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Day Two

August 18, 2000

PROCEEDINGS

DR. THRALL: It's my pleasure to reconvene the FIFRA SAP Open Meeting on the EPA Health Effects Division's proposed classification of the human carcinogenic potential of malathion.

I'll begin by re-introducing the Panel members. I don't think there are very many new players here this morning, but we'll do this anyway. I am Mary Anna Thrall. I am a member of the SAP and I am acting as your Chairperson today. I am a Veterinary Clinical Pathologist and a Professor in the Pathology Department at Colorado State University.

And I'll just go ahead and start here on my right. Dr. Capen?

DR. CAPEN: Yes. I am Charles Capen, Professor and Chairman of the Department of Veterinary Biosciences at Ohio State University, a permanent member of the Scientific Advisory Panel. My expertise is in pathology, endocrinology and toxicology.

DR. BRUSICK: My name is David Brusick. I work

1 with Covance Laboratories as Vice President for
2 Toxicology. And most of my research and scientific
3 interest has been in genetic toxicology and carcinogenic
4 mechanisms.

5 DR. CHEN: My name is James Chen. I am at the
6 National Center for Toxicological Research in FDA. My
7 expertise is biostatistics.

8 DR. GAYLOR: Dave Gaylor. I'm with Sciences
9 International, Inc. My areas are biostatistics and risk
10 assessment.

11 DR. MCCONNELL: I am Gene McConnell from
12 Toxpath, Incorporated. I am a veterinary pathologist and
13 toxicologist. My areas of expertise are in the design,
14 interpretation and conduct of animal bioassays.

15 DR. THRALL: Dr. Williams?

16 DR. WILLIAMS: Gary Williams. I am an M.D.
17 Pathologist and Professor of Pathology at New York
18 Medical College. And my area of interest is chemical
19 carcinogenesis and safety assessment.

20 DR. EVERITT: I'm Jeff Everitt. I'm a Senior
21 Scientist at CIIT in Research Triangle Park, North
22 Carolina. My area of expertise is toxicologic pathology

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1 and comparative medicine.

2 DR. BOORMAN: I'm Gary Boorman. I'm a
3 Veterinary Pathologist. I'm with the National Toxicology
4 Program, which is located at the National Institute of
5 Environmental Health Sciences. My experience and
6 background are pathology of -- especially cancer in
7 rodents and in design of rodent studies.

8 DR. NEEDLEMAN: I'm Herbert Needleman. I'm a
9 Professor of Psychiatry and Pediatrics at the University
10 of Pittsburgh. And my studies involve the influence of
11 lead at low dose on children's brains and behavior.

12 DR. ROBERTS: I'm Steve Roberts. I'm a
13 Toxicologist, Professor and Director of the Center for
14 Environmental and Human Toxicology at the University of
15 Florida.

16 DR. THRALL: Thank you. Mr. Paul Lewis, who is
17 our designated federal official this morning, will go
18 over some administrative procedures with us.

19 MR. LEWIS: Thank you, Dr. Thrall. I want to
20 again thank all the Panel members for agreeing to serve
21 at this SAP meeting and for deliberations dealing with
22 malathion.

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1 I just want to remind everyone that again this
2 meeting will be following Federal Advisory Committee
3 requirements. Such that being the case, we have a public
4 docket, where all the material that was presented
5 yesterday and to be presented today will be available on
6 that public docket. And again, the background documents,
7 agenda and the like are also available on our web site.

8 In terms of the format for the meeting today, we
9 will be continuing our deliberation based on following up
10 on the questions being posed to the Panel. We're going
11 to first begin by having the agency provide some follow
12 up discussion based on comments made by the Panel. Prior
13 to that we'll also have introductions by officials.

14 We will be distributing to the Panel additional
15 material that the agency has -- will be providing to the
16 Panel. It will also be available in the Docket. In
17 addition, some additional material that was provided to
18 us this morning from public commenters will be going to
19 the Panel and to the Docket.

20 Thank you. And thank you, again, Dr. Thrall,
21 for agreeing to serve as Chair for this session.

22 DR. THRALL: Thank you, Mr. Lewis. We'll now

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1 have some welcoming remarks by Dr. Galson, who is the
2 Director of the Office of Science Coordination and
3 Policy.

4 DR. GALSON: Thanks, Dr. Thrall, and welcome
5 back everyone. We're looking forward to a very
6 productive day today. I neglected to make a comment
7 yesterday that I wanted to just add today.

8 I think most of you know that we have two types
9 of members on the Science Advisory Panel. We have
10 permanent members and ad hoc members. The permanent
11 members, although we wish they were really permanent, are
12 serving four year terms, and the ad hoc members are
13 selected for each meeting as a consequence of their
14 special skills that we believe they'll add to the review
15 in question.

16 We have a new member of our permanent Panel, who
17 is attending their first meeting today, and that is Dr.
18 Roberts. And I apologize for not acknowledging him.
19 We're extremely grateful that he has agreed to join us as
20 a permanent member. He has undergone quite an extensive
21 month's long vesting process, including being nominated
22 by the National Institutes of Health's National Science

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1 Foundation to the agency, and then gone through a lot of
2 layers of review.

3 We know that he's going to really help us out
4 and, again, we're extremely grateful of his time for
5 being here.

6 Thanks. I also want to introduce Dr. Richard
7 Hill of my office who is going to be sitting in for me
8 this morning. I've got to go, but I'll be back after
9 lunch.

10 Thanks a lot.

11 DR. THRALL: Dr. Finnercrisp, do you have any
12 comments?

13 DR. FINNERCRISP: Are we ready to get on to the
14 business at hand, or should I just say hi?

15 DR. THRALL: I think we're ready for business.

16 DR. FINNERCRISP: Okay. I thought I would
17 mention that in response to several issues that were
18 raised yesterday that the agency has been busy doing its
19 homework and acquiring information in three categories.
20 We will distribute to the Panel, and put in the Docket
21 after we get some more copies made, a series of fact
22 sheets having to do with mosquito control. So it's

1 responsive to Gene's request about alternatives. We'll
2 share those with you in a few minutes when we get the
3 extra copies.

4 Ms. Shepherd mentioned a series of studies by
5 Dr. Plasiak, and we've acquired the references that Bob
6 Simon had submitted to the agency. We've asked Dr.
7 Brusick to have a look at those today to provide some
8 perspective as to whether or not they would be useful or
9 critical to completion of our hazard assessment on the
10 cancer potential.

11 And thirdly, if you will recall there were two
12 epidemiological study cites in the comments offered by
13 NCAMP. And Dr. Jerry Blondell, the epidemiologist in the
14 Health Effects Division, is here to provide you all a
15 brief overview of the contents of those two citations,
16 and some other things that he has had time to acquire by
17 the same authors.

18 DR. THRALL: Thank you.

19 DR. FINNERCRISP: So we're prepared.

20 DR. THRALL: Good. I think I'll turn it over to
21 Dr. Copley now. Dr. Dementi, did you have a comment?

22 DR. DEMENTI: Yeah. I had one follow up from

1 yesterday's meeting, myself. And this had to do with Dr.
2 Williams' question about whether all the tumors or most
3 of the tumors were benign. And I think that my response
4 was really not adequate on that question. Actually, I
5 think malignancy constitutes a fair fraction of what we
6 have here.

7 In the mouse liver, for instance, a substantial
8 fraction of the tumors in the low dose group are
9 carcinomas, and some eight of the 16 original carcinomas
10 were downgraded to adenomas.

11 In the case of the rat liver, we originally had
12 five carcinomas diagnosed in the high dose group -- I
13 mean in the study. They were all downgraded by the PWG
14 to adenomas. But I have concerns about that, and I would
15 like some further examination of those slides.

16 At issue also is the thyroid C-cell tumorigenic
17 response in the rat. I think that progression in that
18 case to carcinoma is at issue in this instance. In the
19 case of the thyroid follicular cell response, we have an
20 enrichment of carcinomas in that case.

21 In the case of the oral tumor response, half of
22 those were malignant. In the case of the nasal tumor

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1 response, one of the four was originally diagnosed as a
2 carcinoma. It was then downgraded later by a peer review
3 to an adenoma.

4 In the case of testicular tumors, admittedly all
5 of those appeared to be benign. But there is a concern
6 in humans that testicular tumors do progress in humans to
7 malignancy. And leukemia by definition is a malignancy.

8 And then as to the question of irrelevance of
9 benign versus malignant tumors -- I'm quoting now from
10 the Office of Science and Technology Policy paper that I
11 cited yesterday concerning that we combined adenomas and
12 carcinomas. And this is one of the reasons.

13 This practice can make the total neoplastic
14 response, benign and malignant, clearly significant
15 despite the lack of statistical significance in the
16 tumors diagnosed as malignant. These pathologists
17 believe that truly benign tumors in rodents are rare and
18 that most tumors diagnosed as benign really represent a
19 stage in the progression to malignancy.

20 And in the case of the mouse study, that was an
21 18 month study. We had abundant benign tumors in the
22 high dose group. After two years I strongly suspect many

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1 of those would have gone to carcinomas.

2 So that's a full response to your question
3 yesterday.

4 DR. THRALL: Dr. Williams?

5 DR. WILLIAMS: Well, we're going to be taking up
6 a number of these tumor types later in the day, so I
7 don't want to address that.

8 But, I mean, as a pathologist I found your
9 reasoning rather difficult to follow. You know, you went
10 from the interstitial cell tumors of the rat testes,
11 which are unequivocally benign, to make the suggestion
12 that this somehow suggests progression to malignancy in
13 humans. Interstitial cell tumors of the testes are
14 exceedingly rare in humans. The principal tumor types
15 are seminomas and others. I mean, there's no connection,
16 and I just don't understand why you're making
17 associations like that.

18 DR. DEMENTI: I was only citing a published work
19 that said that tumors -- testicular tumors -- in humans
20 progress. That's all I'm saying.

21 DR. WILLIAMS: Yeah, I know. But, I mean, we're
22 -- the questions I was asking were trying to elicit

1 facts. And, you know, you're now raising questions about
2 the pathology working group.

3 Now as a matter of fact, we had some extensive
4 discussions about that yesterday, and among the
5 pathologists on the group here, our overwhelming -- I
6 mean, our absolute consensus is that those were reliable
7 reevaluations. And the reason, you know, this question
8 came up -- and Dr. Boorman responded to it yesterday.

9 But the reason diagnoses change is not because
10 one pathologist is taking a blatantly malignant tumor and
11 changing the diagnosis to a benign tumor. But it's the
12 equivocal tumors in the gray zone that are at issue. And
13 those are the ones that when an initial pathologist is
14 reading a study, there can be what we call a diagnostic
15 drift. And then the way that's reconciled is to bring a
16 group in to have them all look at the same lesions
17 concurrently and form a consensus diagnosis.

18 And we felt that the pathologists that were
19 represented on those pathology working groups were very
20 credible, outstanding pathologists, and that the outcome
21 is exactly what we would have anticipated.

22 So, I mean, when you say to me in response to my

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1 question about benign tumors that you have concern that
2 they're really benign, I can't accept that. I have to go
3 by what the best data are that have been offered to us.

4 DR. DEMENTI: Okay. But I left the audience
5 with the impression that I agreed that benign -- that
6 these tumors were basically benign. And I'm saying that
7 there is a lot of evidence here that it goes beyond that,
8 and also that rodent pathologists believe that these
9 things do progress.

10 So each study has its own characteristics. But,
11 also, you know, I, as a toxicologist, would like to know
12 more about the tumors that are right on the periphery of
13 a diagnosis between adenoma and carcinoma. What are the
14 features of that tumor. And furthermore, maybe another
15 section of that liver, right next to that slice that had
16 an equivocal call, may be more enlightening as to just
17 whether it is or is not one thing or another.

18 But to know more about what that is is a
19 question that I have.

20 DR. THRALL: Dr. McConnell?

21 DR. MCCONNELL: You don't want to get into a
22 discussion of this now, do you?

1 DR. THRALL: I think not.

2 DR. MCCONNELL: Okay.

3 DR. THRALL: Let's start out with having EPA
4 give us some information that we requested yesterday, and
5 then we'll get into the specific questions. And we'll
6 talk more about these tumors.

7 Could I turn it over to you, Dr. Copley?

8 DR. COPLEY: Thank you very much. Penny did
9 almost all the introductory stuff I was going to mention
10 about the material. Am I on?

11 DR. THRALL: Uh-huh.

12 DR. COPLEY: Am I loud enough? Okay. Am I loud
13 enough now? Okay. I'm still going to introduce Jerry
14 Blondell, who is our epidemiologist in the Health Effects
15 Division. And he is sitting right over there by Dr.
16 Finnercrisp. And he has a lot of the information that we
17 printed off the two web sites that were mentioned last
18 night, and he also has some of the other information that
19 was discussed yesterday.

20 I also was requested to get information on the
21 metabolism. I brought in the study. I think I'm going
22 to let Judy Housworth make a comment about the metabolism

1 study, since she's the one that had mentioned it
2 yesterday.

3 DR. HOUSWORTH: Thank you. When I was talking
4 yesterday --

5 MR. LEWIS: Dr. Housworth --

6 DR. THRALL: Do you want to introduce yourself?

7 DR. HOUSWORTH: Dr. Housworth. July Housworth.

8 MR. LEWIS: From?

9 DR. THRALL: And who do you represent?

10 DR. HOUSWORTH: Kemy Nova.

11 MR. LEWIS: Thank you.

12 DR. HOUSWORTH: Yesterday when I was talking
13 about the metabolism study, I was talking from memory.
14 There is no pharmacokinetics data in that study. It is a
15 typical guideline of an EPA metabolism study.

16 The study author, which was what I was
17 remembering or recalled, had noted that he felt that the
18 urinary data indicated an overload of the metabolic
19 capacity of the liver and possibly some effect on the
20 excretory properties of the kidney. That was just a
21 conclusion he made from the urinary data.

22 We have no plasma data except at 72 hours, which

1 indicates quite a discrepancy in the amount in plasm
2 between the low dose and the high dose, and about 20
3 times the amount in the liver at 800 milligrams compared
4 to the low dose.

5 DR. THRALL: Dr. McConnell?

6 DR. MCCONNELL: All right. Well, refresh me
7 now. Yesterday I went away with the idea that we had
8 saturation. I think that was the term you used.

9 DR. HOUSWORTH: Yes, I did.

10 DR. MCCONNELL: At 800. Is that now not the
11 case?

12 DR. HOUSWORTH: No. What the question I'm
13 answering is whether or not we have pharmacokinetics data
14 -- if we have time data indicating a plateau in the
15 plasma -- and we do not.

16 DR. MCCONNELL: So you cannot say that there was
17 saturation at 800?

18 DR. HOUSWORTH: I can't from plasma data,
19 because we don't have it, and there is only the
20 appearance of it from the urinary data.

21 DR. MCCONNELL: So you can't say it with any
22 kind of data?

1 DR. HOUSWORTH: No, I cannot.

2 DR. MCCONNELL: Okay. So there is no such thing
3 as saturation. There may be, but we don't have any data
4 to support that.

5 DR. HOUSWORTH: There may be. Right.

6 DR. MCCONNELL: Okay.

7 DR. HOUSWORTH: That was just the conclusion of
8 the study author.

9 DR. MCCONNELL: All right.

10 DR. THRALL: Dr. Housworth, I think there might
11 be another question for you.

12 DR. WILLIAMS: Right. Gary Williams. What was
13 the basis for the suggestion that there was metabolic
14 overload by the pathologist?

15 DR. HOUSWORTH: By the chemist or the -- if you
16 look at the urinary data for the low dose, there is
17 obvious --

18 DR. WILLIAMS: Well, what data are these now?

19 DR. HOUSWORTH: From the metabolism study.

20 DR. WILLIAMS: Metabolism, okay. Yeah.

21 DR. HOUSWORTH: Right. A radio labelled
22 malathion metabolism study.

1 DR. WILLIAMS: Right.

2 DR. HOUSWORTH: If you look at it over time at
3 the low dose, there is a peak rather quickly in the data
4 within 72 hours.

5 DR. WILLIAMS: Uh-huh.

6 DR. HOUSWORTH: If you look at the data for the
7 high dose group, it is low to begin with and then it
8 reaches the high level, which maintains at that high
9 level almost over the whole extent of the study.

10 DR. WILLIAMS: Right.

11 DR. HOUSWORTH: It begins to come down at 72
12 hours. And that's what he was basing his conclusion on.

13 DR. WILLIAMS: Okay. Did your pathologist draw
14 any inferences from the presence of -- in the two year
15 study -- well, actually it's already present at one year,
16 the hepatomegaly and cellular hypertrophy in the liver?

17 DR. HOUSWORTH: Could I ask Dr. Hardesty to talk
18 about that?

19 DR. WILLIAMS: Sure.

20 DR. HARDESTY: This is Jerry Hardesty. I don't
21 think the pathologist --

22 DR. THRALL: Dr. Hardesty, you're going to have

1 to speak up a little bit.

2 DR. HARDESTY: I don't think the pathologist
3 drew any inferences from it, but there was a clear no
4 effect level for hypertrophy in both studies. I don't
5 have the data in front of me right now, but I think that
6 it was at 800 parts per million in the mouse and at 500
7 parts per million in the rat.

8 DR. WILLIAMS: That's the way I read it, yeah.

9 MALE SPEAKER: I don't understand that
10 statement. It started at that level, or it was not --

11 DR. HARDESTY: No. It was not present at that
12 level. It was present at the higher doses.

13 DR. WILLIAMS: Thanks.

14 DR. THRALL: Dr. McConnell?

15 DR. MCCONNELL: And that is confirmed. I went
16 through it some more last night. By the liver weight
17 there is like this with liver weight increase in both the
18 rat and mouse.

19 DR. THRALL: Dr. McConnell, your hand signals
20 won't be picked up by the tape recorder.

21 DR. MCCONNELL: There is a -- let's see. How
22 can I do that? That's how you make an Italian mute, you

1 know. Tie their hands behind their back.

2 There is a sharp delineation between 800 and the
3 two high dose groups. Is that clear enough?

4 DR. THRALL: Thank you.

5 DR. MCCONNELL: And that was hard.

6 DR. HOUSWORTH: I have a point of clarification
7 for the metabolism study. That was conducted on Sprague
8 Dawley rats rather than Fischer rats, which may or may
9 not have had a bearing.

10 DR. COPLEY: Were there any other areas that I
11 was suppose to follow up on that anybody feels I haven't
12 addressed yet? Okay.

13 Should I have Jerry discuss the epidemiology at
14 this point?

15 DR. THRALL: I think so.

16 DR. COPLEY: Okay.

17 DR. THRALL: I think so.

18 DR. BLONDELL: Dr. Jerry Blondell with the
19 Health Effects Division at EPA. I did bring copies of
20 the two publications that were mentioned yesterday. One
21 of them is a meeting abstract in the American Journal of
22 Epidemiology. It was from the annual Society for

1 Epidemiologic Research meeting. And the other was a
2 publication in cancer research.

3 The first study did mention that there were
4 specific insecticides -- well, first of all, let me say
5 that those studies have to do with non-Hodgkin's lymphoma
6 and pesticide exposure. The first study mentions a
7 number of correlations, including significant
8 associations with non-Hodgkin's lymphoma, chlordane,
9 diazinon, difenate and malathion.

10 This study in terms of the evidence for
11 malathion has not been subsequently published. That's
12 not to say that there haven't been subsequent
13 publications on that cohort. There have. The first
14 publication subsequent to that was related to 24D that
15 was published. And I also brought a copy of that
16 article. And in the article where they analyze for 24D,
17 they say analysis of organophosphate use. Adjusted for
18 use of 24d showed an independent association with
19 non-Hodgkin's lymphoma and will be described more
20 thoroughly in a future report.

21 Well, to date there is no future report that I
22 know of. The most recent report actually was an

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1 association with DDT and combining pooled analysis of
2 three studies, which included this analysis that was done
3 in Nebraska which this first article was based on.

4 And, again, they talk about the fact that the
5 most notable increase was found among farmers who use DDT
6 for more than five days a year. However, additional
7 adjustment for use of organophosphates, phenoxiecidic
8 (phonetic) acids and individual pesticides, lindane,
9 malathion and atrazene reduced the odds ratio for the DDT
10 association. And that led to the conclusion, no strong
11 consistent evidence was found for an association between
12 exposure to DDT and non-Hodgkin's lymphoma. Still no
13 specific study, however, that addresses malathion based
14 on this Nebraska evidence.

15 The other study that was discussed -- that was
16 mentioned was a study in Iowa and Minnesota. This was
17 one that we reviewed very carefully, particularly because
18 of the association with 24D. And as a matter of fact,
19 this was one of the studies that the Science Advisory
20 Panel reviewed a few years back when it considered the
21 evidence of -- the epidemiologic evidence for
22 carcinogenicity of 24D specifically for non-Hodgkin's

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1 lymphoma.

2 This study had eight -- well, let's see.
3 Actually -- yeah, eight different analyses that looked at
4 malathion in one way or another and the possible
5 association with non-Hodgkin's lymphoma. And let me sort
6 of specify what those eight were to give you a sense of
7 what we're looking at here.

8 One of them was looking at pesticides that were
9 used as animal pesticides versus -- or excuse me.
10 Insecticides that were used for animals -- treatment of
11 cattle, for example -- and insecticides used on crops.
12 So that's one division.

13 Another division is whether the pesticide was
14 ever handled, or handled just prior to 1965.

15 And then the other one -- the other division
16 that comes into all of this -- is whether there was
17 protective clothing, handled without protective
18 equipment, and then finally whether there was first the
19 individual states, Iowa and Minnesota, whether there was
20 a difference between those two.

21 Out of those eight possibilities, there were two
22 having to do with malathion that were statistically

1 significant, and both of those were handled before 1965.
2 However, in that same data there was also an association
3 with carbaryl, DDT, diazinon, lindane and one of the
4 herbicides, chlorambin (phonetic).

5 So the problem is that there is a tremendous
6 amount of multi cholinergic. That is, there are several
7 correlations and without adjusting one for the other, you
8 can't be sure whether malathion is really responsible for
9 this association that was seen with non-Hodgkin's
10 lymphoma or whether it was one of these many other things
11 that also have significant associations.

12 And so one of the reasons that the National
13 Cancer Institute went ahead to do the agricultural health
14 study was to get beyond these case control studies,
15 overcome the problem of recall bias, where you're asking
16 people to remember what it was they used prior to 1965,
17 for example, which is often a source of concern because
18 of the bias and people's memory. Their ability to
19 remember things.

20 So they are doing this major study that was --
21 some of you who were at the triazine meeting here just a
22 couple of months ago -- the atrazine meeting, I should

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1 say, a couple of months ago knows that Dr. Erin Blair
2 discussed the fact that they have an agricultural health
3 study -- a prospective study -- in Iowa and North
4 Carolina to tease out the differences in what's going on
5 with these different pesticides.

6 And the main reason for doing that study was
7 these earlier studies that came up with these various
8 inconsistent results on non-Hodgkin's lymphoma. And
9 since Dr. Blair was here, I thought I would read from a
10 recent publication in 1997 summarizing -- reviewing
11 cancer and pesticides, by Drs. Sheila Zom, Mary Ward and
12 Erin Blair from the State of the Art Reviews on
13 Occupational Medicine. They had a paragraph on
14 organophosphate pesticides which I think summarizes their
15 conclusions about the state of the knowledge.

16 Organophosphates and insecticides, whose use has
17 grown as the use of organo chorines has decreased, have
18 been linked to leukemia, non-Hodgkin's lymphoma and lung
19 cancer. Analyses for individual organophosphates have
20 shown an excess leukemia risk among farmers exposed to
21 crotozyfos (phonetic), dichlorvos, famper (phonetic) and
22 excess non-Hodgkin's lymphoma risk among those exposed to

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1 diazinon, dichlorvos and malathion. These associations,
2 however, have not taken into account each subject's
3 potential for multiple exposures.

4 And so that's kind of where we are today. We
5 need really to get more information so we can adjust for
6 these confounding factors of multiple pesticide exposure.
7 And I would be happy to provide copies of any of these
8 articles.

9 DR. THRALL: Questions from the Panel? Gene?

10 DR. MCCONNELL: Yeah. That was most useful, Dr.
11 Blondell. A couple of us that happened to grow up on
12 farms were talking about this last night. We both were
13 from the midwest. I remember using malathion one time in
14 a chicken coop, and I think we used it to spray some pigs
15 for lice one time.

16 But I don't think of malathion as a big
17 pesticide in the midwest where these studies were done,
18 but I would like to hear more. Isn't malathion, in
19 addition to the mosquito control, used primarily in
20 orchards? How is it used, I guess would be a better way
21 to ask that question.

22 DR. BLONDELL: No. It has a wide variety of

1 uses on animals and crops. And judging at least in Iowa
2 and Minnesota the number of cases and controls and so on
3 -- well, actually I guess -- okay. Yeah, the numbers are
4 pretty low. They had six cases -- well, let's see. Six
5 cases -- six controls in Iowa. Although this is use
6 prior to 1965. Let me go to one of the other studies
7 that covers everything, if I can.

8 No. They did have 21 and 30. It roughly is
9 about the same as the other insecticides. I wouldn't say
10 that it's much higher or much lower. It's sort of in
11 between. So, you know, it's used.

12 DR. MCCONNELL: Okay. But I guess what it comes
13 down to -- and I appreciate the problems that you have,
14 because it's very seldom that a farmer or anyone else
15 uses a single pesticide. You know, I just don't
16 understand how you're going to sort that out, in fact.

17 So is it fair to say that we can't say there is
18 no association. Can we say there is a lack of
19 association? Or is the proper thing to say that this is
20 an unanswerable question, at least at this time, so we
21 can't say whether there is an association or not with
22 malathion and any malignant disease in humans? In other

1 words, inadequate data?

2 DR. BLONDELL: I would certainly say that the
3 data is inadequate. However, there is an association,
4 but we can't at this point account for whether the
5 association is due to malathion or the other factors.

6 DR. MCCONNELL: Right. Yeah. I remember -- you
7 know, I was on the 24D Panel and we worked hard on that
8 study. Okay.

9 DR. THRALL: All right. Any other questions?
10 Thank you very much. All right. Dr. Copley, shall we --
11 are we ready to go ahead and address issue number two
12 then at this point?

13 DR. COPLEY: All right. I just wanted to
14 mention something else that somebody had asked yesterday,
15 and I'm not sure if it was adequately answered. And it
16 had to do with cholinesterase in general in the rat
17 studies. When we compared the three month, six month, 12
18 month and 24 month cholinesterase values, they did get
19 more severe with time. The inhibition worsened.

20 Okay. The issue for the next set of questions
21 is: the HED CARC classified malathion as suggestive.
22 This is based on the occurrence of liver tumors in male

1 and female B6C3F1 mice and female Fischer 344 rats at
2 excessive doses, and the presence of a few rare nasal
3 respiratory epithelial tumors in male and female rats,
4 and nasal and oral tumors could not be distinguished as
5 either treatment related or due to random occurrence.

6 The first question relating to this is: does
7 the SAP consider the statistically significant trend and
8 pair-wise increases in liver tumors in the male mouse at
9 8,000 and 16,000 parts per million (adenomas of 14 out of
10 55 and 49 out of 51 for the males and females -- I'm
11 sorry -- for the two high doses, as compared to four out
12 of 54 in the controls) to be related to malathion
13 treatment? Why or why not? And what weight should be
14 placed on these data since there is evidence of excessive
15 toxicity based on the marked brain and red blood cell and
16 plasma cholinesterase inhibition and decreased body
17 weight gain?

18 DR. THRALL: Thank you. Dr. Gaylor?

19 DR. GAYLOR: My comments are going to also apply
20 to question 2.2, which is for the females, because the
21 results are quite similar and I think the issues are
22 exactly the same for both males and females. Well, I

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1 guess we'll have to address question 2.2 for females
2 separately. But my comments apply to both.

3 And before I answer the specific question, I
4 want to make a statement about the statistical analysis
5 that was done on these data and other data that we will
6 discuss today. In this case there was very little
7 difference in mortality across the dose groups. And so
8 what you do makes little difference.

9 What was done here was they counted the number
10 of animals at risk at the time of the first tumor. Well,
11 this is a pretty crude procedure that was used up to 20
12 years ago. Since 1980 the IARC procedure and the Peto,
13 et al. procedures more or less have been the standard,
14 and the Peto Prevalence Test has been used in the
15 analyses for a number of these tumors in this study -- or
16 in these studies.

17 The problem with the Peto test is that it
18 requires the pathologist to designate whether a tumor is
19 seen as a result of being a fatal tumor that kills the
20 animal and that's why you observe the tumor, or whether
21 it's nonfatal or so called incidental. The animal dies
22 of other causes or is sacrificed and you see the tumor.

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1 This is very difficult for the pathologists.
2 Most of them objected to this from the very beginning.
3 NTP tended to analyze data as considering all the tumors
4 as incidental or fatal. If the results came out the
5 same, it was nice. If they didn't, it was a problem.

6 More recently the NTP is using what is called
7 the Poly-3 test. We talked about that a little bit
8 yesterday. What the Poly-3 means, it's an adjustment for
9 animals -- for an animal at risk. The weight that is
10 given the animal. The three just means it's timed to the
11 third power. A lot of tumors in rodents, and also in
12 humans, the incidence increases with age or time to the
13 third power.

