog metamorphosis assay.

6 Now, in this case, if you look at
7 the...the measures that are being taken is, in the
8 mammals, there's T4, TSH, and thyroid histopathology.
9 And one of the...one of the concerns that I have is
10 that serum T4 is affected by many chemicals, and it's
11 probably being affected through liver metabolism. A
12 concern that I have, though, is that if phenobarbital
13 is the positive control and it acts by activating the
14 liver, we can't rule out...another example would be
15 linuron that is being presumed to increase liver
16 metabolism, but it doesn't increase TSH. So, T4 levels
17 go down to a significant degree, not trivial, in a dose
18 dependent manner, but TSH isn't increased.

19 This profile looks exactly like PCBs.
20 So, PCB exposure decreases T4, doesn't change TSH,
21 doesn't activate the thyroid gland, but we know from
22 many different studies that it can affect thyroid
23 hormone signaling in the developing brain, in the liver
24 and heart and other tissues.

25 So...so, we can't rule out the

1 possibility that T4 decline, in the absence of an
2 increase in TSH, is informative. And so, we can't...we
3 can't rule that out.

4 The amphibian assay is important in this
5 regard, because it captures endpoints of thyroid
6 hormone action. There are differences...there may be
7 differences in metabolism between amphibians and...and
8 mammals that...that...that I'm not sure, as I think
9 about it, complementarity and redundancy, I'm not sure
10 that it's entirely...it is complementary. There's no
11 doubt about that, because the amphibian metamorphosis
12 assay captures endpoints of thyroid hormone action, but
13 I...but I don't think we can say that it's redundant
14 entirely, because metabolic differences may exist that
15 may be important.

16 So, for just final points here, serum T4
17 in the pubertal assays is a reasonable measure of the
18 impact of a chemical on the HPT axis, but failure of
19 TSH to respond to lower T4 I don't think can be assumed
20 to be benign. So...so, we can't ignore that whether
21 the amphibian...whether the amphibian assay reveals an
22 effect of that chemical or not.

23 So, the pubertal assays don't have a
24 measure of thyroid hormone action, and that's a
25 weakness, but I don't think that's a weakness that can

1 be solved immediately, because I...I can't think of
2 anything that's a validated assay at this point that
3 would...that would be able to stand in there.

4 The amphibian metamorphosis assay
5 captures measures of thyroid hormone action but can't
6 necessarily be assumed to be directly related to
7 mammals because of these cases of metabolism.

8 I think the more we know about it, the
9 better we're going to feel about the relationship
10 between those two assays.

11 Next slide.

12 So, I don't need to...you...you want to
13 have a conversation about the general presentation
14 before we move into the last part of these questions,
15 or...okay.

16 So, in terms of minimizing false
17 positives and false negatives, this...I think at this
18 point, it's difficult to estimate, because we don't
19 really know. I think that it's a valid point, for
20 example, that Dr. Denver pointed out earlier that
21 there...there is the possibility that...that chemicals
22 can have a generalized effect that would be similar to
23 this non-thyroidal illness that we see in humans, and
24 that's a genuine possibility.

25 And I don't know...I don't think

1 that...that we know enough yet to be able to estimate
2 how many of these chemicals that cause a reduction in
3 T4 with no increase in TSH are false positives or in
4 that case. So...so, it's going to be difficult to
5 estimate that.

6 On the other hand, we do know a
7 very...you know, clearly, of examples where T4
8 declines, TSH doesn't increase, but there are adverse
9 consequences down stream.

10 Okay, the next slide.

11 Are there unnecessary redundancies for
12 the MOAs here? I think the answer is just no. I mean,
13 I'm not sure how many redundancies there are, but it
14 would be, certainly, not too many.

15 Okay, one more.

16 Different combinations of validated
17 assays would be more effective. This can be
18 interpreted two ways. One is currently validated
19 assays or two, gee, wouldn't it be nice. And in terms
20 of current validated assays, I'm not sure that there
21 are any that can be just immediately added on to
22 supplement weaknesses here, but capturing some measures
23 of thyroid hormone action in pubertal assays would be
24 important. I think simple ideas are...serum
25 cholesterol levels, heart and cardiovascular functions.

1 In vitro assays, I think, might also be
2 important for thyroid hormone receptor binding.
3 Because the TR-alpha and TR-beta mediate different
4 kinds of effects on the thyroid system, it's important
5 to separate these two things out. For example, 1, the
6 beta receptor mediates negative feedback. An effect on
7 the alpha receptor that's selective wouldn't be
8 captured, even in...in serum TSH levels. And, also,
9 the transactivational assays would be important.

10 Okay, that...that concludes the
11 presentation on our part for question 1 and question 2.
12 We...we believe that we can point to a good number of
13 redundancies, particularly with the in vivo assays.

14 And...and same with compliments, a good
15 number of redundancies in...or...or compliments in the
16 in vivo assays. The in vitro assays are the place that
17 probably there is less. The question is, is there
18 enough. We don't know. Is there too many? I don't
19 think so. I don't think we show that there
20 is...there's really too many in...in any of the
21 categories.

22 But I think we might want to discuss now
23 questions 1 and 2 together. They're...they're
24 connected.

25 **DR. PORTIER:** Does anybody want to jump

1 in? Okay, Dr. Denver.

2 **DR. DENVER:** I just want to follow up on
3 a point that Dr. Zoeller made about potential
4 differences in metabolism across species, and...and we
5 really don't know very much about that.

6 One thing we do know, though, and
7 I...and I was referring to one of the most common modes
8 of action, thyroid disruption is competition for
9 binding to transthyretin, the serum binding protein,
10 well, you know, a well characterized mode of action, at
11 least for PCBs and...and related compounds.

12 And it's important to note that
13 the...the specificity of transthyretin across species
14 is actually quite different. In mammals, it's for T4,
15 and in amphibia and, actually, most non-mammalian
16 vertebrates, it's for T3.

17 And so, what that suggests is that you
18 may have very different compounds that would cause
19 thyroid disruption through that mode of action in
20 amphibia and would be picked up in amphibia and other
21 wildlife that wouldn't show up in mammals. And, on the
22 other hand, you would have compounds that would disrupt
23 thyroid function in mammals that wouldn't show up in
24 amphibia.

25 **DR. PORTIER:** I think I want to push it

1 a little bit more on the false positive/false negative.
2 Jan? That's the question Jan was going to ask, too.
3 Okay. I want to get a little bit clearer on...on the
4 feeling of the panel on...on this
5 especially...let's..let's take the issue of false
6 negatives.