14 An animal that has a tumor is given full weight,
15 obviously. It lived long enough to get a tumor, or if it
16 made it to the end of the study -- the two year study or
17 18 month study -- it's given full weight. If an animal
18 only made it half way through a study, say 12 months in a
19 24 month study, it is given a weight of one half to the
20 third power, or it's counted as 1/8 of an exposure. If
21 it made it to 18 months, it's 3/4 of the way through a
22 two year study and it's given the weight of 3/4 to the

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1 third power or about the weight of a half.

2 It's a very simple procedure. It's very easy to
3 use. And I would suggest that at least this program in
4 EPA look into using this so called Poly-3 adjustment for
5 adjusting animals at risk in a study. It's more
6 important later on when we talk about the monocellular
7 leukemia in the male rat.

8 That's just a general statement that applies
9 particularly to liver tumors, because some liver tumors
10 may be -- may cause death or may not. And fatal and
11 nonfatal doesn't mean benign and latent. That's not
12 separated in the categories because it's separated in the
13 categories according to the way you're able to observe
14 tumors.

15 Okay. We're being asked are these -- do we
16 consider the liver tumors in male mice, and also female
17 mice, to be related to malathion exposure, why or why
18 not. I think the answer to that is clearly yes. It's
19 not asking us whether it's a direct effect of malathion,
20 or an indirect effect of malathion, or a secondary
21 effect.

22 I think clearly there are liver tumors. There

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1 is a high incidence in the two upper doses. With the
2 pair-wise comparisons there is a statistically
3 significant trend, and clearly there is an increase in
4 liver tumors. Now why they occur, we're not being asked
5 to address, as I understand this question.

6 And then the second part of the question is what
7 weight should be placed on these data since there is
8 evidence of excessive toxicity based on marked brain and
9 red blood plasma and cholinesterase inhibition and
10 decreased body weight.

11 Well, as others have already stated, we're not
12 aware of a relationship between cholinesterase inhibition
13 and tumor production, either increasing or decreasing
14 tumor production. So, you know, I think there is too
15 much emphasis that has been placed possibly on the
16 cholinesterase inhibition as related to tumor production.
17 Certainly it's a major physiological function in the
18 animals, but what it has to do with tumors is not clear.
19 In fact, people are saying it has no connection.

20 The decreased body weight obviously -- and it's
21 fairly sizable in the male mouse. There was a decrease
22 in body weight of 15 percent at the second highest dose

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1 and 18 percent at the highest dose. However, I take it
2 these body weights are at the end of the study. Those
3 tend to be fairly unreliable, especially if you have
4 tumors growing, sick animals and all sorts of things
5 going on. It's better to look at body weight at around
6 12 months before tumors begin to be produced. Although I
7 guess that body weight depression was throughout
8 adulthood.

9 So it certainly indicates an increase -- or the
10 animals are under stress. We tend to use 10 percent as
11 kind of a cut off for being at or above the maximum
12 tolerated dose. So certainly the maximum tolerated dose
13 was exceeded here. It's not of question that we didn't
14 give high enough doses. It's more of a problem of are
15 the doses too high.

16 So the second part of the question asked what
17 weight should be placed on these data. I don't think we
18 can say we give these the weight of 50 percent, so it's
19 either all or none. Do we just totally discount and
20 ignore the fact that liver tumors were produced, or do we
21 say yes, these need to be considered. I don't think we
22 can ignore them. I think we have to consider the fact

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1 that malathion at high doses produced liver tumors.

2 I would like to know, you know, if we had
3 cytotoxicity at the high dose and we had increased cell
4 turnover and that was the reason that these tumors were
5 produced, then we wouldn't have to worry about this at
6 low doses. But as I understand, we're not being asked to
7 consider that.

8 I believe -- so my recommendation would be, or
9 my suggestion would be, that the EPA, in establishing a
10 point of departure for the low dose risk assessment,
11 should consider liver tumors in mice as one of their
12 endpoints for establishing a point of departure. It
13 doesn't mean that that would be the point of departure
14 that would be used. There might be another tumor type.
15 And we're not being asked whether it should go linear or
16 nonlinear. That's beyond the question.

17 But I think the liver tumors are going to have
18 to be considered.

19 DR. THRALL: Thank you, Dr. Gaylor. Dr. Chen?

20 DR. CHEN: James Chen. Also my comment applies
21 to question in male and female study. I noticed that Dr.
22 Gaylor has answered the second part of the question about

1 what weight should be placed on post data.

2 I agree with what -- most of Dr. Gaylor's
3 statement about -- I believe the liver tumor occur in the
4 800 ppm and the 1,600 ppm are related to the malathion
5 exposure and because there are increasing dose response
6 trend. And also the incidence of the two groups are much
7 higher than the control, and also higher than the
8 historical control group.

9 In the second part of the question about how
10 much weight should be placed on this data, so if we kind
11 of consider that the design is adequate, then this data
12 should be placed on zero weight. Say we put a zero
13 weight on the liver tumor. Then I don't see that we can
14 put any weight on the remaining tumors, because once the
15 two high dose groups, the 800 ppm and 1,600 ppm, are kind
16 of determined to be excessive, then the other tumors
17 would be excessive, too.

18 So in my opinion we should -- the dose would be
19 also excessive to other tumors. So in that case, the
20 implication would be that 800 ppm would be the MTD of
21 this particular study, which we talked about the survival
22 rate or body weight or the MTD is not exactly at 800 ppm.

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1 So how much weight should be placed on this.
2 Dr. Gaylor say we cannot put 50 percent. Either put zero
3 or 100 percent. But what I think, we should put some.
4 How much weight, it's really hard to kind of come up with
5 what it needs to be when we're aware of those tumors that
6 occur at the high dose, since body weight, particularly
7 at 1,600 ppm, kind of the body weight reduction I think
8 is at least 20 percent in the 1,600 ppm group.

9 But they do have a dose response trend. There's
10 an increase in dose response trend. Also, the tumor rate
11 at the two low dose groups, 100 ppm and 800 ppm, are
12 higher than the control group, although not significant.

13 DR. THRALL: Thank you, Dr. Chen. Dr.
14 Needleman?

15 DR. NEEDLEMAN: I'm in agreement with what Dr.
16 Gaylor said. I've expressed myself on that before. I
17 have little else to add, except to point out that in the
18 late '70's there was a book called Exploratory Analysis
19 by Masteller and --

20 **(END OF TAPE 1, SIDE A)**

21 DR. NEEDLEMAN: -- and the analyst in this study
22 removed the upper groups after the data had been

1 collected. They were transforming the study from a
2 confirmatory hypothesis testing study to an exploratory
3 study. It's okay to do that, but you can no longer say
4 that you're testing a hypothesis. The post hoc
5 examination of the data rules out the possibility of
6 saying that you're testing a hypothesis.

7 I have expressed myself before about the reasons
8 I think that the upper dose groups should be given full
9 weight in the analysis.

10 DR. THRALL: Dr. Boorman?

11 DR. BOORMAN: I would like to stimulate a little
12 discussion on the term liver tumors versus liver
13 adenomas. And one of the things that caught my attention
14 is if you look at the carcinomas in the males, there was
15 none in the controls. There was four at 100. But at
16 800, which is within a reasonable dose, there was only
17 two. And two at the next dose and none at the high dose.
18 And if you look at the female mice, there was one
19 carcinoma in the controls, zero at 100, two and then one
20 and then two. So neither in the males nor the females is
21 there statistical evidence of a carcinoma.

22 And so I agree with the comments made by Drs.

1 Gaylor, Needleman and Chen. But I think to use the term
2 liver tumors, implying adenomas plus carcinomas, may be
3 misleading, because there is very little evidence that
4 the carcinomas are being induced by malathion. And some
5 might argue that there is even evidence that they're
6 being inhibited, because they at least in the males go
7 down. I wouldn't go that strong.

8 But I think that I would like to stimulate at
9 least a little bit of discussion. And my suggestion
10 would be to substitute that this is based on the
11 occurrence of liver adenomas rather than liver tumors.
12 But this may engender a lot of discussion.

13 DR. GAYLOR: And I want to respond to that.

14 DR. BOORMAN: Sure. Please.

15 DR. GAYLOR: You can't tell by looking at these
16 crude tumor rates what is going on here. In fact, you
17 raise a good question here. For carcinomas in the male
18 mice, a Poly-3 analysis may indeed show something. You
19 know, I kind of doubt it, but it could. But that's what
20 is required here.

21 The reason it's falling off is animals are dying
22 off before they have time to progress to carcinomas.

1 That may be one reason why you're not seeing any
2 carcinomas at the high dose. Survival is so poor.

3 MALE SPEAKER: Is survival poor in mice?

4 DR. GAYLOR: I'm sorry. Not in the mice. But,
5 you know, that still could be going on. It may be that
6 carcinomas are only showing up in the animals that live
7 to near the end of the study. That's probably not going
8 on with the mice, though. It could be in the rats.

9 DR. BOORMAN: Yeah, it's speculation. Right,
10 that's rats.

11 DR. GAYLOR: Probably that's a possibility in
12 the rats, but probably not in the mice. But there,
13 again, a Poly-3 for a proper adjustment for survival
14 would remove that, whether that's an issue or not.

15 DR. THRALL: Dr. Copley?

16 DR. COPLEY: Yeah. I just wanted to make a
17 comment on something Dr. Gaylor had mentioned earlier
18 about body weight. In the DER that we provided on the
19 mouse, which is reference number seven, body weights are
20 decreased from the very beginning of the study all the
21 way through. They're not just endpoint changes in this
22 particular study at the 8,000 parts per million dose and

1 the 16,000 parts per million dose.

2 DR. GAYLOR: That's even more crucial.

3 DR. COPLEY: So it's showing that it does --
4 it's not just an endpoint. It's a variation that is hard
5 to determine. You can see it much earlier.

6 DR. GAYLOR: Because what is important is the
7 body weight early in the study. But the relationships
8 between tumor incidence and body weight, you have to look
9 at body weights from three months up to 12 months.
10 That's where it's most important.

11 DR. THRALL: Dr. Dementi?

12 DR. DEMENTI: Yes. What concerns me is the
13 lumping together of the 8,000 and 16,000 ppm groups. At
14 the 8,000 ppm level, there was no marked cholinesterase
15 inhibition. In fact, as I tried to explain yesterday,
16 there is no substantial evidence that cholinesterase was
17 even inhibited. There was a 20 percent inhibition I
18 think in females and 23 percent in males, which was not
19 statistically significant. So you need to make a
20 distinction between what cholinesterase is doing at 8,000
21 and 16,000.

22 Also I sought to note that in females the body

1 weight deficit was 9.7 percent, not quite 10 percent.
2 But 10 is the figure that's being cited as the cutoff
3 point. But I think you really need to focus a little
4 more on females at 8,000 ppm, which is solidly positive
5 for tumorigenic response. But yet I don't think there is
6 marked evidence in that group as it is in the other
7 group.

8 DR. THRALL: Dr. Williams?

9 DR. WILLIAMS: Yeah, thank you. Gary Williams.
10 Well, let me start with this point on body weight,
11 because I think we're losing sight of a very important
12 point that Dr. Copley made yesterday.

13 What is important is not the terminal body
14 weights, because at that point you have a lot of sick
15 animals, etc. What is important is the body weight gain
16 reduction. And if you look at the curves -- which I have
17 open in front of me and I've done this calculation, which
18 I think anybody who spent any time on this study should
19 have done -- the weight gain in the controls is about 14
20 grams over the course of the study.

21 The weight gain in the high dose group -- I'm
22 talking about males now -- is six grams, less than 50

1 percent of the weight gain of the controls. The weight
2 gain in the 8,000 ppm is only seven grams, 50 percent
3 reduction in body weight gain. That is a profound toxic
4 effect.

5 Now I want you to be absolutely clear that when
6 we are talking about toxicity here, we're not talking
7 about cholinesterase inhibition. We're talking about
8 gross toxicity to these mice. And there is no doubt, I
9 think, in the opinion of all of us here that these were
10 severely intoxicated animals at these two high doses.

11 DR. THRALL: Dr. Roberts? Oh, Dr. Everitt?

12 DR. EVERITT: Yeah. I would like to go on
13 record as saying I'm looking at systemic toxicity.
14 Personally I believe the acetyl cholinesterase may be a
15 bio marker of exposure, but I'm not putting a whole lot
16 of weight into the degree of acetyl cholinesterase
17 inhibition as manifested the toxicity.

18 There is substantial depression of body weight.
19 There is very significant depression of feed consumption
20 at the outset of the study in those groups. And at the
21 end of that study, there is very significant elevation of
22 hepatic weights in the 8,000 part per million group also.

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1 There is a 19 percent increase in liver weight. So we
2 have significant indication that there is systemic
3 toxicity.

4 In the rats where we have 100 percent incidence
5 of death, that's maybe the only time you're see
6 pathologists and statisticians agree on anything, because
7 you have 100 percent death. That's got to be significant
8 toxicity. We don't know why those animals died. They
9 died without cholinergic signs, but they're obviously
10 under systemic toxicity.

11 DR. ROBERTS: Steve Roberts. Getting back to
12 something I mentioned yesterday, in my mind there are two
13 questions here: a qualitative question and perhaps a
14 quantitative dose response question. In terms of
15 weighing from a qualitative standpoint, you count the
16 high doses. I think you have to. I mean, they're
17 clearly associated with malathion exposure. And if you
18 want to answer the qualitative question about whether or
19 not it's tumorigenic, you have to count them.

20 I think the issue then in terms of weighing, in
21 my mind, is whether or not they are suitable for dose
22 response analysis. And I have some real questions about

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1 that because of the loss of weight and because of the
2 evidence of toxicity. And in fact the EPA's carcinogen
3 guidelines talk about use of high toxicity doses and
4 don't rule them out for a qualitative answer in terms of
5 whether or not it's a carcinogen, but do caution against
6 their use for dose response purposes.

7 And I share the concerns about using those doses
8 for dose response analysis, but not for answering a
9 qualitative question.

10 DR. THRALL: Dr. Williams?

11 DR. WILLIAMS: Gary Williams, yes. I would like
12 to follow up on that, particularly since at the end of
13 the day I'm one of the respondents to the question on the
14 weight of evidence and each of these tumor types has to
15 go into that. So I've been thinking a lot about these,
16 particularly the mouse liver tumors, because this is in
17 fact the main and probably the only unequivocal tumor
18 response in all of these studies that have been done.

19 Now we've talked about the -- you know, the
20 severe effect on body weight gain. I would like to
21 subscribe to what Dr. Boorman said about the pathology.
22 And these are predominantly benign tumors. And it's not

1 that we don't, Dr. Dementi, count benign tumors as part
2 of a carcinogenic effect. I would still call this a
3 carcinogen, even if they had only benign tumors.

4 But the significance is in what it tells us
5 about the biological processes that are leading to the
6 tumors. When we are administering to animals DNA
7 reactive or genal toxicity chemicals, we get a high
8 incidence of malignant tumors. On the other hand,
9 chemicals that operate by a different mechanism, such as
10 I'm going to suggest for this one, produce predominantly
11 or exclusively benign tumors as we're seeing here.

12 Now what is going on in these mice?
13 Unfortunately, we don't have good mechanistic studies as
14 Dr. Gaylor called attention to a moment ago. It would be
15 very nice to have some cell proliferation data and other
16 things that we know influence the development of these
17 kinds of tumors. But what we do have is clear evidence
18 of metabolic overload, which is why I queried that aspect
19 earlier.

20 Now in this case, let me say we cannot look at
21 the terminal liver weights, because these animals all
22 have tumors, so those weights don't really mean anything.

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1 But what we do have that is valuable is the 12 month
2 liver weights. In there, there is a clear increase in
3 absolute and relative liver weights in the 8,000 and the
4 16,000 parts per million group. And in the high dose
5 group, it's almost a 50 percent increase in absolute
6 liver weight.

7 So given the fact that we know that malathion is
8 predominately metabolized in the liver, when this
9 chemical is coming in by the oral route at these high
10 doses, this is the scenario I'm envisioning. The animals
11 are being presented with a tremendous load of malathion
12 that they have to metabolize, which is broken down by the
13 carboxyl esterases for excretion in the urine. And there
14 is probably a lot of enzyme induction going on, leading
15 to liver enlargement hypertrophy. And those are
16 conditions that we know from many other studies with
17 agents like phenobarbital and others lead to increases in
18 rodent liver tumors.

19 And so I feel that we've got a plausible
20 mechanism here, as well as a clear indication that these
21 tumors are occurring only at highly toxic doses in these
22 mice. And if I have to go choose between 100 and zero

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1 weight, I'm going for zero.

2 DR. THRALL: Gene?

3 DR. MCCONNELL: When you're finished with the
4 discussion, I think it's appropriate to read Dr. Hard's
5 comments, or I can read them at your pleasure.

6 DR. THRALL: Okay. Go ahead, then, with your
7 comment, Dr. Brusick.

8 DR. BRUSICK: I think I would like to also go
9 into the group that if we're going to use the zero or
10 100, I would go with the all or none -- I would go with
11 none. I agree that we cannot -- qualitatively it appears
12 that these tumors are related to exposure to high
13 concentrations of malathion. But trying to extrapolate
14 those down to the intended purpose of these studies,
15 which is to provide some degree of information about risk
16 at low levels of exposure for human beings, that
17 information is really not relevant.

18 One of the reasons that makes me believe that is
19 that scientifically -- or the scientific community has
20 for a long time believed that there is a maximum
21 tolerated dose that was selected for the purpose, I
22 believe, of establishing some sort of cutoff, that above

1 that point there is a lot of confounding factors that we
2 don't understand that can cause effects that really have
3 very little or no relevance to lower dose levels. And
4 that's the whole purpose of doing a MTD.

5 So if we're exceeding a MTD, then I really
6 strongly believe that that information, if it isn't zero,
7 has very, very little weight going into a weight of
8 evidence that is really going to come out of this for the
9 purpose of looking at low level exposures for human
10 beings.

11 DR. THRALL: Thank you, Dr. Brusick. Dr.
12 McConnell, did you want to read the comments in?

13 DR. MCCONNELL: Right. I think that, you know,
14 to be fair to Dr. Hard, we should.

15 My view is that little weight should be accorded
16 to the increases in liver tumors in mice, because there
17 is no evidence of carcinogenicity at lower doses. The
18 increase occurred at doses exceeding the MTD and the
19 hepatic carcinogenesis in B6C3F1 mice is not a very
20 persuasive index of carcinogenicity of the compound.

21 So I think that's in concert with what you've
22 heard from most of the people here.

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1 DR. THRALL: Dr. Needleman?

2 DR. NEEDLEMAN: I think Dr. Williams gave a very
3 plausible mechanism for effects at high dose. But I just
4 want to point out that when you truncate the distribution
5 and you're left with 54 animals in each cell, the power
6 of finding a rare event is very small. The reason that,
7 as I understand, we give high doses is just that. That
8 with a small sample size, you're likely to miss rare
9 events.

10 And I've done some preliminary power analyses on
11 this sample, and with 54 subjects in each group, the
12 power to find a small effect is something like .5. A 50
13 percent chance of missing an effect is really there. So
14 there is another reason for giving high dose exposures.

15 DR. THRALL: Dr. Williams?

16 DR. WILLIAMS: Gary Williams. Just a brief
17 addendum to that. I agree entirely with your point. I
18 think we should take into -- we are taking into account
19 the findings in the high dose animals. And it's
20 meaningful to me that there were no other tumors other
21 than in the liver. I mean, if under these highly toxic
22 conditions we found a host of other tumors, that would

1 change the whole picture. But what all I'm seeing here
2 is an effect on the tissue, the organ responsible for the
3 bio transformation of this compound.

4 DR. THRALL: Dr. Gaylor?

5 DR. GAYLOR: I want to make a statement about
6 dose response modeling. EPA and others are not now doing
7 sort of dose response modeling. They're not taking the
8 tumor data and trying to extrapolate it, say, with a
9 multi stage model of the low dose. It's just
10 establishing a dose where the compound shows an increase
11 in tumor incidence. The default is the 10 percent
12 incidence. A bench mark of 10 percent.

13 And then EPA will apply a margin of exposure
14 analysis to this and take into account how much weight --
15 or how much weight this margin of exposure can take into
16 account and look at mode of action, if that information
17 is available, how big a margin of exposure is needed
18 between doses that produce tumors and human exposure
19 levels -- or recommended human exposure levels. So the
20 dose response modeling is rather limited. I mean, you do
21 some in the high dose range to estimate a bench mark
22 dose. Penny's shaking her head no. Maybe she

1 needs to comment on this.

2 I mean, if we decide these tumors are not
3 relevant because it's a high dose toxic effect and
4 wouldn't occur at low doses, then EPA doesn't have to
5 deal with the issue. But if we say there may be some
6 relevance, maybe the margin of exposure doesn't -- maybe
7 it doesn't get you out of the problem.

8 Can I ask Penny to comment?

9 DR. FINNERCRISP: Why am I shaking my head?

10 DR. THRALL: Dr. Finnercrisp?

11 DR. FINNERCRISP: Well, Dave is right about the
12 modeling within the range of observed data to identify
13 some bench mark, LED-10 or ED-10 or whatever it turns out
14 to be. But then there are two choices. One is straight
15 line through the origin from that if one thinks one
16 should be probablistic or equivalent to a probablistic
17 risk assessment, and the other is the margin of exposure
18 if one has determined it's appropriate to presume a
19 nonlinear dose response.

20 So the choice would be made in good measure on
21 the weight of the evidence and the nature of the data and
22 the decision to be made after you do the qualitative

1 component of the assessment process. And whether or not
2 you have mode of action data.

3 MR. HILL: Richard Hill, EPA. I would like to
4 just jump ahead a little bit in regard to Dave's
5 comments. The agency position is that this compound has
6 suggestive evidence of carcinogenicity. Overall, looking
7 at all tumor types and amassing whatever information that
8 we do have on mode of action, etc., suggestive evidence
9 of carcinogenicity says we think there is a signal there,
10 but there is not enough information to make a judgment in
11 regard to human carcinogenicity. And the effect is that
12 we would not recommend using tumor data to evaluate risk
13 in a quantitative sense.

14 So that's where the agency's position is. And
15 the Panel, of course, is to evaluate whether or not that
16 is an appropriate conclusion for this database.

17 DR. GAYLOR: So suggestive wouldn't cause you to
18 do a point of departure or margin of exposure
19 extrapolation?

20 MR. HILL: That's correct.

21 DR. FINNERCRISP: Right, at all.

22 DR. GAYLOR: If we said likely, then we'd have

1 -- then you would have to?

2 MR. HILL: Yes.

3 DR. GAYLOR: But suggestive you don't.

4 MALE SPEAKER: Can I point out that you're
5 discussing the question at the end of the day here now?

6 DR. THRALL: Why don't we wait on that.

7 DR. GAYLOR: I'm not trying to make a judgment
8 as to what --

9 MR. HILL: Yeah. I was just trying to clarify
10 the discussion that Dave brought up, which is very
11 interesting.

12 DR. GAYLOR: He's telling us what will happen.

13 DR. FINNERCRISP: Or not.

14 DR. THRALL: Dr. Chen?

15 DR. CHEN: Yeah. I would like to make a comment
16 about the incidence rate of the two low dose groups. The
17 dose-response trend test shows a significant increase in
18 dose related effects. In those two low dose groups, for
19 adenoma is 15 percent and 13 percent in the control
20 group, and in the 8,000 ppm group it is much higher.

21 And so those are -- even if it is not
22 statistically significant it may be biologically

1 relevant. It shows there is some activity there. So
2 when we say statistically significant, usually one of the
3 applications is to try to get the NOEL. So the
4 statistician can make -- do have some message there.

5 And also I would like to respond to Dr.
6 Williams' comment about liver tumor is the only positive
7 finding. Later on I kind of disagree about some of the
8 negative response about the testicular and leukemia,
9 which maybe does have some suggestion and in my opinion
10 not completely negative.

11 DR. THRALL: Dr. Copley?

12 DR. COPLEY: Yeah. I would just like to remind
13 the Panel of one of the comments I made yesterday having
14 to do with the control values of 7 percent, which is
15 quite low for this laboratory where the range is from 14
16 to 22 percent. And the range at the 100 and 800 parts
17 per million doses is at the low end of the historical
18 control range for this laboratory.

19 DR. CHEN: Yeah. Which -- can I? Jim Chen.
20 Usually concurrent control, in my opinion, is the most
21 reliable kind of standard. And if control is in the low
22 end, so is the low dose and medium dose group. And I

1 seem hard to kind of think control is in low end.

2 DR. THRALL: Dr. Dementi?

3 DR. DEMENTI: Yes. Yesterday I labored to try
4 to establish that the historical control group here is
5 virtually useless. There are only five groups, a total
6 of 205 mice in that historical control group. And it has
7 not had the benefit of the PWG. In other words, I
8 personally don't think much reliance should be placed
9 upon it. Now maybe that's something you all should talk
10 about.

11 And this may be sort of a naive question. But
12 yesterday you decided the study was an acceptable study.
13 Today you're saying that both of the high dose groups
14 were excessive. Are those two decisions inconsistent? I
15 mean, is it really an acceptable study if the two high
16 dose groups are excessive and you're discounting the
17 findings of those two high dose groups, given the fact
18 that the next dose level down is tenfold lower, 800 ppm.
19 There is a big gap in there from 800 to 8,000 ppm.
20 There's a void. A wasteland in essence.

21 DR. THRALL: It's my impression that yesterday
22 we decided that it was the 800 ppm that was acceptable in

1 this study.

2 Dr. Williams, you had a comment?

3 DR. WILLIAMS: Yeah. First of all for clarity,
4 what I said was not that there were no other findings. I
5 said this is the main tumor finding.

6 Now secondly, on this issue of historical
7 controls, regardless of what the experience of this
8 particular laboratory, IRDC -- and of course any
9 laboratory will only have a historical control base
10 dependent on the number of bioassays that they've been
11 asked to do.

12 But all of us sitting here are familiar with
13 this mouse, and we know that this is very low for the
14 incidence of liver tumors in male B6C3F1 mice.

15 DR. GAYLOR: An 18 month study?

16 DR. WILLIAMS: Yeah. Okay. Now the point that
17 Dr. Chen made, I have to point out, applies only to the
18 males. If you look at the same incidence in the females,
19 you don't have increases in adenomas. Yet the females
20 have at the high doses, just as with the males, the
21 increases in adenomas.

22 So I don't think that those numbers in the low

1 dose groups in the males are of, quote, biological
2 significance. I think they're within the historical
3 range for the B6C3F1 mouse and they're not supported by
4 the findings in the female, which also responded at the
5 high doses with increases in liver tumors.

6 DR. THRALL: Dr. Gaylor?

7 DR. GAYLOR: I don't think much of historical
8 data in general. There are too many things that can
9 differ: diets and body weights and perhaps the pathology
10 and so on. I mean, it's somewhat useful, but of
11 secondary importance to concurrent controls. That's the
12 reason we run controls, because the concurrent controls
13 really should and do carry the most weight.

14 But mathematically the way this experience was
15 designed, you look at a spread in doses from 100 parts
16 per million up to 16,000 parts per million.
17 Mathematically what happens is basically that the 100
18 parts per million group looks like a control group. I
19 mean, that's sort of the way the mathematics would handle
20 this.

21 So the combined tumor incidence in male tumors,
22 we had four in the controls and 10 at 100 parts per

1 million. I would basically say 10 tumors in the 100 part
2 per million is basically a control value and the four is
3 probably on the low side. And here again, historical
4 controls -- we were told yesterday and it's still not
5 very clear whether these are 18 month historical
6 controls. I guess they were.

7 DR. COPLEY: Yes. These historical controls are
8 from the testing facility for an 18 month study.

9 DR. GAYLOR: For 18 months. But when we say we
10 know a lot about the B6C3F1, that's true, but what we
11 generally know is what goes on at 24 months. But I would
12 agree with Dr. Williams. I think the controls here look
13 a little low compared to the 100 part per million.

14 DR. THRALL: Dr. Everitt?

15 DR. EVERITT: I just want to make one comment on
16 the biology hepatocellular response in the B6C3F1 mouse.
17 The other thing that we do know as mouse pathologists is
18 that we generally have some idea of how many carcinomas
19 you generally see in a relationship to the number of
20 adenomas in a study.

21 And there are some unusual features in this
22 particular study, in that we have an extremely high

1 adenoma response compared to the carcinoma response. In
2 conjunction with the knowledge that malathion is
3 predominantly metabolized through the liver, and knowing
4 that we have hypertrophy, and knowing that we have
5 significant liver enlargement, I think we need to also
6 keep that in mind, because the natural history and the
7 continuum of the mouse liver response is fairly well
8 known.

9 Now I should point out that in the common
10 textbook that is used by many toxicologic pathologists on
11 the B6C3F1 mouse, there is a table that gives adenoma and
12 carcinoma incidence on virtually throughout the course of
13 a chronic study weekly. And, you know, at all through
14 the stages of the response in this mouse, you generally
15 do not have this ratio of adenomas to carcinomas.