7 **DR. LASLEY:** I think the safeguard to
8 false negatives is the redundancy. If...if you have
9 redundant systems and they're sensitive...and I think
10 we...we have selected the more sensitive assays that
11 are validated...then I think that's the only safeguard
12 you can really have.

13 **DR. PORTIER:** Yes?

14 **DR. KULLMAN:** Dr. Kullman, Seth Kullman.
15 I think also represented are a range of both
16 specificities and sensitivities within the assays
17 across the board, that where some may not provide both,
18 I think there...there's a number of different ways that
19 chemicals may interact with either complete specificity
20 or incomplete specificity versus the sensitivity, and I
21 think we saw some...some good examples of that when we
22 were given the presentation this morning on a variety
23 of different compounds, both strong and weak agonists
24 and antagonists to several of these systems.

25 Not all the systems lit up the same way

1 or as well or were activated or...or depressed the same
2 way, but, certainly, there would seem to be the ability
3 to capture a range of both positive, negative...well,
4 maybe not so negative...but...but strong and...and
5 weaker agonists and antagonists.

6 **DR. PORTIER:** Dr. Belcher, you look like
7 you're ready to make a comment. Nope? Dr. Zoeller.

8 **DR. ZOELLER:** So, for the thyroid
9 system, one thing that's important, I think,
10 to...to...at least for me when I think about it, is the
11 Tier...the goal of Tier 1 is to just see if some...if
12 there's some chemical that might interfere with, in the
13 case of thyroid hormone, thyroid hormones signaling at
14 any point in time. So, it's just a...it's a...it's a
15 very quick, simple assay that would give a broader
16 picture.

17 In the case of this issue of thyroid
18 hormone decline in the absence of a TSH increase, in a
19 pregnant female, the first trimester and, you know, the
20 first 7.5...what am I thinking...16 days in a rat
21 is...the fetus can't make thyroid hormone. And so,
22 really, in terms of the mother, it doesn't really
23 matter what's happening. As long as T4 levels decline,
24 whether TSH goes up or not is irrelevant, and the fetus
25 is going to be deprived of thyroid hormone regardless

1 of the mechanism by which T4 declines.

2 So, I think that...that if the tier is
3 to be viewed as an indicator of what could be really an
4 important endocrine disruption event that would have to
5 be explored more fully in a Tier 2, and that's where
6 you would get hold of this kind of issue, it's
7 important not to ignore a decrease in T4 regardless of
8 the other kinds of events that you see happening in
9 that assay.

10 **DR. PORTIER:** Dr. Eldridge?

11 **DR. ELDRIDGE:** Eldridge, yes. With
12 respect to the reproductive parameters, our...our
13 little group with this charge question felt pretty
14 comfortable that...that the redundancy does help
15 obviate false negatives with two important things. One
16 is that it's...it's perhaps more important to avoid
17 false negatives than anything else. In other words,
18 it's...it's necessary to not let an active material go
19 unidentified.

20 And the other thing is, of course, you
21 can test lots of little mechanisms, and we were
22 thinking of many little mechanisms that are not picked
23 up here, but the...the group of assays that are
24 identified at this time before us seem to be providing
25 a lot of redundancy on most of the important effects.

1 The...the problem of false positives is
2 a different kind of issue. The...unfortunately, the
3 false positives are most likely to happen with the
4 large-scale, extensive, complicated in vivo testing,
5 because that's where more known specific actions can
6 take place.

7 And so, the Agency, then, is...is on
8 tightropes to make a call on things, because repeating
9 a binding assay is fairly simple if you're not sure if
10 that worked, but repeating a...an in vivo study because
11 of...of uncertainty of indirect actions, it's a lot
12 more difficult.

13 So, this...this causes us to caution the
14 Agency to be very careful and very willing to look at
15 the entire spectrum of results as it decides how to
16 proceed once a positive happens, especially in these
17 large-scale, difficult to perform in vivo tests.

18 **DR. PORTIER:** Dr. Lasley? Any more
19 discussion on false positives? Because as you...as you
20 mentioned, I mean, that's where the potential for
21 expense, animal use can build up. Right?

22 **DR. ELDRIDGE:** Yes, Eldridge. And once
23 is expensive, but...but I think most of us have
24 experience with larger-scale animal testing versus
25 smaller-scale specific testing like a receptor binding,

1 and...and we all know how difficult it is to get a very
2 precise answer, to get it to happen the same way every
3 time in...in a case like that. So, it...it's a much
4 more complicated system to get definitive answers, and
5 if you're going to start testing chemicals at or near
6 the MTD, you're almost begging for some effects to
7 happen.

8 **DR. FURLOW:** So...David Furlow, UC
9 Davis. So, a couple things. We touched on some of
10 these points earlier. Maybe that...that's why it's not
11 so fleshed out this afternoon, but I guess the MTD
12 issue is something that still concerns me.

13 So, is there a possibility that if
14 you're working at the MTD and then half below that,
15 then you may get general toxicity, but if you went to
16 lower doses, you may reveal endocrine disrupting
17 effects? I think...I don't think that's really be
18 talked a lot about here, and I...I am actually quite
19 concerned about that. Right?

20 So, if you throw something out because
21 it's generally toxic at the dose where it's causing 10
22 percent of the body weight to drop, and you say well,
23 okay, there's no endocrine disrupting effect, I mean,
24 maybe some other folks can weigh in on this, but I
25 guess I'm a little bit worried that you may be masking

1 something by working at those high concentrations. I
2 don't think we've really talked about that maybe
3 enough.

4 **DR. LASLEY:** Lasley. No, we didn't...we
5 didn't consider that. We took the question with the
6 assumption that these were the assays, the validated
7 assays would be employed as they stand, and we would
8 accept that information, but we didn't really consider
9 what would be or should be improved with individual
10 assays.

11 **DR. ZOELLER:** I...I would at least want
12 to...this is Tom Zoeller...to echo that concern. I
13 think it's...I think there are a number of important
14 published cases where this is true. And so, I worry
15 that, you know, I mean, it's a tough call, because if
16 you're only going to use a couple of doses, right in
17 the beginning, we don't know where you are unless you
18 do a full range testing. On the other hand, you have
19 to be aware that this kind of situation is going to
20 crop up.

21 **DR. PORTIER:** On the redundancy issue,
22 we...you demonstrated that we have redundancies on the
23 in vivo but very little redundancy on the in vitro
24 testing. Does that bother you? Does that...I mean, it
25 seemed to indicate that that was okay, but I'd like us

1 to discuss that maybe a little bit more.

2 **DR. LASLEY:** Lasley here. I...I was
3 surprised, actually, when we broke the numbers down,
4 because I thought it would be perhaps even the other
5 way, but I think the reason is before that is the fact
6 that the in vitro assays are more mature, they're easy
7 to handle, they're more specific, and it's possible
8 that you just don't need as many of them to get the
9 same kind of information.

10 So, I think that's possible. On the
11 other hand, just with the previous conversation, where
12 we have concerns about levels and doses and what's
13 happening, I think that's the area where improvements
14 could be made by adding more...more efficient, more
15 redundancy in the in vitro assays.

16 **DR. PORTIER:** Dr. Brown?

17 **DR. BROWN:** Brown. I'm not sure that we
18 even have all the assays that we need, yet alone
19 redundancies. So, I mean, in the ideal world that Dr.
20 Zoeller referred to, what would we like to have? Well,
21 we probably would like to have some more in vitro type
22 assays that would span a wider spectrum of...of
23 endpoints, because those tend to be, as Dr. Lasley
24 said, the more specific, the more sensitive assays that
25 really target a specific endpoint that's actually, you

1 know, absolutely measurable as opposed to the in vivo
2 assays where we're left with redundancies but I think,
3 in fact, we need those redundancies, because we're not
4 as sure of what those endpoints are really telling us.

5 **DR. PORTIER:** Okay, before we go on to
6 the last component, I just wanted to check with EPA.
7 Did you get what you needed out of this conversation?

8 **DR. TOUART:** Just a clarification point
9 in terms of MTD effects. I think part of the comment
10 that Dr. Furlow made, and that's if we see an effect at
11 the high concentration which may exceed an MTD and we
12 have toxic effect, that we might discount what would be
13 seen at a lower concentration. I think that, in
14 general, the interpretation would be at the lower
15 concentration. If there are no indications of...of
16 toxicity at that level, you would like to be able to
17 interpret any. That's part of the...the purpose of
18 having more than one concentration in the...in the in
19 vivo screens, in case the...the high dose is washed
20 out.

21 In those cases where all doses have
22 some, you know, overt or systemic toxicity, I think
23 that the indication would be that we might need to...to
24 repeat that. The intent is that...that we...we will
25 have tested up to, you know, a...a limit dose or a

1 maximum, you know, level to make sure that we've
2 covered, but the context is we don't want to exceed
3 a...a...a maximum tolerated dose.

4 **DR. PORTIER:** Dr. Chambers?

5 **DR. CHAMBERS:** Okay, but most remain
6 concerned about this MTD approach, though, because I
7 understand what the rationale is to try to get...to get
8 a worst case scenario so that you can identify effects.
9 However, all of the animal's defenses or many of the
10 animal's defenses are compromised at that particular
11 point, and that's why you start seeing some toxicity.

12 And so, any kind of positive effect in
13 the endocrine parameters here could just reflect the
14 overall toxicity. That's been mentioned by others,
15 too, and if the only positive you get is at the MTD
16 dose, what are you going to do? Are you going to look
17 to the lower doses to...to claim that it's a positive
18 effect? Because I don't know that you can if the only
19 positive effect is at the MTD dose, reflect the overall
20 toxicity.

21 **DR. TOUART:** This is Les Touart again.
22 Respond to that. I think, again, I think the concept
23 is we want to be, you know, below one, an MTD, but we
24 want to be approaching it in...in that context.
25 If...if we do see, you know, toxicities and at that

1 level is the only one where an endocrine response is
2 occurring but the next lower level it's not, then
3 that's a little bit of a...of a...of a quandary of
4 sorts, you know, for us.

5 So, I think any advice in terms of...of
6 how to step down from that, whether we might need an
7 additional, you know, level in something like the
8 pubertals where there are only two concentrations, you
9 know, those are some things, you know, to consider, but
10 any advice in a better approach, then, in trying
11 to...to use an MTD in a screening, you know, level mode
12 or in interpreting that, I think, would be helpful.

13 **DR. PORTIER:** David?

14 **DR. FURLOW:** I mean, I don't know if
15 this is the point for give and take sort of thing, but
16 if I...I mean, so, I guess, not being a toxicologist by
17 training, thinking of the MTD and just going...I guess
18 the ra...I guess I don't understand the rationale for
19 just going and say a half a concentration below. I
20 mean, in...I understand we want to limit the number of
21 animals. I am, certainly, actually am sympathetic to
22 that, but, I mean, 10-fold below or 100-fold below,
23 but...or just half below, how does at least a
24 toxicologist come to setting up the minimal dose
25 response curve, and how did you come up with just one-

1 half? Is that true for just the pubertals? Is that
2 how it goes? It's MTD and then one-half the MTD?

3 That was my understanding, but I may
4 be...I may be missing something there.

5 **DR. TIMM:** I think that the protocol has
6 used a quarter of MTD or a half of MTD, and I think
7 maybe looking at the data, that generally shows the
8 right sort of spread, but, again, it depends upon the
9 dose response curve with the compound and a lot of
10 other factors. So, it's, you know, it's a rule of
11 thumb that...that seems like it works okay, but you're
12 right, to do those levels is...is difficult. You have
13 to...you have to peg it pretty well.

14 **DR. PORTIER:** Dr. Bucher?

15 **DR. BUCHER:** So, just to carry this
16 conversation on a little bit further, what kind of
17 information do you expect that there will exist on
18 these 73 chemicals in addition to the...the...the
19 success or failure of this tiered approach is that it
20 depends heavily on the 73 chemicals, and you picked the
21 73, because they have infor...well, because there's
22 high exposure. So, presumably, they'll have a range of
23 other types of toxicity information available.

24 How are you going to figure that into
25 the...to...to determining whether the pubertal assays

1 are...are going to do the job for you or not given the
2 fact that, you know, the information that may exist for
3 these may allow very good dose selection in the male
4 and the female pubertal or it may not? I mean, do you
5 have any sense of...of what your 73 chemicals look like
6 in that regard?