16 So there is also a little bit of difference in
17 the biology here that implies that we have some growth
18 control problem in the liver analogous to what Dr.
19 Williams, you know, put out earlier for a potential what
20 could be going on there of linking metabolism with this
21 unusual response.

22 DR. COPLEY: I would just like to make a comment

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1 on the historical control information. It's in the
2 package in the new CARC document. We have the original
3 tumor values, which would be the ones read by the same
4 pathologist before the PWG. And on those the controls
5 are 2 percent, 11 percent and 4 percent, going from
6 controls up through 800. So they're even lower than
7 these values, and those would be the appropriate values
8 to compare against the historical controls, because
9 neither of them had PWG review.

10 DR. THRALL: Dr. Gaylor?

11 DR. GAYLOR: I wanted to go back and revisit the
12 observation that Dr. Boorman called to our attention.
13 That is, in the male mice for carcinomas that there
14 appeared to be a few more at the lower doses and none
15 were seen at the higher dose.

16 In this case it might be a result of the
17 decreased body weight, because we know there is a high
18 correlation between early body weight and tumor
19 incidence. So not that it's important to do here, but if
20 an adjustment was made for body weight, either by using
21 your historical data from Sealkoff in 1995, a publication
22 in Fundamental Applied Toxicology -- one could make an

1 adjustment for the changes in body weight -- or a
2 technique by Gaylor and Kodell that was published in '99,
3 where the animals are just subdivided into strata of low
4 body weights, middle body weights and high body weights
5 and you do your dose response analysis within those
6 strata and then combine the statistics.

7 Maybe that would answer why the carcinomas
8 tapered off. It may be related to body weight. I don't
9 know, and I'm not suggesting that it's important to try
10 to answer that question here.

11 DR. THRALL: It's my sense that we have answered
12 question 2.1 and possibly 2.2 as well. Do you want to go
13 ahead and read 2.2, and we'll see if there are any
14 additional comments on that?

15 DR. COPLEY: Does the SAP consider the
16 statistically significant trend and pair-wise increases
17 in the liver tumors in female B6C3F1 mice at 8,000 and
18 16,000 parts per million to be related to malathion
19 exposure? Why and why not? And what weight should be
20 placed on these data since there is evidence of excessive
21 toxicity based on severe cholinesterase inhibition and
22 decreased body weight gain at both doses?

1 DR. THRALL: Okay. Are there any additional
2 comments as regards to question 2.2? Dr. Gaylor?

3 DR. GAYLOR: Well, I think we have sort of a
4 disagreement on how much weight. I mean, we've heard
5 arguments that we should consider the mouse liver tumor,
6 and we heard arguments that maybe we should totally
7 discount the mouse liver tumor because of the toxicity at
8 the two high doses.

9 So I don't think the Panel can come to -- it
10 doesn't sound like the Panel is going to come to a
11 consensus. But it should be noted that we have a split
12 in the Panel. I'm not suggesting that we vote. Maybe
13 you want to vote. I don't know.

14 DR. THRALL: No. I think in the report the
15 report will just reflect that there is a difference of
16 opinion.

17 DR. NEEDLEMAN: May I?

18 DR. THRALL: Yes, Dr. Needleman?

19 DR. NEEDLEMAN: I apologize for repeating
20 myself, but I just want to emphasize that if you trim the
21 sample by cutting off the top two, you can no longer say
22 that you have confirmed the hypothesis. You've now

1 converted it to an exploratory study and you cannot use
2 it to make a judgment. You have not confirmed any
3 hypothesis at all.

4 DR. THRALL: Dr. Boorman?

5 DR. BOORMAN: I hesitate to do this and probably
6 at the end of the day we'll be sorry I brought it up.
7 But this is a picky point that sort of bothers me. On
8 the female mice where they talk about the statistically
9 significant trend, I think the trend in the female mice,
10 if you look at the total tumors -- one, one, two -- it's
11 really driven by the high dose.

12 And I guess if we're making judgments about low
13 dose and stuff, I wonder if Dr. Gaylor had any comments
14 on the trend test?

15 DR. GAYLOR: It's driven by the two high doses.

16 DR. BOORMAN: Yeah, exactly.

17 DR. GAYLOR: Well, that's true throughout here
18 in all the tumors we're looking at. When we talk about a
19 trend test, this becomes a real problem. I don't want to
20 do a Gene sharp curve here, but trend doesn't -- I mean,
21 we do a trend test but that doesn't really tell us
22 whether that trend starts at the very low dose or whether

1 it starts at a higher dose.

2 DR. BOORMAN: You answered my question. Thank
3 you very much. That's what I wanted to hear.

4 DR. GAYLOR: But as Dr. Needleman pointed out,
5 you know, we're looking at rare events in 50 animals.
6 We're not going to see trends unless we get a 20 percent
7 incidence, and then you only have a 50/50 chance of
8 seeing them with low backgrounds. So that's a typical
9 problem we're aware of.

10 DR. THRALL: Dr. Williams?

11 DR. WILLIAMS: Well, I would like to bring up
12 the point again about -- and it comes up in this
13 question. Are these related to malathion exposure? Now
14 malathion is a specific chemical entity. What was tested
15 here was technical grade malathion, which contains 3
16 percent impurities. Those impurities, in my reading of
17 the literature, several of them have been documented to
18 be toxic in their own right.

19 And I point out that when animals are given
20 8,000 ppm technical grade malathion with 3 percent
21 impurities, you're actually testing 240 ppm impurities,
22 which is higher than the low dose in this study for

1 malathion.

2 So I really don't know which of these effects is
3 attributable to malathion or to the impurities. And I
4 just don't think we should lose site of that, because
5 there is an important, I mean, not only scientific issue
6 here, but a practical one, because in the environment I
7 would assume that whatever residues persist of malathion,
8 they may be segregated from the impurities. And if
9 you're talking about, you know, the need for monitoring
10 or guaranteeing safety quantitatively on malathion, I'm
11 not sure that we have data that bears directly on that.

12 DR. THRALL: This came up yesterday. Do we know
13 what those impurities are? Can we state what they are,
14 rather than --

15 FEMALE SPEAKER: Confidential business
16 information. The company is not willing to share them
17 and by law, need not.

18 DR. WILLIAMS: Yeah. Well, we don't know for
19 the current studies, and that's why I was asking a little
20 bit about the history. Because I have a paper dealing
21 with the toxicity of impurities which presumably, given
22 the date of the paper, would have been the American

1 Cyanamid original product.

2 But it does give you an idea of what kind of
3 impurities are there. I mean, they're all basically what
4 you would anticipate from incomplete chemical reactions
5 in the synthesis of the parent product. I mean, we're
6 not talking about solvents or contaminants, but actually
7 incomplete reaction products.

8 DR. THRALL: Dr. Copley?

9 DR. COPLEY: Technical grade malathion is what
10 is going into the formulations, and that's one reason why
11 we require the tests to be on the technical rather than
12 the pure.

13 DR. WILLIAMS: I understand.

14 DR. COPLEY: Because this way we're testing for
15 the impurities that are going to be there when the public
16 is exposed to it.

17 So I guess the question we're really asking --
18 and perhaps I should be more specific in it. Is this
19 malathion product that was tested this technical grade.
20 That's what we're asking about, not the malathion pure.

21 DR. WILLIAMS: Good.

22 DR. COPLEY: So it doesn't really matter what

1 impurities are which. It's this whole thing together.
2 How would you classify it.

3 DR. THRALL: Dr. McConnell?

4 DR. MCCONNELL: Since Dr. Williams opened that
5 box, I have one point I would like to add to that. I was
6 going to mention it later, but I'll do it now.

7 Dr. Brusick yesterday shared the paper with me
8 on the in vivo mutagenesis studies that were conducted in
9 Berkeley. And while those studies certainly have a lot
10 of awards on them, there was one useful piece of
11 information, albeit the exposures they used were
12 incredibly high in terms of these studies, because they
13 gave them material interperintly (phonetic), which will
14 have a rapid absorption.

15 There was one useful piece of information in
16 there. There were two studies that were comparable in
17 mice where they gave this material. In the one study, it
18 showed an effect. In the other study, it did not show an
19 effect at comparable doses. The only difference was that
20 the one material was pure malathion. The other material
21 was technical.

22 So that might give us a clue that in fact these

1 other components of the technical material might indeed,
2 at extremely high levels, have an effect.

3 DR. THRALL: All right. Are there any other
4 comments? Dr. Dementi?

5 DR. DEMENTI: Yes. Dr. Needleman's comment I
6 agree with entirely. He said it in a more elegant way
7 than I've said it my paper. But if you delete or ignore
8 the top two doses for risk assessment purposes as having
9 any practical use, then what is left in the study is not
10 a complete study.

11 In fact, in the 800 ppm dose level, all tissues
12 were not examined histopathologically. We only examined
13 all tissues at the top dose level and in the control. So
14 a lot of tissues have not even been examined at that dose
15 level, and you only have two doses there.

16 And then as far as a MTD is concerned, again
17 quoting from the Office of Science and Technology Policy,
18 it says use of the maximum tolerated dose (the MTD), the
19 largest doses, that is, doses far exceeding human
20 exposure levels, have been strongly recommended by
21 several national and international bodies in order to
22 overcome the inherent low sensitivity of bioassays. I'm

1 missing a dose level in there.

2 DR. THRALL: Dr. Williams?

3 DR. WILLIAMS: Okay. I'll reiterate my position
4 here. I am not excluding from consideration the top two
5 doses. I believe that this test material has been tested
6 in extremis at 8,000 and 16,000 parts per million. And
7 the only thing it did was increase the incidence of liver
8 tumors in the mouse. I'm taking into account that in
9 those two dose groups there were no other tumors produced
10 even at colossal exposures.

11 So I think my conclusion is that in the mouse
12 this test substance is not carcinogenic in any other
13 tissue other than the liver.

14 DR. THRALL: All right. Can we go ahead then
15 with question 2.3 at this time? Are we ready to do that?
16 Okay. Dr. Everitt?

17 DR. EVERITT: I'll address that.

18 DR. THRALL: We're going to read the question
19 first.

20 DR. COPLEY: The CARC considered the April 2000
21 PWG report for Fischer -- female Fischer 344 rat liver
22 tumors to be valid and used these values in the cancer

1 hazard assessment.

2 Question 2.3.1: Does the SAP agree that the
3 female rat liver tumor PWG report should be considered
4 valid and that these values should be used in the hazard
5 assessment for malathion? If yes, why, and if not, why
6 not?

7 DR. THRALL: Okay. Dr. Everitt?

8 DR. EVERITT: Okay. I'll begin with some
9 discussion of that. I strongly feel that PWG is a good
10 thing in toxicologic pathology, particularly for lesions
11 that have a biological continuum. All of us that work in
12 toxicologic pathology that evaluate Fischer rats and
13 B6C3F1 mice struggle with issues of classification in
14 certain organ systems. And the liver is certainly one of
15 those.

16 And I think it's fairly universally accepted in
17 the toxicologic pathology community that the concept of
18 the pathology working group is a good thing, and that
19 when one can come up with a consensus of a PWG diagnosis,
20 it should hold more weight than the individual opinion of
21 an individual toxicologic pathologist.

22 The PWG that was conducted for this study

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1 appears to have been conducted in full concordance with
2 the criteria set out in PR Notice 94-5, if I'm not
3 mistaken, unless any of my colleagues have any concerns
4 with that. It appears that the review group were well
5 experienced toxicologic pathologists, and that they were
6 brought together in such a manner, and read the slides in
7 very typical blinded fashion, that would really be
8 amenable to working with the diagnosis that they
9 struggled with in the liver, which was to at one time
10 with a group of pathologists bring together to address
11 the question of is something a focus of cellular
12 alteration or an adenoma.

13 Most toxicologic pathologists don't struggle as
14 much with separating out hepatic carcinomas from hepatic
15 adenomas. But there is always a struggle, even among the
16 most experienced hepatic pathologists and people that
17 worked many years in experimental rodent liver systems,
18 for any given lesion in a study that there are marginal
19 lesions.

20 And I think that there is concern that has been
21 at least eluded to during the past day and a half that
22 there has been downgrading of lesions. And I would like

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1 to just bring up, in my personal experience I've now sat
2 on probably upwards of 75 pathology working groups, many
3 of which deal with liver, because it's one of the common
4 areas we deal with in rodent toxpath.

5 There is always a concern about thresholds,
6 where any individual pathologist draws the line on these
7 marginal hepatic --

8 (END OF TAPE 1, SIDE B)

9 DR. EVERITT: -- working group. And in my
10 experience, this is actually remarkable consensus that
11 this group had. It should lend its strength to the
12 process that was conducted here.

13 There are two other issues surrounding this.
14 One is the issue of were the slides selected properly for
15 making this separation and downgrading. In other words,
16 were slides selectively chosen. And there is concern
17 that not all foci were chosen to be reviewed by the
18 pathology working group.

19 I think it's also well accepted that there are
20 many, many foci of cellular alteration in rodent livers.
21 A very, very small majority of these go on to further
22 progression within this biological continuum, and only a

1 certain number of those, principally the larger ones, are
2 diagnostically challenging to the pathologist.

3 So I agree with what was done by the pathology
4 working group. I don't think there was necessarily any
5 reason to go to the small foci and have all the foci
6 necessarily reviewed by the group.

7 I also would like to point out that to do
8 further sectioning of livers brings up a lot of other
9 questions on the introduction of bias. So the way the
10 pathology working group was conducted, I believe, is
11 probably the working norm of most toxicologic
12 pathologists.

13 So with that, I'll just open it up to colleagues
14 for what their opinions may be.

15 DR. THRALL: Dr. Roberts?

16 DR. ROBERTS: Just a quick question. Perhaps
17 the agency can clear this up. Dr. Copley, when you
18 presented the basic criteria of how these things operated
19 yesterday, you did say that when the slides are re-read
20 or reevaluated that all slides are evaluated.

21 And so I'm just curious. How common is it to do
22 as Dr. Everitt said, where there is some selection that

1 goes on? Is this unusual or is it commonplace when you
2 do these re-reads?

3 DR. COPLEY: The PR Notice specifically states
4 ~~that~~ all the slides for a particular tissue need to be
5 re-read by a peer review pathologist. And that was done.
6 And from that -- all it says is any places where the peer
7 review pathologist and the study review pathologist
8 differ, those are the ones that would have to go.

9 And in this case, they sent all the positive
10 tumor findings. So they sent a lot more slides, because
11 they didn't distinguish whether there was a difference or
12 not a difference between the two pathologists. They sent
13 everything. And then they went down a couple levels and
14 sent things that I guess that they said they thought
15 could potentially have been misdiagnosed and then they
16 wouldn't have gotten picked up.

17 DR. THRALL: Dr. McConnell?

18 DR. MCCONNELL: Yes. I agree entirely with
19 everything that Dr. Everitt said. I would just add that
20 having been involved myself and Dr. Mormon in the
21 evolution of the pathology working group over time, this
22 just wasn't -- I wanted to bring out that this just

1 didn't happen. You know, this was an evolutionary
2 process, and probably Dr. Mormon had more to do with how
3 these things -- how the pathology working group evolved
4 than anyone else on this planet. So you can blame him
5 for it or give him credit for it, whichever is
6 appropriate.

7 But the point I'm trying to make, as Gary and I
8 used to say, what we hoped to accomplish with the
9 pathology working group diagnoses or consensus diagnoses
10 was that if any other pathologist ever came in and
11 reviewed that study, that hopefully and probably they
12 would come up with the same number of tumors that we had
13 seen, or that the pathology working group had found and
14 diagnosed.

15 Although we realized that the mix between
16 adenoma and carcinoma might change in their hands, what
17 we were attempting to accomplish was that they wouldn't
18 find some other tumor in that study of a different organ
19 than we had missed. That was the number one reason why
20 we had this process, or developed this process.

21 And the second was that when the EPA or any
22 other regulatory agency got down to using this data, that

1 they could be fairly well assured that at least the total
2 number of tumors was close to what reality is.

3 That's all I have.

4 DR. THRALL: Other comments from Panel members
5 regarding this question? Dr. Needleman?

6 DR. NEEDLEMAN: First I have a question. I
7 never encountered this apparatus before a couple weeks
8 ago. Was it a part of the initial design, or was it
9 brought in after the data was collected?

10 DR. COPLEY: This particular one, as I had
11 mentioned before, was completed by Kemy Nova this year.
12 The study is several years old, so it was done after the
13 fact.

14 DR. NEEDLEMAN: So it was after the fact.

15 DR. COPLEY: The PWG quite frequently is done
16 after the fact.

17 DR. NEEDLEMAN: I understand. I'm going to
18 begin with an anecdote. When I was at a pediatrics
19 counsellor, there was great debate over the utility and
20 the danger of a tonsillectomy. At one time almost all
21 children were submitted to it, and then there was an
22 agreement that nobody should get it.

1 And when I was a resident, we were told about a
2 study in which 100 children were referred to a panel of
3 otolaryngologists and 50 were said to be candidates for a
4 tonsillectomy and 50 were rejected. Then the 50 that
5 were rejected were given to a group of otolaryngologists
6 and 25 were selected. And then the third round, 12 were
7 selected.

8 I bring this up to show that judgment under
9 uncertainty is a very hazardous business. The human
10 brain is not designed to make good estimates -- good
11 quantitative estimates. There is a very good book on
12 this by Conaman and Torski called Judgment Under
13 Uncertainty, two pre-imminent cognitive psychologists,
14 who have examined human decision making under these
15 circumstances.

16 And we're terrible at it. And the other thing
17 is that we don't know that we're terrible at it. We have
18 an incredible belief in our accuracy. And it's been
19 disproved again and again and again.

20 Now there is another concept. It's called
21 regression to the mean. And that is, if you have a group
22 of data and you plot a regression line, some will be

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1 above and some will be below it. And then if you come
2 back and run the same test again, the people in the high
3 end will regress to the mean, and the people in the low
4 end will regress to the mean. Now in this experiment, a
5 group of diagnoses of cancer were re-studied and there
6 was a smaller number of malignancies diagnosed. That
7 could be regression to the mean. So I think that this
8 whole issue is clouded.

9 Now the other thing is, as I said before, this
10 was done after the fact. This group of diagnoses was
11 selected out and revisited. Once again, this is an
12 exploratory enterprise and cannot be used to confirm a
13 diagnosis either of carcinogenesis or not carcinogenesis.

14 DR. THRALL: Would a pathologist like to respond
15 to that?

16 DR. BOORMAN: Part of my training was at the
17 Medical School in Ann Arbor, Michigan. And what they
18 routinely did when they did biopsies and frozen biopsies,
19 is they got panel decisions and people had to write it
20 down.

21 I am -- and perhaps mistakenly -- firmly
22 convinced that you have more accuracy when you have more

1 than one opinion. Because I think that individuals are
2 subject to variation from the mean. And I think that
3 we're trying to get closer to the truth.

4 I guess that's just my opinion. I think that it
5 is not uncommon in other situations when you're talking
6 about treatment to get more than one decision.

7 DR. NEEDLEMAN: I agree with that completely.
8 And if a group of pathologists had look at this at one
9 time and then come to a consensus, that would be better
10 than any single or two pathologists. But then when you
11 revisit it with another group and you find that the
12 diagnosis is diminished, that could well be regression to
13 the mean, or it could be this problem we have with
14 decision making.

15 That is, if you're brought in as a consultant to
16 look at a diagnosis, the consultant has to say something
17 different than the group before. I mean, it's
18 traditional and you find the change in diagnoses. And it
19 could be explained simply by regression to the mean.

20 DR. THRALL: Okay. That was a discussion
21 between Drs. Boorman and Needleman, for the record. Dr.
22 McConnell?

1 DR. MCCONNELL: I just wanted to add one thing,
2 Herb. And that is that I can't speak to deciding whether
3 tonsils need to be removed or not. It's not my area,
4 although mine were removed.

5 There are criteria, and they're well defined,
6 and they're written down, not necessarily in stone. But
7 there are criteria for diagnosing a hyperplasia versus a
8 adenoma versus a carcinoma. And these are in text and
9 other kinds of readily acceptable material. And I'm sure
10 those were used in this particular case, which I think
11 takes some of the bias out of it.

12 And as Dr. Everitt suggested and in my
13 experience, too, I've seen just as many cases where
14 neoplasms are upgraded as downgraded. I think that just
15 happened to be a fluke in this particular study that
16 those were downgraded, not because of any inherent or
17 perceived bias on the part of the pathologists.

18 DR. THRALL: So perhaps this is less subjective
19 than determining if someone should have a tonsillectomy
20 or not?

21 DR. MCCONNELL: I don't know. I can't comment
22 on that. Herb is the expert on that.

1 DR. THRALL: Dr. Williams?

2 DR. WILLIAMS: Yeah. Gary Williams. Well, I
3 think the main point I would like to make is that the
4 diagnosis doesn't make any difference. These are all
5 liver tumors, and no liver tumors are going away. And
6 whether these are benign or malignant by histologic
7 criteria, we're still going to accept them as tumors.

8 So in that sense, nothing is changed. And I
9 think something for people who haven't spent a lot of
10 time dealing with rodent liver tumors is that
11 biologically they're all benign. You practically never
12 find a metastatic or an invasive liver tumor as in
13 contrast to humans. And so we're dealing only with
14 histologic criteria for what is benign and what is
15 malignant.

16 Now you have extremes. We have at one end
17 tumors that are, you know, blatantly pleomorphic and a
18 lot of cellular abnormalities that are easy to call
19 carcinoma, even though they won't invade or metastasize.
20 And then at the other end, you've got small, well
21 differentiated lesions that some people say are -- may
22 call them a carcinoma. Some may call them an adenoma.

1 But what happens here is that once the initial
2 diagnoses are made, these controversial lesions are
3 revisited by a group. And they all try to harmonize the
4 diagnostic criteria they are applying, and then they say,
5 okay. Now we all think these are adenomas.

6 But in the end, it doesn't make any difference.
7 They are still tumors.

8 DR. THRALL: Dr. Copley?

9 DR. COPLEY: I would like to make two comments.
10 One is, since the PWG itself goes into their evaluation
11 blind, they don't know whether they are changing or not
12 changing what the original results were. They don't know
13 what the total dose -- they don't have any idea what dose
14 groups they're looking at. They don't know how many were
15 in the dose groups.

16 The only person actually who would know that
17 information is the original pathologist, but he's not --
18 he's given coded slides as well. So unless he recognizes
19 that particular tissue, he's not going to know what he's
20 doing.

21 Another thing, about at least this particular
22 one that the report said, is before they went into the

1 PWG report, they reviewed the criteria from the article
2 that they reviewed -- that they were using the criteria
3 from.

4 ----- And the third thing is, we've gotten at least
5 half a dozen PWG reports that I was able to find just by
6 using a search. Half of them were not -- half of them
7 went down as to whether they considered it to be
8 treatment related effects or not treatment related
9 effects. I mean, not exactly half. But we had some
10 where they increased the actual severity and it ended up
11 being called treatment related tumors, and in the other
12 cases it did the opposite.

13 DR. THRALL: Dr. Dementi?

14 DR. DEMENTI: On this particular study, six of
15 the adenomas were downgraded to hepatocellular foci --
16 hepatocellular alteration. In other words, the tumor
17 count did change. Six of them went into no man's land.
18 And there were, as I recall, like in the 6,000 ppm dose
19 group, three of those that were downgraded to
20 hepatocellular alteration. So for all practical
21 purposes, that dose group becomes no different from the
22 control in terms of what is seen there. But in fact

1 something is seen there. Hepatocellular alterations are
2 seen in that dose group.

3 And I really think this committee should
4 consider -- and I think you're suppose to consider --
5 hepatocellular alterations in your overall assessment of
6 the carcinogenicity. And I think our guidelines require
7 you to look at these as key events in the process.

8 -- Hepatocellular alterations of moderate degree of
9 severity were the ones chosen to be looked at by the
10 chairman of this committee. But when they evaluated
11 these and reported them, they did not rank them as to
12 their severity. So we cannot say in looking at this data
13 whether the ones that were downgraded were in fact of a
14 moderate degree of severity.

15 But I think if we assume that the ones that were
16 adenomas would in fact be of moderate degree of severity,
17 then as I understand it in the control, there are none of
18 these of moderate degree of severity, but like six in the
19 6,000 ppm group. Which means that group is quite
20 different from the control, but it doesn't get any
21 reflection in the statistics -- or in the analysis of
22 this. It's just treated as if it were the same as the

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1 control.

2 And also I might note that liver tumors, as I
3 understand it in the NTP database in the female F344 rat,
4 are very rare. In other words, I think the carcinoma
5 incidence is like .1 percent. So every tumor is very
6 important in this study.

7 DR. THRALL: Dr. Everitt?

8 DR. EVERITT: Yeah. I would like to make one
9 comment there. We'll add a reference. There are good
10 references on this. The subject of foci and hepatic
11 tumor progression in rodents has been the subject of week
12 long conferences that I've been at. It's far beyond the
13 discussion we can have here today. We will add some
14 references that can be used for the relationship between
15 foci and adenomas.

16 But it's a very complex subject. I think,
17 though, that we as a committee -- and there are other
18 pathologists on this group -- felt that the way the
19 reviewing pathologist chose those lesions most likely to
20 be of the diagnostic dilemma that fell between large foci
21 of cellular alteration and hepatic adenoma were probably
22 done according to standards that are the normal practice

1 of toxicologic pathology.

2 And that is using the diagnostic criteria that
3 had been established for the Fischer rat and the B6C3F1
4 mouse. And that is a subjective -- in many cases
5 subjective on size, okay. And so the question comes up,
6 was there bias drawn in how the slides were selected.
7 There was no indication that that was in fact the case.

8 DR. DEMENTI: My concern is more with whether you
9 shouldn't include in your evaluation the incidence of
10 hepatocellular alterations in your overall assessment of
11 the carcinogenicity. And our guidelines say that you
12 should consider key events.

13 DR. EVERITT: But those are done on a -- my
14 understanding is that three neoplastic lesions or lesions
15 that are felt to be important in the spectrum of the
16 carcinogenic process, particularly for organs for which
17 we believe there is a biological continuum or done case
18 by case based upon the tumor outcome and the types of
19 lesions that are seen in the premia plastic spectrum.

20 In other words, even for the purposes of hepatic
21 carcinogenesis, the focus is not a focus. There are many
22 times of foci. There are many kinds of compound specific

1 lesions that one gets as a potential premia plastic
2 lesion in the rodent liver. And there is no indication
3 in this study that that was done with bias. And in fact
4 we've seen the incidence even of foci in this study.

5 DR. COPLEY: Yeah. And I would like to just
6 comment on that, because I did mention yesterday that the
7 incidence of foci in this study from the original review,
8 there was no dose related increase. I just haven't been
9 able to lay my hands on the numbers this morning.

10 DR. THRALL: Thank you, Dr. Copley.

11 DR. DEMENTI: Wait a minute.

12 DR. THRALL: Dr. Dementi?

13 DR. DEMENTI: Those of moderate degree of
14 severity were notably more numerous in the control than
15 in the dose group. I don't think there were any in the
16 control of moderate severity. And when that lesion was
17 chosen as the one to send forward to the PWG, in my view
18 designates it as a key event under the EPA's guidelines
19 for use of key events.

20 They don't say it has to be premia plastic or it
21 has to meet some -- they just say, is that a key event.
22 And it is a key event. That's why the tumors were

1 downgraded.

2 DR. EVERITT: I'm sorry. Which EPA guideline
3 says a larger focus is a key event? I would just like to
4 see the reference of that.

5 DR. DEMENTI: As I understand, the EPA
6 guidelines instruct that you should use key events in
7 your assessment of the carcinogenicity along with tumor
8 incidence. And I'm just arguing the point that
9 hepatocellular alterations of moderate degree of severity
10 satisfy as a key event in this process.

11 DR. EVERITT: But, Dr. Dementi, remember these
12 were done blindly. That would take all of your problems
13 out of it, would it not?

14 DR. DEMENTI: No. I'm just talking about the
15 incidence of hepatocellular alterations should be
16 considered along with adenomas in your assessment. And I
17 talked with a NTP scientist about this. He said that
18 hepatocellular alterations -- they alone were identified
19 in this rat study. You would not use them in an
20 assessment as an indication of carcinogenicity. But he
21 said if there are adenomas present, you would use them.
22 And this man is a noted authority.

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1 DR. THRALL: Dr. McConnell?

2 DR. MCCONNELL: Yeah. Well, I've just been
3 provided a table here, Table 11, that does show the
4 incidence of these foci or alterations.

5 MR. LEWIS: Dr. McConnell, could I ask you to
6 put that maybe on overhead to present?

7 DR. MCCONNELL: Certainly.

8 MR. LEWIS: Great.

9 DR. MCCONNELL: And it's quite obvious that -- I
10 don't care what you did with them. If you called them
11 all tumors, it's not going to change anything.

12 DR. DEMENTI: Are they of moderate degree of
13 severity, though? Are they of moderate degree of
14 severity or just all hepatocellular alterations, period.
15 Are they of the type that were chosen out to send to the
16 PWG, that's what I'm saying.