7 **DR. TOUART:** This is Les Touart in
8 response. The majority of the compounds are
9 pesticides, and most of those are FUGIs pesticides
10 where there is a fair amount of mammalian data in terms
11 of acute oral toxicities, other, you know, feeding
12 studies, 9-day feeding study type...type...type data.
13 So, there's a fair amount of information to help...to
14 help focus, you know, where one might be maximum, but,
15 again, there's always going to be, I think, some
16 difficulties if you're trying to approach to a, you
17 know, a level that's at the threshold of...of toxicity
18 but below it, because the context under the conditions
19 that one study and life stage that may have been tested
20 versus the other, you have that situation.

21 On the...in the aquatic, you know,
22 studies, it's a...it's a little bit different, you
23 know, approach, and we do have more than the two dose
24 levels. We're generally using three concentrations.
25 We also have a limit which we don't test above 100 ppm,

1 because that's a very high concentration, and we don't
2 feel that for compounds, it's, you know, you're not
3 going to go above that, you know, approach anything.

4 And, also, we're not going to test above
5 the...the...the limits of solubility for the...for the
6 material in terms of what the organism would be able to
7 be exposed or what we could maintain concentrations
8 for, but we still would...would try to...to use levels
9 that are below toxicity that would have been manifest
10 in, you know, fish acute toxicity studies. Or for the
11 frogs, we would usually be, you know, utilizing
12 whatever information we had on...on the aquatic
13 organisms, or we would have to do some level of range
14 finding in terms of identifying toxicity going into
15 the...into the screen proper.

16 **DR. BUCHER:** And are you going to be
17 putting out guidance with regard to that last point?

18 **DR. TOUART:** This is Les Touart again.
19 In response to the...for the fish and the frog in
20 the...in the...the test method, there is some guidance
21 associated establishing that the...the dose levels
22 and...and...to use. I think that the caveat with that
23 in terms of interpretation. Again, you know, it's
24 a...it's a fairly, you know, narrow window that we
25 might...might be looking at, and if we do see

1 toxicities of what might be perceived as toxicities
2 through more systemic, you know, routes, you know, that
3 isn't going to have to weigh into the interpretations
4 of...of what those effects in general.

5 If...if...if the consideration is
6 that...that we're dealing at...at...you know, in
7 general toxic levels, we will try and discount those
8 levels and...and move to the levels where we...we don't
9 believe that's occurring to determine what other
10 activities might be going on.

11 **DR. CHAMBERS:** To follow on Dr. Bucher's
12 earlier point, if...if these are mostly chemicals that
13 are very well characterized, because they're registered
14 pesticides already, and you have the databases, are the
15 doses for these particular endocrine disruption tests,
16 are those using the information from all that database?

17 **DR. TOUART:** Les Touart. I...I think
18 the...the general situation is...is we would like
19 the...interpret those...those data and utilize those
20 data, but, again, the...the life stages, you know, may
21 be different in terms of...of the toxicities in terms
22 of pubertal. I'm not as familiar with all the...the
23 full data set that...that we have on...on even the
24 mammalian, you know, set to determine if we have
25 comparable, you know, information in terms of toxicity

1 for the...for the pubertal life stage or in terms of
2 the...the stages that would be done at Hershberger and
3 uterotrophic, you know, kind of context.

4 On the aquatic side, you know, we would,
5 you know, have fish, you know, toxicity data. We may
6 have fishery life stage, you know, data to...to also,
7 you know, utilize in trying to establish the normal.

8 I think, you know, another thing in
9 terms of the intent for...for endocrine screening is
10 we...we're looking at...at evaluating levels of...of
11 toxicity, you know, that are going to be in a...in a
12 range below what our traditional toxicity tests and
13 stuff are already identifying, you know, as...as
14 concern levels and stuff, but in...in a screening, we
15 do want to test at...at as...the highest levels as
16 would be appropriate or practical within...within these
17 assays to determine if we're seeing some level
18 of...of...of a response in a screening, and then we're,
19 you know, the intent is to use Tier 2 to actually do
20 the...the dose responses and find out what
21 the...the...the lower bounds of that are.

22 But if...if we miss it in the screening,
23 then...then that would be, you know, a miss and...and
24 become a false negative in the context.

25 **DR. CHAMBERS:** I do appreciate what

1 you're saying, but what concerns me is that if...if
2 some of the pesticide modes of action are really well
3 characterized already, say, they're neurotoxicants, and
4 you know the levels at which neurotoxicity occurs, and
5 you force the levels for these endocrine tests much,
6 much higher than that in order to find that, is that
7 going to happen? You're shaking your head. No?

8 **DR. TIMM:** Yeah, this is Gary Timm. No,
9 I mean, clearly, if...there is a large database on...on
10 the pesticides, and it would include 90-day
11 synchronics, it would include two-generation tests for
12 the presence of pesticides, two-generation mammalian
13 assays. But they may be old. They may not have
14 endocrine-sensitive endpoints in them, so things may
15 have been missed. Probably developmental tox studies
16 as...as well.

17 So, there's a lot of data that
18 would...would pertain to this life stage, I think, for
19 setting dose levels in this particular case. In some
20 cases, they are known neurotoxicants and you're right.
21 I mean, you would not force...your MTD would be set by
22 whatever your...your database looks like. No, you're
23 not going to run up above a dose level that has been
24 seen to be an effect level in...in, for instance, a
25 neurotox study.

1 When you get to the more beta poor
2 chemicals, then, obviously, setting a dose level
3 becomes a much more difficult sort of thing, and there
4 may have to be some range finding studies of some sort
5 to be done as just part of a general...general tox
6 study design.

7 And for the...for the large volume
8 inerts, there is a program, a voluntary testing
9 program, that has been...it's both domestic and in
10 conjunction with OECD where they are getting a minimum
11 data set. And so, some of that information could be
12 used, though they're not starting from scratch on
13 those, either. So, we would hope that that would be
14 taken into account when industry sets those levels, and
15 I'm sure it would be.

16 **DR. PORTIER:** I think we'll go on to
17 part C. Dr. Lasley?

18 **DR. LASLEY:** Lasley. Short answer is
19 yes. I think we've already heard a very long list
20 of...of...wish list of things that people would like to
21 see: perhaps more specific assays for puberty,
22 trans...transaction assay for androgens, perhaps
23 improved steroidogenic cells for steroidogenesis,
24 perhaps adding some development or organizational
25 tests, certainly including more or better negative

1 controls, and certainly specific thyroid assays if they
2 can be found.

3 But in general, I think, there's room
4 for increased, more specific in vitro assays and
5 certainly, I think, perhaps improved and more specific
6 in vitro assays to replace some that are there that are
7 a little difficult to interpret.

8 So, yes, there's room for improvement.
9 I don't think anyone thought that this was a...a final
10 list of assays or a final tier at this particular date.

11 **DR. ELDRIDGE:** Eldridge. I'd like to
12 add to that just to feel that...that the SAP process
13 seems to work pretty well and that I'd recommend that
14 the Agency continue using the SAP as...as new tests and
15 new parameters come along as a way to assemble a group
16 of people to render advice, because this is a...a
17 regularly constituted panel that can be called again
18 and again, and it would be fairly simple to arrange it
19 this way.

20 So, we would hope that this whole
21 process would be ready to evolve and able to evolve as
22 new technology, especially as new technology comes out
23 and also after you begin to get some results on the 73
24 compounds that are on your list. I think there would
25 be a lot of times when you'd want to come back to this

1 panel for more advice.

2 **DR. KULLMAN:** Seth Kullman. I don't
3 have any comments on specific assays to add, but I
4 would like comment on the fact of looking at the
5 standardization of the assays that are actually
6 currently on the books, and it appears from some of the
7 discussions that we've had that there's some...some
8 possibility to standardize some of these assays to a
9 greater degree, make them more amenable to
10 interlaboratory comparisons, and really provide a
11 mechanism to tighten up on how these assays are run,
12 depending on the...the labs and agencies that are going
13 to be performing them.

14 **DR. PORTIER:** Anybody else want to
15 comment on this? Dr. Furlow?

16 **DR. FURLOW:** Since hepatic toxicity
17 could be one of the reasons why many of these hormone
18 systems are affected, I wonder if it's possible to
19 include a...a panel, just a general hepatic toxicity
20 screen, either gene expression of p450...is there...is
21 there a sort of a panel of genes and enzyme products
22 from the liver that could be included to...to look at
23 what might be going on? I mean, Dr. Zoeller
24 already...already showed you enzymes affected
25 indirectly that could then affect thyroid homeostasis.

1 And so, that might be something to add.

2 And the other thing, too, to reduce the
3 number of animals or to tighten up some of the data, I
4 mean, certainly about gene expression studies,
5 quantitative PCR has, you know, sort of been alluded
6 to. Maybe in some of the...some of the proposals,
7 that's something that might be coming on line, but
8 certainly, in the amphibian system, there are...there
9 are some very nice, very strongly induced, and very
10 specifically thyroid hormone lead and cell thyroid
11 hormone induced genes that could be looked at with
12 quantitative PCR that may make it more sensitive and
13 actually tighten up the data and give you a better,
14 say, okay, this is where we are in response to thyroid
15 hormone signaling.

16 So, you know, those are my biases,
17 because I work on gene expression, but I...but I think
18 they actually do have some value, value added. Those
19 are my main things.

20 I guess the...the...the major thing I,
21 additionally, that I would also recommend in...in
22 trying to get around sort of the false positive
23 question we've had over and over again in the pubertal
24 would be if you can find the negative. Right? So, the
25 al...alcohol maybe has been suggested, but I...I guess

1 I would...I'd feel a lot more comfortable if you did
2 have some sort of negative in...in the...in the
3 pubertals before going forward.

4 **DR. PORTIER:** Dr. Cooke?

5 **DR. COOKE:** Gerard Cooke, yes. When
6 considering a weight of evidence approach, there are
7 some other things that you...you could incorporate
8 which...Dr. Chambers' suggestion that there's a lot of
9 data available on the 73 chemicals that you're going to
10 choose such as exposure data and tissue distribution
11 data and bioavailability data which you could then run,
12 when you're running through the testing, on a weight of
13 evidence approach, you could say well, okay, we...we've
14 got all these yes and noes and...and maybes that might
15 trigger to...to test which may have been done and may
16 have already been proved negative, some of the
17 endpoints, and then you can go back and look at the
18 tissue distribution data and the bioavailability data
19 and say these would have prevented us from having to go
20 to...to...to a test. I mean, that gives you credence
21 for your Tier 1 tests.

22 **DR. PORTIER:** Dr. Vandenberg?

23 **DR. VANDENBERGH:** Yes, Vandenberg. I'd
24 like to really emphasize something that Bill Lasley
25 said a moment ago about the...the effects of hormones

1 do occur both as an organizational phenomenon very
2 early in life and then activational, and what we're
3 dealing with here is almost all activational. And I
4 think that somehow...and I can't come up with a nice
5 simple little assay for you, because it's a complicated
6 question...but it needs to be addressed that we're
7 going to see long-term effects in the animal and
8 probably in the human population as a result of some
9 relatively minor changes during fetal development.

10 And those effects include things like
11 the brain is organized between masculine and feminine
12 areas. It includes a variety of different organ
13 systems that are affected by this.

14 I know that's a very complicated story.
15 It's probably going to end up being in your care, too,
16 but I think it's...it's something that is well worth
17 exploring.

18 **DR. PORTIER:** Dr. Furlow?

19 **DR. FURLOW:** Some of these developmental
20 things get me going. So, in...in five words...no, five
21 minutes or less, I wasn't here for the presentation, so
22 that...that may have been covered, but the intrauterine
23 to lactational assay was not accepted, and I haven't
24 read through all the reviews, but, you know, what,
25 beyond amphibian metamorphosis assay, then, what other

1 kinds of developmental assays is the EPA considering
2 or...or not considering?

3 I mean, is your experience with the
4 intrauterine to lactational so disheartening that you
5 don't want to go...go beyond? I...I think it's
6 incredibly important, personally. So...and...and to
7 rely totally on the amphibian assay as the only
8 developmental one and...and a very specific one,
9 thyroid hormone, at that...may...may...may not be a
10 good idea.

11 **DR. TIMM:** Yeah, this is Gary Timm. We
12 did bring the...the whole question of whether the
13 inutero/lactational assay should be in Tier 1 or not
14 before the SAP about a year ago, and, you know, it was,
15 I think, the consensus probably of EPA staff and the
16 consensus of the panel that gee, it would be great to
17 do it, but it is so long, so expensive, so complicated
18 that it really did not fit the definition of a Tier 1
19 screen, and we...we felt that a better design of Tier 2
20 than what we have was where we should put our energy,
21 and that...in fact, that's what we're doing.

22 We're looking at a...a one-generation
23 assay that utilizes more animals than...utilizes
24 virtually all the animals to increase the...the
25 representation of the...the litter so you characterize

1 the...the effects within litters much better
2 than...that what the current two-gen does. So, it's a,
3 I think, a more effective test and adds more endocrine
4 sensitive endpoints, and it's a shorter-term test than
5 the current two-gen.