17 DR. THRALL: Okay. We'll spend just a couple of
18 minutes on this table and then we're going to break.

19 Dr. Finnercrisp?

20 DR. FINNERCRISP: May I offer some clarification
21 about what guidelines, if any, say what about all of
22 this?

1 DR. THRALL: Please.

2 DR. FINNERCRISP: There is nothing in any of the
3 EPA guidelines that infer the use of preanal plastic
4 observations quantitatively in determining tumor
5 incidence.

6 What we do talk about, is if we have an
7 understanding of the ideology of a particular tumor type,
8 and we have made a decision that it is appropriate to
9 include that tumor type in a qualitative and quantitative
10 risk assessment, and we have determined enough is known
11 about the mode of action, we may use the data on the
12 preanal plastic lesion, or its no effect level, or its
13 bench mark dose, depending upon how one may have modeled
14 it, as a point of departure in doing quantitative risk
15 assessment. It is never ever suggested to some foci
16 along with adenomas and carcinomas in determining tumor
17 incidence.

18 DR. THRALL: Thank you, Dr. Finnercrisp, for
19 clarifying that.

20 DR. MCCONNELL: Well, as you can see -- to me,
21 unless I'm missing this totally, I just don't see how
22 those numbers would help in clarifying the issue.

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1 DR. DEMENTI: What are those numbers?

2 DR. COPLEY: Brian, those numbers are actually
3 from the original study report. That's the foci that
4 were diagnosed by the pathologist when we first got the
5 study report in 1994.

6 DR. DEMENTI: But are they the incidence of
7 hepatocellular alterations of moderate degree of
8 severity? The ones that were sent to the PWG?

9 DR. COPLEY: What this has is the basophilic,
10 eosinophilic and clear cell. It doesn't specify by
11 severity.

12 DR. DEMENTI: Okay.

13 DR. COPLEY: This is total foci.

14 DR. DEMENTI: So it doesn't break it -- make the
15 distinction between the more advanced moderate degree of
16 severity ones versus the others. I realize that the
17 total incidence of hepatocellular alterations was quite
18 numerous. But certain ones were chosen out to send to
19 the PWG, and they're the ones I'm talking about.

20 DR. EVERITT: Yeah. All I'm saying is, my
21 understanding is that we don't grade severity of the
22 various histologic subtypes of foci. We leave it for the

1 reviewing pathologist in the PWG structure to choose
2 lesions based upon the ones that would be deemed to be
3 diagnostic dilemmas.

4 ----- And what I'm saying is, there is no indication
5 that that was done with undue bias. It was done
6 according to how we generally conduct these rodent PWGs,
7 looking a hepatic lesions. That's all I'm trying to say.

8 ----- DR. DEMENTI: Okay.

9 DR. EVERITT: It's not the norm to start getting
10 into the subdivision of these foci. And that would be a
11 topic well beyond anything we could cover today with this
12 group.

13 DR. DEMENTI: Well, I'm just trying to make the
14 point that those of moderate degree of severity -- as I
15 recall, there were none in the control. But with the
16 downgraded adenomas in the 6,000 ppm group, plus the ones
17 that were there -- there were like six in that group.
18 And we're treating these livers as if they were perfectly
19 normal statistically.

20 And I'm saying there were these hepatocellular
21 alterations there and that should be properly addressed.

22 DR. EVERITT: But one more comment. Dr.

1 Dementi, are you thinking that there might be small ones
2 in the control group that would be missed by the
3 reviewing pathologist?

4 DR. DEMENTI: No. What I'm saying is, only
5 those of moderate degree of severity was sent to the PWG.
6 They did not see the small ones.

7 DR. EVERITT: But those are the only ones that
8 are diagnostic dilemmas, is what I'm saying.

9 DR. DEMENTI: And that's why they should be
10 considered.

11 DR. EVERITT: And they were.

12 DR. DEMENTI: No. I mean in your statistical
13 treatment of the data, along with tumors.

14 DR. THRALL: Dr. Williams?

15 DR. WILLIAMS: Yeah. As a matter of fact, I
16 agree with Dr. Dementi on this point. Because there is a
17 continuum of events in hepatocellular neoplasia
18 progressing from the foci to larger lesions called
19 adenomas and then carcinomas. And typically in the kind
20 of research that I do, we quantify all stages of this
21 process. And it really does tell us something about dose
22 response and kinetics.

1 And I think it's entirely possible that at the
2 6,000 ppm there may indeed be a population of foci that
3 are larger than at lower doses. But I have to look at
4 that in the context that at 6,000 ppm in rats that this
5 compound is producing hepatomegaly again, just as it did
6 in the mice.

7 And this is a -- I think it's the same thing
8 going on in the rat as in the mouse. It's metabolic
9 overload in the liver that is accelerating the
10 spontaneous neoplastic process, and that you will get all
11 along the line, if careful study is done, increases in
12 various stages of neoplasia. And I think probably,
13 although we don't have the evidence here, something might
14 have been going on at 6,000.

15 But I still consider it irrelevant to human
16 hazard.

17 DR. DEMENTI: Well, I used the 6,000 because
18 it's the most glaring example. The point is that it
19 occurred at other doses, too. And you really need to
20 break out and look at the hepatocellular alteration in
21 all groups, as well as the tumors, to properly evaluate.
22 That is, hepatocellular alteration of moderate degree of

1 severity in the control and other groups.

2 DR. WILLIAMS: Well, I have some sympathy with
3 that, but not today. I mean --

4 DR. DEMENTI: This is a critical call.

5 DR. WILLIAMS: Well, I know. But where -- okay.
6 I mean -- I don't know. I guess -- are you --

7 DR. THRALL: Identify yourselves before you
8 speak.

9 DR. WILLIAMS: Williams. I don't know. Are you
10 powerless to get this kind of data before we meet in this
11 room? Well, I guess I'm not going to get an answer to
12 this right now.

13 DR. THRALL: I think perhaps -- I think that the
14 consensus of the Panel is that we believe that the female
15 rat liver tumor PWG report is valid. That's my sense.

16 And I think it's time to take a break. It's 20
17 until 11. Let's reconvene at 11 o'clock. Check out time
18 at this hotel is 12, so you may want to do that now.

19 **(Whereupon, a brief recess was taken.)**

20 DR. THRALL: All right. If everyone could be
21 seated who wants to be seated, we'll reconvene. And Mr.
22 Lewis has some comments for us to begin with.

1 MR. LEWIS: Thank you, Dr. Thrall. I just want
2 to reiterate what I mentioned before at the beginning of
3 today's meeting that there may be some additional
4 material that will be presented today from the agency and
5 from the public. I want to again emphasize that any
6 additional material that will be distributed to the
7 Panel, and obviously to the public, everything should go
8 to myself.

9 Please give that to me, and I'll make sure that
10 the appropriate administrative procedures are followed in
11 terms of distribution to the Panel and for the docket.
12 Include also a cover note saying who it's from and what
13 the material is.

14 Thank you very much.

15 DR. THRALL: Thank you, Mr. Lewis. At the
16 outset, Dr. Herzy has requested to make a few remarks.
17 And so if you could come forward and identify yourself
18 and who you represent, we'll deal with that.

19 DR. HERZY: Yes. I'm Dr. William -- is this on?

20 DR. THRALL: You're not on.

21 DR. HERZY: I'm Dr. William Herzy. I am Senior
22 Vice President of the National Treasury Employees Union,

1 Chapter 280. We represent the professional employees at
2 EPA headquarters. I'm also an EPA employee, a Senior
3 Scientist in the Office of Pollution Prevention and
4 ..Toxics.

5 And I just had a question relevant to a
6 grievance that we filed -- the union filed -- yesterday
7 with respect to the events that are taking place today.
8 And the question I had is for Dr. Copley.

9 Did I hear you say that the PWG's mandate under
10 PR 94 was to review the slides in which there were
11 diagnostic differences between the study pathologist and
12 the review pathologist? And if that was the mandate of
13 the PWG?

14 DR. COPLEY: No. I brought a copy of the PR
15 Notice with me. Let me just find it. Here it is.

16 DR. WILLIAMS: Is this pertinent to our
17 discussion?

18 DR. HERZY: Yes. My understanding -- if I
19 understood Dr. Copley correctly, if in fact that was the
20 mandate of the PWG, the six adenomas that were at issue
21 in the rat liver tumor findings had been agreed to by the
22 original pathologist -- study pathologist -- and a review

1 pathologist. And if there was no difference between
2 those two pathologists in the diagnosis, I'm not clear as
3 to why the PWG then reviewed those. That's the issue.

4 DR. COPLEY: Okay. That part is in the NTP
5 report, because it says to use the NTP technical report's
6 process. And so I took that out. It says at least or at
7 minimum. That's the minimum that they have to be given,
8 not the maximum. And they can give them the whole animal
9 for every animal in the study, if they want to.

10 DR. HERZY: Okay.

11 DR. COPLEY: But the minimum has to be the
12 disagreements between those two.

13 DR. HERZY: Okay.

14 DR. COPLEY: And I think there is a NTP report
15 floating around that I could actually get the exact
16 wording from, or actually we have --

17 DR. WILLIAMS: We have the NTP here.

18 DR. COPLEY: Yes. Dr. Boorman?

19 DR. BOORMAN: Yeah. One of the things that we
20 often do in a pathology working group, is we will take,
21 for example, some normals where the study pathologist and
22 the reviewing pathologist agree that there is no lesion

1 in question. We will take some lesions where there are
2 no disagreement between the study pathologist and the
3 reviewing pathologist on a benign lesion and on a
4 malignant lesion. And in addition we include all of the
5 -- you know, I should say in general we include all of
6 the discrepancies.

7 And so that's our process. So we include both
8 -- some of the cases where there are no disagreements.
9 And that also gives you some indication of the reviewing
10 pathologist and the study pathologist and how they stand
11 in the PWG.

12 DR. THRALL: Thank you. Dr. McConnell?

13 DR. MCCONNELL: But it was my understanding, Dr.
14 Copley, that in this case they looked at all of the
15 lesions, correct, in the liver?

16 DR. COPLEY: The peer review pathologist --

17 DR. MCCONNELL: Did. The peer review
18 pathologist.

19 DR. COPLEY: Well, that's required.

20 DR. MCCONNELL: In fact, he looked at every
21 liver?

22 DR. COPLEY: Right.

1 DR. MCCONNELL: But even if there was no
2 diagnosis --

3 DR. COPLEY: But they're talking about the PWG
4 itself.

5 DR. MCCONNELL: Okay.

6 DR. COPLEY: The PWG only got those that had
7 adenomas, carcinomas, gross lesions in the liver and
8 severe or moderate alteration.

9 DR. MCCONNELL: So they did see all the lesions
10 that could be called a neoplasm?

11 DR. COPLEY: Correct. But the question was, did
12 it say that they should only look at the differences. Or
13 how was it worded?

14 DR. HERZY: Thank you for clarifying it for me.

15 DR. THRALL: Dr. McConnell --

16 DR. MCCONNELL: And I'll make this quick.

17 DR. THRALL: Okay. You wanted to go back to
18 some information regarding lesion size in the liver.
19 Okay.

20 DR. MCCONNELL: At the break I was provided with
21 a table, and I guess it is in the report -- the original
22 data report -- that shows the foci -- or areas of

1 cellular alteration -- and that they were indeed graded.
2 The plus one, plus two, plus three is increasing degrees
3 of severity. And, you know, my looking at that -- and
4 I'm not a statistician. But eye balling that, nothing
5 jumps out at me that the severity in the controls versus
6 other doses is that much different.

7 You might disagree, but to me eye balling that
8 as a pathologist, that's not much of a deal there.

9 DR. THRALL: Dr. Dementi?

10 DR. DEMENTI: That data, is that that comes out
11 of the PWG -- the final PWG? That's what went into the
12 PWG.

13 DR. MCCONNELL: I don't know.

14 DR. DEMENTI: Right, I know it. But I wanted to
15 make that point. Okay.

16 DR. MCCONNELL: But I don't think the PWG graded
17 these, nor would I expect them to. That wasn't the issue
18 for the PWG. I mean, that would be a separate issue. I
19 mean, if you had some question that this was important --
20 but like I said before, even if I saw that, I certainly
21 wouldn't call something a carcinogen based on increase in
22 severity of areas of cellular alteration.

1 DR. DEMENTI: But see, the problem is certain
2 adenomas got downgraded by the PWG to be lesions. And we
3 don't have the incidence after the PWG of those of
4 moderate degree of severity. That is, those that were
5 chosen initially to go to the PWG.

6 DR. MCCONNELL: Well, I can assure you that if
7 there was something that had been called an adenoma
8 originally, and it was downgraded to a cellular
9 alteration, it would not be a plus one. It would be a
10 plus two or three, all right.

11 DR. DEMENTI: That's my presumption, too.

12 DR. MCCONNELL: All right.

13 DR. DEMENTI: And so then I sort of added them
14 up on my own, and I get incidence that don't indicate
15 there are any in the control that is of moderate degree
16 of severity.

17 DR. MCCONNELL: Well, there are 14 on that
18 slide.

19 DR. DEMENTI: Of moderate degree of severity.

20 DR. MCCONNELL: Yeah. In a scale of three --
21 maybe they had a scale of four. But at least that might
22 be mild, by the way. A plus two might be mild rather

1 than plus -- than moderate.

2 DR. DEMENTI: Okay.

3 DR. MCCONNELL: But it's not important what you
4 call them.

5 DR. DEMENTI: What I have to say is in my
6 written submission to the committee. Could I just read
7 this one paragraph?

8 The PWG report says the purpose of the PWG
9 review was to determine the incidence of hepatocellular
10 neoplasms in female rats following currently accepted
11 nomenclature and diagnostic criteria. Goodman, et al.
12 More correctly, in my view, the PWG would be expected to
13 determine incidence of lesions recognized as critical in
14 the natural history of neoplasia, that is, hepatocellular
15 alternations, adenomas and carcinomas, as these would
16 prove essential as key events and neoplasms to evaluate
17 under EPA's draft guidelines.

18 An important observation from this study before
19 and after the PWG in support of the concept of the
20 natural history of neoplasia, and why all three of its
21 elements need to be considered in the assessment under
22 EPA's draft guidelines, is this. All carcinomas were

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1 downgraded to adenomas, and not another lesion, and when
2 adenomas were downgraded, they were downgraded to
3 hepatocellular alterations, and not another lesion.
4 Hence, in this study five carcinomas, the entire lot,
5 were downgraded to adenomas, while six of the original
6 adenomas were downgraded to hepatocellular alterations,
7 which I consider the key events in this drama.

8 In this case it appears that final incidence of
9 hepatocellular alterations of moderate degree of severity
10 are needed, as these lesions were selected out by the PWG
11 Chairman to forward to the PWG as the most suspect among
12 such lesions to be reclassified as adenomas by the PWG.

13 And that's my point.

14 DR. THRALL: Dr. Everitt?

15 DR. EVERITT: Dr. Thrall, can I make a
16 suggestion, and sort of to move on? I mean, there are
17 going to be differences of opinion on this. Can we just
18 ask the question of, does anybody on the Panel feel that
19 knowing the severity of the focus grade that would have
20 been given to the downgraded adenomas -- would that
21 change anybody's thinking on how we look at the data.
22 And if not, why don't we just, you know, move on.

1 DR. THRALL: Move on.

2 DR. EVERITT: And agree there will be a
3 difference of opinion between the Panel and Dr. Dementi.

4 DR. THRALL: Okay. All right. Does everyone
5 agreed with Dr. Everitt? All right. We're going to move
6 on. And, again, I think that we answered question 2.3.1.
7 The SAP believes that the PWG report is valid.

8 So, Dr. Copley, can we go on to 2.3.2?

9 DR. COPLEY: Yes. Does the SAP consider the
10 statistically significant trend and pair-wise increases
11 in liver tumors in female Fischer 344 rats at 12,000
12 parts per million to be related to malathion exposure?
13 If not, why not? What weight should be placed on this
14 data, since there is evidence of excessive toxicity based
15 on severe cholinesterase inhibition in all three
16 compartments and mortality?

17 DR. THRALL: Dr. McConnell?

18 DR. MCCONNELL: Okay. Yes, we agree that the
19 increase in liver adenomas is related. But I would like
20 to emphasize that it's related to the test substance as
21 contrasted to malathion itself, okay?

22 DR. THRALL: Point taken.

1 DR. MCCONNELL: I think that's very important.
2 But there are no carcinomas, okay. So, again, it falls
3 in line with what Dr. Williams was referring to and might
4 be a hint in terms of the mode of action of these tumors.

5 It's important to note that the liver weight was
6 also increased at 6,000 ppm, as well as 12,000 ppm, at 12
7 months. And as I suggested yesterday, the 12 month data
8 is better to use for liver weights than the weight at the
9 end of the study. For example, at 6,000 the liver weight
10 was increased approximately 10 percent in the females and
11 at 12,000, 18 percent. In the males it was 23 percent at
12 6,000 and 35 percent.

13 And then the last part of the question was
14 should the data -- the evidence of excessive toxicity. I
15 do not think that the -- or for me, at least, I did not
16 consider the cholinesterase issue to impact on whether
17 these tumors were associated with that or not. I was
18 more concerned with the obvious toxicity as indicated by
19 survival weight gain, and most importantly, the liver
20 increased weight and the presence of liver hypertrophy at
21 that dose.

22 And I'll stop there.

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1 DR. THRALL: Dr. Everitt, do you have any
2 additional comments? All right. You agree with Dr.
3 McConnell. Are there any other -- do any other Panel
4 members which to respond to this question?

5 DR. MCCONNELL: I might -- should I read Dr.
6 Hard's?

7 DR. THRALL: Yes, please.

8 DR. MCCONNELL: Okay. I agree that the data on
9 female rat liver tumors emanating from the April 2000 --
10 well, this was 3.2. Excuse me.

11 I do not believe that the apparent trend and
12 pair-wise increases in liver tumors in female 344 rats at
13 12,000 ppm to be considered a carcinogenic response to
14 malathion because of the following: the PWG, by
15 definition a group of expert pathologists, found no
16 increased incidence of liver tumors at any dose up to and
17 including the highest dose of 6,000 ppm that was not
18 compromised by excessive toxic.

19 The PWG diagnosed no case of liver carcinoma at
20 any dose, all tumors being adenomas. There was no
21 increase in the incidence of foci of hepatocellular
22 alternation at any dose, and thus no effect of malathion

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1 initiation and progression of lesions important in the
2 carcinogenesis continuum.

3 The percent incidence of liver adenomas at toxic
4 dose, 12,000 ppm at 13 percent, is not much higher than
5 the upper limit of the testing facility's historical
6 control range of 5.4 percent. Furthermore, incidence
7 from excessive doses that cause toxicity and mortality
8 cannot necessarily be expected to fall within a
9 historical or concurrent control range based on data
10 accumulated from normal animals.

11 The major metabolite of malathion and malaoxon,
12 which is also the active cholinesterase inhibiting
13 entity, tested in the same strain of rat at the same
14 testing facility, did not produce an increase in liver
15 tumors.

16 And finally in my view, no weight at all should
17 be placed on any data from the 12,000 ppm dose group,
18 because it was at a dose producing excessive toxicity
19 leading to mortality.

20 DR. THRALL: Thank you. All right. Question
21 2.4, Dr. Copley?

22 DR. COPLEY: The committee could not determine

1 whether the nasal tumors in rats were due to treatment or
2 random occurrence because -- and what I had mentioned
3 yesterday. Do you want me to re-read the reasons why we
4 considered either way?

5 DR. THRALL: Please.

6 DR. MCCONNELL: No.

7 DR. COPLEY: Okay.

8 DR. THRALL: Gene says no.

9 DR. COPLEY: You have it.

10 DR. THRALL: We have it. Go ahead.

11 DR. COPLEY: Okay. It should be noted that the
12 biological significance of the olfactory epithelial tumor
13 is unknown, since it is from a different cell of origin
14 from these types of tumors -- and as we heard yesterday,
15 it's a glandular tumor -- and should not be combined with
16 other tumors of the respiratory nasal cavity. The
17 biological significance of this in relation to tumors of
18 the respiratory epithelium is unknown. It should be
19 pointed out that there were five nasal sections per rat.
20 Historical control studies usually have only one, two or
21 three sections.

22 The first question is: does the SAP agree that

1 nasal respiratory epithelial tumors in the rat are rare
2 tumors in light of the number of sections in the current
3 study as compared to the historical control database?
4 Why or why not?

5 DR. THRALL: Dr. Boorman?

6 DR. BOORMAN: The question as phrased refers to
7 tumors of the nasal section. And so my answer is going
8 to deal first with that and then more specifically with
9 the tumors that were found in this study.

10 Tumors in the nasal section in the Fischer 344
11 rat are uncommon, but not rare in recent national
12 toxicology program historical controls. And we will
13 include a reference from Hasman, et al. in 1998, where if
14 you look at a feeding study there was -- now this is in
15 the nasal cavity. There were zero adenomas, one squamous
16 cell papilloma and five squamous cell carcinomas that
17 were found in the nasal sections. If you look at male
18 rats for the inhalation studies, there was one adenoma
19 and no papillomas or carcinomas were found in the
20 squamous epithelium.

21 If you look at the female rats in a feed study,
22 there was one adenoma and one squamous cell carcinoma.

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1 If you look at the inhalation study, there was one
2 adenoma.

3 (END OF TAPE 2, SIDE A)

4 DR. BOORMAN: -- epithelial origin are not rare.
5 However, the tumors in question are the adenomas of the
6 respiratory epithelium. And I think it's fair to say
7 that those are rare. There were none in the feeding
8 study in male rats and one in an inhalation study out of
9 900 male rats. There was one out of 1,300 in a feeding
10 study in female rats and one out of 900 in an inhalation
11 study. And that's in a 1998 publication.

12 I also in a very nonscientific survey pulled all
13 the blue books or two year studies that were published in
14 1999 that were on my desk. And I threw out two studies,
15 Pentachlorophenol, et al. and Frefferol (phonetic)
16 Alcohol, which appeared to have a slight nasal tumor
17 response. Of the remaining studies, there were about
18 1,300 animals.

19 In those I looked at all of the groups, and I
20 found four tumors in the male rats, none in the female
21 rats. There was one adenoma of the respiratory
22 epithelium, two squamous cell carcinomas, and I was

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1 excited to find one olfactory epithelial tumor which is
2 no longer relevant to the discussion.

3 And I can make that data available. And what I
4 will probably do, is just provide the study that had the
5 one adenoma in the male and mention the females.

6 So to answer the question, I would say that
7 adenomas of the nasal respiratory epithelium are rare in
8 our historical control database, but I think that you
9 need to refer to adenomas, because papillomas and
10 squamous cell carcinomas occur more frequently.

11 DR. COPLEY: Say that again? You need to refer
12 only to adenomas, is what you just said, correct?

13 DR. BOORMAN: Right.

14 DR. COPLEY: Okay.

15 DR. BOORMAN: What you found was adenomas of the
16 respiratory epithelium. There are other epithelial
17 tumors.

18 DR. COPLEY: Right.

19 DR. BOORMAN: And what I didn't mention is there
20 is also mesenchyma tumors, chondromas, sarcomas and fiber
21 sarcomas that occur uncommonly in the nasal cavity.

22 DR. COPLEY: But we were talking about the

1 epithelial adenomas.

2 DR. BOORMAN: Right. And we -- to make a long
3 answer short, we agreed that they are rare.

4 DR. THRALL: Dr. Everitt, do you have anything
5 to add?

6 DR. EVERITT: Yeah. I would like to just make
7 one comment and then read something from Dr. Hard. The
8 comment I would like to make is that it is very unusual
9 to have sectioned the nose comprehensively in a dose feed
10 study. Taking five sections of the nasal passages is not
11 something that is routinely conducted by many
12 laboratories.

13 In my own institution, we have done it and we
14 have published many papers saying that it is useful to
15 do. But we don't have a good database of the results. I
16 will make that available. I didn't have time to do it in
17 preparation for this meeting. But I will go back and see
18 if we have found control respiratory epithelial adenomas
19 in our database. I have to go back to studies that were
20 published out of our institution. The original
21 pathologist has left, so it will take me a little while
22 to do that. But I will make that available.

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1 But I want to just bring up something that
2 Gordon Hard brought up, and I'm going to read his answer.
3 In considering the significance of the nasal tumors, I
4 want to bring attention to a feature in the malaoxon
5 study that I feel is of likely significance in the
6 malathion bioassay.

7 Under microscopic pathology the study
8 pathologist described a clearly dose related increase in
9 the incidence of foreign material, food particles and
10 hair in the nasal lumens of male and female rats rising
11 from less than 10 percent in controls to close to 50
12 percent in high dose animals, closely mirrored by the
13 incidence of nasal lumen inflammation at the high dose.

14 The authors of the report speculate that this
15 abnormal aspiration might have been indicative of a
16 neurological effect secondary to the inhibition of
17 cholinesterase activity. As severe depression of
18 cholinesterase activity was observed in the malathion
19 study, it seems reasonable to suggest that a similar
20 aspiration abnormality occurred particularly at the
21 higher doses of this compound.

22 In my experience, aspirated foreign material

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1 into the rat nose can be an inciting factor in the
2 occurrence of random, small nasal tumors.

3 I bring this up because it's well known in rats
4 that chronic inflammation can effect both nasal and oral
5 tumorigenesis. And with the uncertainty in the
6 databases, I think we have to at least keep an open mind
7 that secondary effects may be a very plausible
8 explanation for, you know, this unusual finding where we
9 only have an occasional tumor noted in a group.

10 DR. THRALL: Thank you.

11 DR. BOORMAN: Mary Anna, can I make one more
12 comment?

13 DR. THRALL: Yes.

14 DR. BOORMAN: I had forgotten to mention that
15 two out of three tumors in the malathion study are in
16 section five, the section that we do not have in the NTP
17 database. And so I think that also needs to be included
18 for the record.

19 DR. THRALL: Thank you. Dr. Capen?

20 DR. CAPEN: Yeah. I think I would agree with
21 what both Dr. Boorman and Dr. Everitt have said. And I
22 think the difference in the number of sectioning levels

1 plays an important role in the difference in incidence
2 that, you know, have been reported in this study.

3 DR. THRALL: Thank you. Do any other Panel
4 members have any responses to this question? Yes, Dr.
5 Williams?

6 DR. WILLIAMS: Gary Williams. I guess I do have
7 a kind of gut reaction, although it's not statistically
8 supported, that there is something going on in the nasal
9 mucosa at the high doses, because these three tumors
10 occurred only at the high doses. So that suggests to me
11 that it is not a completely random event, or they might
12 have been spread over other dose groups.

13 Now, Jeff, you read in a hypothesis for these
14 tumors. But why are we relying on the malaoxon study?
15 Was there not similar findings in the malathion study?

16 DR. EVERITT: I don't have the data in front of
17 me. I don't believe that the degree of findings were the
18 same. Does anybody have Jim Swenberg's report?

19 DR. WILLIAMS: Well, I read his report and they
20 do mention toxicity in the nasal mucosa. I think it's
21 predominantly, as I recall, in the olfactory mucosa.

22 DR. EVERITT: Let me -- I didn't make it clear.

1 I missed the most important part of answering my
2 question. And that is, I don't think we can ascribe one
3 way or the other what the cause of these neoplasms is.
4 ~~So~~ I'm not insinuating that it's a random occurrence.
5 I'm just saying that this is a rare occurrence. They do
6 sporadically occur.

7 I'm just saying that the strength of the
8 database is very uncertain for this site, and that there
9 are differences in the incidence of this tumor that can
10 be related to other, you know, potential factors.

11 But my conclusion personally is that we cannot
12 ascribe an ideology to these tumors.

13 DR. BOORMAN: You're getting to the next
14 question.

15 DR. WILLIAMS: This is the next question.

16 DR. EVERITT: Oh, I'm sorry. Okay.

17 DR. THRALL: Dr. Boorman, did you have -- did
18 you want to make a comment before we go on? Okay. All
19 right. Next question?

20 DR. COPLEY: Okay. Does the SAP agree that the
21 increase in these nasal respiratory epithelial tumors in
22 Fischer rats cannot be conclusively attributed to either

1 treatment with malathion -- technical -- or random
2 occurrence? If the SAP feels that this increase can be
3 attributed to treatment, why?

4 ----- And I would just like to comment on the thing
5 that he mentioned that the malaaxon was not -- I went
6 back and I looked at the same things. I didn't see it in
7 the malathion study -- the nasal debris.

8 ----- DR. EVERITT: Yeah, I got ahead of myself. I
9 agree with that statement that the ideology of these
10 tumors cannot be definitively ascertained. But I share
11 the same concern that Dr. Williams has, that it's a rare
12 occurrence and it was in the high concentration groups.

13 I just wanted to point out, with the uncertainty
14 in the database when you have a single uncommon
15 occurrence, as you start pulling out more and more of
16 these blue books, you start seeing that rare things seem
17 to keep popping up. So when you have a single finding --
18 a single tumor finding -- there is uncertainty.