6 So, that's what we're doing. And
7 it...the philosophy clear back in the EDSTAC days...and
8 I...I don't think anyone in the, you know, research
9 labs or...or the literature has shown that we would
10 miss things.

11 I mean, what we're looking for in Tier 1
12 is a signal that there is a problem with the endocrine
13 system, that a chemical is causing some perturbation of
14 the endocrine system. Identifying the adverse effects
15 and getting a dose response relationship between
16 the...the chemical and the adverse effects are what we
17 do in Tier 2.

18 So, we're...we're happy if we can get
19 the signal in Tier 1 that we have a problem, and
20 we're' even happier if it gives us some ideas about how
21 to...how to proceed in Tier 2, but...but...but that's
22 maybe more wishful thinking than always the case.

23 Obviously, we want Tir 1 to be an
24 effective filter and keep the things that are...are not
25 a problem out of Tier 2 and flag the ones that are a

1 problem to us so that they can go on to Tier 2.

2 **DR. TOUART:** Just to talk about some
3 other assays that are kind of in development, you know,
4 but we really haven't considered them as far
5 as...as...as Tier 1 just because of the...the length of
6 time, and I think any time you start dealing with
7 organizational type studies, you generally have to
8 carry these out long enough for individuals
9 to...to...to mature and...and the like, and that's been
10 the...the big limitation in the context of our Tier 2s
11 are established to do that.

12 But you want an assay that's being
13 developed at the OECD level. There's a fish sexual
14 development, you know, test. And...and that assay
15 looks at...at the fish in the EN through early
16 development, and with species like the medaka and
17 zebrafish, we do have genetic sex monitors so that we
18 can indicate, you know, the difference between the
19 genotypic and phenotypic, you know, sex changes.

20 And that's in development, but these are
21 60-day, you know, plus type...type tasks and really
22 extensions of...of something like the existing early
23 life stage test which is a...a traditional test.

24 In...in the development or pursuit of
25 the Avian 2-generation test, we investigated an egg

1 injection, you know, method as a means of doing kind of
2 a range finding for...for looking at...at that, but to
3 do the egg injection, you...you're doing...letting
4 these birds, you know, hatch and then reach maturity
5 before you...you can collect the markers to indicate
6 that you had some effect, you know, by the...the, you
7 know, hormonal disruption that was in the embryo.

8 So...so these are some...some context,
9 but, again, the...the difficulties with those have
10 been, you know, we can't find something that...that,
11 you know, would really be in, you know, the kinds of
12 time frame that some of our other assays are which are
13 still, you know, in...in a relative sense, not...not
14 short assays, I mean, when you're dealing with 21 days
15 or...or longer.

16 So, you know, that's the context. If
17 there are some suggestions of...of assays that might
18 exist or might, you know, be on the horizon or areas
19 that might be worth pursuing, I think that's something
20 to consider, but, again, the problem right now is...is
21 we don't really have a viable, you know, candidate that
22 probably can move forward with in this case.

23 **DR. VANDENBERGH:** I'm going to make one
24 more comment along that line, the...the Tier 2 test,
25 and that is it's been since '96 that we've been working

1 on getting the Tier 1s organized, and it looks like
2 it's getting closer and closer. I'm sure that the
3 public and, as you mentioned, the Congress is a little
4 concerned about how long it's been taking to do that.

5 Is there a plan afoot now so that you've
6 got a schedule of what needs to be done to set up one
7 or more Tier 2 tests? Because I assume that maybe
8 before too long, you'll have Tier 1 data coming in that
9 there were some effects.

10 **DR. TOUART:** Yes, it's, you know, some
11 of the advancements and evolutions, improvements
12 of...of the rodent 2-generation, you know, assay, the
13 generation test, you know, this exists, and we consider
14 that very valid. There are some additional endpoints
15 that have been added, and there are some others that
16 are maybe still under consideration, and...and if those
17 are perceived to be valid, those would be added into
18 that method.

19 On the...for the other, you know, toxic
20 groups, we do have projects ongoing in developing fish
21 2-generation, an...an avian 2-generation, you know,
22 assay. We're looking at an amphibian, what we're
23 calling a growth reproduction assay, because we haven't
24 figured out a...a viable paradigm for...for doing a
25 full life cycle and having the frog reproduce, and

1 we're...we're using a...a...a Xenopus species, you
2 know, in the pursuit of...of that which we have been
3 able to...to spawn within the laboratory, at least on a
4 consistent basis.

5 The anticipation, you know, for
6 these...and we also have a...an invertebrate that
7 we're...we...we're using in Tier 2 to determine, since
8 there is ability for vertebrate active, you know,
9 materials that interfere with the invertebrate, you
10 know, hormonal system, so we felt that anything that
11 tested positive we wanted to evaluate in...in that
12 context, so we do have a 2-generation mysid, you know,
13 test that we're...we're looking at in developing.

14 In developing the eco, you know, assays,
15 we're really, first of all, looking at value added of
16 the 2-generation test in terms of what more it gives us
17 than existing methods that...that guidelines exist for
18 avian reproduction and fish, you know, life cycle
19 testing and the mysid life cycle testing. On the frog
20 side, we really have no full chronic, so that has
21 to...has to be developed.

22 The time lines that...that we have right
23 now is anticipating trying to have these studies
24 through in a laboratory, you know, testing by 2010.
25 That's optimistic that everything looks right with the

1 first time.

2 We do have some initial, you know,
3 trials that have been completed or on their way in
4 terms of establishing a standardized method that could
5 then go into interlaboratory testing.

6 We have partnered with some
7 international colleagues. Especially, Japan has been
8 interested and have been very helpful in pursuit of
9 the...the fish 2-generation test and, you know, are
10 ramping up to assist in the pursuit of the amphibian
11 growth reproduction, you know, assay.

12 The avian 2-generation is the one that's
13 the...the...the most limited, because the...the U.S.,
14 you know, and our program is the only one that's really
15 putting forth the...the resources, but we have projects
16 associated with some other partners, including the
17 Department of Army and the USGS who have, you know,
18 their own in...interest in...in assisting in developing
19 these longer-term type tests in avian species.

20 **DR. BROWN:** Brown. I guess I'd like to
21 go back to the rationale for the...the 73 chemicals
22 that have been selected, and I...I just do not...don't
23 know exactly what the rationale was for the selection
24 of these compounds.

25 I mean, obviously, they're...they're

1 pesticide, heavy on pesticides which are probably also
2 in the environment, considerable amounts in the
3 environment, but as I recall, going back to some of
4 the...a couple of the other groups in which I
5 participated in...in this overall process, the emphasis
6 seemed to be on selecting compounds from a wide diverse
7 range of different chemical classes rather than kind of
8 focusing on...on...on single classes where I would
9 assume the pesticides, in general, tend to fall in
10 similar chemical classes, a few chemical classes rather
11 than a wider range.

12 **DR. TIMM:** Gary Timm. Well, first of
13 all, one has to remember that the...what we're required
14 to do by law, and we are required to screen pesticides.
15 So, that was...was one of the things that we would have
16 foremost in our minds, that, you know, if you don't do
17 anything else, do what the law tells you to do.

18 And we had originally attempted to use a
19 high sequence screening that...to help us sort out
20 through some other...other candidates, as...as I
21 mentioned in my remarks yesterday. That didn't work
22 terribly well.

23 We took, really, off-the-shelf methods
24 that the pharmaceutical industry found satisfactory,
25 and, of course, they're looking for...they're looking

1 for very powerful compounds. They're looking for the
2 ethanol estradiols in the world. They don't want a
3 birth control pill that's the size of a football.

4 So, they're not looking for...for weak
5 stuff, but the stuff that...that we have is several
6 orders of magnitude less potent, typically, than...than
7 your pharmaceutical levels, so it's that we had to...to
8 optimize those assays, and, you know, at the time we
9 were making decisions about picking chemicals, that
10 hadn't happened yet.

11 So, we didn't...didn't rely on that
12 technology. We moved to a strictly exposure-based
13 system, because we also did this pilot study that I
14 mentioned where we looked at existing data and we said,
15 you know, that stuff isn't...the payoff that we would
16 get from looking at existing data as...as to hits
17 that...of chemicals that we should proceed with wasn't
18 worth going through the data. We, you know, on the 30
19 chemicals, there was a lot of old stuff there. There
20 was nothing that would really tell us to move forward,
21 and this was...mainly, this was all pesticide actives.

22 So, we said we...we should focus on
23 pesticide active. We should also use high production
24 volume inerts, because they're pesticide chemicals
25 under the law as well, and we will use just strictly an

1 exposure base for this first 50 to 100. We started off
2 with slightly over 100 and...and we winnowed it down,
3 looking at these exposure databases, to 73.

4 And that...we proposed the methodology,
5 got comments on the methodology. People were not wild
6 about it, because everybody really would like to have
7 had a hazard basis but said, you know, given everything
8 else, this is a reasonable approach.

9 We...we've done it. We put out a
10 preliminary list. We're...we've taken comments on that
11 list, and so, a final list will come out along with
12 the...the orders for testing and the...the final
13 battery. And that's, you know, the target for all that
14 stuff is...is August of this year.

15 **DR. PORTIER:** Well, this has been fun
16 discussion, but we need to kind of come back and
17 finalize our program here. I think we've covered all
18 of the questions that EPA has...has asked. I just want
19 us to take this one last opportunity to go through the
20 panel and see if there's any topic that we haven't
21 touched on that you'd like to make sure we discuss and
22 include in our...our report.

23 And...and yesterday, if I heard right,
24 EPA did open the door that we can make recommendations
25 on where we think short-term research might want to be

1 directed. Clearly, the in vitro methodology is an area
2 that's going to show up in our report, but I just
3 wondered if there were other things that haven't been
4 discussed yet that we should put on the table and
5 discuss in these final minutes.

6 Dr. Lasley?

7 **DR. LASLEY:** Well, I'm not sure that
8 these things weren't brought up or discussed, but I...I
9 think there's clearly some avenues that are opening up.
10 I mean, there are new endocrine disruptors being
11 described in the literature, and these are going to go
12 beyond estrogen, androgen, and testosterone. Specific
13 are...are thyroid and, specifically, the glucocorticoid
14 assays.

15 And I think the technology in signal
16 transduction assays is...is growing by leaps and
17 bounds, and I think this will serve well to...to fill
18 in the area of in vitro assays and...and take some
19 pressure off some of the less specific in vivo assays.

20 So, I think these are two areas that,
21 you know, are definitely going to come up.

22 **DR. PORTIER:** Yes, Dr. Zoeller?

23 **DR. ZOELLER:** You know, I...I've said
24 this before, but I guess I'll say it again within in
25 this context, but I do think that...that the thyroid

1 system is...is certainly the least represented in the
2 tier, and, you know, maybe depending on your research
3 bias, it's either the more important axis or maybe the
4 less important axis, but, certainly, in terms of public
5 health, there's a lot of good reason to believe that
6 thyroid function is important.

7 And having...having specific and
8 sensitive measures of thyroid hormone disruption at
9 the...at the receptor tissue response would be a really
10 valuable thing to have. I don't think anybody would
11 dispute that, but I think that there are probably a few
12 ideas that are...that are at least manageable within
13 the context of Tier 1 that would be good to develop.

14 It's clearly not there, but just in
15 terms of development, if there...if there are specific
16 research avenues that EPA were going to take, it seems
17 to me that that's something that really needs to be
18 built up into the tier.

19 **DR. PORTIER:** Dr. Timm?

20 **DR. TIMM:** Gary Timm. I'm aware that
21 the Japanese have developed a transductional activation
22 assay for TR-alpha and TR-beta. I...I don't know how
23 far along it is in terms of, I mean, they've run a
24 bunch of chemicals through it, but validation of such a
25 system would be difficult if you don't have a number of

chemicals that are...are flagged as...as interfering with the receptor.

So, I don't think it's progressed very far, but...but, at least, a start on that technology exists.

DR. PORTIER: You were asked. Last chance for comments. Dr. Furlow? I knew I could count on you.

DR. FURLOW: Yeah, well. It's...this has been touched on, but I guess one other concern I have. It's impacted my...the research I do in my own lab, and that is...and that is the somewhat controversial of...of strain differences, and I...I do understand that in...in your experience, the experience of the EPA group, this is...this hasn't made a big difference, but I guess for future research, I notice in discussions of...of strain differences and...and sensitivity of these different compounds, though, that when that was discussed in either the...the ISRs or...or answers to the peer reviewers, basically, the...the answer was well, you know, yes, there are strain differences, and it would take a really long time to figure out the basis of those strain differences and whether or not, you know, what strain is...is appropriate for what...what assay.