19 DR. THRALL: Dr. Boorman, any additional
20 comments?

21 DR. BOORMAN: No additional light on the
22 subject.

1 DR. THRALL: Okay. Any -- yes, Dr. Gaylor?

2 DR. GAYLOR: Dr. Gaylor. I agree with Dr.
3 Williams here. I have some concern that with seeing
4 three rare tumors -- I'm talking about the nasal, the
5 respiratory epithelium adenomas. Those three. You will
6 hear statisticians say if you have less than four tumors,
7 you don't worry about it. Well, when we say that, we're
8 talking about groups of 50 animals. If no tumors in 50
9 controls, you have to have four tumors in a treated group
10 to reach statistical significance.

11 What we have here, and what you have to do here,
12 is being willing to look at both males and females and
13 combine that information and not look at it separately.
14 If you look at one tumor in the male and two tumors in
15 the females, you don't achieve any statistical
16 significance.

17 But when you do a popular method of analysis,
18 where you use the data -- combine the data. Not combine
19 it up front. But you combine the statistical outcomes,
20 which really goes back to what Mendel and Hansel said in
21 their review. It's the stratify. In this case would be
22 sex and look at the overall conclusion.

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1 What we have here are actually -- in males and
2 females combined in the three lower doses, we have 300
3 animals exposed with no -- I'm not using any historical
4 data here. I'm using concurrent data. We have 300
5 animals at the three lower doses with no tumors of this
6 type. In the two higher doses, we have 200 animals with
7 three tumors of this rare type.

8 And when you do the dose response trend test in
9 the males and in the females and combine the results of
10 those two, you come up with a statistical significance
11 level of a .02 level. Now I can submit this as an
12 appendix, I guess, to our report, if you think that's
13 necessary.

14 So I would agree there is maybe something going
15 on here to see three rare tumors. And, again, we have
16 the high dose. You know, we still have the high dose
17 problem. And is it due to irritation. Is it due to --
18 but I don't think we can disregard the fact that we have
19 three -- and three tumors become statistically
20 significant because we have more than 50 animals per dose
21 group that we're looking at.

22 DR. BOORMAN: Mary Anna, can I make one brief comment?

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1 DR. THRALL: Yes.

2 DR. BOORMAN: I think it gets back to what Dr.
3 Needleman said. I think we -- I agree with you that when
4 you have two tumors in the high dose and one in the next
5 dose, we just can't dismiss them. The problem with the
6 statistical approach, to me I would suggest that if you
7 had one in the 800, then you just split your groups
8 different, in that you split your groups for your
9 analysis based under these --

10 DR. GAYLOR: I didn't split them. I was -- I
11 didn't split the groups. I did a dose response trend
12 test.

13 DR. BOORMAN: Okay.

14 DR. GAYLOR: I didn't look at the data. I
15 didn't do that split. I was just pointing out that
16 that's kind of why this comes out significant.

17 DR. BOORMAN: Oh, okay.

18 DR. GAYLOR: But I did a dose response.

19 DR. BOORMAN: Okay, fair enough.

20 DR. GAYLOR: But it's an after the fact of
21 combining males and females. We don't do that, but you
22 could argue why should males and females be different.

1 DR. BOORMAN: No, it's a minor point.
2 Conceptually I agree with you. I was just worried about
3 the post hoc combining. And I think it's not wrong to do
4 it, but I think that we need to put it in the light that
5 Dr. Needleman said, that this is sort of the after the
6 fact.

7 DR. COPLEY: And I would like --

8 DR. BOORMAN: So notwithstanding, I agree.

9 DR. COPLEY: I would just like to understand
10 something, Dr. Gaylor. When you combine these, does that
11 make any difference -- I mean, does it make any
12 difference in the fact that the males and females are
13 responding differently toxicologically? Not profile wise
14 or qualitatively, but quantitatively, because the high
15 dose in the females has roughly the same toxicity as the
16 6,000 in the males.

17 So is that important in the way you combine
18 them?

19 DR. GAYLOR: No. I'm not combining the data up
20 front. I'm doing a statistical trend test on the males.
21 I'm doing a statistical trend test on the females. And
22 I'm combining -- I guess you could say it's sort of a

1 combination of the P values. You have two P values and
2 you combine these to get one P value -- one significance
3 level.

4 So it's just taking the data at face value.
5 It's just taking the tumor incidence at face value and
6 it's not -- it's just saying, here's two estimates of
7 dose response slopes and what do we get. That's our
8 conclusion overall.

9 DR. THRALL: Dr. McConnell?

10 DR. MCCONNELL: Yeah. I want to agree with Dr.
11 Williams that intuitively I am interested in the tumors
12 in that they occurred in the higher two doses and I give
13 some credence to that.

14 However, I reserve the right to change my mind
15 if Dr. Everitt shows me that there is a similar incidence
16 in his studies -- in the controls in his formaldehyde
17 studies where they did take this section at the anterior
18 end of the nose. Because I think, as Gary pointed out,
19 Mormon pointed out that two of those lesions were found
20 in that section five, and that's a section that is not in
21 the historical database, number one.

22 And number two, you actually have 40 percent

1 more tissue to look at in this study than the historical
2 database. So those two things together to me give me a
3 little caution in the importance of these regions.

4 DR. GAYLOR: Gaylor. Well, that's the reason I
5 only use concurrent data.

6 DR. MCCONNELL: Yeah. I didn't trust the
7 historical data on this.

8 DR. THRALL: Dr. Williams?

9 DR. WILLIAMS: Yeah, Gary Williams. Could I ask
10 another question? The malaoxon study that was also done
11 concurrently at Huntington, did they section this level
12 five?

13 DR. MCCONNELL: That's a good question.

14 DR. WILLIAMS: I'm kind of asking that because
15 it may be due to something other than malathion/malaoxon.
16 But you see where I'm getting at, Gene? Obviously there
17 are no tumors there, now whether it was because the right
18 sections weren't taken or there was nothing going on.

19 DR. MCCONNELL: Sure.

20 DR. COPLEY: Well, we had a re-review of the
21 histopathology, but I don't have any evidence that it was
22 re-cut. Oh, wait a minute. I'm sorry. Malaoxon, yes.

1 This isn't malaixon. That's malathion.

2 I don't think we requested re-cuts in the
3 malaixon.

4 DR. MCCONNELL: Well, I've had a little bit to
5 do with this myself. It was sections two and four, I
6 think, in the malathion study, and there was not a
7 reexamination of malaixon.

8 DR. COPLEY: Right.

9 DR. THRALL: Okay. Question 2.4.3?

10 DR. COPLEY: So what exactly is the SAP's
11 response to 2.4.2?

12 DR. THRALL: Dr. Everitt, do you want to
13 summarize the response to 2.4.2, then, for us?

14 DR. EVERITT: I think -- I don't know if there
15 is a consensus. I guess I agreed with the statement that
16 said that the increase in nasal respiratory epithelial
17 tumors cannot be conclusively attributed to either
18 treatment with malathion or random occurrence.

19 I reserve the same concern that Dr. Williams has
20 that, you know, these tumors were only found in the high
21 concentration group. But I make my statement based upon
22 what I call an extremely weak database for historical

1 controls, in that I personally know of no dose feed study
2 in Fischer rats cut this way and the fact that these
3 tumors have been occasionally reported.

4 DR. THRALL: Dr. Gaylor?

5 DR. GAYLOR: I disagree with the statement that
6 you can't conclude that these are not due to malathion.
7 Just using the available data on these studies without
8 referring to any historical data, these data show a
9 statistically significant dose response trend for the rat
10 concerning both sexes.

11 DR. THRALL: So you have --

12 DR. GAYLOR: So I would say, yes, it appears
13 these are related to malathion exposure. Now what it
14 means because they're are at the high dose and maybe it's
15 due to irritation, that may be -- you know, that may be
16 the explanation.

17 But I would say statistically there is a
18 significant dose response trend. It's significant at the
19 .02 level. That's pretty high. It's not absolute.

20 DR. EVERITT: One clarification. You're saying
21 that in light -- keeping the issue of excessive toxicity
22 out there. So in other words, that's with the

1 concentration?

2 DR. GAYLOR: I'm saying that the tumor incidence
3 shows a statistically significant trend. Now what that
4 means is -- that's pathology.

5 DR. BOORMAN: Can I get a clarification? The
6 way the questions are phrased, 2.4.2 deals with female
7 rats and 2.4.3 deals with male rats. Your conclusion
8 applies to both males and females, if I'm hearing you
9 correctly?

10 DR. GAYLOR: That's right.

11 DR. COPLEY: No.

12 DR. GAYLOR: Well, no. Question 2.4.2 says
13 tumors in Fischer rats. It doesn't say male or female.

14 DR. COPLEY: It's the nasal respiratory
15 epithelial tumors in the males and females, and 2.4.3 has
16 to do with that olfactory epithelium rat.

17 DR. EVERITT: But the statistics you're basing
18 upon the combination of males and females?

19 DR. GAYLOR: Right.

20 DR. BOORMAN: Okay, thank you. Sorry.

21 DR. COPLEY: Marion Copley. What about the
22 comment that Dr. McConnell made about controls in a study

1 where section five is being taken?

2 DR. MCCONNELL: I will make sure that gets in
3 there, but I have to await Dr. Everitt's getting back to
4 us with what he found in a comparable study. I assume
5 those were Fischer rats.

6 DR. EVERITT: Yeah. I'm hedging because they
7 are not my studies. These are studies that were
8 conducted by Dr. Kevin Morgan at CIT and, you know, I
9 need to check and see if it's comparable and what the
10 actual database would be. But it would be very limited.
11 I mean, we're talking about a single study.

12 DR. MCCONNELL: This was a single study.

13 DR. EVERITT: Right. But if we found a tumor in
14 controls, if there is one there, it's not going back and
15 finding it. If it's been reported, then it would be
16 worth knowing that.

17 DR. MCCONNELL: Sure.

18 DR. THRALL: And these were animals in which the
19 cut was at level five?

20 DR. EVERITT: Well, if I'm not mistaken, this is
21 the scheme that has been published by John Young. It's a
22 standard cutting scheme. It's just not a standard

1 numbering system.

2 DR. MCCONNELL: Right.

3 DR. EVERITT: So we would cut the same way. We
4 would number differently. So it will be the same
5 section, but our numbers would be different. But I
6 believe this is a standard cutting scheme that has been
7 published in FAT by John Young.

8 Am I right or wrong?

9 DR. MCCONNELL: I assume. It's the same picture
10 that Young has in his paper, essentially.

11 DR. COPLEY: Actually this picture has section
12 five superimposed on the rest of it. The picture
13 originally was four sections. I'm pretty sure I have a
14 copy of the article here, who it was published by, and I
15 can't remember her name. It was somebody who -- it was a
16 cell proliferation.

17 DR. MCCONNELL: Yeah. But I can assure you that
18 if there were five sections taken in your study, and five
19 sections in Dr. Everitt's study, that it will be close
20 enough to compare.

21 DR. COPLEY: This was by Sandra Elridge, and it
22 was Effects of Propylene Oxide on Nasal Epithelial Cell

1 Proliferation. That's what we had sent to the company
2 as --

3 DR. EVERITT: Yeah. Dr. Elridge was a post hoc
4 at CIT.

5 DR. COPLEY: Okay.

6 DR. EVERITT: And I believe it's a CIT study, so
7 I'm assuming that it's our cut. But that's why I'll go
8 back and check our database.

9 DR. MCCONNELL: It would even be more pertinent
10 then.

11 DR. COPLEY: Uh-huh.

12 DR. THRALL: Okay. I think we have responded as
13 much as we can to that. So 2.4.3?

14 DR. COPLEY: What, if any, is the significance
15 of the adenoma of the olfactory epithelium in the one
16 Fischer 344 rat at 6,000?

17 DR. THRALL: Dr. McConnell?

18 DR. MCCONNELL: Okay. Well, obviously it's not
19 an olfactory tumor. We've established that it is a
20 Mormon's land tumor. In my opinion, no significance
21 should be given to a single tumor in any organ unless
22 there is concomitant arguments for that, i.e.,

1 hyperplasia in that same tissue. Therefore, I do not
2 think it's related to the exposure.

3 Second, I would add that I do not think it is
4 appropriate to combine that tumor with the other nasal
5 tumors, because it is a different histogenic -- it has a
6 different histogenic origin.

7 And I'll stop there.

8 DR. THRALL: Dr. Williams?

9 DR. WILLIAMS: I concur. I have nothing to add.

10 DR. THRALL: Okay. Any other Panel members wish
11 to comment? Okay. Question 2.5?

12 DR. COPLEY: The CARC could not determine
13 whether the oral cavity squamous cell tumors in Fischer
14 344 rats were due to treatment or random. The one
15 papilloma in males at 100 parts per million was
16 considered incidental.

17 It should be pointed out that the oral
18 epithelium (often palate) is usually present on nasal
19 sections and that there were five nasal sections per rat.
20 Historical control studies usually have one two to three.
21 However, the CARC determined that a re-cut would not
22 alter their conclusion.

1 Does the SAP agree that the oral squamous cell
2 tumors in Fischer 344 rats are rare tumors in light of
3 the number of sections in the current study as compared
4 to the historical control database? Why or why not?

5 DR. THRALL: Dr. Brusick?

6 DR. BRUSICK: Dr. Everitt and I had a brief
7 discussion regarding oral cavity tumors last night, and I
8 think I'll defer to him to provide, you know, a more
9 accurate and reliable discussion.

10 DR. EVERITT: Actually, I'm going to -- I had
11 some talks with Dr. Boorman, too, who made the Panel
12 aware of the NTP database, and I'm going to discuss the
13 findings in light of the recent NTP database revisions.

14 And that's that tumors of the oral cavity in the
15 Fischer 344 rat are uncommon but not rare. In a recent
16 publication by Hasman, Haley and Morris, which is in
17 ToxPath, volume 26, ten squamous cell tumors were
18 reported in the oral cavity of male Fischer rats in dose
19 feed studies out of 1,354 animals in the group, and 15
20 squamous tumors in an inhalation study. These are in
21 control animals. And this give an overall tumor
22 incidence of about 1 percent.

1 I think what is of interest here is the fact
2 that the incidence is actually higher in the inhalation
3 study controls than in the dose feed controls. And I
4 think this reflects back on the difficulty in assessing
5 the site and in the validity of some of these database
6 conclusions, in that inhalation studies are probably
7 examined a little bit more comprehensively for this site
8 than our dose feed studies in traditional chronic study
9 evaluations.

10 But in the female Fischer rat, there is even
11 more tumors. There were 18 squamous cell tumors in dose
12 feed groups and 14 tumors in inhalation study controls in
13 the same kind of animals. So it's running about 1.2
14 percent in control animals.

15 So I think this particular tumor has probably
16 traditionally been under appreciated as far as its actual
17 incidence. And I should make note of the fact that that
18 isn't with this extensive five sectioning pattern.
19 That's with the standard NTP sectioning pattern.

20 DR. THRALL: Dr. Boorman?

21 DR. BOORMAN: I'm real smooth here with the
22 microphone, after knocking over water and now candy.

1 I think the other thing that is worth pointing
2 out is the range in the controls goes from zero to 4
3 percent with some groups, and zero to 6 percent in other
4 groups. And if you look at the possibilities in any of
5 the groups, in the females it's 6 percent in the
6 inhalation studies. Four percent is the top. Six
7 percent for the males inhalation and 4 percent for the
8 feeding. So that we could have two or three tumors in a
9 control group of 50 animals.

10 Brian Dementi has discussed a lot the fact that
11 the tumors in the study are restricted to the palate.
12 What we're talking about here is oral cavity any site.
13 And so I want to be sure that that's clear.

14 DR. THRALL: Dr. Dementi?

15 DR. DEMENTI: Yes. May I comment on that? The
16 histopathology in this case comes out of the nasal
17 histopathology. There was not an oral histopathology
18 done on this study.

19 And as I evaluate NTP's database myself, I find
20 that almost all of the squamous cell tumors were of the
21 tongue and of the oropharynx. And in my discussions with
22 folks down there, I have been unable to identify a single

1 palate squamous cell tumor in the NTP database. There is
2 one lesion said to be of the oral cavity which has no
3 further descriptive. It could possibly be of the palate,
4 but that's the only one from the descriptors they have
5 that could be of the palate.

6 And I think that it is inappropriate to use
7 historical control data for tissues that were not
8 examined in the study. The tongue and oropharynx and
9 other oral tissues were simply not examined. And also,
10 we have no certainty that out of a nasal histopathology
11 assessment that we even have a fair assessment of the
12 palate.

13 I don't know that you folks in pathology all
14 know whether in a nasal tissue assessment you can count
15 on the assessment having been adequate for the palate.
16 But if so, it's only for the palate. I mean, the other
17 oral tissues have not been examined, and it's irrelevant
18 to use incidence for the tongue and so forth when that
19 tissue has not been examined.

20 And then I must say I find I remarkably disagree
21 with the CARC saying that regardless of what
22 histopathology assessment of the oral cavity would come

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1 up with, it wouldn't change their assessment. I mean,
2 good golly. I think you've got four extremely rare
3 tumors there already. And I say extremely rare in the
4 sense of they're being of the palate. In other words,
5 they are extremely rare in the palate.

6 And the thought that if you went in and examined
7 the other tissues and found a few more of these and none
8 in the control, I don't see how the committee here can
9 say that that wouldn't make any difference on what their
10 conclusion is. And I just can't believe that.

11 DR. THRALL: Dr. Everitt, would you like to
12 respond?

13 DR. EVERITT: Yeah. I can't make any refinement
14 of the database. In other words, I don't have
15 information that would say what the incidence of palate
16 tumors are versus oral cavity tumors. Generally those
17 are combined, to the best of my knowledge, in most
18 databases.

19 However, I would say that these tumors are
20 generally -- palatial tumors would generally be found in
21 studies that do a five section nasal study. As you can
22 see, you've got that area visible at trim, okay. So it

1 would be unusual, I would think, to miss palatial tumors
2 in the gross trim.

3 Okay. As far as what the actual incidence of
4 palatial tumors, I would just say it's not broken down in
5 the databases, and I don't think we can go by hearsay.
6 As far as I know, we have to look at oral cavity as a
7 whole when we assess this.

8 But what I am stating is that I think this is an
9 under appreciated site in the database that these
10 databases are not very robust as far as our ability to
11 determine these individual tumor findings for this site.

12 DR. DEMENTI: Well, two of these lesions are
13 malignancies -- squamous carcinomas. And my point is, I
14 can't understand why you would not want to see an
15 examination of the full oral cavity. If you've got four
16 already in the palate --

17 DR. EVERITT: No, no. I'm sorry.

18 DR. DEMENTI: Given the fact that the animals --

19 DR. EVERITT: You are examining the oral cavity,
20 but you're doing that -- that's a macroscopic assessment
21 at rodent necrose. In other words, when we determine
22 target organs of toxicity, I don't believe -- I mean, I

1 don't believe that there is a sectioning scheme that
2 would allow you to definitively map oral cavity squamous
3 lesions. What would happen is, lesions would be
4 sectioned as they were macroscopically visible, or the
5 section that would be taken is the sectioning scheme that
6 was utilized in this study.

7 DR. DEMENTI: Well, I don't know quite what --
8 exactly what you're saying. But the point is, the
9 oropharynx and the tongue were not examined, and other
10 oral tissues were not examined in the study. And also my
11 point --

12 DR. THRALL: Dr. Dementi, I think what he's
13 saying is that when you look in the mouth at necrose, you
14 would see oral tumors. We won't see them in the nose,
15 and that's why they take multiple sections. Right?

16 DR. DEMENTI: And none of these were seen.
17 That's the point. All four of these were not visible
18 macroscopically. And Dr. Bolte responded to a question
19 that I had. You know, do we have assurance that the oral
20 cavity was evaluated and why weren't these seen
21 macroscopically. And his response was that they were
22 endophytic in their growth pattern. That is, they were

1 growing inwardly in such a way that they couldn't be seen
2 macroscopically.

3 DR. THRALL: Dr. McConnell?

4 DR. MCCONNELL: Yeah. I would just add that
5 it's practically impossible, if not impossible, to sample
6 the oral cavity in the sense I think you're talking
7 about, Dr. Dementi, in that it would entail taking
8 sections through the cheek, through the tongue and
9 through the soft palate, etc.

10 It's like sampling the peritoneum. You know,
11 how would you do that. In a practical sense, it's
12 impossible. So one has to rely on gross observations.
13 And I assume that this study was done according to EPA
14 guidelines and that the oral cavity was examined. And if
15 the oral cavity is examined in a confident way, as long
16 as the controls and the dose groups are treated
17 similarly, no bias is introduced, in my opinion, and you
18 can rely on the observation that no tumors were seen, to
19 mean that no tumors were seen.

20 Obviously, if I took 25 different samples
21 throughout the oral cavity, something else might come up.
22 But that's just not practical and probably not even

1 possible, and it certainly would not be cost effective,
2 either intellectually or monetarily.

3 DR. DEMENTI: Well, the four squamous cell
4 tumors that were identified microscopically were not seen
5 grossly.

6 DR. MCCONNELL: Yeah. And the hard palate is an
7 interesting tissue. I am surprised a little bit that
8 they were all endophytic. A squamous cell carcinoma
9 should have been macroscopically visible. I'm surprised
10 that it was not.

11 DR. DEMENTI: And Dr. Bolte also says that in
12 inhalation studies the oral cavity is examined
13 microscopically. So it's a realistic thing.

14 DR. MCCONNELL: No. I --

15 DR. DEMENTI: That's what he said in his letter
16 to me.

17 DR. MCCONNELL: Okay. Well, I would bet you if
18 he were here today, he will modify that and say it's
19 examined grossly, and it's examined microscopically in
20 that the palate is part of a nasal section.

21 DR. DEMENTI: It's just the oral cavity is
22 examined microscopically. That's what he said in his

1 letter to me.

2 DR. MCCONNELL: Okay.

3 DR. THRALL: Yes, Dr. Roberts?

4 DR. ROBERTS: I would just like to make sure I
5 understand the response of the pathologists on the Panel
6 on this -- the question regarding oral squamous cell
7 tumors in Fischer 344 rat.

8 Have I heard correctly that those tumors are --
9 if we consider the oral cavity as a whole, those tumors
10 are uncommon but not rare, but that we're not able to
11 answer whether those tumors as they occur might occur
12 specifically in the palate, which was observed here are
13 rare?

14 We can't answer that question based on the data
15 that we have in front of us?

16 DR. DEMENTI: Exactly.

17 DR. ROBERTS: Is that correct?

18 DR. DEMENTI: Exactly.

19 DR. BOORMAN: Yeah. If you look at squamous
20 cell carcinomas in control groups of 50, they occur at
21 zero to 2 percent. But in the female rats, carcinomas
22 have occurred at 4 percent in one control group and up to

1 6 percent in another control group in an inhalation
2 study. We generally in our sections like that -- those
3 are sections of the nasal cavity. But you can see from
4 the photograph that that's the palate that we examine.

5 And I think Dr. Dementi is raising an
6 interesting question. We say oral cavity any site. I
7 have not gone back. We have a total of about 50 tumors
8 here in roughly 4,000 animals. And I would need to go
9 back and try to, you know, find out where the site is. I
10 don't know if that's relevant, and I don't know if we
11 would have that data. I don't know if all of our
12 pathologists would specifically say whether it's palate.
13 Some of these tumors occur at the base of the tongue.

14 DR. THRALL: Dr. Everitt, I've got a question.
15 The terms rare and uncommon, are those subjective terms?
16 Is there a certain percentage that can be applied to
17 those terms?

18 DR. EVERITT: Yeah, I'm sorry. I shouldn't use
19 that. But I think it's safe to say -- I don't know how
20 to split out for the same reasons Dr. Boorman mentioned
21 on palate. But oral cavity squamous cell tumors in the
22 Fischer rat run about 1.2 percent.

1 DR. THRALL: Dr. Williams?

2 DR. WILLIAMS: Yeah, just one point of
3 clarification on the pathology. The squamous cell
4 carcinoma of the alveolus of the tooth should not be
5 lumped with the tumors of the hard palate. It really is
6 a different type of tumor. So there were not two
7 carcinomas of the palate. There was one.

8 DR. DEMENTI: I seem to recall Dr. Swenberg said
9 they were combinable. But I don't have -- I would have
10 to dig out his papers.

11 DR. WILLIAMS: Well, let's hear from some other
12 people. I think they're a different type of tumor.

13 DR. DEMENTI: I will say one thing. There was
14 one of the palate tumors finally diagnosed as being of
15 the palate was originally diagnosed as being of the
16 alveolus of the tooth. Dr. Swenberg changed it to the
17 palate. So, I mean, it suggests those two tissues were
18 very close.

19 DR. WILLIAMS: Was that a PWG?

20 DR. DEMENTI: That was a peer review.

21 DR. WILLIAMS: A peer review. And do you accept
22 that? Do you accept that one?

1 DR. DEMENTI: Do I?

2 DR. EVERITT: Well, let me read Dr. Swenberg's
3 answer, okay, to question 2.5. A single squamous cell
4 carcinoma originating from the tooth alveolus was
5 diagnosed in a 150 ppm female. A single small squamous
6 cell carcinoma was diagnosed on the hard palate in a
7 12,000 ppm female, and a single squamous cell papilloma
8 was diagnosed at a 6,000 ppm female. A squamous cell
9 papilloma was also diagnosed in the palate of a low dose
10 male. These neoplasms are not significantly different
11 from the controls.

12 DR. THRALL: So the bottom line response, I
13 think the consensus of the Panel is that the tumors are
14 uncommon but not rare.

15 DR. BOORMAN: It might be helpful, rather than
16 using terms that are not -- that may mean things to
17 different people. To say -- and give the actual
18 percentages and the ranges. And we can do that from the
19 Hasman article.

20 And I think that we need to point out, as Dr.
21 Dementi said, that these are oral cavity any site. And I
22 would be glad to add a couple of sentences, or even go

1 back and look at some of these and see how much we can
2 define that. Dr. Dementi has pointed out that he has
3 talked to some of the people at our place trying to find
4 this out, and maybe I can provide more detail.

5 DR. THRALL: Good. Dr. Copley?

6 DR. COPLEY: Yeah. I just wanted to clarify
7 something --

8 DR. THRALL: I don't think you're on.

9 DR. COPLEY: Okay. Now am I? Okay. I just
10 wanted to clarify something that Dr. Williams had said.
11 The reason why a PWG wasn't required is this wasn't a
12 re-read of the existing slides, for the most part. We
13 requested re-cuts of all the tissues, except for the ones
14 that they already had. So they ended up with -- three
15 out of the five slides per animal were brand new
16 slides.

17 So we said do these cuts and have them all read
18 by the same pathologist. And I think that the study
19 pathologist, Bolte, was involved with this with Dr.
20 Swenberg. So it wasn't that they were re-reading all the
21 slides.

22 DR. DEMENTI: Could I make one last comment? To

1 the extent that the nasal tumors might be viewed as a
2 local effect by inhalation or whatnot, in the oral cavity
3 the food is in intimate contact with the oral cavity
4 through the chewing process.

5 And the fact that there are these four extremely
6 rare squamous cell tumors, as I can best determine in my
7 discussions with people at NTP, and given that the
8 abundance of such tumors often occur on the tongue and
9 oropharynx. But the fact that they are seen in this
10 study in the palate creates a greater imperative for you
11 to look for them in the oral cavity because they are so
12 rare in the palate.

13 DR. BOORMAN: Can I ask a question? One of the
14 things that we can look at in the data, Dr. Dementi, is
15 in our experience with some of the chemicals that induce
16 oral cavity tumors, we also find tumors of the esophagus
17 and the fore stomach.

18 Is there any hint or suggestion of tumors in the
19 fore stomach? Because that would poke holes in your
20 argument.

21 DR. DEMENTI: There is, I think, extensive
22 squamous cell hyperplasia in the fore stomach, but no

1 tumors. And I think the study pathologist attributed
2 that to some sort of reflux -- acid reflux in the stomach
3 or something, because the rats weren't eating properly or
4 something. But there was squamous cell hyperplasia in
5 the fore stomach. The other site, I don't know the
6 answer.

7 DR. BOORMAN: The esophagus is probably not a
8 fair question, because unless you see the tumor grossly,
9 you're not going to know. If you found something, it
10 would be significant. A lack of finding in the esophagus
11 is probably -- it doesn't mean as much, simply because
12 it's something that could be missed.

13 DR. DEMENTI: Well, I think you, yourself, ought
14 to look at the squamous cell hyperplasia in the stomach
15 for your own assessment.

16 DR. THRALL: Dr. Williams?

17 DR. WILLIAMS: Gary Williams. Can I ask Dr.
18 Gaylor a question, since he fell silent on this issue?
19 Previously when you were looking at tumor data, you made
20 the observation that the low dose group in these studies,
21 because of the tremendous spread of doses, is tantamount
22 to another control group. And one of the findings that

1 we have here is in this 100/50 treatment group in males
2 one of these tumors showed up.

3 Would you consider that indicative of a
4 spontaneous tumor?

5 DR. MCCONNELL: Are you consistent, in other
6 words.

7 DR. GAYLOR: I don't have the calculation for
8 that.

9 DR. THRALL: You're not on.

10 DR. WILLIAMS: You've been censored.

11 DR. GAYLOR: Yeah. If we would have had a tumor
12 at that lowest dose of 50 parts per million with the
13 nasal tumor, that would have wiped out the dose response
14 trend. So without doing the calculation, that's my
15 guess. Well, we've got four tumors. We've got one in a
16 dose that is very close to the zero dose relative to the
17 other doses.

18 So I didn't -- and I didn't know what tumors to
19 really -- I didn't do an analysis on these. I didn't
20 know what tumors to combine or not to combine. And as
21 Dr. Needleman has pointed out, looking at the data and
22 then after the fact deciding what to do is kind of -- it

1 kind of puts you in a bad position.

2 So statistically I didn't think there was
3 anything going on here with the oral squamous cell
4 tumors, but I could be wrong.

5 DR. THRALL: Okay. So Dr. Boorman has agreed to
6 try to find out more information on the location of these
7 oral tumors and hopefully that can be included in the
8 report.

9 Okay, next question?

10 DR. COPLEY: Okay. Does the SAP agree that a
11 re-cut of tissue would not significantly alter the
12 conclusions of this study? If yes, why? If no, why
13 not?

14 DR. THRALL: Dr. Williams?

15 DR. WILLIAMS: Okay. Now I was -- have been
16 uncertain actually of what that question meant. Often
17 when you talk about a re-cut, it means you're cutting
18 things that have already been cut.

19 DR. COPLEY: Okay. Re-cut possibly was not the
20 best word to use.

21 DR. WILLIAMS: Yeah.

22 DR. COPLEY: Do you feel that we should go back

1 and request sectioning of the oral cavity?

2 DR. WILLIAMS: Right.

3 DR. COPLEY: Do you feel that results from that
4 would alter -- I'm not saying that they might not find a
5 tumor more here or there. But do you think it would
6 alter the conclusions?

7 DR. WILLIAMS: Right. Well, I was going to
8 respond in that vain.

9 DR. COPLEY: Okay.

10 DR. WILLIAMS: Because that's obviously what Dr.
11 Dementi has been advocating. And I don't think it would.
12 I think there is every possibility you would find
13 additional tumors. I mean, I don't know if these things
14 even qualify as tumors, I mean, if you can't see them
15 grossly. But anyhow you would find additional lesions
16 in all probability. But since there is no dose
17 response here, I would have to assume that they would
18 be distributed over all groups in the study and
19 that it wouldn't impact the interpretation of the
20 study.

21 I don't see any merit in it.

22 DR. THRALL: Dr. McConnell?

1 DR. MCCONNELL: Yeah, I agree. I would only add
2 that I just think it's an impossible task. I wouldn't
3 know how to sample the oral cavity in a manner that would
4 add to the bottom line. I just think it would be an
5 impossible task. I could take a routine section from the
6 tongue. I could take a routine section from the gum,
7 etc. Cheek.

8 DR. DEMENTI: Oropharynx.

9 DR. MCCONNELL: And oropharynx. I could do all
10 those things, but, again, I'm still sampling. When you
11 think about your sections that are about two millimeters
12 thick, the tissue you take, it's still a very, very small
13 percentage of the oral cavity that you're sampling, even
14 after doing all of that.

15 So I just don't think it would add anything. I
16 think you have to realize that in a practical sense you
17 have to look in that particular tissue at a good gross
18 observation at the time of necrose and that will have to
19 suffice, and I think indeed does answer the question as
20 to whether there is a carcinogenic potential of
21 xenobiotics.

22 DR. THRALL: Additional comments? Yes?

1 DR. WILLIAMS: I'll just make one -- this is now
2 a scientific observation. But investigators have gone to
3 heroic effects to attempt to induce oral cavity cancer
4 with tobacco products. And they have been resoundingly
5 unsuccessful. For whatever reason, the oral cavity in
6 rats doesn't appear to be very responsive, even to potent
7 genal toxic agents.

8 DR. THRALL: All right. Next question?

9 DR. COPLEY: Does the SAP agree that the
10 increase in the oral tumors in Fischer 344 rats cannot be
11 conclusively attributed to either treatment with
12 malathion technical or random occurrence? If the SAP
13 feels that this increase can be attributed to treatment,
14 why?

15 DR. THRALL: Dr. Williams?

16 DR. WILLIAMS: I don't think that the tumors are
17 attributable to treatment for reasons we've already
18 discussed several times.

19 DR. THRALL: Okay. Dr. Everitt, do you have
20 anything to add? Any other Panel members? Okay. Next
21 question?

22 DR. COPLEY: This is question 2.6 and it was

1 incorrectly listed as 2.5 in the background document.
2 You had two 2.5's.

3 Does the SAP agree with the proposed
4 classification of malathion as suggestive? Why or why
5 not?

6 DR. THRALL: Dr. Copley, the Panel has requested
7 that we respond -- I'm sorry. I should have mentioned
8 this before. That we respond to issue three before we
9 get into question 2.5.

10 DR. COPLEY: That's fine.

11 DR. THRALL: So if you could just go ahead and
12 address question three -- issue three, question three,
13 then we'll go back.

14 DR. WILLIAMS: Could I just ask -- Dr. Thrall,
15 Dr. Williams over here.

16 DR. THRALL: Yes.

17 DR. WILLIAMS: Are we trying to push through and
18 finish without lunch?

19 DR. THRALL: No. But there's been a request
20 that we not break for lunch until about 12:30, since we
21 had a break at 11.

22 DR. WILLIAMS: Oh.

1 DR. THRALL: Is that okay with everybody?

2 DR. WILLIAMS: Except we've got two biggies here
3 now.

4 DR. THRALL: So you think this might be an
5 appropriate place --

6 DR. WILLIAMS: And we're not going to finish
7 either of them in 15 minutes.

8 DR. THRALL: Okay. Then in that case, let's
9 break.

10 DR. COPLEY: I skipped 2.5.4. Although I think
11 you actually did answer it, but I would like to have it
12 said at one time.

13 DR. EVERITT: And especially for the record in
14 terms of stating the question.

15 DR. COPLEY: Correct.

16 DR. EVERITT: And have the Panel comment on it.

17 DR. THRALL: Okay., 2.5.4.

18 DR. COPLEY: Yes. What, if any, is the
19 significance of the squamous cell carcinoma of the
20 alveolus of the tooth in the one female Fischer rat at
21 100 parts per million?

22 DR. THRALL: Dr. Boorman?

1 DR. BOORMAN: We've stated before in the
2 discussion -- I think that to attribute a solitary tumor
3 at a low dose treatment is not consistent with good
4 science.

5 DR. THRALL: Okay. Dr. McConnell?

6 DR. MCCONNELL: I concur with that. And if you
7 will, I'll read Dr. Gordon Hard's comment into the
8 minutes.

9 It is my view that the squamous cell carcinoma
10 of the tooth alveolus in one female F344 rat at 100/50
11 ppm is not related to treatment with malathion. The
12 study pathologist reported a squamous cell carcinoma of a
13 tooth alveolus in one male rat in the historical control
14 database of 227 males, presumably F344 strain, at the
15 test facility, although none were observed in 226
16 companion females.

17 Furthermore, periodontal disease was reported in
18 the malathion study, a condition which itself creates
19 abnormal environmental factors.

20 DR. THRALL: Okay. Do any other Panel members
21 wish to respond to that? All right.

22 I think, so that we can stick a little closer to

1 the published schedule that we will break for lunch now.
2 And we will -- it's 12:20. Let's reconvene at 1:15 and
3 continue then. Thank you.

4 (Whereupon, a lunch recess was taken.)

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AFTERNOON SESSION

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DR. THRALL: Okay. Mr. Lewis has some introductory announcements.

MR. LEWIS: Thank you, Dr. Thrall. Two points, one for the Panel members. We estimate that we're going to end today at about 4 o'clock. It's a little earlier than we have on the agenda. So if anyone wants to try to catch an earlier flight back to your home, please contact Patrick McQue from the SEP office and let him know that you want to change a flight. He will contact Shirley Perceival to make those changes.

Concerning some of the public comments that came into the SAP, you probably heard several Panel members make remarks based on Dr. Gordon Hard and Dr. James Swenberg. Neither one of them was able to provide their remarks at the meeting, but they provided written comments. The comments are already in the Docket. And I've asked the Panel members to review those comments and to add any additional remarks or to enter them into the record relevant to the particular question being posed here today. So that's why you are hearing Dr. McConnell and others providing remarks based on Mr. Hard and Dr.

1 Swenberg.

2 Thank you. Dr. Thrall?

3 DR. THRALL: All right. We are ready for -- as
4 I mentioned before, the Panel has requested that we
5 address issue three before we address question 2.5. So
6 if you could go ahead and read issue three and question
7 three.

8 DR. COPLEY: There were several neoplastic
9 lesions that the CARC considered and determined not to be
10 indicative of a carcinogenic potential of malathion
11 technical. These included mouse liver tumors at low
12 doses in males, male rat oral tumors that were
13 incorrectly listed as nasal tumors in the background
14 document, male rat thyroid follicular cell tumors, male
15 rat thyroid C-cell tumors, rat interstitial cell
16 testicular tumors, male rat liver tumors, male rat
17 leukemia, female rat pituitary gland tumors and female
18 rat uterine tumors of various types. The CARC considered
19 and determined that leukemia in male rats was also not
20 related to malaaxon treatment. All the previous were
21 malathion.

22 And the question is, does the SAP agree that

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1 these tumors are not related to malathion treatment and
2 as such do not contribute to the weight of the evidence?

3 And the next slide actually lists all the tumors
4 if you want to take them on a one by one basis.

5 DR. THRALL: Thank you. Dr. Brusick, did you
6 want to lead off with this?

7 DR. BRUSICK: Actually, I'm going to in the
8 interest of time defer to Dr. McConnell and let him begin
9 the discussion.

10 DR. THRALL: Okay. Dr. McConnell?

11 DR. MCCONNELL: Thank you. And in the interest
12 of time, I'm going to read Dr. Hard's comments, because I
13 essentially agree with them.

14 I do not consider that any of the listed tumors
15 are related to malathion exposure and therefore should
16 not be considered in the weight of the evidence. This
17 view is based variously on lack of statistical or
18 biological significance in group incidence, lack of dose
19 response relationships and/or incidence within concurrent
20 and historical control ranges.

21 Having said that, however, I think it is
22 appropriate to go through each one of these tumor types

1 and give them some serious consideration. I'm not going
2 to do them, however, in the order that they are listed.
3 I think there are a couple that we can deal with very
4 quickly and save our time for discussion of the ones that
5 might be more controversial in some people's eyes.

6 The first tumor that I thought that at least for
7 me I could write off very quickly was the female rat
8 uterine tumors. In looking at the table -- and this is
9 on page 18. I'm using page 18 of submission 013991 from
10 Jess Rowland, subject malathion. That's what I'm using
11 for my answers to this question.

12 In looking at those uterine tumors, for me there
13 is nothing at all that stands out.

14 DR. THRALL: Dr. McConnell, do you want to speak
15 more directly into the microphone?

16 DR. MCCONNELL: I'm sorry. For me there is
17 nothing that stands out on the endometrial lesions or
18 other tumors in the uterus. I wouldn't even know how to
19 lead such a discussion, and therefore I'm just going to
20 suffice it to say I see no reason to consider any of
21 those as treatment related.

22 DR. THRALL: All right. If we're going to take

1 these one at a time, then maybe other Panel members could
2 comment on female uterine tumors? Any other comments?
3 Dr. Williams?

4 DR. WILLIAMS: Well, this applies -- Gary
5 Williams. I mean it applies to the uterine tumors as
6 well as all of these others that we're going to look at.

7 But the point has been made a number of times in
8 the literature, including by Dr. Hasman at NIEHS, that in
9 a bioassay when you're sampling 40 different tissues and
10 processing them looking for tumors, and where there are
11 known spontaneous backgrounds, there is just a certain
12 statistical chance that in a treatment group there will
13 be a statistically significantly larger number of tumors
14 than in a control group.

15 And I think for the most part that's entirely
16 what we're dealing with here and with these other sites.
17 And it can go down as well as up.

18 DR. THRALL: All right. Are there any other
19 comments?

20 DR. MCCONNELL: Only on the uterine tumors?

21 DR. THRALL: On uterine tumors?

22 DR. BOORMAN: I agree.

1 DR. THRALL: Okay.

2 DR. MCCONNELL: All right. Then next let's go
3 to the testicular tumors while we're in the reproductive
4 phase of this discussion.

5 Now in regard to these tumors, these are the
6 interstitial or tumors of the testes which are so common
7 in the Fischer rat. As all of you know, practically all
8 of the animals by 24 months will have lesions that could
9 be considered interstitial cell tumors, depending on
10 one's criteria for diagnosis. But in the usual sense
11 where a lesion is considered a tumor if it's greater than
12 three contiguous seminiferous (phonetic) tubules, we
13 typically see close to 100 percent in these animals.

14 The only thing that made this significant, in my
15 opinion, was because the animals died earlier, so that
16 there was -- when you do one of these Peto's Prevalence
17 Tests, it did show significance. However, as you will
18 recall, these animals died after 18 months. And I think
19 at 18 months even, if you -- and there is some good data
20 to support this. If you section these testicles, you'll
21 find close to that incidence of lesions that would
22 qualify as interstitial cell tumors.

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1 So I think what we're seeing here is a function
2 of early death and has nothing to do with the
3 experimental procedures or the protocol or the exposure.

4 DR. THRALL: All right. Are there any other
5 comments regarding interstitial cell tumors? Yes, Dr.
6 Capen?

7 DR. CAPEN: Yeah. Just to be consistent I
8 think, you know, we should clarify that these are
9 adenomas at best. And I've seen a number of studies
10 where lesions that are diagnosed according to the
11 morphologic criteria as adenomas, if you remove the
12 chemical for a period of three to six months, many of
13 these go away.

14 So, you know, at least in my judgment a lot of
15 these are probably just areas of hyperplasia. But even,
16 you know, I think to clarify the termination, since we
17 have used either adenoma or carcinoma to indicate benign
18 or malignant, we should indicate that certainly I would
19 suspect that the vast majority of these are adenomas.

20 DR. THRALL: Dr. Gaylor?

21 DR. GAYLOR: Gaylor. For the first time in my
22 life I think I've paid attention to testicular tumors.

1 I've usually had the same attitude that 100 percent of
2 the animals, or nearly that many, get tumors, and so
3 what, in the male rat.

4 But the EPA did do a proper statistical analysis
5 of these data -- the Peto Prevalence Test. Considering
6 these tumors as nonfatal is an appropriate test to
7 conduct. The analysis apparently shows a statistically
8 significant trend in the -- if you want to call it the
9 time to tumor or a reduced latency. Even at 500 parts
10 per million there is seen a significant difference
11 between the 500 parts per million group and the control
12 group in the time that tumors occur.

13 And I disagree with all the statements made on
14 page 22 in the EPA report. Their interpretation, in my
15 mind, is totally incorrect. They said in one of these
16 statements that the apparent statistical significance of
17 the tumor incidence at the two high doses could be
18 attributed to the high mortality at these doses resulting
19 in earlier observation of tumor, and significance was
20 considered to be an artifact of the Peto's Prevalence
21 analysis.

22 The whole point of a Peto's Prevalence analysis

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1 is to remove this artifact of early death. In fact, what
2 we have here is -- it wasn't a designed experiment. But
3 these animals died -- starting dying at around 18 months.
4 We have a beautiful sacrifice experiment here going on.
5 We have animals dying weekly, basically, and we're able
6 to look at whether or not these animals have tumors.

7 So we have -- we couldn't have designed a better
8 study if we wanted to look at time to tumor. The Peto
9 Prevalence analysis is to look at survival. It's an
10 analysis that takes that into account.

11 The next statement says sufficient data not
12 available to determine if there was a decrease in the
13 latency period. There was no serial sacrifice to
14 determine latency. In fact, the first tumor occurred in
15 the control group during week 54. Actually, we've got a
16 great serial sacrifice study here. It wasn't a planned
17 one, but in fact that's what happened.

18 And then it says this tumor type is not useful
19 in overall evaluations since its occurrence is similar at
20 all dose levels. That's true at 24 months. Basically
21 nearly 100 percent of the animals have tumors in all dose
22 groups. What this test is telling us is that back at 18

1 months, before we have all the animals with tumors, back
2 at 18 months, 20 months and so on, we do have a
3 significant dose response trend in the proportion of the
4 animals that have interstitial cell tumors.

5 So if you look at the data at 19 months, 20
6 months, 21 months and so on, you'll see dose response
7 trends. By the time you get out to 24 months and all the
8 animals have this tumor, then of course you don't see it.
9 But it's telling us that there are dose response effects
10 and that the tumors are occurring earlier in the high
11 dose group and even at the 500 part per million group.

12 So I have some concern here. Again, it's a very
13 common tumor and you could argue that it's so common that
14 it doesn't mean anything. That's up to the pathologist.
15 But statistically malathion had an effect here on time to
16 tumor.

17 DR. MCCONNELL: Dave, can I ask you a question
18 here? In this statistical evaluation, does what went on
19 at 6,000 and 12,000 ppm impact on the statistics at 500?

20 DR. GAYLOR: No. It does on the trend test. A
21 separate pair-wise test was done. Just looking at the
22 500 part per million group, it's saying that this tumor

1 occurred earlier at 500 parts per million than it did in
2 the control group. So that gives me some concern.

3 Does anybody else want to speak to this?

4 DR. THRALL: Dr. Williams?

5 DR. WILLIAMS: Dave, could you just help me
6 understand how this can be? I mean, because when I look
7 at the numbers, essentially it's saying every animal --
8 virtually every animal, either when it died or was
9 killed, had an interstitial cell tumor?

10 DR. GAYLOR: You're looking at the total?

11 DR. WILLIAMS: Yeah.

12 DR. GAYLOR: Total study. If you go back and
13 look at those animals that are dying, say, at 18 months
14 -- you know, I don't have the data in front of me and I
15 don't know.

16 DR. WILLIAMS: Well, they had to have it, too,
17 if it's all.

18 DR. GAYLOR: Sure, they got it. Yeah. So
19 basically what's happening, maybe back at 18 months, is
20 there are no or few of these tumors in the control group
21 and at 500 parts per million there are a few. And at the
22 higher doses there is more.

1 And if you take a cut in time back here at 18
2 months, 19 months, 20 months or whatever, the data is
3 available. But you can't tell -- you can't tell from
4 this overall summary.

5 DR. BOORMAN: What I need to do is, I would like
6 the information on the information of animals at risk and
7 the number of animals examined at 18 months. Because I
8 have no idea whether we're at 10 controls or one animal
9 or three animals.

10 DR. GAYLOR: We're looking at all 50. We're
11 doing what NTP does basically.

12 DR. BOORMAN: But I'm asking how many animals
13 were examined at 18 months?

14 DR. GAYLOR: Well, whatever had died at that
15 point in time.

16 DR. BOORMAN: But that's the question. If
17 somebody could provide that.

18 DR. GAYLOR: Well, sure. They've got that.

19 DR. WILLIAMS: Well, what makes the difference
20 when they all had it anyhow?

21 DR. GAYLOR: But they don't all have it at 18
22 months.

1 DR. WILLIAMS: But 52 out of 55 had it.

2 DR. BOORMAN: But let's get the numbers.

3 DR. WILLIAMS: So in other words, it can't be --

4 DR. COPLEY: I don't have the numbers yet.

5 They're looking for it. But I would like to ask a
6 hypothetical question.

7 If all the animals were born with interstitial
8 cell tumors, and they were all living for a year or 18
9 months, you don't know they have these tumors. And
10 that's how an interstitial cell tumor is. It won't kill
11 them. It will grow there and you don't know you have it
12 until you open up the animal and look. So all animals
13 are born with it, because they happen to bred this strain
14 that has it.

15 And they are testing a chemical on them. The
16 high dose animal all dies. The next to the high dose
17 animals die later. What will your Peto show? Because
18 you don't diagnose those tumors until those animals are
19 dead. What will your Peto show?

20 DR. BOORMAN: Marion, can I interrupt to make a
21 point? What Dr. Gaylor is saying -- he's saying that
22 when you examine the animals at 18 months there are

1 different rates in the different groups. And if that's
2 true, I would like to see the data. Because in our
3 experience, we find almost all animals after 12 or 14
4 months have interstitial cell lesions.

5 And if it's just a reflection of when you're
6 examining the animals, that's one thing. Dr. Gaylor has
7 evidence that at 18 months it's zero percent in the
8 control.

9 DR. GAYLOR: No, no, no, no. No.

10 DR. BOORMAN: Then if it's just a function of
11 when the animals are examined, whenever you look at a
12 Fischer rat, probably after 15 months, they'll have
13 interstitial cell tumors. All of them. One hundred
14 percent essentially. Or 90 percent. Because it's a
15 very, very, very common lesion. It's a very slow growing
16 lesion.

17 And as Dr. Capen said, it's probably
18 hyperplasia. It's proliferation of the interstitial
19 cells. And we arbitrarily -- if it's a certain size, we
20 designate them as benign tumors. We have never in my
21 experience diagnosed a malignant interstitial cell tumor.
22 We had one out of hundreds of thousands of rats that we

1 thought was a malignant tumor. We went back to look at
2 it -- I was writing the book chapter -- and it was so
3 otolithic we could not be sure.

4 So we don't have any evidence that any of these
5 tumors ever go to malignancy. These are lesions that
6 occur at nearly 100 percent. We have a couple hundred
7 thousand controls in our database and none of them are
8 malignant. And they may all be hyperplasia.

9 My argument would be if no matter what the
10 statistics would say, biologically I have a hard time
11 attributing any significance to this.

12 DR. WILLIAMS: Gary Williams. Just one minor
13 point. And they are also usually multiple. And if you
14 do multiple sections, you find these small niduses of
15 proliferating interstitial cells in all of these animals.

16 DR. CHEN: Yeah. I agree with what Dr. Boorman
17 say about those tumors may not be important. But what I
18 have a problem is about the reason explained in the
19 report. The Peto Test is not significant, even we see
20 the 500 dose group at 500 ppm and control group almost
21 have same kind of tumor incidence rate. But what I just
22 tell you, those 500 group occur much earlier than the

1 control group. That's all it tells. The incidence is
2 the same.

3 However, okay, I answer the question about how
4 many animals in 18 months. There is a table of how many
5 animals survive. And the way it seems to me, at 22 weeks
6 the control group had five animals die. At 22 weeks.
7 And 500 ppm group has nine animals, which kind of can
8 make some comparison. The 6,000 group has 19 out of 52,
9 but in the 22 weeks, the control group has 13 animals
10 die. And 500 ppm group has 12 animals die.

11 So what I tell you is if we just do comparison
12 of the control in the 500 group, and what I tell you
13 giving the incidence is correct, those 13 animals, what
14 we observed in the control group, have the lower tumor
15 rate than the 12 animals in the 500 ppm group. That's
16 all in that week, 23.

17 DR. BOORMAN: But if you look at week 78 -- and
18 this is on page 23 of the document. At 78 weeks there
19 was zero controls that were dead, zero at the low dose,
20 three at the 500 and one at the 6,000. So your
21 significance would be based on zero controls, three at
22 the mid dose and then the next to high dose is one, and

1 there are 15.

2 DR. CHEN: Okay. Let me answer your question.
3 In the Peto test the way -- if you don't observe any
4 animal die in that same control group, then there is no
5 comparison. It will wash out.

6 DR. EVERITT: I think the only point is that
7 there is a very, very steep mortality curve that then
8 goes to 100 percent mortality in this study, and does
9 that have an effect on the Peto Prevalence Test.

10 DR. CHEN: No, it doesn't. It only say that
11 tumor occurs maybe only about one or two weeks apart.

12 DR. EVERITT: But when you have a tumor that at
13 the end of a study is 100 percent incidence essentially,
14 and you have a very steep mortality and a very compressed
15 period of observation for that Peto Prevalence Test, and
16 you have extremely high mortality by the end of the
17 study, isn't that going to effect things? I mean it's
18 not a very robust situation.

19 DR. GAYLOR: Well, it makes it even harder for
20 the Peto's Test to come up significant when they all end
21 up with 100 percent tumors. That test is just telling us
22 that at some point before two years there is a difference

1 in the tumor incidence curves, that tumors are occurring
2 a little bit earlier in the higher dose groups than they
3 are in the controls. Now what that means to you --

4 DR. EVERITT: I'm just suggesting that we don't
5 put much weight to that in that it's 100 percent
6 incidence of a tumor by the end of a study. You're in a
7 study in which you have a very steep mortality curve, not
8 just a very -- you know, a very severe mortality. It's a
9 very steep curve, okay, and so you're looking at a very
10 -- it's not like many other tumors where you're looking
11 at time of latency to the tumor.

12 DR. BOORMAN: It's not like a serial sacrifice.

13 DR. COPLEY: I think I found --

14 DR. GAYLOR: It's not true at 500 dose group.

15 DR. COPLEY: I think I found something that
16 might help. And it's a 12 month sacrifice of 15 rats.
17 And at the 12 month time point, 15 rats in both control
18 and high dose group were examined histopathologically.
19 The combined incidence of unilateral and bilateral
20 interstitial cell tumors were 83 percent, 79 percent, 92
21 percent, 98 percent and 96 percent in groups one through
22 five. And this is at 12 months. So that is an interim

1 sacrifice across 15 animals.

2 DR. GAYLOR: That's not much difference.

3 DR. THRALL: Could you repeat those percentages
4 one more time?

5 DR. COPLEY: It's in the DER that somebody was
6 reading from on page 67, if anybody wants to find it,
7 second paragraph. And it's at a 12 month time point.
8 The combined incidence of unilateral and bilateral
9 interstitial cell tumors were 83 percent, 79 percent, 92
10 percent, 98 percent and 96 percent of the 15 animals.

11 DR. MCCONNELL: That's starting very high in the
12 controls and it's getting a little bit higher in the high
13 dose group. That's all we're saying.

14 DR. EVERITT: I'm just suggesting that it may be
15 statistically significant using that particular test.
16 But I think to most pathologists we're looking at a
17 situation that is probably biologically meaningless.

18 DR. GAYLOR: That's fine. We're not arguing
19 that.

20 DR. THRALL: Okay. Let's go to the next tumor.

21 DR. MCCONNELL: All right. Gosh, if I thought
22 that one was going to be easy, what am I going to do now.

1 Well, I had an encouraging remark just made to me. He
2 said that was his hardest one.

3 So, anyhow, I think since it will be easier for
4 you to follow along, we'll do them as they occur in this
5 document that I referred to earlier. So table nine, male
6 rat thyroid follicular tumor rates. I think I have to
7 preface what I'm going to say here in that while it is
8 appropriate to diagnose these tumors as adenomas and
9 carcinomas and divide that, the most proper way to
10 analyze the data, and I think the best way to analyze the
11 data, is to look at the combined situation.

12 Because these are a continuum. They're often
13 one man's adenomas and another man or woman's carcinoma.
14 And with the exception of if you would happen to find
15 some of these that were truly aggressive and it
16 metastasized outside of the organ, which is also rare, I
17 think the best way to analyze this data is looking at the
18 combined tumor.

19 Now if I understand this table correctly, the
20 combined situation is not significant for any of the
21 pair-wise tests, but does become significant at a .035
22 level for a trend test. For me, this was not very

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1 persuasive in suggesting that that observation was
2 related to the treatment of the chemical, and because the
3 incidence are so low and in fact where the animal
4 survived at about the same -- they were almost identical,
5 the 500 ppm versus the zero ppm.

6 I'm sure this trend -- this prevalence test
7 became significant because the high dose group animals
8 died earlier. And the potential with the statistics
9 would be that these animals, if they had been allowed to
10 live longer, probably would have even had a higher
11 incidence. I guess that's what makes it significant.

12 However, from a biologist standpoint, I do not
13 think this would be related to the malathion exposure.

14 DR. THRALL: Other comments? Yes, Dr. Gaylor?

15 DR. GAYLOR: I agree that the EPA has done the
16 proper statistical analysis here. And in spite of the
17 higher -- just the opposite, I think, of what Dr.
18 McConnell just said. In spite of the higher mortality at
19 the higher doses, we still detected a significant trend
20 here and the Peto test takes into account the number of
21 animals at risk based on the differences in mortality.
22 So it takes that into account in spite of the higher

1 mortality.

2 But it was a significant trend. There is no
3 pair-wise -- as was pointed out, there is no pair-wise
4 differences. So it's -- you know, it's a statistically
5 significant result. It's an isolated result. But I
6 don't think you can argue both ways. We just argued we
7 had a high incidence -- a high background of incidence.
8 Maybe that isn't what you were saying. We had a high
9 incidence with testicular tumors, so we're going to
10 disregard those. Now we've got a low incidence, so we're
11 going to disregard those. I don't think that's what you
12 meant. You just meant it was kind of a low incidence
13 compared to the controls, is that right?

14 DR. MCCONNELL: Yeah.

15 DR. THRALL: Dr. Capen?

16 DR. CAPEN: Yeah. Just a word. I think it's
17 important to point out that there apparently are no TSH
18 mediated pre-neoplastic or non-neoplastic lesions of
19 hyperplasia in either the male or female rats. And as I
20 remember seeing a table in the three month sub-chronic
21 study, there was no evidence of centrealaubidier
22 (phonetic) hypertrophy that would be suggestive of

1 hepatic microsomalimzime (phonetic) induction. I assume
2 that we don't have any thyroid hormone or TSH values from
3 the study. At least I haven't heard any of them
4 presented.