1 And so, I understand the...the time and
2 convenience and the time pressure and...and the money
3 pressure you guys are on, but I guess, for future down
4 the road, I'd like to...I'd like to put in a plug for
5 trying to understand what those genetic differences are
6 if there...there's research that can be done, either
7 supported by the EPA or other agencies to try to figure
8 out what...what is it that makes one strain more
9 sensitive to chemical X than others.

10 Is it simply...is it simply the liver,
11 or is it any number of things, receptors, et cetera?
12 And so, I'd just kind like to put in a plug for that
13 and...and also just make sure that just, again, to tell
14 the EPA I think you guys need to keep paying attention
15 to that, because I...I'd hate...that is a place where
16 you could have false negatives.

17 I know in my...my own research, we study
18 glucocorticoids, and looking at muscle mass loss in
19 C5756s or, essentially, we're almost a factory to
20 dexamethazone. We give it to 5Cs, and bang, within a
21 week, their muscles are shrinking like crazy. So, you
22 know, why is that? We're trying to figure that out,
23 and, actually, if we figure out the genetics of that,
24 it might be very interesting from a basic science
25 question.

1 But I also...also think it's a very
2 important question in terms of toxicity testing
3 broadly, even beyond endocrine disruption. So, as a
4 plug for future research, I mean, you...you could even
5 criticize, easily, the *Xenopus laevis* assay from that
6 standpoint as well. I mean, this is not a North
7 American species.

8 This is an animal that's adapted that's
9 completely aquatic, et cetera, and even if you...you
10 know, I know there were some...some discussion in
11 looking at *Xenopus laevis* versus *Tropicales*, *Tropicales*
12 is harder to raise and et cetera, but, you know, you
13 could...you could criticize any of these assays from
14 that standpoint. I...I understand that, but I think
15 it's something that if...I know it can't be done in the
16 short term, but I think it's something that, as a
17 priority in toxicology research, I think it's something
18 that we ought to think about moving forward.

19 **DR. TIMM:** May we interject? Ralph
20 Cooper as a...an observation that is, I think,
21 pertinent to some of the discussion we've been having,
22 so I would like to turn the mike over to him for a few
23 minutes.

24 **DR. COOPER:** Ralph Cooper, EPA. There
25 was two discussions about some things that might be

1 added, one of them, I think, in the thyroid axis with
2 some of the maybe materials you could add a few
3 endpoints that might be useful in interpreting thyroid
4 mode of action. One of them was cholesterol.

5 And then there was the comment about
6 looking at the liver as we're trying to evaluate liver
7 function in this...in tier protocols, and I wanted to
8 mention that the clinical chemistry panel has included
9 those, and I think rather than just say that that's in
10 there...and I can't list all the things that are
11 included in it...but if you could give us some insight
12 as to a), how to use those measurements when we
13 evaluate the data, I think that that would be very
14 useful.

15 So, that's part of that working
16 protocol, whether or not that would help us out with
17 that.

18 **DR. PORTIER:** So noted. Not seeing any
19 enthusiastic hands to continue the discussion, I think
20 I'm going to ask EPA if they got out of this...enough
21 out of this last discussion. And we're certainly going
22 to write. Hopefully, we're going to capture everything
23 in our minutes, and...and you'll see that, but any
24 final comments?

25 **DR. TIMM:** Gary Timm. I...I...I

1 think...I think we have a fairly clear sense of what
2 the panel feels about...about the battery that we
3 proposed, despite some misgivings, certainly, that we
4 have heard from...from people yesterday.

5 I think there was certainly concern that
6 the battery was too redundant and that it...it
7 should...it was...it's costly, but what I heard today
8 is that we would lose valuable components if we...if we
9 did remove anything that...that we had proposed, and I
10 guess that...that's a very, very useful message for us
11 to...to take home.

12 And we also appreciate, once again,
13 I...I think reminding us of some of the problems
14 that...that still exist that we can work on, and we
15 look forward to moving ahead and appreciate your...your
16 input.

17 **DR. PORTIER:** Dr. Eldridge?

18 **DR. ELDRIDGE:** But I would follow that
19 up by suggesting that, as time passes and technology
20 improves and you also collect more information, that
21 some redundancies that may appear to be candidates for
22 omission. Unless you could find better tests, more
23 specific tests, and...and other ways of getting at the
24 questions, particularly with regard to specificity,
25 and...but because there's always going to be this

1 concern about the large-scale in vivo testing,
2 and...and so, finding ways to...to reduce that
3 would...so, the suggestion is to keep alert for
4 potential ways to reduce the redundancies if you can
5 find better specific substitutes.

6 **DR. PORTIER:** Okay. I think, at that
7 point, we're finished with our regular program and all
8 the questions, and we've made the rounds. So, I'm
9 going to turn it over to the Federally Designated
10 Official to formally close the meeting.

11 **MR. DOWNING:** Thank you very much.
12 Well, as we draw our day to a close, we find we've come
13 to the conclusion of the meeting of the FIFRA SAP on
14 the Endocrine Disruptor Screening Program Proposed Tier
15 1 Screening Battery.

16 I want to thank everyone for their
17 participation in this meeting. I think it's been
18 excellent, and we've had a lot of really excellent
19 presentations as well as the wonderful exchange of
20 ideas. I think the Endocrine Disruptor Screening
21 Program folks have a good sense of the panel's thoughts
22 about all that.

23 I would like to mention that the
24 presentations and the slides, even those that we've
25 seen this afternoon, will be available on the OPP

1 docket shortly. I'll say maybe tomorrow, as well as,
2 of course, within 90 days, we will be preparing our
3 final report, the meeting minutes, essentially, which
4 will also be published.

5 Thank you. Good to know.

6 All the documents that were presented
7 yesterday are now on the docket, she tells me, so we're
8 getting better and better and quicker and quicker at
9 this. So, anyway, that is available as well, as I say,
10 the documents today will be up there shortly as well.

11 Well, with that, then, I will draw to a
12 conclusion of this meeting of the FIFRA SAP. And,
13 again, thanks to everyone and thanks to the audience
14 for hanging in there with us as well, and we will be
15 adjourned.

16 **DR. PORTIER:** And if the panel will meet
17 in the break room in, say, 10 minutes. Give you a
18 chance to get your stuff together.

19 (**WHEREUPON**, the meeting was adjourned at 3:38 p.m.)
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SUBMITTED ON March 26, 2008



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