5 DR. THRALL: Dr. Chen?

6 DR. CHEN: Yeah. I would like to make a comment
7 about the trend test when the P value is only 3.5
8 percent. This may be one of the incidence what Dr.
9 Williams is talking about, because we do conduct more
10 than 20 to 30 tumor types. We conduct several tests. So
11 if the tests increase, then there is a chance of false
12 positive increase. And usually I kind of -- if the trend
13 test is only 3.5 percent, I kind of suspicious about the
14 significance of this finding.

15 DR. THRALL: Okay. Any other comments about
16 thyroid tumors?

17 DR. COPLEY: Follicular cell thyroid tumors.

18 DR. THRALL: Follicular cell thyroid tumors?

19 DR. MCCONNELL: Yeah. Now we'll go to the
20 C-cell tumors.

21 DR. THRALL: C-cell tumors.

22 DR. MCCONNELL: Okay. And that's table 10. And

1 I guess the reason that we were asked to look at this was
2 because at the 500 ppm in a comparison of the carcinoma
3 versus the adenoma there was a significant pair-wise
4 difference.

5 Again, I would caution, however, that the
6 thyroid C-cell tumors are a little bit similar, not in
7 terms of incidence, but in terms of a morphologist
8 diagnosis to the interstitial cell tumor of the
9 testicular, in that when one makes this diagnosis, it's
10 fairly arbitrary and probably does not have much to do
11 with the natural history of this lesion.

12 Therefore, again, I am more persuaded by the
13 combined incidence of this particular lesion than I am to
14 an analysis of either the adenoma or carcinoma, unless I
15 saw a highly significant trend for one or the other. And
16 of course with this particular study because of the high
17 mortality, I can probably find that out at the 6,000 and
18 12,000 ppm.

19 So when one looks at the combined incidence of
20 these tumors, for me, I don't see anything going on with
21 regard to the biology or the statistics.

22 DR. THRALL: Dr. Capen, would you like to

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1 comment on that?

2 DR. CAPEN: Yeah. I think I would agree that
3 certainly it is a very common spontaneous tumor in
4 certain strains of rats with a variable incidence of both
5 hyperplasia adenomas and carcinomas. Certainly the main
6 control signal for this cell population is the calcimine
7 concentration. We have no indication that there are
8 changes in blood calcium. At least I'm not aware of any
9 xenobiotic chemical that has ever been shown to
10 significantly increase the incidence of C-cell tumors in
11 rats. But Dr. Boorman might know of one. But it
12 certainly would be very uncommon.

13 DR. BOORMAN: It's very uncommon. There is a
14 possibility of one in the first couple of bioassays that
15 might have been related to C-cell tumors, but it's a very
16 old study. And so essentially in the last 20 years there
17 has been no chemical that induces C-cell tumors.

18 DR. GAYLOR: I would like to address that. In
19 1985 Huff, et al. of the NTP went back and reevaluated
20 the NCI malaixon studies. And for the combined adenoma
21 and carcinoma for thyroid C-cell in the male Fischer rat
22 -- and the female -- they came up with an equivocal

1 finding. They called it equivocal.

2 DR. BOORMAN: If you split --

3 DR. GAYLOR: They're adding adenomas and
4 carcinomas together.

5 DR. BOORMAN: And generally what we do is when
6 we -- we have four levels. We have clear evidence, some
7 evidence, equivocal evidence and no evidence. And
8 generally the regulatory agencies look at equivocal
9 meaning that it's closer to a negative.

10 So I don't think that -- I stick with my
11 statement.

12 DR. GAYLOR: Yeah. It's low. And also the
13 single carcinoma increasing at 500 parts per million in
14 the Kemy Nova study is somewhat -- you know, it's sort of
15 isolated. But we got two kind of isolated and weak
16 events here and they've been noted, and I think that's
17 probably all we can say about them.

18 DR. THRALL: Okay. Next tumor?

19 DR. MCCONNELL: Yeah, 10B. Essentially I have
20 the same comments, and I won't reiterate them other than
21 to say that the combined --

22 MALE SPEAKER: That's 10B?

1 DR. MCCONNELL: Yeah, 10B.

2 MALE SPEAKER: What is it?

3 DR. MCCONNELL: Thyroid C-cell tumors in male
4 rats. That the combined analysis is the one that should
5 be used for this tumor in terms of determining whether
6 there is a treatment or not treatment related effect.

7 I was interested in that the 6,000 and 12,000
8 ppm doses were not listed on the one in my handout. But
9 I see them up there, and I guess that that doesn't help
10 me that much anyhow.

11 DR. COPLEY: Excuse me. There are two tables in
12 there. One has it with it and one has it without.

13 DR. MCCONNELL: Oh.

14 DR. COPLEY: It's exactly the same thing. They
15 did the statistics, which from what Dr. Needleman says is
16 something we shouldn't have done. We did the statistics.
17 We dropped off those other animals.

18 DR. MCCONNELL: Okay. All right.

19 DR. COPLEY: So look at the one with it.

20 DR. MCCONNELL: That's right. And, again, it's
21 just that one, so I have the same comment.

22 DR. THRALL: Okay. Next tumor?

1 DR. MCCONNELL: The next one is table 11, female
2 rat.

3 DR. THRALL: Tumor type?

4 DR. MCCONNELL: Pituitary pardistalis
5 (phonetic). Same comment as before, that I think the
6 combined incidence is the best approach to this for the
7 reasons I have stated for the other tumors. Again, this
8 is a tumor with a very high background incidence
9 approaching 50 percent in many studies.

10 In this particular study, the 500 ppm was
11 significant in terms of the Peto's Prevalence Test. The
12 other dose groups did not show anything. I hope this
13 doesn't offend my statistician sitting next to me here.
14 But this is one of those, in my opinion, a statistic
15 fluke.

16 DR. THRALL: Okay. Any other comments about the
17 pituitary tumors pardistalis (phonetic)? Okay.

18 DR. MCCONNELL: And then I think we're left with
19 the leukemia, if I'm not mistaken. Mononuclear cell
20 leukemia. Have we covered all the other ones?

21 The mononuclear cell leukemia in the Fischer
22 rat, as all of you know --

1 (END OF TAPE 3, SIDE A)

2 DR. MCCONNELL: -- that it is influenced by many
3 things. It can be increased as well as decreased, and
4 therefore the data have to be looked at very carefully in
5 terms of deciding whether something is treatment related
6 in either direction. I'm working from table 16 in that
7 same document that I was given.

8 And looking at this data, the part that I guess
9 the reason it was presented to us was because of what was
10 observed in the 100/50 ppm group. In that group there
11 was a -- I guess it was significant pair-wise at the .025
12 level, but was not significant at 500 ppm, nor at 6,000
13 and 12,000, nor was there any evidence of a change with
14 regard to the Peto's Prevalence Test.

15 Therefore, I don't think that this observation
16 is related to the exposure of the test material.

17 DR. THRALL: Dr. Gaylor?

18 DR. GAYLOR: The Peto Prevalence Test is
19 inappropriate for this tumor, because as stated, maybe 80
20 percent of these tumors are the cause of death and you
21 see the tumor when the animal dies.

22 So what needs to be done with this -- with the

1 mononuclear cell tumor is a Poly-3 test. And I can't --
2 I can't tell looking at these. We don't know when these
3 animals are dying and what the tumor incidence is with
4 time. The proper analysis needs to be done and then, you
5 know, just off hand I don't think there is anything going
6 on here.

7 But I really can't -- I would have to reserve
8 that judgment until I saw the results of either using the
9 Peto test considering these as all fatal tumors, or
10 better still using this Poly-3 test. So I don't think we
11 can tell from the presentation of the data.

12 DR. THRALL: Dr. Chen?

13 DR. CHEN: Chen. I agree with Dr. Gaylor about
14 the proper test. Use either Poly-3 test or Peto fatal
15 tumor test, or just use a lab table test. And what
16 original kind of confused me is about table 16B. The
17 denominator is number with the MCL. But what really the
18 denominator -- the proper denominator should be number of
19 animal still alive at that particular time. And in that
20 case, then you will see kind of -- maybe you will not see
21 that steep response rate. And in that case, the 600 ppm
22 or 500 ppm, you may not get a significant.

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1 And so, of course, what about when the average
2 time to tumor and you can see other than the highest dose
3 of 12,000 ppm would have a difference of the time to
4 tumor difference. Usually that's what -- if you do a
5 Peto test, probably you're going to get -- may not get a
6 trend, but probably can get a significant in that
7 particular group.

8 But the 16B, the way kind of tabulate seems you
9 have an increase in response, but really the denominator
10 should be the number of still alive at that time.

11 DR. COPLEY: That wasn't the purpose of this
12 table. This table was meant to demonstrate -- or meant
13 to ask the question, is there increased severity on the
14 MCL. Not -- I mean on the MCL itself, not increased
15 frequency. They were not looking at incidence. And
16 you're correct. If we were doing that type of
17 evaluation, this would not be the way it was done.

18 Statistics were not done on this table. It was
19 only to visually see if you could determine, and whether
20 it was -- and then we would have to decide afterwards, is
21 it scientifically correct to use MCL as a cause of death
22 as an indicator of severity. It was a question that was

1 posed at our meeting.

2 DR. CHEN: Thank you.

3 DR. THRALL: Any other comments regarding MCL?
4 Okay.

5 DR. COPLEY: What was the bottom line after all
6 of that?

7 DR. MCCONNELL: The bottom line was that -- at
8 least for me was that I didn't think that there is any
9 effect of malathion on the incidence of mononuclear cell
10 leukemia in either the male or the female Fischer rat.

11 DR. GAYLOR: And Gaylor's bottom line is we
12 can't tell until we do a statistical analysis.

13 DR. THRALL: Yes, Dr. Roberts?

14 DR. ROBERTS: Roberts. Is it possible to get
15 that analysis? I mean, is that something that we could
16 ask to have done and provided to the committee, or do we
17 just say we just can't decide because the analysis wasn't
18 done?

19 DR. MCCONNELL: It would take somebody a few
20 hours to do it.

21 MALE SPEAKER: I would just ask the
22 representative from Kemy Nova, Judy Housworth, to see if

1 she could pull up something on the MCL. I don't know if
2 she has it in her package or not.

3 DR. MCCONNELL: Well, we can give her a few
4 minutes to try to find that while we finish discussing
5 this question, if that's all right.

6 DR. THRALL: Yes. Dr. Williams?

7 DR. WILLIAMS: Gary Williams. I think this
8 tumor type really exemplifies the statistical problem
9 that I was referring to earlier. Because as Dr. Boorman
10 can probably tell you in greater detail, NTP has
11 encountered any number of bioassays in which there has
12 been one or another group with a statistical increase,
13 but could never be determined to be treatment related.

14 Now what I want to share with you is an
15 experience with another organo chlorine which EPA knows
16 as trichlorfon, which in the bioassay that was done when
17 it was -- I guess it's an herbicide, is it? I'm not
18 exactly sure what its use is. But it's the precursor to
19 dichlorvos. But anyhow it produced in one sex at one
20 dose a statistically significant increase.

21 Now trichlorfon was given another name of
22 triphenate (phonetic) and came back as a treatment for

1 alzheimer's. And the regulatory authorities wanted,
2 because of this finding of mononuclear cell leukemia,
3 another bioassay done. Bottom line, it didn't confirm
4 the finding from the first study.

5 So I think that just shows how, again, with a
6 high incidence tumor like this, when you're sampling a
7 lot of groups, you can always find -- there is always a
8 possibility for one increase.

9 DR. GAYLOR: Gaylor. We're aware of that, and
10 that's why NTP and I agree for something like mononuclear
11 cell tumors we would require significance at the .01
12 level before we get very excited about it. So we conduct
13 a more stringent statistical test on the common tumors to
14 minimize that problem. It doesn't eliminate it, but to
15 minimize it.

16 DR. THRALL: All right. Any other comments?

17 DR. MCCONNELL: On?

18 DR. THRALL: On --

19 DR. MCCONNELL: Mononuclear?

20 DR. THRALL: Not necessarily MCL, but regarding
21 question three?

22 DR. MCCONNELL: Well, I was going to summarize

1 that.

2 DR. THRALL: Okay.

3 DR. MCCONNELL: And say that in the totality of
4 looking at these other lesions that we've been asked to
5 look at, other kinds of tumors, that for me nothing stood
6 out as being related to malathion. And I'm in concert
7 with Dr. Williams in regard that these kind of things
8 usually show up on bioassays. They are important to
9 discuss, and they're important to evaluate and put to
10 bed, if you will, so that one has evaluated all the data.

11 But I see nothing here that suggests to me that
12 any of these tumors were related to the treatment.

13 DR. THRALL: Dr. Gaylor?

14 DR. GAYLOR: I want to bring up another tumor
15 that has not been addressed. They're in the report. And
16 that's the adrenal tumor. And the reason I bring that up
17 is that it appeared in two studies in the male rat. In
18 the old NCI study at the mid dose of 2,000 parts per
19 million, there was a statistically significant increase
20 in adrenal tumors, significant at the .01 level. And in
21 the Kemy Nova study at a mid dose at the 6,000 parts
22 million, also the adrenal tumors were statistically

1 significant on a pair-wise comparison with the controls
2 at the .01 level.

3 So here we have a tumor that we can't argue --

4 MALE SPEAKER: Dave, can I just -- are you
5 talking about pheochromocytomas or adrenal --

6 DR. GAYLOR: Just call it adrenal. I don't -- I
7 don't know.

8 MALE SPEAKER: It makes a difference.

9 DR. GAYLOR: I don't know. It was -- they were
10 just referred to as adrenal tumors in the NCI study. And
11 I think we have the Kemy Nova study. We ought to be able
12 to --

13 DR. COPLEY: Excuse me. Could you tell us what
14 you're getting that from so we can find it?

15 DR. GAYLOR: What I'm getting at? What I'm
16 getting at is adrenal tumors --

17 DR. THRALL: No, no.

18 DR. COPLEY: Where?

19 DR. THRALL: She said where are you getting it.

20 DR. GAYLOR: Oh, where I'm getting this from.

21 DR. COPLEY: Not what. I'm sorry. I meant what
22 are you reading?

1 DR. GAYLOR: I'll see if I can find it. The
2 adrenal tumors from the NCI report number 192 (1979).

3 MALE SPEAKER: Yeah. Those were pheochrome
4 cystomas.

5 DR. GAYLOR: Okay. And there were two out of 49
6 in the controls and 11 out of 48 in the 2,000 parts per
7 million. And the Kemy Nova -- what are Kemy Nova adrenal
8 tumors?

9 DR. COPLEY: No, which document is it that we
10 gave you? Otherwise, I have no way of finding it.

11 DR. GAYLOR: We've got so many documents.

12 DR. COPLEY: Well, they all have six letter --
13 six number things right on the very top stamped on it.
14 And that will help me locate it.

15 DR. GAYLOR: Well, give me a minute. It's the
16 Kemy Nova study on the Fischer 344 rat with malathion.
17 Twelve out of 70 controls had adrenal. And I don't know.
18 It just said adrenal. Sixteen out of 55 at the 6,000
19 parts per million. So it must be -- it's in the Kemy
20 Nova report. It's not in any summary data, because it's
21 been totally ignored. So it wasn't in any summary
22 documents that were given us. I would have to go back.

1 DR. WILLIAMS: Are you aware of this, Dr.
2 Dementi? You know this data.

3 DR. DEMENTI: I'm aware of the pheochrome
4 cystoma. It was a questionable finding in the early NCI
5 study. I mean, are you asking me what does he have there
6 in his hand?

7 DR. WILLIAMS: No. I'm interested. -- they were
8 pheochrome cystomas?

9 DR. DEMENTI: Yes.

10 DR. WILLIAMS: Not particle tumors?

11 DR. DEMENTI: That was the term used, yes.
12 Pheochrome cystomas.

13 DR. WILLIAMS: And the second study that he's
14 referring to, were those also?

15 DR. DEMENTI: I don't know what he's talking
16 about.

17 DR. GAYLOR: I'm talking about the Kemy Nova
18 study. I'm not a pathologist. I don't know. They call
19 them adrenal tumors. I don't know.

20 MALE SPEAKER: We don't quite know what you're
21 talking about.

22 DR. WILLIAMS: Nor do we.

1 DR. BOORMAN: If you look -- and I don't know if
2 it's the same. This is the reexamination of the NCI
3 Histopathology. And if you look at the pheochrome
4 cystomas, in the males they go zero, two, zero, five, and
5 in the females they go one, two, zero, zero. So there is
6 nothing on the reexamination if this is the same study.

7 DR. GAYLOR: Are you talking about the Kemy Nova
8 study?

9 DR. BOORMAN: I'm talking about the NCI study.
10 There is nothing in the NCI study on the reexamination
11 done by Hasman and Huff.

12 MALE SPEAKER: And one other guy.

13 DR. GAYLOR: Well, the numbers -- so the old --
14 the numbers I was looking -- well, I was looking at the
15 1979 report. So I'm looking at the original data in the
16 1979 report. And you say that's been re-read?

17 DR. BOORMAN: If we're talking about the same
18 thing. This is a reexamination. I'll bring the table
19 over to you. It did not hold up on the reexamination.

20 DR. GAYLOR: So what did you just read off?

21 DR. BOORMAN: I'll bring it over.

22 DR. GAYLOR: Well, read it off. Read it off for

1 everybody.

2 DR. BOORMAN: If we're talking about the same
3 thing, this is table two on the report by Cuff, McConnell
4 and Hasman and everybody else. It's out of the pool
5 controls of 2 out of 50. The low dose is zero out of 46.
6 The high dose is 5 out of 44. That's for the male
7 Osborne-Mendel rats.

8 For the female, the pool controls are 2 out of
9 46, zero out of 50 and zero out of 45.

10 DR. GAYLOR: I'm looking at Fischer 344.

11 DR. BOORMAN: Then I'll look at that.

12 DR. GAYLOR: Yeah, I agree. In Osborne-Mendel I
13 didn't see anything.

14 DR. BOORMAN: I don't know if it's worthwhile.
15 The male Fischer 344 rats are five out of 49, 10 out of
16 48 and 6 out of 46. The females are 3 out of 48, 2 out
17 of 47, 3 out of 49. So you have something that was not
18 seen in the male or female Osborne-Mendel rats. It was
19 not seen in the female Fischer rats. And from this
20 table, I can't tell if 5 out of 49 is statistically
21 significant from 10 out of 48. But the high dose is 6
22 out of 46.

1 DR. GAYLOR: Read the male -- read the male
2 again for the 344?

3 DR. BOORMAN: I'll bring it over.

4 MR. LEWIS: Dr. Boorman, also can you cite this
5 for the record what document you're referring to?

6 DR. BOORMAN: Yeah. It was one that was
7 provided to us. It's on the docket.

8 DR. THRALL: While they're looking that up,
9 there were comments made as to whether it mattered that
10 these were pheochromocytomas versus adrenal tumors.
11 Would someone want to address that for the record?

12 DR. CAPEN: Yeah, I would like to comment.

13 DR. THRALL: Okay, Dr. Capen?

14 DR. CAPEN: The two parts to the adrenal are
15 functionally embryologically structurally different.
16 They respond to different signals. The adrenal medullary
17 tumors are a very common tumor in many strains of
18 laboratory rats in contrast to the adrenal cortical
19 tumor.

20 DR. THRALL: So if they are pheochromocytomas,
21 then it's going to sort of fall into these other
22 categories as far as tumor incidence in this type of rat?

1 DR. CAPEN: Right.

2 DR. THRALL: Dr. Williams?

3 DR. WILLIAMS: Yes, Gary Williams. Well, we'll
4 eventually see what emerges here. But I had tabulated
5 the finding under discussion from the original report,
6 because I tried to find every statistically significant
7 event. And this increase that is 10 out of 48 in the low
8 dose group versus 5 out of 49 in the controls was
9 statistically significant at .02 by life table analysis.

10 So it doesn't meet that high threshold that Dr.
11 Gaylor eluded to a moment ago of .01 for a commonly
12 occurring tumor.

13 DR. THRALL: All right. And now, Dr. Boorman,
14 are you ready to tell us for the record what the document
15 is?

16 DR. BOORMAN: This is Gary Boorman. And for the
17 record, it is the article by Huff, Bates, Ustes, Hasman
18 and McConnell. It appeared in Environmental Research,
19 volume 37, pages 154 to 173 (1985). And this was
20 provided to us as part of our material.

21 DR. THRALL: Okay. Dr. Gaylor, do you want to
22 address this now?

1 DR. GAYLOR: Yeah. I'll drop the adrenal tumor.
2 The reevaluation done by NTP would indicate that there
3 was nothing in the adrenal in that old study. And I'm
4 still a little -- I'm still not clear where this number
5 came from. But, again, it would be a single isolated
6 event from the Kemy Nova study if indeed it is true.

7 So I'm not concerned. It didn't show up in two
8 studies like I thought it had.

9 DR. THRALL: Okay, thank you. So have we
10 adequately summarized our response regarding question
11 number three? Last chance for any additional comments
12 regarding this. All right.

13 We are ready then for question 2.5. Okay, Dr.
14 Roberts?

15 DR. ROBERTS: I'm sorry. Did we get an answer
16 about whether or not we were going to get any statistical
17 recalculation?

18 DR. THRALL: I think someone was searching.

19 MALE SPEAKER: They didn't have it.

20 DR. THRALL: They don't have it.

21 DR. ROBERTS: So the answer is no.

22 MALE SPEAKER: On the MCL, right?

1 DR. GAYLOR: MCL. I mean, they could supply
2 that before we write our report, but we wouldn't have it
3 today.

4 DR. THRALL: Okay. So Dr. Gaylor will do those
5 statistics?

6 DR. GAYLOR: No. I don't have the data.

7 DR. WILLIAMS: We can rely on Kemy Nova's
8 statistics, I think. I don't see any reason why we
9 can't.

10 DR. ROBERTS: Yeah. I just wanted to know --
11 just get a definitive answer whether or not they were
12 going to provide -- whether we could look for that
13 information or not.

14 DR. WILLIAMS: And I would hope that the agency
15 would verify the statistics that Kemy Nova does.

16 DR. THRALL: Okay. Question 2.5?

17 DR. COPLEY: This is the 2.6 that I had
18 originally called 2.5. Okay. Does the SAP agree with
19 the proposed CARC classification of malathion as
20 suggestive? Why or why not? And the suggestive was
21 based on the description I had given yesterday from the
22 cancer assessment guidelines.

1 DR. THRALL: Okay. And Dr. Williams will lead
2 this discussion.

3 DR. WILLIAMS: Yes. I don't agree with the
4 classification. And I looked at the criteria for
5 classification and tried to fit into that the findings
6 that we have. And those findings are increases in benign
7 liver tumors in rats and mice at the highest doses, and
8 possibly now this reduction in the latency period for the
9 interstitial cell tumors in the male Fischer rats.

10 I considered whether these data would fit your
11 category of likely. But I considered that not
12 appropriate, because as I read the criteria, they require
13 strong experimental evidence. And I wanted to comment on
14 that, because to me strong experimental evidence of
15 carcinogenicity is when the chemical induces in the
16 animals a type of tumor not seen in the controls. And we
17 don't have that at all here.

18 A somewhat lesser effect is when the chemical
19 increases a type of tumor seen in the controls. And we
20 have that. And at a lower level I would place reduction
21 of latency. And we have possibly an example of that.

22 And then finally just for completeness, another

1 criteria that is frequently used is an increase in the
2 multiplicity of tumors with no increase in incidence in
3 any of the treated groups. And we haven't been
4 confronted with a situation like that today.

5 So I found that there was neither strong
6 experimental evidence for carcinogenicity, nor did the
7 evidence implicate the tumor increases to be due to a
8 mode of action that was relevant to humans. And I think
9 to the contrary we have information that leads us to
10 believe, certainly for the rodent liver tumors, that the
11 mode of action for their increases is not relevant. And
12 notably there is no evidence for a DNA reactive
13 mechanism.

14 The category that EPA settled on was suggestive,
15 which I found I couldn't support, because the tumor
16 increases occurred only under conditions of toxicity that
17 are not relevant to human exposures. In particular, the
18 exposures at which the benign liver tumors were
19 increased, the animals exhibited profoundly reduced body
20 weight gain, hepatomegaly and liver cell hypertrophy.
21 And these latter findings, as I discussed, are indicative
22 of metabolic overload.

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1 And therefore I favored the categorization of
2 inadequate for those findings, i.e., the liver tumors and
3 now the reduced latency for the interstitial cell tumors.

4 For all of the other exposures at which no
5 tumors were increased, I believe that these and the much
6 lower environmental exposures to malathion -- and I think
7 here we should recognize the fact that just by rough
8 calculations, these high doses that are being used in
9 these animal studies were somewhere in the order of a
10 million fold higher than environmental exposures.

11 I find that the low doses used in the bioassays
12 at which there were no increases in tumors are unlikely
13 to constitute a human cancer hazard.

14 DR. THRALL: Thank you. Dr. Everitt, do you
15 have additional comments?

16 DR. EVERITT: I would concur. I had trouble
17 myself trying to pigeonhole our thoughts in our
18 discussions today into these five categorizations. But I
19 feel strongly that we have trouble interpreting the
20 extremely high concentrations that I think exceed the
21 maximum tolerated dose. And so I feel like the
22 assessment is inadequate to utilize that material.

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1 But I think at the lower concentrations, I feel
2 that the liver tumor response that we see is atypical,
3 probably associated with functional impairment of
4 metabolism. And I think that I would think it's unlikely
5 to pose a human cancer hazard. I do not feel that we
6 should put their suggestive evidence of carcinogenicity
7 on the weight of mouse liver tumor evidence in this study
8 in the absence of finding hepatic carcinomas.

9 DR. THRALL: Other Panel members? Dr. Gaylor?

10 DR. GAYLOR: Our two previous speakers failed to
11 mention the nasal epithelial adenomas. I think we have
12 some suggestion there that at least there is again
13 statistical evidence for these rare tumors. Now, again,
14 it's high dose.

15 I have a hard time placing things in categories
16 while ignoring the dose. And if you could pump 10,000
17 parts per million of malathion into people for a
18 lifetime, you would have some strange people running
19 around. And I think it's likely some of them would have
20 tumors.

21 And even -- and I'm not so certain whether there
22 is anything going on at 500 or 800 parts per million.

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1 And, again, if you could pump that into people for a
2 lifetime, maybe you would see tumors. But I would say
3 it's highly unlikely you would see tumors in humans as
4 environmental exposures, particularly with intermittent
5 exposures.

6 So I find it hard to pick a category without
7 addressing dose. We've heard that the metabolism to
8 malaaxon is going to be basically the same in humans and
9 animals. Now, of course, there is a question of where
10 that gets saturated. If we don't use the two high doses,
11 if we say we're going to ignore the results at the two
12 high doses -- and, you know, I appreciate the arguments
13 for that.

14 Then we have to say, well, then we don't have an
15 adequate study. We really don't have a MTD. A MTD is
16 probably some -- I don't know, I'm guessing -- 2 to 4,000
17 parts per million, and we have 800 parts per million. So
18 I don't know what I'm saying.

19 It's very difficult to put it in a category.
20 But I would go with the suggestive, because I'm a little
21 bit concerned about -- even though the interstitial tumor
22 is very common, and the only thing we're seeing there is

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1 an earlier occurrence, I don't really know what's going
2 on in the mononuclear cell. The thyroid follicular cell
3 showed a dose response in the male rat for adenoma and
4 carcinoma combined. C-cell is pretty -- the thyroid C-
5 cell is pretty weak.

6 So there are some things going on. Some of
7 those are probably statistical artifacts, but are all
8 four of them statistical artifacts? Who knows. So I
9 would go with the suggestive category.

10 DR. THRALL: Yes, Dr. Needleman?

11 DR. NEEDLEMAN: I have expressed my disquiet
12 with the evaluation of the data before, so I won't go
13 over it in any depth. Just in a very summary fashion.

14 I read CARC I first, and I found it persuasive.
15 And I saw that EPA came to a conclusion that it was a
16 likely carcinogen. That seemed to be sensible. Then I
17 read CARC II and it said it was downgraded. And I have
18 spoken about the selective post hoc. I said elimination
19 on the basis of exposure, and then the elimination on the
20 basis of outcome. So you have two reevaluations at
21 different aspects of the study.

22 Now I did this. I said suppose I had to write

1 this up for publication. I was given the assignment of
2 writing these proceedings up to simply submit it to a
3 journal. I could write the message very clearly. I
4 could write the results. And then I would have to say,
5 and then we excluded this group because we defined them
6 as excessive dose, and we excluded these diagnoses on the
7 basis of a reevaluation.

8 I would have a great deal of difficulty writing
9 that in a coherent fashion, and I wonder what the fate of
10 that paper would be. I think I can tell you what it
11 would be in the journals I serve on. So I believe that
12 there are big mythologic solecisms at work here in the
13 reevaluation of the database that has been produced by
14 the registrant.

15 And one other thing. I was given a paper today
16 from Mutation Research, which says that malathion does
17 produce breakages in DNA. That's from 1999. I think
18 that has to be read by all of us, too.

19 DR. THRALL: Yes, Dr. Williams?

20 DR. WILLIAMS: Right. Can I try to clarify
21 again for the record, because Dr. Gaylor has used the
22 word ignore, and Dr. Needleman has used the word exclude,

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1 that in my assessment I'm not ignoring or excluding
2 anything. I'm accepting those rodent liver tumors, and
3 I'm arriving at what I think is their implication for
4 human cancer hazard.

5 Now the thing about the EPA guideline, these
6 categories are different from what are used, for example,
7 by the NTP. The NTP categories have no reference to
8 human risk whatsoever. They would just be grading animal
9 tumors. And if we were doing an NTP categorization, it
10 would probably look quite different than this one. But
11 this one weaves in human risk assessment into the
12 categorization.

13 And suggestive says that the findings raise a
14 concern for carcinogenic effects in humans. And nothing
15 I see here raises any concern in my mind about potential
16 cancer hazards to humans. And that's why I'm not in the
17 suggestive ballpark.

18 DR. THRALL: Dr. Brusick?

19 DR. BRUSICK: I don't think I could be
20 comfortable with the unlikely category, simply because
21 once we interpret the data and use whatever method for
22 exclusion or ignoring or not weighing it or extrapolating

1 it, I don't think, in my opinion, the data that we have
2 left, the portions of the studies that remain, are
3 adequate to claim an unlikely interpretation.

4 DR. THRALL: Dr. McConnell?

5 DR. MCCONNELL: Yes. I think it's important
6 that all of us get on the record. Can you hear me? I
7 think it's important that all of us get on the record,
8 because this is the bottom line.

9 And that being the case, I think there are two
10 things here. I think I agree with the evaluation of
11 unlikely based on the animal data. But I was less than
12 persuaded, even though we had very little presentation on
13 the epidemiology, that what we heard certainly is
14 inadequate to say anything about the human situation
15 under human exposure conditions.

16 So I guess I would lean toward unlikely if I had
17 to base it strictly on animal data, and inadequate if I
18 had to consider human data.

19 DR. THRALL: Thank you. Dr. Roberts?

20 DR. ROBERTS: Yeah. As I look at the data, I
21 think that the positive responses at high doses create
22 the qualitative descriptor. I mean, it is tumorigenic at

1 high doses. And I think that qualitative description --
2 you can't hear me?

3 DR. COPLEY: Not well.

4 DR. ROBERTS: Not well. Okay, how is this,
5 better? That qualitative description I think leads to
6 the suggestion. At the same time, I think when we look
7 at those high doses, I agree with many of the comments
8 that have been made earlier, as well as my own points
9 that I don't think those doses are suitable for dose
10 response extrapolation. I think there are a lot of
11 problems with trying to infer dose response information
12 from those.

13 One of the difficulties, as I look at this in
14 trying to understand dose response, is we don't have data
15 from intermediate doses. We don't have a mode of action
16 that would give us perhaps some insight into what the
17 shape of the dose response curve should perhaps look
18 like.

19 And while I find Dr. Williams' postulated
20 mechanism of metabolic overload attractive -- and I think
21 that's very reasonable, and if I had to bet money on it,
22 that would be a very reasonable place to bet. But we

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1 don't have, at least presented to us, any information
2 about what's going on metabolically at any of these
3 doses.

4 So I'm left with the situation that I think we
5 have very little data to work with to come up with any
6 kind of a quantitative dose response information on
7 malathion beyond the suggestion of carcinogenicity
8 provided by those high dose data.

9 So I think that's unfortunately kind of the
10 situation where we are. It may earn this label
11 qualitatively, but going beyond that and coming up with
12 kind of dose response information, I think, is very
13 difficult given what we have. We could perhaps make some
14 qualitative statements that based on the nature of the
15 response that responses -- cancer responses in humans
16 would be very unlikely.

17 But I don't think we've got enough data to do
18 anything more specific than that.

19 DR. THRALL: Dr. Boorman?

20 DR. COPLEY: What was your final answer on the
21 qualitative aspects of it, since that's really what we're
22 asking for?

1 DR. ROBERTS: Yeah. I thought that the
2 description -- I guess I'm back to suggestive. I thought
3 that the description provided by Dr. Hill earlier -- in
4 other words, there is enough there to say suggestive, but
5 certainly not enough to try and quantify a cancer risk.
6 It seems pretty reasonable after taking a look at all of
7 this.

8 DR. THRALL: Dr. Boorman?

9 DR. BOORMAN: One of the things that I was
10 struck by was that we're giving fairly high doses, and I
11 think nobody here is arguing that the animal should have
12 been dosed at higher doses. And there is really a lack
13 of malignant tumors in a variety of sites. It was an
14 extensive examination.

15 The real believable effect is in the liver. And
16 one of the striking things about the liver was it was
17 essentially restricted to benign, proliferative lesions.
18 And whether these are actual adenomas or hyperplasias, we
19 don't know. But I think that if it had potent
20 carcinogenic activity, it would certainly have been
21 manifested in the liver by the appearance of malignant
22 lesions, which we didn't see.

1 And so I'm sort of at the level that I think
2 that the data is inadequate for an assessment of the
3 human carcinogenic potential. I think that there is not
4 enough evidence there.

5 And I think EPA has done a very good job looking
6 at all of the different sites and tissues. I think Brian
7 Dementi has been very concerned and called attention to a
8 lot of areas, which I think is the way these important
9 chemicals should be treated.

10 But in the end I think that, you know, the
11 occasional nose tumors and stuff like that -- one in the
12 males and two in the females -- don't come to the level
13 of suggestive for me. And I'm sympathetic with what Dr.
14 Williams suggested that perhaps it's unlikely at low
15 doses, but I don't know enough for dose response
16 relationships to really make that statement.

17 So I would probably end up with the data are
18 inadequate for an assessment.

19 DR. THRALL: Thank you. Dr. Capen?

20 DR. CAPEN: Yeah. I think I would come down
21 about the same level. I certainly couldn't support
22 suggestive evidence of carcinogenicity for the reasons

1 that largely Dr. Boorman has summarized. I think I would
2 come down on data are inadequate.

3 DR. THRALL: Thank you. Dr. Chen?

4 DR. CHEN: Yeah. I would support EPA
5 classification about data that suggests some
6 carcinogenicity evidence based on the liver tumor
7 particularly in male mice study. And even if we see the
8 two high dose are significant, the two low dose, in my
9 opinion, still show some indication of the
10 carcinogenicity.

11 Unless -- we just talk about the two low dose,
12 and in my opinion 800 ppm is not a MTD. So unless --
13 there is no evidence of these two mechanisms about high
14 dose and low dose effect. And also there is some
15 evidence of mutagenicity. So we look at it based on no
16 threshold control study.

17 So it does have some suggestion about some
18 carcinogenicity.

19 DR. THRALL: Dr. Dementi, did you have a comment
20 a while ago?

21 DR. DEMENTI: I was going to ask, to the extent
22 that you all consider the data inadequate, are you

1 calling for more studies?

2 MALE SPEAKER: No.

3 MALE SPEAKER: No.

4 MALE SPEAKER: No.

5 DR. THRALL: Yes, Dr. Everitt?

6 DR. EVERITT: I would make the case that perhaps
7 it would be worth getting some handle on this suggestion
8 that if we think we know the metabolism of malathion that
9 it might help in the interpretation of the hepatic
10 response if we at least knew what was happening in some
11 relatively straightforward metabolism studies.

12 I'm not suggesting that a bioassay be repeated.
13 But I think knowing the mode of action would allow us to
14 get a determination perhaps of the shape of the dose
15 response curve. And I think all of us on the committee
16 are feeling that the concentration setting on this
17 chronic bioassay is less than optimal. And, you know, at
18 the risk of being the Monday morning quarterback,
19 certainly nobody would have necessarily chosen this
20 concentration setting regiment knowing what turned out.

21 And I think that perhaps some relatively limited
22 straightforward metabolism studies might shed some light

1 onto some of the things that Dr. Williams is suggesting
2 for a potential mode of action. Which I totally agree
3 with everything that has been said. It's really kind of
4 speculative, including what I've said.

5 DR. THRALL: Dr. McConnell?

6 DR. MCCONNELL: Yeah. When I said no further
7 studies, I was talking about two year bioassays, okay.
8 But I do support what Dr. Everitt said. It would be
9 enlightening to see a well conducted study such as he's
10 talking about. But I hope you envision that there would
11 be some cell proliferation component to that such a
12 study, because I think that might help in the mode of
13 action.

14 DR. COPLEY: May I just ask for clarification on
15 what Dr. Everitt said? When you talked about metabolism
16 studies, are you talking about male, female, rat or mouse
17 or any?

18 DR. EVERITT: Well, I would suggest that at
19 least in the mouse, where we have what I would call -- I
20 think what we have is an unusual situation for evaluation
21 where we have an extremely -- I don't want to use the
22 word extremely. We have a high incidence of benign

1 neoplasms that appears to be restricted to concentrations
2 that we have been arguing for the past day and a half,
3 are they exceeding the maximum tolerated dose.

4 Well, most people feel that certainly the 16,000
5 exceeded anybody's definition of the MTD, and presumably
6 the 8,000 in both sexes. And so with that in mind, the
7 next concentration down, nobody is satisfied that we've
8 tested at the highest concentration we ideally would want
9 to see.

10 And so we're struggling with this. And perhaps
11 knowing what the metabolic profile is for hepatic
12 metabolism, and knowing are we in fact at that 800 ppm
13 saturating important pathways for, you know, hepatic
14 activation, I think would be important information for a
15 mode of action.

16 DR. THRALL: Yes, Dr. Williams?

17 DR. WILLIAMS: I can't sit quiet if we're
18 designing research, because that's what I love.

19 Okay. What you want here is something of the
20 order of a 90 day study spanning a nice tight dose range,
21 going down from your high doses and filling in those, you
22 know, gaps between 800. And then you plug in several

1 parameters for DNA damage in the liver. It could either
2 be an in vivo/in vitro UDS or P-32 post labelling.

3 You have sentinel groups for metabolism along
4 the way. You do either BUdR or P-32 -- or, I mean PCNA
5 for cell proliferation. You measure enzyme induction.
6 Then you can nail down the kind of mechanism that I was
7 eluding to.

8 DR. THRALL: All right. Any other comments?

9 DR. WILLIAMS: I'll be happy to do it.

10 DR. THRALL: Okay. Dr. Dementi?

11 DR. DEMENTI: I had one question. When you were
12 talking about statistics on the leukemia data, was that -
13 - which set of data was that for that you were asking us
14 to give you? Is that the mortality?

15 DR. GAYLOR: Gaylor. You look at -- what you
16 have to have is the age that every animal is removed from
17 the study, which you have. Whether or not it had a
18 mononuclear cell tumor. And this is in the Fischer 344
19 rats from the Kemy Nova study.

20 That's all the information you need, and you can
21 do this Poly-3 test or you can do the log rank. Probably
22 that's what they have available in their arsenal.

1 There's a log rank test or the Peto or the Cox test. You
2 probably have, you know, people at EPA who run that. Do
3 that.

4 DR. DEMENTI: In other words, the data is
5 showing an increased percentage of animals --

6 DR. GAYLOR: I can't tell what the data is
7 telling us on mononuclear cell tumor without knowing at
8 what age those tumors are being detected and how many
9 animals at risk and the animals at risk for a fatal tumor
10 and the number of animals that are alive at different
11 points in time.

12 So that data is impossible for me to interpret
13 without that analysis.

14 DR. DEMENTI: In other words, that data, though,
15 is the data that someone was seeking statistically?

16 DR. GAYLOR: Yeah. That data is available.

17 DR. DEMENTI: So I'm just saying --

18 DR. GAYLOR: It would take me half a day to do
19 it.

20 DR. DEMENTI: I understand. But somebody is
21 going to do that.

22 DR. GAYLOR: Well, I hope so.

1 MALE SPEAKER: Our statistician isn't here right
2 now. But you're talking about the middle line of those
3 three?

4 DR. GAYLOR: No, no, no, no.

5 MALE SPEAKER: It doesn't even -- it goes down.

6 DR. GAYLOR: No, I'm not talking about the
7 middle line. I'm talking about the analysis.

8 MALE SPEAKER: The top line.

9 DR. GAYLOR: No. Well, yeah, top line. But
10 those denominators --

11 (END OF TAPE 3, SIDE B)

12 DR. GAYLOR: -- hand off my chin. What we need
13 is an analysis of the tumor incidence. We need to know
14 the number of animals at risk in each of the dose groups.
15 And the Cox test or the Peto Fatal Tumor test -- or what
16 else? Oh, the log rank test. There are three tests that
17 give essentially the same results and take into account
18 the mortality across dose groups.

19 And that analysis needs to be conducted. And it
20 could be done with -- well, and the Poly-3 test is
21 another test. So there are three or four tests that
22 should give similar results that take into account

1 mortality for fatal tumors.

2 MR. LEWIS: Dr. Gaylor, could I suggest that
3 within the next week that you provide to the agency what
4 you're requiring, and I can share it with the entire
5 Panel and with the agency also. Just a brief description
6 of what's being required.

7 DR. GAYLOR: I'm requiring a standard typical
8 statistical analysis that is done worldwide, that's been
9 available for 20 years, and should be in the EPA arsenal
10 of statistical techniques that they use for analyzing
11 data. In fact -- I don't know. They've used these --
12 they've done these analyses.

13 I'm not asking for anything unusual here. I'm
14 just asking for a standard statistical analysis that NTP
15 does. FDA does.

16 MR. LEWIS: I just want to make sure we're not
17 left with a lot of ambiguity here. Is the Panel asking
18 for something to be done that they want to see the
19 results of before they're going to be able to finalize
20 what they've just told us, or is this just information
21 you want? What's going to be done with this information?
22 We have to be very, very clear on what the process is

1 from now until the committee meets to finalize its
2 report.

3 DR. GAYLOR: Well, I would look at the results
4 and make some statement in our written report. I think
5 whether that comes out positive or negative will not
6 change how people view malathion as to whether they
7 consider the data inadequate, unlikely or suggestive. I
8 don't think that single outcome is going to change the
9 bottom line.

10 MR. LEWIS: Okay.

11 DR. GAYLOR: It's just going to be another
12 paragraph that should be in the report.

13 MR. LEWIS: Okay, thanks.

14 DR. THRALL: So maybe it would be useful, Dr.
15 Williams, for you to sort of summarize. There was
16 obviously no consensus here. But perhaps you can sort of
17 summarize the response to question 2.5 by the various
18 Panel members and how it will appear in the report.

19 DR. WILLIAMS: Well, as I heard it -- and I was
20 just consulting -- Dr. Finnercrisp has been tabulating.
21 I assume that's on the written record.

22 But I heard Dr. Needleman voicing support for

1 likely, the original CRC. And I didn't hear anyone else
2 supporting that point of view. There were then several
3 in support of suggestive, which supports the EPA
4 position. And then there were a lesser number of us that
5 were in favor of inadequate or not likely.

6 So what I heard is that reasons were brought
7 forward for every option available to us, except for
8 carcinogenic to humans. Apparently no one thinks that is
9 the case. So I think we just -- I'm not sure that it has
10 value to saying how many people were for each, but rather
11 just capturing what reasons were given for recommending
12 whatever categorization. Because finally we're only
13 advisory to the EPA, and then they have to decide how
14 gave them the best advice.

15 DR. THRALL: Yeah. And the reasons for those
16 different opinions will be in the report.

17 DR. WILLIAMS: Yes. Right.

18 DR. THRALL: Okay. All right. I think we've
19 gone as far as we can on question 2.5. Now there was one
20 other item, and that was Dr. Brusick was going to
21 summarize some information that was not available to us
22 earlier?

1 DR. BRUSICK: Right. I was given two
2 manuscripts that have been published and two abstracts.
3 Let me just sort of go backward just a little bit and
4 indicate that there are a couple of sets of data. There
5 is the data that came in to EPA with the registrant's
6 submission that covered the battery of tests required by
7 EPA. All these results were negative. Dr. DeGeorge
8 indicated that at FDA, as part of their evaluation of
9 malathion for different reasons, they have some short
10 term tests that are all negative.

11 And I think on the basis of that -- or those
12 results, the conclusion was that mutagenicity doesn't
13 play a role in any of the tumors that were seen even at
14 the high dose.

15 There was, as I had indicated, however, a review
16 that was done that showed several things. To summarize
17 very briefly from this review that was done by the -- in
18 California. I have to go back and find it, but I did
19 refer to it earlier. There were some findings showing
20 that gene mutation tests, whether they be in bacteria or
21 cells or cultures and so on, were uniformly negative,
22 indicating that there wasn't a likely production of

1 adducts to the DNA that would result in base-pair
2 substitutions or friendship mutations and things of that
3 sort.

4 But in vitro tests for sister chromatid exchange
5 and chromosome aberrations were very often positive with
6 malathion and malaoxon, whether they were done in vitro
7 lymphocytes or CHL cells. There were about 10 to 12
8 studies, most of them were positive either for chromosome
9 aberrations or for sister chromatid exchange or both.

10 And then there were some in vivo studies for the
11 micronucleus that showed at high dose levels -- acute
12 high dose levels in the mouse. Under certain conditions
13 -- interparietal injection -- you could get evidence for
14 chromosome breakage. So there was in the published
15 literature indications that under certain conditions you
16 could have chromosome breakage.

17 Then there was the discussion about, or the
18 suggestion that there were some other papers by a Dr.
19 Plasiak in Poland. Now I've got two papers for Dr.
20 Plasiak, as well as an abstract. Both of these came from
21 publications which I think would have been reviewed. I
22 mean, the methodology looks reasonable. Then the

1 interpretation, as far as I can tell, having just looked
2 at these very briefly, seems reasonable.

3 In mutation research the evaluation there would
4 have been reviewed -- peer reviewed by individuals who
5 are very familiar with this assay, as well as the other
6 journal, which is Pesticide Biochemistry and Physiology.
7 I'm not as familiar with that journal.

8 The methods that were used -- it's called the
9 comet assay. And essentially the comet assay exposes
10 cells. These were cells that were -- these were studies
11 that were done in vitro with malathion, 99.8 percent pure
12 amaloxone (phonetic), exposing the cells and looking for
13 evidence of single strand and double strand breaks in
14 this assay. It's an assay in which you expose the cells
15 and then you subject them to electrophoresis. And if you
16 have broken DNA, you get a nice little tail, and then the
17 length of that tail is an indication of the amount of DNA
18 strand breakage. It's called the comet assay, a single
19 cell gel electrophoresis assay.

20 The results with malathion in this assay up to
21 the toxic levels that could be used were negative. And
22 this, as I said, was almost absolute pure malathion. But

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1 with malaoxon, they reported positive results, and the
2 results looked very good. Dose response -- it's not a
3 high dose toxic effect, but multiple doses showed
4 increasing rates of DNA damage.

5 In the second study that they performed, which
6 is kind of interesting, they used a score bait to see if
7 they could interfere with the DNA damaging effect for the
8 following reason. And I'll just read two or three
9 sentences.

10 Because malaoxon differs from its parent
11 compound biooxygen (phonetic) atoms added in place of the
12 sulphur, it is reasonable to consider an oxidative origin
13 of observed damages. Oxygen atoms can be a source of
14 reactive oxygen species which have potential to cause
15 damage to DNA.

16 And I think, again, if in fact we're looking at
17 something that is a reactive oxygen species, you would
18 expect it to produce some single strand breaks in DNA,
19 which could be interfered with by all sorts of radical
20 scavengers like ascorbate. Those would be the initial
21 lesions that might give rise to sister chromatid exchange
22 and chromosome breakage, but not gene mutation. So it

1 sort of all hangs together.

2 The other thing that they showed in their other
3 paper was that these -- this DNA damage, if you expose
4 the cells, wait a little while and then look for DNA
5 damage, it's virtually all repaired. So, again, single
6 strand breaks due to reactive oxygen species present,
7 they're very, very rarely repaired.

8 So, again, I think this is an indication that
9 the metabolite malaoxon may be able to react in some way
10 with DNA. It's active oxygen species or something that
11 is produced along with it during metabolism that might
12 have this effect. But the phenomenon in in vivo is
13 probably not going to be any relevance to anything
14 because it's unlikely that those reactive oxygen species
15 at low doses are going to do anything to any significant
16 extent. And if they would, it would be repaired readily.

17 But at massive doses it's very possible you
18 could overwhelm the ability to scavenge the reactive
19 oxygen species or to repair the damage and there could be
20 some effects. If they are present, most likely it would
21 be chromosomal sister chromatid exchange type damage.

22 So in a sense that's the data. I don't think

1 that it has -- that it changes what was already out in
2 the literature or any conclusions. But it does provide a
3 little bit more information to sort of put the pieces
4 together and makes it tie together, and sort of gives
5 some logic to some of the findings that maybe, you know,
6 malathion per se in an animal wouldn't give you a lot of
7 a positive response that Gene mentioned in the
8 micronucleus test, because very little of it -- if it's
9 absolutely pure, very little of it is converted to
10 malaaxon. But if you use technical grade, you've already
11 got a bunch of that there, and it goes in and you'll see
12 this chromosome damage.

13 There was another abstract. I think I just need
14 to mention it. It's an incomplete study, but it was part
15 of the information that was given to us. And this is by
16 another group, Dick Albertini at the University of
17 Vermont, who looks at gene mutation in human T-lymphocyte
18 cells in vitro.

19 And they have done some studies where they have
20 analyzed 101 mutants -- HPTR mutants -- from human
21 lymphocytes, 24 from controls and 77 from malathion
22 treated cell cultures, trying to sequence the HPRT

1 mutants to see if there is a different gene -- a
2 different base or configuration involved in the mutants
3 versus the controls, which would indicate that you've got
4 a chemical induction versus another alternative which is
5 selection of preexisting mutations.

6 And until this analysis is finished, it's not
7 really -- you can't reach any conclusions. There were no
8 conclusions as to whether the malathion treated mutants
9 really were new induced mutants in these cells, which
10 would be the first time a gene mutation response was
11 found, or whether you're really looking at an enrichment
12 of preexisting mutations in that population.

13 So that's the new data.

14 DR. THRALL: Dr. McConnell?

15 DR. MCCONNELL: Yeah. I think to be fair to Dr.
16 Hard that we probably ought to put into the record
17 whatever it was his final analysis was, whether it's
18 likely or unlikely.

19 DR. THRALL: Do you have that?

20 DR. MCCONNELL: I don't have it in front of me.
21 I hope somebody has their's handy. I was looking for it
22 and I misplaced it.

1 DR. GAYLOR: Dr. Thrall?

2 DR. THRALL: Yes?

3 DR. GAYLOR: I think I would object to that,
4 because, you know, having served on study sections and
5 things, you don't get to vote unless you're there. I
6 mean, he hasn't heard all of our deliberations on, you
7 know, these various tumor types.

8 So I don't think that would be an informed
9 opinion at this point.

10 DR. THRALL: But it's my understanding that his
11 report will be -- that will be in our report, right? Or
12 will he have a chance to modify that?

13 MR. LEWIS: Basically, as I mentioned before,
14 Dr. Hard and Dr. Swenberg are two individuals that
15 provided written comments to the SAP in terms of this
16 session. So basically it's written comments that are
17 provided to the Panel and that the Panel can react or
18 respond to. Dr. Hard will not be part of the Panel
19 report writing process.

20 DR. THRALL: I see.

21 MR. LEWIS: All they are are public comments,
22 just like other people provide public comments, that you

1 as Panel members are at liberty to consider or not
2 consider.

3 DR. MCCONNELL: I'm at your pleasure.

4 DR. THRALL: I would suggest that they be read.

5 DR. MCCONNELL: Okay.

6 DR. GAYLOR: Well, I wasn't objecting to that.
7 I thought it became part of our conclusions.

8 MR. LEWIS: No.

9 DR. GAYLOR: Yeah.

10 MR. LEWIS: Again, he's just a public commenter
11 like the other people you had yesterday.

12 DR. THRALL: Okay.

13 MR. LEWIS: It's the same procedure.

14 DR. GAYLOR: Say that again?

15 MR. LEWIS: Dr. Hard is a public commenter,
16 similar to the people we heard yesterday, so all you're
17 doing is just -- you basically reviewed a public comment
18 from Dr. Hard and are just summarizing the remarks.

19 DR. GAYLOR: Okay.

20 DR. THRALL: Do you want to do that?

21 DR. MCCONNELL: Sure. It's quite short.

22 I do not agree that the evidence for

1 carcinogenicity of malathion is suggestive. My view is
2 that the weight of the evidence leads to support for not
3 likely to be carcinogenic in humans. Justification for
4 this is provided in my responses to the preceding
5 questions.

6 In short, I do not believe that there is a
7 positive and significant tumor response at any organ site
8 after discounting dose groups in which there was
9 excessive toxicity.

10 DR. THRALL: All right. Are there any final
11 comments from the Panel regarding any of the questions or
12 anything else that you want to have appear in the report?

13 All right. Then I would ask EPA if they have
14 any further questions of us, or have we, in your opinion,
15 answered these as best we can? Obviously, they are
16 questions for which there is no consensus.

17 DR. COPLEY: I have a copy of the rat report,
18 and it mentions what statistical analyses were done. And
19 I would just like to read them and have you tell me
20 whether this is what you had in mind, since you had
21 mentioned some of these tests.

22 And it was the Cox test and the Gehan, Breslow,

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1 Cruxel, Wallace analysis based on the incidence and
2 survival. Is that something different than you were
3 talking about? I know you mentioned Peto with fatal,
4 which I know is a different test. But you had mentioned
5 some other tests as well.

6 DR. GAYLOR: The Gehan, Breslow test is a log
7 rank type test, so, yeah, that's find.

8 DR. THRALL: Dr. Gaylor?

9 DR. GAYLOR: Yes?

10 DR. THRALL: Could you speak up?

11 DR. GAYLOR: The answer is yes. The Gehan,
12 Breslow test would be adequate for looking at the
13 mononuclear cell tumor.

14 DR. THRALL: And is that one of the tests that
15 you had?

16 DR. COPLEY: That's what the method says.

17 DR. GAYLOR: Did you have that?

18 DR. COPLEY: I don't have Appendix P here to
19 actually look at the table to see if there were any stars
20 in that particular table.

21 DR. GAYLOR: So maybe it's been done. It would
22 be awfully easy to miss. We had so much to look at.

1 DR. THRALL: Okay.

2 DR. CHEN: Can I make a comment?

3 DR. THRALL: Dr. Chen?

4 DR. CHEN: Yes. In those tests -- you mentioned
5 the Cox and the Gehan test. I believe they look at the
6 mortality, whether they have a differential mortality.
7 But what we suggest would be, you can use the same test
8 and test the leukemia. Just use the same test to test
9 for leukemia.

10 DR. THRALL: We're checking. It may be that
11 that was done on this test.

12 DR. CHEN: Okay.

13 DR. THRALL: Okay. Yes?

14 MR. O'SHAUGHNESSY: I just wanted to make one
15 brief point.

16 MR. LEWIS: Sir, come up to the microphone.

17 DR. THRALL: Do you want to come up to the table
18 and use the microphone and identify yourself?

19 MR. O'SHAUGHNESSY: Donald O'Shaughnessy from
20 Kemy Nova. I made a quick call back to verify what is on
21 our CSF for technical malathion. It's referring back to
22 the mutagenicity discussion. And I have verified that

1 zero is the value for malaoxon in the technical.

2 I just wanted to also point out that
3 mutagenicity studies are generally regarded as support
4 for a mechanism for carcinogenicity, if there is
5 carcinogenicity. Malaoxon was tested at vastly higher
6 doses than you would get from metabolism at those doses
7 and it was not in fact carcinogenic. So in fact any
8 mutagenicity would have no bearing.

9 DR. THRALL: Okay. Any other questions of the
10 Panel from EPA?

11 DR. COPLEY: I just want to be clear on the
12 things that we still have outstanding. And one of them
13 is the statistics on the MCL, which we actually may be
14 able to resolve today. And I can't remember if there was
15 actually anything else that we were suppose to provide to
16 the Panel.

17 DR. THRALL: I don't believe so.

18 DR. COPLEY: So that if we get this resolution
19 today, then some of the people that had concerns about
20 this, they may actually be able to come to a conclusion?

21 DR. THRALL: I don't think so.

22 DR. COPLEY: Okay.

1 DR. THRALL: I think that that was asked a while
2 ago, and the response was that those statistics will
3 probably not alter anyone's opinion as far as answering
4 question 2.5 or 2.6, whatever it was.

5 DR. COPLEY: Okay.

6 DR. THRALL: All right. Then I would like to
7 thank the Panel members for working very hard and
8 responding in a very clear way, I think, to these
9 questions. And I would like to thank EPA for their very
10 clear reports to us.

11 And with that, I would -- and, Dr. Finnercrisp,
12 do you have any final comments?

13 DR. FINNERCRISP: Ditto.

14 DR. THRALL: Okay, very good. Then we are
15 adjourned.

16 (Whereupon, the meeting was concluded.)

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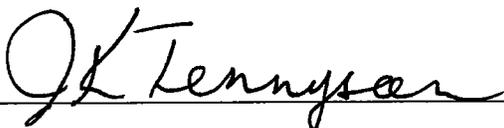
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